Hepatitis B
and
Hepatitis D

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Hepatitis B
Hepatitis B

• 42 nm, partially double-stranded circular DNA virus.
• 350-400 million carriers world-wide;
  – causes 500000 to 1 million deaths a year.
• 1.25 million carriers in USA.(0.5 %);
  – > 8% in Alaskan Eskimos.
• Represents 5-10% of liver transplants worldwide.
• New infections: decreasing in frequency
  – 260,000/y in 1980’s;
  – now 73,000/y
• Greatest decline among children & adolescents (vaccine effect).
Hepatitis B

- Highest rate of disease in 20 to 49 year-olds
- 20-30% of chronically infected americans acquired infection in childhood.
- High prevalence in:
  - Asian-Pacific with 5-15% HBsAg(+)
  - Eastern European immigrants

**Transmission:**
- In USA predominantly sexual and percutaneous during adult age.
- In Alaska predominantly perinatal.
Global Distribution of CHB Carriers

HBsAg Prevalence

- Low < 2%
- Intermediate 2-8%
- High > 8%

Hepatitis B Transmission

• **Sexual:**
  – Heterosexual in 41% of acute cases.
  – Men having sex with men have 10% risk.

• **Percutaneous** (mostly illicit drug use):
  – 15% of acute HBV cases

• **Perinatal:**
  – 10% of acute cases (mother-child)

• **Transfusion:**
  – 1/63000 transfusions.

• **Other:** organ transplant, tattoo, piercing, acupuncture, ...
Risk of Seroconversion after percutaneous exposure to infected source (without prophylaxis)

## Seroprevalence of HBV, HCV & HIV

<table>
<thead>
<tr>
<th>Seroprevalence</th>
<th>HBV</th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Population</td>
<td>0.42%</td>
<td>1.8%</td>
<td>0.31-0.42%</td>
</tr>
<tr>
<td>HCW population</td>
<td>Higher</td>
<td>Same</td>
<td>Same</td>
</tr>
</tbody>
</table>

- HBV: Hepatitis B Virus
- HCV: Hepatitis C Virus
- HIV: Human Immunodeficiency Virus
- HCW: Healthcare Workers
<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous</td>
<td>6-30%</td>
<td>1.8%</td>
<td>0.2-0.5%</td>
</tr>
<tr>
<td>Mucosal</td>
<td>Transmission documented</td>
<td>Transmission documented</td>
<td>0.09%</td>
</tr>
<tr>
<td>Nonintact Skin</td>
<td>Transmission NOT documented</td>
<td>Transmission NOT documented</td>
<td>&lt; 0.1%</td>
</tr>
<tr>
<td>Human Bite</td>
<td>Transmission documented</td>
<td>Transmission documented</td>
<td>Transmission documented</td>
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</table>
# Infective Material Causing HCWs Infection

<table>
<thead>
<tr>
<th></th>
<th>HBV</th>
<th>HCV</th>
<th>HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documented</strong></td>
<td>Blood</td>
<td>Blood Immunoglobulins</td>
<td>Blood Blood products Body fluids</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>Blood products</td>
<td>Blood products Bloody fluids Semen Vaginal Fluids</td>
<td>Semen Vaginal fluid Cerebrospinal fluid Breast milk Serosal fluids Amniotic fluid Exudates Saliva in dental exam</td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>Urine Feces</td>
<td>Saliva Urine Feces</td>
<td>Saliva Urine Feces</td>
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</tbody>
</table>
## Postexposure Prophylaxis for Percutaneous or Mucosal exposure to HBV

<table>
<thead>
<tr>
<th>Status of Exposed</th>
<th>HBsAg(+) Source</th>
<th>HBsAg(-) Source</th>
<th>Not tested/Unknown Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unvaccinated</td>
<td>HBig 0.06 mL/kg or 5mL IM x 1 Vaccinate (0,1,6,12 mo)</td>
<td>Vaccinate</td>
<td>Vaccinate</td>
</tr>
<tr>
<td>Vaccine responder</td>
<td>No treatment</td>
<td>No treatment</td>
<td>No treatment</td>
</tr>
<tr>
<td>Vaccine non-responder</td>
<td>HBig 0.06 mL/kg or 5 mL IM x 2, 30 d apart Re-vaccinate</td>
<td>No treatment</td>
<td>If “high risk” source, treat as HBsAg(+)</td>
</tr>
<tr>
<td>Vaccinated; unknown response</td>
<td>Test anti-HBs titer</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If &gt; 10 mIU/mL: No treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If &lt; 10 mIU/mL: HBig 0.06 mL/kg or 5 mL IM x 1 + Re-vaccinate x3 dose and test titer</td>
<td>No treatment</td>
<td>Test anti-HBs titer</td>
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</table>
Intra-dermal HBV Vaccination for Vaccine Non-Responders


1. **Week 0**: give adult hepatitis B vaccine Engerix B, 0.25cc intra-dermal in forearm
2. **Week 2**: give adult hepatitis B vaccine Engerix B, 0.25cc intra-dermal in other forearm
3. **Week 4**: draw HBsAb (post hepatitis B vaccine)
   - HBsAb > 10 mIU/mL = Immune, no further vaccine
   - HBsAb < 10 mIU/mL = repeat steps 1, 2, 3

If HBsAb < 10 mIU/mL after second series of intradermal hepatitis B vaccine refer to Employee Health for counseling
   - some protocols give 16 weekly intradermal doses of 0.25 mL Engirex B (80 mcg total).
HBsAg(+) Healthcare Worker

• CDC says:
  – “Those who are HBeAg(+) should not perform exposure-prone procedures without previous counseling and advice from an expert review panel regarding under which circumstances they should be allowed to perform those procedures”.
  – They should notify the patient about their HBV status prior to the procedure.

• In Europe different countries use HBV-DNA varying from 200 IU/mL to < 2000 IU/mL to allow performance of exposure-prone procedures. Monitoring for compliance is needed.
Hepatitis B Transmission in Pregnancy
HBV & Pregnancy

• Pregnancy is well tolerated by HBV carriers
• HBV reactivation with exacerbation of disease is rare during pregnancy or post-partum.
• Intrauterine transmission of HBV is rare, but may occur during “threatened abortion” by transplacental leakage.
• Transmission by amniocentesis is low (<= 4%).
• If mother is HBeAg(+), risk of vertical transmission is 90% without prophylaxis.
• Post-partum “flare up” is common and due to decrease of cortisol levels. Up to 12-17% may have post-partum “e” seroconversion.
Maternal HBV Viral Load in HBeAg(+) mothers and Risk of Vertical Transmission

Han et al. AASLD Abstr 170, 2011

<table>
<thead>
<tr>
<th>Viral Load (copies/mL)</th>
<th>&lt; $10^6$</th>
<th>$10^6 - 10^{6.99}$</th>
<th>$10^7 - 10^{7.99}$</th>
<th>$\geq 10^8$</th>
</tr>
</thead>
<tbody>
<tr>
<td># Mothers</td>
<td>174</td>
<td>298</td>
<td>531</td>
<td>239</td>
</tr>
<tr>
<td># Neonates infected</td>
<td>0</td>
<td>9</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>% Neonates Infected</td>
<td>0</td>
<td>3</td>
<td>5.5</td>
<td>9.6</td>
</tr>
</tbody>
</table>

$< 10^6$ copies mL is $< 200000$ IU/mL
HBV & Pregnancy

• If mother has HBV-DNA < $10^8$ IU/ml:
  – neonatal immuno-prophylaxis prevents transmission in 95%, when done as follows:
    • HBIG 0.5 mL IM within 12 h of birth +
    • HBV immunization with 1st dose of 0.5 mL IM within 12 h of birth, in a different site from HBIG, and then vaccinate @ 1, 2, and 12 months.

• If mother is “highly infectious” with HBV-DNA > $10^8$ IU/mL
  – risk of HBV transmission is 30-40% despite [HBIG + HBV immunization]

• If mother is infected with HBeAg(-) and HBV-DNA > $10^8$ IU/mL (“very high load precore mutant HBV”):
  – infant is at risk of fulminant hepatitis B during initial 2 to 4 months of life.
HBV & Pregnancy

• Treatment, with Telbivudine, of mothers with HBV-DNA > 2x10^6 IU/mL, starting in wks-20 to 32 (usually 28) and until wk-4 post-partum,
  – decreases transmission of HBV to the neonate from 8% to 0%.
• EASL recommends to treat mothers, who are not in need of treatment but who have HBV-DNA > 10^{6-7} IU/mL, with Lamivudine, Telbivudine, or Tenofovir, to prevent perinatal transmission.
  – Treat from pregnancy week 24 until week 8-12 post-partum
• In the recent “Management of chronic HBV in Asian Americans”, the authors recommend to consider oral anti-viral during the 3rd trimester in pregnancy with viral load >/= 200,000 IU/mL (Dig Dis Sci: 56(11); 2011).
HBV & Pregnancy

• Cesarean section decreases vertical transmission rate, but:
  – is not indicated because [HBIG + HBV immunization +/- Antiviral] is very effective.

• Mothers with HBV/HDV co-infection:
  – may vertically transmit both infections to the neonate.
  – HBIG + HBV immunization can protect from both.

• Post-vaccination testing of infant should be done at age 9-15 months.
Hepatitis B in the General Population
Spectrum of Disease

Acute HBV infection
- 90% neonates
- 25–30% children
- <10% adults

Chronic infection
- 15–40%

Fulminant hepatic failure
Progressive chronic hepatitis
Inactive carrier state

Cirrhosis

 Decompensated cirrhosis
Death
HCC

Hepatitis B
High-Risk Groups

- Persons born in high prevalence area $\geq 2\%$
- Active homosexual men
- Promiscuous heterosexuals
- Person with hx of STD
- Healthcare & Public Safety workers
- Attendant/family of institutionalized mentally handicapped
- Person with HCV or HIV
- Person with chronic elevation of ALT or AST.
- Persons undergoing cytotoxic or immunosuppressive therapy.
- Intravenous drug abuser
- Person requiring frequent transfusions
- Inmate in long-term correctional facility
- Hemodialysis patient
- Traveler $>6$ months to endemic area
- Sexual partner or household contact of HBsAg(+) person
- All pregnant women
- Persons born in US from parents from areas with prevalence $\geq 8\%$, who were not vaccinated as infants
Hepatitis B Vaccination

- All children and adolescents
- All high-risk groups
- Post-Vaccination testing:
  - Healthcare & Public-Safety workers (1 month after 3rd dose)
  - Infants from HBsAg(+) mother (at age 9-15 months)
  - Hemodialysis patients (1 month post 3rd dose, and then yearly).
  - Sexual partner of HBsAg(+) persons (1 month after 3rd dose)
HBV Vaccine in HIV Infected

- If safe, consider delaying until CD4(+) cells are \( \geq 200 \text{ cells/mm}^3 \) or until HIV suppression is achieved.
- Protocol:
  - Double dose vaccine @ 0, 1, 2, and 12 months or
  - Intradermal HBV vaccination for up to 16 doses.
HBV Vaccination for People who Inject Drugs
WHO: July 2012

• Rationale:
  – Evidence shows that both a rapid schedule as well as providing incentives to people who inject drugs helps increase uptake and completion of HBV vaccination.
    • Vaccinations should be provided at a location and time convenient for people who inject drugs.

• Protocol:
  – Rapid schedule at days: 1, 7, and 21
Recommendations for HBsAg(+) Persons

• **PRECAUTIONS**
  • Have sexual contacts vaccinated
  • Use barrier sexual protection unless partner is immune
  • Not share razors, toothbrushes
  • Cover open cuts & scratches
  • Clean blood spills with detergent or bleach
  • Not donate blood, semen, organs.

• **ENCOURAGEMENTS**
  • Can participate in all activities, including contact sports.
  • Should be included in usual daycare and school activities, without isolation from others.
  • Can share food & utensils, and kiss others.
  • Breast feeding is recommended if the baby is being immunized with HBIG + vaccine.
Acute HBV
Acute Hepatitis B

- **Incubation**: 1-4 months
- **Prodrome**: arthralgia, arthritis, skin rash
- **Symptoms**: malaise, anorexia, jaundice, nausea, fatigue, low-grade fever, myalgia, change in taste and smell. Tender hepatomegaly in most patients; splenomegaly in 5-15%.
- **Infrequently**: confusion, edema, coagulopathy, coma (Fulminant Failure in 0.5%)
Acute Hepatitis B

**Diagnosis:**
- anti-HBc IgM antibody (+) usually with signal/noise ratio > 5.08 (s/n ratio </= 5.08 suggest reactivation of chronic infection);
- Frequently HBsAg (+) in early phase and anti-HBs(+) in late phase.
- HBV-DNA usually around 1000 IU/mL (in reactivation of chronic HBV usually </= 1 million IU/mL)

**Evolution to Chronicity:**
- a) Infants: 90%,
- b) Children 1-5: 25-50% (30%) ,
- c) Adults & older children: 5%
Acute Hepatitis B

- **Treatment:**
  - Supportive;
  - Anti-virals in “protrated hepatitis”, or failure to regenerate/sub-massive necrosis.
    - Lamivudine or Entecavir has been recommended for these cases.
  - In one study of 80 patients with severe acute HBV infection receiving either lamivudine or no therapy, mortality was significantly higher in the control group at 25.0% vs the lamivudine group at 7.5% ($P = .034$)
    - (Dig Dis Sci 2010;55:775-83)
  - Duration:
    - At least 3 months after development of anti-HBs, with HBsAg loss,
    - 12 months after anti-HBe seroconversion without HBsAg loss.
Age of Acquisition of Acute Hepatitis B 1989 estimates
Acute Hepatitis B Virus Infection with Recovery
Typical Serologic Course

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>HBeAg</th>
<th>anti-HBe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM anti-HBc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-HBs</td>
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</tbody>
</table>

Weeks after Exposure
Chronic HBV
Chronic Hepatitis B

- In low prevalence areas (USA) 30-50% history of acute hepatitis (rare in high prevalence)
- **Symptoms**: frequently asymptomatic; sometimes RUQ or epigastric pain or acute-like hepatitis episodes.
- **Extrahepatic**: serum-sickness, polyarteritis nodosa, membrano- or membranoproliferative-glomerulonephritis, mixed cryoglobulininemia, IgA nephropathy, papular acrodermatitis.
Extra hepatic Manifestations of HBV

- **Arthritis-Dermatitis**
  - **Manifestations:** fever, arthralgias, rash, angioneurotic edema, and, less commonly, hematuria and proteinuria is seen as a prodromal manifestation of acute hepatitis B and rarely in patients with chronic hepatitis B.
  - **Arthralgia:** proximal interphalangeal joints, knees, ankles, shoulders, and wrists are the joints most commonly affected.
  - **Laboratory:** HBsAg titers in the blood are high and complement levels are low.
    - HBsAg has been detected in synovial membranes, and complement levels in synovial fluid are low.
    - Evidence of activation of the complement system by HBsAg–anti-HBs complexes.
Extra hepatic Manifestations of HBV

• **Polyarteritis Nodosa**
  – As many as 30% of patients with polyarteritis nodosa are infected with HBV.
  – Occurs in less than 1% of patients with HBV infection,
    • after acute or recent hepatitis B or,
    • more commonly, in association with chronic HBV infection.
  – **Manifestations**: arthralgias, mononeuritis, fever, abdominal pain, renal disease, hypertension, central nervous system abnormalities, and rash.
  – **Pathogenesis**: Medium to small arteries and arterioles with fibrinoid necrosis and perivascular infiltration due to deposition of circulating immune complexes that contain HBsAg.
    • No apparent relationship exists between the severity of the vasculitis and the severity of the hepatic disease, and the hepatic disease often is relatively mild despite high levels of viral replication.
Extra hepatic Manifestations of HBV

• **Polyarteritis Nodosa**
  
  – **Diagnosis:**
    
    • Arteriography of mesenteric or renal vessels showing cork-screwing and aneurisms.
    
    • Biopsy of affected organ showing arteritis of medium size arterioles.

  – **Course:** variable, but the prognosis is gravest for patients with substantial proteinuria (>1 g/day), renal insufficiency (serum creatinine > 1.6 mg/dL), gastrointestinal involvement, cardiomyopathy, and involvement of the central nervous system.

  – **Management:** antiviral agents, given alone or in combination with plasmapheresis.
Extra hepatic Manifestations of HBV

• **Glomerulonephritis**
  
  • Most common types:
    – membranous glomerulonephritis and membranoproliferative glomerulonephritis.
  
  • Pathogenesis:
    – Renal biopsy with immune complex deposition and cytoplasmic inclusions in the glomerular basement membrane.
    – The immune complexes activate complement and production of cytokines with a subsequent inflammatory response.
  
  • Manifestations:
    – Nephrotic syndrome is the most common presentation.
    – In affected children, renal failure at presentation is almost always mild, and a history of clinical liver disease is uncommon.
    – Liver biopsy specimens almost always demonstrate varying degrees of chronic hepatitis.
Extra hepatic Manifestations of HBV

• **Glomerulonephritis**

• **Diagnosis:**
  – serologic evidence of HBV antigens or antibodies, the presence of immune-complex glomerulonephritis in a renal biopsy specimen, and the demonstration of glomerular deposits of one or more HBV antigens, such as HBsAg, HBcAg, or HBeAg, by immunohistochemistry.
  – Most patients have detectable HBeAg in serum and, in addition, demonstrate low serum C3 and occasionally low C4 levels.

• **Evolution:**
  – Children: The renal disease typically resolves in months to several years. Often, resolution occurs in conjunction with HBeAg seroconversion. Rarely, however, renal failure may ensue.
  – Adults: natural history has not been well defined, but several reports suggest that glomerular disease is often slowly and relentlessly progressive.

• **Treatment:**
  – Interferon alpha. Linked to long-term control of HBV replication.
  – Therapy with nucleoside analogs has resulted in improved renal function and diminished proteinuria.
Extra hepatic Manifestations of HBV

• **Cryoglobulinemia:**
  - Type II and type III cryoglobulinemia have been associated with hepatitis B, but the association is uncommon.
    - Type II cryoglobulins consist of a polyclonal IgG and monoclonal IgM,
    - Type III cryoglobulins contain polyclonal IgG and rheumatoid factor.
      • Frequency of cryoglobulinemia is higher in with chronic HCV infection (54%) than with chronic HBV infection (15%).
  - Manifestations:
    - systemic vasculitis (purpura, arthralgias, peripheral neuropathy, and glomerulonephritis),
    - often paucisymptomatic or asymptomatic.

• Treatment:
  - Interferon has been used successfully to treat symptomatic HBV cryoglobulinemia.
  - Experience with nucleoside analog therapy has not been reported.
Chronic Hepatitis B
Natural History

• Evolution to Chronicity after Acute HBV:
  – 90% of infants infected at birth
  – 30% of children infected at age 1-5 y
  – 6% of infected after age 5 y

• Cumulative cirrhosis risk:
  – 8-20% at 5 y.

• Risk of decompensation in untreated HBV cirrhosis:
  – 20% at 5 y

• Survival for untreated decompensated cirrhosis:
  – 14-35% at 5 y.

• Death from chronic HBV liver disease
  – 15-25% of chronically infected

• Risk of HCC in HBV cirrhosis:
  – 2 – 5% per year.

• USA yearly mortality from HBV
  – 5000 per year
In a survey of 17 liver centers across the US, approximately 56% of HBV carriers were of Asian descent.

- **Patient Type**
  - U.S.-born
  - Foreign-born (Asia)

- **Mode Transmission**
  - Sexual, Parenteral
  - Perinatal (vertical)

- **Percent Developing Chronic HBV**
  - 2-10%
  - 80-90%

Progression to Chronic Hepatitis B Virus Infection

Typical Serologic Course

<table>
<thead>
<tr>
<th>Weeks after Exposure</th>
<th>IgM anti-HBc</th>
<th>Total anti-HBc</th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>anti-HBe</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>52</td>
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Acute (6 months)
Chronic (Years)
Age of Acquisition of Chronic Hepatitis B 1989 estimates

- Adult: 59
- Perinatal: 24
- Children 1-10 y: 6
- Adolescent: 12

Legend:
- Adult
- Perinatal
- Children 1-10 y
- Adolescent
## HBV Genotypes

**Test genotype with: INNO-LiPA HBV Genotyping**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Areas of prominence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>North West Europe, USA, Central Africa</td>
</tr>
<tr>
<td>B</td>
<td>Taiwan, Japan, Indonesia, China, Vietnam</td>
</tr>
<tr>
<td>C</td>
<td>East Asia, Taiwan, Korea, China, Japan, Vietnam</td>
</tr>
<tr>
<td>D</td>
<td>Mediterranean area, India</td>
</tr>
<tr>
<td>E</td>
<td>West Africa</td>
</tr>
<tr>
<td>F</td>
<td>Central and South America</td>
</tr>
<tr>
<td>G</td>
<td>France, USA</td>
</tr>
<tr>
<td>H</td>
<td>Mexico, Central and South America</td>
</tr>
</tbody>
</table>

HBV Genotypes and Place of Birth

Test genotype with: INNO-LiPA HBV Genotyping

Clinical Associations with Genotypes

- Time to HBeAg seroconversion and probability of HBsAg loss:
  - B < C
- Response to treatment with interferon-α:
  - A > B ≥ C > D
- Precore/core promoter mutant frequency:
  - precore mutation not selected with A and F
- Liver disease activity and risk of progression:
  - B < C
- Evolution to chronic liver disease:
  - A < D
- Hepatocellular carcinoma risk:
  - B > C in younger age group in Taiwan, but
  - B < C in older age group in Japan
Characteristics of HBV genotype C

• HBe seroconversion at older age
  – (< 20 vs 48 years)
• Higher rate of HBe reversion, HBe(-) to (+).
• Greater risk of reactivation
• More severe histology
• Higher incidence of HCC
• Lower response to regular IFN
Prognostic Factors For Progression To Cirrhosis

<table>
<thead>
<tr>
<th>Factors</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>.0001</td>
</tr>
<tr>
<td>HBV-DNA persistance</td>
<td>.0001</td>
</tr>
<tr>
<td>Virus genotype C</td>
<td>.001</td>
</tr>
<tr>
<td>Recurrent acute flares</td>
<td>.001</td>
</tr>
<tr>
<td>Histologic Staging</td>
<td>.0002</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>.001</td>
</tr>
<tr>
<td>HCV, HDV co-infection</td>
<td>.001</td>
</tr>
<tr>
<td>HIV co-infection</td>
<td>.02</td>
</tr>
</tbody>
</table>

Development of Pre-Core and Core-promoter Mutants
Meaning of Different HBV Markers

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<thead>
<tr>
<th>HBeAg(+)</th>
<th>HBV-Genotype</th>
<th>HBV-DNA</th>
<th>Basal Core Promoter (BCP) Mutation</th>
<th>Precore Mutation</th>
</tr>
</thead>
</table>
| - Indicates high viral replication  
- Risk factor for: chronic hepatitis, cirrhosis, and HCC.  
- Natural resolution over time (8-10%).  
- Slower rate of progression of liver disease. | - A responds better to IFN; B & C are intermediate; D has poor response.  
- B: high risk of HCC in young Taiwanese and old Japanese.  
- C: higher risk of HCC in BCP mutants | - If > 200000 IU/mL in pregnancy, increase fetal transmission despite vaccination +/- HBIG.  
- Progression to cirrhosis increases if > 2000 IU/mL.  
- Risk of HCC increases if > 200000 IU/mL | - Increases disease progression in Genotypes B and C.  
- Increases HCC risk in Genotype C. | - Most common in HBeAg(-).  
- Associated with ALT elevation and persistent necro-inflammation at lower HBV-DNA.  
- Fast progression to liver disease.  
- No natural resolution over time. |
Meaning of Different HBV Markers

• **Quantitative HBsAg:** Quantitative hepatitis B surface antigen (HBsAg) reflects the amount and the transcriptional activity of covalently closed circular DNA inside hepatocytes.
  – Detects all three forms of circulating HBsAg: virion-associated HBsAg, subviral particles and HBsAg produced from integrated sequence.
  – Changes very slowly with time and remain at a low level among inactive carriers.

• Provides information concerning disease activity over and above an estimation of viral replication.
  – **INACTIVE CARRIER:** European HBeAg(-) and HBV-DNA < 2000 IU/mL and HBsAg < 1000 IU/mL
  – **LOW RISK OF HCC:** Asian HBV-DNA < 2000 IU/mL and HBsAg < 1000 IU/mL
  – **LIKELY TO CLEAR HBsAg:** Asian with HBsAg < 100 IU/mL
  – **Peg-IFN RESPONSE HBeAg(+)**:
    • GOOD: at week 24, HBV-DNA < 20000 and HBsAg < 1500;
    • POOR: HBsAg > 20000 @ wk 24 or no decline @ wk 12 or 24
  – **Peg-IFN RESPONSE HBeAg(-)**:
    • GOOD: HBsAg > 10% drop @ week 24, or > 1 log drop @ wk 48;
    • POOR: HBV-DNA < /= 2 log drop @ wk 12, or HBsAg no decline @ wk 12
Natural History of HBV: Development of HBeAg-negative CHB

Phases of HBV infection:
- Replicative or immune tolerance phase
- HBeAg clearance phase
- Low-replicative phase
- HBV reactivation

Wild-type HBV

Variant HBV

### HBeAg-positive vs HBeAg-negative
#### Chronic Hepatitis B

<table>
<thead>
<tr>
<th>HBeAg (+)</th>
<th>HBeAg (–)</th>
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<tbody>
<tr>
<td>High HBV DNA</td>
<td>Lower HBV DNA</td>
</tr>
<tr>
<td>HBeAg produced</td>
<td>No HBeAg produced</td>
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<tr>
<td>Less difficult to treat</td>
<td>Difficult to treat</td>
</tr>
<tr>
<td>Slower rate of progression to liver disease</td>
<td>Fast rate of progression to liver disease</td>
</tr>
<tr>
<td>Natural resolution over time (8-10%)</td>
<td>No natural resolution over time</td>
</tr>
<tr>
<td>Clinical outcome measures: HBV DNA, ALT, “e” &amp; “s” seroconversion</td>
<td>Clinical outcome measures: HBV DNA, ALT normalization</td>
</tr>
</tbody>
</table>

Prevalence of HBeAg-negative CHB

- Prevalence of HBeAg-negative CHB in HBsAg-positive patients differs according to region and is determined primarily by the infecting genotype:\(^1\)
  - up to 90% in Mediterranean regions
  - \(\sim 30\text{–}55\%\) in Asia Pacific
  - \(\sim 30\text{–}50\%\) in Northern Europe
  - up to 40% in the United States
- Prevalence of HBeAg-negative CHB is increasing worldwide:\(^2\)

---

Testing for HB Pre-core & Core-Promoter Mutant

• Commercial Test: Inno-LiPA HBV PreCore
• Suspect and Test for “mutant” HBV when HBV-DNA is > 2000 IU/mL and patient is HBeAg(-). Patient may have:
  – HBV wild-type in “inactive carrier state” (normal ALT: males =/< 30 U/L, females =/< 19 U/L): no need to treat, or
  – Precore or Core-promoter mutant HBV in “immunotolerant state” (normal ALT): no need to treat, or
  – Precore or Core-promoter mutant HBV in “immunoactive state” (elevated ALT): needs treatment.
Chronic Hepatitis B

• **Diagnosis:**
  – *HBsAg* (+) & HBV-DNA (+) for > 6 months, with
  – anti-HBc IgM (-) but anti-HBc total (+) [excludes incubation]

(1 IU = 5 copies, and 1 pg = 2.86 x 10^5 copies/ml)
States of Chronic Hepatitis B

- Inactive Carrier
- Immunotolerant
- Immunoactive or Immunoreactive
- Occult Hepatitis B and Immunosuppression Mediated HBV flare-up
HBV Viral Load Conversion

- $1 \text{ pg} = 2.86 \times 10^5 \text{ copies/mL}$
- $1 \text{ pg} = 5.72 \times 10^4 \text{ IU/mL}$
- $1 \text{ copy} = 0.2 \text{ IU}$
- $1 \text{ IU} = 5 \text{ copies}$
- $2000 \text{ IU} = 10000 \text{ copies} = 0.035 \text{ pg}$
- $20000 \text{ IU} = 100000 \text{ copies} = 0.35 \text{ pg}$
Viral Load and ALT Thresholds to Consider Treatment

• The likelihood of hepatic injury is determined by the presence of:
  – elevated liver enzymes (ALT > 1-2 X the ULN),
  – Moderate to severe necro-inflammation or fibrosis,
  – by a meaningful elevation of HBV-DNA.

• For treatment purposes normal ALT values are:
  – Males up to 30 U/L
  – Females up to 19 U/L
Viral Load and ALT Thresholds to Consider Treatment

• The threshold of HBV-DNA viral load which is likely to be associated with tissue damage (meaningful elevation) is different according to AASLD with “Wild Virus” (HBeAg(+)) and in pre-core or core promoter “Mutant Virus” (HBeAg(-)).

• For treatment purposes, meaningful HBV-DNA values are:
  – Wild-type HBeAg(+): 20,000 IU/mL (2000 IU/mL EASL)
  – Mutant HBeAg(-): 2,000 IU/mL
Viral Load and ALT Thresholds to Consider Treatment

• When a patient is HBeAg(-) and has an HBV-DNA > 2,000 IU/mL but less than 20,000 IU/mL:
  – check for the presence of pre-core or core-promoter mutations because the infection with a “mutant” virus may need treatment if ALT is elevated or if ALT elevates in the future.
Viral Load and ALT Thresholds to Consider Treatment

• Exceptions to ALT & HBV-DNA rules:
  
  – **CIRRHOSIS**: In patients with cirrhosis, liver damage may continue in absence of ALT elevation and even with relatively low viral replication (> 2000 U/L vs any detectable > 60 U/L) (EASL: any detectable HBV-DNA)
  
  – **HBeAg(+) AGE 30 or First Degree relative with HCC**: In patients older than 30 or with Fam Hx of HCC, liver damage may occur with viral load > 2000 U/L even in absence of ALT elevation. A FibroScan with kPa > 8 or APRI > 1.5 identify who needs liver biopsy to directly assess presence or absence of liver injury. Treat if >/= F2.

  • (EASL: age > 30, or Family hx of cirrhosis or HCC; If HBeAg(-) with HBV-DNA 2000 to <20000 do not need immediate Bx.)
Chronic Hepatitis B states

• **Inactive Carrier state**

  • **Normal ALT and**
    
    – **HBe(+) or “Wild-type”:**
      
      HBV-DNA < 20000 IU/mL, (EASL: < 2000)
    
    – **Mutant-HBe(-):**
      
      HBV-DNA < 2000 IU/mL,

    *(in HBe(-): if HBV-DNA > 2000 IU/mL but < 20000 IU/mL, needs testing for PreCore or Core-promoter mutation to classify, but management will not change)*
Chronic Hepatitis B states

- **Follow-up of Inactive Carrier state**
  - Repeat ALT every 3 months x 1 year; then every 6-12 months. After age 40, add HBV-DNA every year.
    - If HBsAg titer < 1000 IU/mL the interval may be longer.
  - If ALT elevates > ULN and HBV-DNA remains low: investigate cause & consider liver Bx
  - If ALT elevates > ULN (male > 30 U/L, female > 19 U/L) & HBV-DNA increases to > 20000 IU/mL: treat
  - If ALT remains normal but HBV-DNA elevates > 2000 IU/mL:
    - Liver Fibrosis assessment +/- Bx if Hbe(+) older than 30 or Fam Hx HCC;
    - Liver Bx if APRI > 1.5 or FibroScan > 8 kPa
    - Treat if F0-4, otherwise observe (immunotolerant state).
Chronic Hepatitis B states

- **Immunotolerant state**

- **Normal ALT and**
  - HBe(+) or Wild-type: HBV-DNA > 20000 IU/mL, (EASL > 2000)
  - Mutant-HBe(-): HBV-DNA > 2000 IU/mL

- **NOTE:**
  - AASLD: Consider Liver Bx in older than 40 years & HBV-DNA > 2000 IU/mL, (May be immunoactive). Bx if APRI > 1.5; FibroScan > 8 kPa
  - EASL: Consider liver Bx in HBe(+) after age 30, or if family history of cirrhosis or HCC; Bx in APRI > 1.5 or FibroScan > 8 kPa.
  - If HBe(-), no need for Bx unless HBV-DNA > 20000
Chronic Hepatitis B states

- **Follow-up of Immunotolerant state**
  - ALT every 3-6 months
  - If ALT elevates > ULN (male > 30 U/L, female > 19 U/L) & HBV-DNA still > 20000 IU/mL: consider liver Bx and/or treat
  - If person is or reaches age =/> 40: consider liver Bx to assess histologic activity and decide about treatment
Chronic Hepatitis B states

• **Immunooactive state**
  
  • Elevated ALT (> ULN)
    - HBe(+) or Wild-type:
      
      HBV-DNA > 20000 IU/mL (EASL: > 2000)
    
    - **Mutant-HBe(-):**
      
      HBV-DNA > 2000 IU/mL
  
• **Treat**
# Management of Patients in “Gray Zone”
(Expert Opinion)

## EVALUATION

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<td>Male gender</td>
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<tr>
<td>Male ALT &gt; 30 U/L</td>
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<tr>
<td>Female ALT &gt; 19 U/L</td>
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<tr>
<td>BCP Mutation</td>
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<tr>
<td>HCC in 1st degree relative</td>
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<tr>
<td>Albumin &lt; 3.5 g/dL or Platelets &lt; 130K</td>
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</table>

## DECISION

<table>
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<th>Action</th>
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<td>&lt; 3</td>
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<tr>
<td>&gt;/= 3 &amp;</td>
<td>Monitor without therapy</td>
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<tr>
<td>HBV-DNA&lt;/= 2000 IU/mL</td>
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</tr>
<tr>
<td>&gt;/= 3 &amp;</td>
<td>Treat</td>
</tr>
<tr>
<td>HBV-DNA &gt; 2000 IU/mL</td>
<td></td>
</tr>
</tbody>
</table>
Occult Hepatitis B

- **Definition:** HBV-DNA in liver and/or serum in absence of HBsAg
  - may be anti-HBc(+), anti-HBs(+), or be negative for both (20%).
- **Causes:**
  - a) Persistent HBV cccDNA in hepatocyte nucleus after “clearance” of clinical infection, with viral control mediated by:
    - 1) T-cell mediated immune surveillance, or
    - 2) Viral interference (i.e.: co-infection with HCV or schistosoma), or
    - 3) Epigenetic mechanisms like transcriptional repression.
  - b) Infection with virus with antigenically modified S protein or with mutation inhibiting S gene expression: “a” determinant mutant virus (most common G145R mutation)
Occult Hepatitis B

- **Highest risk groups for occult HBV:**
  - Natives from highly HBV-endemic areas,
  - chronic HCV co-infected,
  - HIV co-infected,
  - hemodialysis patients,
  - hemophiliacs,
  - former/current IV drug abusers
Occult Hepatitis B

• **Clinical Relevance:**
  – a) Transmission of infection by blood transfusion (seen in Taiwan and India),
  – b) Reactivation due to immunosuppression:
    • Rituximab, Alemtuzumab, Infliximab, liver transplant, hematological malignancies, HIV infection, stem cell transplantation, chemotherapy, kidney or heart transplantation,
  – c) Acceleration of liver damage in chronic HCV and cryptogenic liver disease,
  – d) Increased risk of HCC

• **Prevention of Transmission of Occult HBV**
  – Test donated blood for HBV-DNA in highly endemic areas.
    • Do not use blood if HBV-DNA is (+).
Prevention of HBV Reactivation by Immunosuppression

• **Management of Pre-Immunosuppression HBV markers:**
  – Test for HBsAg & anti-HBc before immunosuppression;
  • If HBsAg(+):
    – Risk of reactivation, even when HBV-DNA is negative, is 40%
    – Investigate checking HBV-DNA quantitation and ALT;
      » If HBV-DNA is (+): treat accordingly with Entecavir or Tenofovir (Lamivudine OK if HBV-DNA < 2000 IU/mL)
      » If HBV-DNA is (-): Any oral anti-HBV antiviral can be an option.
  – Continue antiviral until 12 months after end of therapy.
  – Monitor HBV while immunosuppressed to detect evidence of resistance.
Prevention of HBV Reactivation by Immunosuppression

• Management of Pre-Immunosuppression HBV markers:
  – Test for HBsAg & anti-HBc before immunosuppression;
    • If only HBc(+):
      – Risk of reactivation with anti-HBc(+) and HBV-DNA(-), is 4%.
      – Investigate checking HBV-DNA quantitation;
        » If HBV-DNA is positive, treat with Entecavir or Tenofovir (Lamivudine OK if HBV-DNA < 2000 IU/mL)
        » If HBV-DNA is (-):
          • A) Start pre-immunosuppression prophylaxis with Lamivudine or other anti-HBV drug and continue antiviral until 12 months after end of therapy, or
          • B) monitor while on immunosuppressive therapy q 1-3 months for reappearance of HBsAg or HBV-DNA; If HBV reactivates, treat.
Treatment of HBV
Chronic Hepatitis B
Treatment Candidates

- **Cirrhotic:**
  - Any ALT value
  - HBV-DNA > 2000 IU/mL (EASL: any detectable HBV-DNA.)

- **Non-cirrhotic with HBsAg(+) > 6 months, and:**
  - ALT > ULN, or Liver Bx with moderate or severe activity, plus
    - **a) Wild HBe(+):** HBV-DNA > 20000 IU/mL (EASL > 2000) or
    - **b) Mutant-HBe(-):** HBV-DNA > 2000 IU/mL
Therapeutic Strategies in HBeAg-negative CHB

- Treatment course of limited duration
  - off-therapy sustained responses
  - best achieved with IFN-based treatment
  - long-term clinical benefit without need of continuous medication

- Long-term maintenance therapy
  - effective HBV suppression maintained as long as the patient is on-therapy
  - best achieved with NAs
  - high rates of relapse once treatment is stopped
  - long-term suppression of HBV DNA can lead to increased survival benefit, but is compromised by risk of drug resistance

Chronic Hepatitis B
Treatment Options

- **Interferon:**
  - non-cirrhotic, and
  - ALT > 2 x ULN, and HBV-DNA < 12 x 10^6 IU/mL (200 pg/mL, or 57 x 10^6 copies/mL)

- **Peg-IFN:**
  - non-cirrhotic, and
  - HBV-DNA < 3.6 x 10^9 IU/mL (EASL: < 2x 10^8 IU/mL)
  - ALT > 1 x ULN (EASL: ALT > 2-5 X ULN)
  - Genotype A > B >/= C > D
  - Older age
  - Liver Bx with Activity >/= A_2
Chronic Hepatitis B
Treatment Options

- **Entecavir or Tenofovir**:  
  - They are preferred due to “high barrier” for viral resistance, needing several viral mutations before resistance develops.  
  - Given if patient is a not candidate for interferon but is a candidate for treatment, or because of physician/patient preference.  
  - Lamivudine, Telbivudine, Emtricitabine, and Adefovir have a low barrier for resistance and/or lower antiviral activity. For these reasons they are not first-line therapies.
Chronic Hepatitis B
Treatment Options in Special Groups

• **In Pregnancy:** in the following order
  - Tenofovir
    - category B & conditionally safe for lactation depending on dose or patient-group.
  - Telbivudine
    - category B & possibly unsafe for lactation.
  - Lamivudine
    - category C & unsafe for lactation

• **In Patients with HIV co-infection:**
  - All HBV patients should be check for HIV before therapy.
  - If CD₄ > 500/mL, only use Peg-IFN, Adefovir, or Telbivudine unless the anti-HBV drug is being use as part of HAART.
  - If on HAART: Tenofovir + (Emtricitabine or Lamivudide)
  - Use of other HBV drugs, as monotherapy, may facilitate HIV resistance.
Chronic Hepatitis B
Treatment Options in Special Groups

- **Woman in child-bearing age wishing to eradicate virus before pregnancy:**
  - Peg-Interferon

- **Renal Insufficiency:**
  - Entecavir

- **Decompensated Cirrhosis:**
  - Entecavir
    - 1 mg/d (not 0.5 mg/d); risk of lactic acidosis if MELD > 20.
  - Tenofovir may be considered.
Chronic HBV

Goals of Therapy

• **Ideal:**
  - Clear HBsAg and cure disease; (infrequently reached).
Chronic HBV

Goals of Therapy

- **Practical:**
  - **HBe(+)**: Convert to “inactive carrier state” with:
    - HBV-DNA < 20000 IU/mL and
    - sero-conversion to HBe(-)/anti-HBe(+), confirmed 1-3 months later;
    - ideally < 20 IU/mL (complete response)
  - **Mutant-HBe(-)**: Convert to “inactive carrier state” with:
    - HBV-DNA < 2000 IU/mL
    - ideally < 20 IU/mL (complete response)
  - **Cirrhotic**: Convert to:
    - HBV-DNA < 2000 IU/mL
    - ideally < 20 IU/mL (complete response)
Chronic HBV Therapy

Points to Keep in Mind

• **Sustained loss of HBeAg requires:**
  – to confirm seroconversion by a second test 1-3 months post-seroconversion.
  – to continue oral agent for at least 6 months (EASL: 12 months) after confirmation of the loss of HBeAg and development of anti-HBe.

• **Long therapy with oral agents increases frequency of drug-resistance.**

• **If patients were HBe(-) pre-treatment, therapy will be life-long or until patient lososes HBsAg.**
Definitions of Virological Response to Interferon / Peg Interferon

- **Primary Non-Response:**
  - Not well defined

- **Virological Response:**
  - HBV-DNA < 2000 IU/mL at any time.
  - Evaluated during therapy at 6 & 12 months.
  - Evaluate after EOT at 6 and 12 months.

- **Sustained Off-treatment Virological Response:**
  - HBV-DNA < 2000 IU/mL >/= 12 months after EOT.

- **Use of HBsAg titer to predict response to Peg-IFN:**
  - **HBeAg(+):** If week 12 HBsAg titer is > 20000 IU/mL the NPV is 84-100%; consider discontinue therapy (?)
  - **HBeAg(-):** In genotype D, if HBsAg titer decline is < 0.5 log and HBV-DNA decline < 2 log, NPV is 90%; discontinue (?).
Definitions & Management for Treatment with Oral Antivirals

- **Primary non-response**: drop of HBV-DNA < 1 log after 12 wks of therapy or < 2 log after 24 weeks of therapy.
  - Check for viral resistance (INNO-Lipa HBV DR v2).
  - May be compliance issue, or host pharmacologic effect.
  - Change to more potent drug or add second drug without cross-resistance.

- **Partial Response**: HBV-DNA drop > 1 log, with HBV-DNA > 2000 IU/mL, after 24 weeks of therapy.
  - Predicts high risk for resistance. (Resistance risk is low if HBV-DNA is < 200 IU/mL).
  - Change or add second drug without cross-resistance.

- **Complete On-therapy Response**:
  - HBV-DNA < 20 IU/mL
Definitions for Treatment with Oral Antivirals

• **Virologic Breakthrough:**
  a) Increase of HBV-DNA > 1 log from nadir, at any time, while on therapy, or
  b) Reappearance of HBV-DNA(+) after 2 negative HBV-DNA, at least 1 month apart, while still on therapy.
    – Check for viral resistance (INNO-Lipa HBV DR v2).
    – May be compliance problem.
    – Change to more potent drug or add second drug without cross-resistance.

• **Virologic Relapse:**
  – Increase in serum HBV-DNA > 1 log IU/mL after discontinuation of therapy, on at least 2 determinations 4 weeks apart.
Definitions for Treatment with Oral Antivirals

- **Sustained Virological Response:**
  - Persistence of clinical response 12 months after end-of-therapy, to a predefined goal (like HBV-DNA < 2000 IU/mL in HBeAg(-) or < 20000 IU/mL in HBeAg(+)).

- **Complete Off-Therapy Response:**
  - SVR plus loss of HBsAg

- **Histological Response:**
  - Decrease in necro-inflammation by =/> 2 Ishak or HAI score without worsening of fibrosis.

- **Commercial Test for Drug Resistance:**
  - Inno-LiPA HBV DR v2 (Lamivudine, Telbuvidine, Emtricitabine and Adefovir)
# Drug Cross-Resistance Profile
(Reverse transcriptase mutations)

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Entecavir</th>
<th>Adefovir</th>
<th>Tenofovir</th>
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<tbody>
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<td>S</td>
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# Treatment Options for Antiviral Resistance

<table>
<thead>
<tr>
<th>Resistance to</th>
<th>Rescue Therapy</th>
</tr>
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</table>
| Lamivudine or Telbivudine | **Add:** Tenofovir, or Adefovir (?), or  
**Switch to:** Tenofovir + Emtricitabine (Truvada) |
| Adefovir | **Add:** Entecavir, or Lamivudine (?), or  
**Switch to:** Entecavir, or Tenofovir, or if Lamivudine resistant to (Tenofovir + Emtricitabine) (Truvada) |
| Entecavir | **Add:** Tenofovir, or Adefovir (?), or  
**Switch to:** Tenofovir or (Tenofovir + Emtricitabine) |
| Tenofovir | **Add:** Entecavir, Telbivudine, Lamivudine, or Emtricitabine |
Undetectable HBV-DNA at 1 year
HBeAg(+) Patients
Seroconversion to anti-HBe at 1 year
HBeAg(+) Patients
Undetectable HBV-DNA at 1 year HBeAg(-) Patients
Loss (%) of HBsAg after 1 year of Different Therapies
3 year F/U after Virological Response* with Peg-IFN HBeAg(+) & HBe(-) Patients

* Within 6 months after EOT
Long term F/U of Interferon Responders
Loss of HBsAg after HBe seroconversion (Europeans & Americans)
Rates of Antiviral Resistance
Peg-IFN

- Approved in 2002 for adults.
- Immunomodulatory therapy.
- Dose Peg-IFN alpha 2a: 180 mcg/week x 48 weeks, SQ.
- For both HBeAg(+) and (-).
- Does not induce viral resistance
- May cause transient and potentially severe ALT elevations
- Best candidates:
  - Viral load < 2 x 10^8 IU/mL
  - Genotypes A > B >/= C > D
  - ALT > 2 x ULN; ideal if > 5 x ULN
  - Females > males
  - Older age
Peg-IFN

- **Contraindicated:**
  - Decompensated cirrhosis
  - Pregnancy
  - Autoimmune disorder
  - Post organ-transplant

- **Side effects:**
  - Very Common (> 10%): anorexia, malaise, arthralgia, myalgia, alopecia
  - Common (1-10%): anxiety, depression, neutropenia, infections, thyroid disease, visual disorder
  - Uncommon (< 1%): Suicidal ideation, pancytopenia, peripheral neuropathy
Hepatitis B Therapy and ALT Flares

- Exacerbations of hepatitis during hepatitis B therapy
  - Characterized by transient and potentially severe increases in serum ALT

- Transient acute exacerbations of hepatitis B (ALT elevation >10-fold higher than the upper limit of normal) were observed
  - HBeAg negative: 12% and 7% during and after treatment
  - HBeAg positive: 18% and 12% during and after treatment

- Marked transaminase flares while on PEGASYS therapy have been accompanied by other liver test abnormalities
  - Dose reduction should be considered in patients experiencing transaminase flares
  - If ALT increases are progressive despite reduction of PEGASYS dose or are accompanied by increased bilirubin or evidence of hepatic decompensation, PEGASYS should be immediately discontinued

Entecavir

- Oral deoxyguanidine nucleoside analog approved in 2005
- Active in wild, HBe(-), and YMDD
- **Dose:** - 0.5 mg/d in HBe(+ or (-); 
  - 1 mg/day in YMDD mutant and in decompensated cirrhosis;
  - modify in renal impairment.
- No interaction with Lamivudine, Adefovir, nor Tenofovir.
- Should be taken in empty stomach.
- In HIV co-infection, may induce HIV drug resistance; OK to use while in HAART.
- In Lamivudine- or Telbivudine- resistant HBV, these drugs must be discontinue when Entecavir is initiated.
Entecavir

• **Side Effects:**
  – Lactic acidosis (highest risk with MELD > 20),
  – severe hepatomegaly
  – **Headache, fatigue, nausea.**

• **Viral Response after 1 y therapy:**
  – HBe(+) = 82%,
  – HBe(-) = 48%

• **Resistance:**
  – YMDD mutant (Lamivudine resistant): 7% @ 1 y, 26% @ 3y, & > 50% @ 5y.
  – In Naïve: 1.2% @ 5 y.
  – Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.
Tenofovir Disoproxil

- Oral adenosine nucleotide analog; approved in 2008.
- Dose: 300 mg/day; adjusted by renal function
- Effective in: wild and YMDD mutant; HBeAg(+) and (-)
- Causes 4-5 log drop HBV-DNA @ 48 weeks
- No resistance in up to 4 years
- Side Effects:
  - Lactic acidosis
  - Severe hepatomegaly
  - Osteomalacia, decreased mineral density
  - Renal insufficiency, Fanconi Syndrome (both rare)
Comparison of Entecavir & Tenofovir
Lok A. Hepatology 2010: 52(2):743-747

<table>
<thead>
<tr>
<th></th>
<th>ENTECAVIR</th>
<th>TENOFOVIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBe(+) 1y HBV-DNA log drop</td>
<td>6.9</td>
<td>6.2</td>
</tr>
<tr>
<td>HBe seroconversion</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>HBe(-) 1y HBV-DNA log drop</td>
<td>5</td>
<td>4.6</td>
</tr>
<tr>
<td>HBsAg loss</td>
<td>&lt; 1%</td>
<td>0%</td>
</tr>
<tr>
<td>Genotypic resistance Nucleoside-Naive</td>
<td>1.2% (year 5)</td>
<td>0% (year 3)</td>
</tr>
<tr>
<td>Lam-experienced</td>
<td>51% (year 5)</td>
<td>N/A</td>
</tr>
<tr>
<td>Safety in Pregnancy</td>
<td>Class C</td>
<td>Class B</td>
</tr>
<tr>
<td>Adverse Events</td>
<td>None</td>
<td>Osteopenia, nephrotoxicity</td>
</tr>
</tbody>
</table>
Telbivudine (LdT)

- Telbivudine: specific inhibitor HBV polymerase; approved in 2006.
- Oral beta-L-deoxynucleoside of thymidine
- Causes 2-3 log HBV-DNA drop by wk 4; not effective in YMDD mutant.
- Dose: 600 mg/d
- Side Effects:
  - Lactic acidosis,
  - Severe hepatomegaly,
  - CPK elevation with myopathy,
  - Peripheral neuropathy (especially if combined with Peg-IFN)
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.
Lamivudine

• Nucleoside analogue; Approved in 1998.
• Dose: 100 mg/day (300 mg/d in HIV-HBV co-infection); correct by creatinine clearance.
• Side effects:
  – Lactic acidosis,
  – Severe hepatomegaly
  – Mild increase in ALT
• High rate of resistance.
Adefovir Dipivoxil

- Oral adenosine nucleotide analog.
- Moderately active in wild, HBe(-), and YMDD mutant.
- Good choice for HBe(-) mutant, and as second drug for YMDD mutant, and as monotherapy in HIV co-infection.
- Decreases levels of intrahepatic cccDNA.
- Used together with Peg-IFN, increases rate of HBe seroconversion and of HBsAg loss.
- Dose 10 mg/day; correct by renal fx.
- Escape mutants are sensitive to Lamivudine.
- Nephrotoxic in 1%; creatinine raise and waste of phosphate & glucose (Fanconi)
- When changing from Lamivudine to Adefovir, continue both long term to decrease resistance to adefovir.
HBV prevention Post-OLTx
HBsAg(+) Recipient
Benefits of HBIG Prophylaxis

HBsAg(+) Recipients

% Survival

<table>
<thead>
<tr>
<th>Time</th>
<th>No Prophylaxis</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>5 years</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>10 years</td>
<td>73</td>
<td>81</td>
</tr>
</tbody>
</table>
Benefits of HBIG Prophylaxis
HBsAg(+) Recipient

- Anti-HBs titer goals post-OLTx (in HBIG monotherapy):
  - a) first week:  >500 IU/L,
  - b) week 2-4:  >500 IU/L in high-replic; >100-150 in low-replic
  - c) day 28-180: >250 IU/L in high-replic; >100-150 in low-replic
  - d) thereafter: >100-150 IU/L

- Escape occurs b/o:
  - a) “inadequate anti-HBs titer”, or
  - b) “pre-S/S mutation” causing reduced binding of anti-HBs.
Definitions for Oral Antivirals

Pre-OLTx anti-HBV Therapy

- **High replicators** > $10^4$ copies/mL or > **2000 IU/mL**:
  - high risk for graft re-infection and death;
  - all cirrhotics with > $10^4$ copies/mL (2000 IU/mL) need therapy with “high resistance-barrier agent” (Tenofovir, Entecavir, or Lamivudine+Adefovir).

- **Low replicators** < $10^4$ copies/mL (< **2000 IU/mL**):
  - moderate/low risk re-infection & death;
  - if < $10^2$ copies/mL, may be candidates for post-OLTx [short-term HBIG + oral agent], or [oral “high resistance-barrier” agent monotherapy].
Combination HBIG + Oral agent

**Low replicators** ($\leq 10^4$ copies/mL or < 2000 IU/mL), **Fulminant HBV, and HBV+Delta**

Angus PW. Liver Transpl 2000;6:429-433; Gane EJ. Gastroenterology 2007;132:931-937

- **Anhepatic phase**: HBIG 936 IU IM (3 mL Nabi-HB)
- Start/continue oral agent post-OLTx: Either (Adefovir + Lamivudine), Entecavir, or Tenofovir, or the combination that was effective before transplant. Continue oral agent **for life**.
- **First week**: daily 936 IU HBIG (3 mL Nabi-HB) IM x 7 days.
- **Thereafter**: HBIG 936 IU IM q month (3 mL Nabi-HB)
- If pre-OLTx HBV-DNA was < $10^4$ IU/mL, and after 1 year HBV-DNA is still “non-detectable”, consider to discontinue HBIG after vaccination + boosters (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, if patient responds with anti-HBs > 100 mIU/mL.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Combination HBIG + Oral agent

**High Replicators** (> $10^4$ copies or > 2000 IU/mL)

- **Anhepatic phase**: HBIG 10000 IU IV
- Continue effective oral agent, with high resistance barrier, post-OLTx **for life**. Give either (Adefovir + Lamivudine), Entecavir, Tenofovir, or combination regimen that was effective pre-Tx.
- **First week**: daily 10000 IU HBIG IV x 6 days
- **Thereafter**: 936 IU IM q month (3 mL Nabi-HB), starting on day 7 post-op.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
<table>
<thead>
<tr>
<th>Recipient’s viral load</th>
<th>Anhepatic Phase</th>
<th>First week</th>
<th>Thereafter</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV-DNA &lt; 1000 IU/mL</td>
<td>HBIG 1872 IU (6 mL Nabi-HB), IM</td>
<td>HBIG 936 IU (3 mL Nabi-HB), qd IM, x 7 days</td>
<td>HBIG 936 IU (3 mL Nabi-HB), IM q month for &gt;= 6 months. Immunize after 6 months, and if anti-HBs response &gt; 100 IU/L, d/c HBIG</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td>HBV-DNA &gt; 1000 IU/mL</td>
<td>HBIG 1872 IU (6 mL Nabi-HB), IM</td>
<td>HBIG 936 IU (3 mL Nabi-HB), qd IM, x 7 days</td>
<td>HBIG 936 IU (3 mL Nabi-HB), q month IM for life, (could consider vaccination after 18 months of HBIG and D/C HBIG if anti-HBs &gt; 100 IU/L but 5-6% relapse if HBIG is discontinued)</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
</tbody>
</table>
Anti-HBc(+) organ
given to HBsAg(-) Recipients
Anti-HBc(+) organ donors

Risk of HBV acquisition

• Anti-HBc (+) or anti-HBs (+) donors:
  – Overall 33-100%

• Anti-HBc(+) organ given to:
  – HBV naïve recipient: 30-72%.
  – Anti-HBc(+) recipient: 13%.
Anti-HBc(+) Organ Donors

Risk of HBV Infection

Dodson et al. Transplantation 1997

No HBV prophylaxis was given
Anti-HBc(+) Donor To Naïve Recipient

Effect of Prophylaxis

UCLA Experience

Ghobrial RM; Transplant Hepatology CAQ Course - 2006

% of Anti-HBc(+) to Naïve

- No Therapy: 29%
- Lamivudine: 44%
- HBIG: 17%
- HBIG + Lam: 0%

Bar chart showing the percentage of Anti-HBc(+) to Naïve recipients under different prophylaxis conditions.
Anti-HBc(+) organ donors

• **Primary candidates:**
  • HBsAg(+) recipients

– Follow protocols for Low, or High Replicators as described in previous section (“HBsAg(+) Recipient”).
Anti-HBc(+) organ donors

- **Secondary candidates:**
  - 1) anti-HBs(+) recipients (with titer > 10 IU/L),
  - 2) anti-HBc(+) recipient, and
  - 3) critically ill.

- Before OLTx or other Tx:
  - Order HBV-DNA in donor’s serum (to detect “pre-S/S mutant virus” = HBsAg(-) mutant), and
  - Check or order recipient’s “peak” anti-HBs titer (if not known, obtain pre-op anti-HBs titer)
Anti-HBc(+) organ donors

Secondary candidates management:

- Donor’s serum HBV-DNA(+) & any Recipient’s peak anti-HBs titer (despite absence of HBsAg):
  - Highly active oral agent (Lamivudine+Adefovir combination, or Tenofovir or Entecavir, for life);
  - Booster Vaccinate after 1 year [if HBV-DNA(-)] (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, until anti-HBs > 100 IU/mL (but continue oral agent for life)
Anti-HBc(+) organ donors

– Secondary candidates management:

– Donor’s serum HBV-DNA (-) & Recipient’s peak anti-HBs titer > 100 IU/L:
  • Lamivudine 150 mg BID (until anti-HBs > 100 mIU/mL, or for life).
  • Booster vaccinate x 1 dose, after 1 year, and check anti-HBs.
  • Discontinue oral agent after if good anti-HBs response is maintained (> 100 mIU/mL)?

– Donor’s serum HBV-DNA (-) & Recipient’s peak anti-HBs titer is < 100 IU/L:
  • Lamivudine 150 BID (until anti-HBs > 100 mIU/mL, or for life).
  • Booster Vaccinate after 1 year [if HBV-DNA(-)] (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, until anti-HBs > 100 mIU/mL.
  • Discontinue oral agent if good anti-HBs response is achieved (> 100 mIU/mL)?
Anti-HBc(+) liver donors

— **Secondary candidates management:**

— **Choice of oral agent:**
  
  • If donor HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  
  • If donor HBV-DNA in serum is negative, give Lamivudine 150 mg BID (corrected by renal function).

— **Monitoring:**

  • HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  
  • HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
Anti-HBc(+) liver/other organ donors

- **Tertiary candidates:**
  - HBV naïve patients [anti HBc(-) & anti-HBs(-)]
    - Before OLTx, check/order HBV-DNA in donor’s serum.
      - If Donor’s serum HBV-DNA is (+):
        - High resistance barrier oral agent (Entecavir, or Tenofovir) for life; [to give HBIG will not help if donor’s HBsAg was (-)]
        - Vaccinate after 1 year [if HBV-DNA(-)]; Independently of response, give oral agent for life.
      - If Donor’s serum HBV-DNA is negative:
        - Lamivudine 150 mg BID (until anti-HBs > 100 mIU/mL, or for life)
        - Vaccinate after 1 year [if HBV-DNA(-)], with 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
        - Discontinue oral agent if good anti-HBs response is achieved (> 100 mIU/mL)?
Anti-HBc(+) liver donors

• **Tertiary candidates:**
  – **Choice of oral agent:**
    • If HBV-DNA in serum is (+) give Tenofovir or Entecavir.
    • If HBV-DNA in serum is negative, give Lamivudine.
  – **Monitoring:**
    • HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
    • HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.
# UofL Protocol: Anti-HBc(+) organ given to HBsAg(-) Recipient

<table>
<thead>
<tr>
<th>Recipient Status</th>
<th>Donor Status</th>
<th>Oral Agent (adjust dose by renal function)</th>
<th>Immunization</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak anti-HBs &gt; 10 mIU/mL, or anti-HBc(+)</td>
<td>Serum HBV-DNA(+)</td>
<td>High “barrier-resistance”, [(Adefovir+Lamivudine), Entecavir, or Tenofovir] for life.</td>
<td>HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td>Peak anti-HBs &gt; 100 mIU/mL</td>
<td>Serum HBV-DNA(-)</td>
<td>Lamivudine 150 BID, until anti-HBs &gt; 100 mIU/mL, or for life</td>
<td>HBV-vaccine 40 mcg, until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td>Peak anti-HBs 10-99 mIU/mL, or anti-HBc(+)</td>
<td>Serum HBV-DNA(-)</td>
<td>Lamivudine 150 BID, until anti-HBs &gt; 100 mIU/mL, or for life</td>
<td>HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td>anti-HBs &lt; 10 mIU/mL, and anti-HBc(-)</td>
<td>Serum HBV-DNA(+)</td>
<td>High “barrier-resistance”, [(Adefovir+Lamivudine), Entecavir, or Tenofovir] for life.</td>
<td>HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
<tr>
<td>anti-HBs &lt; 10 mIU/mL, and anti-HBc(-)</td>
<td>Serum HBV-DNA(-)</td>
<td>Lamivudine 150 BID, until anti-HBs &gt; 100 mIU/mL, or for life</td>
<td>HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs &gt; 100 mIU/mL</td>
<td>HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life</td>
</tr>
</tbody>
</table>
Hepatitis D
Hepatitis D

- 36-43 nm Deltavirus with negative-stranded circular RNA which depends on HBV to propagate
- Causes immune-mediated liver injury; anti-HBs is protective; anti-HD is not protective.
- Can be acquired as Co-infection (HBV + HDV together) or as Super-infection (HDV over chronic HDV)
- **Prophylaxis:** HBV vaccination.
HDV Co-Infection

• Severity similar to acute HBV but less chronicity (5% vs 2%). Fulminant mostly with genotype III
• Most patients very symptomatic and jaundiced.
• Classically two bouts of elevated ALT/AST a few weeks apart.
• **DX**: anti-HBcIgM(+) & anti-HD IgM(+) followed by anti-HD IgG(+).
HDV Super-Infection

• Evolves to chronic HBV+HDV in 80%; FHF in some; the rest clears HBV & HDV.
• Most patients evolve to cirrhosis over a decade; 15% benign course; few have rapid progression to cirrhosis in < 2 years.
• **DX:** HBsAg(+), anti-HBcIgM(-), anti-HD IgM(+) followed by strong anti-HD IgG(+).
HBV – HDV Super-infection

Typical Serological Course

- **Time after Exposure**
- **Titer**

- **Jaundice**
- **Symptoms**

- **Total anti-HDV**
- **IgM anti-HDV**
- **ALT**

- **HBsAg**
- **HDV RNA**
Chronic HDV Treatment

• Interferon high dose (9 MU TIW) for 48 months or at least 12 months after normalization of ALT.

• Liver Transplant with HBIG post-op; graft re-infection in 9-12 %
Thank You
HDV Coinfection with HBV

Coinfection with HBV

HDV RNA

HBsAg
HDAg
Anti-HBc
Anti-HBs
Anti-HD
igM Anti-HBc

Titer

Weeks after Exposure
Chronic Hepatitis D

Persistent Infection after Superinfection of HBV Carrier

HDV RNA

HBsAg

Anti-HBc

HDAg

Anti-HD

Titer

Years

Weeks

Time
Regular Interferon
Interferon in HBV

- **Usual dose:** 5M QD or 10M TIW x 16-32 wks in HBe(+), or 48-96 wks in HBe(-)
- **Best in:** HBV-DNA < 12 x 10^6 IU/mL (57 x 10^6 copies/mL), ALT > 5xULN, females, adult acquisition.
- Flare up in 30-50%; can cause decompensation
- Sero-conversion maintained in most
- Genotype A responds better than g-D in both, HBe(+) (46 vs. 24%) & HBe(-) (59 vs. 29%)
- Good response slows progression and decreases HCC risk.
Meta-Analysis of IFN in HBe(+)  
Survival After HBeAg Clearance in HBeAg-positive CHB

Proportion of patients surviving

Proportion of patients free of hepatic complications

*According to the proportional hazards model
Long term F/U of Interferon Responders

Loss of HBsAg (Europeans & Americans)

Pegylated Interferons
Comparison of Safety, Depression and QofL during Pegasys 180 monotherapy in Chronic HCV and HBV (HBeAg(+) and(-))

Pooled data of 448 HBV and 827 HCV pts.

Safety at: 1, 2, 4, 6, 8, & 12 weeks and then q 6 weeks until 24 weeks post-EOT

QofL at: 12, 24, 48, and 72 weeks.
Tolerability of Pegasys in Chronic HBV vs. HCV
Marcellin et al. AASLD Abstr.# 1158, 2004

![Graph showing quality of life and depression levels in HCV and HBV patients with and without HBeAg.](image)
Conclusions
Abstr # 1158

- Treatment with Pegasys 180 mcg/week is associated with lower rates of side effects and depression, and with less impact in Quality of Life, in patients with chronic HBV compared with those with chronic HCV.
## Adverse Events with PEGASYS® Monotherapy in CHB

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>PEGASYS in CHB (n=448)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>54%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36%</td>
</tr>
<tr>
<td>Headache</td>
<td>27%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>26%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10%</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>8%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8%</td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
</tr>
</tbody>
</table>

Peg-Interferon in HBeAg(+)
Pegasys 180 x 24 wks in HBe(+) Week 48 (SVR ?) Data
Cooksley W et al. J Viral Hepat 2003, 10:298-305
Pegasys 180 x 48 wks in HBe(+)  
Week 72 (SVR ?) Data  
Lau G et al. Hepatology 2004; 40:171A
HBV DNA Levels Over Time

On-treatment

Follow-up

- PEGASYS® + placebo
  - HBeAg seroconversion
  - EOT= 27%; EOF= 32%

- PEGASYS® + lamivudine
  - HBeAg seroconversion
  - EOT= 24%; EOF= 27%

- Lamivudine
  - HBeAg seroconversion
  - EOT= 20%; EOF= 19%

* all numbers shown are \( \log_{10} \) reduction from baseline

Lau et al. AASLD. 2004.
HBeAg Seroconversion Rates Over Time

On-treatment

Follow-up

PEGASYS® + placebo

PEGASYS® + lamivudine

lamivudine

Study week

Lau et al. AASLD. 2004.
Effect of HBV Genotype

HBe Seroconversion 24 wks after EOT

Cooksley W et al. EASL 2005
Effect of Pre-Treatment ALT HBe Seroconversion 24 wks after EOT

Cooksley W et al. EASL 2005
Effect of Baseline HBV-DNA
HBe Seroconversion 24 wks after EOT

Cooksley W et al. EASL 2005
Peg-Intron 100x 32w + 50x20w in HBe(+) Week 78 Data

![Bar chart showing the percentage of patients with different outcomes after treatment with Peg-Intron or Peg-Intron + Lam.](chart.png)
CONCLUSIONS

Peg-IFN in HBeAg(+) Chronic HBV

• One third of chronic HBeAg(+) infected patients achieve sustained seroconversion
• Loss of HBsAg occurs in 3 to 4% in the first year. Additional HBsAg loss is expected in long-term follow up.
• Genotypes A, B, and C respond better than genotype D
• Test genotype with: INNO-LiPA HBV Genotyping
• Viral loads of up to $2 \times 10^8$ IU/mL ($1.17 \times 10^9$ copies/mL) respond best.
• Patients with ALT > 5xULN respond best
Peg-Interferon in HBeAg(-)
Pegasys 180 x 48 wks in HBe(-) Week 72 Data

![Graph showing HBV-DNA < 20K, ALT = NI, HBsAg(-) with data for Pegasys (177), Pegasys + Lam (179), and Lamivudine (181).]
HBV DNA Levels Over Time

Mean HBV DNA (log_{10} cp/mL)

On-treatment

Follow-up

PEGASYS + placebo

PEGASYS + lamivudine

lamivudine

Study week

0 6 12 18 24 30 36 42 48 54 60 66 72

On-therapy HBV DNA Suppression and LAM Resistance

YMDD mutation development at end of treatment

- 32/179 = 18%
- 1/173 = <1%

* All numbers shown are log_{10} reduction from baseline.
Effect of Genotype

HBV-DNA < 20,000 @ 24 wks after EOT

Marcellin P et al. EASL 2004
CONCLUSIONS
Peg-IFN in HBeAg(-) chronic HBV

• More than 40% of patients achieve conversion to low replicative state
• Genotypes A, B, and C respond better than genotype D
• Test genotype with: INNO-LiPA HBV Genotyping
• Loss of HBsAg occurs in 3-4% after first year of therapy and in 11% by year 4 (Marcellin P, EASL 2008). Additional HBsAg losses may occur with further follow-up
• Resistance to Lamivudine is very rare during combination therapy with Peg-interferon
Prediction of Sustained Response to Peg-Ifn α2a in HBeAg(-) Patients

- HBeAg(-) patients treated with Pegasys 180 +/- RBV x 48 wks.
- Measurement of decline in HBsAg (Abbott Architect) & HBV-DNA (TaqMan) @ wks 4, 8, 12, 24, 48, 60, 72.
- Sustained response defined as HBV-DNA < 2000 IU/mL and Normal ALT @ wk 72.
- Best predictors for sustained response (SR) were 12 wk parameters.

<table>
<thead>
<tr>
<th>HBsAg decline</th>
<th>HBV-DNA drop &gt;/= 2 log</th>
<th>Recommendation</th>
<th>SR Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>STOP</td>
<td>0%</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>Continue</td>
<td>24%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>Continue</td>
<td>25%</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Continue</td>
<td>39%</td>
</tr>
</tbody>
</table>
Lamivudine
Lamivudine x 48 wks in HBe(+)  

![Graph showing the comparison between Lamivudine and Placebo in HBe(+) patients.](image-url)
Lamivudine in HBe(+) x 3 y

Seroconversion HBe(-)

2 years: 27
3 years: 40
Lamivudine Resistance
YMDD mutants

YMDD mutants over different years:
- 1 YEAR: 24
- 2 YEAR: 42
- 3 YEAR: 53
- 5 YEAR: 70

Chart showing the percentage of YMDD mutants over time.
CONCLUSIONS
Lamivudine in Chronic HBV

- Lamivudine induces loss of HBeAg in 17, 27, and 40% after 1, 2, and 3 years of therapy, respectively
- Therapy with Lamivudine decreases progression of fibrosis and can reverse hepatic decompensation
- Decompensated cirrhotics have a 1 y survival of 79%; most deaths occur within initial 6 months.
- Loss of HBsAg is extremely rare
- Resistance to Lamivudine occurs rapidly, and reaches 70% after 5 years of therapy
- Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.
Adjustment of Adult Lamivudine dose by Creatinine Clearance

- $\geq 50$ mL/min: 100 mg/day
- 30-49 mL/min: 100 mg x1, then 50 mg/day
- 15-29 mL/min: 35 mg x1, then 25 mg/day
- 5-14 mL/min: 35 mg x1, then 15 mg/day
- < 5 mL/min: 35 mg x1, then 10 mg/day
Adefovir
Adefovir Dipivoxil

- Oral adenosine nucleotide analog.
- Moderately active in wild, HBe(-), and YMDD mutant.
- Good choice for HBe(-) mutant, and as second drug for YMDD mutant, and as monotherapy in HIV co-infection.
- Decreases levels of intrahepatic cccDNA.
- Used together with Peg-IFN, increases rate of HBe seroconversion and of HBsAg loss.
- Dose 10 mg/day; correct by renal fx.
- Escape mutants are sensitive to Lamivudine.
- Nephrotoxic in 1%; creatinine raise and waste of phosphate & glucose (Fanconi)
- When changing from Lamivudine to Adefovir, continue both long term to decrease resistance to adefovir.
Adjustment of Adult Adefovir dose by Creatinine Clearance

- $\geq 50$ mL/min: 10 mg/day
- 20-49 mL/min: 10 mg every other day
- 10-19 mL/min: 10 mg every third day
- Hemodialysis: 10 mg a week after dialysis
Adefovir x 48 wks in HBe(+)  

- HBV-DNA<400: Adefovir 21, Placebo 0
- HBe(-): Adefovir 12, Placebo 6
- ALT= NI: Adefovir 48, Placebo 16
- Histol. Improv: Adefovir 53, Placebo 25
Adefovir x 3 y in HBe(+)  
Marcellin P et al. AASLD Abst 1135, 2004

![Bar chart showing the percentage of HBe(-) and HBV-DNA<1000 at 1 year, 2 years, and 3 years after treatment.]
Adefovir x 48 wks in HBe(-)

Adefovir Resistant Mutants (%)
Adefovir + Lamivudine in Lam-Resistant HBV

Gastroenterology 2007;133:1445-1451

[Bar graph showing the percentage of HBV-DNA levels (<35 c/mL, 35-2000, >2000) and resistance across 12, 24, 36, and 48 months.]

- HBV-DNA < 35 c/mL
- HBV-DNA 35-2000
- HBV-DNA > 2000
- Resistance
High rate of HBsAg loss and HBsAg seroconversion in chronic hepatitis B patients on combination therapy with Peginterferon alfa-2a (Pegasys®) and Adefovir (Hepsera®): HBsAg titer predicts HBsAg loss or seroconversion. (Abstr LB 14)

- **Population:** 73 patients with chronic HBV; 34 HBe(+), 38 HBe(-).
- **Treatment:** 48 weeks of Peg-IFNa2a 180 mcg/w + Adefovir 10 mg/d; then 24 weeks without therapy.
- **Results:**
  - a) No difference in baseline HBV-DNA in seroconvertors & non-seroconvertors.
  - b) Baseline HBsAg titer (IU/mL) was lower in patients who loss HBsAg and seroconverted.
High rate of HBsAg loss and HBsAg seroconversion in chronic hepatitis B patients on combination therapy with Peginterferon alfa-2a (Pegasys®) and Adefovir (Hepsera®): HBsAg titer predicts HBsAg loss or seroconversion. (Abstr LB 14)

**CONCLUSION:**

- Combination of Peg-IFN + ADV causes higher rates of seroconversion than current monotherapies.
- Baseline HBV-DNA does not predict HBsAg loss nor seroconversion.
- Baseline HBsAg levels predict HBsAg loss and seroconversion.
- Larger studies are needed to confirm these findings.
CONCLUSIONS
Adefovir in Chronic HBV

• Adefovir is effective in controlling replication of HBe(+), HBe(-), and YMDD mutant HBV.
• Response increases with length of therapy but is slower than that to Lamuvidine
• Resistance to Adefovir is relatively low, but is higher in HBeAg(-) mutant.
• When Adefovir id added to Lamivudine in YMDD mutant HBV, resistance is low.
• Decompensated cirrhotics have a 1 y survival of 84% with adefovir; clinical benefits seen after 6 months of therapy.
Entecavir
Entecavir

- Oral deoxyguanidine nucleoside analog
- Active in wild, HBe(-), and YMDD
- **Dose**: - 0.5 mg/d in HBe(+) or (-); - 1 mg/day in YMDD mutant; - modify in renal impairment.
- No interaction with Lamivudine, Adefovir, nor Tenofovir.
- Should be taken in empty stomach.
- In HIV co-infection, may induce HIV drug resistance.
- In Lamivudine- or Telbivudine- resistant HBV, these drugs must be discontinue when Entecavir is initiated.
Entecavir

- **Side effects**: headache, fatigue, nausea
- **Viral Response after 1 y therapy**:  
  - $\text{HBe}(+) = 82\%$,  
  - $\text{HBe}(-) = 48\%$
- **Resistance**:  
  - YMDD mutant (Lamivudine resistant): $7\% @ 1\ y, 26\% @ 3\ y, & > 50\% @ 5\ y$.  
  - In Naïve: $1.2\% @ 5\ y$.  
  - Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.
Adjustment of Adult Entecavir dose by Creatinine Clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Naive</th>
<th>Lam Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 50 mL/min</td>
<td>0.5 mg/day</td>
<td>1 mg/day</td>
</tr>
<tr>
<td>30-39 mL/min</td>
<td>0.25 mg/day</td>
<td>0.5 mg/day</td>
</tr>
<tr>
<td>10-29 mL/min</td>
<td>0.15 mg/day</td>
<td>0.3 mg/day</td>
</tr>
<tr>
<td>&lt; 10mL/min, Hemodialysis, Peritoneodialysis</td>
<td>0.05 mg/day</td>
<td>0.1 mg/day</td>
</tr>
</tbody>
</table>
Entecavir x 48 & 96 wks in HBe(+)  
Gastroenterology 2007;133:1437-1444

1 of 354 patients developed Entecavir resistance & 13 had virologic breakthrough
Entecavir x 48 wks in HBe(-)
Bristol-Myers Squibb package insert

- HBV-DNA<300: 90% (Entecavir), 72% (Lamivudine)
- ALT=NI: 78% (Entecavir), 71% (Lamivudine)
- Histol improv: 70% (Entecavir), 61% (Lamivudine)
Entecavir x 48 wks in YMDD mutant

Bristol-Myers Squibb package insert

![Bar chart showing treatment outcomes for Entecavir and Lamivudine.](chart.png)
CONCLUSIONS
Entecavir in Chronic HBV

• Entecavir is effective in controlling viral replication in HBe(+), HBe(-), and YMDD mutant chronic HBV
• Entecavir controls viral replication, normalizes ALT, and improves histology faster than Lamivudine
• Resistance has been reported more in YMDD mutant (Lamivudine resistance) and is very high after 5 years (is not a good choice); is very uncommon in Lam-naïve.
• When changing from Lamivudine to Entecavir, DO NOT OVERLAP therapies (D/C Lam).
• When changing from Adefovir to Entecavir, overlap for at least 3 months.
Telbivudine (LdT)

- Telbivudine: specific inhibitor HBV polymerase.
- Oral beta-L-deoxynucleoside of thymidine
- Causes 2-3 log HBV-DNA drop by wk 4; not effective in YMDD mutant.
- Dose: 400-600 mg/d
- May cause CPK elevation
- **Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.**
Adjustment of Adult Telbivudine dose by Creatinine Clearance

- >/50 mL/min: 600 mg/day
- 30-49 mL/min: 400 mg/day
- 10-29 mL/min: 200 mg/day
- Hemodialysis: 200 mg after each dialysis
Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

- Double blind, prospective, randomized 1:1
- 2 years of Telbivudine vs Lamivudine
- **Patients:**
  - 1367 [921 HBeAg(+) & 446 HBeAg(-)] with
    - Liver Bx c/w Ch. HBV, HBV-DNA > 10^5 copies/mL, ALT > 1.3 ULN
- **1st end-point:** HBV-DNA < 10^5 + [normal ALT or loss HBeAg]
- **2nd end-point:**
  - a) Histologic response: Drop histol. Activ > 2 pts,
  - b) Viral response: Drop of HBV-DNA or HBV-DNA(-) by PCR
  - c) Normalization of ALT
  - d) Loss of HBeAg, or HBe seroconversion
Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

HBeAg(+)
Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

HBeAg(-)
Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

CONCLUSION

• Telbivudine is faster and more effective than Lamivudine in HBeAg(+) and HBeAg(-) chronic HB

• There is incremental effect from 1 year to 18 months of therapy.
Telbivudine vs. Adefovir
HBeAg(+) patients

- **log drop HBV-DNA at week 24:**
  - Telbivudine = 6.3, Adefovir = 4.97

- **HBV-DNA < 300 copies/mL @ wk 24:**
  - Telbivudine = 38.6%, Adefovir = 12.4%

- **Loss of HBeAg:**
  - Telbivudine = 16%, Adefovir = 10%

- **Normalization of ALT:**
  - No difference.
Tenofovir Disoproxil

- Oral adenosine nucleotide analog
- Dose: 300 mg/day; adjusted by renal function
- Effective in wild and YMDD mutant
- Causes 4-5 log drop HBV-DNA @ 48 weeks
- No resistance in up to 130 wks
Tenofovir x 72-130 wks in YMDD mutant


Tenofovir x 48w
Adefovir x 48w
Other Oral Agents
Emtricitabine (FTC)

• Oral cytosine nucleoside analog
• **Dose**: 200 to 300 mg/d; adjust by renal function.
• Resistance by YMDD mutation in 12% at 48 weeks.
• **Side effects**: lactic acidosis, fatty liver, fat redistribution, neutropenia.
• Resistance to Lamivudine increases risk of resistance to Entecavir, Telbivudine, and Emtricitabine; do not give them together.
Emtricitabine x 48 wks in HBe(+) or (-)
Schiffman et al. AASLD 2004, Abstr# 22
Clevudine

- Oral pyrimidine analog (L-FMAU = 2-fluoro-5-methyl-beta-L-arabino furanosyl uridine)
- Is phosphorylated inside the cell and is slowly removed: sustained viral inhibition.
- Causes 3-4 log drop in HBV-DNA by wk 4.
- Dose: 30-50 mg/day
Clevudine x 12-24 wks in HBe(+)
Percutaneous Injuries in Healthcare Workers (HCWs)

- Frequency has decreased over the last decade
  - In 1998 were 590164 reported percutaneous hospital-based exposures in the US. It is estimated that 39% were not reported.
- Currently estimated at 384000 - 600000 percutaneous injuries per year at US Hospitals (> 1000/day)
- Only 43% are reported.
- In 2004, the U.S. work-productivity cost was 188.5 million dollars.
- Highest rate is in OR Nurses (39.7 exposures/FTE/year).
- By the end of their training, 99% of surgical residents will have at least 1 needle stick injury; more than 50% will not be reported.
- Frequency with hollow-needles has decreased (due to safer devices) but with solid-needles has increased.
Percutaneous Injuries in Healthcare Workers (HCWs)

- Worldwide, in the year 2000, needle injuries caused 66,000 cases of HBV, 16,000 cases of HCV, and 1,000 cases of HIV in HCWs.
- Factors that increase risk:
  - Poor organization climate or administrative support
  - High workload
  - Poor training in use of safer device
  - Believe that following precautions with place patient at risk
  - HCW’s state of mental anguish or social dysfunction
Frequency of sharp injuries by surgeons in Teaching Hospitals - England 1992

<table>
<thead>
<tr>
<th>Frequency</th>
<th>CT Surgery</th>
<th>OB/GYN Surgery</th>
<th>General Surgery</th>
<th>Other Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1/month</td>
<td>60%</td>
<td>63%</td>
<td>54%</td>
<td>19%</td>
</tr>
<tr>
<td>&lt; 1/month, &gt; 1/year</td>
<td>40%</td>
<td>31%</td>
<td>23%</td>
<td>35%</td>
</tr>
<tr>
<td>&lt; 1/year</td>
<td>0</td>
<td>6%</td>
<td>23%</td>
<td>47%</td>
</tr>
<tr>
<td>Always Reports</td>
<td>0</td>
<td>6%</td>
<td>14%</td>
<td>28%</td>
</tr>
</tbody>
</table>
Frequency of sharp-injuries and re-contact* exposure in Teaching Hospital – US 1992
JAMA 1992;267:2899-2904

<table>
<thead>
<tr>
<th>Procedures with Injury</th>
<th>CT Surgery</th>
<th>GYN Surgery</th>
<th>General Surgery</th>
<th>Orthopedic Surgery</th>
<th>Trauma Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures with Injury</td>
<td>9%</td>
<td>10%</td>
<td>8%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Re-contact</td>
<td>3%</td>
<td>4%</td>
<td>1%</td>
<td>0.3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Re-contact:** instrument contacted patient after HCW injury, or bone fragment or wire fixed to patient injured the HCW
<table>
<thead>
<tr>
<th></th>
<th># HCW</th>
<th># Infected Patients</th>
<th># Patients tested in look-back</th>
<th>% Infected Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>3</td>
<td>3</td>
<td>3527</td>
<td>0.09%</td>
</tr>
<tr>
<td>HBV</td>
<td>12</td>
<td>91</td>
<td>3079</td>
<td>2.96%</td>
</tr>
<tr>
<td>HCV</td>
<td>11</td>
<td>38</td>
<td>9678</td>
<td>0.36%</td>
</tr>
</tbody>
</table>
Factors Affecting Viral Bloodborne Pathogens Transmission to HCWs

- Prevalence of the pathogen in the population served by the healthcare facility.
- Frequency of exposure
- Type of exposure (percutaneous, mucosal, nonintact skin)
- Infectivity of the virus (HBV > HCV > HIV)
- Titer of the virus in the body fluid or inanimate object.
- Availability of pre-exposure prophylaxis (HBV), and post-exposure prophylaxis (HBV, HIV)
Risk of HBV Infection in HCWs

- HBV is much more infectious than HCV and HIV.
- HBV can be transmitted by percutaneous, mucosal, or nonintact skin exposure.
- Inanimate objects (fomites) can transmit HBV: finger-stick devices, jet gun injectors, multi-dose vials, endoscopes.
- Infectious HBV can survive up to for 7 days in contaminated surfaces.
- OSHA-required HBV vaccination of HCWs since 1991, has decreased HBV infections by 95% between 1983 to 1995.
- Only 75% of HCWs have received HBV vaccination.
Risk Minimization

• All HCWs with reasonably anticipated exposure to blood or contaminated body fluids must receive from the healthcare facility:
  – yearly education about bloodborne pathogen transmission and risk minimization.
  – HBV vaccination (and post vaccination testing) at no cost. Quantitative anti-HBs titers should be tested 1-2 months after final (3\textsuperscript{rd}) vaccine dose.
  – If anti-HBs titer is < 10 mIU/mL, the 3-dose vaccination should be repeated, and anti-HBs titers repeated. Failure to obtain titers > 10 mIU/mL after the second 3-dose vaccine series classifies the patient as “non-responder”.
  – If HCW refuses HBV vaccination, he/she must sign mandated declination form.
Risk Minimization

- engineering controls proven to reduce exposure risk
  - leak-proof containers to transport blood,
  - impervious needle-disposal containers,
  - needles IV medication systems,
  - blunted suture needles
- “Personal Protective Equipment”, that HCWs must use it when performing procedures with blood exposure risk
  - impervious gowns,
  - gloves,
  - face/eye shields
Effect of Lamivudine on HBV Vertical Transmission from Highly Infectious Mothers
Xu WM et al. AASLD Abstr # 246, 2004
Xu WM et al. J. Viral Hepat 2009:16, 94-103

- Multicenter, double blind, randomized, placebo controlled.
- **Population**: 114 pregnant women with HBsAg(+) & HBV-DNA > 200 million IU/mL (Chiron bDNA).
- **Treatment**: Lamivudine 100 mg/d vs. placebo starting @ wk 32 until 4 wks post-partum
- All neonates received: HBIG 200 IU + HBV vaccine @ birth, 4 & 24 weeks.
- **End-point**: HBsAg(+) & HBV-DNA(+) @ age 53 wks
RESULTS # 246

- HBsAg(+): LAM 18, PLACEBO 39
- anti-HBs(+): LAM 84, PLACEBO 61
- HBV-DNA(+): LAM 20, PLACEBO 46
CONCLUSION
Abstr # 246

• In mothers with HBV-DNA > 200 million IU/ml, the addition of Lamivudine 100 mg/d in the 8 weeks prior to delivery plus 4 weeks post-partum, to the regimen of HBIG & Vaccination, decreased the rate of vertical transmission of HBV.

• No safety concerns were observed on mothers nor infants.

• Lamivudine was well tolerated.
Testing for HB Pre-core & Core-Promoter Mutant

- 70% of anti-HBe(+)/HBeAg(-) have HBV-DNA \( \leq 20000 \) IU/mL; may have “wild” or “mutant” HBV. **Testing for Pre-core/Core-promoter mutation should be done.**
- Commercial Test: Inno-LiPA HBV PreCore
- If HBV-DNA is < 2000 IU/mL and patient is HBeAg(-). Patient may have:
  - Wild HBV “inactive carrier state”: **no need to treat**, or
  - Precore or core-promoter HBV “inactive carrier state”: **no need to treat**.