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Chronic viral hepatitis Delta

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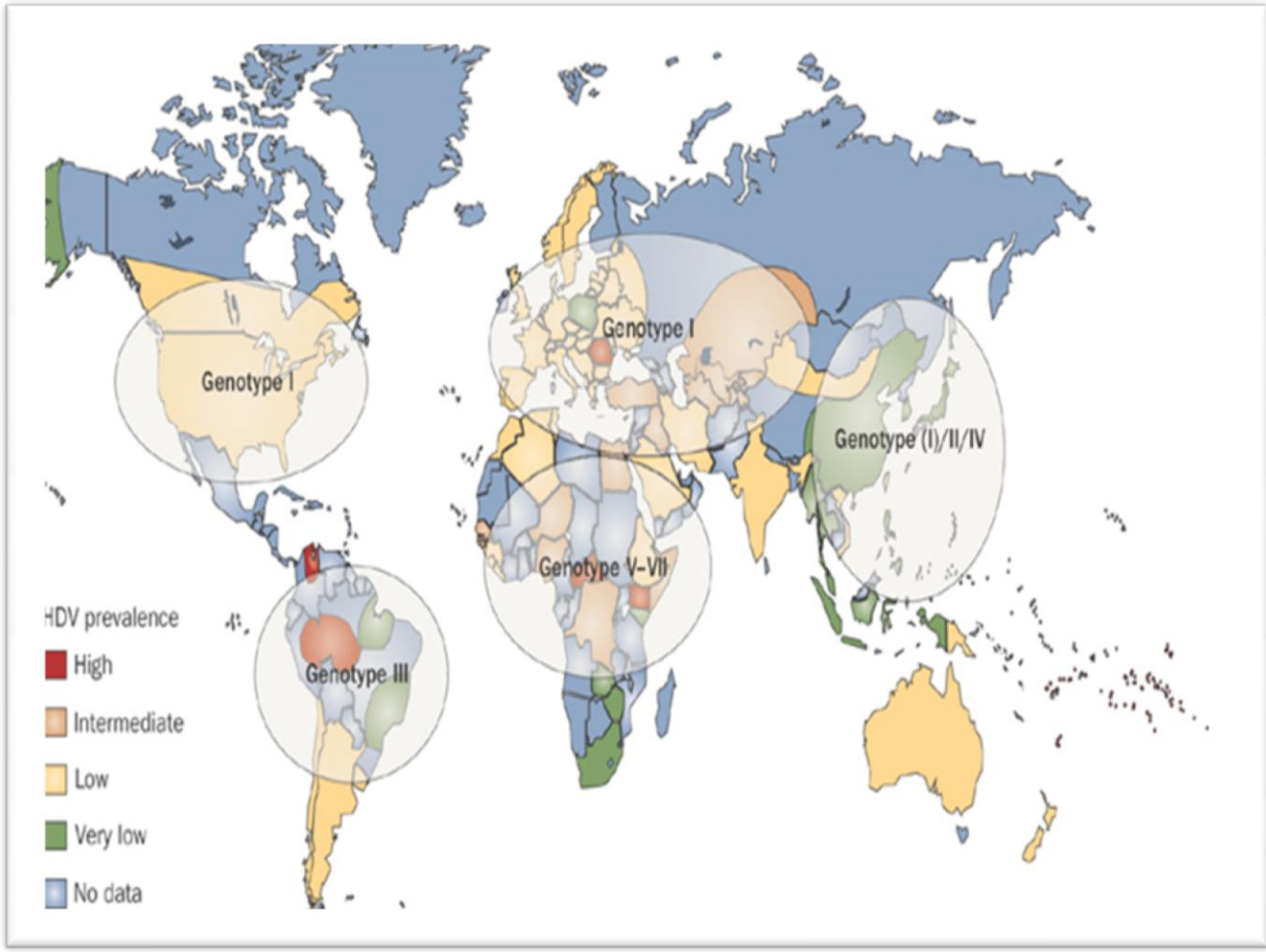
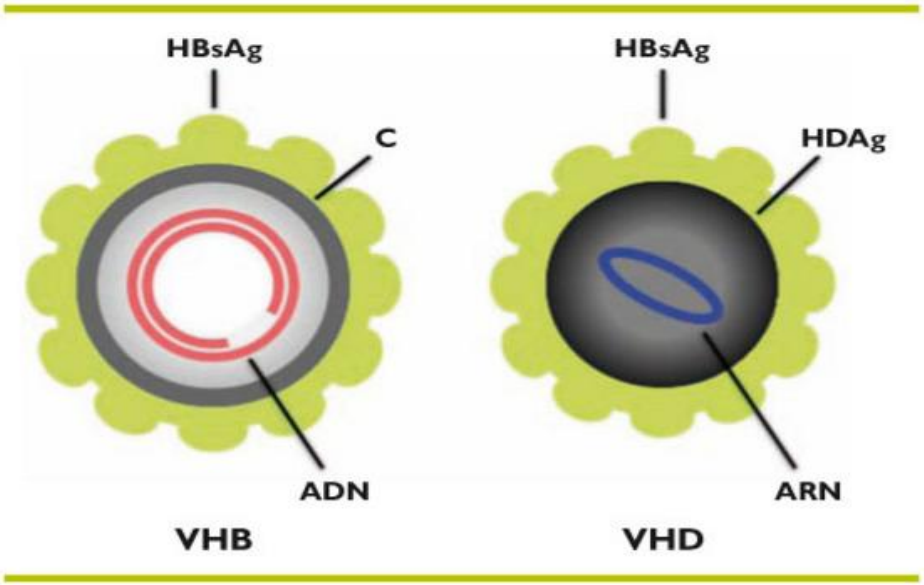
Epidemiology of HDV

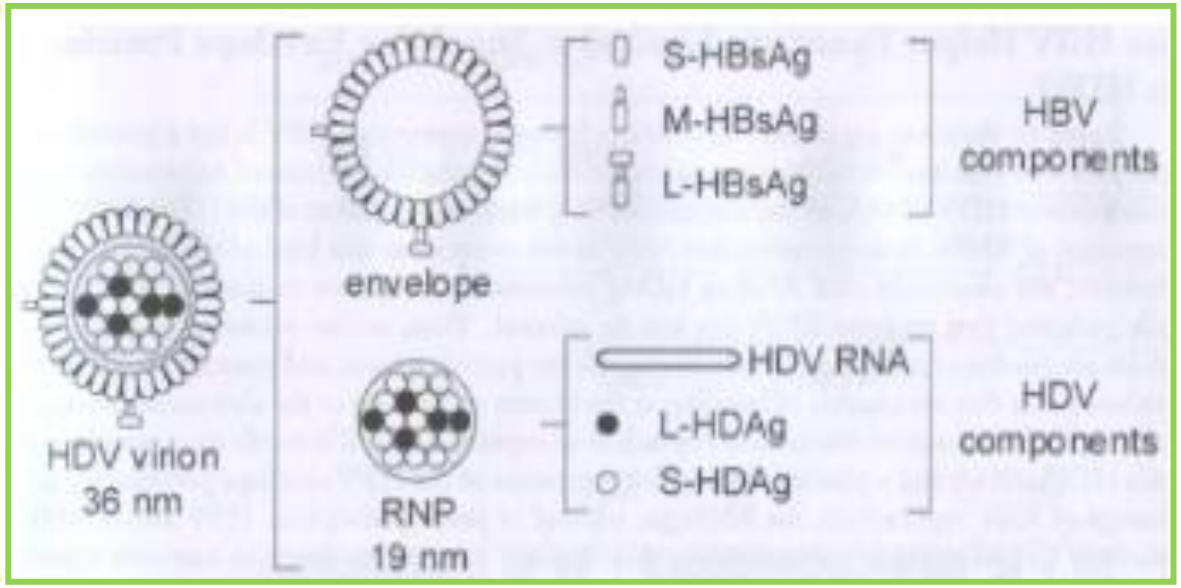
- Approximately 15 million people are infected with HDV worldwide.
- Areas with the **highest prevalence** include southern Italy; North Africa; the Middle East; the Amazon Basin; and the American South Pacific islands.
- HDV infection is more common in adults than in children.
- Children from underdeveloped, HDV-endemic countries are more likely to contract HDV infection through breaks in the skin, due to the presence of skin lesions.
- Risk factors for HDV include *intravenous drug use* and *multiple blood transfusions*.
- *Sexual* transmission is less efficient than with HBV.



Heidrich B, Deterding K, Tillmann HL, . Virological and clinical characteristics of delta hepatitis in Central Europe. *J Vi*
Hepat. Dec 2009;16(12):883-

Virology in HDV infection





- HDV is a small, 1.7Kb RNA virus contained in a protein envelope consisting of hepatitis B surface antigen (HBsAg). HDV is defective, in obligatory dependence on the hepatitis B virus (HBV), and can thrive only in patients with hepatitis B surface antigen (HBsAg)
- The only function of HBV required from HDV is the HBsAg coat for morphogenesis.
- HDV can replicate independently within the hepatocyte, but it requires HBsAg for propagation.
- Hepatic cell death may occur due to the direct cytotoxic effect of HDV or via a host-mediated immune response.

Sureau, Camille. Hepatitis Delta Virus: HDV-HBV Interactions. Hepatitis Delta Virus (2006

Replication of HDV

- Replication of HDV is restricted to the liver.
- Although replication of HDV can occur within hepatocytes in the absence of HBV, HBV is necessary for coating the HDV virions and allowing their spread from cell to cell.
- HBsAg and L-HDAg are needed for HDV assembly. Envelope proteins derived from the pre-S and S antigens of HBV encapsidate HDV RNA and HDAg. HDAg is necessary for viral proliferation.
- HBsAg, HDAgs, and HDV RNA are the main particles of HDV. Assembly can only occur in the presence of the helper virus HBV.
- In most cases of HDV infection, HBV replication is suppressed to low levels by HDV . Liver damage in these patients is essentially due to HDV only.
- Occasionally, HBV and HDV replicate simultaneously, each virus contributing to the liver damage, thereby resulting in more severe liver disease

Hadziyannis SJ. Review: Hepatitis delta. Journal of Gastroenterology and Hepatology, 1997, 12(4):289-298.

Natural History on HDV infection

HDV infection occurs into two forms:

- The first form is caused by the **co infection of HBV and HDV**; this usually results in a more severe acute hepatitis with a higher mortality rate than is seen with acute hepatitis B alone but rarely results in chronic infection.
- A second form is a result of a **super infection of HDV in a HBV** carrier and can manifest as a severe “acute” hepatitis in previously asymptomatic HBV carriers or as an exacerbation of underlying chronic hepatitis B.

  - Unlike coinfection, HDV superinfection in HBV carriers almost always results in chronic infection with both viruses.
  - In chronic HDV infection, HBV replication is often suppressed, patients are mostly hepatitis B “e” Ag negative, and anti-HBeAg positive. Occasionally, HDV RNA and HBV DNA may coexist.
  - A higher proportion of persons with chronic HBV/HDV coinfection develop cirrhosis, hepatic decompensation, and liver cancer compared to those with chronic HBV infection alone.

Clinical outcomes in HDV

- Three phases of chronic hepatitis D have been proposed:

a) an **early active phase** (active HDV replication and suppression of HBV),

b) a **second moderately active** phase (with decreasing HDV and reactivating HBV),

c) a **third late phase** (with development of cirrhosis and hepatocellular carcinoma caused by replication of either virus or with remission resulting from marked reduction of both viruses).

- Progression to cirrhosis usually takes 5 - 10 yrs, but it can appear 2 years after onset of infection. About 60 to 70% of patients with chronic hepatitis D develop cirrhosis.
- HCC may actually be more a secondary effect of the associated cirrhosis than a direct carcinogenic effect of the virus.

Hadziyannis SJ. Hepatitis delta: an overview. In: Rizzetto M, Purcell RH, Gerin JL, and Verme G, eds. Viral Hepatitis and Liver Disease, Turin, Edizioni Minerva Medica, 1997, 283-289.

A clinical score for hepatitis delta

BEA score or Baseline Event-anticipation score is an easy to apply clinical score that predicts the development of liver-related complications (decompensation, hepatocellular carcinoma, liver transplantation and/or death) in chronic hepatitis delta patients.

A clinical score to define patients with mild, intermediate and a severe course of liver disease in hepatitis delta.

This simple score is based on the:

- patient's sex (male),
- age (>40 years),
- country of origin (Mediterranean),
- INR (>1.2),
- thrombocyte counts (1 point <100,000/ml; 2 points if <50,000/ml)
- bilirubin (>ULN).

BEA-A	**Mild risk**	**0-1 point**
BEA-B	**Moderate risk**	**2-4 points**
BEA-C	**Severe risk**	**> 5 points**

Less than 2 points is associated with an excellent 5-10 year course, whereas all patients with 5 or more points developed liver-related complications within 5-7 years of follow-up.

Development and evaluation of a baseline-event-anticipation score for hepatitis delta. ***Calle Serrano*** *B, Großhennig A, Homs M, Heidrich B, Erhardt A, Deterding K, Jaroszewicz J, Bremer B, Koch A, Cornberg M, Manns MP, Buti M, Wedemeyer H. J Viral Hepat. 2014 Mar 27. doi: 10.1111/jvh.12251.*

Diagnosis of HDV infection

Due to dependence of HBV on HDV, the diagnosis of hepatitis D can be suspected only in patients with markers of HBV infection.

The diagnosis of HDV infection should be considered in the following clinical situations:

- **Acute hepatitis B**: HDV **coinfection** should be excluded in patients at risk (intravenous drug users or patients from endemic country) or in those with severe and/or prolonged illness, often with a double elevation of liver enzymes.
- **Acute hepatitis with undetermined origin in a chronic HBV careier**. If all cause of acute hepatitis have been excluded, including an exacerbation of HBV, as often seen in anti-Hbe positive chronic hepatitis B, HDV may responsible for a sudden increase of liver enzymes in the setting of socalled **superinfection of** a **know careier** of **HBV**.
- **HBs-positive chronic hepatitis.** HDV testing should be performed in all HBsAg-positive patient emigrating from countries with high prevalence of infection and in those who have a history of injection drug use. This should be mandatory when HBsAg-positive patients are considered for antiviral therapy.

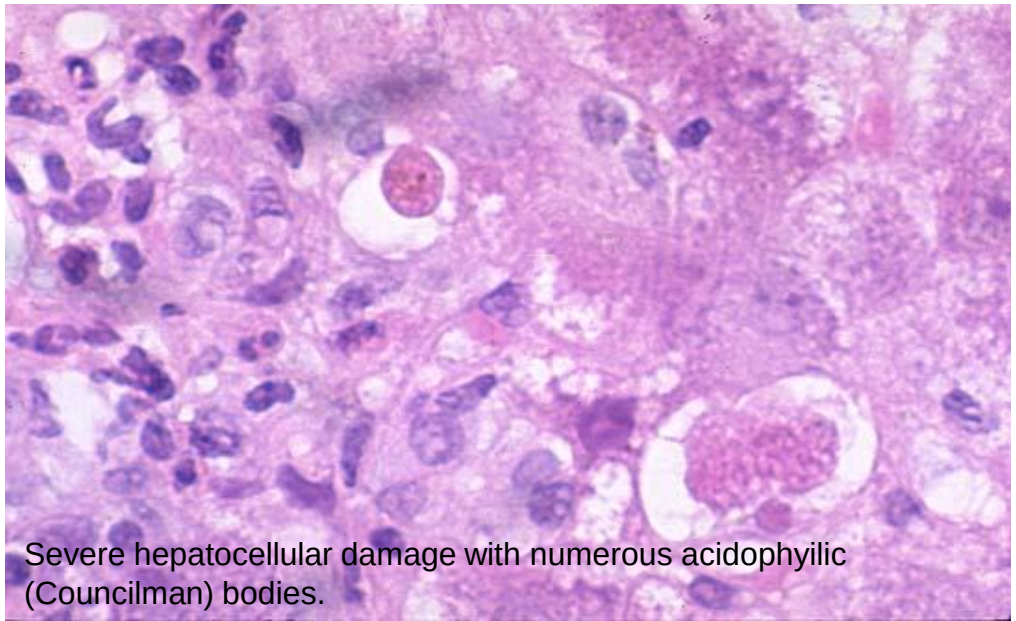
Diagnostic Markers in HDV Infection

Diagnostic Marker	Importance
Anti-HD IgG antibody	Positive in all individuals exposed to HDV, persists long-term, and may persist even after viral clearance
Anti-HD IgM antibody	Positive in acute infection and negative in past infection but persists in a large proportion of patients with chronic infection. Used as surrogate marker for HDV replication but not 100% sensitive or specific
HDV RNA qualitative	Marker of HDV replication; positive in patients with chronic infection; negative in spontaneous or treatment-induced viral clearance
HDV RNA quantitative	Useful method to monitor treatment response

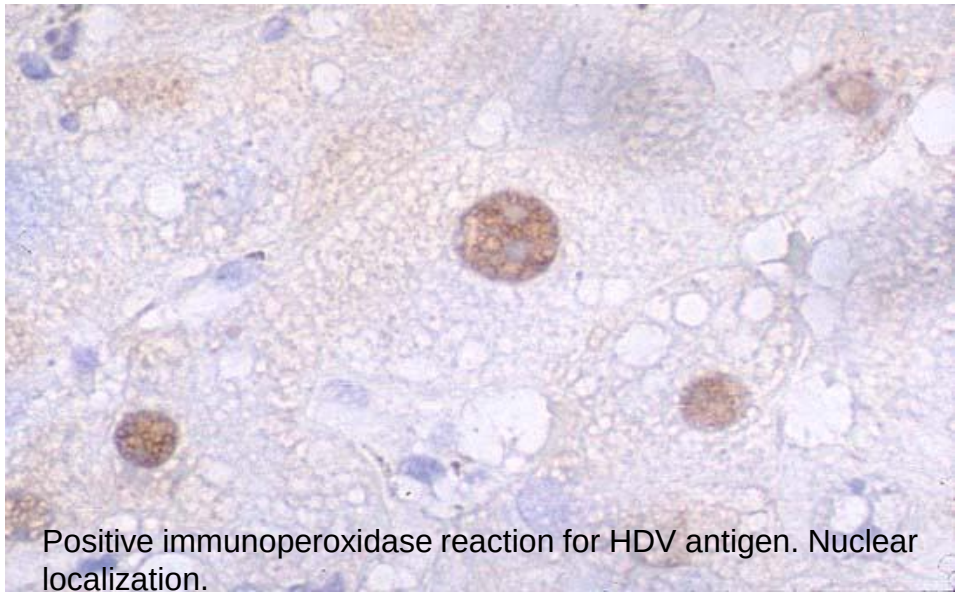
Virologic Characteristic	**Coinfection**	**Superinfection**
HBV infection	Acute, self-limited	Chronic
Hepatitis B surface antigen	Positive, transient	Positive, persistent
IgM anti-HBc	Positive, transient	Negative
Anti-HBs	Raises after clearance of hepatitis B surface antigen	Negative
HDV infection	Acute, self-limited	Acute 20%, chronic 80%
Liver hepatitis D antigen	Positive, transient	Positive, may be negative at a late stage
Serum HDV RNA	Positive, transient	Positive, persistent
Antibodies to hepatitis D antigen	Late acute phase, low titer	Rapidly increasing, persistent in high titers
IgM antibodies to hepatitis D antigen	Transient	Rapidly increasing, persistent in high titers

Liver biopsy in HDV chronic hepatitis

- Consider liver biopsy if the serologic diagnosis of hepatitis is non-conclusive.
- Hepatitis D virus (HDV) antigen immunohistochemical analysis of liver tissue is the criterion standard for establishing a diagnosis of persistent HDV infection.
- Histologic features are very similar to those observed in patients with HBV infection.
- *Acidophilic bodies and degeneration of hepatocytes with acidophilic cytoplasm are present. The few inflammatory cells (lymphocytes) likely represent the direct cytotoxicity of HDV. Results of immunohistochemical staining for HDV antigen are positive*.



Severe hepatocellular damage with numerous acidophyilic (Councilman) bodies.



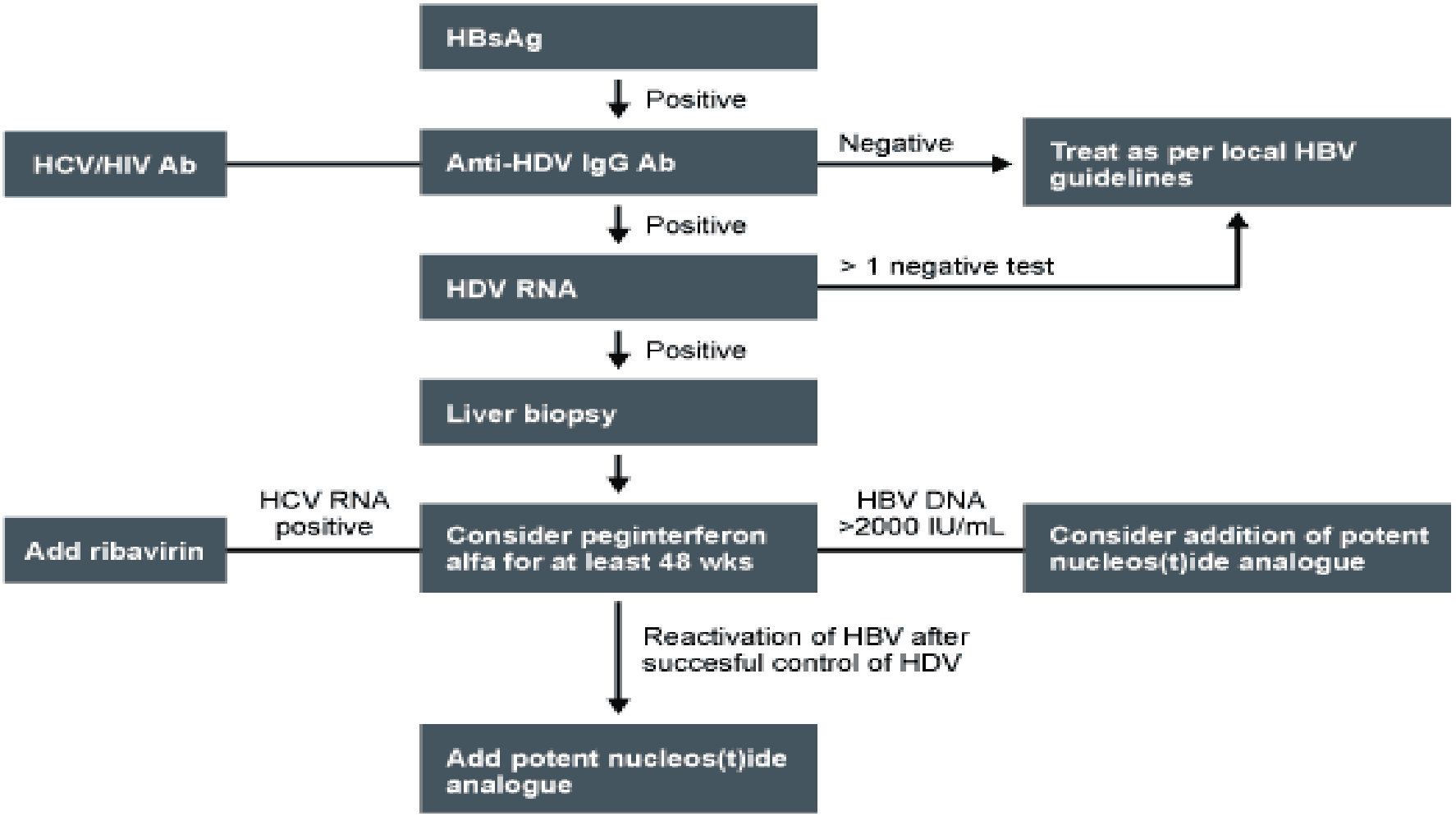
Positive immunoperoxidase reaction for HDV antigen. Nuclear localization.

The treatment of chronic hepatitis D

The aim of treatment of hepatitis D is to eradicate or to achieve long-term suppression of both HDV and HBV.

- **The primary endpoint** of treatment is the suppression of HDV replication, which is accompanied by normalization of the serum alanine transferase (ALT) level and amelioration of necroinflammatory activity on liver biopsy. Suppression of HDV replication is documented by loss of detectable HDV RNA in serum and of HDAg in the liver.
- **A secondary endpoint** is the eradication of HBV infection, with HBsAg to anti-HBs seroconversion. There is very little information to support that current treatment is effective in achieving this goal. Eradication of HBV infection with development of anti-HBs will protect the individual from reinfection with HBV as well as HDV. Patients who have cleared HDV but who remain HBsAg positive are still at risk of reinfection with HDV.

Algorithm for the management of an HDV-infected patient



Ab, antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Antiviral therapy in chronic hepatitis Delta

Standard Therapies

- **Interferon alfa-2a** has been used to treat hepatitis D virus (HDV) infection. Dosages varying from 3-10 mU 3 times per week for as long as 12 months have been used. At the end of therapy, loss of HDV RNA and normalization of liver enzymes was seen in 20-50%.
- Treatment with interferon can be continued after the 1-year period if well tolerated and efficacy is demonstrated.
- **Pegylated IFN a** (PEG-IFN a) therapy is associated with HDV RNA negativity in 25%-40% of cases after 1 year. Monitoring HDV RNA and HBsAg levels may help in guiding therapy

Novel Therapies

- **Lonafarnib**, a prenylation inhibitor, which prevents the assembly of the hepatitis D virion by blocking the combination of the hepatitis B surface antigen with the large hepatitis D antigen, and nuclei acid polymers (in particular REP-2139), which block the assembly of HBV subviral particles.
- **Myrcludex B**, a synthetic N-acylated pre-S1 lipopeptide which blocks in vivo and in vitro the receptor function of Na+ -taurocholate co-transporting polypeptide.

Manesis EK, Schina M, Le Gal F, et al. Quantitative analysis of hepatitis D virus RNA and HBsAg serum levels in chronic delta hepatitis improves treatment monitoring. *Antivir Ther*. 2007;12(3):381-8

Prognosis of HDV hepatitis

- The prognosis is excellent for patients with coinfection in whom treatment eradicates both viruses.
- The prognosis is variable for patients who are superinfected. It depends on the duration and severity of HBV infection, alcohol consumption, comorbid illnesses, and age.
- In patients who undergo liver transplantation for chronic liver disease secondary to HBV and hepatitis D virus (HDV) infection, HDV seems to suppress the replication of HBV in the transplanted liver and may help to prolong graft survival. However, fulminant hepatitis from recurrent HBV and HDV infection in the transplanted liver has resulted in patient death or the need to retransplant

Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. *Lancet* 2011; 378: 73–85