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A. Wranke, Lourdes Maria Borzacov, Raymundo Paraná, Cirley Lobato ...+21 more authors

Institutions: Hannover Medical School, Universidade Federal de Rondônia, Federal University of Bahia, Aga Khan University ...+7 more institutions

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Clinical and virological heterogeneity of hepatitis delta in different regions world-wide: The Hepatitis Delta International Network (HDIN)

Anika Wranke[1], Lourdes M. Pinheiro Borzacov[3], Raymundo Parana[4], Cirley Lobato[5], Saeed Hamid[6], Emanoil Ceausu[7], George N. Dalekos[8], Mario Rizzetto[9], Adela Turcanu[10], Grazia A. Niro[11] Farheen Lubna[6], Minaam Abbas[13], Patrick Ingiliz[12], Maria Buti[14], Peter Ferenci[15], Thomas Vanwolleghem[16], Tonya Hayden[18], Naranjargal Dashdorj[19], Adriana Motoc[7], Markus Cornberg[1,2], Zaigham Abbas[13], Cihan Yurdaydin[17], Michael P. Manns[1,2], Heiner Wedemeyer[1,2] , Svenja Hardtke[1,2]on behalf of the Hepatitis Delta International Network*

*Study-Group:

Beatriz Calle Serrano, Michael Wöbse, Benjamin Heidrich, Marion Muche, Nikolaos Gatselis, Kalliopi Zachou, Erwin Ho, Antonina Smedile, Rosanna Fontana, Robert Gish, Dana Obretin, Rafael Stern

[1]Gastroenterology, Hepatology and Endocrinology, Hannover Medical School,

[2]German Centre for Infection Research (DZIF), HepNet Study-House, Hannover, Germany

[3]Research Centre for Tropical Medicine of Rondônia - CEPEM/SESAU, and Federal University of Rondônia; Brazil

[4]Hepatology Centre of the University Hospital Professor Edgar Santos, Federal University of Bahia, Brazil

[5]Hospital das Clínicas do Acre, Rio Branco, Brazil

[6]Department of Hepatogastroenterology, Aga Khan University, Karachi, Pakistan

[7]Infectious Diseases, Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania,

[8]Department of Medicine and Research Laboratory of Internal Medicine, Medical School, University of Thessaly, Larissa, Greece

[9]Department of Internal Medicine - Gastroenterology, University of Torino, Italy

[10]State University of Medicine "Nicolae Testemitanu", Chisinau, Republic of Moldova

[11]Divisione di Gastroenterologia, Ospedale Generale Regionale “Casa Sollievo della Sofferenza”, San Giovanni Rotondo, Italy

[12]Centre for Infectiology Berlin (CIB)

[13]Ziauddin University Hospital Karachi, Pakistan

[14]Liver Unit, Valle d'Hebron University Hospital and Ciberhed del Instituto CarlosIII, Barcelona, Spain

[15]Department of Internal MedicineIII, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

[16]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Edegem,Belgium

[17]Medical Faculty, Ankara University, Ankara, Turkey

[18]Centres for Disease Control and Prevention/Div of viral hepatitis; Atlanta, USA

[19]Onom Foundation, Ulaanbaatar, Mongolia

Corresponding authors: Heiner Wedemeyer & Svenja Hardtke

Carl-Neuberg-Straße 1, 30625 Hannover, Germany

Tel: +49 511 532 6057

FAX: +49 511 532 6820

E-mail: hardtke.svenja@mh-hannover.de

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List of abbreviations

HDV: hepatitis delta virus; HDIN: Hepatitis Delta International Network; HBV: hepatitis B virus; HBeAg: hepatitis B e antigen; HDV-RNA: Hepatitis delta viral ribonucleic acid; HCC: hepatocellular carcinoma; IFNa: alpha interferon; NUC: nucleos(t)ide analogue; CRF: case report form; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; INR: International Normalized Ratio (alias Quick); ALT: alanine aminotransferase, AST: aspartate transaminase; IU/L: international units per litre; LLN: lower limit of normal; ULN: upper limit of normal

Conflict of interest

All authors: no conflict

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ABSTRACT

Chronic hepatitis D (delta) is a major global health burden. Clinical and virological characteristics of patients with hepatitis D virus (HDV) infection and treatment approaches in different regions world-wide are poorly defined.

Methods:

The Hepatitis Delta International Network (HDIN) registry was established in 2011 with centres in Europe, Asia, North- and South America. Here, we report on clinical/ virological characteristics of the first 1576 patients with ongoing or past HDV infection included in the database until October 2016 and performed a retrospective outcome analysis. The primary aim was to investigate if the region of origin was associated with HDV replication and clinical outcome.

Results:

The majority of patients was male (n=979, 62%) and the mean age was 36.7 years (range 1-79, with 9% of patients younger than 20 years). Most patients were HBeAg-negative (77%) and HDV-RNA positive (85%). Liver cirrhosis was reported in 48.7% of cases which included 13% of patients with previous or ongoing liver decompensation. Hepatocellular carcinoma (HCC) developed in 30 patients (2.5%) and 44 (3.6%) underwent liver transplantation. Regions of origin were independently associated with clinical endpoints and detectability of HDV RNA. Antiviral therapy was administered to 356 patients with different treatment uptakes in different regions. Of these, 264 patients were treated with interferon-a and 92 were treated with HBV-Nucs only.

Conclusions: The HDIN registry confirms the severity of hepatitis delta but also highlights the heterogeneity of patient characteristics and clinical outcomes in

different regions. There is an urgent need for novel treatment options for HDV infection.

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2. Hepatitis delta
3. Hepatitis epidemiology
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Key Point Box:

- This is the thus far largest multicentre, cross-sectional cohort of hepatitis delta patients
- Our data highlights the diversity of hepatitis delta patient characteristics in different regions world-wide
- We here confirm the particular severity of hepatitis delta
- There is an urgent need for novel treatment options for HDV infection

1. INTRODUCTION

Hepatitis delta is caused by infection with the hepatitis D virus (HDV) and is considered to be the most severe form of chronic viral hepatitis. HDV lacks the ability to synthesize its own envelope proteins and is dependent on the presence of the HBV envelope proteins to package its genome and produce infectious particles. HDV infection can therefore only occur in patients with hepatitis B, either as simultaneous co-infection or super-infection. As compared to HBV mono-infection, hepatitis delta has been associated with a more rapid progression of liver disease to cirrhosis and hepatic decompensation and an increased incidence of hepatocellular carcinoma [1-3].

Worldwide, about 240 million individuals are considered to be HBsAg positive [4], including 2–8 % being co-infected with HDV, resulting in 10–20 million individuals suffering from hepatitis delta [5]. The prevalence of hepatitis delta varies significantly among different regions of the world.

Turkey and other Eastern European and Mediterranean areas are still considered as endemic areas [4,6,7]. A particularly high prevalence of HDV infection has been reported in Pakistan, Mongolia, north-western Brazil, Polynesia and parts of central Africa [8-15]. In central Europe and North America hepatitis delta is mainly a problem in immigrant populations and in people who inject drugs [16,17].

At least eight different HDV genotypes have been described [5] which are possibly associated with different clinical courses. The most common HDV genotype 1, is responsible for most cases of hepatitis delta in Europe, North America and South Asia and has been associated with greater severity of liver disease [18-20]. Genotypes 2 and 4 are mainly prevalent in East Asia and the Yakutia region of Russia, while HDV genotype 3 is seen exclusively in the north-western parts of South America, especially in the Amazon Basin. Genotypes 5-8 have been described in

sera of African-origin patients [21]. HDV genotype 3 infection is linked to a particularly poor prognosis [22-24]. However, there is limited data comparing patient characteristics and the clinical courses of hepatitis delta in different regions of the world. This information could help to better understand if host or viral factors lead to distinct outcomes in liver disease, which could explain pathophysiological features of HDV infection. The aim of the HDIN registry is to characterize descriptively clinical and virological features of patients with HDV infection in different geographical regions of the world. Moreover, we aimed to collect information on antiviral therapy uptake to better define requirements and needs for alternative treatment approaches, in addition we performed retrospective outcome analysis to determine parameters associated with clinical liver related endpoints, liver cirrhosis or being HDV RNA positive.

2. METHODS

2.1. Inclusion criteria and process

All patients had to be HBsAg positive and anti-HDV positive for at least 6 months. Detailed description of the inclusion process and definitions of liver related complications and cirrhosis are given in the supplementary information. For the study we used the STROBE Statement-checklist of items that should be included (Supplementary Table 1).

2.2. Statistics

Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, Illinois, USA). All parameters were described as median values including their Interquartile range (IQR). P-values <0.05 were considered as significant. Continuous values were analysed by T-Test. For non-parametric (distribution-free) variables, Mann-Whitney-U-tests were used. A chi square-test was used for the comparison of discrete variables. The Fisher exact test was considered if there were less than five patients. To determine the odds ratios (OR) for the development of the endpoints we used logistic regression models for univariate and multivariate analysis. Possible interactions were considered by evaluating the same orientation of ODs in uni- and multivariate analysis (supplement).

2.4. Ethics

The study was approved by the Ethics Committee of the Hannover Medical School 1023-2011 and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. More detailed information are given in the supplement.

3. RESULTS

3.1 Patients

The analysis was based on data entered by 19 individual centres (Supplementary Table 2) from 15 countries including Austria, Belgium, Brazil, Georgia, Germany, Greece, Italy, Mongolia, Pakistan, Republic of Moldova, Romania, Russia, Spain, Turkey and the United States. In total, 1605 patients were enrolled.

Patients with incomplete data were excluded from analysis. Thus, the following analysis was based on 1576 patients.

The network included 598 (38%) female and 979 (62%) male patients with a median age of 36.7 years (Table 1). Patients were divided according to their country of birth into Eastern Mediterranean (e.g.Turkey, Greece), Eastern Europe and Central Asia, Central and Southern Europe, South Asia (mainly Pakistan) and South America (mainly Brazil) (Figure 1). Most of the patients were born in Eastern Europe (n=678) or South Asia (n=398), followed by South America (n=193), Eastern Mediterranean (n=161) and Central Europe (n=90). Only 13 patients were born in Africa.

3.2. Serological and virological parameters

HBeAg-positive hepatitis delta was detected in 22.8% of patients. Moreover, 85.3% were HDV-RNA positive, but only 59.8% of patients had a positive HBV-DNA result. Anti-HCV was detected in 6.3% of the patients, but HCV RNA was detectable in only 13 patients (3.3%) (Table 1). Quantitative values for HDV RNA, HBV DNA or HCV RNA data were not available.

3.3. Haematological and biochemical parameters

The haematological and biochemical parameters displayed a wide variability (Table 1). Low platelet counts (<100 000/µl) were found in 23% of patients, high INR (>1.2) values in 23% and low albumin (<3.5 g/l) in 19% of patients.

3.4. Regional characteristics

Patients from Central Europe had a mean age of 46.4 years (range: 14-71) whereas patients from Eastern Europe (35.7 years; range: 1-79) and South Asia (32.7 years; range: 11-70) were younger (both p<0.01) (Supplementary Table 3). HBeAg was negative in the far majority of cases, although patients from South Asia were more likely to be HBeAg positive (35.2%) compared to patients from other regions (10.3% - 16.1%). HDV-RNA was found to be more often positive in patients from South Asia (86.9%) and Eastern Europe (86.4%) (CE 58,9%, SA 46,1%). In South Asia 60.8% of the patients were HBV-DNA positive compared to 14.0% in South America (p<0.01). Analysis of HCV co-infection showed that 6.3% of the patients were anti HCV positive. Patients from Central Europe were more frequently anti HCV positive (22.2%) compared to the other regions. Patients from Eastern Europe had the highest bilirubin levels (1.9 mg/dl range 0.1-21) (Table 2a). More than 40% of the patients from South Asia had low Albumin of <3.5 g/l compared to 17.3% from South America and 18.3% from Central Europe (both p<0.01) (Figure 2b). Low platelet counts of < 100 000/µl were detected in 23% of all patients. Especially in central Europe and South America even more than 35% of patients had low platelet counts below 100 000/µl compared to 28.4% in Eastern Mediterranean, 27.7% in South Asia and 20.8% in Eastern Europe (p<0.01) (Figure 2c). INR above >1.2 was detected in 68% of patients from South America compared to 32% in South Asia and Central Europe (both p<0.01) (Figure 2d). Regarding the different fibrosis scores, there were

only a few differences among the regions. Most patients had a Baseline-Event-Anticipation (BEA)-score of B, an APRI score of 0.5 – 2 and a MELD <15 points (not shown).

3.4. Antiviral treatment regimes

In contrast to the previous analysis in which the patients were grouped according to their country of birth, the antiviral treatment analysis was based on regions of the participating centres, as access to therapy is determined by the country of residence. Overall, antiviral therapies had been administered to 356 patients (28%, n=1251). 264 patients received IFNa-based therapies (107 pegylated IFNa and 78 conventional IFNa) with (n=79) concomitant or subsequent nucleos(t)ide analogues (NUCs), 92 were treated with NUCs alone, and 895 did not receive any antiviral therapy. No information about antiviral therapy was available for 325 patients. Most of the patients treated with NUCs alone received either lamivudine (n=82) or entecavir (n=76) (supplement Figure 1). In Central Europe nearly half of the patients were treated, while countries in South Asia rarely administered antiviral therapy. In all regions patients were mainly treated with IFNa-based therapies (Figure 3).

Next, we analyzed the patients who were treated and how these patients differed with regards to their baseline characteristics. Surprisingly, patients who were treated had a lower biochemical disease activity compared to non-treated patients. These findings were confirmed by analysing patients, treated with NUCs or IFNa only. In addition, patients who received treatment had a significantly higher age ($p<0.01$) and a lower platelet count ($p<0.01$), particularly those who were treated with NUCs. Most of the patients who were treated had an APRI score between 0.5-2, AST/ALT ratio of <1, MELD score < 15 and were BEA B (not shown).

3.5 Factors associated with HDV RNA-positivity, liver cirrhosis and development of clinical endpoints

3.5.1. Factors associated with HDV RNA positivity

Among the cohort of 1576 anti HDV positive patients, 718 were assigned as HDV RNA positive. Previous antiviral treatment for hepatitis delta was associated with a negative HDV RNA result (OR 0.5; 95% CI 0.3-0.7), which could be confirmed in subsequent multivariate analysis (Table 2). A positive HDV RNA result was associated with high albumin levels and platelet counts as well as high levels of AST in univariate and multivariate analysis. Interestingly, also the region of origin was associated with the HDV RNA status: Central Europe as country of origin was associated with negative HDV RNA (OR: 0.2), whereas South Asia was associated with positive HDV RNA (OR: 2.9).

3.5.2. Liver cirrhosis

Liver cirrhosis was detected in 635 patients (48.7%). Factors significantly associated the presence of cirrhosis in univariate and multivariate logistic regression analyses are shown in Table 3. Backward logistic regression model analysis revealed that quantitative platelet count, AST, alcalic phosphatase, NUCs and age were independently associated with the presence of cirrhosis (Table 3). The region of origin was not associated with the presence of cirrhosis in multivariate analysis.

3.5.3. Development of clinical endpoints

Previous decompensation occurred in 159 patients. Hepatocellular carcinoma was present in 30 patients at screening. Liver transplantation had to be performed in

44 patients. In South America 30.4% of the patients developed a clinical event, compared to patients from other regions (EM 11.3% ($p<0.01$), EE 16.3% ($p<0.01$), CE 12.6% ($p<0.01$), SAS 7.5% ($p<0.01$)) (Figure 4). Altogether, 178 patients (14.7%) had at least one liver related endpoint in the past or at the first available visit. Factors significantly associated with clinical endpoints are shown in Table 4. Treatment with IFN was univariately and multivariately associated with lack of endpoints compared to treatment with NUCs $P<0.01$: OR 0.1; 95% CI 0.06-0.3. In addition we performed a multivariate backwards analysis which showed that high age, low albumin and high creatinine as well as South America as country of origin were associated with the presence of liver related endpoints (Table 4).

DISCUSSION

Here we present the first data from the so far largest multicentre, cross-sectional cohort of hepatitis delta patients. The Hepatitis Delta International Network included more than 1500 patients from 19 centres in 15 countries located on four continents. We confirmed the particular severity of hepatitis delta, highlighted the enormous heterogeneity of the clinical and virological features of HDV infection in different regions world-wide and unravelled significant limitations considering access to antiviral therapy.

In line with previously studied cohorts of HBV mono-infected and HCV infected patients [25,26] our analysis confirmed that men are more often HDV infected than women. However, remarkable differences in the age of HDV patients became evident when comparing different regions and countries. Hepatitis delta patients were particularly young in Eastern Europe and South Asia. This could indicate differences in epidemiological features of HDV infection, e.g. infections in early childhood versus infections at older ages but may also reflect differences in health systems when patients present with symptoms at clinical sites. Moreover, the particular young age of South American patients may indicate the severity of HDV genotype 3 while age differences between European and Asian patients, who are mostly infected with HDV genotype 1, suggests that genetic or environmental factors contribute to distinct disease outcomes.

The relatively high frequency of advanced stages of liver cirrhosis and the resulting abnormal laboratory results (e.g. thrombocytopenia (45%), elevated INR (23%)) are alarming. Importantly, the frequency of cirrhosis and hepatic decompensations reported for patients included in the HDIN data base is in line with

previously published single-centre experiences, which mainly described European HDV genotype 1-infected patients [30,31] and reported cirrhosis in 34-56% of cases [1,7,32-36]. Recently, this high probability of liver related complications was also confirmed in the Swiss HIV/HDV cohort [37]. Unfortunately we had no information about the HIV status of the patients in this registry. Grade 3 elevations of liver aminotransferases indicating severe biochemical disease activity, was reported only in a minority of HDIN patients. Thus, acute infections or severe flares of chronic hepatitis delta disease are currently only a minor problem – which is different to early reports on the characteristics of HDV infected patients published in the 1980s and 1990s [38].

The retrospective outcome analysis confirmed factors associated with the presence of cirrhosis and endpoints like age, albumin and platelet count. One new aspect of this study was that the region of origin from hepatitis delta patients should be taken into consideration during treatment decisions as for example South American origin was associated with the presence of liver related endpoints in our analysis. This indicated once more that patients with hepatitis delta who were born in different region worldwide have significant differences in characteristics cannot compared in studies. Besides, this study confirmed that the treatment with IFN was associated with a benign clinical outcome as previously shown by Wranke et al.[36]

One particular strength of the HDIN database is the opportunity to compare HDV-infected patients and the severity of liver disease in different countries and regions. Strikingly, patients from South America had the most advanced stages of liver disease. This might be explained by the predominance of HDV genotype 3 infections in this region but could also indicate distinct genetic or environmental factors present in the Amazonian region which possible contribute to a more progressive course of disease. Overall, our data are in line with a previous report

from Manaus [39]. Furthermore, patients from Eastern parts of Europe were more likely to have high values of AST and ALT indicating increased inflammatory activity. Currently, the reasons for this observation are unclear but environmental factors and concurrent drug or alcohol abuse may be involved. Genetic factors may also be in parts responsible. For example, differences among different regions in hepatitis activity and the response to IFNa-based antiviral therapy in HCV infection can be explained partly by distinct single nucleotide polymorphisms (SNPs) near the interferon lambda-3 (IFNλ3) gene (interleukin 28B). However, different IFNλ3, rs12979860 genotypes did not significantly affect the outcome of pegylated IFNa therapy in hepatitis delta [40,41]. Whether genetic factors influence the course of hepatitis delta has yet to be determined. Similarly, more studies are needed to explain other surprising findings, e.g. the particularly low albumin levels in patients from Pakistan and the remarkably high INR values in patients from South America.

As expected, patients followed in European centres were most likely to receive antiviral therapy (41%). In contrast, both IFNa as well as NUCs were given less often in South Asia and Eastern Europe. One possible explanation could be the limited access to antiviral therapy and costs of treatment. A focus of future studies with the HDIN database must be to compare different outcomes of antiviral therapy and to determine to what extent patients benefit from reducing HDV-RNA levels or suppressing HDV replication to undetectable levels. This will be important as previous reports show that large differences in clinical endpoints can be achieved with antiviral therapy [7,32,42-44]. In this registry, NUC therapy was associated with a higher likelihood to be negative for HDV RNA, which would be in line with the data of Soriano et al. [45] but in contrast to the recently published data of the HIV Swiss cohort [46]. Most patients in our cohort were treated with lamivudine. Of note, lamivudine-induced HBsAg variants, e.g. 196l or 196S, may inhibit secretion of HDV

particles [47,48] which could explain a high likelihood for a negative HDV RNA result. Still, the association between NUC therapy and HDV RNA negativity could simply reflect a bias that more patients with advanced cirrhosis who show lower HDV RNA values receive antiviral therapy with NUCs.

Although we present the thus far largest cohort of patients infected with HDV and HBV, this study has obvious limitations. We report a cross-sectional, retrospective analysis of baseline characteristics but have not yet analysed the long-term outcome of HDV infection. Due to the lack of laboratory results especially virological parameters further analysis have to be done and results may be distort. Even though data from sites in 15 different countries were available, we have to admit that patients who were born in Eastern European were overrepresented (678; 40%), whereas there were limited data on patients born in Africa were limited or even followed in African centres. This fact may be biased some interpretations. We also highlight that our cohort is not a population-based cohort but heavily biased as patients were followed at academic centres. The obvious referral bias may therefore lead to an overestimation of disease severity. Moreover, parameters determined during routine clinical practice differ between sites and regions. HDV-RNA values were also available only for a minority of patients and were analysed by different in-house assays. Inter-assay variability of HDV-RNA PCRs has been shown to be very large [50], and thus, it is not possible to compare HDV levels in this cohort without central HDV-RNA testing. Finally, determination of HDV-genotypes is not part of routine diagnostics in most countries and was therefore reported only in a minority of patients.

In conclusion, we show that hepatitis delta still represents a severe and not uncommon health burden, which is globally spread. HDV-associated liver disease and patient characteristics show remarkable heterogeneity in different countries and

regions, which may be explained by viral, host and environmental factors. This probably needs to be taken into consideration for the development of alternative antiviral therapies. Currently, treatment uptake is very low in some countries which highlights the fact that reducing the barriers to available therapies must have priority to reduce the morbidity and mortality caused by HDV.

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Table 1) Baseline characteristics of the included patients

	Overall n=1576	Number of subjects Tested
Age (years) mean ± SD	36.7 ± 13.6	
Range	1-79	
Male % (n)	62% (979)	
HDV RNA positive % (n)	85.3 (719)	842
HBeAg % (n)	22.8 (275)	1205
HBV DNA positive % (n)	59.8 (528)	883
HCV RNA positive % (n)	1.0 (13)	395
Anti HCV positive % (n)	6.3 (78)	1228
Hemoglobin (g/dl) median ± SD (range)	13.5 ± 2.3 (3.9-21.7)	1380
Thrombocytes (10^3/µL) median ± SD (range)	154 ± 81 (2-917)	1406
INR median ± SD (range)	1.2 ± 0.3 (0.2-3.8)	1049
ALT (U/L) median ± SD (range)	119 ± 289 (6-6729)	1436
AST (U/L) median ± SD (range)	104 ± 242 (2-4000)	1223
Bilirubin (mg/dl) median ± SD (range)	1.4 ± 1.4 (0.04-21)	1327
Alkaline Phosphatase (U/L) median ± SD (range)	115 ± 82 (2-1627)	1118
Albumin (g/dl) median ± SD (range)	3.9 ± 1.3 (0.1-38)	986
Creatine (mg/dl) median ± SD (range)	0.8 ± 0.2 (0.07-3.4)	1046
Sodium (mmol/L) median ± SD (range)	139 ± 12.6 (24-414)	728

Table 2) Parameters associated with positive HDV RNA (n=718) in univariate and multivariate analysis

Parameter	Significance (univariate)	Significance (multivariate)*
Age	P=0.04: OR 0.9; 95% CI 0.9-0.9	not significant
Alcalic phosphatase	P=0.03: OR 1.0; 95% CI 1.0-1.0	not significant
ALT	P<0.01: OR 1.0; 95% CI 1.0-1.0	not significant
AST	**P<0.01: OR 1.0; 95% CI 1.0-1.0**	**P<0.01: OR 1.0; 95% CI 1.0-1.02**
Albumin	**P<0.01: OR 0.4; 95% CI 0.3-0.5**	**P= 0.05: OR 0.6; 95% CI 0.4-0.99**
Thrombocytes	P<0.01: OR 0.9; 95% CI 0.9-0.9	P= 0.02: OR 0.99; 95% CI 0.99-0.99
Country of origin (SA)	P<0.01: OR 0.4; 95% CI 0.2-0.8	not significant
Country of origin (EM)	P<0.01: OR 0.5; 95% CI 0.3-0.8	not significant
Country of origin (CE)	**P<0.01: OR 0.2; 95% CI 0.1-0.3**	**P<0.01: OR 0.2; 95% CI 0.1-0.5**
Country of origin (SAS)	**P<0.01: OR 4.6; 95% CI 2.8-7.6**	**P<0.01: OR 2.9; 95% CI 1.4-5.98**

*all parameters with P<0.05 were considered for multivariate analysis

Table 3) Parameters associated with liver cirrhosis (n=635) in univariate and multivariate analysis

Parameter	Significance (univariate)	Significance (multivariate)*
Age	P<0.01: OR 1.02; 95% CI 1.01-1.03	P<0.01: OR 1.0; 95% CI 1.0-1.04
Therapy (IFN vs. NUCs)	p<0.01, OR 0.27, 95% CI 0.2-0.5	P<0.01: OR 0.3; 95% CI 0.1-0.7
Bilirubin	P<0.01: OR 2.4; 95% CI 2.0-3.0	not significant
Alcalic phosphatase	P<0.01: OR 1.0; 95% CI 1.0-1.0	P=0.03: OR 1.01; 95% CI 1.0-1.02
Creatinin	P<0.01: OR 2.6; 95% CI 1.5-4.8	not significant
ALT	P<0.01: OR 1.0; 95% CI 1.0-1.0	not significant
AST	P<0.01: OR 1.0; 95% CI 1.0-1.02	P=0.04: OR 1.01; 95% CI 1.0-1.02
Thrombocytes	P<0.01: OR 0.9; 95% CI 0.9-0.9	P<0.01: OR 0.98; 95% CI 0.97-0.99
Country of origin (SAS)	P<0.01: OR 0.5; 95% CI 0.4-0.6	not significant
Country of origin (EE)	P<0.01: OR 1.6; 95% CI 1.3-2.0	not significant
INR	P<0.01: OR 35.4; 95% CI 17.3-72.3	not significant
Albumin	P<0.01: OR 0.6; 95% CI 0.5-0.7	not significant

*all parameters with P<0.05 were considered for multivariate analysis

Liver cirrhosis were defined clinically, histologically or if one of the following parameters were positive: APRI>2, MELD>15.

Table 4) Parameters associated with different endpoints (n=178) in univariate and multivariate analysis

Parameter	Significance (univariate)	Significance (multivariate)*
Sex (gender)	P=0.02: OR 1.5; 95% CI 1.1-2.1	not significant
Age	P<0.01: OR 1.0; 95% CI 1.0-1.05	P=0.04: OR 1.04; 95% CI 1.0-1.1
Therapy (IFN vs. NUCs)	**P<0.01: OR 0.1; 95% CI 0.07-0.2**	**P<0.01: OR 0.1; 95% CI 0.06-0.3**
Thrombocytes	P<0.01: OR 0.9; 95% CI 0.9-0.9	not significant
INR	P<0.01: OR 8.8; 95% CI 5.2-14.8	not significant
Bilirubin	P<0.01: OR 1.4; 95% CI 1.2-1.5	not significant
Alcalic phosphatase	P<0.01: OR 1.0; 95% CI 1.0-1.0	not significant
Albumin	P<0.01: OR 0.4; 95% CI 0.4-0.6	P<0.01: OR 0.4; 95% CI 0.2-0.8
Creatinin	P<0.01: OR 4.5; 95% CI 2.2-9.3	P<0.01: OR 11.2; 95% CI 1.9-67.6
Country of origin (SA)	P<0.01: OR 3.2; 95% CI 2.2-4.6	not significant
Country of origin (SAS)	**P<0.01: OR 0.4; 95% CI 0.2-0.6**	**P<0.01: OR 7.8; 95% CI 3.1-19.6**

*all parameters with P<0.05 were considered for multivariate analysis

Previous liver related complications like ascites, encephalopathy, oesophageal bleeding, HCC and LTX. Altogether, 178 patients (14.7%) developed a liver related endpoint in the past or at the first available visit.

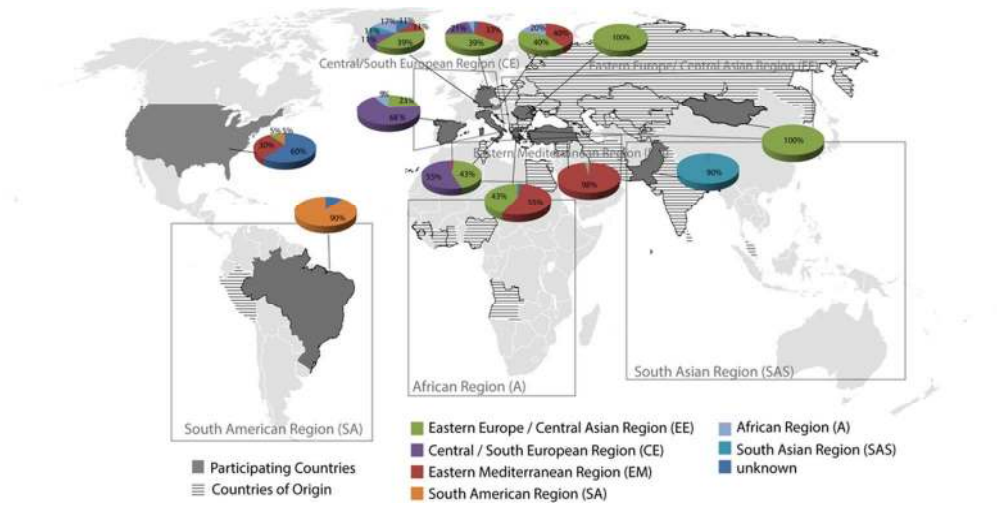
Figure legends:

Figure 1:
Participating countries of the HDIN marked in dark grey. Countries of birth of patients (stripes) were group into 6 different regions: Eastern Europe /Central Asia (EE, green), Central and South Europe (CE, purple), Eastern Mediterranean (EM, red), South America (SA, orange), Africa (A, light blue) and South Asia (SA, turquoise). Pie charts are showing the composition of the patient population per participating country.

Figure 2 (a,b,c,d):
Patients were grouped according to their country of birth into 6 regions (African region not shown because of too small patient numbers). Albumin, Platelets and INR were divided into two groups according to common clinical cut-offs.

Figure 3:
Antiviral treatment analysis was based on regions of the participating centers, reflecting the different treatment options and policies. Red bars showing patients treated with Nucs only. Blue bars showing patients treated with IFNa alone or IFNa in combination with NUCs.

Figure 4:
Clinical endpoints (decompensation (e.g. ascites, encephalopathy and variceal bleding), HCC and transplantation) grouped according to the country of birth of the patients. Bars demonstrate the percentage of patient /per region who had at least one clinical endpoint.



Participating countries of the HDIN marked in dark grey. Countries of birth of patients (stripes) were group into 6 different regions: Eastern Europe /Central Asia (EE, green), Central and South Europe (CE, purple), Eastern Mediterranean (EM, red), South America (SA, orange), Africa (A, light blue) and South Asia (SA, turquoise). Pie charts are showing the composition of the patient population per participating country.

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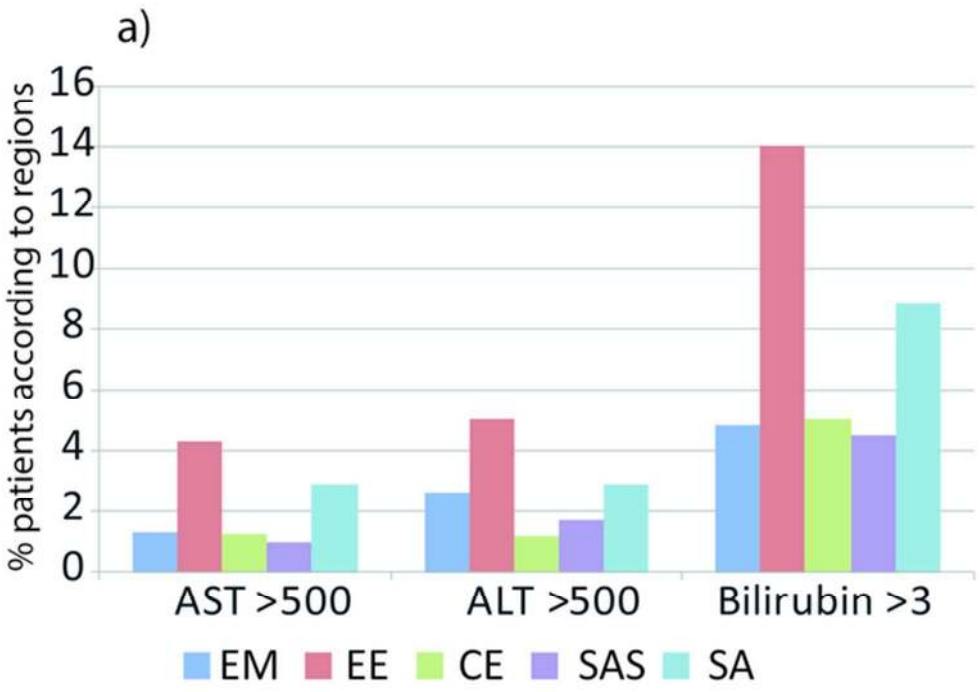

Patients were grouped according to their country of birth into 6 regions (African region not shown because of too small patient numbers). ALT, AST, Bilirubin, Albumin, Platelets and INR were divided into two groups according to common clinical cut-offs.

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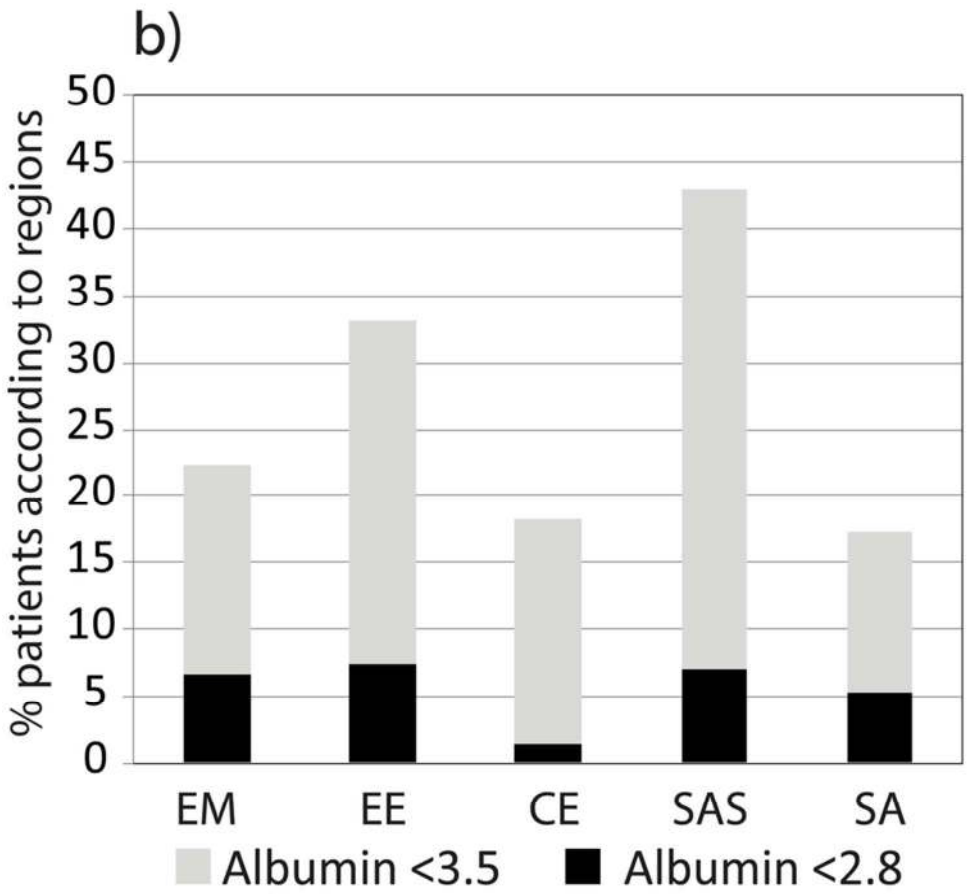

Patients were grouped according to their country of birth into 6 regions (African region not shown because of too small patient numbers). ALT, AST, Bilirubin, Albumin, Platelets and INR were divided into two groups according to common clinical cut-offs.

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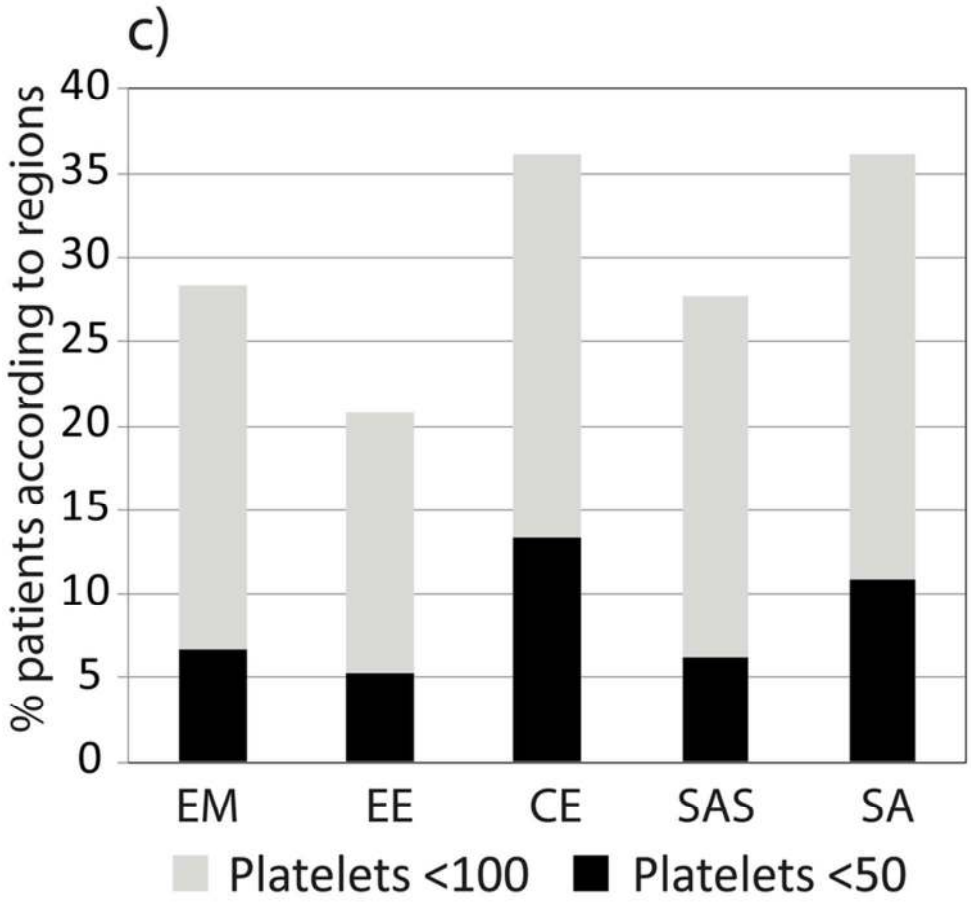

Patients were grouped according to their country of birth into 6 regions (African region not shown because of too small patient numbers). ALT, AST, Bilirubin, Albumin, Platelets and INR were divided into two groups according to common clinical cut-offs.

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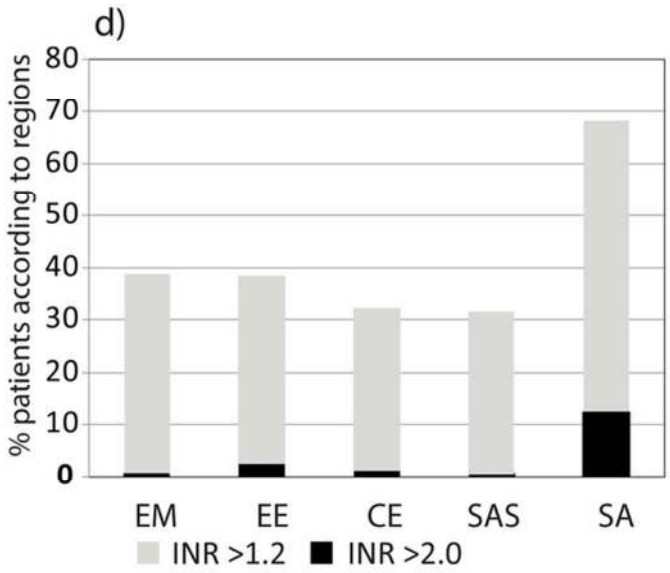

Patients were grouped according to their country of birth into 6 regions (African region not shown because of too small patient numbers). ALT, AST, Bilirubin, Albumin, Platelets and INR were divided into two groups according to common clinical cut-offs.

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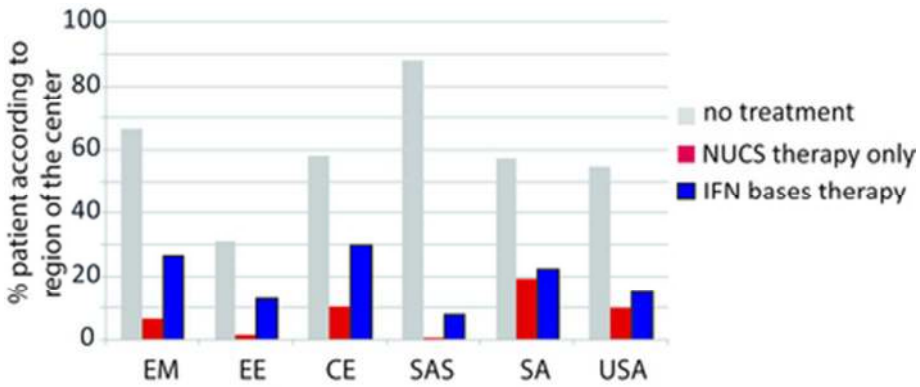

Antiviral treatment analysis was based on regions of the participating centers, reflecting the different treatment options and policies. Red bars showing patients treated with Nucs only. Blue bars showing patients treated with IFNa alone or IFNa in combination with NUCs.

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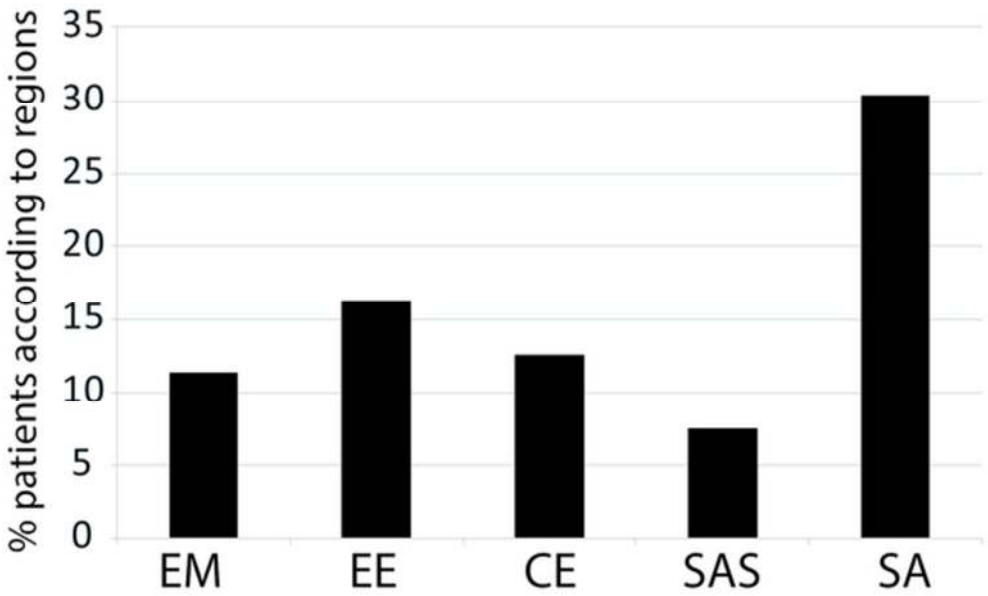


Clinical endpoints (decompensation (e.g. ascites, encephalopathy and variceal bleding), HCC and transplantation) grouped according to the country of birth of the patients. Bars demonstrate the percentage of patient /per region who had at least one clinical endpoint.

50x30mm (300 x 300 DPI)

Supplementary table 1: strobe guidelines

	Recommendation	Comment to the study
Title and abstract	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Results of the register based on a retrospective analysis.
	(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Background, analysis and results are included in the abstract
Background/ rationale	Explain the scientific background and rationale for the investigation being reported	Current studies were explained.
Objectives	State specific objectives, including any prespecified hypotheses	Open questions based on the introduction have been raised.
Study design	Present key elements of study design early in the paper	We provide information on the study design (retrospective), established questions, which should be analyzed and introduced a statistical plan.
Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Detailed description of the registry and the inclusion process were described.
Participants	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	The inclusion process was described and information on the participating countries was provided. Follow up data were not analyzed in this study.
	(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	All variables were presented. Endpoints were descripted. Modifiers were statistically minimized.
Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	A detailed statistical analysing plan was provided.
Bias	Describe any efforts to address potential sources of bias	Shown in the discussion.
Study size	Explain how the study size was arrived at	We showed all participating countries and their numbers of patients.
Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	For all quantitative variables units were shown. No other grouping was performed.
Statistical methods	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical methods were descripted.
	(*b*) Describe any methods used to examine subgroups and interactions	Descripted in the statistic section.
	(*c*) Explain how missing data were addressed	Missing values were excluded.
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	Not applicable
	(*e*) Describe any sensitivity analyses	Sensitivity was considered by multivariate analysis.

Participants	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Numbers of patients were documented and missing values were provided.
	(b) Give reasons for non-participation at each stage	Not applicable

	(c) Consider use of a flow diagram	Diagrams of missing values were provided.
Descriptive data	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Detailed patients characteristics were provided. Potential confounders were discussed.
	(b) Indicate number of participants with missing data for each variable of interest	Missing values were shown.
Outcome data	*Cohort study*—Report numbers of outcome events or summary measures over time	Previous endpoints were descripted.
Main results	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	For univariate and multivariate analysis confidence intervals were analysed. Confounders were minimized by statistical methods.
	(*b*) Report category boundaries when continuous variables were categorized	Category boundaries were provided.
	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	The long term outcome was not analysed.
Other analyses	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	All steps were descripted.
Key results	Summarise key results with reference to study objectives	Every result was reported.
Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Any possible limitation and bias were discussed.
Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Results were associated with current available studies and discussed.
Generalisability	Discuss the generalisability (external validity) of the study results	Results were interpreted based on current data, therewith generalizability was discussed.
Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding was descriped.

Supplementary table 2: HDIN participating centers

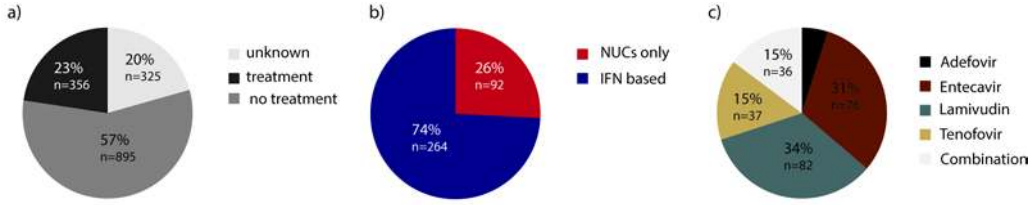
Site	**Country**	**Number of patients**
Hannover	Germany	136
Berlin	Germany	11
Berlin Charité	Germany	3
Rotondo	Italy	19
Florence	Italy	3
Torino	Italy	40
Atlanta	USA	20
Larissa	Greece	44
Karachi 1	Pakistan	134
Karachi 2	Pakistan	263
Bucharest	Romania	122
Barcelona	Spain	34
Rondônia	Brazil	93
Rio Branco	Brazil	121

Ankara	Turkey	78
Vienna	Austria	5
Ulaanbaatar	Mongolia	299
Chisinau	Moldova	133
Antwerp University Hospital	Belgium	18

Supplementary table 3: Mean age and gender distribution according to the different regions

Region	Age (years) mean + SD (range)	Gender Male % (n)
EM	42.5 ± 11.2 (16-78)	70.8% (114)
EE	35.7 ± 14.2 (1-79)	53.8% (365)
CE	46.4 ± 11.9 (14-71)	71.1% (64)
SAS	32.7 ± 11.7 (11-70)	70.9% (282)
SA	39.5 ± 13.1 (12-77)	60.6% (117)

Supplementary figure 1



Antiviral treatment regimens of the included patients. a) all patients were grouped into treated or not treated patient as well as unknown antiviral treatment (included previous and ongoing treatment). b) treated patients were grouped into therapy based on NUCs alone or IFNa treatment strategies (with or without NUCs). c) Specification of NUCs either alone or in combination with were determined.

Supplementary methods

Inclusion process and definitions

All participating centres signed a Participation Form and the laboratory normal range and the patient data were collected in an online CRF provided and supported by the Hannover Clinical Trial Centre. Patients could be included retrospectively as well as prospectively in the registry. For prospective inclusion we provided an informed consent in English as a template for the participating centers. All participating centres signed the following participation form: "I hereby confirm the participation of the above mentioned centre in the Hepatitis Delta International Network. I am aware that I am responsible to create an informed consent which is easy to understand for my patients in accordance with the template I have received from the Hepatitis Delta International Network." The following items were collected: Patient basic data, demographics, concomitant conditions, physical examination, haematology, biochemistry/virological parameters, liver-related complications like ascites, encephalopathy and variceal bleeding, development of HCC or, liver transplantation, as well as previous and ongoing antiviral therapy. Thereafter, database extraction was performed and all data were monitored centrally. Queries were sent to the centres. Here, we present the baseline characteristics of the included patients. Previous liver related complications were defined as ascites, encephalopathy,

oesophageal bleeding, HCC and liver transplantation (LTX). Liver cirrhosis was diagnosed based on liver histology (F5/F6 according to the ISHAK-score) or by transient elastography (>13.0 kPa). If these data were not available, presence of cirrhosis was considered if patients had already clinical evidence of hepatic decompensation in the past or if at least two of the following criteria were present: AST/ALT ratio >1; cholinesterase <lower limit of normal (LLN); platelets <100,000/mL; international normalized ratio (INR) >1.5; and/or splenomegaly (largest dimension >12 cm) or if one of the following parameters were positive: APRI>2, MELD>15.

Statistical analysis plans

For analyzing three final test variables (endpoints, cirrhosis and HDV RNA positive) we first analyzed the following categorial parameteres in univariate regression models: gender, therapy (NUCS vs. IFN), country of origin: SA, EM, EE, CE, SAS. All other parameters were analyzed continuously: age, thrombocytes, INR, AST, ALT, bilirubin, alcalic phosphotase, albumin and creatinine. Virological variables and special laboratory results like CHE were due to limited numbers of cases not considered for the analysis. All parameters that were univariate significant ($p<0.05$) associated with the test variables were included into multivariate regression models.