Hepatitis D: Epidemiology and Clinical Features

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Estimates of Global HDV Infection: ~5% of HBsAg+ Persons

N=282 studies

<table>
<thead>
<tr>
<th>Anti-HDV among HBsAg+</th>
<th>AFR</th>
<th>AMER</th>
<th>EMR</th>
<th>EUR</th>
<th>SEAR</th>
<th>WPR</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>6.0</td>
<td>5.9</td>
<td>3.5</td>
<td>3.0</td>
<td>3.2</td>
<td>4.1</td>
<td>4.5</td>
</tr>
<tr>
<td>#, thousands</td>
<td>3,835</td>
<td>416</td>
<td>836</td>
<td>445</td>
<td>1,267</td>
<td>4,935</td>
<td>11,992</td>
</tr>
</tbody>
</table>

(95% CI: 9-19 million)

N=634 studies

Anti-HDV
48 million
(95% CI: 44–52)

Taiwan, Pakistan, Mongolia, Italy, Turkey, Amazon basin, and Central Africa
## HDV in the U.S.

<table>
<thead>
<tr>
<th>Population</th>
<th>N HBsAg+</th>
<th>Years of Study</th>
<th>Assay Used</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHANES</td>
<td>--</td>
<td>1999-2012</td>
<td>International Immunodiagnostics HDV Ab assay</td>
<td>0.02% (n=10)</td>
</tr>
<tr>
<td>Veterans</td>
<td>25,603 (n=2175 tested for HDV)</td>
<td>1999-2013</td>
<td>Not stated</td>
<td>3.5%</td>
</tr>
<tr>
<td>HBRN – U.S. wide</td>
<td>1507 (adults) 181 (peds)</td>
<td>2016</td>
<td>DiaSorin</td>
<td>3.2% 1.1%</td>
</tr>
<tr>
<td>Mid-Western healthcare system</td>
<td>1007 (n=217 tested for HDV)</td>
<td>2012-2106</td>
<td>Not stated</td>
<td>3.3%</td>
</tr>
<tr>
<td>Baltimore IDU</td>
<td>86</td>
<td>2005-6</td>
<td>Diagnostic Bioprobes Srl</td>
<td>11%</td>
</tr>
<tr>
<td>CA Hepatology</td>
<td>499</td>
<td>2008</td>
<td>Quest Diagnostics</td>
<td>8.4%</td>
</tr>
<tr>
<td>NHANES</td>
<td>113</td>
<td>2011-2016</td>
<td>DiaSorin</td>
<td>42% (n=43)</td>
</tr>
</tbody>
</table>

# Anti-HDV Detection

## Performance of Cusabio and DiaSorin EIA kits compared to that of reference laboratory methods

<table>
<thead>
<tr>
<th>ELISA kit</th>
<th>+/+</th>
<th>+/-</th>
<th>-/-</th>
<th>-/+</th>
<th>Sensitivity (% [95% CI])</th>
<th>Specificity (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cusabio</td>
<td>26</td>
<td>5</td>
<td>50</td>
<td>6</td>
<td>81.3 (63.0–92.1)</td>
<td>90.9 (79.3–96.6)</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>32</td>
<td>0</td>
<td>55</td>
<td>0</td>
<td>100 (86.7–100)</td>
<td>100 (91.9–100)</td>
</tr>
</tbody>
</table>

- **ARUP Laboratories**
  - Cusabio (China)
  - DiaSorin (Italy)

Another study compared Q-MAC to HDV RNA or Western blot detection and found:

- **Q-MAC**: 100% sensitive and 94% specific compared to HDV RNA or Western blot detection.
- **DiaSorin**: 7.1% FN rate and 21% FP rate and compared to QMAC.

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Chow S, CVI, 2016
Challenges in Estimating HDV Burden

- Lack of studies in “general population” of CHB
  - Most come from special groups: hepatology clinics, PWIDs, MSM with higher risk for HDV

- Variability in performance characteristics of anti-HDV tests
  - Risk of both over-estimating and underestimating

- Most studies focus on anti-HDV detection, with limited data on % with HDV viremia (to elucidate resolved versus persistent HDV infection)
Transmission of HDV

- Perinatal: possible but presumably extremely rare

- Children: Intrafamilial (especially in endemic areas)

- Adolescents/Adults: most common in developed countries → IDU, sex
  - Medical care, folk remedies, scarification
Risk Profiles: Global and in U.S.

Meta-regression of 376 population samples from 95 countries

Comparator general population or asymptomatic HBsAg+ from same region

NIDDK cohort
91/652 HDV+ (comparator HDV neg)

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**Table**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adjusted OR(^a)</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-DNA below 2,000 IU/mL</td>
<td>7.8</td>
<td>3.6–17.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALT &gt; 40 U/L</td>
<td>7.4</td>
<td>3.9–14.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IVDU</td>
<td>25.2</td>
<td>4.0–161.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>HDV endemic country of origin</td>
<td><strong>5.8</strong></td>
<td>3.1–10.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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*Stockdale A, J Hepatol 2020
Da B, AJG, 2020*
Changing Epidemiology Related to HBV Vaccination

*Italy, multicenter, seroprevalence surveys*

### Age-specific Prevalence of anti-HDV in HBsAg+ Persons

<table>
<thead>
<tr>
<th>Year</th>
<th>0-29 yrs</th>
<th>30-49 yrs</th>
<th>&gt; 50 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>25%</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>1992</td>
<td>14%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>1997</td>
<td>8%</td>
<td>10%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Overall prevalence:
- 1987: 23%
- 1992: 14%
- 1997: 8%

*Gaeta, Hepatology 2000*
Changing Epidemiology Related to Immigration

HBRN: North American HBsAg+ participants

Anti-HDV prevalence by Country of Origin

Highest among those born in Africa (7%), East Mediterranean (27%) and Europe regions (5%)

Lowest among those born in the Western Pacific (1.9%) and SE Asia (0%)
# Recommendations for HDV Screening

## Targeted approach

### Persons born in regions with reported high HDV endemicity

<table>
<thead>
<tr>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa (West Africa, horn of Africa)</td>
</tr>
<tr>
<td>Asia (Central and Northern Asia, Vietnam, Mongolia, Pakistan, Japan, Taiwan)</td>
</tr>
<tr>
<td>Pacific Islands (Kiribati, Nauru)</td>
</tr>
<tr>
<td>Middle East (all countries)</td>
</tr>
<tr>
<td>Eastern Europe (Eastern Mediterranean regions, Turkey)</td>
</tr>
<tr>
<td>South America (Amazonian basin)</td>
</tr>
<tr>
<td>Other (Greenland)</td>
</tr>
</tbody>
</table>

- Persons who have ever injected drugs
- Men who have sex with men
- Individuals infected with HCV or HIV
- Persons with multiple sexual partners or any history of sexually transmitted disease
- Individuals with elevated ALT or AST with low or undetectable HBV DNA

Screen all HBsAg-positive patients at least once
Diagnosis of HDV Infection

Screening test = Anti-HDV

Confirmation of viremia = HDV RNA test

WHO standard for HDV RNA NAT established in 2013

Anti-HDV assays not standardized
Variability in accuracy
No FDA-approved assays

Not routinely done
Variable Proportion of anti-HDV Positive Patients with Chronic Viremia

<table>
<thead>
<tr>
<th>Region</th>
<th>Anti-HDV Prevalence</th>
<th>HDV RNA Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>6.0</td>
<td>41 (32-51)</td>
</tr>
<tr>
<td>Eastern Med</td>
<td>3.5</td>
<td>49 (30-69)</td>
</tr>
<tr>
<td>European</td>
<td>3.0</td>
<td>64 (54-73)</td>
</tr>
<tr>
<td>Southeast Asian</td>
<td>3.2</td>
<td>50 (31-70)</td>
</tr>
<tr>
<td>West Pacific</td>
<td>4.1</td>
<td>73 (58-69)</td>
</tr>
<tr>
<td>Americas</td>
<td>5.9</td>
<td>64 (22-98)</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>4.5</td>
<td>58 (52-64)</td>
</tr>
</tbody>
</table>

Viremia rates reflect rate of spontaneous and treatment-associated clearance

Stockdale A, J Hepatol 2020
Patterns of Infection and Risk of Chronicity

**Coinfection**
- More severe acute disease
- Clinically indistinguishable from acute HBV
- Like acute HBV, most will clear spontaneously (both HBV and HDV)
- Higher frequency of acute liver failure

**Super-infection**
- More severe chronic disease
- Presents at “flare” in patient with known CHB
- Severity is variable
- Low rates of spontaneous clearance
HDV and HBV Levels in Chronic HDV

- About 70–90% of patients with HDV co-infection are HBeAg negative, and most have low serum HBV DNA

~50%: HDV RNA high HBV DNA low

~30%: HDV RNA and HBV DNA are similar

Least frequent: HDV RNA low HBV DNA high

Schaper et al, J Hepatol; Wedemeyer H, Lancet 2011
Clinical Outcomes of HDV Infection

**COINFECTION**

- Fulminant: 2-20%
- Recovery: 90-95%

**SUPERINFECTION**

- Chronicity: 2-7%
- Chronicity: 90-95%

**CIRRHOSIS**

- Recovery: 5-10%
- Fulminant: 10-20%

**HEPATOCELLULAR CARCINOMA**

- 70-80%
- Mortality rate 2-20% higher than HBV
- 2-4% per year

CalleSerrano, Manns & Wedemeyer, Seminars in Liver Disease 2012
HDV-Specific Factors Associated with Cirrhosis

- Presence of HDV RNA
- Anti-HDV IgM
- Older age
- HBeAg-negative
- HDV genotype
  - (HBV genotype)

French cohort

Taiwan cohort

Fattovich G, Gut 2000
Romeo Gastroenterology 2009
Su C Gastroenterology 2006
Wranke A, Hepatology, 2017
Roulot D, J Hepatol 2020
Risk of Cirrhosis and HDV Viremia

French cohort N=1,112

**Multivariate analysis of factors independently associated with cirrhosis:**

- Male sex: HR; 1.03 per year
- Country of origin. Northern Africa/Middle East HR (vs France) HR: 2.0
- HDV viremia HR: 6.11

Roulot D, J Hepatol 2020
HDV Associated with Higher Likelihood of Liver-Related Outcomes Compared to HBV

N=634 studies
Systematic review and meta-analysis

**HDV positive** vs. **HDV negative**

- **Cirrhosis**
  - HDV positive: 40.50% (22.09–60.43)
  - HDV negative: 14.22% (8.46–21.17)
  - OR = 3.84 (1.79–8.24)

- **HCC**
  - HDV positive: 5.67% (2.28–10.46)
  - HDV negative: 4.42% (1.81–8.09)
  - OR = 1.66 (0.74–3.74)

- **Death**
  - HDV positive: 17.17% (4.29–36.25)
  - HDV negative: 9.97% (2.81–20.84)
  - OR = 1.99 (0.06–6.65)
HCC Risk by Type of Study

**Prospective**
- Sheng 2007: RR = 1.57 [0.09; 26.52], Weight = 3.5%
- Manesis 2013: RR = 1.71 [0.22; 13.10], Weight = 5.3%
- Brancaccio 2019: RR = 2.34 [0.91; 5.99], Weight = 9.7%
- Tamura 1993: RR = 2.87 [1.17; 7.06], Weight = 9.8%
- Colombo 1991: RR = 9.00 [0.94; 85.94], Weight = 4.7%
- Bueguelin 2017: RR = 9.30 [3.03; 28.58], Weight = 8.8%

**Random effects model**
Heterogeneity: $I^2 = 5\%$, $\tau^2 = 0.2578$, $p = 0.38$

**Retrospective**
- Caturelli 2003: RR = 0.22 [0.07; 0.69], Weight = 8.7%
- Liaw 2004: RR = 0.43 [0.09; 2.03], Weight = 7.0%
- Mallet 2017: RR = 1.53 [1.39; 1.68], Weight = 12.4%
- Kushner 2015: RR = 2.90 [1.48; 5.70], Weight = 10.8%
- Fattovich 2000: RR = 3.20 [1.01; 10.12], Weight = 8.7%
- Ji 2012: RR = 3.90 [1.84; 8.26], Weight = 10.5%

**Random effects model**
Heterogeneity: $I^2 = 80\%$, $\tau^2 = 1.1077$, $p < 0.01$
Hepatitis D: Summary

- Prevalence estimates are limited by lack of testing and accuracy of test available
  - Epidemiology influenced by HBV vaccination and immigration
- Diagnostic tests—new WHO standard for HDV RNA and increased focus on performance of anti-HDV assays
- Proportion with chronic viremia variable (40-70%)
  - Patterns of HBV and HDV replication heterogeneous
- Higher risk for progression to cirrhosis and to develop HCC
  - HDV viremia important driver of risk
  - HDV and HBV genotypes may be relevant