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# Ten-Year Follow-Up After 96 Weeks Treatment With Peginterferon Plus Tenofovir in Hepatitis D (HIDIT-II): Improved Clinical Outcome After Combination Therapy

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## ABSTRACT

**Background:** Chronic delta hepatitis represents a major health burden. Until recently, pegylated interferon-alfa-2a (PEG-IFNα) therapy was the only treatment option for patients infected with hepatitis D virus (HDV). The aim of this study was to evaluate 10-year long-term clinical and virological outcomes after 96 weeks of treatment with PEG-IFNα with or without tenofovir disoproxil fumarate (TDF).

**Methods:** We conducted a retrospective follow-up study of the Hep-Net-International-Delta-Hepatitis-Intervention-Study 2 (HIDIT-II trial). Patients had received 96 weeks of treatment with either PEG-IFNα-2a plus TDF or PEG-IFNα-2a alone. Patients were included if they had completed the 96-week treatment period and had at least one follow-up visit (PEG-IFNα-2a + TDF; $n = 51$, PEG-IFNα-2a alone; $n = 56$).

**Results:** Patients who received PEG-IFNα-2a + TDF were younger (37 vs. 42 years) and no significant differences were observed in other baseline characteristics between the two treatment arms. A total of 26 patients (24%) developed one or more

**Abbreviations:** AST, aspartate transaminase; AUC, area under the curve; CHD, chronic hepatitis D; CI, confidence interval; EASL, European Association for the Study of the Liver; EOT, end of treatment; FU, follow-up; GGT, gamma glutamyl transferase; HBsAg, hepatitis B surface antigen; HBV DNA, hepatitis B viral DNA; HBVcccDNA, hepatitis B virus covalent closed circular DNA; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HDV RNA, hepatitis delta viral RNA; HIDIT-II, Hep-Net-International-Delta-Hepatitis-Intervention-Study 2; HR, hazard ratio; INR, International Normalized Ratio; ISGs, interferon stimulated genes; LTX, liver transplantation; MELD, Model of end stage liver disease; NA, nucleoside analogue; PEG-IFNα, pegylated interferon-alfa-2a; ROC, receiver operating characteristics; SD, standard deviation; TDF, tenofovir disoproxil fumarate.

The first two authors contributed equally to this article.

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liver-related endpoints after a mean time of 8.4 years. The incidence of endpoints was significantly lower in the combination group (14% vs. 34%, $p = 0.02$). The development of liver-related endpoints was also associated with non-response to therapy (HDV RNA and HBsAg), elevated HBV DNA at week 72, and baseline age, cirrhosis, platelets, INR, AST, GGT, bilirubin and albumin according to the Cox regression model.

**Conclusions:** The long-term follow-up of this large randomised clinical trial demonstrates that combination therapy with TDF and virological response to PEG-IFNα-2a (undetectable HDV RNA and HBsAg loss) were associated with better clinical outcomes.

**Trial Registration:** NCT00932971, EudraCT 2008-005560-13

## 1 | Introduction

Hepatitis delta is considered to be the most severe form of viral hepatitis in humans [1–4]. Until recently, pegylated interferon alfa (PEG-IFNα) was the only treatment option for chronic hepatitis D (CHD) with a documented beneficial effect on clinically relevant endpoints [2, 5–7]. Despite the demonstrated efficacy of bulevirtide in reducing HDV RNA in clinical studies, the reduction of HBsAg was observed only in combination therapy with PEG-IFNα [8]. Moreover, the availability of this drug is limited in the majority of regions globally. The recent EASL guideline on CHD management recommends considering a course of therapy with PEG-IFNα for a period of 48 weeks in patients with compensated liver disease [9]. The 5- and 10-year follow-up assessments of the largest randomised controlled clinical trial, the HIDIT-1 study [10], confirmed the beneficial effects of PEG-IFNα on endpoints and further emphasized that off-treatment month 6 undetectable viremia does not necessarily indicate a sustained viral response, and late relapse is common in CHD patients treated with IFN [5, 11]. However, off treatment HDV RNA negativity at any time point was found to be associated with the absence of clinical events. This suggests that a single timepoint of undetectable HDV RNA may be sufficient for a favourable disease course [5]. A beneficial effect of nucleoside analogues (NA) in CHD has been reported in 2 studies from Spain for prolonged TDF-treatment in patients with HIV [12, 13]. Based on these data a complementary randomised controlled study was conducted with the more potent NA tenofovir (TDF) which did not show a greater decline in HBsAg levels with PEG-IFNα + TDF combination therapy compared to PEG-IFNα monotherapy [14], although there was a trend for undetectable HDV RNA being more frequently observed in the combination versus. monotherapy groups (48% vs. 33%, $p = 0.125$), respectively. The current study assessed the 10-year follow-up of PEG-IFNα combined with TDF versus. PEG-IFNα monotherapy.

## 2 | Patients and Methods

### 2.1 | Patients and Data Collection

The Hep-Net International Delta Hepatitis Interventional Trial-II (HIDIT-II), a multicentre randomised study was conducted between 2009 and 2017. According to the original HIDIT-II trial by Wedemeyer et al. [14], patients with chronic HDV infection and compensated liver disease who were aged 18 years or older were eligible for inclusion. All patients were HBsAg positive for at least 7 months, anti-HDV positive for at least 3 months, and HDV RNA positive at the local laboratory at the screening visit. In the original study, patients were excluded if alanine aminotransferase (ALT) levels exceeded 10 times the upper limit of normal or if platelet counts were below 90,000 per μL. Prior interferon therapy or treatment with NA within the preceding 6 months also constituted the exclusion criteria. This resulted in 120 patients with chronic hepatitis D being randomised to receive either PEG-IFNα (180 μg once a week) plus TDF (300 mg daily) for 96 weeks or PEG-IFNα (180 μg once a week) plus placebo for 96 weeks. For the present retrospective 10-year follow-up analysis, all patients who had completed the 96-week treatment period in the HIDIT-II study and had at least one follow-up visit were eligible for inclusion ($n = 107$) (Figure 1). Data for these patients were collected retrospectively based on a structured CRF from July 2022 to August 2024. The participating sites documented clinical and virological information annually. Laboratory parameters were evaluated at the local level. HDV RNA in the HIDIT-II study (visits until follow up week 356) was quantified using the Cobas TaqMan system with an in-house assay (Roche Diagnostics, Mannheim, Germany) [14, 15]. Subsequently, retrospectively assessed HDV RNA was subjected to local testing. Any retreatment was at the attending physician's discretion; no randomisation took place. Cirrhosis was defined histologically according to Ishak scores of F5-F6 or if the elastography result was greater than 15.2 kPa [16] or ARFI > 1.8 m/sec [17]. Additional criteria were based on the original manuscript [14, 15].

### 2.2 | Ethics

The Ethics Committee of the Hannover Medical School approved the HIDIT-II study and the retrospective follow-up assessment (Vote no.5292 and 10,273_BO_K_2022). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the respective national competent Authorities. All patients provided written informed consent before enrolment or were anonymized at the responsible centres.

### 2.3 | Statistical Analyses

Statistical analyses and the creation of figures were performed using SPSS software (SPSS Inc., Chicago, IL, version 28). All parameters were described as mean +/− SD. $p$ values < 0.05 were considered statistically significant. Continuous variables were analysed by t-tests. For nonparametric parameters Mann-Whitney U-tests were used. A chi-square-test was calculated



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**Key Summary**

- Summarise the established knowledge on this subject
  - Hepatitis delta is the most severe form of viral hepatitis.
  - Treatment with pegylated interferon alpha (PEG-IFNα) has been demonstrated to result in off-treatment HDV RNA responses in 17%–43% of patients and has been associated with improved clinical long-term outcome.
  - Nevertheless, the additional impact of combination therapy with Tenofovir on both virological response and the clinical long-term outcome remains to be determined.
- What are the significant and/or new findings of this study?
  - Patients chronically infected with HDV receiving combination therapy of PEG-IFNα with Tenofovir developed less liver-related endpoints and had a greater decline in HDV RNA at EOT than patients receiving monotherapy with PEG-IFNα.
  - Virological response to PEG-IFNα (HDV RNA, HBsAg) favourably affected the long-term outcome of HDV infection
  - HBV DNA had an impact on long-term clinical outcomes.

for the comparison of discrete variables. In case of an expected cell count ≤ 5, Fisher's exact test was used instead. Parameters that were associated with a better clinical long-term outcome in univariate time-dependent Cox-regression models ($p < 0.05$) were additionally compared in multivariate analysis. Multivariate Cox-regression analyses were performed using the likelihood ratio-test for backward selection. Hazard ratios (HRs), including their 95% confidence intervals (CIs), were calculated for the Cox-regression models. Using Kaplan-Meier analysis the cumulative event free survival was calculated. Different risk groups were compared by log rank-tests. Patients lost to follow-up, deceased, or reaching an endpoint were censored at their last recorded visit.

## 3 | Results

### 3.1 | Patients' Characteristics

In total, 107 patients completed the 96-week therapy and had at least one follow-up visit ($n = 56$; PEG-IFNα + placebo, $n = 51$; PEG-IFNα + TDF) (Figure 1). There were no significant differences in baseline characteristics between the two treatment arms, except for a slightly but significantly younger age profile (37 vs. 42 years, $p = 0.04$) in the PEG-IFNα + TDF arm (Table 1). The mean follow-up period was 8.4 years (ranging from 1.8 to 13.1 years), with 46 having a follow-up of 5–10 years and 42 patients with a FU of more than 10 years. After the 96 weeks treatment period, re-treatment with interferon-based therapy was administered to 22 patients and four patients received bulevirtide. Further analyses regarding re-treatment are provided in the supplement.

### 3.2 | Virological Outcome

By end of treatment (EOT) at week 96, 48 patients (45%) were found to have undetectable HDV RNA. During the follow-up period, 26 patients (54%) experienced a post-treatment relapse, with one patient becoming positive again after more than 5 years (Figure 2). For a comprehensive overview of the HDV RNA course, please refer to the provided supplement. A reduction in the levels of HBsAg from baseline to EOT was observed in 15 patients (14%). Of these patients, 11 demonstrated persistent

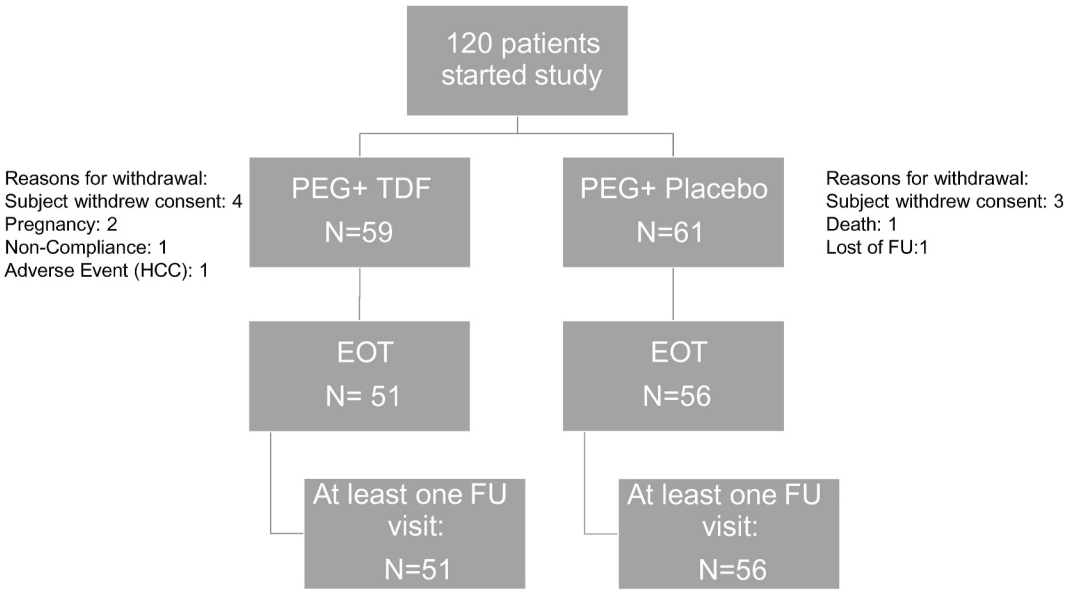



**FIGURE 1** | Study flow chart. Flow chart illustrating patient selection from the original HIDIT-II trial to the long-term follow-up cohort. The figure indicates the number of patients screened, randomised to PEG-IFNα + TDF or PEG-IFNα + placebo, the number completing 96 weeks of treatment, and those included in the follow-up analysis. Reasons for exclusion (e.g., loss to follow-up, missing data) are also shown. EOT = end of treatment; HBV = hepatitis B virus; HDV = hepatitis D virus; PEG-IFNα = pegylated interferon alfa; TDF = tenofovir disoproxil fumarate.



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**TABLE 1** | Baseline characteristics of the study population.

| Variable | PEG-IFNα + TDF ($n$ = 51) | PEG-IFNα + placebo ($n$ = 56) | $p$-value |
|---|---|---|---|
| Male, $n$ (%) | 35 (69%) | 37 (66%) | 0.78 |
| **Age (years), mean ± SD (range)** | **37.6 ± 12.3 (20–64)** | **42.1 ± 10.4 (20–60)** | **0.04** |
| AST (IU/L), mean ± SD (range) | 75.8 ± 53.2 (29–293) | 76.4 ± 42.2 (30–226) | 0.46 |
| ALT (IU/L), mean ± SD (range) | 116.8 ± 106.1 (32–540) | 113.6 ± 69.7 (33–339) | 0.65 |
| Bilirubin (mg/dL), mean ± SD (range) | 0.83 ± 0.43 (0.23–1.9) | 0.80 ± 0.43 (0.20–1.9) | 0.92 |
| Albumin (g/dL), mean ± SD (range) | 4.2 ± 0.5 (3.1–5.2) | 4.2 ± 0.4 (3.3–5.1) | 0.89 |
| Platelets ($10^3$/μL), mean ± SD (range) | 180.6 ± 84.6 (84–633) | 161.7 ± 49.6 (70–276) | 0.17 |
| INR, mean ± SD (range) | 1.10 ± 0.13 (0.9–1.3) | 1.06 ± 0.10 (0.9–1.2) | 0.50 |
| MELD, mean ± SD (range) | 7.9 ± 1.6 (6–14) | 7.8 ± 1.4 (6–12) | 0.77 |
| HDV RNA ($\log_{10}$ IU/mL), mean ± SD (range) | 4.9 ± 1.3 (0–6.9) | 4.8 ± 1.1 (2.6–6.3) | 0.78 |
| HBV DNA ($\log_{10}$ IU/mL), mean ± SD (range) | 2.2 ± 1.4 (0–6.9) | 2.3 ± 1.6 (0–8.4) | 0.67 |
| HBsAg ($\log_{10}$ IU/mL), mean ± SD (range) | 3.9 ± 0.5 (2.8–4.8) | 3.7 ± 0.6 (1.7–4.6) | 0.38 |
| Cirrhosis, $n$ (%) | 21 (41%) | 21 (38%) | 0.69 |

*Note:* Values are mean ± SD (range) unless otherwise stated. Bold indicates a statistically significant difference between groups ($p < 0.05$).
Abbreviations: Units: INR = international normalised ratio; IU = international units; MELD = Model for End-Stage Liver Disease; SD = standard deviation.

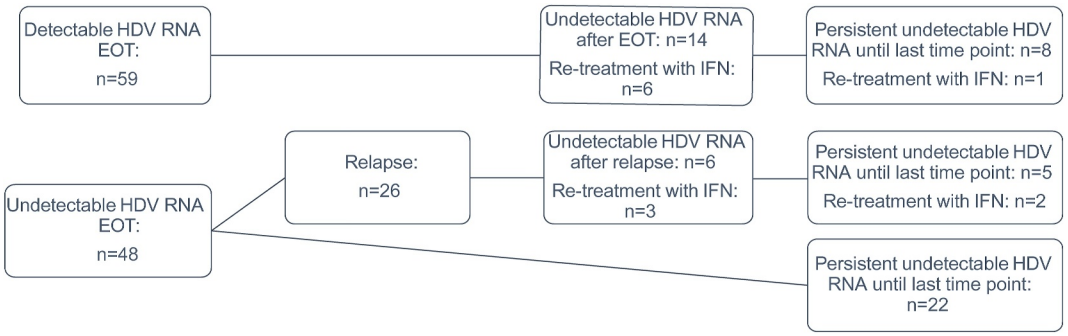



**FIGURE 2** | HDV RNA kinetics during follow-up. Long-term HDV RNA levels from end of treatment (EOT) up to 10 years of follow-up. Shown are individual patient trajectories for those with undetectable HDV RNA at EOT and those with detectable HDV RNA. Relapse was defined as reappearance of detectable HDV RNA after EOT among patients who were HDV RNA–negative at EOT. EOT = end of treatment; HDV = hepatitis D virus; RNA = ribonucleic acid.

HBsAg loss during FU. Four additional patients exhibited undetectable HBsAg during subsequent follow-up. Consequently, a total of 15 (14%) patients showed loss of HBsAg, with eight allocated to the placebo arm and seven to the PEG-IFNα + TDF arm. There were no differences in HDV RNA relapse ($p = 0.91$) or undetectable HBsAg ($p = 0.93$) between the two treatment arms. However, a significantly higher proportion of patients with TDF exhibited undetectable HDV RNA at EOT ($n = 28$ (55%) versus. $n = 20$ (36%), $p = 0.05$) (Table 2). Decline in HDV RNA at EOT (defined as log HDV RNA baseline divided by log HDV RNA at EOT) was significantly higher in the PEG-IFNα + TDF arm compared to the placebo arm (Δ3.1 vs. Δ2.4; $p = 0.02$). Furthermore, a significant difference was observed in HBV DNA levels between the two treatment arms at week 72 ($p = 0.01$) and EOT ($p = 0.02$), with the placebo arm demonstrating higher values. Seven patients in the placebo arm and none in the PEG-IFNα + TDF arm showed evidence of HBV DNA levels exceeding 2000 IU/mL at EOT.

### 3.3 | Clinical Outcome

A progression to cirrhosis from baseline was detected in 29 patients after a mean of 1.8 years (ranging from 0.9 to 6.8 years) after baseline. After EOT, a total of 26 patients (24%) developed one or more liver-related endpoints. However, six patients received IFN re-therapy prior to the development of an endpoint, and were therefore excluded from further analysis. Consequently, a total of 20 endpoints occurred after a mean time of 4.1 (1.4–8.9) years (Table 3). For further analysis, only the first event was considered, which included decompensation ($n = 8$), HCC ($n = 8$), LTX ($n = 2$) and death ($n = 2$). The number of endpoints developed by patients in the PEG-IFNα + placebo arm was higher than that in the PEG-IFNα + TDF arm ($n = 15$ (27%) versus $n = 5$ (10%), $p = 0.02$). In the Cox regression model, therapy with TDF was associated with an improved long-term clinical outcome (log rank: $p = 0.04$) (Figure 3a).



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**TABLE 2** | Characteristics at end of treatment (week 96).

| Variable | PEG-IFNα + TDF ($n$ = 51) | PEG-IFNα + placebo ($n$ = 56) | $p$-value |
|---|---|---|---|
| **Undetectable HDV RNA, $n$ (%)** | **28 (54.9%)** | **20 (35.7%)** | **0.05** |
| **HBV DNA ($log_{10}$ IU/mL), mean ± SD** | **1.05 ± 0.66** | **1.61 ± 1.77** | **0.02** |
| HBsAg ($log_{10}$ IU/mL), mean ± SD | 3.09 ± 1.46 | 3.29 ± 1.28 | 0.15 |
| ALT (IU/L), mean ± SD | 61.6 ± 69.5 | 74.9 ± 88.1 | 0.20 |
| Undetectable HBsAg, $n$ (%) | 7 (13.7%) | 6 (10.7%) | 0.63 |

*Note:* Values are mean ± SD (range) unless otherwise stated. Bold indicates a statistically significant difference between groups ($p < 0.05$).
Abbreviations: Units: IU/mL = international units per millilitre; SD = standard deviation.

**TABLE 3** | Follow-up characteristics.

| Variable | PEG-IFNα + TDF ($n$ = 51) | PEG-IFNα + placebo ($n$ = 56) | Total ($n$ = 107) | $p$-value |
|---|---|---|---|---|
| Follow-up, mean ± SD (range) | 8.6 ± 3.3 (1.8–13.1) | 8.2 ± 3.4 (2.2–13.1) | 8.4 ± 3.3 (1.8–13.1) | 0.55 |
| **Overall endpoints, $n$ (%)** | **7 (13.7%)** | **19 (33.9%)** | **26 (24.3%)** | **0.02** |
| **Endpoints prior to initiation of re-treatment, $n$ (%)** | **5 (9.8%)** | **15 (26.8%)** | **20 (18.7%)** | **0.02** |
| Decompensation, $n$ (%) | 4 (7.8%) | 7 (12.5%) | 11 (10.3%) | 0.32 |
| HCC, $n$ (%) | 2 (3.9%) | 8 (14.3%) | 10 (9.3%) | 0.06 |
| LTX (liver transplantation), $n$ (%) | 1 (2.0%) | 6 (10.7%) | 7 (6.5%) | 0.07 |
| Death, $n$ (%) | 2 (3.9%) | 6 (10.7%) | 8 (7.5%) | 0.17 |
| Development of cirrhosis, $n$ (%) | 1 (6.7%) | 2 (10.0%) | 3 (8.3%) | 0.73 |
| Increase in MELD, $n$ (%) | 5 (9.8%) | 5 (8.9%) | 10 (9.4%) | 0.88 |
| HDV RNA relapse after EOT | 15/28 (53.6%) | 11/20 (55.0%) | 26/48 (54.2%) | 0.91 |
| Undetectable HDV RNA at last available visit, $n$ (%) | 15 (49.9%) | 14 (48.3%) | 29 (48.6%) | 0.91 |
| HDV RNA ever undetectable, $n$ (%) | 32 (62.7%) | 30 (53.6%) | 62 (57.9%) | 0.47 |
| Undetectable HBsAg, $n$ (%) | 7 (13.7%) | 8 (14.3%) | 15 (14.0%) | 0.93 |
| Positive anti-HBs, $n$ (%) | 2 (3.9%) | 5 (8.9%) | 7 (6.5%) | 0.26 |
| Re-treatment with IFN, $n$ (%) | 12 (23.5%) | 10 (17.9%) | 22 (20.6%) | 0.47 |
| Re-treatment with NAs, $n$ (%) | 19 (37.3%) | 24 (42.9%) | 43 (40.2%) | 0.55 |
| Re-treatment with bulevirtide, $n$ (%) | 3 (5.9%) | 1 (1.8%) | 4 (3.7%) | 0.27 |

*Note:* Bold indicates a statistically significant difference between groups ($p < 0.05$). Endpoints include hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, and liver-related death.

#### 3.3.1 | Associations of Virological Response and Long-Term Outcome

Significantly higher levels of quantitative HDV RNA at EOT ($p = 0.02$) and week 120 ($p = 0.03$) were observed in patients who developed an endpoint (Figure 4a). Furthermore, undetectable HDV RNA at EOT was associated with a lower incidence of clinical complications ($n = 4$ (8%) versus $n = 16$ (27%), $p = 0.01$, log rank: $p < 0.01$) as was undetectable HDV RNA at least once during the observation period ($n = 6$ (10%) versus $n = 14$ (31%), $p < 0.01$, log rank: $p < 0.01$) (Figure 3b). Nevertheless, the incidence of clinical endpoints did not demonstrate a significant difference when comparing responders who remained free of relapse with non-responders/relapsers ($n = 3$ (14%) versus $n = 17$ (20%); $p = 0.37$). A greater reduction in HDV RNA from baseline to weeks 4 and 48 was further associated with a lower incidence of endpoints ($p < 0.01$ and $p = 0.04$) (Figure 4b). In addition, an association was observed between HBV DNA log at week 72 and the development of endpoints ($p < 0.01$). A total of 15 patients exhibited HBsAg clearance, and no patients achieving HBsAg developed an endpoint ($p = 0.04$). In the Kaplan-Meier analysis, undetectable HBsAg was found to be significantly associated with a favourable long-term clinical outcome (log rank: $p = 0.03$) (Figure 3c).

#### 3.3.2 | Factors Associated With Clinical Long-Term Outcome

In order to identify potential risk factors for the development of liver-related endpoints, a Cox regression analysis was performed (Figure 5, Table 4). In univariate Cox regression analysis, baseline cirrhosis ($p < 0.01$; HR: 4.25), age at baseline ($p < 0.01$; HR: 1.1), undetectable HDV RNA at EOT ($p = 0.01$; HR: 0.24), undetectable



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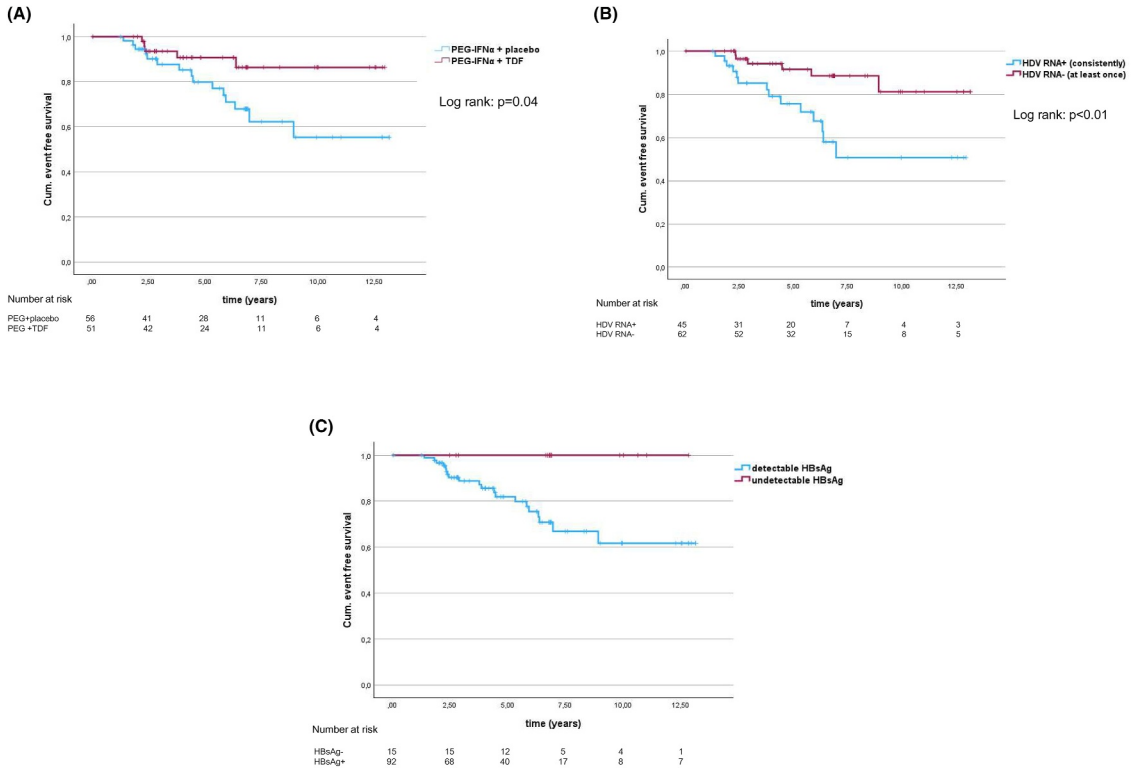



**FIGURE 3** | Kaplan–Meier analysis of long-term clinical outcomes. Kaplan–Meier survival curves comparing clinical outcomes between treatment arms and virological subgroups: (A) endpoint-free survival in patients treated with PEG-IFNα + TDF versus PEG-IFNα + placebo; (B) endpoint-free survival according to HDV RNA status at any time during follow-up; (C) endpoint-free survival stratified by HBsAg loss. Endpoints were defined as the first occurrence of hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, or liver-related death. Numbers at risk are displayed below each curve. HCC = hepatocellular carcinoma; HDV = hepatitis D virus; HBsAg = hepatitis B surface antigen; PEG-IFNα = pegylated interferon alpha; TDF = tenofovir disoproxil fumarate.

HDV RNA at least once during the observation period ($p < 0.01$; HR: 0.26), log HBV DNA at week 72 ($p < 0.01$; HR: 1.60) and therapy with PEG-IFNα + TDF ($p = 0.05$; HR: 0.36) were associated with the development of endpoints. A multivariate analysis was conducted to compare undetectable HDV RNA at EOT and undetectable HDV RNA at any timepoint, given their demonstrated similarity. This analysis showed that the presence of negative HDV RNA at any timepoint was a more effective prognostic indicator for predicting the occurrence of an endpoint ($p < 0.01$). Consequently, this factor was included in the subsequent multivariate Cox analysis, which indicated age ($p < 0.01$; HR: 1.07), undetectable HDV RNA at least once ($p < 0.01$; HR: 0.19) and therapy with PEG-IFNα + TDF ($p = 0.03$; HR: 0.24) as independent predictors of the development of endpoints. In order to ascertain whether combination therapy could have an added effect on non-responders, the Kaplan-Meier analysis was conducted comparing PEG-IFNα + placebo with PEG-IFNα + TDF in patients with detectable HDV RNA at EOT. This analysis indicated that non-responding patients treated with combination therapy still had a better long-term follow-up (log rank: $p = 0.05$) (Figure 6).

## 4 | Discussion

Here, we present the 10-year long-term results of the multicentre HIDIT-II study, the world's largest investigator-initiated hepatitis D treatment trial to date. Data from the original study and 5-year follow-up have already been published [14, 15]. Patients treated with the combination of PEG-IFNα and TDF had a better long-term clinical outcome and a higher decline in HDV RNA at EOT. Furthermore, undetectable HDV RNA at EOT or at any timepoint during the observation period, combination therapy with TDF and lower HBV DNA at week 72 were univariately associated with a favourable long-term clinical outcome, along with non-cirrhotic status at baseline and younger age. Age and therapy with PEG-IFNα and TDF as well as negative HDV RNA at any timepoint remained significant after multivariate Cox regression analysis. Therefore, our study is the first randomised trial to show a reduced incidence of liver-related endpoints in patients with hepatitis delta treated with TDF in combination with PEG-IFNα.

The mechanism underlying the observed TDF-associated benefits remains uncertain. Given that HDV does not encode its own viral enzymes, it is unlikely that TDF exerts a direct antiviral effect on HDV replication, which is consistent with previous studies showing limited efficacy of NAs against HDV [9, 10]. Only two studies in HIV-coinfected patients have demonstrated suppressed HDV RNA under prolonged TDF therapy [12, 13]. One possible explanation is that long-term NA use reduces the recycling of HBV DNA to the nucleus, lowering the HBVcccDNA pool and thereby decreasing HBsAg production over time [18]. Another potential mechanism is immune reconstitution in the context of effective antiretroviral therapy [19]. Additionally, emerging in vitro and in vivo data suggest



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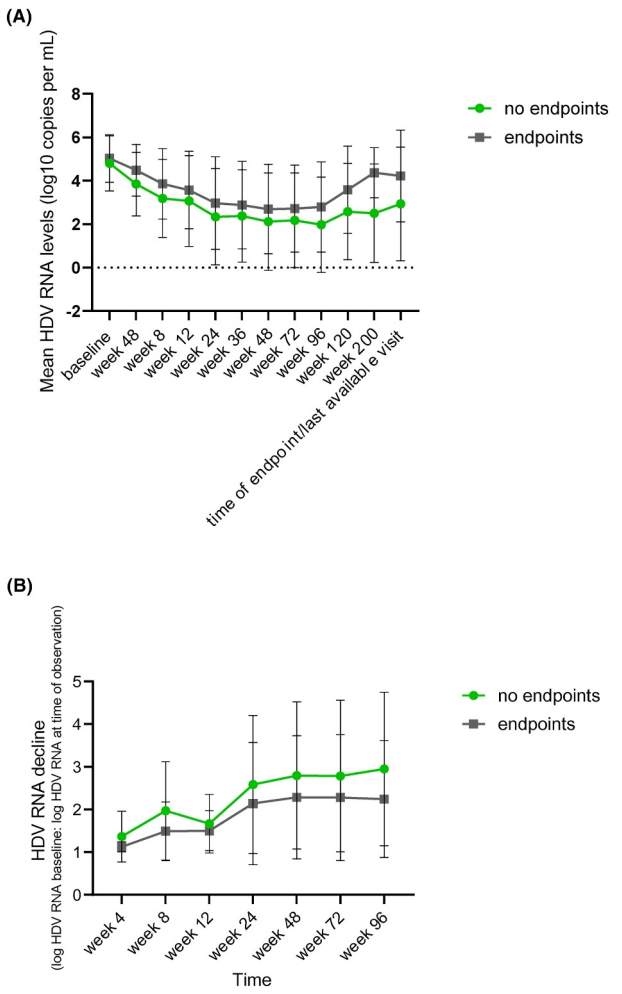



**FIGURE 4** | Virological response in patients with and without clinical endpoints. (A) Mean HDV RNA levels over time. Patients who developed a clinical endpoint had significantly higher HDV RNA levels at week 96 (end of treatment, EOT) ($p = 0.02$) and at week 120 ($p = 0.03$). (B) HDV RNA decline over time. HDV RNA decline, defined as $\log_{10}$ HDV RNA at baseline divided by $\log_{10}$ HDV RNA at the respective observation time point, was associated with a lower incidence of endpoints at weeks 4 and 48 ($p < 0.01$ and $p = 0.04$, respectively). Endpoints were defined as hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, or liver-related death. EOT = end of treatment; HCC = hepatocellular carcinoma; HDV = hepatitis D virus.

that TDF may exert immunomodulatory effects—including chemokine and cytokine induction—and may enhance interferon lambda signalling with subsequent upregulation of interferon-stimulated genes (ISGs) [20, 21]. These properties could theoretically amplify the immunological effects of PEG-IFNα when used in combination.

However, given the study's design, it is not possible to distinguish whether the observed benefits are attributable to TDF alone or to its combination with PEG-IFNα. Some patients received treatment with TDF alone based on the physician's discretion after EOT. These patients exhibited no survival benefit; however, they were generally older and had more advanced disease, as shown in previous studies, which even considered NA treatment prognostically unfavourable [2, 22]. A finding that can be refuted in our study, given the comparable baseline characteristics of the treatment groups.

However, it remains unclear whether the beneficial effect of TDF was primarily driven by lower HDV RNA levels, reduced HBV DNA replication, or by additional non-virological mechanisms. Data on quantitative HDV RNA measurements and their correlation with clinical outcomes remain limited; however, available evidence is consistent. The 10-year long-term analysis of the HIDIT-I study showed that patients with undetectable HDV RNA at any time had a favourable long-term follow-up [5], a result confirmed in our current analysis. Further studies have likewise demonstrated the prognostic value of suppressed HDV both during the natural disease course and following therapy [23–25]. Collectively, these observations highlight HDV RNA suppression as a central therapeutic target, in line with recently published data [6].

In addition to these HDV-related factors, HBV-related mechanisms may play a role. A subgroup analysis of non-responders indicated that TDF may exert an effect beyond measurable HDV suppression, suggesting that HBV dynamics could contribute. Therefore, it is important to note that dominant viral replication can shift over time [26] and advanced disease stages may be associated with decreased HDV but increased HBV replication [27]. This may be particularly relevant given that 39% of patients in our cohort had cirrhosis, and higher HBV DNA levels were associated with endpoints in the univariate analysis. These data are in line with data from the 90s

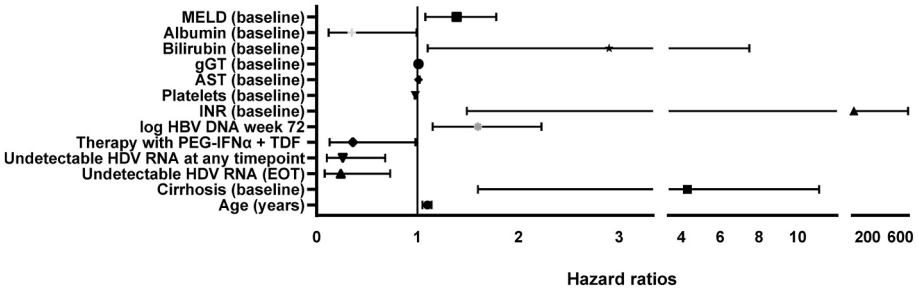



**FIGURE 5** | Factors associated with the development of clinical endpoints. Cox regression analysis demonstrating the association between individual clinical and virological parameters and the risk of developing a clinical endpoint during long-term follow-up. AST = alanine aminotransferase; EOT = end of treatment; GGT = gamma-glutamyltransferase; HBV DNA = hepatitis B virus deoxyribonucleic acid; HDV RNA = hepatitis D virus ribonucleic acid; INR = international normalised ratio; PEG-IFNα = pegylated interferon alfa; TDF = tenofovir disoproxil fumarate.



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**TABLE 4** | Parameters associated with clinical long-term outcome in univariate and multivariate Cox regression analyses.

| Parameter | Univariate HR [95% CI] | *p*-value | Multivariate HR [95% CI] | *p*-value |
|---|---|---|---|---|
| Baseline cirrhosis | **4.25 [1.63–11.09]** | **< 0.01** | 2.72 [0.94–8.09] | 0.07 |
| Age (years) | **1.10 [1.05–1.14]** | **< 0.01** | **1.07 [1.02–1.12]** | **< 0.01** |
| Undetectable HDV RNA at EOT | **0.24 [0.08–0.73]** | **0.01** | — | — |
| Undetectable HDV RNA at least once | **0.26 [0.10–0.68]** | **< 0.01** | **0.19 [0.06–0.57]** | **< 0.01** |
| HBV DNA ($log_{10}$ IU/mL) week 72 | **1.60 [1.15–2.23]** | **< 0.01** | 1.37 [0.88–2.13] | 0.16 |
| Therapy with PEG-IFNα + TDF | **0.36 [0.13–0.98]** | **0.05** | **0.24 [0.07–0.86]** | **0.03** |
| MELD (baseline) | **1.39 [1.08–1.78]** | **0.01** | — | — |
| Platelets (baseline) | **0.98 [0.97–0.99]** | **< 0.01** | — | — |
| INR (baseline) | **32.14 [1.49–694.89]** | **0.03** | — | — |
| AST (baseline) | **1.01 [1.00–1.02]** | **0.04** | — | — |
| GGT (baseline) | **1.01 [1.00–1.01]** | **< 0.01** | — | — |
| Bilirubin (baseline) | **2.88 [1.10–7.51]** | **0.03** | — | — |
| Albumin (baseline) | **0.35 [0.12–0.99]** | **0.05** | — | — |

*Note:* Bold indicates statistical significance ($p < 0.05$). Multivariate analysis included only variables with $p < 0.05$ in univariate analysis.
Abbreviations: CI = confidence interval; EOT = end of treatment; HR = hazard ratio.

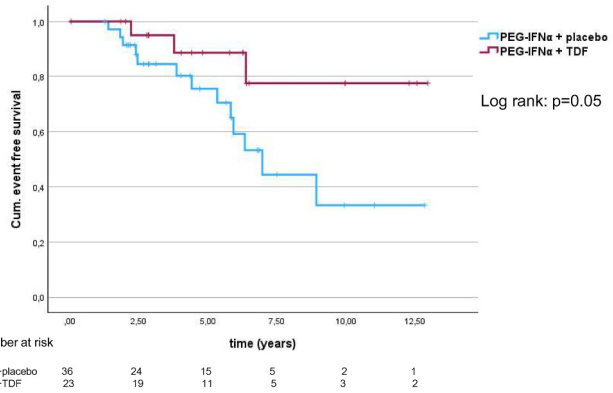



**FIGURE 6** | Kaplan–Meier analysis in patients with detectable HDV RNA at EOT. Kaplan–Meier curve showing clinical outcomes in patients with detectable HDV RNA at the end of treatment, comparing PEG-IFNα + TDF versus PEG-IFNα + placebo. Endpoints were defined as hepatic decompensation, hepatocellular carcinoma (HCC), liver transplantation, or liver-related death. Numbers at risk are shown below the curve. EOT = end of treatment; HCC = hepatocellular carcinoma; HDV = hepatitis D virus; PEG-IFNα = pegylated interferon alfa; TDF = tenofovir disoproxil fumarate.

suggesting that HBV replication may contribute to liver damage and that concurrent high-level HBV and HDV replication may be associated with more severe disease [28], highlighting the relevance of effective HBV DNA suppression with NA.

Nevertheless, the ultimate therapeutic goal remains HBsAg loss, which was also shown to be prognostic in the present study. This underscores the continued relevance of PEG-IFNα-based therapy, even in the era of bulevirtide, since significant declines in HBsAg have thus far only been achieved when PEG-IFNα is included [8].

The limitations of the present study must be considered. From the fifth year following treatment, data were collected retrospectively by the respective centres without a standardised follow-up protocol, which may have introduced potential recall and documentation bias and resulted in different follow-up durations. Furthermore, different HDV RNA assays were used across centres. Consequently, the present study focussed on HDV RNA measurements obtained within the initial 5 years, which were centralised, although limitations were also present there [29]. Additionally, re-treatment after the 96-week study period was performed according to the discretion of the treating physicians rather than a uniform protocol. Therefore, all re-treated patients were excluded from long-term outcome analyses.

In conclusion, our analysis of the HIDIT-II 10-year long-term outcome demonstrated that combination therapy with PEG-IFNα + TDF was associated with a more favourable clinical long-term outcome and a pronounced virological response. Consequently, this therapeutic approach should be considered in all cases of CHD. The findings further highlight that despite the availability of bulevirtide, PEG-IFNα remains an important component of therapy—particularly for achieving HBsAg loss.

### Author Contributions

Anika Wranke and Julia Kahlhöfer had full access to all the data in the study and were responsible for the integrity of the data and the accuracy of the data analysis. Concept and design: Cihan Yurdaydin, Heiner Wedemeyer, Julia Kahlhöfer and Anika Wranke. Acquisition, analysis, and interpretation of data: Anika Wranke, Julia Kahlhöfer. Drafting of the manuscript: Cihan Yurdaydin, Heiner Wedemeyer, Julia Kahlhöfer and Anika Wranke. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Anika Wranke. Administrative, technical, or material support: All authors.

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## Ethics Statement

The study was approved by the Ethics Committee of the Hannover Medical School 10,273_BO_K_2022 and all other centre sites. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

## Consent

All authors approved the manuscript for publication.

## Conflicts of Interest

Cihan Yurdaydin reports personal fees from AbbVie, Gilead, Eiger, Eiger InnovTheraputics, Roche and reseach grants from Gilead. Florin A Caruntu declares a grant/research support from HORIZON-HLTH-2021-Disease-04-07. Kathrin Sprinzl declares personal fees from Gilead Science, Ipsen. Hans H. Bock reports personal fees from AbbVie, Gilead, Ipsen; principal investigator in clinical trials for Gilead, GSK. George V. Papatheodoridis declares that he has served as advisor for: Abbvie, Albireo, Astra Zeneca, BioArs, Elpen, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Takeda, Vir and a lecturer for: Abbvie, Astra Zeneca, BioArs, Elpen, Genesis, Gilead, GlaxoSmithKline, Janssen, Ipsen, Merck Sharp & Dohme, Novartis, NovoNordisk, Roche Research grants: Abbvie, Gilead, Takeda, Vianex. Uta Merle reports personal fees from CSL Behring, CytoSorbents Europe GmbH, Falk, Gilead, Microbiotica and Univar. Münevver Demir declares that she received research grants from Merz and Echosens and was a lecturer for: Gilead, AbbVie, Falk, Advanz, Ipsen, Merz, Boehringer, Sanofi and Astra Zeneca. Markus Cornberg personal fees from AbbVie, AiCuris, Gilead, GlaxoSmithKline, Janssen, Merck/MSD, Novartis, Roche, Swedish Orphan Biovitrum Falk. Heiner Wedemeyer reports research grants from Abbvie, Biotest, Gilead, HORIZON, personal fees from AbbVie, Aligos, Altimmune, Biotest, BMS, BTG, Dicerna, Enanta, Gilead, Janssen, Merck/MSD, MYR GmbH, Roche, Vir Biotechnology, Intercept, Falk, Norgine, Pfizer, principal investigator in clinical trials for principal investigator in clinical trials for Abbvie, Altimmune, Bristol-Myers-Squibb, Gilead, Janssen, MYRGmbH, Norvartis, Vir Biotechnology and role in the DGVS executive board. Julia Kahlhöfer, Kendal Yalcin, Selim Gürel, Ulus S. Akarca, Jan-Hendrik Bockmann, Onur Keskin, Ramazan Idilman, Svenja Hardtke and Anika Wranke declare no conflict of interests.

## Data Availability Statement

The data that support the findings of this study are available on reasonable request from Anika Wranke.

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