



VHPB TECHNICAL MEETING

# **The changing context of Hepatitis Delta**

*Background document*

**28-29 October 2021** – 16h until 19h

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VHPB Secretariat

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## **MEETING OBJECTIVES**

- Overview of current epidemiology of hepatitis Delta and discussing potential associated risk factors (e.g. HIV & Migrants from endemic countries)
- (New) Diagnostic tools and screening recommendations for hepatitis Delta
- Discuss prevention of hepatitis Delta
- Discuss treatment of hepatitis Delta
- Discuss the public health impact of hepatitis Delta
- As hepatitis Delta is an opportunistic infection to HBV, discussing HBV related issues is not excluded from the program

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## **PARTICIPANTS (± 50/MEETING)**

- Global scientists, opinion leaders, infectiologists, hepatologists, vaccinologists, paediatricians and public health representatives, who are experts in the field of viral hepatitis or health organisations involved in the prevention and control of viral hepatitis
- VHPB advisors
- Observers

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## **INTENDED IMPACT**

Emphasizing the importance of Hepatitis Delta, by gathering state-of-the-art information about its epidemiology, diagnosis, prevention, treatment and public health impact and the discuss the way forward to eliminate Hepatitis Delta.

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## **OUTLINE OF THE MEETING**

Presentations on selected topics about the changing context of hepatitis Delta will be pre-recorded by the speakers and made available latest one week before the meeting. The topic will be covered in separate 3h sessions, on Thursday-Friday 28-29 October 2021.

*NOTE: This pre-meeting document contains general background information on the topic of the VHPB meeting. It contains a list of selected abstracts/references from a Pubmed MEDLINE search of June 2021 on different search terms 24/06/2021: (Hepatitis D[Title/Abstract]) AND (("2016/01/01"[Date - Publication] : "2021/06/24"[Date - Publication])) depending on the topic discussed in a session of the meeting.*

*The references are sorted by publication year (most recent first). **References published in 2020 and 2021 are displayed.** This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully, it will give an overview of what has been published on the topics of the meeting.*

### Key facts

- **Hepatitis D virus (HDV) is a virus that requires hepatitis B virus (HBV) for its replication.**
- **Hepatitis D virus (HDV) affects globally nearly 5% of people who have a chronic infection with hepatitis B virus (HBV).**
- **HDV infection occurs when people become infected with both hepatitis B and D simultaneously (co-infection) or get hepatitis D after first being infected with hepatitis B (super-infection).**
- **Populations that are more likely to have HBV and HDV co-infection include indigenous populations, recipients of haemodialysis and people who inject drugs.**
- **Worldwide, the number of HDV infections has decreased since the 1980s, due mainly to a successful global HBV vaccination programme.**
- **The combination of HDV and HBV infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards liver-related death and hepatocellular carcinoma.**
- **Hepatitis D infection can be prevented by hepatitis B immunization, but treatment success rates are low.**

#### Overview

Hepatitis D is an inflammation of the liver caused by the hepatitis D virus (HDV), which requires HBV for its replication. Hepatitis D infection cannot occur in the absence of hepatitis B virus. HDV-HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards hepatocellular carcinoma and liver-related death.

Vaccination against hepatitis B is the only method to prevent HDV infection.

#### Geographical distribution

In a study published in the *Journal of Hepatology* in 2020 (1), conducted in collaboration with WHO, it was estimated that hepatitis D virus (HDV) affects nearly 5% of people globally who have a chronic infection with hepatitis B virus (HBV) and that HDV co-infection could explain about 1 in 5 cases of liver disease and liver cancer in people with HBV infection. The study has identified several geographical hotspots of high prevalence of HDV infection including Mongolia, the Republic of Moldova, and countries in western and central Africa.

#### Transmission

The routes of HDV transmission, like HBV, occur through broken skin (via injection, tattooing etc.) or through contact with infected blood or blood products. Transmission from mother to child is possible but rare. Vaccination against HBV prevents HDV coinfection and hence expansion of childhood HBV immunization programmes has resulted in a decline in hepatitis D incidence worldwide.

Chronic HBV carriers are at risk of infection with HDV. People who are not immune to HBV (either by natural disease or immunization with the hepatitis B vaccine) are at risk of infection with HBV, which puts them at risk of HDV infection.

Those who are more likely to have HBV and HDV co-infection include indigenous people, people who inject drugs and people with hepatitis C virus or HIV infection. The risk of co-infection also appears to be potentially higher in recipients of haemodialysis, men who have sex with men and commercial sex workers.

#### Symptoms

In acute hepatitis, simultaneous infection with HBV and HDV can lead to a mild-to-severe hepatitis with signs and symptoms of indistinguishable from those of other types of acute viral hepatitis infections. These features typically

appear 3–7 weeks after initial infection and include fever, fatigue, loss of appetite, nausea, vomiting, dark urine, pale-colored stools and jaundice (yellow eyes). even fulminant hepatitis, but recovery is usually complete and development of fulminant hepatitis is infrequent and chronic hepatitis D is rare (less than 5% of acute hepatitis).

In a superinfection, HDV can infect a person already chronically infected with HBV. The superinfection of HDV on chronic hepatitis B accelerates progression to a more severe disease in all ages and in 70–90% of persons. HDV superinfection accelerates progression to cirrhosis almost a decade earlier than HBV mono-infected persons. Patients with HDV induced cirrhosis are at an increased risk of hepatocellular carcinoma (HCC); however, the mechanism in which HDV causes more severe hepatitis and a faster progression of fibrosis than HBV alone remains unclear.

## **Diagnosis**

HDV infection is diagnosed by high levels of anti-HDV immunoglobulin G (IgG) and immunoglobulin M (IgM), and confirmed by detection of HDV RNA in serum.

However, HDV diagnostics are not widely available and there is no standardization for HDV RNA assays, which are used for monitoring response to antiviral therapy.

## **Treatment**

Pegylated interferon alpha is the generally recommended treatment for hepatitis D virus infection. Treatment should last for at least 48 weeks irrespective of the patient's response. The virus tends to give a low rate of response to the treatment; however, the treatment is associated with a lower likelihood of disease progression. This treatment is associated with significant side effects and should not be given to patients with decompensated cirrhosis, active psychiatric conditions and autoimmune diseases.

More efforts are needed to reduce the global burden of chronic hepatitis B and develop medicines that are safe and effective against hepatitis D and are affordable enough to be deployed on a large scale to those who are most in need.

## **Prevention**

While WHO does not have specific recommendations on hepatitis D, prevention of HBV transmission through hepatitis B immunization, including a timely birth dose, additional antiviral prophylaxis for eligible pregnant women, blood safety, safe injection practices in health care settings and harm reduction services with clean needles and syringes are effective in preventing HDV transmission. Hepatitis B immunization does not provide protection against HDV for those already infected with HBV.

## **WHO response**

In May 2016, the World Health Assembly adopted the first Global health sector strategy on viral hepatitis, 2016–2021. The strategy highlights the critical role of universal health coverage and the targets of the strategy are aligned with those of the 2030 Sustainable Development Goals. The strategy has a vision of eliminating viral hepatitis as a public health problem and this is reflected in the global targets of reducing new viral hepatitis infections by 90% and reducing deaths due to viral hepatitis by 65% by 2030. Actions to be taken by countries and WHO Secretariat to reach these targets are outlined in the strategy.

Furthermore, to support countries in moving towards achieving the global hepatitis goals under the 2030 Sustainable Development Agenda, WHO is working in the following areas:

- raising awareness, promoting partnerships and mobilizing resources;
- formulating evidence-based policy and data for action;
- increasing health equities within the hepatitis response;
- preventing transmission; and
- scaling up screening, care and treatment services.

For World Hepatitis Day 2021, WHO is highlighting on the theme “Hepatitis Can’t wait” to acknowledge the urgency of hepatitis elimination with a view to achieving the 2030 elimination targets.

Tan, M., A. S. Bhadoria, F. Cui, A. Tan, J. Van Holten, P. Easterbrook, N. Ford, Q. Han, Y. Lu, M. Bulterys, and Y. Hutin. "[Estimating the Proportion of People with Chronic Hepatitis B Virus Infection Eligible for Hepatitis B Antiviral Treatment Worldwide: A Systematic Review and Meta-Analysis.](#)" *Lancet Gastroenterol Hepatol* 6, no. 2 (Feb 2021): 106-19.

**BACKGROUND:** In 2016, of the estimated 257 million people living with chronic hepatitis B virus (HBV) infection worldwide, only a small proportion was diagnosed and treated. The insufficiency of information on the proportion of people infected with HBV who are eligible for treatment limits the interpretation of global treatment coverage. We aimed to estimate the proportion of people with chronic HBV infection who were eligible for antiviral treatment worldwide, based on the WHO 2015 guidelines. **METHODS:** In this systematic review and meta-analysis, we searched Medline, EMBASE, and the Cochrane databases from Jan 1, 2007, to Jan 31, 2018, for studies describing HBsAg-positive people in the population or health-care facilities. We extracted information from published studies using a standardised form to estimate the frequency of cirrhosis, abnormal alanine aminotransferase (ALT), HBV DNA exceeding 2000 IU/mL or 20 000 IU/mL, presence of HBeAg, and eligibility for treatment as per WHO and other guidelines as reported in the studies. We pooled proportions through meta-analysis with random effects. The study was registered with PROSPERO, CRD42020132345. **FINDINGS:** Of the 13 497 studies, 162 were eligible and included in our analysis. These studies included 145 789 participants. The pooled estimate of the proportion of cirrhosis was 9% (95% CI 8-10), ranging from 6% (4-8) in community settings to 10% (9-11) in clinic settings. Examining the proportion of participants who had characteristics used to determine eligibility in the WHO guidelines, 1750 (10.1%) of 17 394 had HBV DNA exceeding 20 000 IU/mL, and 20 425 (30.8%) of 66 235 had ALT above the upper limit of normal. 32 studies reported eligibility for treatment according to WHO or any other guidelines, with a pooled estimate of eligibility at 19% (95% CI 18-20), ranging from 12% (6-18) for studies in community settings to 25% (19-30) in clinic settings. **INTERPRETATION:** Many studies described people with HBV infection, but few reported information in a way that allowed assessment of eligibility for treatment. Although about one in ten of the 257 million people with HBV infection (26 million) might be in urgent need of treatment because of cirrhosis, a larger proportion (12-25%) is eligible for treatment in accordance with different guidelines. Future studies describing people with HBV infection should report on treatment eligibility, according to broadly agreed definitions. **FUNDING:** WHO and US Centers for Disease Control and Prevention.

Hayashi, T., Y. Takeshita, Y. J. Hutin, H. Harmanci, P. Easterbrook, S. Hess, J. van Holten, E. O. Oru, S. Kaneko, C. Yurdaydin, and M. Bulterys. "[The Global Hepatitis Delta Virus \(Hdv\) Epidemic: What Gaps to Address in Order to Mount a Public Health Response?](#)", *Arch Public Health* 79, no. 1 (Oct 19 2021): 180. <https://dx.doi.org/10.1186/s13690-021-00693-2>.

**BACKGROUND:** Co-infection between hepatitis B virus (HBV) and hepatitis delta virus (HDV) causes the severest chronic hepatitis and is associated with a high risk of cirrhosis and hepatocellular carcinoma (HCC). The Global Health Sector Strategy on Viral Hepatitis called for the elimination of hepatitis (- 65% mortality and - 90% incidence) by 2030. Our aims were to summarize key points of knowledge and to identify the gaps that need to be addressed to mount a public health response to HDV. **METHODS:** We performed a current literature review in terms of epidemiology by WHO regions, genotypes distribution and their pathogenicity, factors associated with HDV infection, mortality due to HDV infection, testing strategies and treatment. **RESULTS:** Prevalence of infection and genotypes are heterogeneous distributed, with highest prevalence in foci around the Mediterranean, in the Middle East, and in Central, Northern Asia and Eastern Asia. Persons who inject drugs (PWID) and migrants from highly endemic areas are highly affected. While antibody detection tests are available, HDV RNA tests of current infection are not standardized nor widely available. The few therapeutic options, including lofartinib, are not widely available; however several new and promising agents have entered clinical trials. **CONCLUSION:** HDV infection is an poorly known cause of chronic liver disease. To mount a public health response, we need a better description of the HDV epidemic, standardized testing strategies and better treatment options.

Rizzetto M and T Stroffolini (2021). "[Forty-Five Years after the Discovery of the Hepatitis D Virus: Where Do We Stand?](#)" *Viruses* 13(4).

The discovery of the Australia Antigen in the mid-1960s led, in a few years, to the identification of the virus of Hepatitis B [...].

Rizzetto M, S Hamid and F Negro (2021). "[The changing context of hepatitis D.](#)" *J Hepatol* **74**(5): 1200-1211. The global epidemiology of hepatitis D is changing with the widespread implementation of vaccination against hepatitis B. In high-income countries that achieved optimal control of HBV, the epidemiology of hepatitis D is dual, consisting of an ageing cohort of domestic patients with advanced liver fibrosis who represent the end stage of the natural history of HDV, and of a younger generation of immigrants from endemic countries who account for the majority of new infections. As observed in Europe in the 1980s, the distinctive clinical characteristic of chronic hepatitis D in endemic countries is the accelerated progression to cirrhosis and hepatocellular carcinoma. Despite some recent progress, the therapeutic management of HDV remains unsatisfactory, as most patients are not cured of HDV with currently available medicines. This review article describes the current epidemiology and clinical features of chronic hepatitis D, based on the literature published in the last 10 years.

Papatheodoridi M and GV Papatheodoridis (2021). "[Is hepatitis delta underestimated?](#)" *Liver Int* **41 Suppl 1**: 38-44.

Hepatitis D virus may be underestimated because it is a significant problem in HBsAg-positive patients, especially those who inject drugs, have HIV or HCV co-infections and/or live in certain endemic regions. In the past few decades, the prevalence of HDV was expected to have decreased as a result of improvements in public healthcare policies and universal HBV vaccination programs. However, HDV has continued to spread in low-income countries, with local outbreaks and migration to less endemic areas, so that its prevalence has remained stable or even increased in certain regions. As a result, research has been focused on the epidemiology of HDV. Contradicting data from three large recent meta-analyses have reported that the prevalence of HDV may be between 0.16% and 1.00% in the global general population, and 4.5% and 14.6% in HBsAg-positive patients, with an estimated 12 to 70 million HDV patients worldwide. The exact prevalence and estimated number of HDV patients is still a subject of debate for several reasons, including the unreliable assessment of the infection and a lack of real-world screening. HDV infection is associated with an increased risk of progression to cirrhosis and the development of HCC compared to patients with HBV mono-infection, a risk which is even higher in patients with HIV co-infection. Morbidity and mortality from HDV-related cirrhosis should not be overlooked. In conclusion, hepatitis D virus is probably underestimated and certainly underdiagnosed, and screening for HDV should be performed in all HBsAg-positive patients in clinical practice.

Papatheodoridi M and GV Papatheodoridis (2021). "[Current status of hepatitis delta.](#)" *Curr Opin Pharmacol* **58**: 62-67.

Hepatitis D virus (HDV) infection in patients chronically infected with hepatitis B virus (HBV) causes the most severe form of chronic viral hepatitis and continues to represent a major health problem. The latest data show that the global prevalence is much higher than previously considered. Therefore, screening with the detection of anti-HDV antibodies is mandatory for all chronic HBV patients. In spite of the severity of liver disease, the only recommended treatment today is pegylated interferon-alpha, which has limited efficacy. Novel host-targeting molecules are now under investigation. The current phase 2 clinical trials include pegylated interferon-lambda, bulevirtide, lonafarnib, and REP-2139. This review focuses on the current status of epidemiology, diagnosis, and treatment of HDV infection.

Masood U and S John (2021). **Hepatitis D.** *StatPearls*. Treasure Island (FL), StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.

Hepatitis D virus (HDV) was discovered in 1977 in patients with chronic Hepatitis B virus (HBV) infection. Originally thought to be an unrecognized HBV antigen, the HDV nuclear antigen was later discovered to be a part of a new pathogen, initially known as the delta agent. HDV is considered a hybrid virus as it uses Hepatitis B surface antigen (HBsAg) as its envelope protein rendering it the ability to infect only patients that concomitantly harbor HBV. Due to unknown reasons, HBV replication is suppressed in HDV-infected individuals.

Decker A, C Neumann-Haefelin and R Thimme (2021). [Hepatitis A-E](#) *Internist (Berl)* **62**(2): 163-174.

Hepatitis viruses A-E cause acute and chronic liver inflammation and thus lead to significant morbidity and mortality worldwide. They differ significantly in their biology, course of disease and therapy options. While hepatitis A virus only causes acute infection, hepatitis B can become chronic, even reactivate or

occur as coinfection with hepatitis D virus. Whereas these infections are preventable through vaccination, a vaccine does not exist against HCV. However, new direct antiviral agents reliably lead to cure of chronic hepatitis C. Hepatitis E virus frequently causes acute or in case of immunosuppression-even chronic hepatitis. Continual screening of patients with elevated liver enzymes or risk groups using simple serological markers can enable virus-specific therapy of mostly asymptomatic chronic virus hepatitis, preventing the development of liver cirrhosis and hepatocellular carcinoma.

Vignon A, S Denolly, J Perez-Vargas and FL Cosset (2020). "[\[The hepatitis delta virus: an easily turncoat pathogen?\]](#)." *Med Sci (Paris)* **36**(1): 27-29.

Taylor JM (2020). "[Infection by Hepatitis Delta Virus.](#)" *Viruses* **12**(6).

Hepatitis delta virus (HDV) and hepatitis B virus (HBV) are blood-borne viruses that infect human hepatocytes and cause significant liver disease. Infections with HBV are more damaging when there is a coinfection with HDV. The genomes and modes of replication of these two viruses are fundamentally different, except for the fact that, in nature, HDV replication is dependent upon the envelope proteins of HBV to achieve assembly and release of infectious virus particles, ones that use the same host cell receptor. This review focuses on what has been found of the various ways, natural and experimental, by which HDV particles can be assembled and released. This knowledge has implications for the prevention and treatment of HDV infections, and maybe for an understanding of the origin of HDV.

Tallan A and Z Feng (2020). "[Virus spread in the liver: mechanisms, commonalities, and unanswered questions.](#)" *Future Virol* **15**(10): 707-715.

The liver is home to five known human hepatitis viruses (hepatitis A virus-hepatitis E virus). Despite being phylogenetically unrelated, these viruses replicate and spread in the liver without causing apparent cytopathic effects, and all have evolved strategies to counteract antibody-mediated inhibition of virus spread. In this review, we discuss the current understanding regarding the spread mechanisms for these viruses with an attempt to extract common principles and identify key questions for future studies.

Sonneveld MJ and RJ de Knegt (2020). "[Editorial: rapid disease progression in hepatitis delta-can we turn the tide?](#)" *Aliment Pharmacol Ther* **51**(1): 172-173.

Shen DT, DZ Ji, HY Chen, H Goyal, S Pan and HG Xu (2020). "[Hepatitis D: not a rare disease anymore: global update for 2017-2018.](#)" *Gut* **69**(4): 786-788.

Khuroo MS and AA Sofi (2020). "[The Discovery of Hepatitis Viruses: Agents and Disease.](#)" *J Clin Exp Hepatol* **10**(4): 391-401.

Discovery of five hepatitis viruses A to E has followed distinctive definable phases. Human experiments at Willowbrook identified two forms of hepatitis namely infectious hepatitis and serum hepatitis. The discovery of Australia antigen in 1965 led to rapid scientific developments in viral hepatitis. SH antigen was detected in sera of patients with serum hepatitis and soon SH antigen and Australia antigen were found to be identical and selectively associated with serum hepatitis. In 1970, 42-nm Dane particles were detected in Australia antigen positive sera and linked to the virus of serum hepatitis. Subsequently, a new antigen-antibody system (e-antigen/antibody) was detected in such patients and associated with infectivity. Then, DNA polymerase was found in concentrated pellets containing Australia antigen. Hepatitis B virus (HBV) DNA cloning and sequencing of HBV followed these developments. In 1973, 27 nm hepatitis A virus (HAV)-like particles were visualized in stool samples obtained during acute phase of illness after inoculation of MS-1 strain in volunteers. Cloning and sequencing of HAV followed. In 1977, a new antigen-antibody system ( $\delta$  antigen-antibody system) was identified by chance associated with HBV. Based on animal transmission studies,  $\delta$  agent was found to be another virus called hepatitis D virus that is defective, requires the helper functions of HBV and interferes with HBV replication. The search for hepatitis C virus started when non-A, non-B hepatitis was recognised in multiply transfused patients with subsequent successful animal transmission. HCV was identified by a novel immunoscreening approach involving screening of cDNA libraries from infectious sera. The story of hepatitis E is historically linked to discovery of waterborne epidemic non-A, non-B hepatitis from Kashmir, India. Virus-like-particles of the agent were identified in stool samples of a human volunteer after a self-experimentation. HEV cDNA was detected in bile-enriched infectious samples and full-length HEV RNA genome was subsequently cloned and sequenced.

Miao Z, S Zhang, X Ou, S Li, Z Ma, W Wang, MP Peppelenbosch, J Liu and Q Pan (2020). [Estimating the Global Prevalence, Disease Progression, and Clinical Outcome of Hepatitis Delta Virus Infection](#) *J Infect Dis* **221**(10): 1677-1687.

BACKGROUND: Hepatitis delta virus (HDV) coinfects with hepatitis B virus (HBV) causing the most severe form of viral hepatitis. However, its exact global disease burden remains largely obscure. We aim to establish the global epidemiology, infection mode-stratified disease progression, and clinical outcome of HDV infection. METHODS: We conducted a meta-analysis with a random-effects model and performed data synthesis. RESULTS: The pooled prevalence of HDV is 0.80% (95% confidence interval [CI], 0.63-1.00) among the general population and 13.02% (95% CI, 11.96-14.11) among HBV carriers, corresponding to 48-60 million infections globally. Among HBV patients with fulminant hepatitis, cirrhosis, or hepatocellular carcinoma, HDV prevalence is 26.75% (95% CI, 19.84-34.29), 25.77% (95% CI, 20.62-31.27), and 19.80% (95% CI, 10.97-30.45), respectively. The odds ratio (OR) of HDV infection among HBV patients with chronic liver disease compared with asymptomatic controls is 4.55 (95% CI, 3.65-5.67). Hepatitis delta virus-coinfected patients are more likely to develop cirrhosis than HBV-monoinfected patients with OR of 3.84 (95% CI, 1.79-8.24). Overall, HDV infection progresses to cirrhosis within 5 years and to hepatocellular carcinoma within 10 years, on average. CONCLUSIONS: Findings suggest that HDV poses a heavy global burden with rapid progression to severe liver diseases, urging effective strategies for screening, prevention, and treatment.

Rizzetto M (2020). ["The Discovery of the Hepatitis D Virus: Three Princes of Serendip and the Recognition of Autoantibodies to Liver-Kidney Microsomes."](#) *Clin Liver Dis (Hoboken)* **16**(Suppl 1): 1-11.

## Epidemiology and management

Farci P, GA Niro, F Zamboni and G Diaz (2021). ["Hepatitis D Virus and Hepatocellular Carcinoma."](#) *Viruses* **13**(5). Hepatitis D virus (HDV) is a small, defective RNA virus that depends on hepatitis B virus (HBV) for virion assembly and transmission. It replicates within the nucleus of hepatocytes and interacts with several cellular proteins. Chronic hepatitis D is a severe and progressive disease, leading to cirrhosis in up to 80% of cases. A high proportion of patients die of liver decompensation or hepatocellular carcinoma (HCC), but the lack of large prospective studies has made it difficult to precisely define the rate of these long-term complications. In particular, the question of whether HDV is an oncogenic virus has been a matter of debate. Studies conducted over the past decade provided evidence that HDV is associated with a significantly higher risk of developing HCC compared to HBV monoinfection. However, the mechanisms whereby HDV promotes liver cancer remain elusive. Recent data have demonstrated that the molecular profile of HCC-HDV is unique and distinct from that of HBV-HCC, with an enrichment of upregulated genes involved in cell-cycle/DNA replication, and DNA damage and repair, which point to genome instability as an important mechanism of HDV hepatocarcinogenesis. These data suggest that HBV and HDV promote carcinogenesis by distinct molecular mechanisms despite the obligatory dependence of HDV on HBV.

Castaneda D, AJ Gonzalez, M Alomari, K Tandon and XB Zervos (2021). ["From hepatitis A to E: A critical review of viral hepatitis."](#) *World J Gastroenterol* **27**(16): 1691-1715.

Viral infections affecting the liver have had an important impact on humanity, as they have led to significant morbidity and mortality in patients with acute and chronic infections. Once an unknown etiology, the discovery of the viral agents triggered interest of the scientific community to establish the pathogenesis and diagnostic modalities to identify the affected population. With the rapid scientific and technological advances in the last centuries, controlling and even curing the infections became a possibility, with a large focus on preventive medicine through vaccination. Hence, a comprehensive understanding of hepatitis A, B, C, D and E is required by primary care physicians and gastroenterologists to provide care to these patients. The review article describes the epidemiology, pathogenesis, clinical presentation, diagnostic tools and current medication regimens, with a focus on upcoming treatment options and the role of liver transplantation.

Vlachogiannakos J and GV Papatheodoridis (2020). ["New epidemiology of hepatitis delta."](#) *Liver Int* **40** Suppl 1: 48-53.

Hepatitis D virus (HDV) is a defective pathogen that needs hepatitis B virus (HBV) for infection. Co-infection of HBsAg-positive individuals with HDV is commonly associated with a more rapid progression

to cirrhosis, a higher incidence of hepatocellular carcinoma (HCC) and increased mortality. Initial studies have shown that about 5% of chronic HBV carriers worldwide (15-20 millions) were also infected with HDV. However, recent studies suggest that the prevalence of HDV is at least two- to three-fold higher than previous estimations. Improved diagnostic techniques have shown that HDV infection remains endemic in certain areas of the world. Injection drug users, individuals with high-risk sexual behaviour and patients co-infected with human immunodeficiency virus (HIV) represent the major reservoir of the disease in the Western world. Although the burden of HDV infection significantly decreased in Europe in the nineties, there has been no further decrease in the last decade, probably because of migration from HDV endemic countries. Until new and more effective therapies are available, public health measures should be reinforced by increasing prophylactic HBV vaccination programs, preventing transmission of the virus among parenteral drug users and implementing universal HDV screening of all HBV-infected individuals.

Stockdale AJ, B Kreuels, MYR Henrion, E Giorgi, I Kyomuhangi, C de Martel, Y Hutin and AM Geretti (2020). "[The global prevalence of hepatitis D virus infection: Systematic review and meta-analysis](#)." *J Hepatol* **73**(3): 523-532.

**BACKGROUND AND AIMS:** There are uncertainties about the epidemic patterns of HDV infection and its contribution to the burden of liver disease. We estimated the global prevalence of HDV infection and explored its contribution to the development of cirrhosis and hepatocellular carcinoma (HCC) among HBsAg-positive people. **METHODS:** We searched Pubmed, EMBASE and Scopus for studies reporting on total or IgG anti-HDV among HBsAg-positive people. Anti-HDV prevalence was estimated using a binomial mixed model, weighting for study quality and population size. The population attributable fraction (PAF) of HDV to cirrhosis and HCC among HBsAg-positive people was estimated using random effects models. **RESULTS:** We included 282 studies, comprising 376 population samples from 95 countries, which together tested 120,293 HBsAg-positive people for anti-HDV. The estimated anti-HDV prevalence was 4.5% (95% CI 3.6-5.7) among all HBsAg-positive people and 16.4% (14.6-18.6) among those attending hepatology clinics. Worldwide, 0.16% (0.11-0.25) of the general population, totalling 12.0 (8.7-18.7) million people, were estimated to be anti-HDV positive. Prevalence among HBsAg-positive people was highest in Mongolia, the Republic of Moldova and countries in Western and Middle Africa, and was higher in injecting drug users, haemodialysis recipients, men who have sex with men, commercial sex workers, and those with HCV or HIV. Among HBsAg-positive people, preliminary PAF estimates of HDV were 18% (10-26) for cirrhosis and 20% (8-33) for HCC. **CONCLUSIONS:** An estimated 12 million people worldwide have experienced HDV infection, with higher prevalence in certain geographic areas and populations. HDV is a significant contributor to HBV-associated liver disease. More quality data are needed to improve the precision of burden estimates. **LAY SUMMARY:** We combined all available studies to estimate how many people with hepatitis B also have hepatitis D, a viral infection that only affects people with hepatitis B. About 1 in 22 people with hepatitis B also have hepatitis D, increasing to 1 in 6 when considering people with liver disease. Hepatitis D may cause about 1 in 6 of the cases of cirrhosis and 1 in 5 of the cases of liver cancer that occur in people with hepatitis B. Hepatitis D is an important contributor to the global burden of liver disease.

Stockdale AJ, B Kreuels, MRY Henrion, E Giorgi, I Kyomuhangi and AM Geretti (2020). "[Hepatitis D prevalence: problems with extrapolation to global population estimates](#)." *Gut* **69**(2): 396-397.

Stockdale AJ, Y Hutin and AM Geretti (2020). "[Reply to: "Revisiting the estimation of hepatitis D global prevalence"](#)." *J Hepatol* **73**(5): 1280-1281.

Miao Z and Q Pan (2020). "[Revisiting the estimation of hepatitis D global prevalence](#)." *J Hepatol* **73**(5): 1279-1280.

Hercun J, C Koh and T Heller (2020). "[Hepatitis Delta: Prevalence, Natural History, and Treatment Options](#)." *Gastroenterol Clin North Am* **49**(2): 239-252.

Half a century after its discovery, hepatitis delta remains a pertinent global health issue with a major clinical impact in endemic regions and an underestimated prevalence worldwide. Hepatitis delta virus infection follows a challenging clinical course and is responsible for significant liver-related morbidity. Although the only currently available treatment (pegylated interferon) does not provide consistent results, emerging therapeutic options are promising. This article explores the epidemiology, natural history, as well as current and potential therapeutic options for hepatitis delta virus infection.

Do A and NS Reau (2020). "[Chronic Viral Hepatitis: Current Management and Future Directions.](#)" *Hepatol Commun* **4**(3): 329-341.

The past decade has seen transformation in the strategies for identifying and managing viral hepatitis, most dramatically the transformation of hepatitis C virus from a mostly chronic affliction to a curable disease that is accessible to wide populations through direct-acting antiviral therapies. More recently, shifting of hepatitis C virus burden to younger patients driven by intravenous drug use has shaped screening recommendations. Future work focusing on effective screening, linkage to care, treatment initiation, and post-cure management will allow countries to work toward meeting goals of eliminating viral hepatitis as a major public health threat. Concurrently, hepatitis B virus has also seen advances in management using oral nucleos(t)ide therapies with high-resistance barriers. However, virologic cure remains elusive in the setting of viral genetic persistence within the hepatocyte nucleus, even with suppressive antiviral therapy. Future directions include a refined definition of "cure," new biomarkers, and development of therapies targeting multiple pathways in the viral pathogenic and replication pathway. Progress is additionally being made on the management of hepatitis D infection. This review summarizes the recent evolution in disease characteristics, associated affected population, and changes in our understanding of management for these infections. We also discuss future directions in the management of viral hepatitis, including discussion on issues related to management before and after antiviral therapy. Conclusion: We summarize recent advances in the identification and management of viral hepatitis, which hold the potential to markedly reduce disease burden and therefore associated liver-related complications. However further work is needed to adequately identify and manage these diseases.

Cornberg M, AS Lok, NA Terrault and F Zoulim (2020). "[Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference\(†\).](#)" *J Hepatol* **72**(3): 539-557.

Representatives from academia, industry, regulatory agencies, and patient groups convened in March 2019 with the primary goal of developing agreement on chronic HBV treatment endpoints to guide clinical trials aiming to 'cure' HBV. Agreement among the conference participants was reached on some key points. 'Functional' but not sterilising cure is achievable and should be defined as sustained HBsAg loss in addition to undetectable HBV DNA 6 months post-treatment. The primary endpoint of phase III trials should be functional cure; HBsAg loss in  $\geq 30\%$  of patients was suggested as an acceptable rate of response in these trials. Sustained virologic suppression (undetectable serum HBV DNA) without HBsAg loss 6 months after discontinuation of treatment would be an intermediate goal. Demonstrated validity for the prediction of sustained HBsAg loss was considered the most appropriate criterion for the approval of new HBV assays to determine efficacy endpoints. Clinical trials aimed at HBV functional cure should initially focus on patients with HBeAg-positive or negative chronic hepatitis, who are treatment-naïve or virally suppressed on nucleos(t)ide analogues. A hepatitis flare associated with an increase in bilirubin or international normalised ratio should prompt temporary or permanent cessation of an investigational treatment. New treatments must be as safe as existing nucleos(t)ide analogues. The primary endpoint for phase III trials for HDV coinfection should be undetectable serum HDV RNA 6 months after stopping treatment. On treatment HDV RNA suppression associated with normalisation of alanine aminotransferase is considered an intermediate goal. In conclusion, regarding HBV 'functional cure', the primary goal is sustained HBsAg loss with undetectable HBV DNA after completion of treatment and the intermediate goal is sustained undetectable HBV DNA without HBsAg loss after stopping treatment.

Cheung A and P Kwo (2020). "[Viral Hepatitis Other than A, B, and C: Evaluation and Management.](#)" *Clin Liver Dis* **24**(3): 405-419.

Viral hepatitis can cause a wide spectrum of clinical presentations from a benign form with minimal or no symptoms to acute liver failure or death. Hepatitis D coinfection and superinfection have distinct clinical courses, with the latter more likely leading to chronic infection. Management of chronic hepatitis D virus is individualized because of the paucity of treatment options and significant side effect profile of currently available treatments. Sporadic cases of hepatitis E caused by contaminated meats are becoming increasingly prevalent in immunocompromised hosts. Human herpesviruses are an important cause of disease also in immunocompromised individuals.

Boyd A and G Wandeler (2020). "[Hepatitis D virus: is it all in the family?](#)" *Gut* **69**(7): 1162-1163.

## COUNTRY EXAMPLES

**New Zealand** - Jackson K, M Littlejohn, E Gane and S Locarnini (2021). "[Molecular Phylogenetics of Hepatitis D Virus in New Zealand and the Implications for Pacific Island Countries.](#)" *Intervirology* **64**(2): 102-107.

Hepatitis delta virus (HDV) is considered a satellite virus that requires hepatitis B virus surface antigen for infectivity. HDV is endemic in some Pacific Island (PI) countries, including Kiribati and Nauru, with a unique genotype 1, "Pacific clade." The aims of this study were to determine the HDV genotypes in New Zealand and investigate the link of strains to other PI countries and the rest of the world through phylogenetics. Sequencing and phylogenetic analyses were performed on 16 HDV-positive serum samples from 14 individuals collected between 2009 and 2014 at Auckland Hospital. Thirteen of 14 strains were confirmed as genotype 1 and 1 was genotype 5. Eleven of the 13 genotype 1 strains clustered with the Pacific clade. These were isolated from subjects born in Samoa, Kiribati, Tuvalu, and Niue. Another genotype 1 strain isolated from a Maori health-care worker clustered most closely with a European strain. There was an African genotype 1 and genotype 5 from African-born subjects with HIV coinfection. This study supports the probable transmission of HDV Pacific clade around the PI from Micronesia to Polynesia. The data also confirm the need to screen hepatitis B surface antigen-positive individuals for HDV.

**Tuva** - Isaeva OV, LY Il'chenko, AA Saryglar, AA Karlsen, KK Kyuregyan and MI Mikhailov (2021). "[Clinical course and outcomes of chronic viral hepatitis D in patients from Republic of Tuva as endemic region.](#)" *Vopr Virusol* **66**(1): 74-83.

INTRODUCTION: Hepatitis D (delta,  $\delta$ ) is caused by an RNA virus (hepatitis D virus, HDV) from genus Deltavirus, and is the most severe and difficult to treat disease among both viral hepatitis and infectious diseases in general. The development of HDV infection in the host organism is possible only in the presence of hepatitis B virus (HBV). Coinfection with HBV and HDV is associated with a more rapid progression of chronic viral hepatitis (CVH) to liver cirrhosis (LC) and an unfavorable outcome in comparison with HBV monoinfection. Data on the influence of clinical, biochemical and virological factors on the infectious process in patients with hepatitis D are limited due to the insufficient amount of research on this theme. The study aimed to determine demographic, clinical, biochemical, and virological factors influencing the course and progression of CVH D in patients followed during 10 years, residing in the territory of the Tuva Republic, one of the endemic regions of the Russian Federation. MATERIAL AND METHODS: Changes in clinical and laboratory parameters were analyzed in dynamics in 121 HDV infected patients with a different course of the disease, who were under observation from 2009 to 2019. Three groups of patients were identified: group 1 - 61 patients with disease progression of chronic hepatitis to LC (Child-Pugh class B-C), group 2 - 49 patients with non-progressive chronic hepatitis, and group 3 - 11 patients with slowly progressive LC (class A). Demographic data, the presence of detectable HBV DNA, indicators of the functional state of the liver: alanine aminotransferase (ALT/GPT), aspartate aminotransferase (AST/GOT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), and total bilirubin content were analyzed. The severity of hepatic encephalopathy was assessed by the duration of the numbers connection test (NCT). RESULTS: All patients belonged to the same ethnic group (Tuvinians), were infected with HDV genotype 1 and were positive for HDV RNA throughout the entire follow-up period. There were no significant differences in sex ratio and mean age at the time of inclusion in the study between the groups. In group 1, the average number of years from inclusion in the study to the formation of LC was  $3.65 \pm 2.3$  years, years to the lethal outcome:  $4.5 \pm 3$  years. Significantly higher levels of AST/GOT, ALP, GGT, total bilirubin (TB) and NCT grade were found in group 1 compared to group 2. ALT/GPT levels did not differ significantly in these groups. When comparing groups with disease progression and slowly progressive LC (groups 1 and 3), no significant differences were found in any of the clinical and biochemical parameters. ALT/GPT, GGT, TB and NCT values were significantly higher in patients with slowly progressive LC (group 3) compared to group 2. No differences in AST/GOT and ALP levels were found between these groups. Detectable HBV DNA was significantly more frequent in patients with progressive disease and with chronic viral hepatitis than in patients with slowly progressive LC. There were no significant differences in the frequency of HBV DNA detection in patients from groups 1 and 2. CONCLUSION: The results obtained on a relatively homogeneous cohort demonstrated that age and gender are not the factors influencing the progression of chronic viral hepatitis D to cirrhosis. The lack of detectable HBV DNA is associated with the slow progression of LC. The revealed differences in clinical and biochemical parameters reflect the degree of functional liver damage in chronic viral hepatitis D and HDV-associated cirrhosis.

**Vietnam** - Hoan NX, M Hoechel, A Tomazatos, CX Anh, SR Pallerla, LTK Linh, MT Binh, BT Sy, NL Toan, H Wedemeyer, CT Bock, PG Kremsner, CG Meyer, LH Song and TP Velavan (2021). "[Predominance of HBV Genotype B and HDV Genotype 1 in Vietnamese Patients with Chronic Hepatitis.](#)" *Viruses* **13**(2).

Hepatitis delta virus (HDV) coinfection will additionally aggravate the hepatitis B virus (HBV) burden in the coming decades, with an increase in HBV-related liver diseases. Between 2018 and 2019, a total of 205 HBV patients clinically characterized as chronic hepatitis B (CHB; n = 115), liver cirrhosis (LC; n = 21), and hepatocellular carcinoma (HCC; n = 69) were recruited. HBV surface antigen (HBsAg), antibodies against surface antigens (anti-HBs), and core antigens (anti-HBc) were determined by ELISA. The presence of hepatitis B viral DNA and hepatitis delta RNA was determined. Distinct HBV and HDV genotypes were phylogenetically reconstructed and vaccine escape mutations in the "a" determinant region of HBV were elucidated. All HBV patients were HbsAg positive, with 99% (n = 204) and 7% (n = 15) of them being positive for anti-HBc and anti-HBs, respectively. Anti-HBs positivity was higher among HCC (15%; n = 9) compared to CHB patients. The HBV-B genotype was predominant (65%; n = 134), followed by HBV-C (31%; n = 64), HBV-D, and HBV-G (3%; n = 7). HCC was observed frequently among young individuals with HBV-C genotypes. A low frequency (2%; n = 4) of vaccine escape mutations was observed. HBV-HDV coinfection was observed in 16% (n = 33) of patients with the predominant occurrence of the HDV-1 genotype. A significant association of genotypes with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) enzyme levels was observed in HBV mono-infections. The prevalence of the HDV-1 genotype is high in Vietnam. No correlation was observed between HDV-HBV coinfections and disease progression when compared to HBV mono-infections.

**Egypt** - Elbahrawy A, MK Ibrahim, A Eliwa, M Alborai, A Madian and HH Aly (2021). "[Current situation of viral hepatitis in Egypt.](#)" *Microbiol Immunol*.

An estimated 8-10 million people suffer from viral hepatitis in Egypt. Hepatitis A virus (HAV) and hepatitis E virus (HEV) are major causes of viral hepatitis in Egypt since  $\geq 50\%$  of the Egyptian population are already exposed to HAV infection by the age of 15 years. In addition,  $> 60\%$  of the Egyptian population tested seropositive for anti-HEV in the first decade of life. They mainly cause self-limiting hepatitis, however cases of fulminant hepatitis and liver failure were reported in Egypt. Hepatitis B virus (HBV), hepatitis C virus (HCV), and hepatitis D virus (HDV) are the main causes of chronic hepatitis, liver cirrhosis, and liver cancer (HCC) in Egypt. Globally, Egypt has the highest age standardized death rate due to cirrhosis from 1990 until 2017. The prevalence rate of HBV (1.3-1.5%) has declined after national infantile immunization. Coinfection of HBV patients with HDV is common in Egypt since HDV antibodies (IgG) range from 8.3% to 43% among total HBV patients. After the conduction of multiple national programs to control HCV infection, a lower rate of HCV prevalence (4.6%) was recently reported. Data about the incidence of HCV after direct antiviral agents (DAA) treatment are lacking. Hepatocellular carcinoma (HCC) incidence of 29/1000/year in cirrhotic patients after DAA treatment, is reported. A higher rate of infiltrative pattern among HCC patients after DAA treatment is also recognized. Viral hepatitis is one of the major public health concerns in Egypt that need more attention and funding from health policymakers. This article is protected by copyright. All rights reserved.

**Africa** - Dakurah OB, CRT Tamandjou, M Zunza, W Preiser and TG Maponga (2021). "[Viral hepatitis associated hepatocellular carcinoma on the African continent, the past, present, and future: a systematic review.](#)" *BMC Cancer* **21**(1): 715.

**BACKGROUND:** Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths in Africa. In Africa, the major causes of HCC include chronic infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV). Knowledge of the changes in the incidence of viral hepatitis-associated HCC over time and the factors responsible for such changes is key in informing policies for the prevention of viral hepatitis-associated HCC in Africa. **AIM:** The study aimed to systematically summarize the changes in the prevalence of viral hepatitis among HCC patients and the overall effect of the prevalence of viral hepatitis on the incidence of HCC over the past four decades in Africa (1980-2019). **METHODS:** A literature search was conducted in MEDLINE (PubMed), Google Scholar, Science Direct, Scopus, Web of Science, and African wide web for articles published on viral hepatitis-associated HCC in Africa from 1980 to 2019. The abstracts of the articles were screened for eligibility and those meeting the inclusion criteria were retrieved and reviewed. **RESULTS:** A total of 272 studies were included in the analysis. Viral hepatitis-related HCC incidence changed by 1.17% (95% confidence interval (CI): 0.63-1.71,  $p < 0.001$ ), 0.82% (95% CI: 0.45-1.18,  $p < 0.001$ ), and 3.34% (95% CI: 2.44-4.25,  $p < 0.001$ ) for every 1% change in the prevalence of HBV, HCV, and hepatitis D virus (HDV) respectively, per decade. The incidence of HBV-related HCC decreased by -0.50% (95% CI: -0.74 - -0.25,  $p < 0.001$ ) over the last 40 years, while HCV-related HCC

increased. CONCLUSION: Overall, the incidence of viral hepatitis-associated HCC has not declined, mainly due to no decline in the prevalence of HCV, HDV, and the high number of chronic hepatitis B carriers on the African continent. There is an urgent need for the allocation of resources for the implementation of treatment and preventive programs for HBV, HCV, HDV, and HCC in Africa. This systematic review is registered with PROSPERO®, number CRD42020169723.

**Nigeria** - Abdulkareem LO, DA Ndububa, AO Uhumwangho and T Yunusa (2021). "[Hepatitis D virus antibodies and liver function profile among patients with chronic hepatitis B infection in Abuja, Nigeria.](#)" *J Infect Dev Ctries* **15**(1): 141-146.

INTRODUCTION: Hepatitis D virus (HDV) is a satellite virus of hepatitis B virus (HBV). An estimated 5% of HBV infected individuals worldwide have HDV infection. There is paucity of studies in Nigeria on the burden of HDV infection. This study aimed at determining the prevalence rate of HDV antibodies among individuals with chronic hepatitis B (CHB) infection and comparing the liver function test (LFT) and disease severity among the anti-HDV positive (anti-HDV+) and anti-HDV negative (anti-HDV-) individuals. METHODOLOGY: A cross-sectional study of 180 CHB infected individuals who were clinically evaluated and tested for HDV antibodies using the Enzyme-linked Immunoassay method. Their LFT profile and Child-Turcotte-Pugh (CTP) were also assessed. Data were analyzed using the SPSS version 17. RESULTS: Their mean age was  $35.2 \pm 10.4$  years. There were 150 (83.3%) and 30 (16.7%) individuals with uncomplicated and complicated CHB infection respectively. Thirty-four (18.9%) of the participants were anti-HDV+. The mean serum ALT, AST, albumin and INR of the anti-HDV+ subjects were  $16.5 \pm 13.8$  IU/L,  $26.3 \pm 32.6$  IU/L,  $38.9 \pm 7.6$  g/L, and  $1.2 \pm 0.2$  respectively. The mean values for the same parameters of the anti-HDV- subjects were  $10.8 \pm 9.5$  IU/L,  $13.4 \pm 11.2$  IU/L,  $41.4 \pm 6.0$  g/L and  $1.1 \pm 0.2$  respectively ( $p < 0.05$ ). The mean CTP scores in the anti-HDV+ and anti-HDV- subjects were  $6.1 \pm 2.1$  and  $5.5 \pm 1.2$  respectively ( $p = 0.03$ ). CONCLUSIONS: Anti-HDV sero-prevalence rate was 18.9% and anti-HDV+ CHB patients had worse LFT results compared to those who were anti-HDV-.

**Sakha** - Yushchuk ND, SS Sleptsova, SI Malov, IF Bilukina, SI Semenov, LA Stepanenko, OB Ogarkov, ED Savilov and IV Malov (2020). "[Assessment of external risk factors of hepatocellular cancer development and markers of genetic predisposition to its development in the ethnic group of yakut - men.](#)" *Ter Arkh* **92**(1): 56-61.

AIM: To establish the main external and genetically determined risk factors for the development of hepatocellular cancer in the ethnic group of male Yakuts living in the Republic of Sakha (Yakutia) [RS (Y)] in the epidemiologically unfavorable conditions of the incidence of viral hepatitis. MATERIALS AND METHODS: A total of 97 male Yakuts were examined, including 44 people diagnosed with hepatocellular cancer and 53 people diagnosed with chronic viral hepatitis. HCC risk factors were identified by analyzing medical records and questioning patients. In the experimental and control groups, genetic studies of single nucleotide polymorphisms of genes mapped on the X-chromosome and involved in the activation of antiviral immunity along the TLR7 signaling pathway were performed. RESULTS AND DISCUSSION: In 100% of patients with hepatocellular cancer, infection with hepatitis B, C, D viruses or co-infection with these agents was detected. Every fourth patient with HCC in the RS (Y) was infected with hepatitis D. The course of hepatocellular cancer associated with HDV was characterized by rapid progression of liver cirrhosis, development of portal hypertension, bleeding from varicose veins of the stomach and esophagus (36.4%) and edematous ascitic syndrome (63.6%). In addition to viral agents, additional risk factors for liver cancer were identified, such as alcohol abuse, overweight, diabetes mellitus, and smoking. Among the studied variation sites of genes localized on the X-chromosome and encoding the reaction of innate antiviral immunity, no genetic marker was found with a sufficient degree of confidence determining the likelihood of hepatocellular cancer developing. CONCLUSIONS: The high incidence of hepatocellular carcinoma of the male population in the RS (Y) is due to the widespread prevalence of parenteral viral hepatitis, especially viral hepatitis D. Due to the introduction of mass vaccination of the population against hepatitis B in the Russian Federation in the foreseeable future in the RS (Y) we should see a decrease in the proportion of hepatocellular cancer associated with hepatitis B and D viruses, and therefore the focus should be on the treatment and prevention of hepatitis C virus and non-infectious risk factors.

**Iran** - Yousefi M, GR Sharifzadeh, A Ebrahimzadeh, Z Azarkar, MH Namaei, G Azarkar, S Ahmadi Ghezeldasht, R Rezaee, N Valizadeh Zare, A Mosavat and M Ziaee (2020). "[Prevalence and Associated Risk Factors of HTLV-1 and Co-infections of Blood-Borne Viruses in Birjand, Iran's Eastern Border.](#)" *Arch Iran Med* **23**(10): 672-677.

**BACKGROUND:** Blood-borne viruses (BBVs) are one of the most important public health concerns. South Khorasan has a long border with Afghanistan and concern has risen there about blood-borne oncogenic viral infections. The aim of the present study was to evaluate the prevalence and associated risk factors of human T-lymphotropic virus 1 (HTLV-1) and co-infections of BBVs in Birjand, Iran's eastern border. **METHODS:** In this cross-sectional study, 3441 subjects were tested for sero-prevalence of HTLV-1 by ELISA. The data on demographic features, HTLV-1-related risk factors and other characteristics of the population were analyzed by Pearson chi-square and logistic regression tests. Finally, the co-infection of BBVs was evaluated in the study. **RESULTS:** The prevalence of HTLV-1 was 0.3% (95% CI: 0.12-0.48). Notably, the sero-prevalence of HIV, hepatitis B virus (HBV), hepatitis D virus (HDV), and hepatitis C virus (HCV) in our previous studies was reported at 0%, 0.2%, 1.2% and 1.6%, respectively. The results indicated that the occurrence of HTLV-1 infection was associated only with the history of hospitalization (odds ratio [OR]: 0.27, 95% CI: 0.07-0.97, with  $P = 0.04$ ). The co-infection of HBV with HCV was the most common (2.35%), while a co-infection rate of 1.17% was found for both HBV/HTLV-1 and HBV/HDV. **CONCLUSION:** Although a higher prevalence of the viruses was expected, it was close to the overall Iranian population. With respect to close relationship with an HTLV-1 endemic area (Mashhad and Neyshabour), the prevalence is very low; however, more attention is needed. Our findings reinforce the importance of increasing knowledge about BBV-related health risk behaviors to prevent the emergence of new cases, especially in low-risk populations.

**China** - Wu S, Y Zhang, Y Tang, T Yao, M Lv, Z Tang, G Zang, Y Yu and X Chen (2020). "[Molecular epidemiology and clinical characteristics of hepatitis delta virus \(HDV\) infected patients with elevated transaminases in Shanghai, China.](#)" *BMC Infect Dis* **20**(1): 565.

**BACKGROUND:** Patients coinfecting with HBV and hepatitis D virus (HDV) have a greater risk of HCC and cirrhosis. The current study was undertaken to assess HDV genotype distribution and determine clinical characteristics of hepatitis delta virus (HDV) among HBsAg positive individuals in Shanghai. **METHOD:** This retrospective study involved 225 serum samples from HBsAg positive hospitalized patients from October 2010 to April 2013. HDV-specific RT-nested PCR was used to amplify HDV RNA. HDV genotypes were characterized by Next-generation sequencing (NGS), followed by phylogenetic analyses. HDV/HBV co-infected patients and HBV mono-infected patients were compared clinically and virologically. **RESULTS:** Out of the 225 HBsAg-positive serum samples with elevated transaminases, HDV-RNA was identified in 11 (4.9%) patients. The HBV loads in the HDV positive group were significantly lower than the HDV negative HBV-infected patients. The aminotransferase enzymes were significantly higher in HDV/HBV co-infected compared to HDV negative patients ( $P < 0.05$ ). Phylogenetic analyses indicated that HDV-2 genotype being the predominant genotype, other HDV genotypes were not observed. HDV/HBV patients were significantly associated with a rather unfavourable clinical outcome. **CONCLUSION:** In summary, the prevalence of HDV infection in patients with elevated transaminases is not low and the predominance of HDV genotype 2 infection in Shanghai. This finding helps us to better understand the correlation of HDV/HBV co-infection. Moreover, Next-generation sequencing (NGS) technologies provide a rapid, precise method for generating HDV genomes to define infecting genotypes.

**Germany** - Steffen G, I Sperle, SA Leendertz, N Sarma, S Beermann, R Thamm, V Bremer, R Zimmermann and S Dudareva (2020). "[The epidemiology of Hepatitis B, C and D in Germany: A scoping review.](#)" *PLoS One* **15**(3): e0229166.

**BACKGROUND:** Germany is considered to be a low prevalence country for viral Hepatitis B, C and D (HBV, HCV, HDV). However, the burden of disease can be high among subpopulations. To meet the world Health Organization (WHO) viral hepatitis (VH) elimination goals, a national strategy was developed by the German government in 2016. We performed a scoping review to understand the baseline epidemiological situation in Germany regarding burden of disease, sequelae and care of HBV, HCV and HDV as a reference to monitor the progress of the national VH elimination and to identify further knowledge gaps and research needs. **METHODS:** The protocol of the systematic review was prepared following the PRISMA statement guidelines for scoping reviews. Relevant search terms were used to identify eligible studies according to the research questions. We searched six online databases for original work published between January 2005 and March 2017. Based on the identified references, a matrix was developed presenting the eligible literature by targeted population group and outcome category. **RESULTS:** 104 publications were eligible for extraction covering 299 outcome results. The population groups targeted in the identified studies included the general population and proxy populations, a range of clinical populations, people who inject drugs, men who have sex with men,

healthcare workers, people in prisons and different migrant/mobile populations. Other vulnerable populations (e.g. sex workers) were not targeted. Overall, good evidence was found for HBV and HCV prevalence and HBV vaccination coverage in the GP and proxy populations. Evidence for these outcomes was weaker in populations at risk for VH. For HBV and HCV incidence and mortality, we identified large evidence gaps in all population groups. Outcomes on VH sequelae and care were mainly covered by studies in clinical populations of people living with viral hepatitis. For HDV the overall evidence available was scarce. CONCLUSIONS: We created a comprehensive evidence-based overview on the current epidemiological situation of viral hepatitis in Germany. We identified knowledge gaps for further research and established a baseline for future monitoring of viral hepatitis elimination goals in Germany.

**Germany** - Sperle I, G Steffen, SA Leendertz, N Sarma, S Beermann, R Thamm, Y Simeonova, M Cornberg, H Wedemeyer, V Bremer, R Zimmermann and S Dudareva (2020). "[Prevalence of Hepatitis B, C, and D in Germany: Results From a Scoping Review.](#)" *Front Public Health* **8**: 424.

Background: One of the five strategic directions in the World Health Organization global health sector strategy on viral hepatitis 2016-2021 is to generate strong strategic information for focused action to understand the viral hepatitis epidemic and focus the response. Knowledge of national prevalence is a cornerstone of strategic information. Germany is considered to be a low prevalence country for viral hepatitis B, C, and D, however the prevalence is likely to be higher among at-risk groups. Methods: The aim of this work was to give a detailed overview of the prevalence of viral hepatitis B (HBsAg, anti-HBc), C (anti-HCV, HCV RNA), and D (anti-HDV, HDV RNA) in different population groups in Germany. Therefore, we analyzed the results of a comprehensive literature search on various aspects of the epidemiological situation of hepatitis B, C, and D in Germany. Eligible publications including information on hepatitis B, C, and D prevalence were extracted from the overall spreadsheet table and summarized and analyzed based on virus and different population groups. A quality appraisal was performed using a checklist developed by Hoy et al. to assess risk of bias in prevalence studies. Results: Overall, 51 publications were identified through the literature search. The overall prevalence of HBsAg in the general (and proxy) population ranged from 0.3 to 1.6%. Among at-risk groups, including clinical populations and health care workers, the HBsAg prevalence ranged from 0.2% (among rheumatic patients) to 4.5% among HIV positive patients. The overall prevalence of anti-HCV in the general (and proxy) population ranged from 0.2 to 1.9%. Among at-risk groups, including clinical populations and health care workers, the anti-HCV prevalence ranged from 0.04% (among health care workers) to 68.0% among people who inject drugs. Conclusions: The hepatitis B and C prevalence in the general population in Germany is low. Prevalence is high to very high among at-risk populations, however for some groups evidence was incomplete or missing completely. To reach the elimination goals in Germany and implement a targeted response, more research among at-risk groups is needed.

**Iran** - Pouri AA, M Ghojzadeh, B Baiaz, FS Hamzavi, B Poursaghari and MH Somi (2020). "[Prevalence of hepatitis D virus among HBsAg-positive individuals, 2015-2016: Azar cohort study.](#)" *Health Promot Perspect* **10**(1): 38-42.

Background: Hepatitis D virus (HDV) is a defective RNA pathogen that requires the presence of the hepatitis B virus (HBV) for infection. Middle East countries are endemic areas for HDV infection. So, it is important to estimate the prevalence of HDV in these countries. This study aimed to estimate the prevalence of HDV in HBsAg positive patients participated in Azar cohort study, North-west of Iran. Methods: In this cross-sectional study, out of 4949 participants of the Azar cohort study, 51 HBsAg positive patients were selected. Five participants did not consent to HDV testing. The presence of anti-HDV IgG was checked in 46 patients (13 chronic hepatitis B and 33 inactive chronic hepatitis B) using enzyme-linked immunosorbent assay (ELISA) kit. The serum level of liver enzymes was measured and a questionnaire about risk factors was completed. Results: In this study, the mean age of HBsAg positive patients was 50.06 (SD 9.14) years and 41.3% were female. Only one out of 46 patients was positive for HDV infection. Thus, the prevalence of HDV infection among hepatitis B virus surface antigen (HBsAg) positive patients was 2.17% (95% CI: 0.1-11.5). The positive anti-HDV patient was in the inactive chronic hepatitis B state and she had a history of hospitalization and dental procedures. Conclusion: The results showed that the prevalence of HDV infection in HBsAg positive patients was 2.1% that was lower than the reported prevalence in many other regions of Iran. Health policymakers and healthcare providers should design coherent and orderly epidemiological studies for planning and monitoring HDV infection.

**Taiwan** - Lee KC, CL Lin, CW Hsu, ML Chang, YC Chen, WR Lin, MW Lai, KH Lin, M Chao, RN Chien and CT Yeh (2020). "[Decreasing seroprevalence of anti-hepatitis D virus antibodies in the antiviral era with inverse association with hepatitis B virus DNA, Taiwan, 2006 to 2019.](#)" *J Med Virol* **92**(1): 124-127.

We examined the seroprevalence change of anti-hepatitis D virus (HDV) antibodies in Taiwan from 2006 to 2019. A total of 1147 patients who had chronic hepatitis B virus (HBV) infection were assessed. Of them, 51 (4.4%) were positive for anti-HDV antibodies. Comparison between anti-HDV-positive and negative groups was performed to examine clinical and virological factors related to anti-HDV positivity. It was found that the median HBV-DNA concentration was  $1.6 \times 10^5$  IU/mL (range,  $<20-4.5 \times 10^{10}$  IU/mL) and  $<20$  IU/mL (range,  $<20-2.0 \times 10^9$  IU/mL) for patients with negative and positive anti-HDV antibodies, respectively ( $P < .001$ ). In addition, a progressive year-to-year decrease of anti-HDV seroprevalence was unveiled. For patients who had HBV-DNA  $>15\,000$  IU/mL, the year-to-year (calculated every 2 years) seropositive rates of anti-HDV were 10.0%, 7.9%, 0.7%, 0.3%, 0%, 0%, and 0% ( $P < .001$ ). For patients who had HBV-DNA  $<15\,000$  IU/mL, the year-to-year seropositive rates were 18.6%, 12.8%, 7.8%, 5.0%, 7.3%, 8.0%, and 3.7% ( $P < .001$ ). In conclusion, seropositive of anti-HDV was inversely associated with HBV-DNA levels. A progressive decrease of anti-HDV seroprevalence was found with no anti-HDV-positive cases detected in high HBV-DNA patient group after 2014.

**Uzbekistan** - Khodjaeva M, N Ibadullaeva, A Khikmatullaeva, E Joldasova, S Said, A Shahnoza, U Ismoilov, GP Caviglia, M Rizzetto and E Musabaev (2020). "[Hepatitis D virus in Uzbekistan.](#)" *Lancet Gastroenterol Hepatol* **5**(3): 238-240.

**Georgia** - Kasradze A, S Shadaker, T Kuchuloria, A Gamkrelidze, M Nasrullah, L Gvinjilia, D Baliashvili, N Chitadze, M Kodani, A Tejada-Strop, J Drobeniuc, L Hagan, J Morgan, P Imnadze and F Averhoff (2020). "[The burden and epidemiology of hepatitis B and hepatitis D in Georgia: findings from the national seroprevalence survey.](#)" *Public Health* **185**: 341-347.

**OBJECTIVES:** The burden of hepatitis B virus (HBV) and hepatitis D virus (HDV) infections is unknown in Georgia. This analysis describes the prevalence of hepatitis B and coinfection with HDV and the demographic characteristics and risk factors for persons with HBV infection in Georgia. **STUDY DESIGN:** This is a cross-sectional seroprevalence study. **METHODS:** A cross-sectional, nationwide survey to assess hepatitis B prevalence among the general adult Georgian population (age  $\geq 18$  years) was conducted in 2015. Demographic and risk behavior data were collected. Blood specimens were screened for anti-hepatitis B core total antibody (anti-HBc). Anti-HBc-positive specimens were tested for hepatitis B surface antigen (HBsAg). HBsAg-positive specimens were tested for HBV and HDV nucleic acid. Nationally weighted prevalence estimates and adjusted odds ratios (aORs) for potential risk factors were determined for anti-HBc and HBsAg positivity. **RESULTS:** The national prevalence of anti-HBc and HBsAg positivity among adults were 25.9% and 2.9%, respectively. Persons aged  $\geq 70$  years had the highest anti-HBc positivity (32.7%), but the lowest HBsAg positivity prevalence (1.3%). Anti-HBc positivity was associated with injection drug use (aOR = 2.34; 95% confidence interval [CI] = 1.46-3.74), receipt of a blood transfusion (aOR = 1.68; 95% CI = 1.32-2.15), and sex with a commercial sex worker (aOR = 1.46; 95% CI = 1.06-2.01). HBsAg positivity was associated with receipt of a blood transfusion (aOR = 2.72; 95% CI = 1.54-4.80) and past incarceration (aOR = 2.72; 95% CI = 1.25-5.93). Among HBsAg-positive persons, 0.9% (95% CI = 0.0-2.0) were HDV coinfecting. **CONCLUSIONS:** Georgia has an intermediate to high burden of hepatitis B, and the prevalence of HDV coinfection among HBV-infected persons is low. Existing infrastructure for hepatitis C elimination could be leveraged to promote hepatitis B elimination.

**Germany** - Juhl D, M Chudy, S Görg and H Hennig (2020). "[Prevalence of antibodies against Hepatitis D virus \(HDV\) in blood donors in Northern Germany.](#)" *Transfus Apher Sci* **59**(3): 102721.

**OBJECTIVE:** To assess the prevalence of HDV infections in German blood donors. **METHOD:** 167 donors with acute/chronic or resolved HBV infection and detectable antibodies against Hepatitis B core antigen (anti-HBc) were tested for antibodies against HDV (anti-HDV) by competitive ELISA. Samples with detectable anti-HDV or with HBsAg and/or HBV DNA were additionally investigated for HDV RNA. **RESULTS:** In nine (5.4 %) of the 167 donors, also HBsAg and HBV DNA were detectable. Anti-HDV was detectable in two of the 167 donors (1.2 %), additional four donors (2.4 %) had a borderline result. All of these donors tested negative for HBsAg and HBV DNA. Neither in samples with anti-HDV nor in HBsAg-/HBV DNA-positive samples, HDV RNA was detectable. **CONCLUSIONS:** At least 1.2 % of anti-HBc-positive blood donors have had an HDV infection. Although there is some evidence for a somewhat higher prevalence of HDV, the overall prevalence of HDV in Northern Germany is low.

**Kiribati** - Jackson K, R Tekoaau, T Holgate, R Edwards, L Yuen, A Lee, S Nicholson, M Littlejohn, S Locarnini and K Tuneti (2020). "[Hepatitis B and D in the Pacific Islands of Kiribati.](#)" *J Clin Virol* **129**: 104527.

BACKGROUND: Historical reports indicate that hepatitis B and hepatitis D are highly endemic in the Pacific Island of Kiribati but current levels are unknown. OBJECTIVES: To determine current prevalence of HBV and HDV in Kiribati, characterize the strains in both mono-infection and co-infection and assess individuals for antiviral therapy. STUDY DESIGN: Sera obtained from 219 patients were screened for HBsAg, HBeAg, HBV DNA, anti-HD, and HDV RNA. 61 HBV isolates were sequenced for genotype, phylogenetic analysis and detection of pre-core and basal core promoter mutations. 82 HDV isolates were also sequenced. RESULTS: 55.7 % HBsAg positive samples had antibodies to HDV and 73.2 % had detectable HDV RNA, indicating that 40.8 % HBsAg-positive individuals had current HBV/HDV co-infection. There were 42 co-infected males and 40 females; the youngest individual was a 4 year-old boy. HBV isolates were genotype D4, and HDV strains formed a distinct Pacific clade of genotype 1. Undetectable HBV DNA loads were statistically more frequent in the co-infected sub-population ( $p < 0.0001$ ). Basal core promoter and pre-core mutations were present in both mono and co-infection. CONCLUSION: Kiribati has one of the highest HBV/HDV co-infection rates in the world. The epidemiology of co-infection in this population was unusual with males and females equally represented and the presence of co-infection in a 4 year old child suggesting neonatal or early horizontal transmission, which is extremely rare. Coinfection with HDV resulted in statistically significant suppression of HBV DNA levels. The HDV strain identified in Kiribati was unique to the Pacific Islands.

**Afghanistan** - Hussein AA, KM Islam Saeed, E Yurdcu and AM Bozdayı (2020). "[Molecular epidemiology of Hepatitis B virus, Hepatitis C virus, and Hepatitis D virus in general population of Afghanistan.](#)" *Turk J Gastroenterol* **31**(9): 658-666.

BACKGROUND/AIMS: This study gives a clue about genotypes, subgenotypes and subtypes of HBV, HCV and HDV viruses in general population of Afghanistan. MATERIALS AND METHODS: A total of 234 HBsAg, 44 anti-HCV and 5 Anti-Delta positive patients belong to 25-70 age group were obtained through a rapid screening test among 5898 residents of Afghanistan. After quantifying viral load, genotyping of 61 HBV, 29 HCV and 1 HDV samples were accomplished by sequencing of a segment of the HBV Pre S, HCV NS5B, and HDV Delta antigen regions respectively. Clinically important variants of the HBV polymerase gene, the "a" determinant of HBsAg, HCV NS5B and NS3 regions were assessed. RESULTS: All HBV isolates were dispersed throughout the genotype D branch and ayw2 was the only subtypes found. The anti-HDV prevalence among HBsAg positive individuals was 2.2% and the single HDV sample, belonged to HDV genotype I. Analysis of HCV isolates revealed subtype HCV-1b in 75.86%, HCV-3a in 20.69% and HCV-3b in 3.44% patients. The observed mutant variants in the MHR of HBsAg were Y100 15%, Q101 5%, G102 15%, T115 45%, P120 5%, T131 5%. Likewise, S213T 10%, Q215P 5% and N248H 100% mutations were detected in the HBV polymerase region. C316N mutation was prevalent in 72.7% of HCV 1b participants. CONCLUSION: Genotypic variation in Afghan patients is in line with the ones existing in neighboring countries and regions. HBV genotypes D1, subtype ayw2, HDV RNA type I, and HCV RNA genotype 1b are likely to be dominant in Afghan patients.

**Spain** - Hernández-Èvole H, Á Briz-Redón and M Berenguer (2020). "[Changing delta hepatitis patient profile: A single center experience in Valencia region, Spain.](#)" *World J Hepatol* **12**(6): 277-287.

BACKGROUND: Delta hepatitis is a rare infection with an aggressive disease course. For almost three decades, however, there have been no epidemiological studies in our traditionally endemic area. AIM: To investigate the prevalence of delta hepatitis in a sample of patients with chronic hepatitis B virus (HBV) infection followed at a Hepatology Unit in Valencia, Spain. METHODS: Retrospective evaluation of anti-hepatitis D virus-immunoglobulin G seroprevalence among patients with chronic HBV infection ( $n = 605$ ) followed at a reference Hepatology Unit in Spain. RESULTS: The prevalence of anti-hepatitis D virus-immunoglobulin G among HBV-infected patients was 11.5%: Male (63%) and median age of 52 years. The majority were born in Spain (67%) and primarily infected through intravenous drug use. However, a significant percent (24.5%), particularly those diagnosed in more recent years, were migrants presumably nosocomially infected. Comorbidities such as diabetes (8.5%), obesity/overweight (55%), and alcohol consumption (34%) were frequent. A high proportion of patients developed liver complications such as cirrhosis (77%), liver decompensation (81%), hepatocellular carcinoma (HCC) (16.5%), or required liver transplantation (LT) (59.5%). Diabetes was associated with progression to cirrhosis, LT, and death. Male sex, increasing age, and alcohol were associated with LT and HCC. Compared to HBV mono-infected patients, delta individuals developed cirrhosis and liver decompensation more frequently, with no differences in HCC rates. CONCLUSION: Patients infected in the 1980's were mostly locals infected

through intravenous drug use, whereas those diagnosed recently are frequently non-Spanish natives from endemic areas. Regardless of their origin, patients are predominantly male with significant comorbidities, which potentially play a major role in disease progression. We confirm a high rate of subsequent liver complications.

**Egypt** - Fouad HM, A Ahmed, EM Reyad, SM ElSadek, RA Khattab and DA El Damasy (2020). "[Hepatitis D virus seroprevalence in Egyptian HBsAg-positive children: a single-center study.](#)" *Arch Virol* **165**(10): 2361-2365.

In this study, we investigated the seroprevalence of anti-hepatitis D virus (HDV) antibodies in hepatitis B surface antigen (HBsAg)-positive children after 25 years of obligatory vaccination of infants against hepatitis B virus. This cross-sectional study included 120 treatment-naïve HBsAg-positive children, with a male-to-female ratio of 1.8:1 and a mean age of  $7.8 \pm 3.8$  years (range, 1-17 years). Mothers were positive for HBsAg in 96.6% of the cases. HBeAg-positive chronic infection was observed in 60% of the cases, HBeAg-positive chronic hepatitis in 12.5%, and HBeAg-negative chronic infection in 26.7%. Anti-HDV antibodies were not detected in any of the cases. Thus, there is a lack of anti-HDV antibodies in HBsAg-positive children, despite the current burden in adults.

**Libya** - Daw MA, AM Daw, NEM Sifennasr, A Draha, A Daw, A Daw, M Ahmed, E Mokhtar, A El-Bouzedi, I Daw, S Adam and S Warrag (2020). "[The epidemiological characterization and geographic distribution of hepatitis D virus infection in Libya.](#)" *Pan Afr Med J* **35**: 120.

INTRODUCTION: North Africa is known to be endemic for hepatitis D virus. However, data on the prevalence of this virus in Libya are scanty. This study aimed to determine the prevalence of hepatitis D virus infection in Libya and analyze the demographic factors associated with the infection, and also to assess the variations across the regions and districts. METHODS: A total of 1873 samples collected from all over the country were tested for antibodies against hepatitis B surface antigen and the results were correlated with demographic and geographic variables. RESULTS: The overall prevalence of hepatitis D virus infection was 1.7%. The prevalence rate was significantly high among those aged over 40 years ( $P < 0.001$ ) and it was associated with intravenous drug use and coinfection with human immunodeficiency virus and/or hepatitis C virus infection ( $P < 0.001$ ). The prevalence rates varied with geographic location and differed markedly within the regions of the country. The highest rate reported was in the central region of Libya, followed by the western and eastern regions. CONCLUSION: Hepatitis D virus infection rate in Libya is considered to be low but is of some concern in some districts. This has been propagated by population displacement and African immigrants, indicating that a continuous epidemiological surveillance program should be implemented.

**Mongolia** - Candia J, E Bayarsaikhan, M Tandon, A Budhu, M Forgues, LO Tovuu, U Tudev, J Lack, A Chao, J Chinburen and XW Wang (2020). "[The genomic landscape of Mongolian hepatocellular carcinoma.](#)" *Nat Commun* **11**(1): 4383.

Mongolia has the highest incidence of hepatocellular carcinoma (HCC) in the world, but its causative factors and underlying tumor biology remain unknown. Here, we describe molecular characteristics of HCC from 76 Mongolian patients by whole-exome and transcriptome sequencing. We present a comprehensive analysis of mutational signatures, driver genes, and molecular subtypes of Mongolian HCC compared to 373 HCC patients of different races and ethnicities and diverse etiologies. Mongolian HCC consists of prognostic molecular subtypes similar to those found in patients from other areas of Asia, Europe, and North America, as well as other unique subtypes, suggesting the presence of distinct etiologies linked to Mongolian patients. In addition to common driver mutations (TP53, CTNNB1) frequently found in pan-cancer analysis, Mongolian HCC exhibits unique drivers (most notably GTF2IRD2B, PNRC2, and SPTA1), the latter of which is associated with hepatitis D viral infection. These results suggest the existence of new molecular mechanisms at play in Mongolian hepatocarcinogenesis.

**Brazil** - Caetano KAA, FPR Bergamaschi, MAS Carneiro, RS Pinheiro, LA Araújo, MA Matos, P Carvalho, MM de Souza, MAD de Matos, NHA Del-Rios, RMB Martins, ARC Motta-Castro, CC Soares, RL Cook and SA Teles (2020). "[Hepatotropic viruses \(hepatitis A, B, C, D and E\) in a rural Brazilian population: prevalence, genotypes, risk factors and vaccination.](#)" *Trans R Soc Trop Med Hyg* **114**(2): 91-98.

BACKGROUND: People living in settlement projects represent an emergent rural population in Brazil. Data on their health is scarce and there are no data on viral hepatitis in this population. This study investigated the epidemiology of viral hepatitis A-E in residents of settlement projects in central Brazil. METHODS: During 2011 and 2012, 923 people living in rural settlements in central Brazil were

interviewed and tested to estimate the prevalence of exposure to viral hepatitis A-E, to identify the circulating hepatitis B virus (HBV)/hepatitis C virus (HCV) genotypes and risk factors for HBV exposure and to evaluate adherence to the hepatitis B vaccination series. RESULTS: Overall, 85.9, 3.9, 0.4 and 17.3% of individuals showed evidence of exposure to hepatitis A virus (HAV), hepatitis E virus, HCV and HBV, respectively. Among HBV-DNA positive samples (n=8), subgenotypes A1 (n=3) and A2 (n=1) and genotype D/subgenotype D3 (n=4) were identified. Hepatitis D virus superinfection was detected in 0/16 HBsAg-positive participants. A total of 229 individuals showed serological evidence of HBV vaccination. In total, 442 settlers were eligible for vaccination, but only 150 individuals completed the vaccine series. All anti-HCV-positive samples (n=4) were also HCV-RNA positive and identified as subtype 1a. CONCLUSIONS: The intermediate endemicity of HAV, the higher prevalence of HBV exposure compared with urban areas and the low compliance with HBV vaccination requires preventive measures focused on rural populations, emphasizing the need for HAV and HBV vaccination.

**Peru** - Cabezas C, O Trujillo, Á Gonzales-Vivanco, CM Benites Villafane, J Balbuena, AO Borda-Olivas, MA Suarez-Jara, FM Peceros and MC Ramirez-Soto (2020). "[Seroepidemiology of hepatitis A, B, C, D and E virus infections in the general population of Peru: A cross-sectional study.](#)" *PLoS One* **15**(6): e0234273.

BACKGROUND: Viral hepatitis (hepatitis A, B, C, D and E) remains a public health problem in Peru, with a high disease burden. There are limited data on the prevalence of viral hepatitis at a national level, and none reported for over two decades. In this study, the prevalence rates of hepatitis A (HAV), B (HBV), C (HCV), D (HDV) and E virus (HEV) infections in the Peruvian population were determined to provide updated baseline data that would help guide the development of strategies aimed at reducing the transmission of viral hepatitis in Peru. METHODS: We conducted a cross-sectional, population-based study in the 25 regions of Peru. The study included participants of both sexes, aged 15-69 years, who had lived for >6 months in a specific region of Peru. Serum samples were analyzed by ELISA for anti-HAV (IgG), anti-HBs  $\geq 10$  mIU/ml, anti-HCV, anti-HDV and anti-HEV (IgG) antibodies, and by chemiluminescence for the HBV surface antigen (HBsAg) and antibodies against the core HBV antigen (anti-HBc IgM and IgG). RESULTS: In a total of 5183 study participants, the prevalence rates of anti-HAV (IgG), HBsAg, total anti-HBc IgG, anti-HBs  $\geq 10$  mIU/ml, anti-HCV and anti-HEV (IgG) were 98.4% [95% confidence interval (CI) 98.0-98.7], 0.4% (95% CI 0.21-0.55), 10.1% (95% CI 9.4-11.0), 60% (95% CI 58.5-61.2), 0.1% (95% CI 0.02-0.25), and 14% (95% CI 13.1-15.0%), respectively. The prevalence of anti-HDV among HBsAg carriers was 15% (3/20). CONCLUSIONS: The prevalence of HAV and HEV in the population aged 15-69 years in Peru is high, while the prevalence of HBV and HDV has changed from intermediate to low endemicity level and the prevalence of HCV is low. These findings would prove useful in the development of new strategies aimed at reducing the transmission of viral hepatitis in Peru, with a view to ultimately eliminating these infections in the future.

**Peru** - Cabezas C, O Trujillo, J Balbuena, M Terrazas, C Manrique-de Lara, L Marin and MC Ramirez-Soto (2020). "[\[Reduction of HBV and HDV infection in two indigenous peoples of Peruvian Amazon after the vaccination against hepatitis B\]](#)." *Salud Publica Mex* **62**(3): 237-245.

OBJECTIVE: To determine the outcome of the vaccination against hepatitis, we determined the prevalence of hepatitis B virus (HBV) and hepatitis D virus (HDV) infections, eight years after introduction of the vaccination. MATERIALS AND METHODS: A cross-sectional study was performed in 2 944 participants of 67 Kandozi and Chapra indigenous peoples in April 2010. Serological screening for hepatitis B surface antigen (HBsAg), antibody anti-HBc IgM and IgG, antibody anti-HBs and anti-HDV were determined by ELISA tests. RESULTS: The prevalence rates of HBsAg, anti-HBc total, anti-HBs  $\geq 10$  mIU/ml and anti-HDV were 2.3, 39.13, 50.95 and 2.11%, respectively. The prevalence rate of HBsAg in children <11 years was 0%. Among carriers of HBsAg, the prevalence rates of HDV and acute HBV infections were 2.11% (all were >14 years) and 11.94%, respectively. HBsAg and anti-HBc total were associated with individuals  $\geq 10$  years ( $p < 0.001$ ). CONCLUSIONS: These findings show the elimination of HBV carriers in children <11 years, eight years following introduction of the vaccination against HBV.

**Peru** - Cabezas C, O Trujillo, J Balbuena, FM Peceros, M Terrazas, M Suárez, L Marin, J Apac and MC Ramirez-Soto (2020). "[Decrease in the prevalence of hepatitis B and D virus infections in an endemic area in Peru 23 years after the introduction of the first pilot vaccination program against hepatitis B.](#)" *PLoS One* **15**(8): e0236993.

In 1991, Peru launched the first vaccination program against hepatitis B in children aged under 5 years in the hyperendemic [hepatitis B virus (HBV) and hepatitis D virus (HDV)] province of Abancay. We conducted a cross-sectional study to determine the prevalence of HBV and HDV infections, 23 years after the launch of the vaccination program, as well as the post-vaccine response against hepatitis B in terms

of prevalence of hepatitis B surface antibody (anti-HBs  $\geq 10$  mUI/ml). Among 3165 participants aged from 0 to 94 years, the prevalence rates of hepatitis B surface antigen (HBsAg), and hepatitis B core antibody (total anti-HBc) were 1.2% [95% confidence interval (CI) 0.85-1.64%], and 41.67% (95% CI 39.95-43.41%), respectively. The prevalence rate of anti-HBs at protective levels ( $\geq 10$  mUI/ml) in individuals who HBsAg and anti-HBc negative was 66.36% (95% CI 64.15-68.51%). The prevalence rate of HBsAg in children aged  $< 15$  years was nil, and among adult HBsAg carriers, the prevalence of hepatitis D antibody (anti-HDV) was 5.26% (2/38; 95% CI 0.64-17.74). These findings showed that HBV prevalence has changed from high to low endemicity, 23 years following implementation of the vaccination program against hepatitis B, and HDV infection was not detected in those aged  $< 30$  years.

**Peru** - Cabezas C, O Trujillo, J Balbuena, L Marin, M Suárez, M Themme, H Rodriguez, P Valencia and L Crispin-Huamani (2020). "[Prevalence of retrovirus, hepatitis B and D infection in the Matsés ethnic group in Loreto, Peru.](#)" *Rev Peru Med Exp Salud Publica* **37**(2): 259-264.

Observational, cross-sectional, populational study to determine the prevalence of infection by hepatitis B virus (HBV), hepatitis D virus (HDV), human immunodeficiency virus (HIV) and human T-lymphotropic virus type 1 and 2 (HTLV-1/2) in the Matsés ethnic group, after immunization against HBV. ELISA and qPCR tests were used in 963 residents. The prevalence of HBsAg, Anti-HBc and Anti-HBs was 3.32%, 36.03% and 58.67% respectively. In 3.1% of the population the viral load was greater than 2000 IU/mL. In children under 10 years, the prevalence of HBsAg and anti-HBc was 0.0% and 2.6%, respectively, while protective antibodies were found in 94.4%. The prevalence of HIV and HTLV-1/2 infection was 1.5% and 0.6%, respectively. It is therefore concluded that there are low rates of HBV and HDV infection in the Matsés child population. Likewise, the presence of HIV and HTLV-1/2 infection is confirmed.

**Germany** - Bockmann JH, M Grube, V Hamed, J von Felden, J Landahl, M Wehmeyer, K Giersch, MT Hall, JM Murray, M Dandri, S Lüth, AW Lohse, M Lütgehetmann and J Schulze Zur Wiesch (2020). "[High rates of cirrhosis and severe clinical events in patients with HBV/HDV co-infection: longitudinal analysis of a German cohort.](#)" *BMC Gastroenterol* **20**(1): 24.

BACKGROUND: Chronic hepatitis delta virus (HDV) infection causes severe liver disease which often leads to cirrhosis and hepatocellular carcinoma (HCC). Aim of this study was to establish the disease severity and prognostic factors for disease outcome by analysing frequencies of clinical events and their correlation with baseline virological and biochemical parameters as well as interferon and nucleos(t)ide analogue treatment choice. METHODS: We studied a single-centre cohort of 49 anti-HDAg-positive patients with HBsAg persistence for at least 6 months. Virological and biochemical parameters, interferon and nucleos(t)ide analogue treatment choice as well as clinical events during follow-up were analysed by retrospective chart review (mean follow-up time 3 years, range 0.25-7.67 years). RESULTS: Severe clinical events occurred in 11/49 hepatitis D patients, including HCC (8/49), death (8/49) or liver transplantation (2/49). HCCs only occurred secondary to liver cirrhosis and their event rates in this cohort of hepatitis D patients did not differ from a matched HBV mono-infected cohort with comparable frequency of liver cirrhosis. A stepwise multivariate logistic regression revealed low platelet count ( $p = 0.0290$ ) and older age ( $p = 0.0337$ ) correlating most strongly with overall clinical events, while serum HDV RNA positivity at baseline did not correlate with any clinical outcome. Interferon-free but not nucleos(t)ide analogue-free patient care correlated with the occurrence of HCC at logistic regression, although only 3/18 interferon-treated patients demonstrated repeatedly negative HDV PCR results post therapy. CONCLUSIONS: Our data indicate that progressive liver disease at baseline plays a major role as predictive factor for overall clinical outcome of hepatitis D patients. In particular, HCC risk may not be underestimated in hepatitis D virus RNA negative hepatitis D patients with advanced liver fibrosis.

**Cameroon** - Besombes C, R Njouom, J Paireau, G Lachenal, G Texier, M Tejiokem, S Cauchemez, J Pépin and A Fontanet (2020). "[The epidemiology of hepatitis delta virus infection in Cameroon.](#)" *Gut* **69**(7): 1294-1300.

OBJECTIVE: To investigate the distribution and risk factors of hepatitis delta virus (HDV) infection in Cameroon. DESIGN: We tested for hepatitis B virus (HBV) surface antigen (HBsAg) and anti-HDV antibody 14 150 samples collected during a survey whose participants were representative of the Cameroonian adult population. The samples had already been tested for hepatitis C virus and HIV antibodies. RESULTS: Overall, 1621/14 150 (weighted prevalence=11.9%) participants were HBsAg positive, among whom 224/1621 (10.6%) were anti-HDV positive. In 2011, the estimated numbers of HBsAg positive and HDV seropositives were 1 160 799 and 122 910 in the 15-49 years age group, respectively. There were substantial regional variations in prevalence of chronic HBV infection, but even more so for HDV (from 1% to 54%). In multivariable analysis, HDV seropositivity was independently associated with living with an

HDV-seropositive person (OR=8.80; 95% CI: 3.23 to 24.0), being HIV infected (OR=2.82; 95% CI: 1.32 to 6.02) and living in the South (latitude <4°N) while having rural/outdoor work (OR=15.2; 95% CI: 8.35 to 27.6, when compared with living on latitude ≥4°N and not having rural/outdoor work). CONCLUSION: We found evidence for effective intra-household transmission of HDV in Cameroon. We also identified large differences in prevalence between regions, with cases concentrated in forested areas close to the Equator, as described in other tropical areas. The reasons underlying these geographical variations in HDV prevalence deserve further investigation.

**Brazil** - Antonio Ferreira-Junior P, EC de-Oliveira, TOG Martin, E Rodrigues Alves-Junior, LJD Silva, F Mello, CJF Fontes and FJD Souto (2020). "[Prevalence of hepatitis B and D virus infection in a district of Mato Grosso, bordering Amazonas and Rondônia states.](#)" *Rev Soc Bras Med Trop* **53**: e20190559.

INTRODUCTION: Brazil's western Amazon basin has the highest prevalence of hepatitis B virus (HBV) infection in the country. Coinfection with hepatitis D virus (HDV) is also endemic. To estimate the prevalence of HBV and HDV markers in a population inhabiting the northwest portion of Mato Grosso state in the western Amazon. METHODS: We performed a cross-sectional study of the seroprevalence of antibodies against HBV core antigen (anti-HBc) in the Três Fronteiras District northwest of Mato Grosso. Anti-HBc-positive subjects were tested for HBV surface antigen (HBsAg). Those positive for this marker were tested for HDV antibodies. Anti-HBc-negative participants were tested for anti-HBsAg. All tests were performed by EIA. RESULTS: A total of 623 individuals in the community were assessed; the majority (67.6%) were male, with a mean age of 30.8 ± 15.4 years. Two hundred and fourteen individuals (34.3%) were anti-HBc-positive, and 47 (7.5%) were HBsAg carriers. Only one individual was anti-HDV-positive. Among the 409 individuals without HBV infection, 18.3% were anti-HBsAg-positive. There was no association between HBV infection and known risk factors. CONCLUSIONS: The study area had intermediate-to-high endemicity for HBV infection, but a low prevalence of HDV. Our serological results suggesting low vaccination-induced protection indicate a need for reinforced immunization programs in the populations of northwest Mato Grosso.

## Clinical manifestation and burden of disease

Zhang Z and S Urban (2021). "[New insights into HDV persistence: The role of interferon response and implications for upcoming novel therapies.](#)" *J Hepatol* **74**(3): 686-699.

Chronic hepatitis D (CHD), a global health problem, manifests as the most severe form of viral hepatitis. The causative agent, HDV, is the smallest known human virus; it replicates its circular single-stranded RNA genome in the nucleus of hepatocytes. HDV requires HBV-encoded envelope proteins for dissemination and de novo cell entry. However, HDV can also spread through cell division. Following entry into hepatocytes, replicative intermediates of HDV RNA are sensed by the pattern recognition receptor MDA5 (melanoma differentiation antigen 5) resulting in interferon (IFN)-β/λ induction. This IFN response strongly suppresses cell division-mediated spread of HDV genomes, however, it only marginally affects HDV RNA replication in already infected, resting hepatocytes. Monotherapy with IFN-α/λ shows efficacy but rarely results in HDV clearance. Recent molecular insights into key determinants of HDV persistence and the accelerated development of specifically acting antivirals that interfere with the replication cycle have revealed promising new therapeutic perspectives. In this review, we briefly summarise our knowledge on replication/persistence of HDV, the newly discovered HDV-like agents, and the interplay of HDV with the IFN response and its consequences for persistence. Finally, we discuss the possible role of IFNs in combination with upcoming therapies aimed at HDV cure.

Wang W, FA Lempp, F Schlund, L Walter, C Decker, Z Zhang, Y Ni and S Urban (2021). "[Assembly and infection efficacy of hepatitis B virus surface protein exchanges in eight hepatitis D virus genotype isolates.](#)" *J Hepatol*.

BACKGROUND & AIMS: Chronic hepatitis D virus (HDV) infections cause the most severe form of viral hepatitis. HDV requires hepatitis B virus (HBV) envelope proteins for hepatocyte entry, particle assembly and release. Eight HDV and eight HBV genotypes are presently distinguished. However, comparing data of replication competence of HDV isolated from different genotypes lacks. Furthermore, it is unknown to what extent combination with different HBV envelopes affect virion assembly and infectivity. METHODS: We subcloned cDNAs of all HDV and HBV genotypes and systematically studied HDV replication, assembly and infectivity using Northern Blot, Western Blot, RT-qPCR, in-cell ELISA. RESULTS: The eight HDV cDNA clones initiated HDV replication with noticeable differences regarding replication efficacy. The eight HBV-HBsAg-encoding constructs all supported secretion of subviral particles, however variations in

envelope protein stoichiometry and secretion efficacy were observed. Co-transfection of all HDV/HBV combinations supported particle assembly, however, the respective pseudo-typed HDVs differed with respect to assembly kinetics. The most productive combinations did not correlate to the natural geographic distribution arguing against an evolutionary adaptation of HDV ribonucleoprotein complex to HBV envelopes. All HDVs elicited robust and comparable innate immune responses. HBV envelope-dependent differences in the activity of the EMA approved entry inhibitor Hepcludex were observed, however efficient inhibition could be achieved at therapeutically applied doses. Lonafarnib, the assembly inhibitor in development also showed pan-genotypic activity. CONCLUSIONS: HDVs from different genotypes replicate with variable efficacies. Variations of HDV genomes and HBV-envelopes both are major determinants for HDV egress and entry efficacy and consequently assembly inhibition by Lonafarnib or entry inhibition by Hepcludex. These differences possibly influence HDV pathogenicity, immune responses and the efficacy of novel drug regimens. LAY SUMMARY: Hepatitis D virus (HDV) needs hepatitis B virus (HBV) to provide envelope protein for virus assembly and de novo entry. Eight HDV and eight HBV genotypes are presently distinguished. In this study, we comprehensively investigated replication competence, envelopment preference and kinetics of virion secretion of all HDV genotypes. We found that different genotypes of HDV replicate with variable efficacies. Genotypic variations in HDV and HBV-envelopes are major determinants for HDV assembly, de novo entry and consequently the efficacy of novel antivirals.

Vieira Barbosa J, R Sahli, V Aubert, A Chaouch, D Moradpour and M Fraga (2021). "[Demographics and outcomes of hepatitis B and D: A 10-year retrospective analysis in a Swiss tertiary referral center.](#)" *PLoS One* **16**(4): e0250347.

BACKGROUND: Hepatitis B virus (HBV) is a major global health challenge with approximately 250-350 million chronically infected individuals. An improved understanding of the demographic features and outcomes of chronic HBV infection and hepatitis D virus (HDV) infection in low-endemic areas may improve prevention, early identification and management both at individual and community levels. Here, we retrospectively analyzed the demographic and clinical characteristics, treatment rates and outcomes of adult patients with chronic HBV infection with or without HDV coinfection examined at Lausanne University Hospital, Switzerland over a 10-year period. METHODS: We analyzed the medical records of all adult patients with chronic HBV and HDV infection examined in our center between 2007 and 2016. Liver-related outcome was defined as the occurrence of cirrhosis, hepatocellular carcinoma, liver transplantation or liver-related death. Analyses were performed using logistic regression and results were reported as odds ratio (OR) and 95% confidence interval (CI). RESULTS: Of 672 consecutive patients, 421 (62.6%) were male, median age was 36 years (interquartile range, 28-46 years), and 233 (34.7%) were of African origin. The prevalence of HDV coinfection was 7.1% and the proportion of anti-HDV-positive patients with detectable HDV RNA was 70.0%. In multivariate analysis, HDV coinfection was the strongest predictor for liver-related outcome (OR 6.06, 95% CI 2.93-12.54,  $p < 0.001$ ), followed by HBeAg positivity (OR 2.47, 95% CI 1.30-4.69,  $p = 0.006$ ), age (OR per 10-year increase 2.03, 95% CI 1.63-2.52,  $p < 0.001$ ) and sex (OR for female 0.39, 95% CI 0.22-0.71,  $p = 0.002$ ). The predictive accuracy of the multivariate model was high (receiver operator characteristic area under the curve 0.81). CONCLUSION: This retrospective study underscores the importance of migration in the epidemiology of chronic hepatitis B in low-endemic areas. HDV coinfection, HBeAg positivity and age predicted liver-related outcomes while female sex had a protective effect.

Sagnelli C, E Sagnelli, A Russo, M Pisaturo, L Occhiello and N Coppola (2021). "[HBV/HDV Co-Infection: Epidemiological and Clinical Changes, Recent Knowledge and Future Challenges.](#)" *Life (Basel)* **11**(2).

Several investigations have been published on Hepatitis Delta Virus (HDV) infection in recent years, from which we have drawn the salient data to provide readers with useful information to improve their knowledge on the subject. HDV genotypes 5-8 have been recently imported to Western countries from central Africa, whose clinical relevance deserves further investigation. Ongoing HDV replication has been identified as an independent predictor of progression to cirrhosis and HCC for patients with HDV chronic hepatitis (HDV-CH). Long-term treatments of HDV-CH with standard or pegylated interferon alfa (peg-IFN- $\alpha$ ) have all been unsatisfactory, leading to a sustained virological response (SVR) only in 20-30% of patients treated, faced with a poor tolerability and frequent serious adverse reactions; the addition of HBV nucleo(s)tide analogues to peg-IFN- $\alpha$  did not improve the rate of SVR. The improved knowledge of the HDV life cycle has allowed the development of direct acting agents towards key-points of the HDV life cycle, namely bulevirtide, lonafarnib and nucleic acid polymers. Preliminary data have shown that

these drugs are more effective than interferon-based therapies, but adverse reactions are also common, which however seem toned down in combination therapy with other antivirals.

Rizzetto M and S Hamid (2021). "[The medical impact of hepatitis D virus infection in Asia and Africa: time for a reappraisal.](#)" *Liver Int* **41**(1): 16-19.

Although hepatitis D is believed to be an important medical problem in Africa and many areas of Asia, the geographical distribution and prevalence rates of infection with the hepatitis D virus (HDV) vary considerably, are often inconsistent and sometimes conflicting. Discrepancies may depend on methodological problems, primarily on different modalities of patients' recruitment; these are analysed in this mini-review, in order to provide a uniform clinical approach when testing patients with chronic HDV disease.

Muhammad H, A Tehreem, MB Hammami, PS Ting, R Idilman and A Gurakar (2021). "[Hepatitis D virus and liver transplantation: Indications and outcomes.](#)" *World J Hepatol* **13**(3): 291-299.

Hepatitis D virus (HDV) is a dependent virus that relies on hepatitis B virus for its replication and transmission. Chronic hepatitis D is a severe form of viral hepatitis that can result in end stage liver disease. Currently, pegylated interferon alpha is the only approved therapy for chronic HDV infection and is associated with significant side effects. Liver transplantation (LT) is the only treatment option for patients with end-stage liver disease, hepatocellular carcinoma, or fulminant hepatitis due to coinfection with HDV. As LT for HDV and hepatitis B virus coinfection is uncommon in the United States, most data on the long-term impact of LT on HDV are from international centers. In this review, we discuss the indications and results of LT with treatment options in HDV patients.

Jang TY, YJ Wei, ML Yeh, SF Liu, CT Hsu, PY Hsu, TW Liu, YH Lin, PC Liang, MH Hsieh, YM Ko, YS Tsai, KY Chen, CC Lin, PC Tsai, SC Wang, CI Huang, ZY Lin, SC Chen, WL Chuang, JF Huang, CY Dai, CF Huang and ML Yu (2021).

"[Role of hepatitis D virus in persistent alanine aminotransferase abnormality among chronic hepatitis B patients treated with nucleotide/nucleoside analogues.](#)" *J Formos Med Assoc* **120**(1 Pt 2): 303-310.

**BACKGROUND:** The biochemical response is a crucial indicator of prognosis in chronic hepatitis B (CHB) patients treated with nucleotide/nucleoside analogues (NAs). The impact of hepatitis D virus (HDV) infection on alanine aminotransferase normalization is elusive. **METHODS:** The longitudinal study recruited 1185 CHB patients who received NAs. These patients were tested for anti-HDV antibody and HDV RNA at the initiation of anti-hepatitis B virus (HBV) therapy and annually for patients who were HDV-seropositive. ALT levels were examined at the first and second year of anti-HBV therapy. ALT abnormality was defined as ALT levels above 40 IU/mL in both male and female, and the risk factors associated with ALT abnormality were analysed. **RESULTS:** Rates of seropositivity for anti-HDV and HDV RNA were 2.0% and 0.8% among 1185 NA-treated CHB patients, respectively. The strongest factor associated with ALT abnormality (>40 IU/mL) after first year treatment with NAs was HDV RNA seropositivity at year 1 (odds ratio [OR]/95% confidence interval [CI]: 31.44/3.49-283.56,  $P = 0.002$ ), followed by liver cirrhosis (2.18/1.51-3.15,  $P < 0.001$ ), detectable HBV DNA at year 1 (OR/CI: 1.99/1.36-2.92,  $P < 0.001$ ), diabetes (OR/CI: 1.75/1.10-2.78,  $P = 0.02$ ), body mass index (BMI) (OR/CI: 1.13/1.09-1.18,  $P < 0.001$ ) and age (OR/CI: 0.97/0.96-0.98,  $P < 0.001$ ). Among patients who were seronegative for HBV DNA at year 1, the strongest factor associated with ALT abnormality was HDV RNA seropositivity at year 1 (OR/CI: 30.00/3.28-274.05,  $P = 0.003$ ), followed by liver cirrhosis (OR/CI: 1.83/1.21-2.75,  $P = 0.004$ ), BMI (OR/CI: 1.16/1.11-1.21,  $P < 0.001$ ) and age (OR/CI: 0.97/0.96-0.99,  $P < 0.001$ ). Similarly, the impact of HDV RNA seropositivity on ALT abnormality was noted in patients without detectable HBV DNA but not in those with hepatitis B viremia at treatment year 2 (OR/CI: 10.16/1.33-77.74,  $P = 0.03$ ). **CONCLUSION:** HDV infection played an important role in ALT abnormality in CHB patients receiving 1-year and 2-year NAs. The impact was particularly noted in patients who had successfully suppressed HBV DNA.

Jang TY, YJ Wei, TW Liu, ML Yeh, SF Liu, CT Hsu, PY Hsu, YH Lin, PC Liang, MH Hsieh, YM Ko, YS Tsai, KY Chen, CC Lin, PC Tsai, SC Wang, CI Huang, ZY Lin, SC Chen, WL Chuang, JF Huang, CY Dai, CF Huang and ML Yu (2021).

"[Role of hepatitis D virus infection in development of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleotide/nucleoside analogues.](#)" *Sci Rep* **11**(1): 8184.

Hepatitis D virus (HDV) infection increases the risk of hepatocellular carcinoma (HCC) in the natural course of chronic hepatitis B (CHB) patients. Its role in patients treated with nucleotide/nucleoside analogues (NAs) is unclear. We aimed to study the role of hepatitis D in the development of HCC in CHB patients treated with NAs. Altogether, 1349 CHB patients treated with NAs were tested for anti-HDV antibody and RNA. The incidence and risk factors of HCC development were analyzed. Rates of anti-HDV

and HDV RNA positivity were 2.3% and 1.0%, respectively. The annual incidence of HCC was 1.4 per 100 person-years after a follow-up period of over 5409.5 person-years. The strongest factor association with HCC development was liver cirrhosis (hazard ratio [HR]/95% confidence interval [CI] 9.98/5.11-19.46,  $P < 0.001$ ), followed by HDV RNA positivity (HR/ CI 5.73/1.35-24.29,  $P = 0.02$ ), age  $> 50$  years old (HR/CI 3.64/2.03-6.54,  $P < 0.001$ ), male gender (HR/CI 2.69/1.29-5.60,  $P = 0.01$ ), and body mass index (BMI, HR/CI 1.11/1.03-1.18,  $P = 0.004$ ). The 5-year cumulative incidence of HCC was 7.3% for patients with HDV RNA negativity compared to that of 22.2% for patients with HDV RNA positivity ( $P = 0.01$ ). In the subgroup of cirrhotic patients, the factors associated with HCC development were HDV RNA positivity (HR/CI 4.45/1.04-19.09,  $P = 0.04$ ) and BMI (HR/CI 1.11/1.03-1.19,  $P = 0.01$ ). HDV viremia played a crucial role in HCC development in CHB patients who underwent NA therapy.

Dandri M, A Bertolotti and M Lütgehetmann (2021). "[Innate immunity in hepatitis B and D virus infection: consequences for viral persistence, inflammation, and T cell recognition.](#)" *Semin Immunopathol.*

Chronic infections with human hepatitis viruses continue to be a major health burden worldwide. Despite the availability of an effective prophylactic vaccine against the hepatitis B virus (HBV) and of antiviral agents efficiently suppressing HBV replication, more than 250 million people are currently chronically infected with this hepatotropic DNA virus, and resolution of chronic hepatitis B (CHB) is rarely achieved. Moreover, coinfection with the hepatitis D virus (HDV), a human RNA satellite virus requiring the envelope proteins of HBV for productive viral spreading, substantially aggravates the disease course of CHB. The molecular mechanisms by which these viruses interact with each other and with the intrinsic innate responses of the hepatocytes are not fully understood. While HBV appears to avoid innate immune recognition, HDV elicits a strong enhancement of innate responses. Notwithstanding, such induction does not hamper HDV replication but contributes to liver inflammation and pathogenesis. Intriguingly, HDV appears to influence the ability of T cells to recognize infected hepatocytes by boosting antigen presentation. This review focuses on current knowledge regarding how these viruses can shape and counteract the intrinsic innate responses of the hepatocytes, thus affecting the immune system and pathogenesis. Understanding the distinct strategies of persistence that HBV and HDV have evolved is central for advancing the development of curative therapies.

Buti M, M Stepanova, A Palom, M Riveiro-Barciela, F Nader, L Roade, R Esteban and Z Younossi (2021). "[Chronic hepatitis D associated with worse patient-reported outcomes than chronic hepatitis B.](#)" *JHEP Rep* 3(3): 100280.

BACKGROUND & AIMS: Health-related quality of life (HRQoL) determined by patient-reported outcomes (PROs) is impaired in chronic hepatitis B (CHB) and C patients, but there are no data regarding patients with chronic hepatitis D (CHD). The aim of this study was to assess PRO scores in untreated patients with CHD and compare them with those obtained for patients with CHB. METHODS: Patients with CHD completed 3 PRO instruments (Chronic Liver Disease Questionnaire [CLDQ], Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-F], and Work Productivity and Activity Impairment [WPAI]), and the results were compared with those of patients mono-infected with CHB. RESULTS: In total, 125 patients were included: 43 with CHD and 82 with CHB. Overall, baseline PROs showed differences between both groups. Several assessments, such as the worry score from CLDQ ( $p = 0.0118$ ), functional well-being from FACIT-F ( $p = 0.0281$ ), and activity impairment from WPAI ( $p = 0.0029$ ) showed a significant trend to worse scores in patients with CHD than with CHB. In addition, the linear regression model supports the finding that having CHD as opposed to having CHB was a predictor of a higher worry score (CLDQ) and a higher activity impairment (WPAI). CONCLUSIONS: In this first assessment in CHD, PROs recorded in patients with CHD showed a significant impairment in some domains of HRQoL questionnaires in comparison with those with CHB. Studies in larger cohorts with lengthier follow-up are needed to fully assess patient-reported quality of life over the course of CHD. LAY SUMMARY: Chronic hepatitis D (CHD) is a viral disease that causes rapid evolution to liver cirrhosis, amongst other severe complications, when compared to patients with chronic hepatitis B (CHB). Health-related quality of life in chronic hepatitis C and CHB has been reported widely, but no studies have been performed on patient-reported outcomes in patients with CHD. Results showed that CHD patients reported worse outcomes in psychological domains such as worry and emotional well-being, as well as in physical domains such as abdominal symptoms, physical well-being, and activity impairment in comparison with patients with CHB.

Zhang Z and S Urban (2020). "[Interplay between Hepatitis D Virus and the Interferon Response.](#)" *Viruses* 12(11).

Chronic hepatitis D (CHD) is the most severe form of viral hepatitis, with rapid progression of liver-related diseases and high rates of development of hepatocellular carcinoma. The causative agent, hepatitis D virus (HDV), contains a small (approximately 1.7 kb) highly self-pairing single-strand circular RNA genome that assembles with the HDV antigen to form a ribonucleoprotein (RNP) complex. HDV depends on hepatitis B virus (HBV) envelope proteins for envelopment and de novo hepatocyte entry; however, its intracellular RNA replication is autonomous. In addition, HDV can amplify HBV independently through cell division. Cellular innate immune responses, mainly interferon (IFN) response, are crucial for controlling invading viruses, while viruses counteract these responses to favor their propagation. In contrast to HBV, HDV activates profound IFN response through the melanoma differentiation antigen 5 (MDA5) pathway. This cellular response efficiently suppresses cell-division-mediated HDV spread and, to some extent, early stages of HDV de novo infection, but only marginally impairs RNA replication in resting hepatocytes. In this review, we summarize the current knowledge on HDV structure, replication, and persistence and subsequently focus on the interplay between HDV and IFN response, including IFN activation, sensing, antiviral effects, and viral countermeasures. Finally, we discuss crosstalk with HBV.

Wedemeyer H (2020). "[The burden of hepatitis D - defogging the epidemiological horizon.](#)" *J Hepatol* **73**(3): 493-495.

Roulot D, Brichtler S, Layese R, BenAbdesselam Z, Zoulim F, Thibault V, Scholtes C, Roche B, Castelnaud C, Poynard T, Chazouillères O, Ganne N, Fontaine H, Gournay J, Guyader D, Le Gal F, Nahon P, Roudot-Thoraval F, Gordien E, Deltavir study group (2020). "[Origin, HDV genotype and persistent viremia determine outcome and treatment response in patients with chronic hepatitis delta.](#)" *J Hepatol*. **73**(5): 1046-1062

Background & aims: HDV infection causes severe chronic liver disease in individuals infected with HBV. However, the factors associated with poor prognosis are largely unknown. Thus, we aimed to identify prognostic factors in patients with HDV infection.

Methods: The French National Reference Centre for HDV performed a nationwide retrospective study on 1,112 HDV-infected patients, collecting epidemiological, clinical, virological and histological data from the initial referral to the last recorded follow-up.

Results: The median age of our cohort was 36.5 (29.9-43.2) years and 68.6% of our cohort were male. Most patients whose birthplace was known were immigrants from sub-Saharan Africa (52.5%), southern and eastern Europe (21.3%), northern Africa and the Middle East (6.2%), Asia (5.9%) and South America (0.3%). Only 150 patients (13.8%) were French native. HDV load was positive in 659 of 748 tested patients (88.1%). HDV-1 was predominant (75.9%), followed by sub-Saharan genotypes: HDV-5 (17.6%), HDV-7 (2.9%), HDV-6 (1.8%) and HDV-8 (1.6%). At referral, 312 patients (28.2%) had cirrhosis, half having experienced at least 1 episode of hepatic decompensation. Cirrhosis was significantly less frequent in African than in European patients regardless of HDV genotype. At the end of follow-up (median 3.0 [0.8-7.2] years), 48.8% of the patients had developed cirrhosis, 24.2% had  $\geq 1$  episode(s) of decompensation and 9.2% had hepatocellular carcinoma. European HDV-1 and African HDV-5 patients were more at risk of developing cirrhosis. Persistent replicative HDV infection was associated with decompensation, hepatocellular carcinoma and death. African patients displayed better response to interferon therapy than non-African patients (46.4% vs. 29.1%,  $p < 0.001$ ). HDV viral load at baseline was significantly lower in responders than in non-responders.

Conclusion: Place of birth, HDV genotype and persistent viremia constitute the main determinants of liver involvement and response to treatment in chronic HDV-infected patients.

Lay summary: Chronic liver infection by hepatitis delta virus (HDV) is the most severe form of chronic viral hepatitis. Despite the fact that at least 15-20 million people are chronically infected by HDV worldwide, factors determining the severity of liver involvement are largely unknown. By investigating a large cohort of 1,112 HDV-infected patients followed-up in France, but coming from different areas of the world, we were able to determine that HDV genotype, place of birth (reflecting both viral and host-related factors) and persistent viremia constitute the main determinants of liver involvement and response to treatment.

Palom A, S Rodríguez-Tajes, CA Navascués, J García-Samaniego, M Riveiro-Barciela, S Lens, M Rodríguez, R Esteban and M Buti (2020). "[Long-term clinical outcomes in patients with chronic hepatitis delta: the role of persistent viraemia.](#)" *Aliment Pharmacol Ther* **51**(1): 158-166.

**BACKGROUND:** Chronic hepatitis delta is a severe liver disease with rapid progression to cirrhosis. The impact of hepatitis delta virus (HDV)-RNA on disease progression and interferon treatment in a real-world cohort has been barely explored. **AIM:** To assess the development of clinical events in a cohort of chronic hepatitis delta patients according to the presence or absence of HDV-RNA **METHODS:** Multicentre study at four academic hospitals in Spain included anti-HDV-positive patients with compensated liver disease with a follow-up  $\geq 12$  months. **RESULTS:** Among 2888 HBsAg-positive subjects, 151 (5.2%) tested positive for anti-HDV, and 118 were included (58% men; median age, 49 years; 73% detectable HDV-RNA and 30% cirrhosis, most often in subjects with HDV-RNA). After a median follow-up of 8 years, subjects with initially detectable HDV-RNA were more prone to developing cirrhosis (31% vs 0%,  $P = .002$ ) and/or liver decompensation (28% vs 3%,  $P = .019$ ). Mortality rate was 0.44 per 1000 person-months. The probability of a clinical event was 6%, 25%, and 80% according to initial baseline-event-anticipation score. HDV-RNA became undetectable in 21 (24%) subjects either due to interferon or spontaneously (48% vs 52%,  $P = .29$ ). Liver decompensation was reduced in interferon-treated patients (13% vs 38%,  $P = .026$ ). **CONCLUSIONS:** Subjects with persistently positive HDV-RNA had a worse prognosis in terms of clinical events. Baseline-event-anticipation score is useful in predicting the risk of developing liver decompensation and hepatocellular carcinoma. Interferon was beneficial in reducing liver decompensation, even in the absence of virological response.

Palom A, M Riveiro-Barciela and M Buti (2020). "[Editorial: rapid disease progression in hepatitis delta-can we turn the tide? Authors' reply.](#)" *Aliment Pharmacol Ther* **51**(1): 174-175.

Kapuria D, G Ben Yakov, C Koh and T Heller (2020). "[Spontaneous Clearance of Chronic Delta Hepatitis.](#)" *Hepatology* **71**(5): 1873-1875.

Jung S, SM Altstetter and U Protzer (2020). "[Innate immune recognition and modulation in hepatitis D virus infection.](#)" *World J Gastroenterol* **26**(21): 2781-2791.

Hepatitis D virus (HDV) is a global health threat with more than 15 million humans affected. Current treatment options are largely unsatisfactory leaving chronically infected humans at high risk to develop liver cirrhosis and hepatocellular carcinoma. HDV is the only human satellite virus known. It encodes only two proteins, and requires Hepatitis B virus (HBV) envelope protein expression for productive virion release and spread of the infection. How HDV could evolve and why HBV was selected as a helper virus remains unknown. Since the discovery of Na(+)-taurocholate co-transporting polypeptide as the essential uptake receptor for HBV and HDV, we are beginning to understand the interactions of HDV and the immune system. While HBV is mostly regarded a stealth virus, that escapes innate immune recognition, HBV-HDV coinfection is characterized by a strong innate immune response. Cytoplasmic RNA sensor melanoma differentiation antigen 5 has been reported to recognize HDV RNA replication and activate innate immunity. Innate immunity, however, seems not to impair HDV replication while it inhibits HBV. In this review, we describe what is known up-to-date about the interplay between HBV as a helper and HDV's immune evasion strategy and identify where additional research is required.

Ferrarese A, S Sciarone, M Gambato, G Germani, M Senzolo, P Boccagni, U Cillo, P Burra and FP Russo (2020). "[Letter: clinical outcomes of patients with hepatitis D infection in the liver transplant setting.](#)" *Aliment Pharmacol Ther* **51**(4): 482-483.

Brancaccio G and GB Gaeta (2020). "[Letter: clinical outcomes of patients with hepatitis D infection in the liver transplant setting-authors' reply.](#)" *Aliment Pharmacol Ther* **51**(4): 484.

Baskiran A, S Akbulut, TT Sahin, C Koc, S Karakas, V Ince, C Yurdaydin and S Yilmaz (2020). "[Effect of HBV-HDV co-infection on HBV-HCC co-recurrence in patients undergoing living donor liver transplantation.](#)" *Hepatol Int* **14**(5): 869-880.

**PURPOSE:** To evaluate the effect of hepatitis D virus (HDV) on hepatitis B virus-hepatocellular carcinoma (HBV-HCC) co-recurrence in patients undergoing living donor liver transplantation (LDLT) for HBV alone or HBV-HDV coinfection. **METHODS:** Between 2002 and 2019, 254 HBV-HCC patients underwent LDLT. The patients were divided into two groups after the application of the exclusion criteria: HBV-HCC (Group B;  $n = 163$ ) and HBV-HDV-HCC (Group D;  $n = 31$ ). First, the B and D groups were compared in terms of demographic and clinical parameters. Second, patients with ( $n = 16$ ) and without ( $n = 178$ ) post-transplant HBV-HCC co-recurrences were grouped and compared in terms of the same parameters. **RESULTS:** Although the risk of HBV-HCC co-recurrence in group D was 4.99-fold higher than in group B,

the risk of HBV recurrence alone in group D was 12.5-fold lower than in group B. The AFP (OR = 4.4), Milan criteria (beyond; OR = 18.8), and HDV (OR = 8.1) were identified as the independent risk factors affecting post-transplant HBV-HCC co-recurrence. The Milan criteria (OR = 2.1) and HBV-HCC co-recurrence (OR = 10.9) were identified as the risk factors affecting post-transplant mortality. HBV-HCC co-recurrence developed in 26.5% of patients in Group B and 100% in Group D (OR = 40;  $p = 0.001$ ). HCC recurrence alone developed in 10% of patients without HBV recurrence in group B and 0% of patients without HBV recurrence in group D (OR = 5.7). CONCLUSION: This study showed that the risk of HBV recurrence alone was reduced by 12.5-fold in the presence of HDV; however, the HCC recurrence occurred in all patients with HDV when HBV recurrence developed.

Argirion I, P Mahale, RM Pfeiffer, J Koshiol and TR O'Brien (2020). "[Cirrhotic controls in a pooled analysis of hepatitis D and hepatocellular carcinoma.](#)" *J Hepatol* **73**(6): 1583-1584.

Alves Vasconcelos MP, DV Dall'Ácqua, H Wedemeyer, SS Witkin, MC Mendes-Corrêa and JM Villalobos-Salcedo (2020). "[Noninvasive Models for Predicting Liver Fibrosis in Individuals with Hepatitis D Virus/Hepatitis B Virus Coinfection in the Brazilian Amazon Region.](#)" *Am J Trop Med Hyg* **103**(1): 169-174.

Hepatitis D virus (HDV) genotype III is endemic in the western Amazon basin and is considered to cause the most severe form of chronic viral hepatitis. Recently, noninvasive fibrosis scores to determine the stage of liver fibrosis have been evaluated in individuals positive for HDV genotype I, but their utility in HDV genotype III-positive patients is unknown. In this retrospective study conducted in an outpatient viral hepatitis referral clinic in the Brazilian Amazon region, the aspartate aminotransferase (AST) to Aspartate aminotransferase to Platelet Ratio Index (APRI) and Fibrosis Index for Liver Fibrosis (FIB-4) values were calculated and compared with histological fibrosis stages. Among the 50 patients analyzed, the median age at liver biopsy was 35.6 years, 66% were male, and all had compensated liver disease. Histological staging revealed fibrosis stages 0, 1, 2, 3, and 4 in four (8%), eight (16%), 11 (22%), 11 (22%), and 16 (32%) patients, respectively. The area under the receiver operating curve (AUROC) of AST-to-alanine aminotransferase (ALT) ratio, APRI, and FIB-4 for detection of significant fibrosis ( $F \geq 2$ ) was 0.550 ( $P = 0.601$ ), 0.853 ( $P < 0.001$ ), and 0.853 ( $P < 0.0001$ ), respectively. Lower AUROC values were obtained for cirrhosis: the AST-to-ALT ratio was 0.640 ( $P = 0.114$ ), APRI was 0.671 ( $P = 0.053$ ), and FIB-4 was 0.701 ( $P = 0.023$ ). The optimal cutoff value for significant fibrosis for APRI was 0.708 (sensitivity 84% and specificity 92%) and for FIB-4 was 1.36 (sensitivity 76% and specificity 92%). Aspartate aminotransferase to Platelet Ratio Index and FIB-4 were less useful to predict cirrhosis. In contrast to recent reports from Europe and North America, both APRI and FIB-4 may identify significant fibrosis in HDV-III-infected patients from northwestern Brazil.

Argirion I, P Mahale, RM Pfeiffer, J Koshiol and TR O'Brien (2020). "[Cirrhotic controls in a pooled analysis of hepatitis D and hepatocellular carcinoma.](#)" *J Hepatol* **73**(6): 1583-1584.

Alfaiate D, S Clément, N Goossens and F Negro (2020). "[Reply to: "Cirrhotic controls in a pooled analysis of hepatitis D and hepatocellular carcinoma"](#)." *J Hepatol* **73**(6): 1585-1586.

Alfaiate D, S Clément, D Gomes, N Goossens and F Negro (2020). "[Chronic hepatitis D and hepatocellular carcinoma: A systematic review and meta-analysis of observational studies.](#)" *J Hepatol* **73**(3): 533-539.

BACKGROUND & AIMS: Chronic hepatitis D (CHD) is the most severe form of chronic viral hepatitis but its role in the development of hepatocellular carcinoma (HCC) remains debated. We conducted a systematic review and meta-analysis of epidemiological studies to examine whether CHD is associated with an increased risk of HCC. METHODS: We searched PubMed, Embase and Web of Science, as well as study references and conference proceedings. We considered cohort and case-control studies allowing the calculation of effect estimates for the association between CHD (exposure) and HCC (outcome) in comparison to chronic hepatitis B. Data extraction and quality evaluation (using the Newcastle-Ottawa scale) were performed independently by 2 authors. Data were pooled using random-effects models. RESULTS: Ninety-three studies (68 case-control studies including 22,862 patients and 25 cohort studies including 75,427 patients) were included. Twelve studies accounted for confounders, in either study design or analysis (10 of which were cohorts), and 11 cohorts were prospective. The overall analysis showed a significantly increased risk of HCC in patients with CHD, despite substantial study heterogeneity (pooled odds ratio 1.28; 95% CI 1.05-1.57;  $I(2) = 67.0\%$ ). The association was particularly strong in the absence of heterogeneity for prospective cohort studies (pooled odds ratio 2.77; 95% CI 1.79-4.28;  $I(2) = 0\%$ ), and studies with HIV-infected patients (pooled odds ratio 7.13; 95% CI 2.83-17.92;

I(2) = 0%). CONCLUSIONS: We found a significantly higher risk of HCC in patients with CHD. Although further studies are needed to definitively exclude a potential bias due to antiviral treatments, our findings highlight the rationale for improved screening of hepatitis D virus infection in patients with chronic hepatitis B, and the urgent need for novel and effective antiviral therapies. LAY SUMMARY: Hepatitis D virus (HDV) is a defective pathogen requiring hepatitis B virus (HBV) to complete its life cycle. Chronic hepatitis D is the most severe form of chronic viral hepatitis, increasing the risk of cirrhosis, liver decompensation and death compared to HBV mono-infection. However, the association between HDV infection and increased risk of hepatocellular carcinoma is debated. We conducted a systematic review and found that patients with HDV infection had a significantly higher risk of developing hepatocellular carcinoma than those with HBV mono-infection.

Akande KO, A Fowotade and O Adekanmbi (2020). "[The effect of Hepatitis D co-infection on the immunologic and molecular profile of Hepatitis B in asymptomatic Chronic Hepatitis B patients in southwest Nigeria.](#)" *J Immunoassay Immunochem* **41**(3): 272-280.

Introduction: Hepatitis D infection causes severe form of viral hepatitis in humans and only affects those with hepatitis B either as a co-infection or superinfection. The aim of this study was to determine the prevalence of Hepatitis D and its effect on the immunologic and molecular profile of Hepatitis B among asymptomatic Chronic Hepatitis B patients in Abeokuta. Methodology: A cross-sectional study of 99 chronic HBV patient who met the inclusion criteria. All the patients were tested for HBsAg, anti HCV, HDV antigen, anti HDV, HBsAg quantification, and HBV DNA quantification. Associations were tested for and P value less than 0.05 was considered significant. Results: The participants included 53 (58%) male and 38 (42%) females with ages ranging from 18 to 69 (means  $39 \pm 11$ ) years. Ten (11%) participants were positive for HDV-Ag while 1 (1.1%) was positive for anti-HDV. Five (5.5%) were positive for HIV 1 & 2 while 1 (1.1%) was positive for anti HCV. HBV DNA quantification ranged from 15 to 17,000,000 IU/ml while HBsAg quantification ranged from 0.25 to 45,520 IU/ml. There was no statistically significant relationship between HDV-Ag and age ( $p = .51$ ), sex ( $p = .73$ ), HBV DNA ( $p = .8$ ) and HBsAg quantification ( $p = 1$ ). Conclusion: The prevalence of HDV-Ag among asymptomatic treatment naïve chronic hepatitis B patients in Abeokuta was 11% and there was no significant difference in the levels of HBV DNA and HBsAg among those with or without hepatitis D.

Abbas Z, MA Qadeer, HA Mandviwalla and M Abbas (2020). "[The Severity of Hepatitis D in Young Adults of Age 18-25 Years.](#)" *Cureus* **12**(10): e10855.

Background Current literature on the prevalence and characteristics of hepatitis D virus (HDV) infection in young adults is limited. This study aims to determine the disease characteristics and severity in young adults. Methods The case records of HDV RNA positive patients of age 18-25 years were analyzed. Results Out of 119 patients, 105 (88%) patients were male. HBV-DNA was detectable in 83 (70%). Hepatitis B e-antigen (HBeAg) was non-reactive in 99 (83%). Cirrhosis was identified in 45 (37.8%) individuals; nine (7.5%) were classified as Child class B or Child class C. Twenty-four (20.2%) had a Model For End-Stage Liver Disease (MELD) score of  $\geq 10$ , out of these 16 had a score of 15 or more. The risk of decompensation was calculated according to the Baseline-event-anticipation (BEA) score; eight (6.7%) patients were at BEA-A (mild risk), 105 (88.2%) were at BEA-B (moderate risk), and six (5.0%) were at BEA-C (severe risk). Notable findings in patients with cirrhosis included splenomegaly, low total leucocyte counts, low platelets, high bilirubin, elevated aspartate aminotransferase, gamma-glutamyl transferase and international normalization ratio, low albumin, high AST to Platelet Ratio Index (APRI), and high BEA score. The splenic size, platelet count, and albumin levels were independently associated with cirrhosis ( $p < 0.001$ ,  $< 0.001$ , and  $0.003$ ). A model using a combination of platelet count, albumin, and spleen size was developed to accurately predict cirrhosis in this cohort. It had an area under the receiver operating characteristics (AUROC) of 0.935. Conclusions HDV-infected young adults, age 18-25 years, were at moderate to severe risk of disease progression. About one-third of patients had already developed cirrhosis indicating the aggressive nature of the disease.

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## THE CHANGING CONTEXT OF HEPATITIS DELTA

### Screening and diagnosis of hepatitis Delta

Yu Z, X Ma, W Zhang, X Chang, L An, M Niu, Y Chen, C Sun and Y Yang (2021). "[Microarray Data Mining and Preliminary Bioinformatics Analysis of Hepatitis D Virus-Associated Hepatocellular Carcinoma.](#)" *Biomed Res Int* **2021**: 1093702.

Several studies have demonstrated that chronic hepatitis delta virus (HDV) infection is associated with a worsening of hepatitis B virus (HBV) infection and increased risk of hepatocellular carcinoma (HCC). However, there is limited data on the role of HDV in the oncogenesis of HCC. This study is aimed at assessing the potential mechanisms of HDV-associated hepatocarcinogenesis, especially to screen and identify key genes and pathways possibly involved in the pathogenesis of HCC. We selected three microarray datasets: GSE55092 contains 39 cancer specimens and 81 paracancer specimens from 11 HBV-associated HCC patients, GSE98383 contains 11 cancer specimens and 24 paracancer specimens from 5 HDV-associated HCC patients, and 371 HCC patients with the RNA-sequencing data combined with their clinical data from the Cancer Genome Atlas (TCGA). Afterwards, 948 differentially expressed genes (DEGs) closely related to HDV-associated HCC were obtained using the R package and filtering with a Venn diagram. We then performed gene ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis to determine the biological processes (BP), cellular component (CC), molecular function (MF), and KEGG signaling pathways most enriched for DEGs. Additionally, we performed Weighted Gene Coexpression Network Analysis (WGCNA) and protein-to-protein interaction (PPI) network construction with 948 DEGs, from which one module was identified by WGCNA and three modules were identified by the PPI network. Subsequently, we validated the expression of 52 hub genes from the PPI network with an independent set of HCC dataset stored in the Gene Expression Profiling Interactive Analysis (GEPIA) database. Finally, seven potential key genes were identified by intersecting with key modules from WGCNA, including 3 reported genes, namely, CDCA5, CENPH, and MCM7, and 4 novel genes, namely, CDC6, CDC45, CDCA8, and MCM4, which are associated with nucleoplasm, cell cycle, DNA replication, and mitotic cell cycle. The CDCA8 and stage of HCC were the independent factors associated with overall survival of HDV-associated HCC. All the related findings of these genes can help gain a better understanding of the role of HDV in the underlying mechanism of HCC carcinogenesis.

Surana P, J Hercun, V Takyar, DE Kleiner, T Heller and C Koh (2021). "[Platelet count as a screening tool for compensated cirrhosis in chronic viral hepatitis.](#)" *World J Gastrointest Pathophysiol* **12**(3): 40-50.

BACKGROUND: Simple tools for clinicians to identify cirrhosis in patients with chronic viral hepatitis are medically necessary for treatment initiation, hepatocellular cancer screening and additional medical management. AIM: To determine whether platelets or other laboratory markers can be used as a simple method to identify the development of cirrhosis. METHODS: Clinical, biochemical and histologic laboratory data from treatment naive chronic viral hepatitis B (HBV), C (HCV), and D (HDV) patients at the NIH Clinical Center from 1985-2019 were collected and subjects were randomly divided into training and validation cohorts. Laboratory markers were tested for their ability to identify cirrhosis (Ishak  $\geq 5$ ) using receiver operating characteristic curves and an optimal cut-off was calculated within the training cohort. The final cut-off was tested within the validation cohort. RESULTS: Overall, 1027 subjects (HCV = 701, HBV = 240 and HDV = 86), 66% male, with mean (standard deviation) age of 45 (11) years were evaluated. Within the training cohort (n = 715), platelets performed the best at identifying cirrhosis compared to other laboratory markers [Area Under the Receiver Operating Characteristics curve (AUROC) = 0.86 (0.82-0.90)] and sensitivity 77%, specificity 83%, positive predictive value 44%, and negative predictive value 95%. All other tested markers had AUROCs  $\leq 0.77$ . The optimal platelet cut-off for detecting cirrhosis in the training cohort was  $143 \times 10^9/L$  and it performed equally well in the validation cohort (n = 312) [AUROC = 0.85 (0.76-0.94)]. CONCLUSION: The use of platelet counts should be considered to identify cirrhosis and ensure optimal care and management of patients with chronic viral hepatitis.

Martínez-Campreciós J, A Rando-Segura, M Buti, F Rodrigo-Velásquez, M Riveiro-Barciela, A Barreira-Díaz, P Álvarez-López, P Salmerón, A Palom, D Tabernero, N Palomo, A Nindia, G Barbosa, E López, V Ferreira, N Saiago, A Kuchta, R Ferrer-Costa, R Esteban, I Molina and F Rodríguez-Frías (2021). "[Reflex viral load testing in dried blood spots generated by plasma separation card allows the screening and diagnosis of chronic viral hepatitis.](#)" *J Virol Methods* **289**: 114039.

Dried blood spots (DBS) have been proposed as an alternative diagnostic technique for chronic viral hepatitis. The aim of this observational study was to correlate serologic HBV, HCV, and HDV status and reflex the respective viral load testing by PSC-DBS samples from capillary blood vs conventional plasma samples in patients with chronic viral hepatitis. Besides, we apply these tests in a prospective study for chronic viral hepatitis diagnosis in a rural region of sub-Saharan Africa. In total, 124 HBsAg-positive patients, 75 anti-HCV positive, 2 with HBV-HCV coinfection, and 13 anti-HDV positive were included. PSC-DBS sensitivity/specificity was 98.4 %/96.2 % for HBsAg detection, 98.7 %/100 % for anti-HCV, and 84.6 %/100 % for anti-HDV. HCV-RNA was quantified in all viremic patients using DBS. Only 42 of 78 (53.8 %) samples with HBV-DNA viremia were quantifiable by DBS. Sensitivity increased to 95.7 % in patients with HBV-DNA levels >2000 IU/mL. There was a high correlation between DBS and venous blood. The prevalence of HBsAg among the 93 individuals tested in Angola was 11 %, and 60 % of cases had detectable HBV-DNA viremia. As a conclusion, PSC-DBS is useful for chronic viral hepatitis screening and reflex molecular diagnosis showing globally high sensitivities and correlation with conventional blood samples.

Da BL, F Rahman, WC Lai, DE Kleiner, T Heller and C Koh (2021). "[Risk Factors for Delta Hepatitis in a North American Cohort: Who Should Be Screened?](#)" *Am J Gastroenterol* **116**(1): 206-209.

INTRODUCTION: The American Association for the Study of Liver Diseases recommends hepatitis D virus (HDV) screening in certain high-risk groups; however, the effectiveness is unknown. METHODS: A study of North American patients with hepatitis B (HBV) referred to the NIH was performed to identify risk factors associated with HDV infection. Active HDV was "confirmed" by serum HDV RNA or histologic HDV antigen staining. RESULTS: Six hundred fifty-two were studied, of which 91 were HDV "confirmed." Independent risk factors for HDV included: intravenous drug users, HBV-DNA <2,000 IU/mL, alanine aminotransferase >40 U/L, and HDV endemic country of origin. DISCUSSION: North American patients with HBV and significant risk factors should be screened for HDV.

Usman Z, S Velkov, U Protzer, M Roggendorf, D Frishman and H Karimzadeh (2020). "[Reply to the Letter of Charre et al. "Mis-Genotyping of Some Hepatitis D Virus Genotype 2 and 5 Sequences Using HDVdb"](#)"." *Viruses* **12**(11).

We thank Charre and colleagues for spotting the mis-annotation of sequences in our database, which was caused by human error [...].

Usman Z, S Velkov, U Protzer, M Roggendorf, D Frishman and H Karimzadeh (2020). "[HDVdb: A Comprehensive Hepatitis D Virus Database](#)"." *Viruses* **12**(5).

Hepatitis D virus (HDV) causes the most severe form of viral hepatitis, which may rapidly progress to liver cirrhosis and hepatocellular carcinoma (HCC). It has been estimated that 15-20 million people worldwide are suffering from the chronic HDV infection. Currently, no effective therapies are available to treat acute or chronic HDV infection. The remarkable sequence variability of the HDV genome, particularly within the hypervariable region has resulted in the provisional classification of eight major genotypes and various subtypes. We have developed a specialized database, HDVdb (<http://hdvdb.bio.wzw.tum.de/>), which contains a collection of partial and complete HDV genomic sequences obtained from the GenBank and from our own patient cohort. HDVdb enables the researchers to investigate the genetic variability of all available HDV sequences, correlation of genotypes to epidemiology and pathogenesis. Additionally, it will contribute in understanding the drug resistant mutations and develop effective vaccines against HDV infection. The database can be accessed through a web interface that allows for static and dynamic queries and offers integrated generic and specialized sequence analysis tools, such as annotation, genotyping, primer prediction, and phylogenetic analyses.

Terrault NA and MG Ghany (2020). "[Enhanced Screening for Hepatitis D in the USA: Overcoming the Delta Blues](#)"." *Dig Dis Sci*.

Shen DT, H Goyal and HG Xu (2020). "[Differences in delta virus hepatitis diagnosis methods and its effect on the hepatitis D prevalence](#)"." *Gut* **69**(10): 1893.

Pereira RCR, CAM Heming, TR Tejo, TCL de Oliveira, R da Silva and DB Parente (2020). "[Use of the LI-RADS classification in patients with cirrhosis due to infection with hepatitis B, C, or D, or infected with hepatitis B and D](#)"." *Radiol Bras* **53**(1): 14-20.

**OBJECTIVE:** To evaluate liver lesions, in accordance with the LI-RADS classification, using contrast-enhanced multiphase dynamic computed tomography in patients with hepatitis B, coinfecting or not with hepatitis D, or with chronic hepatitis C, as well as to determine the level of agreement between radiologists. **MATERIALS AND METHODS:** We evaluated 38 patients with hepatitis B, coinfecting or not with hepatitis D, or with chronic hepatitis C, all of whom underwent contrast-enhanced multiphase dynamic computed tomography. For each examination, two radiologists selected up to three hepatic lesions, categorizing them in accordance with the LI-RADS classification and evaluating signs of chronic liver disease and portal hypertension. To determine the level of agreement between radiologists, we calculated the kappa statistic ( $\kappa$ ). **RESULTS:** Radiologist 1 and radiologist 2 selected 56 and 48 liver lesions, respectively. According to radiologist 1 and radiologist 2, respectively, 27 (71%) and 23 (61%) of the 38 patients had at least one liver lesion; 13 (34%) and 12 (32%) had a LI-RADS 5 lesion ( $\kappa = 0.821$ ); 19 (50%) and 16 (42%) had a hypervascular lesion ( $\kappa = 0.668$ ); and 30 (79%) and 24 (63%) had splenomegaly ( $\kappa = 0.503$ ). Both radiologists identified chronic liver disease in 31 (82%) of the patients ( $\kappa = 1.00$ ). **CONCLUSION:** Lesions categorized as LI-RADS 5 were detected in approximately 32% of the patients, with almost perfect agreement between the radiologists. The level of agreement was substantial or moderate for the other LI-RADS categories.

Lin GY, YL Wu, CS Wang, CY Ko, CH Chen, PJ Chen, PH Peng and CW Hsu (2020). "[Performance of commercially available anti-HDV enzyme-linked immunosorbent assays in Taiwan.](#)" *Virology* **17**(1): 76.

**BACKGROUND:** Hepatitis D virus (HDV) infection is a major global health issue around the world. There are approximately 15-20 million individuals infected with HDV worldwide. HDV infection usually causes increased mortality compared with infection with hepatitis B virus (HBV) alone. However, testing for the detection of HDV is not widely available in Taiwan. Therefore, the General Biologicals Corporation (GB) HDV Ab kit was developed for detecting anti-HDV antibodies. **METHODS:** A total of 913 serum and 462 EDTA-treated plasma samples were obtained from HBsAg-positive individuals in three hospitals in Taiwan from June 2014 to November 2017. We used three commercially available ELISA kits, DiaPro HDV Ab, DiaSorin ETI-AB-DELTA-2 and GB HDV Ab, which were utilized strictly according to the instructions of the manufacturers. **RESULTS:** A comparative study of the results from the GB HDV Ab kit and the other commercial ELISA kits (DiaPro and DiaSorin) was performed to determine their efficacy for anti-HDV detection. The results indicated that the sensitivity of the GB HDV Ab kit for serum and EDTA samples was 100% compared to that of the DiaPro and DiaSorin kits, whereas the specificity for serum and EDTA samples was 99.3 and 98.1%, respectively. In addition, the overall agreement of the results of the GB HDV Ab kit for the serum and EDTA samples was 99.3 and 98.3%, respectively. It is worth noting that the performance of the GB HDV Ab kit was not affected by interference from triglyceride, bilirubin, hemoglobin, or human anti-mouse antibody. The limit of detection of the GB HDV Ab kit is approximately 100-fold lower than that of the other two commercial kits. **CONCLUSIONS:** The GB HDV Ab kit, which presented equivalent sensitivity and specificity compared to both certified anti-HDV kits, would be a suitable kit for HDV diagnosis in Taiwan.

Isaeva OV, LY Ilchenko, VS Kichatova, IA Potemkin, EP Amon, AA Saryglar, AS Al-Sharabi Shukri, AA Kyuregyan and AA Mikhailov (2020). "[Detection of markers of hepatitis B and D virus infection in biological media and dried blood spots.](#)" *Klin Lab Diagn* **65**(2): 95-99.

The aim of this study was to assess the rates of detection of the major markers of infection with hepatitis B and Delta (D) viruses in serum, saliva and dry blood dots (DBS) as a possible option for serological studies among the population of the endemic region in conditions of limited laboratory resources. For this purpose, paired samples of blood serum and DBS, blood serum and saliva from patients with chronic hepatitis B with Delta agent living in the Republic of Tyva, which is endemic for this disease. HBsAg was detected in 289 (100%) serum samples, in 88/92 (95.7%) saliva samples, in 60/80 (75%) DBS samples, stored three years at room temperature, and in 111/117 (94.9%) DBS stored one year at the same conditions. Anti-HBcore was detected in 209 (100%) serum samples, while in saliva and DBS samples this marker was detected in only 13.04% (12/92) and 19.7% (23/117), respectively. Anti-HDV antibodies in serum were detected in 209 (100%) samples collected from patients in 2017-2018. In saliva and DBS anti-HDV were not detected in any sample. This difference in the detection rates of anti-HBcore and anti-HDV might be accounted for the fact that the HBV core protein is a very strong immunogen, inducing the production of anti-HBcore in high concentrations. Probably, the concentration of anti-HDV is much lower, which explains its absence in saliva and DBS in patients with hepatitis B+D. Samples of biological media (saliva), as well as DBS can serve as an alternative material for the detection of HBsAg in screening and research prevalence studies. Meanwhile, the definition of anti-HDV in such media is not possible due

to the false negative results. Due to the high probability of superinfection with HDV in patients with HBV in endemic areas, the detection of HBsAg in alternative media (saliva or DBS) should be followed by testing for anti-HDV in serum samples.

Edwards SK, F Ceccherini-Silberstein and RKJ Tan (2020). "[Research news in clinical context.](#)" *Sex Transm Infect* **96**(3): 235-236.

Da BL, P Surana, V Takyar, DE Kleiner, T Heller and C Koh (2020). "[Vibration-controlled transient elastography for the detection of cirrhosis in chronic hepatitis D infection.](#)" *J Viral Hepat* **27**(4): 428-436.

Noninvasive detection of cirrhosis via vibration-controlled transient elastography (VCTE) has revolutionized the management of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection. However, VCTE has not been studied in chronic hepatitis D virus (HDV) infection and accuracy remains in question due to the significant hepatic inflammation associated with this infection. Consecutive HBV, HCV and HDV patients who underwent VCTE (2006-2019) were evaluated. Diagnosis of cirrhosis was made via liver biopsy or clinical findings. VCTE was compared with other noninvasive serum fibrosis tests using AUROC curves. The performance of VCTE in HBV/HCV/HDV was also compared. We evaluated 319 patients (HBV-112; HCV-132; HDV-75), 278(87%) patients had histology for evaluation. HDV patients had evidence of higher hepatic inflammation as evidence by aspartate aminotransferase, alanine aminotransferase and histology activity index. Cirrhotic HDV patients had higher mean liver stiffness measurements compared with noncirrhotic patients (29.0 vs 8.3 kPa,  $P < .0001$ ). VCTE demonstrated excellent diagnostic accuracy for the detection of cirrhosis with an AUROC of 0.90 compared with APRI (0.83), FIB-4 (0.88), AAR (0.73) and RPR (0.85). Performance of VCTE in HDV was comparable with HBV (0.93) and HCV (0.94). At the optimized cut-off value of  $\geq 14.0$  kPa for determining cirrhosis in HDV, VCTE had a sensitivity of 0.78, specificity of 0.86, NPV of 0.93 and PPV of 0.64. Hence, VCTE is a useful noninvasive test in HDV for determining cirrhosis despite the presence of significant hepatic inflammation.

Da BL, P Surana, DE Kleiner, T Heller and C Koh (2020). "[The Delta-4 fibrosis score \(D4FS\): A novel fibrosis score in chronic hepatitis D.](#)" *Antiviral Res* **174**: 104691.

**BACKGROUND:** Chronic Hepatitis D virus (HDV) infection results in the most severe form of viral hepatitis with a rapid progression to cirrhosis. However, non-invasive fibrosis tests that can accurately predict cirrhosis have not been adequately validated. We aimed to develop a clinically useful non-invasive score that can accurately detect cirrhosis. **MATERIAL AND METHODS:** Patients with chronic HDV diagnosed by liver histology or serum PCR were evaluated. Data regarding demographics, laboratory, imaging, vibration-controlled transient elastography (VCTE), and liver biopsy were collected. The total cohort was randomized into a training and validation cohort. The training cohort was used to develop a novel score, the Delta-4 fibrosis score (D4FS) which was then compared to other non-invasive tests in the validation cohort by area under receiver operating characteristics (AUROC). **RESULTS:** 77 patients with chronic HDV were evaluated: mean age 42.6 (SD:11.1) years, 59.7% male, and 57.1% Asian. The total cohort was then separated into a training (n = 45) and validation (n = 32) cohort with no significant differences in terms of clinical characteristics between the two. From the training cohort, the D4FS was derived from variables of statistical and clinical interest (gamma-glutamyl transpeptidase (GGT), platelet count, alanine aminotransferase (ALT), and liver stiffness measurement (LSM)). The D4FS demonstrated the best AUROC in the validation cohort (0.94) followed by VCTE (0.90), FIB-4 (0.86), APRI (0.81), and AAR (0.71). **DISCUSSION:** The D4FS is a clinically useful non-invasive fibrosis score that can accurately detect cirrhosis in patients with chronic HDV infection. Further studies should be performed to further validate clinical utility.

Charre C, F le Gal, P Dény and C Scholtès (2020). "[Comment: Mis-Genotyping of Some Hepatitis D Virus Genotype 2 and 5 Sequences Using HDVdb.](#)" *Viruses* **12**(10).

Evidence that Hepatitis D virus (HDV) genotype is involved in HDV infection pathogenesis is increasing. Indeed, HDV genotypes have been shown to be linked to different outcomes in terms of liver fibrosis and treatment response. Herein, we show that the promising HDVdb genotyping tool available online can lead to wrong genotyping results. The current HDVdb algorithm should be carefully considered as a "beta-version" and warrants algorithm core corrections, as soon as possible, for an optimal and beneficial use.

Berg MG, A Olivo, K Forberg, BJ Harris, J Yamaguchi, R Shirazi, Y Gozlan, S Sauleda, L Kaptue, MA Rodgers, O Mor and GA Cloherty (2020). "[Advanced molecular surveillance approaches for characterization of blood borne hepatitis viruses.](#)" *PLoS One* **15**(7): e0236046.

Defining genetic diversity of viral infections directly from patient specimens is the ultimate goal of surveillance. Simple tools that can provide full-length sequence information on blood borne viral hepatitis viruses: hepatitis C, hepatitis B and hepatitis D viruses (HCV, HBV and HDV) remain elusive. Here, an unbiased metagenomic next generation sequencing approach (mNGS) was used for molecular characterization of HCV infections (n = 99) from Israel which yielded full-length HCV sequences in 89% of samples, with 7 partial sequences sufficient for classification. HCV genotypes were primarily 1b (68%) and 1a (19%), with minor representation of genotypes 2c (1%) and 3a (8%). HBV/HDV coinfections were characterized by suppressed HBV viral loads, resulting in sparse mNGS coverage. A probe-based enrichment approach (xGen) aiming to increase HBV and HDV coverage was validated on a panel of diverse genotypes, geography and titers. The method extended HBV genome coverage a median 61% (range 8-84%) and provided orders of magnitude boosts in reads and sequence depth for both viruses. When HBV-xGen was applied to Israeli samples, coverage was improved by 28-73% in 4 samples and identified HBV genotype A1, A2, D1 specimens and a dual B/D infection. Abundant HDV reads in mNGS libraries yielded 18/26 (69%) full genomes and 8 partial sequences, with HDV-xGen only providing minimal extension (3-11%) of what were all genotype 1 genomes. Advanced molecular approaches coupled to virus-specific capture probes promise to enhance surveillance of viral infections and aid in monitoring the spread of local subtypes.

Alves Vasconcelos MP, DV Dall'Ácqua, H Wedemeyer, SS Witkin, MC Mendes-Corrêa and JM Villalobos-Salcedo (2020). "[Noninvasive Models for Predicting Liver Fibrosis in Individuals with Hepatitis D Virus/Hepatitis B Virus Coinfection in the Brazilian Amazon Region.](#)" *Am J Trop Med Hyg* **103**(1): 169-174.

Hepatitis D virus (HDV) genotype III is endemic in the western Amazon basin and is considered to cause the most severe form of chronic viral hepatitis. Recently, noninvasive fibrosis scores to determine the stage of liver fibrosis have been evaluated in individuals positive for HDV genotype I, but their utility in HDV genotype III-positive patients is unknown. In this retrospective study conducted in an outpatient viral hepatitis referral clinic in the Brazilian Amazon region, the aspartate aminotransferase (AST) to Aspartate aminotransferase to Platelet Ratio Index (APRI) and Fibrosis Index for Liver Fibrosis (FIB-4) values were calculated and compared with histological fibrosis stages. Among the 50 patients analyzed, the median age at liver biopsy was 35.6 years, 66% were male, and all had compensated liver disease. Histological staging revealed fibrosis stages 0, 1, 2, 3, and 4 in four (8%), eight (16%), 11 (22%), 11 (22%), and 16 (32%) patients, respectively. The area under the receiver operating curve (AUROC) of AST-to-alanine aminotransferase (ALT) ratio, APRI, and FIB-4 for detection of significant fibrosis ( $F \geq 2$ ) was 0.550 ( $P = 0.601$ ), 0.853 ( $P < 0.001$ ), and 0.853 ( $P < 0.0001$ ), respectively. Lower AUROC values were obtained for cirrhosis: the AST-to-ALT ratio was 0.640 ( $P = 0.114$ ), APRI was 0.671 ( $P = 0.053$ ), and FIB-4 was 0.701 ( $P = 0.023$ ). The optimal cutoff value for significant fibrosis for APRI was 0.708 (sensitivity 84% and specificity 92%) and for FIB-4 was 1.36 (sensitivity 76% and specificity 92%). Aspartate aminotransferase to Platelet Ratio Index and FIB-4 were less useful to predict cirrhosis. In contrast to recent reports from Europe and North America, both APRI and FIB-4 may identify significant fibrosis in HDV-III-infected patients from northwestern Brazil.

## Treatment and prevention of hepatitis Delta

Zhang Z and S Urban (2021). "[New insights into HDV persistence: The role of interferon response and implications for upcoming novel therapies.](#)" *J Hepatol* **74**(3): 686-699.

Chronic hepatitis D (CHD), a global health problem, manifests as the most severe form of viral hepatitis. The causative agent, HDV, is the smallest known human virus; it replicates its circular single-stranded RNA genome in the nucleus of hepatocytes. HDV requires HBV-encoded envelope proteins for dissemination and de novo cell entry. However, HDV can also spread through cell division. Following entry into hepatocytes, replicative intermediates of HDV RNA are sensed by the pattern recognition receptor MDA5 (melanoma differentiation antigen 5) resulting in interferon (IFN)- $\beta/\lambda$  induction. This IFN response strongly suppresses cell division-mediated spread of HDV genomes, however, it only marginally affects HDV RNA replication in already infected, resting hepatocytes. Monotherapy with IFN- $\alpha/\lambda$  shows efficacy but rarely results in HDV clearance. Recent molecular insights into key determinants of HDV persistence and the accelerated development of specifically acting antivirals that interfere with the replication cycle have revealed promising new therapeutic perspectives. In this review, we briefly

summarise our knowledge on replication/persistence of HDV, the newly discovered HDV-like agents, and the interplay of HDV with the IFN response and its consequences for persistence. Finally, we discuss the possible role of IFNs in combination with upcoming therapies aimed at HDV cure.

Urban S, C Neumann-Haefelin and P Lampertico (2021). "[Hepatitis D virus in 2021: virology, immunology and new treatment approaches for a difficult-to-treat disease.](#)" *Gut*.

Approximately 5% of individuals infected with hepatitis B virus (HBV) are coinfecting with hepatitis D virus (HDV). Chronic HBV/HDV coinfection is associated with an unfavourable outcome, with many patients developing liver cirrhosis, liver failure and eventually hepatocellular carcinoma within 5-10 years. The identification of the HBV/HDV receptor and the development of novel in vitro and animal infection models allowed a more detailed study of the HDV life cycle in recent years, facilitating the development of specific antiviral drugs. The characterisation of HDV-specific CD4+ and CD8+ T cell epitopes in untreated and treated patients also permitted a more precise understanding of HDV immunobiology and possibly paves the way for immunotherapeutic strategies to support upcoming specific therapies targeting viral or host factors. Pegylated interferon- $\alpha$  has been used for treating HDV patients for the last 30 years with only limited sustained responses. Here we describe novel treatment options with regard to their mode of action and their clinical effectiveness. Of those, the entry-inhibitor bulevirtide (formerly known as myrcludex B) received conditional marketing authorisation in the European Union (EU) in 2020 (Hepcludex). One additional drug, the prenylation inhibitor lonafarnib, is currently under investigation in phase III clinical trials. Other treatment strategies aim at targeting hepatitis B surface antigen, including the nucleic acid polymer REP2139Ca. These recent advances in HDV virology, immunology and treatment are important steps to make HDV a less difficult-to-treat virus and will be discussed.

Sandmann L and M Cornberg (2021). "[Experimental Drugs for the Treatment of Hepatitis D.](#)" *J Exp Pharmacol* **13**: 461-468.

Chronic hepatitis D virus infection is the most severe form of viral hepatitis. Antiviral treatment is urgently needed to prevent patients from developing end stage liver disease or hepatocellular carcinoma. Treatment options were limited to off-label use of pegylated interferon alfa until conditional approval of bulevirtide by the EMA (European Medicines Agency) in July 2020. However, several other antiviral compounds are currently investigated and represent promising agents for the treatment of chronic HDV infection.

Pu J, JT Zhou, P Liu, F Yu, X He, L Lu and S Jiang (2021). "[Viral Entry Inhibitors Targeting Six-Helical Bundle Core Against Highly Pathogenic Enveloped Viruses with Class I Fusion Proteins.](#)" *Curr Med Chem*.

Type I enveloped viruses bind to cell receptors through surface glycoproteins to initiate infection or undergo receptor-mediated endocytosis. They also initiate membrane fusion in the acidic environment of endocytic compartments, releasing genetic material into the cell. In the process of membrane fusion, envelope protein exposes fusion peptide, followed by insertion into the cell membrane or endosomal membrane. Further conformational changes ensue in which the type 1 envelope protein forms a typical six-helix bundle structure, shortening the distance between viral and cell membranes so that fusion can occur. Entry inhibitors targeting viral envelope proteins, or host factors, are effective antiviral agents and have been widely studied. Some have been used clinically, such as T20 and Maraviroc for human immunodeficiency virus 1 (HIV-1) or Myrcludex B for hepatitis D virus (HDV). This review focuses on entry inhibitors that target the six-helical bundle core against highly pathogenic enveloped viruses with class I fusion proteins, including retroviruses, coronaviruses, influenza A viruses, paramyxoviruses, and filoviruses.

Maravelia P, L Frelin, Y Ni, N Caro Pérez, G Ahlén, N Jagya, G Verch, L Verhoye, L Pater, M Johansson, A Pasetto, P Meuleman, S Urban and M Sällberg (2021). "[Blocking Entry of Hepatitis B and D Viruses to Hepatocytes as a Novel Immunotherapy for Treating Chronic Infections.](#)" *J Infect Dis* **223**(1): 128-138.

BACKGROUND: Chronic hepatitis B and D virus (HBV/HDV) infections can cause cancer. Current HBV therapy using nucleoside analogues (NAs) is life-long and reduces but does not eliminate the risk of cancer. A hallmark of chronic hepatitis B is a dysfunctional HBV-specific T-cell response. We therefore designed an immunotherapy driven by naive healthy T cells specific for the HDV antigen (HDAg) to bypass the need for HBV-specific T cells in order to prime PreS1-specific T cells and PreS1 antibodies blocking HBV entry. METHODS: Ten combinations of PreS1 and/or HDAg sequences were evaluated for induction of PreS1 antibodies and HBV- and HDV-specific T cells in vitro and in vivo. Neutralization of HBV by PreS1-specific murine and rabbit antibodies was evaluated in cell culture, and rabbit anti-PreS1

were tested for neutralization of HBV in mice repopulated with human hepatocytes. RESULTS: The best vaccine candidate induced T cells to PreS1 and HDAG, and PreS1 antibodies blocking HBV entry in vitro. Importantly, adoptive transfer of PreS1 antibodies prevented, or modulated, HBV infection after a subsequent challenge in humanized mice. CONCLUSIONS: We here describe a novel immunotherapy for chronic HBV/HDV that targets viral entry to complement NAs and coming therapies inhibiting viral maturation.

Liu Y, H Ruan, Y Li, G Sun, X Liu, W He, F Mao, M He, L Yan, G Zhong, H Yan, W Li and Z Zhang (2021). "[Potent and Specific Inhibition of NTCP-Mediated HBV/HDV Infection and Substrate Transporting by a Novel, Oral-Available Cyclosporine A Analogue.](#)" *J Med Chem* **64**(1): 543-565.

Analogues of the natural product cyclosporine A (CsA) were developed and assessed as antivirals against infection of hepatitis B virus (HBV) and its satellite hepatitis D virus (HDV). An analogue termed 27A exhibits potent inhibition of HBV/HDV infection by specifically blocking viral engagement to its cellular receptor NTCP, while it lacks immunosuppressive activity found in natural CsA. Intraperitoneal injection or oral intake of 27A protects HDV-susceptible mouse model from HDV infection. 27A serves as a promising lead for the development of novel anti-HDV/HDV agents.

Kirstgen M, K Lowjaga, SF Müller, N Goldmann, F Lehmann, D Glebe, KH Baringhaus and J Geyer (2021). "[Hepatitis D Virus Entry Inhibitors Based on Repurposing Intestinal Bile Acid Reabsorption Inhibitors.](#)" *Viruses* **13**(4).

Identification of Na(+)/taurocholate co-transporting polypeptide (NTCP) as high-affinity hepatic entry receptor for the Hepatitis B and D viruses (HBV/HDV) opened the field for target-based development of cell-entry inhibitors. However, most of the HBV/HDV entry inhibitors identified so far also interfere with the physiological bile acid transporter function of NTCP. The present study aimed to identify more virus-selective inhibitors of NTCP by screening of 87 propanolamine derivatives from the former development of intestinal bile acid reabsorption inhibitors (BARIs), which interact with the NTCP-homologous intestinal apical sodium-dependent bile acid transporter (ASBT). In NTCP-HEK293 cells, the ability of these compounds to block the HBV/HDV-derived preS1-peptide binding to NTCP (virus receptor function) as well as the taurocholic acid transport via NTCP (bile acid transporter function) were analyzed in parallel. Hits were subsequently validated by performing in vitro HDV infection experiments in NTCP-HepG2 cells. The most potent compounds S985852, A000295231, and S973509 showed in vitro anti-HDV activities with IC(50) values of 15, 40, and 70  $\mu$ M, respectively, while the taurocholic acid uptake inhibition occurred at much higher IC(50) values of 24, 780, and 490  $\mu$ M, respectively. In conclusion, repurposing of compounds from the BARI class as novel HBV/HDV entry inhibitors seems possible and even enables certain virus selectivity based on structure-activity relationships.

Hercun J, GE Kim, BL Da, Y Rotman, DE Kleiner, R Chang, JS Glenn, JH Hoofnagle, C Koh and T Heller (2021). "[Durable virological response and functional cure of chronic hepatitis D after long-term peginterferon therapy.](#)" *Aliment Pharmacol Ther.*

BACKGROUND: Hepatitis delta virus (HDV) infection is the most aggressive form of chronic viral hepatitis. Response rates to therapy with 1- to 2-year courses of pegylated interferon alpha (peginterferon) treatment are suboptimal. AIMS: To evaluate the long-term outcomes of patients with chronic hepatitis D after an extended course of peginterferon. METHODS: Patients were followed after completion of trial NCT00023322 and classified based on virological response defined as loss of detectable serum HDV RNA at last follow-up. During extended follow-up, survival and liver-related events were recorded. RESULTS: All 12 patients who received more than 6 months of peginterferon in the original study were included in this analysis. The cohort was mostly white (83%) and male (92%) and ranged in age from 18 to 58 years (mean = 42.6). Most patients had advanced but compensated liver disease at baseline, a median HBV DNA level of 536 IU per mL and median HDV RNA level of 6.86 log(10) genome equivalents per mL. The treatment duration averaged 6.1 years (range 0.8-14.3) with a total follow-up of 8.8 years (range 1.7-17.6). At last follow-up, seven (58%) patients had durable undetectable HDV RNA in serum, and four (33%) cleared HBsAg. Overall, one of seven (14%) responders died or had a liver-related event vs four of five (80%) non-responders. CONCLUSIONS: With further follow-up, an extended course of peginterferon therapy was found to result in sustained clearance of HDV RNA and favourable clinical outcomes in more than half of patients and loss of HBsAg in a third.

Graul AI and LA Sorbera (2021). "[The year's new drugs and biologics 2020.](#)" *Drugs Today (Barc)* **57**(2): 101-177. 2020 will go down in history as a year marked in every respect by the emergence and astonishingly rapid spread of the first major global viral pandemic in a century. It seems like nearly every event or story of

the year was influenced in some way by COVID-19, and in that respect, the year ended on a high note with the authorization for emergency use of the first vaccines to prevent SARS-CoV-2 infection and drugs to treat COVID-19. Despite the pandemic's dominance of the 2020 headlines, productivity was at a record high level across all therapeutic areas, as seen by the number of products in this year's review: approximately 50% more than the previous year. Notable achievements include the launch of the first treatment for hepatitis D; regulatory decisions on a suite of biologics for the prevention and treatment of Ebola virus disease, fruit of the 2016-2018 outbreak in the Democratic Republic of Congo; the approval of the first-ever drug to treat Hutchinson-Gilford progeria syndrome, a rare genetic disorder that leads to premature aging; the first treatment developed specifically for thyroid eye disease, also known as Graves' ophthalmopathy; the first nonhormonal, on-demand, vaginal pH-regulating contraceptive; and the first oral allergen immunotherapy for peanut allergy.

Dhillon S (2021). "[Lonafarnib: First Approval.](#)" *Drugs* **81**(2): 283-289.

Lonafarnib (Zokinvy™) is an orally active farnesyltransferase inhibitor developed by Eiger BioPharmaceuticals under license from Merck & Co. for the treatment of hepatitis D virus (HDV) infections, and progeria and progeroid laminopathies. The drug was originally discovered by Merck & Co as an investigational drug in oncology. In progeria, lonafarnib inhibits farnesyltransferase to prevent farnesylation and subsequent accumulation of progerin and progerin-like proteins in the nucleus and cellular cytoskeleton. In November 2020, lonafarnib received its first approval in the USA to reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS) and for the treatment of processing-deficient progeroid laminopathies (with either heterozygous LMNA mutation with progerin-like protein accumulation, or homozygous or compound heterozygous ZMPSTE24 mutations) in patients  $\geq 12$  months of age with a body surface area (BSA) of  $\geq 0.39$  m<sup>2</sup>. Lonafarnib is under regulatory review in the European Union. Clinical development for the treatment of HDV infections is underway in multiple countries. This article summarizes the milestones in the development of lonafarnib leading to this first approval.

Deterding K and H Wedemeyer (2021). "[\[New therapeutic options for hepatitis D\]](#)." *MMW Fortschr Med* **163**(12): 62-63.

Cheng D, B Han, W Zhang and W Wu (2021). "[Clinical effects of NTCP-inhibitor myrcludex B.](#)" *J Viral Hepat* **28**(6): 852-858.

With extensive research on the pathogenesis and treatment of hepatitis B virus (HBV) and hepatitis D virus (HDV) infections, the current treatment of interferon and nucleoside or nucleotide analogues provides reasonable control of viral replication in chronic hepatitis B (CHB). However, drug resistance may occur as a result of long-term treatment, and continuous covalently closed circular DNA (cccDNA) can cause disease relapse after drug withdrawal. Therefore, there is an urgent need for safe and effective antiviral drugs or methods to treat HBV and HDV infections. Myrcludex B is the first entry inhibitor that can inactivate HBV and HDV receptors, compete with HBV for the sodium-taurocholate co-transporting polypeptide, which has been identified as the bona fide receptor for HBV and HDV, block HBV infection in hepatocytes, and participate in HBV transcriptional suppression. Myrcludex B plays an important role in the inhibition of HBV replication and is a potential drug for phase III clinical trials. In this article, we review the progress on the efficacy and clinical application of myrcludex B in recent years.

Bremer B, OE Anastasiou, S Hardtke, FA Caruntu, MG Curescu, K Yalcin, US Akarca, S Gürel, S Zeuzem, A Erhardt, S Lüth, GV Papatheodoridis, M Radu, R Idilman, MP Manns, M Cornberg, C Yurdaydin and H Wedemeyer (2021). "[Residual low HDV viraemia is associated HDV RNA relapse after PEG-IFNa-based antiviral treatment of hepatitis delta: Results from the HIDIT-II study.](#)" *Liver Int* **41**(2): 295-299.

The role of low levels of HDV-RNA during and after interferon therapy of hepatitis D is unknown. We re-analysed HDV RNA in 372 samples collected in the HIDIT-2 trial (Wedemeyer et al, *Lancet Infectious Diseases* 2019) with the Robogene assay (RA; Jena Analytics). Data were compared with the previously reported in-house assay (IA). We detected HDV-RNA in one-third of samples previously classified as undetectable using the highly sensitive RA. Low HDV viraemia detectable at week 48 or week 96 was associated with a high risk for post-treatment relapse, defined as HDV RNA positivity in both assays at week 120. HDV RNA relapses occurred in 10/15 (67%) patients with detectable low HDV RNA at week 48 and in 10/13 (77%) patients with low viraemia samples at week 96. In contrast, the post-treatment relapse rate was lower in patients with undetectable HDV RNA in both assays during treatment.

Asselah T, D Loureiro, F Le Gal, S Narguet, S Brichler, V Bouton, M Abazid, N Boyer, N Giuly, A Gerber, I Tout, S Maylin, CM Bed, P Marcellin, C Castelnau, E Gordien and A Mansouri (2021). "[Early virological response in six patients with hepatitis D virus infection and compensated cirrhosis treated with Bulevirtide in real-life.](#)" *Liver Int* **41**(7): 1509-1517.

Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis. Bulevirtide (BLV, Hepcludex®) is an HDV/HBV entry inhibitor approved in June 2020 in the European Union for adult patients with chronic hepatitis delta (CHD) and compensated liver disease and positive HDV RNA viral load. This real-life preliminary report described early virological efficacy and safety of BLV in six patients with CHD and compensated liver disease: four patients were treated with the combination of BLV (2 mg/d in subcutaneous injection) and pegylated interferon (PEG-IFN) and two patients with BLV monotherapy. Four patients treated with combined therapy had a decline of a minimum of 1 log(10) and 3/3 of 2 log(10) of HDV-VL at 12 and 24 weeks, respectively. One patient among four had stopped the treatment at 12 weeks because of thrombocytopenia and an HDV-VL relapse was notified 24 weeks after treatment cessation. Three patients among four (3/4) had undetectable HDV-VL during the therapy (<100 IU/ml). One patient (1/2) treated with BLV monotherapy had a decline of HDV-VL by 1 log(10) at 8 weeks and 1/1 by 2 log(10) at 28 week on-treatment. Two patients among four (2/4) with combined therapy had normal ALT reached at 4 and 56 weeks. One patient (1/2) with BLV monotherapy achieves ALT normalization at 4 weeks on treatment. Hepatitis B surface antigen (HBsAg) levels remain unchanged. Three among six (3/6) patients had an elevation of total biliary acids without pruritus. These early data generated confirm the interest in this new treatment. Final results will be important to demonstrate long-term clinical benefit (fibrosis reversibility and reduction in hepato-cellular carcinoma [HCC]).

Anastasiou OE, C Yurdaydin, B Maasoumy, S Hardtke, FA Caruntu, MG Curescu, K Yalcin, US Akarca, S Gürel, S Zeuzem, A Erhardt, S Lüth, GV Papatheodoridis, M Radu, S Liebig, H Bantel, B Bremer, MP Manns, M Cornberg and H Wedemeyer (2021). "[A transient early HBV-DNA increase during PEG-IFN \$\alpha\$  therapy of hepatitis D indicates loss of infected cells and is associated with HDV-RNA and HBsAg reduction.](#)" *J Viral Hepat* **28**(2): 410-419.

HBV-DNA levels are low or even undetectable in the majority HDV-infected patients. The impact of PEG-IFN $\alpha$  on HBV-DNA kinetics in HDV-infected patients has not been studied in detail. We analysed data of a prospective treatment trial where 120 HDV-RNA-positive patients were randomized to receive PEG-IFN $\alpha$ -2a plus tenofovir-disoproxil-fumarate (PEG-IFN $\alpha$ /TDF, n = 59) or placebo (PEG-IFN $\alpha$ /PBO; n = 61) for 96 weeks. At week 96, HBV-DNA was still quantifiable in 71% of PEG-IFN $\alpha$ /PBO-treated patients but also in 76% of PEG-IFN $\alpha$ /TDF-treated patients, despite low HBV-DNA baseline values. Surprisingly, a transient HBV-DNA increase between weeks 12 and 36 was observed in 12 in PEG-IFN $\alpha$ /TDF-treated and 12 PEG-IFN $\alpha$ /PBO-treated patients. This increase was positively associated with HBsAg loss [(P = 0.049, odds ratio (OR) 5.1] and HDV-RNA suppression (P = 0.007, OR 4.1) at week 96. Biochemical markers of cell death (M30 and ALT) were higher during the HBV-DNA peak but no distinct systemic immune pattern could be observed by screening 91 soluble inflammatory markers. In conclusion, an early increase in HBV-DNA during PEG-IFN $\alpha$ -2a therapy occurred in more than 20% of patients, even in TDF-treated patients. This transient HBV-DNA rise may indicate PEG-IFN $\alpha$ -induced cell death and lead to long-term HDV-RNA suppression and HBsAg loss.

Abdrakhman A, A Ashimkhanova and WY Almawi (2021). "[Effectiveness of pegylated interferon monotherapy in the treatment of chronic hepatitis D virus infection: A meta-analysis.](#)" *Antiviral Res* **185**: 104995.

Chronic HDV infection often is associated with aggressive form of liver disease, compared to chronic HBV mono-infection. However, chronic HDV treatment is challenging because currently there is no approved regimen for affected patients. While standard interferon with/without nucleos(t)ide analogues were reported to be inferior to pegylated interferon (peginterferon) as HDV treatment according to few randomized clinical trials. This meta-analysis will summarize the results of studies on the effectiveness of peginterferon as HDV treatment regimen. An electronic search was performed using PubMed, Cochrane Library, Research Gate, and Medline databases. Studies involving patients who received peginterferon therapy for at least 48 weeks and followed up for 24 weeks post-therapy were included. All analyses were conducted using Review Manager 5.3 designed for Cochrane Reviews. The primary efficacy endpoint was virological response (VR) or HDV-RNA negativity at the end of the follow-up period, whereas secondary efficacy endpoints were biochemical response (BR) or ALT normalization and HBsAg clearance with seroconversion to anti-HBs at the end of follow-up period. Data were abstracted from 13 relevant studies with a total of 475 patients who were treated with peginterferon alpha-2a or -2b. At the end of 24-week post-treatment the pooled VR was achieved in 29% of patients with 95% CI [24%; 34%], BR was reached

in 33% of patients [95% CI 27%; 40%] and HBsAg clearance with seroconversion to anti-HBs was achieved in 1% of patients with 95% CI [-0.02; 0.05]. In conclusion, this study showed that peginterferon has limited effectiveness in HDV treatment, since only one-third of chronic HDV patients achieved viral clearance and normalized ALT levels. Moreover, HBsAg clearance with seroconversion to anti-HBs has been rarely observed among chronic HDV patients.

Zhang Z and S Urban (2020). "[Interplay between Hepatitis D Virus and the Interferon Response](#)." *Viruses* **12**(11).

Chronic hepatitis D (CHD) is the most severe form of viral hepatitis, with rapid progression of liver-related diseases and high rates of development of hepatocellular carcinoma. The causative agent, hepatitis D virus (HDV), contains a small (approximately 1.7 kb) highly self-pairing single-strand circular RNA genome that assembles with the HDV antigen to form a ribonucleoprotein (RNP) complex. HDV depends on hepatitis B virus (HBV) envelope proteins for envelopment and de novo hepatocyte entry; however, its intracellular RNA replication is autonomous. In addition, HDV can amplify HBV independently through cell division. Cellular innate immune responses, mainly interferon (IFN) response, are crucial for controlling invading viruses, while viruses counteract these responses to favor their propagation. In contrast to HBV, HDV activates profound IFN response through the melanoma differentiation antigen 5 (MDA5) pathway. This cellular response efficiently suppresses cell-division-mediated HDV spread and, to some extent, early stages of HDV de novo infection, but only marginally impairs RNA replication in resting hepatocytes. In this review, we summarize the current knowledge on HDV structure, replication, and persistence and subsequently focus on the interplay between HDV and IFN response, including IFN activation, sensing, antiviral effects, and viral countermeasures. Finally, we discuss crosstalk with HBV.

Wranke A, S Hardtke, B Heidrich, G Dalekos, K Yalçın, F Tabak, S Gürel, Y Çakaloğlu, US Akarca, F Lammert, D Häussinger, T Müller, M Wöbse, MP Manns, R Idilman, M Cornberg, H Wedemeyer and C Yurdaydin (2020). "[Ten-year follow-up of a randomized controlled clinical trial in chronic hepatitis delta](#)." *J Viral Hepat* **27**(12): 1359-1368.

Hepatitis delta virus (HDV) infection causes the most severe form of viral hepatitis. PEG-interferon alpha-2a (PEG-IFN $\alpha$ -2a) is the only effective treatment but its long-term clinical impact is unclear. The aim of this study was to investigate the long-term outcome after 48 weeks of pegylated interferon alpha-2a therapy. We performed a retrospective follow-up study of the Hep-Net-International-Delta-Hepatitis-Intervention-Study 1 (HIDIT-I trial). Patients had received 48 weeks of treatment with either PEG-IFN $\alpha$ -2a plus adefovir dipivoxil (ADV) (Group I), PEG-IFN $\alpha$ -2a alone (Group II) or adefovir dipivoxil alone (Group III). Liver-related complications were defined as liver-related death, liver transplantation, liver cancer and hepatic decompensation defined as development of Child-Pugh scores B or C or an increase in Model for End-stage Liver Disease (MELD) scores of five or more points in relation to baseline values. Patients were considered for further analysis when they were retreated with PEG-IFN $\alpha$ -2a. Follow-up data (at least 1 visit beyond post-treatment week 24) were available for 60 patients [Group I, (n = 19), Group II (n = 20), Group III (n = 21)]. Mean time of follow-up was 8.9 (1.6 - 13.4) years. 19 patients were retreated with IFN-based therapy: 42% (n = 8) in PEG-IFN $\alpha$ -2a arms and 58% (n = 11) in the adefovir only arm. Clinical complications on long-term follow-up occurred in 17 patients and were associated with nonresponse to therapy and baseline cirrhosis. The annual event-free survival rate in patients with cirrhosis vs noncirrhotic patients at year 5 and 10 was 70% vs 91% and 35% vs 76%. Long-term follow-up of a large randomized clinical trial suggests that off-treatment HDV RNA response to PEG-IFN $\alpha$ -2a treatment leads to improved clinical long-term outcome.

Usai C, S Maestro, G Camps, C Olague, L Suárez-Amaran, A Vales, T Aragon, M Hommel, R Aldabe and G Gonzalez-Aseguinolaza (2020). "[TNF-alpha inhibition ameliorates HDV-induced liver damage in a mouse model of acute severe infection](#)." *JHEP Rep* **2**(3): 100098.

BACKGROUND & AIMS: HDV infection induces the most severe form of human viral hepatitis. However, the specific reasons for the severity of the disease remain unknown. Recently, we developed an HDV replication mouse model in which, for the first time, liver damage was detected. METHODS: HDV and HBV replication-competent genomes and HDV antigens were delivered to mouse hepatocytes using adeno-associated vectors (AAVs). Aminotransferase elevation, liver histopathology, and hepatocyte death were evaluated and the immune infiltrate was characterized. Liver transcriptomic analysis was performed. Mice deficient for different cellular and molecular components of the immune system, as well as depletion and inhibition studies, were employed to elucidate the causes of HDV-mediated liver damage. RESULTS: AAV-mediated HBV/HDV coinfection caused hepatocyte necrosis and apoptosis. Activated T

lymphocytes, natural killer cells, and proinflammatory macrophages accounted for the majority of the inflammatory infiltrate. However, depletion studies and the use of different knockout mice indicated that neither T cells, natural killer cells nor macrophages were necessary for HDV-induced liver damage. Transcriptomic analysis revealed a strong activation of type I and II interferon (IFN) and tumor necrosis factor (TNF)- $\alpha$  pathways in HBV/HDV-coinfected mice. While the absence of IFN signaling had no effect, the use of a TNF- $\alpha$  antagonist resulted in a significant reduction of HDV-associated liver injury. Furthermore, hepatic expression of HDAg resulted in the induction of severe liver damage, which was T cell- and TNF- $\alpha$ -independent. CONCLUSIONS: Both host (TNF- $\alpha$ ) and viral (HDV antigens) factors play a relevant role in HDV-induced liver damage. Importantly, pharmacological inhibition of TNF- $\alpha$  may offer an attractive strategy to aid control of HDV-induced acute liver damage. LAY SUMMARY: Chronic hepatitis delta constitutes the most severe form of viral hepatitis. There is limited data on the mechanism involved in hepatitis delta virus (HDV)-induced liver pathology. Our data indicate that a cytokine (TNF- $\alpha$ ) and HDV antigens play a relevant role in HDV-induced liver damage.

Turon-Lagot V, A Saviano, C Schuster, TF Baumert and ER Verrier (2020). "[Targeting the Host for New Therapeutic Perspectives in Hepatitis D.](#)" *J Clin Med* **9**(1).

Hepatitis D virus (HDV) is a small satellite virus of hepatitis B virus (HBV) requiring HBV infection to complete its life cycle. It has been recently estimated that 13% of chronic HBV infected patients (60 million) are co-infected with HDV. Chronic hepatitis D is the most severe form of viral hepatitis with the highest risk to develop cirrhosis and liver cancer. Current treatment is based on pegylated-interferon-alpha which rarely controls HDV infection and is complicated by serious side effects. The development of novel antiviral strategies based on host targeting agents has shown promising results in phase I/II clinical trials. This review summarizes HDV molecular virology and physiopathology as well as new therapeutic approaches targeting HDV host factors.

Shekhtman L, SJ Cotler, L Hershkovich, SL Uprichard, M Bazinet, V Pantea, V Ceboatarescu, L Cojuhari, P Jimbei, A Krawczyk, U Dittmer, A Vaillant and H Dahari (2020). "[Modelling hepatitis D virus RNA and HBsAg dynamics during nucleic acid polymer monotherapy suggest rapid turnover of HBsAg.](#)" *Sci Rep* **10**(1): 7837.

Hepatitis D virus (HDV) requires hepatitis B surface antigen (HBsAg) for its assembly and release. Current HBV treatments are only marginally effective against HDV because they fail to inhibit HBsAg production/secretion. However, monotherapy with the nucleic acid polymer REP 2139-Ca is accompanied by rapid declines in both HBsAg and HDV RNA. We used mathematical modeling to estimate HDV-HBsAg-host parameters and to elucidate the mode of action and efficacy of REP 2139-Ca against HDV in 12 treatment-naive HBV/HDV co-infected patients. The model accurately reproduced the observed decline of HBsAg and HDV, which was simultaneous. Median serum HBsAg half-life ( $t(1/2)$ ) was estimated as 1.3 [0.9-1.8] days corresponding to a pretreatment production and clearance of  $\sim 10(8)$  [10(7.7)-10(8.3)] IU/day. The HDV-infected cell loss was estimated to be 0.052 [0.035-0.074] days<sup>-1</sup> corresponding to an infected cell  $t(1/2) = 13.3$  days. The efficacy of blocking HBsAg and HDV production were 98.2 [94.5-99.9]% and 99.7 [96.0-99.8]%, respectively. In conclusion, both HBsAg production and HDV replication are effectively inhibited by REP 2139-Ca. Modeling HBsAg kinetics during REP 2139-Ca monotherapy indicates a short HBsAg half-life (1.3 days) suggesting a rapid turnover of HBsAg in HBV/HDV co-infection.

Ongaro M, L Spahr, E Giostra and F Negro (2020). "[Efficacy of new therapies.](#)" *Rev Med Suisse* **16**(704): 1538-1543.

Hepatitis D virus causes chronic hepatitis D. The virus is defective, meaning it requires simultaneous presence of hepatitis B virus within the hepatocytes to complete its viral cycle. Globally, 15 to 20 millions people are estimated to be chronically co-infected by hepatitis B and D viruses. Current therapy remains limited to pegylated interferon alfa, which has an unsatisfactory success rate, several contraindications and many side effects. Drugs directly targeting the hepatitis D virus life cycle are being developed with promising results. These drugs target viral entry into hepatocytes, virion assembly or secretion from infected hepatocytes. This article provides an overview of the newly developed therapies and their efficacy.

Keskin O and C Yurdaydin (2020). "[LETTER TO THE EDITOR: Interferon is not an optimal treatment for chronic hepatitis delta but needs 'fair treatment' by us.](#)" *Hepatology*.

Kamal et al. assessed the impact of hepatitis D virus (HDV) viremia on liver related outcomes (1). The study reveals the real world situation of the management of chronic hepatitis D (CHD) in a country where

the disease is rare. Active viral replication was associated with liver related events in CHD. In their study, 108 patients received interferon (IFN) therapy, and 19 became HDV RNA negative at 24/48 week after IFN treatment. Viral response was not associated with lower risk of liver related events.

Jang TY, YJ Wei, CT Hsu, PY Hsu, TW Liu, YH Lin, PC Liang, MH Hsieh, YM Ko, YS Tsai, KY Chen, CC Lin, PC Tsai, SC Wang, CI Huang, ML Yeh, ZY Lin, SC Chen, WL Chuang, JF Huang, CY Dai, CF Huang and ML Yu (2020). "[Serial serologic changes of hepatitis D virus in chronic hepatitis B patients receiving nucleos\(t\)ides analogues therapy.](#)" *J Gastroenterol Hepatol* **35**(11): 1886-1892.

BACKGROUND AND AIM: The serial serologic changes of hepatitis D virus (HDV) infection among chronic hepatitis B virus (HBV) infected patients who received oral nucleotide/nucleoside analogues are elusive. METHODS: Serum anti-HDV and HDV RNA among chronic hepatitis B (CHB) patients were tested at the time of initiating anti-HBV therapy and subsequently during the follow-up period. RESULTS: The seropositive rate of anti-HDV and HDV RNA among 2850 CHB patients, was 2.7% and 0.9%, respectively. Factors associated with anti-HDV seropositivity were platelet counts (odds ratio [OR]/95% confidence intervals [CI]: 0.995/0.992-0.999; P = 0.006), HBV DNA levels (OR/CI: 0.81/0.70-0.94; P = 0.005), and hepatitis B e-antigen (HBeAg) seropositivity (OR/CI: 0.22/0.05-0.95; P = 0.04). The only factor associated with HDV RNA positivity among anti-HDV seropositive patients was age (OR/CI: 0.95/0.90-1.00; P = 0.03). The spontaneous clearance rate of serum anti-HDV antibody was 3.0 per 100 person-years with a median follow-up period of 3.5 years (range 2-12 years), whereas the seroclearance rate of HDV RNA was 4.3 per 100 person-years among anti-HDV seropositive patients after a median follow-up period of 6.0 years (range 2-11 years). A baseline anti-HDV titer < 0.5 cut-off index was the only factor predictive of anti-HDV seroclearance (hazard ratio [HR]/CI: 30.11/3.73-242.85; P = 0.001). CONCLUSIONS: HDV infection was not common among patients treated for HBV in Taiwan. Seroclearance of anti-HDV and HDV RNA did occur over time, albeit the chance is rare.

De Benedetto I, L Boglione, E Salvador, T Lupia, A De Nicolò, G Di Perri, F Lipani and AM Lucchini (2020). "[Plasmatic and intracellular concentration of entecavir during treatment of a symptomatic flare in HBV-HDV decompensated cirrhosis.](#)" *J Infect Public Health* **13**(2): 315-316.

Caviglia GP and M Rizzetto (2020). "[Treatment of hepatitis D: an unmet medical need.](#)" *Clin Microbiol Infect* **26**(7): 824-827.

BACKGROUND: Therapy of chronic hepatitis D (CHD) is still based on interferon alpha (IFN $\alpha$ ), introduced in clinical practice 30 years ago: results are modest and better therapies are an urgent medical need. AIMS: This article provides a critical overview of the new therapies under investigation for CHD. SOURCES: Review of the recently published medical literature. CONTENT: New therapeutic efforts aim to deprive the hepatitis D virus (HDV) of functions provided to its life cycle by the hepatitis B Virus (HBV) or by the host. Three therapeutic strategies are in evaluation: a) Myrcludex B, a myristolated lipopeptide of the pre-S1 domain of the HBsAg that blocks the entry of the HDV into hepatocytes and controls infection by preventing the spreading of the virus to liver cells not infected by the HBV; b) Lonafarnib, an inhibitor of a host farnesyl-transferase that hinders morphogenesis of the HDV by preventing the farnesylation of the large HD-antigen, necessary for virion assembly; c) REP 2139, a nucleic acid polymer that prevents export of the mature HDV by the presumed inhibition of the synthesis of subviral HBsAg particles with which the virion is coated. Myrcludex B and Lonafarnib increase therapeutic efficacy in combination with Peg-IFN $\alpha$ . In a pilot study, REP 2139 in combination with Peg-IFN $\alpha$  induced the clearance of serum HDV RNA and of the HBsAg in about half of 12 treated patients. IMPLICATIONS: Long-term therapies with either Myrcludex B or Lonafarnib in combination with Peg-IFN $\alpha$  are required to achieve clinical control of CHD. However, with prolonged therapies tolerance becomes a problem; studies are on the way to determine whether Peg-IFN lambda may be better tolerated than Peg-IFN $\alpha$ . The promising preliminary data of REP 2139 in combination with Peg-IFN $\alpha$  await confirmation of the original pilot study.

Burwitz BJ, Z Zhou and W Li (2020). "[Animal models for the study of human hepatitis B and D virus infection: New insights and progress.](#)" *Antiviral Res* **182**: 104898.

Hepatitis B virus (HBV) is a member of the Hepadnaviridae family and infects hepatocytes, leading to liver pathology in acutely and chronically infected individuals. Co-infection with Hepatitis D virus (HDV), which requires the surface proteins of HBV to replicate, can exacerbate this disease progression. Thus, the >250 million people living with chronic HBV infection, including 13 million co-infected with HDV, would significantly benefit from an effective and affordable curative treatment. Animal models are crucial to the development of innovative disease therapies, a paradigm repeated again and again throughout the fields

of immunology, neurology, reproduction, and development. Unfortunately, HBV has a highly-restricted species tropism, infecting limited species including humans, chimpanzees, and treeshrews. The first experimentally controlled studies of HBV infection were following inoculation of human volunteers in 1942, which identified the transmissibility of hepatitis through serum transfer and led to the hypothesis that the etiological agent was viral. Subsequent research in chimpanzees (Desmyter et al., 1971; Lichter, 1969) and later in other species, such as the treeshrews (Walter et al., 1996; Yan et al., 1996), further confirmed the viral origin of hepatitis B. Shortly thereafter, HBV-like viral infections were identified in woodchucks (Summers et al., 1978; Werner et al., 1979) and ducks, and much of our understanding of HBV replication can be attributed to these important models. However, with the exodus of chimpanzees from research and the limited reagents and historical data for treeshrews and other understudied species, there remains an urgent need to identify physiologically relevant models of chronic HBV infection. While large strides have been made in generating such models, particularly over the past two decades, there is still no available model that faithfully recapitulates the immunity and pathogenesis of HBV infection. Here, we discuss recent advancements in the generation of murine and non-human primate (NHP) models of HBV/HDV infection.

Broquetas T, M Garcia-Retortillo, M Micó, L Canillas, M Puigvehí, N Cañete, S Coll, A Viu, JJ Hernandez, X Bessa and JA Carrión (2020). "[Hepatitis B surface antigen and hepatitis B core-related antigen kinetics after adding pegylated-interferon to nucleos\(t\)ids analogues in hepatitis B e antigen-negative patients.](#)" *World J Hepatol* **12**(11): 1076-1088.

**BACKGROUND:** Hepatitis B e antigen-negative chronic hepatitis B patients under nucleos(t)ids analogues (NAs) rarely achieve hepatitis B surface antigen (HBsAg) loss. **AIM:** To evaluate if the addition of pegylated interferon (Peg-IFN) could decrease HBsAg and hepatitis B core-related antigen (HBcrAg) levels and increase HBsAg loss rate in patients under NAs therapy. **METHODS:** Prospective, non-randomized, open-label trial evaluating the combination of Peg-IFN 180 µg/week plus NAs during forty-eight weeks vs NAs in monotherapy. Hepatitis B e antigen-negative non-cirrhotic chronic hepatitis B patients of a tertiary hospital, under NAs therapy for at least 2 years and with undetectable viral load, were eligible. Patients with hepatitis C virus, hepatitis D virus or human immunodeficiency virus co-infection and liver transplanted patients were excluded. HBsAg and HBcrAg levels (log<sub>10</sub> U/mL) were measured at baseline and during ninety-six weeks. HBsAg loss rate was evaluated in both groups. Adverse events were recorded in both groups. The kinetic of HBsAg for each treatment group was evaluated from baseline to weeks 24 and 48 by the slope of the HBsAg decline (log<sub>10</sub> IU/mL/week) using a linear regression model. **RESULTS:** Sixty-five patients were enrolled, 61% receiving tenofovir and 33% entecavir. Thirty-six (55%) were included in Peg-IFN-NA group and 29 (44%) in NA group. After matching by age and treatment duration, baseline HBsAg levels were comparable between groups (3.1 vs 3.2) (P = 0.25). HBsAg levels at weeks 24, 48 and 96 declined in Peg-IFN-NA group (-0.26, -0.40 and -0.44) and remained stable in NA group (-0.10, -0.10 and -0.10) (P < 0.05). The slope of HBsAg decline in Peg-IFN-NA group (-0.02) was higher than in NA group (-0.00) (P = 0.015). HBcrAg levels did not change. Eight (22%) patients discontinued Peg-IFN due to adverse events. The HBsAg loss was achieved in 3 (8.3%) patients of the Peg-IFN-NA group and 0 (0%) of the NA group. **CONCLUSION:** The addition of Peg-IFN to NAs caused a greater and faster decrease of HBsAg levels compared to NA therapy. Side effects of Peg-IFN can limit its use in clinical practice.

Bhuvu M, M Moore and S Sen (2020). "['Double-hit' pegylated interferon-alpha successfully treats Hepatitis B and Hepatitis D co-infection.](#)" *Oxf Med Case Reports* **2020**(10): omaa084.

Hepatitis delta (HDV) infection is either acquired simultaneously with, or as a superinfection to, existing Hepatitis B (HBV). It leads to a serious form of chronic viral hepatitis and accelerated liver-related morbidity and mortality including hepatocellular carcinoma. Current treatment regimes propose Pegylated interferon-alpha for 48 weeks however sustained virological response (SVR) rates remain low. We report a patient who initially responded to Pegylated interferon treatment for HBV-HDV co-infection. Although initial improvement in viraemia from both viruses was seen, SVR was not achieved with ongoing progression of liver injury biochemically. However, the summative effect of a second course of Pegylated interferon 2 years later led to HDV cure (SVR 12 months post-treatment), very low level HBV carrier status (with persistently undetectable viral load) and ongoing biochemical normalization. This case illustrates a successful treatment strategy for persistent HBV-HDV co-infection where proposed treatment regimes elicit an initial response but SVR is not achieved.

Abbas Z, M Saad, M Asim, M Abbas and SA Samejo (2020). "[The effect of twelve weeks of treatment with ezetimibe on HDV RNA level in patients with chronic hepatitis D.](#)" *Turk J Gastroenterol* **31**(2): 136-141.

BACKGROUND/AIMS: Sodium taurocholate co-transporting polypeptide (NTCP) is the receptor for the hepatitis B virus (HBV) and hepatitis D virus (HDV) entry into hepatocytes. Ezetimibe is a cholesterol-lowering drug that possesses the pharmacophore features to inhibit NTCP. This study evaluates the efficacy of ezetimibe in patients with chronic HDV infection in a nonrandomized trial. MATERIALS AND METHODS: This proof of concept phase 2 trial evaluated the efficacy and safety of ezetimibe 10 mg daily in (interferon treatment-experienced or interferon ineligible) patients with chronic hepatitis D (CHD). Forty-four patients with CHD were recruited, 38 male and 6 female patients, mean age  $35.2 \pm 8.7$  (range 19-64). Fifteen (34%) patients were on concomitant nucleoside therapy, and cirrhosis was present in 14 subjects. The primary therapeutic endpoint was a decline in HDV RNA at one log or more from the baseline at week 12. RESULTS: The mean HDV RNA level was  $5.4 \pm 1.3 \log_{10}$  IU/mL. HBeAg was non-reactive in 43 (98%). HBV DNA was undetectable in 28 (64%). One patient stopped treatment at week 4, and one patient did not follow-up. One log or more reduction in the HDV RNA levels was observed in 18/44 (41%) patients. No log reduction occurred in 16 patients, and 8 experienced a log increase. No adverse effects from the concomitant nucleoside analogue use or clinical cirrhosis were observed. The drug exhibited a positive safety profile. CONCLUSION: Treatment of CHD patients with ezetimibe resulted in a one log reduction of viral load in 43% (18/42) of the patients who completed the 12 weeks of therapy.

World hepatitis alliance – [Combination therapies show promise against hepatitis D](#) (2019)

## Hepatitis Delta infection in risk groups

**HIV** - Shen DT, PC Han, DZ Ji, HY Chen, WD Cao, H Goyal and HG Xu (2021). "[Epidemiology estimates of hepatitis D in individuals co-infected with human immunodeficiency virus and hepatitis B virus, 2002-2018: A systematic review and meta-analysis.](#)" *J Viral Hepat* **28**(7): 1057-1067.

Hepatitis delta virus (HDV) is an obligate satellite of hepatitis B virus (HBV). HIV/HDV co-infection is associated with a high rate of hepatic decompensation events and death. We aimed to characterize the epidemiology of HDV infection in HIV/HBV co-infected individuals. We systematically searched PubMed, Embase, Cochrane Library, Web of Science, CINAHL and Scopus for studies published from 1 Jan 2002 to 7 May 2018 measuring prevalence of HDV among the HIV population. Pooled seroprevalence was calculated with the DerSimonian-Laird random-effects model. Our search returned 4624 records, 38 of which met the inclusion and exclusion criteria. These studies included data for 63 cohorts from 18 countries and regions. The overall HDV seroprevalence of HIV-infected individuals was 1.03% (95% CI 0.43-1.85) in 2002-2018 globally. Moreover, the estimated pooled HDV seroprevalence among the general population was 1.07% (95% CI 0.65-1.59) in 2002-2018, which was not significantly different from the HDV seroprevalence of individuals living with HIV ( $p = 0.951$ ). The overall HDV seroprevalence of the HBsAg positive population was 12.15% (95% CI 10.22-14.20),  $p = 0.434$  when compared with the corresponding data of HIV/HBV co-infected individuals. This meta-analysis suggested that there was no difference between the HDV seroprevalence in HIV-infected individuals and the general population.

**PWID** - Lu MY, CT Chen, YL Shih, PC Tsai, MH Hsieh, CF Huang, ML Yeh, CI Huang, SC Wang, YS Tsai, YM Ko, CC Lin, KY Chen, YJ Wei, PY Hsu, CT Hsu, TY Jang, TW Liu, PC Liang, MY Hsieh, ZY Lin, SC Chen, JF Huang, CY Dai, WL Chuang, ML Yu and WY Chang (2021). "[Changing epidemiology and viral interplay of hepatitis B, C and D among injecting drug user-dominant prisoners in Taiwan.](#)" *Sci Rep* **11**(1): 8554.

The spreading of viral hepatitis among injecting drug users (IDU) is an emerging public health concern. This study explored the prevalence and the risks of hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) among IDU-dominant prisoners in Taiwan. HBV surface antigen (HBsAg), antibodies to HCV (anti-HCV) and HDV (anti-HDV), viral load and HCV genotypes were measured in 1137(67.0%) of 1697 prisoners. 89.2% of participants were IDUs and none had HIV infection. The prevalence of HBsAg, anti-HCV, dual HBsAg/anti-HCV, HBsAg/anti-HDV, and triple HBsAg/anti-HCV/anti-HDV was 13.6%, 34.8%, 4.9%, 3.4%, and 2.8%, respectively. HBV viremia rate was significantly lower in HBV/HCV-coinfected than HBV mono-infected subjects (66.1% versus 89.9%, adjusted odds ratio/95% confidence intervals [aOR/CI] = 0.27/0.10-0.73). 47.5% anti-HCV-seropositive subjects ( $n = 396$ ) were non-viremic, including 23.2% subjects were antiviral-induced. The predominant HCV genotypes were genotype 6(40.9%), 1a(24.0%) and 3(11.1%). HBsAg seropositivity was negatively correlated with HCV

viremia among the treatment naïve HCV subjects (44.7% versus 72.4%, aOR/CI = 0.27/0.13-0.58). Anti-HCV seropositivity significantly increased the risk of anti-HDV-seropositivity among HBsAg carriers (57.1% versus 7.1%, aOR/CI = 15.73/6.04-40.96). In conclusion, IUDs remain as reservoirs for multiple hepatitis viruses infection among HIV-uninfected prisoners in Taiwan. HCV infection increased the risk of HDV infection but suppressed HBV replication in HBsAg carriers. An effective strategy is mandatory to control the epidemic in this high-risk group.

**Sports** - McGrew C, DS MacCallum, D Narducci, R Nuti, L Calabrese, R Dimeff, S Paul, SK Poddar, A Rao and D McKeag (2020). "[AMSSM Position Statement Update: Blood-Borne Pathogens in the Context of Sports Participation](#)." *Clin J Sport Med* **30**(4): 283-290.

This AMSSM position statement update is directed toward health care providers of patients involved in sport and exercise. There have been significant advances in clinical and scientific research in the understanding of blood-borne pathogens (BBPs), and this update incorporates these advancements. This document is intended as a general guide to clinical practice based on the current state of evidence, while acknowledging the need for modification as new knowledge becomes available. Confirmed transmission of BBPs during sport is exceedingly rare. There are no well-documented reports of HIV, hepatitis C virus, or hepatitis D virus transmission during sport. There is also no evidence for universal testing for BBPs as a specific requirement for participation in sports. Competitive athletes and nonathletes should follow appropriate general public health agency recommendations for screening for BBPs, considering their individual risk factors and exposures. Standard (universal) precautions must be followed by those providing care to athletes. Exercise and athletic participation can help promote a healthy lifestyle for persons living with BBPs. Those with acute symptomatic BBP infection should limit exercise intensity based on their current health status. Education is the key tool for preventing BBP transmission. Research gaps include evaluation of the prevalence of BBP infections in competitive athletes, the effects of long-term, intense training on infected athletes, and the effects of BBP treatment therapies on performance.

**HIV** - Ferrante ND and V Lo Re, 3rd (2020). "[Epidemiology, Natural History, and Treatment of Hepatitis Delta Virus Infection in HIV/Hepatitis B Virus Coinfection](#)." *Curr HIV/AIDS Rep* **17**(4): 405-414.

PURPOSE OF REVIEW: Limited data exist on the prevalence, determinants, and outcomes of hepatitis delta virus (HDV) infection among HIV/hepatitis B virus (HBV)-coinfected persons. This review provides current evidence on the epidemiology, natural history, and treatment of HDV infection in patients with HIV/HBV coinfection and highlights future research needs. RECENT FINDINGS: Cross-sectional studies in Europe, Africa, South America, and Asia show that the prevalence of HDV among HIV/HBV-coinfected patients ranges from 1.2 to 25%. No studies have evaluated the prevalence of HDV infection among HIV/HBV-coinfected patients in the USA. HDV infection increases the risk of hepatic decompensation and hepatocellular carcinoma among HIV/HBV-coinfected patients. HDV treatment remains limited to pegylated interferon-alpha, which results in sustained virologic response in fewer than 25%. Data on the epidemiology, natural history, and treatment of HDV among HIV/HBV-coinfected persons remain limited. More research is needed to address these knowledge gaps in order to better manage HDV coinfection in HIV/HBV-coinfected patients.

**HCV** - Cappy P, Q Lucas, N Kankarafou, C Sureau and S Laperche (2021). "[No Evidence of Hepatitis C Virus \(HCV\)-Assisted Hepatitis D Virus Propagation in a Large Cohort of HCV-Positive Blood Donors](#)." *J Infect Dis* **223**(8): 1376-1380.

A study reported in 2019 showed that hepatitis C virus (HCV) could help disseminate hepatitis D virus (HDV). To test this finding, 2123 plasma samples positive for anti-HCV antibody were screened for anti-HDV antibodies, and HDV-RNA was searched for in samples positive for anti-HDV antibody. Of 41 samples (1.9%) that tested positive for anti-HDV antibody, 27 (65.9%) were positive and 14 (34.1%) negative for antibody to hepatitis B core antigen (anti-HBc). Anti-HDV antibodies were significantly more present in samples positive for anti-HBc (6.21% vs 0.8% in negative samples;  $P < .001$ ) and in samples negative for HCV RNA (2.9% vs 1.5% for positive samples;  $P = .03$ ). Serological ratios were significantly higher in samples positive for anti-HBc ( $P < .01$ ). No anti-HDV-positive sample was HDV RNA positive. In conclusion, this study found no evidence suggesting a role for HCV in HDV dissemination in humans.

## Hepatitis Delta during pregnancy

Terrault NA, MT Levy, KW Cheung and G Jourdain (2021). "[Viral hepatitis and pregnancy.](#)" *Nat Rev Gastroenterol Hepatol* **18**(2): 117-130.

The management of viral hepatitis in the setting of pregnancy requires special consideration. There are five liver-specific viruses (hepatitis A, B, C, D, E), each with unique epidemiology, tendency to chronicity, risk of liver complications and response to antiviral therapies. In the setting of pregnancy, the liver health of the mother, the influence of pregnancy on the clinical course of the viral infection and the effect of the virus or liver disease on the developing infant must be considered. Although all hepatitis viruses can harm the mother and the child, the greatest risk to maternal health and subsequently the fetus is seen with acute hepatitis A virus or hepatitis E virus infection during pregnancy. By contrast, the primary risks for hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus are related to the severity of the underlying liver disease in the mother and the risk of mother-to-child transmission (MTCT) for HBV and HCV. The prevention of MTCT is key to reducing the global burden of chronic viral hepatitis, and prevention strategies must take into consideration local health-care and socioeconomic challenges. This Review presents the epidemiology of acute and chronic viral hepatitis infection in pregnancy, the effect of pregnancy on the course of viral infection and, conversely, the influence of the viral infection on maternal and infant outcomes, including MTCT.

Chilaka VN and JC Konje (2021). "[Viral Hepatitis in pregnancy.](#)" *Eur J Obstet Gynecol Reprod Biol* **256**: 287-296.

The global prevalence of viral hepatitis is very high and seems to be rising over the years. The infection can profoundly affect pregnant women causing significant maternal and perinatal morbidity and mortality with some strains much worse than others. Hepatitis A (HAV) and E (HEV) which are transmitted mainly through the faecal-oral route present as acute hepatitis during pregnancy and are responsible for most local epidemic outbreaks. HAV infection remains self-limiting during pregnancy, while HEV has a higher prevalence and causes significant morbidity. It is also associated with a very high maternal mortality rate (20 %) and requires special attention in endemic areas. HEV vaccines do exist, but the WHO has yet to approve them for general use. Hepatitis B is the most prevalent form and is part of the antenatal screening program. The presence of HBeAg is associated with high viral loads and infectivity. Antiviral therapy, preferably tenofovir (TDF), is recommended for mothers with viral load  $\geq 200,000$  IU/mL(2), with the neonates receiving both active and passive immunisations. Hepatitis C and D are usually found as chronic infections in the pregnant and non-pregnant populations. Screening for hepatitis C during pregnancy and its subsequent management is still unsettled, but the introduction of direct-acting antiviral (DAA) drugs will change the picture if their safety is established in pregnancy. HDV is an incomplete virus linked to HBV and cannot establish an infection on its own. Controlling HBV is paramount to controlling HDV. HEV is quite prevalent and looked upon as hepatotropic. It seems to be quite prevalent in some blood donor populations and has a high co-infection rate with HCV. It has a high Mother-to-Child-Transmission (MTCT) but causes little or no illness in infected infants, and antenatal screening is not justified. This review summarises the prevalence, clinical picture, maternal, perinatal effects, and the management and prevention of hepatitis A, B, C, D, E and G viral infections during pregnancy.

Seto MT, KW Cheung and IFN Hung (2020). "[Management of viral hepatitis A, C, D and E in pregnancy.](#)" *Best Pract Res Clin Obstet Gynaecol* **68**: 44-53.

Viral hepatitis can cause significant maternal and neonatal morbidity and mortality. Hepatitis A and E mainly present as acute hepatitis during pregnancy, while hepatitis C and D are usually found as chronic infection in pregnant women. Hepatitis A remains self-limiting during pregnancy while hepatitis E has a higher prevalence and manifests with a rigorous course in pregnant women. Screening of hepatitis C during pregnancy and its subsequent management during pregnancy are still a debatable topic. New treatments of hepatitis C and E require further evaluation for use in pregnancy. This review summarizes the prevalence, clinical manifestations, maternal, foetal and neonatal effects, and the management of hepatitis A, C, D and E viral infection during pregnancy.

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