

# The changing context of hepatitis D

Virtual meeting  
*28 and 29 October 2021*

*Day 1*

# Objectives

- Provide an overview of the current epidemiology of hepatitis D and discuss potential associated risk factors (e.g. HIV infection and immigration from endemic countries)
- Review diagnostic tools and screening recommendations for hepatitis D
- *Examine the prevention, treatment and control of hepatitis D*
- *Discuss the public health impact of hepatitis D and the arguments for its inclusion in WHO's elimination goals*
- in all, consider relevant hepatitis B-related issues

# Hepatitis D virus

- Small RNA virus with circular single-stranded RNA genome that replicates in the nucleus of hepatocytes; it is packaged with the envelope protein of HBV which enables binding to the same receptor on liver cells as HBV.
- Partial and complete genomic sequences are collected in a new, regularly updated comprehensive database.\*
- Highly heterogeneous; eight genotypes broadly distributed globally, genotypes 5-8 have recently been imported into Western countries from central and western Africa. In vitro, different genotypes replicate with different efficacies.
- *Coinfection and superinfection*; coinfection rarely leads to chronic infection whereas superinfection does result in chronic infection, with accelerated progression to liver disease and hepatocellular carcinoma and the most severe forms of liver disease although milder clinical forms of disease are also seen.

\* [hdvdb.bio.wzw.tum.de](http://hdvdb.bio.wzw.tum.de)

# Epidemiology and disease burden

- HDV infection and disease - largely both underestimated and underdiagnosed, and impact on public health not well understood.
- Vanishing but not vanished (or vanquished): increasing coverage of hepatitis B vaccination diminishing prevalence rates of HDV infection.
- But, still some 257-296 million people with chronic hepatitis B (WHO) – how many are coinfecting with HDV? Estimates: about 13 million people globally infected with HDV (WHO, 2016); other sources indicate 12 million people with anti-HDV antibodies (rates ranging from 3% in Europe and Asia to 6% in Africa and the Americas), 15-20 million or even 48 million. Reported rates vary according to the test used.
- Risk factors: HIV infection, HCV, MSM and PWID and living in endemic countries. Men are at higher risk than women.
- Dual clinical patterns: little change over time in endemic countries, although association is seen with HBeAg-negative HBV infection; in the West changed pattern - patients are either older with advanced fibrosis or, increasingly, immigrants from endemic countries.

# Epidemiology and disease burden (continued)

- Persistent HDV replication more than doubles the rate of progression to liver disease; HDV RNA is an additional risk factor for progression, possibly accounting for 20% for HCC in cirrhotic patients.
- Attributable fraction of HDV to HCC is unknown, but appears to be significant (e.g. in Mongolia and other countries in central Asia) but chronic hepatitis D poses a significant risk of HCC.
- How much disease that is thought to be caused by HBV is actually due to HDV? Are flares in CHB actually hepatitis D?
- Asymptomatic HBV-HDV carriers may exist. Some instances of HBV-negative but HDV-positive cases have been seen.

# Epidemiology and disease burden: country examples

## France

- A few studies but growing interest, with specialist centres; low prevalence reported - with rates range from 2% in blood donors and 3.7% in new HBV-positive patients to 12.6% in HIV-coinfected subjects.
- A nationwide multicentre study found that most cases of HDV infection were in immigrants, mainly from countries in sub-Saharan Africa or southern and eastern Europe; most were due to genotypes 1 and 5. Risk factors included injecting drug use.

## Germany

- A broad systematic literature review was undertaken to support a national strategy on meeting the 2030 elimination goals for viral hepatitis, but only scarce data on HDV. Low prevalence rates - 1.2% for blood donors and 1.45% for the general population but higher in at-risk populations. Most infected subjects were foreign (origins include Eastern Europe), with more men than women and average age of 37 years. The number of notified cases has increased over the past 20 years. The picture remains incomplete.

# Country examples (continued)

## Georgia

- Although HBV prevalence is rated intermediate to high, data are poor for HDV (and unreliable for determining trends). Knowledge of viral hepatitis generally in the general population is low, and HBV vaccination rates are low, although there is a well-supported national viral hepatitis elimination programme.
- The estimated prevalence of HDV coinfection (RNA-positive) is 0.9%; all cases (mostly men with compensated liver disease) have been due to genotype 1.
- Risk factors include HBsAg positivity, a history of blood transfusion, incarceration and injecting drug use as well as inadequate infection control.
- Challenges include lack of standardization of international HDV management guidelines, unaffordability of new treatments, no access to clinical trials and no financial support from the State or private insurance companies.

# Treatment

[Reference made to variable responses to pegylated IFN, but more information on that and new treatments today.]

# Diagnostic tools and screening

- General lack of reliable tools for diagnosis or detection of markers of HDV infection, although some sensitive assays are available – e.g. qualitative PCR tests, antibody ELISAs, and quantitative microarray antibody capture (Q-MAC) assay. Most available assays underestimate or fail to measure viral load; EuroBioPlex shows promise.
- Standardization of diagnostic tests is needed, together with new tests. They should be optimized not only for genotypes but for genotype subtypes.
- Diagnostic algorithms would be useful, starting with a positive result for HBV infection and for symptomless HBV carriers. The Russian Federation has changed its clinical guidelines for HDV; testing for HDV is mandatory in all cases of HBsAg-positive tests irrespective of clinical presentation.
- Screening is insufficient and, in some countries (e.g. Greece), declining. Few Caucasians, people with HCV or HIV infection are screened for HDV; higher but still low rates are reported for other ethnic groups. Testing rates in lower- and middle-income countries and outside tertiary centres are low. Some maintain that low prevalence rates argue against screening, but how accurate is it to say “low prevalence”?
- Advent of new treatments will provide an additional reason for screening.

# Policy responses

- Generally unremarkable: hepatitis D is scantily covered by WHO's global health sector strategy for viral hepatitis for 2016-2021 – maybe it will be included in the strategy for 2022-2030 and the updated European Action Plan, which are being developed (the ongoing consultation processes offer opportunities for advocacy). Hepatitis D does not feature among the elimination targets for 2030.
- Academic research now accelerating from low levels, with focus on epidemiology, disease burden, new diagnostic tools, medicines and public health approaches
- The European Association for the Study of the Liver (EASL) and AASLD have issued guidelines on HDV management and testing; AASLD recommends testing those at high-risk. EASL is drafting recommendations for the treatment of hepatitis D and for testing all HBsAg-positive people for anti-HDV.

# Issues and needs

- Poor awareness of or knowledge about hepatitis D at clinical, medical, scientific, political and general population levels.
- Poor or lacking data, often old and not updated, result in underestimation of prevalence rates; many studies are small and limited (geographically and scope) and focus on patients with advanced liver disease or at high-risk; denominators are varied (general population or HBsAg-positive cases); not all antibody-positive subjects have active HDV-related liver damage; temporal data (trends) are few.
- These weaknesses translate into needs: more and better designed studies; representative studies; definition of parameters and their behaviour (e.g. the probability of finding HDV antibodies at all stages of the clinical spectrum is low); standardized sera and materials; better data on everything from epidemiology (including genotype-specific data) to antiviral agents in the development pipeline, and the possible links between HDV genotypes or subtypes with clinical outcome are needed. Methods for determining prevalence rates need to be standardized or better defined. The attributable fraction of HDV to cirrhosis and HCC needs to be ascertained (estimated at 20% in one study).

# Issues and needs (continued)

- Commercial, inhouse and new diagnostic tests need to be developed and standardized (for instance, PCR tests for genotypes). Staging liver fibrosis: no reliable non-invasive tests; the delta fibrosis score, a promising test, being developed and tested.
- Needs include developing and support for networks.
- Consensus on nomenclature of subtypes of HDV.
- A strong message was that every new diagnosis of a case of HBV infection should be, as a reflex, tested for HDV.