Hepatitis D

Dr.Hamid Ghorbani
M.D.Infectious disease specialist

ACECR Hepatitis Clinic, Mashhad, Khorasan Razavi, Iran

HEPATITIS DELTA VIRUS

Delta agent was identified by Mario Rizzetto in 1977 as a nuclear antigen distinct from HBsAg, HBcAg, and HBeAg in hepatocytes of some HBsAg carriers in Italy.

It soon became clear that this passenger virus, termed hepatitis D virus (HDV), accompanied HBV infection and required the HBsAg for transmission.

This unique HDV RNA genome resembles plant pathogens. HDV is the only member of the genus Deltavirus.

In nature, HDV is only found in patients who are also infected with HBV,woodchucks and Chimpanzees.

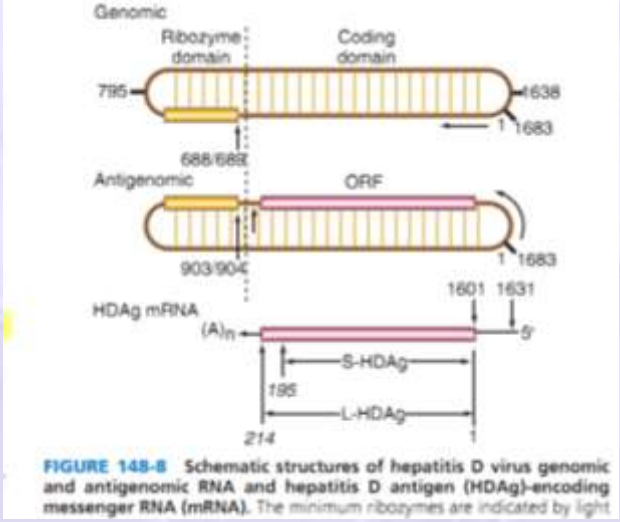


FIGURE 148-8 Schematic structures of hepatitis D virus genomic and antigenomic RNA and hepatitis D antigen (HDAg)-encoding messenger RNA (mRNA). The minimum ribozymes are indicated by light

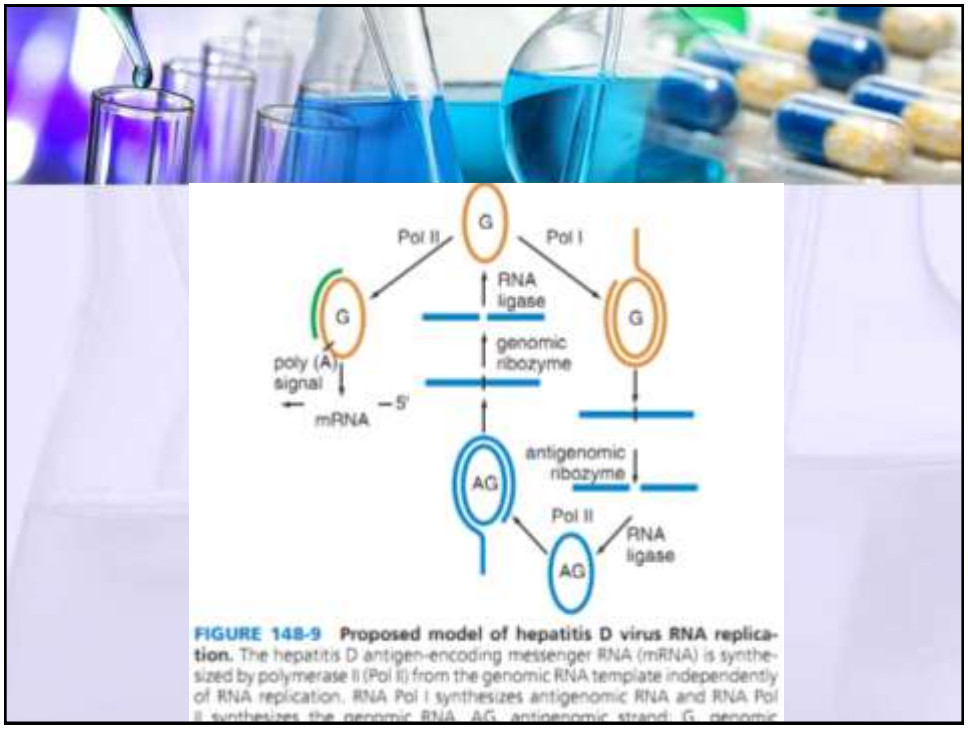


FIGURE 148-9 Proposed model of hepatitis D virus RNA replication. The hepatitis D antigen-encoding messenger RNA (mRNA) is synthesized by polymerase II (Pol II) from the genomic RNA template independently of RNA replication. RNA Pol I synthesizes antigenomic RNA and RNA Pol II synthesizes the genomic RNA. AG, antigenomic strand; G, genomic

Hepatitis D infection

Caused by a defective virus, the hepatitis D virus

Closely associated with HBV infection

Leads to more severe liver disease than chronic HBV mono-infection

No vaccine is available for HDV, but the hepatitis B virus (HBV) vaccination is effective against HDV

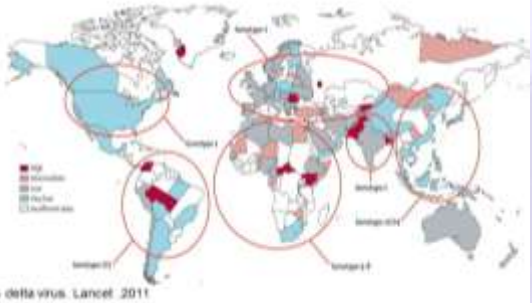
The only form of chronic viral hepatitis for which there is not an established treatment

Is associated with

- an accelerated course of fibrosis progression
- an increased risk of hepatocellular carcinoma
- early decompensation in the setting of cirrhosis.

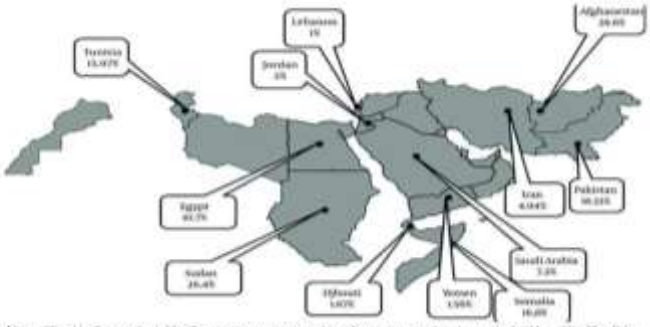
Epidemiology

- Of the 350 million chronic carriers of HBV, more than 15 million have serological evidence of exposure to HDV
- High rates of HDV carriage
  - Central Africa, The Horn of Africa,
  - The Amazon Basin, Eastern and Mediterranean Europe,
  - The Middle East and Parts of Asia



Hughes SA, et al. Hepatitis delta virus. Lancet. 2011

- Afghanistan, Yemen, Pakistan, Egypt are high endemicity for HDV infection
- Many patients are undiagnosed and Checking HDV ab is recommended in HBV patients with flare up during treatment or with low HBV DNA and High level of ALT



Amini N et al. Prevalence of hepatitis d in the eastern Mediterranean region: systematic review and meta analysis. Hepatitis Monthly.

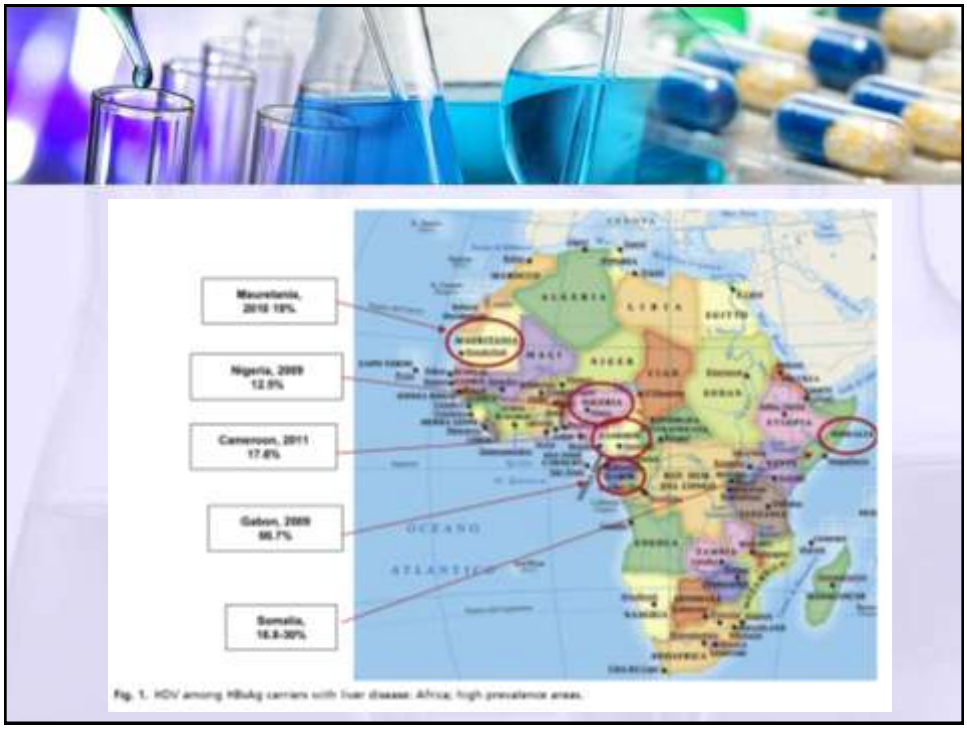
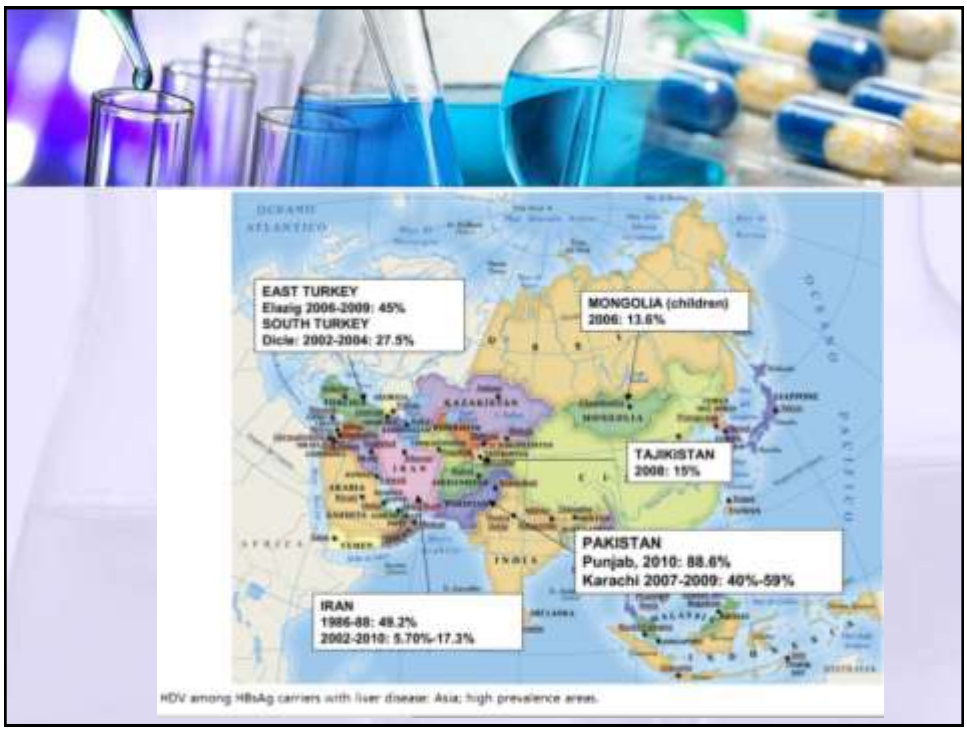


Fig. 1. HDV among HBsAg carriers with liver disease: Africa; high prevalence areas.



HDV among HBsAg carriers with liver disease: Asia; high prevalence areas.

Prevalence in iran

- The pooled HDV prevalence was 7.8% (95% CI: 5.89 - 9.71).
- The prevalence of HDV is less common in Iran than in endemic regions such as Italy and Turkey.
- The most probable route of HDV transmission is hematologic.

Prevalence in Mashhad

- -prevalence in chronic hepatitis B patients:10%
- prevalence in chronic hepatitis B patients with chronic liver disease and cirrhosis:14.2%
- Risk factors:1-transfusion 2-positive family history

Pathogenesis

- HDAg is the only viral protein known to be expressed during HDV infection.
- A high titer of IgM anti-HDV is strongly associated with elevated hepatitis D viremia and the severity of liver injury, whereas a more favorable course to HDV infection is found in individuals with IgG anti-HDV.
- There is no convincing evidence of a protective role of anti-HDV antibodies.

- The mechanisms of liver damage in HDV infection are unclear.
- The adaptive immune response plays an important role in pathogenesis and control of HDV infection, but the precise mechanisms are unknown.
- The presence of HDV-specific T-cell responses correlates with lower ALT levels, suggesting that immune control of viral replication leads to lesser degrees of liver injury.
- The immune response contributes to hepatocellular injury.

Clinical Manifestations

- HDV is spread by blood, blood products, and bodily secretions similar to HBV.
- Following exposure, there is a short incubation period of 3 to 7 weeks.

Acute coinfection with HBV

- 1- **biphasic pattern of ALT levels :** Usually the first episode
- is due to hepatitis B replication and immune response, followed by that of hepatitis D.
- **2-An acute self-limited hepatitis** with complete recovery, similar to other viral hepatitis infections, and chronic infection is seen in only 2%.
- **3-severe or fulminant hepatitis is rare**.

Acute superinfection with HBV

- 1-Severe hepatitis
- 2-Short incubation period
- **3-Chronic hepatitis D in 90**% of the cases.
- 4-Fulminant hepatitis and chronic active hepatitis with cirrhosis. **Fulminant hepatitis,is 10 times** more common in coinfection.
- In patients with chronic HDV, HDV is the dominant virus because it suppresses HBV replication. Thus, most HBV-HDV coinfected patients have low serum HBV DNA levels.

Chronic hepatitis D

- 1-Clinical course of hepatitis is accelerated.
- 2- Cirrhosis occurs in 60% to 80% of chronic hepatitis D patients, and the risk of HCC is about threefold.
- 3- Splenomegaly along with elevated transaminases and high levels of viremia are common.
-
- 4-Unlike HBV, the level of HDV viremia does not seem to correlate with severity of disease.

HIV-HBV-HDV triple infection

- 1-Liver disease is known to be accelerated
- The incidence of HCC and mortality is higher than in patients with HIV alone.

Treatment options

Antiviral Therapy

- Nucleotide and Nucleoside Analogue and Inhibitors
- Interferon Based Therapy
- New Treatment Strategies (Next Presentation)
  - Inhibition of Virus Entrance (Inhibitory Effect on NTCP)
  - Inhibition of Prenylation (Assembly Inhibition)
  - Antisense Oligonucleotides

Liver transplantation

- Patients with evidence of decompensated liver disease or fulminant liver failure should be immediately transferred to a center capable of performing a liver transplantation

- **Combination treatment of peg-IFN with lamivudine, ribavirin, adefovir, and tenofovir was explored but was disappointing, as it did not lead to better viral response rates compared to IFN monotherapy**.

- **The only exception was peg-IFN–adefovir** combination therapy, which was also not associated with higher viral response rates compared to peg-IFN monotherapy but interestingly the decline of quantitative HBsAg levels was more pronounced compared to peg-IFN monotherapy.

HIV-HDV

- A median 6 years of tenofovir treatment was effective in HIV–HDV co-infected patients.

NEW STRATEGIES

Hepatocyte entry inhibitors
Farnesyltransferase inhibitors
Nucleic acid polymers
Small interfering RNAs
Immunological approaches: Toll-like receptor agonists, checkpoint inhibitors, hepatitis B virus vaccines

Table 2. **Characteristics of novel drug treatment for chronic hepatitis D.**

Drug	Mode of action	Administration route	Phase of study
Myrcludex B	Interferes with hepatitis D virus entry into hepatocyte through sodium taurocholate co-transporting polypeptide inhibition	Subcutaneous, daily for 6 months, ± pegylated interferon (peg-IFN)	Ib, IIa
Lonafarnib	Farnesyltransferase inhibitor, inhibits virion assembly	Oral, 2 to 12 months, ± ritonavir ± peg-IFN	II
Rep-2139-Ca	Nucleic acid polymer, binds with high affinity to amphipathic proteins, which are required at various stages of the viral life cycle	Intravenous infusion, once weekly for 4-6 months ± peg-IFN	II

siRNAs

- ARC-520, a siRNA designed to reduce all HBV transcripts via RNA interference, dose-dependently decreased HBsAg levels after one single injection in HBeAg-negative CHB patients in a phase 2a clinical trial.
- A multi-dose extension study (up to 12 doses once-monthly) of the same compound has been conducted. With multiple dosing, additional decline of HBsAg levels was observed,more so in HBeAg-positive than in HBeAg negative patients.
- It was reported that ARC-520 was well tolerated, but the study was put on hold owing to toxicity problem related to the carrier molecule.

Immune system-targeted approaches

- **Vaccine:**
- DNA vaccines,
- Anti-HB immune complexes,
- Immunologically active adjuvants such as beta-glucosylceramide

Toll-like receptors (TLRs)

- As inducers of type 1 IFN responses

-Induction of the innate immune system

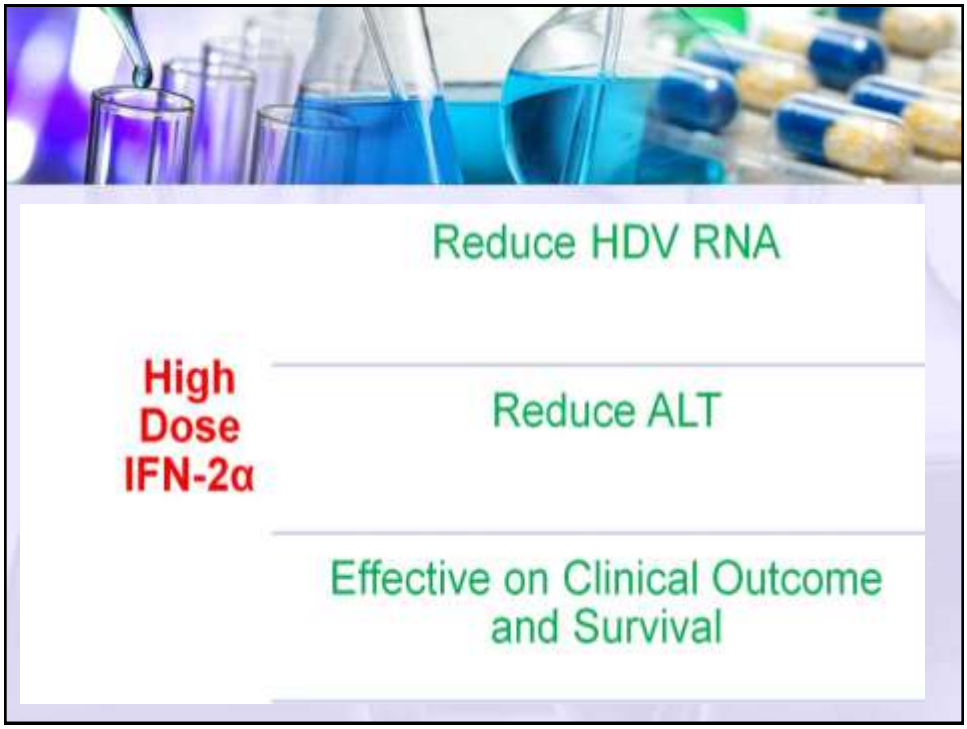
- The oral TLR-7 agonist GS-9620 was well tolerated and led to the induction of peripheral ISG15 production in CHB patients

PD1

- Drugs targeting programmed death protein 1 and its ligand (PD-L1)
- Blocking PD1 appears to be a rational goal to activate the HBV-specific T-cell response.
- In a phase Ib clinical study, the immune checkpoint inhibitor:**NIVOLUMAB**
- Hepatotoxicity and off-target immune activation .
- The future of immune therapy may be using combination immune therapy such as a PD1 blocker with DNA immunization and NA treatment

Choice of therapy

- Antiviral Therapy
  - Interferon Based Therapy
    - Standard Interferon-α (IFN- α)
    - Pegylated Interferon-α (PEG-IFN- α)
    - (IFN- α) VS (PEG-IFN- α)


Reduce HDV RNA
High Dose IFN-2α
Reduce ALT
Effective on Clinical Outcome and Survival


IFN- alfa
Standard IFN-α (High-dose, long-term)
Nine millions units three times a week or
Five millions units daily
Duration of therapy (at least 12 months) can be prolonged if
HBsAg is not cleared and
Treatment well tolerated.
Pascarella S, et al Hepatitis D virus: an update. Liver International. 2011