Hepatitis D, Epidemiology, Management

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Introduction
Introduction

- 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.
Key Points

- HDV infection is particularly frequent among immigrants populations from regions where HDV is endemic, such as Central Africa, Eastern Turkey, Central Asia, some Eastern European countries and the Amazonian region of Brazil.

- Only IFN-alpha has proven antiviral activity against HDV and treatment with PEG-IFN leads to HDV clearance in about 25% of patients.
Transmission routes

• HDV is spread in the same way as HBV, mainly through parenteral exposure.
Risk Factors for HDV infection

- Blood transfusion
- Surgery
- Family history
- Hejamat (traditional phlebotomy)
- Tattooing,
- war injury
- Dentistry interventions and endoscopy.

What Saddam the Iraqi dictator did against our Injured soldiers and health system in prison in Iraq should be more clarified and the prevalence of HDV infection in our soldiers is more common

Alavian SM. We Have More Data Regarding Epidemiology of Hepatitis D in Iran but There are Defects to be Filled Yet! Hepat Mon. 2008
Epidemiology
Epidemiology

Worldwide prevalence of HDV and the geographic distribution of its genotypes

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High rates of HDV carriage

Of the 350 million chronic carriers of HBV, more than 15 million have serological evidence of exposure to HDV

Migration and HDV in Europe

• 8 to 12% of HBs Ag positive in Europe are anti HDV positive

• Most of the European HDV-infected patients were born in highly endemic areas such as:

  Eastern Turkey, Central Asia, Africa, South America especially from Amazonian region of western Brazil and western pacific population

Migration and HDV in Europe

Emerging HDV Epidemiology: Migration

HDV Prevalence
- High
- Intermediate
- Low
- Very Low
- No Data

Pooled HDV Risk Factors Among HBsAg positive patients in Iran, 1983-2008

- Blood transfusion: OR 1.1 (0.40-2.98)
- HBeAg positive: OR 1.26 (0.66-2.4)
- IDU: OR 1.6 (0.78-3.214)
- Hemodialysis: OR 1.72 (0.79-3.76)

Epidemiology of HDV infection in Iran

• The pooled HDV prevalence in HBs Ag positive in Iran was 7.8%.
• In the survey-data analysis, HDV prevalence was 6.61%.
• HDV prevalence was 30.47%, 14.4% (95% , and 4.94% in cirrhotic, chronic-hepatitis, and inactive-carrier patients, respectively.
• Pooled ORs were calculated for several factors common to Iranian HBsAg-positive patients, including history of blood transfusion, intravenous drug abuse, previous hemodialysis, and HBeAg-positive status.
• CONCLUSIONS: The prevalence of HDV is less common in Iran than in endemic regions such as Italy and Turkey; however, it is a severe form of hepatitis in HBsAg-positive patients. The most probable route of HDV transmission is hematologic, which suggests the importance of blood screening for HDV, especially in groups with numerous blood transfusions.

• The virus is highly endemic in Mediterranean countries, the Middle East, Central Africa, and northern parts of south America

Wedemeyer 2010
Epidemiology of HDV infection in EMRO Countries

• The weighted mean of HDV prevalence in the EMRO region was 14.74%, 27.8%, and 36.57%. in asymptomatic HBsAg positive carriers, chronic hepatitis patients, and cirrhosis/hepatocellular carcinoma, respectively.

• Among the asymptomatic HBsAg positive group, HDV prevalence was increased by years in older patients in Saudi Arabia but its prevalence was decreased in Iran.

• No specific pattern was seen according to chronological analysis during years among the EMRO countries.

• HDV infection is endemic in the EMRO countries and it is more common among patients with severe forms of hepatitis. **Due to the high HDV infection rates in the EMRO countries, we recommend blood screening for HDV infection in this region.**

Epidemiology of HDV infection in EMRO Countries

• Regional Distribution of Pooled or Individual Prevalence of Hepatitis D Virus Infection among Patients with Chronic Hepatitis B Patients at EMRO Countries

Pakistan Issue:
The high prevalence could be due to the frequent use of therapeutic injections and drips, contaminated needles, surgical and dental equipment, reusing traditional razors by barbers, use of injectable drugs, and sexual transmission. There is higher seroprevalence of HDV in younger male subjects who are positive for HBsAg.

The most prevalence of HDV infection was in African countries of EMRO regions such as Egypt, Sudan, Tunisia and Somalia.

In conclusion, North Africa must be considered as a high HDV prevalence area in addition to central Africa, southern America, and Mediterranean countries.

### HDV Epidemiology

*Prevalence of HDV in Different Regions and Comparison With HDV prevalence of Iran provinces*

<table>
<thead>
<tr>
<th>Country/Region</th>
<th>Target Population</th>
<th>Prevalence, %</th>
<th>Sample Size</th>
<th>Neighbors City in Iran</th>
<th>Prevalence in Neighbors, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degertekin H et al. (2008) (53)</td>
<td>Turkey/middle east</td>
<td>Meta-analysis</td>
<td>27.1</td>
<td>6734</td>
<td>Tabriz</td>
</tr>
<tr>
<td>Jacobson IM et al. (1985) (56)</td>
<td>Afghanistan/EMRO</td>
<td>high risk group and patients</td>
<td>28.6</td>
<td>362</td>
<td>Mashhad</td>
</tr>
<tr>
<td>Baig S et al. (2009) (57)</td>
<td>Pakistan/EMRO</td>
<td>patients</td>
<td>37</td>
<td>129</td>
<td>Kerman</td>
</tr>
<tr>
<td>Zaki S et al. (2010) (59)</td>
<td>Egypt/EMRO</td>
<td>high risk group and patients</td>
<td>20</td>
<td>100</td>
<td>none</td>
</tr>
<tr>
<td>Gaeta GB et al. (2003) (50)</td>
<td>ItalyEurope</td>
<td>14 referral liver unites</td>
<td>8.3</td>
<td>834</td>
<td>none</td>
</tr>
<tr>
<td>Chen X et al. (1998) (60)</td>
<td>China/Asia</td>
<td>sample infected with HBV</td>
<td>7.72</td>
<td>2681</td>
<td>none</td>
</tr>
</tbody>
</table>

Turkey

• HDV prevalence is much higher in the southeast of the country, being 27% in chronic hepatitis B patients and 46% in hepatitis-B-induced cirrhosis patients. This is in comparison to the HDV prevalence in the West of the country of 5% in chronic hepatitis B patients and 20% in hepatitis-B-induced cirrhosis patients.
Turkey

• There are enough data regarding HDV infection during 20 years and the trend is to decreasing the prevalence.

• The analysis also compared prevalence of HDV before and after 1995. It was observed that HDV prevalence in chronic hepatitis B patients decreased from 38% to 27% in Southeast Turkey and from 29% to 12% in Central Turkey. HDV prevalence in cirrhosis patients has decreased from 66% to 46% in Southeast and from 38% to 20% in West Turkey.
Lebanon

- Hepatitis D was first detected in Lebanon in 1987 when a study reported 57% HDV prevalence in patients with chronic active hepatitis. In 2007, the results of a study in which 258 HBsAg-positive patients from 10 health centers were included showed 1.2% HDV prevalence, which shows a decrease in prevalence since 1987.
Therapy
• No real treatment options!
Treatment Options for HDV

• **Antiviral Therapy**
  - Nucleotide and Nucleoside Analogue and Inhibitors
  - Interferon Based Therapy
  - New Treatment Strategies
    • 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
Treatment Options for HDV

Antiviral Therapy

Nucleotide and Nucleoside Analogue and Inhibitors

Gunsar F et al. Two-year interferon therapy with or without ribavirin in chronic delta hepatitis. Antiviral therapy. 2005
Treatment Options for HDV

- Antiviral Therapy

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

High Dose IFN-2α

Reduce HDV RNA

Reduce ALT

Effective on Clinical Outcome and Survival

Interferon-α

- **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.

**Pegylated-interferon-α**

- **Duration and Dosage**
  - 180 μg weekly
  - 12–18 months

- **Better response** to treatment in comparison with classical IFN-α

- Non-responders to IFN-α may clear HDV RNA after a course with Peg-IFN-α

- **Stopping Rule** suggested, but not guideline

  - Treatment should be stopped in cases with **Less than 3 logs decrease in serum HDV RNA after 24 weeks of treatment**

  - Negativity of HDV RNA and HBV DNA during therapy is not enough for SVR

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Standard and pegylated interferon therapy of HDV infection: A systematic review and meta-analysis. (2012)

Data were abstracted from 14 studies containing 227 chronic HDV-infected patients who received standard or pegylated interferon alpha-2a or -2b.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication year</th>
<th>Country of samples’ origin</th>
<th>Design</th>
<th>Type of interferon</th>
<th>Regimen</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castelnau et al.</td>
<td>2006</td>
<td>US</td>
<td>Prospective</td>
<td>PEG-2 beta</td>
<td>1.5 μg/kg QW×1 year</td>
<td>6-42 months; median 16 months</td>
</tr>
<tr>
<td>Erhardt et al.</td>
<td>2006</td>
<td>Germany</td>
<td>Prospective</td>
<td>PEG-2 beta</td>
<td>1.5 μg/kg QW×48 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>Niro et al.</td>
<td>2006</td>
<td>US</td>
<td>RCT</td>
<td>PEG-2 beta</td>
<td>1.5 μg/kg QW×72 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>Wedmeyer et al.</td>
<td>2011</td>
<td>Germany</td>
<td>RCT</td>
<td>PEG-2 alpha</td>
<td>180 μg QW×48 weeks</td>
<td>6 months</td>
</tr>
<tr>
<td>Canbakan et al.</td>
<td>2006</td>
<td>Turkey</td>
<td>RCT</td>
<td>2 beta</td>
<td>10 MU t.i.w.×48 weeks</td>
<td>96 weeks; mean 3.1 years</td>
</tr>
<tr>
<td>Craxi et al.</td>
<td>1991</td>
<td>Italy</td>
<td>Prospective</td>
<td>2 beta</td>
<td>5 MU/m² t.i.w. 3 months+3 MU/m² t.i.w. 9 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Di Marco et al.</td>
<td>1996</td>
<td>Italy</td>
<td>CCT</td>
<td>2 beta</td>
<td>5 MU/m² t.i.w. 3 months+3 MU/m² t.i.w. 9 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Farci et al.</td>
<td>1994</td>
<td>Italy</td>
<td>RCT</td>
<td>2 alpha</td>
<td>9 or 3 MU t.i.w.×48 weeks</td>
<td>6-48 months</td>
</tr>
<tr>
<td>Gaudin et al.</td>
<td>1995</td>
<td>France</td>
<td>RCT</td>
<td>2 beta</td>
<td>5 MU/m² for 4 months+3 MU/m² for 8 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Günsar et al.</td>
<td>2005</td>
<td>Turkey</td>
<td>RCT</td>
<td>2 alpha</td>
<td>9 MU t.i.w.×2 years</td>
<td>6 months</td>
</tr>
<tr>
<td>Madejon et al.</td>
<td>1994</td>
<td>Spain</td>
<td>RCT</td>
<td>2 alpha</td>
<td>3 MU QD 3 months+1.5 MU QD 9 months or decreasing dose of 18 MU t.i.w. 6 months</td>
<td>18 months</td>
</tr>
<tr>
<td>Rosina et al.</td>
<td>1991</td>
<td>Italy</td>
<td>RCT</td>
<td>2 beta</td>
<td>5 MU/m² t.i.w. 4 months and then 3 MU/m² t.i.w. for 8 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Yurdaydin et al.</td>
<td>2008</td>
<td>Turkey</td>
<td>RCT</td>
<td>2 alpha</td>
<td>9 MU t.i.w.×1 year</td>
<td>6 months</td>
</tr>
<tr>
<td>Yurdaydin et al.</td>
<td>2007</td>
<td>Turkey</td>
<td>Prospective</td>
<td>2 alpha</td>
<td>10 MU t.i.w.×2 years</td>
<td>6 months</td>
</tr>
</tbody>
</table>

CCT=controlled clinical trial; RCT=randomized clinical trial; t.i.w.=Thrice weekly HDV and HB viral load, copy/ml
Pooled SVR rates for pegylated-interferon-α VS Interferon alfa were 29% [95% confidence interval (CI) 19; 41] and 19% (95% CI 10; 29), respectively.

The rates of treatment withdrawal were similar.

The major limitations to this meta-analysis

- The variability of the design of the included studies
- Clinical heterogeneity across treatment regimens
- The few number of patients treated in each study

Final Conclusion

- Literature lacks sufficient evidence to establish precise recommendations for HDV treatment
  - PEG-IFN is more effective than high dose of standard IFN

## Peginterferon plus Adefovir

<table>
<thead>
<tr>
<th>Tx Group (48 Weeks)</th>
<th>Negative Test of HDV RNA at Week 48 of Tx</th>
<th>Sustained Result at 24 Weeks after Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG-IFN-2a+ Adefovir dipivoxil N=31</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td>PEG-IFN-2a N=29</td>
<td>24%</td>
<td>28%</td>
</tr>
<tr>
<td>Dipivoxil N=30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**A decline in HBsAg levels of more than 1 log(10) IU per milliliter from baseline to week 48 was observed in 10 patients in the first group, 2 in the second, and none in the third.**

**Treatment with PEG-IFN alfa-2a for 48 weeks, with or without adefovir, resulted in sustained with HDV infection.**

Summary

• **literature lacks sufficient evidence** to make precise recommendations for treatment of HDV infections

• **12 or 18 months treatment with PEG-IFN** should be used for management of HDV infection.

• **Longer treatment** should be considered if patients are able to tolerate the adverse effects of therapy

• **Patients should be monitored every 3–6 months** after the initiation of treatment as serum levels of HBV DNA and HDV RNA may fluctuate.
Summary

• How to Improve Response Rate
  • Longer Duration
  • Continuous Therapy
  • Pegylated Interferon

• Factors influencing response
  • HDV genotype: non 1 genotype
  • Baseline HDV RNA: < 6 log 10
  • Baseline HBS Ag titer: lower in responder
  • Stage of fibrosis: absence of cirrhosis
Summary

- Peg-IFN-α is still insufficient to cure the majority of chronic hepatitis D patients
Detection of HDV-RNA in anti-HD HBsAg positive individuals

<table>
<thead>
<tr>
<th>HDV-RNA-negative</th>
<th>HDV-RNA-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT levels abnormal</td>
<td>ALT levels abnormal</td>
</tr>
<tr>
<td>HDV-RNA-negative</td>
<td>ALT levels normal</td>
</tr>
<tr>
<td>HDV-RNA-positive</td>
<td>HBV-DNA-negative</td>
</tr>
<tr>
<td>HBV-DNA-positive Disease other than HBV–HDV in inactive HBsAg carrier</td>
<td></td>
</tr>
<tr>
<td>Previous HDV infection</td>
<td></td>
</tr>
<tr>
<td>Treat with IFN-α2a or IFN-α2b (9–10 million units three times per week) or with PEG-IFN-α2a (180 μg weekly) for 12–18 months</td>
<td></td>
</tr>
<tr>
<td>Monitor ALT levels as the large majority of HDV-RNA-positive patients have underlying liver disease</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
</tr>
<tr>
<td>HDV-RNA-negative, ALT levels normal</td>
<td></td>
</tr>
<tr>
<td>HBsAg-positive</td>
<td></td>
</tr>
<tr>
<td>Potential of relapse so only start maintenance therapy after a decline of HBsAg levels of &gt;1 log 10</td>
<td></td>
</tr>
<tr>
<td>HBsAg-negative</td>
<td></td>
</tr>
<tr>
<td>Cured of HBV–HDV</td>
<td></td>
</tr>
<tr>
<td>No response</td>
<td></td>
</tr>
<tr>
<td>HDV-RNA-positive, HBsAg-positive</td>
<td></td>
</tr>
<tr>
<td>Consider retreating or providing long-term treatment with a reduced IFN dosage to control rapidly progressive disease</td>
<td></td>
</tr>
</tbody>
</table>

The new anti-hepatitis D Treatment
HDV Therapy: Problems

- Small series of patients
- Different designs and protocols
- ↓ ALT vs clearance HDV-RNA not consistent
- clearance of HDV-RNA vs histology not consistent
- no advantage to treat up to 24 vs 12 months in controlled series if HBs Ag persist
HDV Therapy: Problems

- IgM anti-HD: surrogate marker of disease activity

- HDV-RNA: not standardized, need for an international reference

- Replication of HDV independent from HBV replication (i.e. from HBV-DNA levels)

- HBV required only to provide the HBsAg capsid
Additional tests – quantitative HBsAg

- HBsAg quantitative
  - HBsAg is associated with HDV RNA levels
  - HBsAg clearance is associated with HDV eradication
  - HBsAg monitoring can be useful during IFN-based treatment

Manesis et al. Antiviral Therapy 2007
The SVR paradigm does not apply to hepatitis D (as long as HBsAg persists)

- In the HBsAg setting, HDV may remain infectious at 10-11 serum dilutions, i.e. at titers far below the sensitivity threshold of current HDV-RNA assays (10 cp/ml)

- Hepatitis D results from a double viral infection. The evaluation of therapeutic goals requires consideration and targeting of two viral infections, adding complexity to the management of the HDV patient

- NO OWN REPLICATION FUNCTION OF HDV to be targeted by antivirals
New Targets for HBV “cure”

Inhibitors of cccDNA:
- cccDNA formation
- cccDNA destruction
- cccDNA silencing

RNA interference

Immune modulation:
- Toll-like receptors agonist
- AntiPD-1 mAb
- Therapeutic vaccine

Inhibitors of nucleocapsid assembly

Polymerase inhibitors:
- Nucleoside analogs
- Non-nucleoside

HBsAg release Inhibitor
- NAP
HDV Therapeutic targets

Ciancio A. & M.Rizzetto, Nat.Rev.Gastroenterol Hepatol 2014
The HDV envelope requires HBV surface antigen proteins provided by HBV. Once inside a cell, however, HDV can replicate its genome in the absence of any HBV gene products.

HDV virion assembly is critically dependent on prenyl lipid modification, or prenylation, of its nucleocapsid-like protein large delta antigen.
Nucleic Acid Polymers (NAPs) in CHB

- NAPs are oligonucleotides that interact with multiple intracellular amphipathic targets

- **NAPs have multiple anti-HBV mechanisms**
  - Block HBV entry
  - Post-entry activity
    - Blocks subviral particle (SVP) formation
  - Restore host immune response

- **NAPs may also have anti-delta effects**
  - block HDV entry
  - Block HDV production from a SVP-related assembly mechanism
  - “liberated” anti-HBs directly target HDV
Nucleic Acid Polymer REP-2139 in patients with HBV/HDV coinfection

- 12 HDV pts in Moldova
- Anti-HDV/RNA +
- HBsAg >1000
- Non-cirrhotic

Results: (1) HBsAg

(2) HDV RNA
Entry Inhibitors in CHB

- Myrcludex B is synthetic N-acylated preS1 lipopeptide which blocks receptor functions of NTCP and virus entry
- Ongoing clinical studies in HBV and HDV infection

Urban, Gastroenterology 2014
Prevention

• Although preventive measures against hepatitis B including vaccination and awareness campaigns with regard to risk factors for the transmission of hepatitis B and D, has decreased the prevalence of hepatitis D, there is no effective way of preventing HDV infection in HBV carriers in endemic areas. This can only be achieved by educating such individuals to prevent further exposures to risk factors.

• In spite of the global trend of decline, significant and persistent transmission is present in some countries.