Hepatitis B

- Of the world’s 6 billion people, one third have been infected with HBV. [Lee W. NEJM 1997;337:1733]
- HBV-infected persons carry a life-time risk for HCC and/or cirrhosis.
- Many persons infected are unaware of the diagnosis.
- Only a minority of those infected receive scheduled follow-up to monitor their disease status.
- The natural history is dynamic.
- HBV-infected persons need life-long regular monitoring for the development of liver disease and HCC.

Geographic Distribution of Chronic HBV Infection

15-40% HBsAg+ progress to Cirrhosis and ESLD

HBsAg Prevalence in Europe

- ≤ 0.2% - Very low
- 0.3-1.0% - Low
- 1.1 - 5.0% - Intermediate
- > 5.0% - High
- NA
**Number of notifications of HBV 1996-2010**

![Graph showing the number of notifications of HBV from 1996 to 2010.](image)

- **Acute**: 11, 31, 157, 158, 108, 342, 545, 707, 856, 798, 854, 919, 803, 645
- **Chronic**: 356, 786, 854, 919, 903
- **Unknown**: 545, 645

**Risk factors (%) for chronic cases of hepatitis B, 2007-2010 (where data available, n=1326, 50%)**

- **Born in endemic country or asylum seeker, 72.8%**
- **Sexually acquired - heterosexual, 4.8%**
- **Sexually acquired - MSM, 2.6%**
- **Sexually acquired - unknown orientation, 2.7%**
- **Baby of HBsAg pos mother, 3.8%**
- **Intellectual disability setting, 3.1%**
- **Household contact with case, 3.1%**
- **Injecting drug user, 1.7%**
- **Other, 2.2%**
- **No known risk factor, 3.6%**
- **Sexually acquired - heterosexual, 4.8%**

**Region of birth (%) for chronic cases of hepatitis B, 2007-2010 (where data available, n=1187, 44%)**

- **Sub-Saharan Africa, 30.8%**
- **Central Europe, 20.1%**
- **Eastern Europe, 9.5%**
- **South & South East Asia, 10.6%**
- **East Asia & Pacific, 15.3%**
- **North Africa & Middle East, 1.1%**
- **Other, 0.8%**

---

**HBV in Ireland**

- Inward migration from areas of medium – high prevalence rates of infection
- Changing epidemiology
- Newer technologies identifying more patients with low levels of replication
- Clinical significance of low level replication?
  - transmission: public health issue
  - cancer risk

**Factors contributing to changing epidemiology**

- Improved socio-economic conditions
  - Reduced intra-family spread
  - Improved medical practices
- HBV vaccination programmes
  - Implementation in areas of high/intermediate prevalence
  - Lack of uniform vaccination in countries with low prevalence
- Increased population movement both within and into the EU
- Route of transmission shifting from vertical to horizontal
  - IV drug users
  - Hospital-acquired
  - Sexual transmission

**Changing prevalence in Italy of HBeAg+ve to HBeAg-negative disease**

- **1975-1985**
  - HBeAg-positive: 58%
  - Anti-HBe positive: 42%
  - Cases = 538

- **1997**
  - HBeAg-positive: 11%
  - Anti-HBe positive: 89%
  - Cases = 718

**HBV Structure**

- Dane particle (42 nm)
  - Outer coat: HBsAg, polypeptide of 226 aa. Can be found of HBV surface or alone (spheres or tubules)
  - Inner core: ds cccDNA
    - DNA polymerase
    - HBcAg
      - The "e" antigen (HBeAg) results from the processing of HBcAg in infected hepatocytes

**HBV viral antigens**

- Discovered by Blumberg from blood of an Australian aborigine in 1965
  - JAMA 1965;191:541

- There are 4 subtypes of HBsAg protein:
  - adw, ayw, adr, ayr

- "a" is the group determinant and is common to all 4 subtypes

- Antibodies against the "a" determinant are protective

- Presence of HBsAg > 6 months defines chronic infection

**HBV viral antigens**

- All three viral antigens (HBsAg, HBeAg, HBcAg) are immunogenic.

- HBcAg is never detected in the serum as it is contained within the Dane particle

- In acute HBV infection, HBsAg is the first to appear in the blood.

**Persistence of HBV**

**Epidemiology of HBV**

- Incubation is long ~ 45-160 days
- HBV is stable on environmental surfaces for ~7 days
- Percutaneous and mucous membrane exposure to contaminated body fluids
- HBsAg detected in wide variety of body fluids but only saliva, blood and semen have been demonstrated to be infectious
- HBeAg presence confers greater infectivity and higher HBV titre (up to $10^9$ particles/mL)

**There is no cure for HBV**
Routes of transmission of HBV and risk of chronic infection by age

<table>
<thead>
<tr>
<th>Age at infection</th>
<th>mode of transmission</th>
<th>risk of cHBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth</td>
<td>perinatal</td>
<td>90%</td>
</tr>
<tr>
<td>0-5 years</td>
<td>horizontal: person-person interfamily (open cuts) unsafe injections</td>
<td>25-30%</td>
</tr>
<tr>
<td>&gt;5 years</td>
<td>horizontal: person-person interfamily (open cuts) unsafe injections IVDU sexual transmission</td>
<td>5-7%</td>
</tr>
</tbody>
</table>

Children at risk for HBV

- Infants born to HBV-infected women
- Infants and children living in community groups with high HBV endemicity
- Immigrant or adopted children from HBV high prevalent areas
- Household contacts of individuals with chronic HBV
- Adolescents engaging in high-risk behaviours

HBV prevention strategies

- Population
  - Mass vaccination
  - Vaccination of selected groups
  - Screening
    - Vaccination of susceptible individuals
  - Post exposure prophylaxis
  - No vaccination

Case 1: PC

- 42 year old homosexual male
- Presents to GP July 2011 with 6 week history of
  - malaise
  - anergia
  - myalgia, arthralgia
  - one week of jaundice

No history of IVDU, tattoos, body piercings
No alcohol excess

<table>
<thead>
<tr>
<th>Endemicity of infection</th>
<th>Primary Routes of Transmission</th>
<th>Prevalence of Chronic Infection (%)</th>
<th>Percentage of Global Population (%)</th>
<th>Vaccination Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Perinatal</td>
<td>≥56</td>
<td>46</td>
<td>Routine infant starting at birth</td>
</tr>
<tr>
<td></td>
<td>Household</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nascocanal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>Household</td>
<td>2-7</td>
<td>43</td>
<td>Routine infant High-risk group if resources available</td>
</tr>
<tr>
<td></td>
<td>Sexual</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Injecting drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occupational</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nascocanal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Sexual</td>
<td>≤5</td>
<td>12</td>
<td>Sickle-leaf pregnant women Postexposure prophylaxis for infants born to infected women Routine infant Routine adolescent High-risk group</td>
</tr>
<tr>
<td></td>
<td>Injecting drug use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occupational</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LFTS:
- albumen 40
- Bili 137
- ALK 379
- gGT 589
- AST 3180
- ALT 4123

HBV serology
- HBsAg +
- HBeAg +
- HBeAb -
- HCVAb -
- HAV IgM -
- HIV 1 & 2 +
- HBcIgM N/D

Diagnosis: acute HBV infection
Referred to liver OPD

Now feeling much better, still jaundiced

LFTS: bilirubin 220, AST 661, ALT 431, gGT 430, INR 1.6

Virology: HBsAg+, HBeAg-, HBeAb-

Other causes of liver disease excluded

US liver normal

Discussion points

- Acute hepatitis B / Reactivation of chronic hepatitis B?
- Does the patient needs treatment?
- Likelihood of fulminant hepatitis B in immunocompetent adults is <1% and the progression to chronic HBV infection is <5%

Lamivudine Therapy In Patients With Severe Acute Hepatitis B

- 17 immunocompetent patients (12 women, 5 men, age 17-83 years) with severe acute hepatitis B were treated with lamivudine.
- In 12 patients, concurrent corticosteroid therapy was administered.
- One patient developed fulminant hepatitis B and underwent successful urgent liver transplantation 5 days after the lamivudine therapy was initiated.
- Sixteen patients responded well to the treatment and their biochemical parameters improved rapidly. Within 3-7 months, the HBsAg was undetectable in 14 out of 15 investigated patients. Protective anti-HBs antibodies developed in 11 of them in 3-21 months.
- Early treatment with lamivudine alone or with corticosteroids probably decreases the risk of progression to fulminant hepatitis in patients with severe acute hepatitis B.

Lamivudine Treatment For Acute Severe Hepatitis B: A Pilot Study.

- Fifteen patients (10 men, 5 women, mean age 34.3+/-7.3 years) with severe acute HBV infection were treated with lamivudine 100 mg daily for 3-6 months, starting 3-12 weeks after onset of infection.
- Thirteen patients (86.6%) responded to treatment.
- The 11 patients who were serum HBeAg-positive before treatment seroconverted, and HBeAb developed within 12 weeks in 9 of them; HBsAg was undetectable in all 11 tested patients, and protective titer of HBsAb developed within 12-16 weeks in 9 of them.
- Lamivudine induces a prompt clinical, biochemical, serological and virological response in immunocompetent patients with de novo HBV infection. Lamivudine may prevent the progression of severe acute disease to fulminant or chronic hepatitis and should be considered for use in selected patients. A large randomized controlled, double-blind prospective study is needed.

A randomized controlled trial of lamivudine to treat acute hepatitis B.

- Acute hepatitis B patients with serum bilirubin of more than 5 mg/dL were randomized to receive either 100 mg of lamivudine daily for 3 months (group 1, n = 31) or placebo (group 2, n = 40).
- At week 4, HBV DNA levels were significantly lower (P = 0.037) in group 1 (median: 3.6721 log copies/mL) than group 2 (median: 4.2721 log copies/mL).
- The improvement in serum bilirubin, ALT, and INR values was similar in the 2 groups.
- No difference in outcome with severe hepatitis.
- After 12 and 18 months, 93.5% and 92.5%, respectively, of patients in the lamivudine group and 96.7% and 97.5%, respectively, of patients in the placebo group lost HBsAg.
- All HBeAg-positive patients in both groups lost e antigen and anti-HBe developed in 71% and 87.5% of patients in groups 1 and 2, respectively (P = 0.132).


Treatment For Acute Hepatitis B

- Prognosis with acute infection is relatively worse in patients who are immunocompromised, have concomitant infection with hepatitis C or D virus, have preexisting liver disease, or are elderly.
- Treatment can be considered with a severe (INR >1.5) or a protracted course (such as persistent symptoms or marked jaundice (bilirubin >10 mg/dl) for more than four weeks after presentation).

**Acute HBV infection**

- Main risk for acquisition is blood or sexual exposure.
- Risk for chronicity relates to age:
  - Adult: less than 5%
  - Child < 5 years: 20-50%
  - Neonate: 90%
- 30% develop jaundice
- <1% develop acute liver failure
- Incubation period: 1 – 4 months
- Sexual transmission is now the major mode of spread in developed countries (30% cases in USA)

**Acute hepatitis B in Ireland, 2004-2010**

- 10% of cases notified 2004-2010 were acute infections
- 477 acute notifications in this time period (annual average: n= 68)
- 82% of acute cases notified 2004-2010 were male
- Median ages at notification: 33 years for males, 30 years for females.
- Where risk factor data available, 66% of cases were sexually acquired. Approximately half of sexually acquired cases were in men who have sex with men
- Where country of birth available, 75% born in Ireland

**Phases of acute HBV**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>anti-HBc</th>
<th>anti-HBe</th>
<th>anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Viremia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Late active</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Window</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clearance</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Vaccination</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Natural History of HBV

Natural History: “inactive” HBsAg

- Prognosis: benign
- But 20-30% of inactive carriers may reactivate in follow-up
- Multiple episodes of reactivation causes progressive liver disease

**Case 2: CN**

- 44 yr male from Ivory Coast, resident x 3 years
- Referred to haematology clinic with low WCC (3.4, neuts 1.8): racial variant
- Abnormal LFTS noted: AST 132, ALT 140, bilirubin 26
- Repeat LFTS: AST 65, ALT 61, Bilirubin 14
- Liver US: coarse echo pattern to liver, spleen enlarged, low volume ascites
- MRI liver: no liver cancer
- OGD: early (grade 1) oesophageal varices
- Diagnosis: CIRRHOSIS with portal hypertension

- Liver biopsy: macronodular cirrhosis, mild activity. HBsAg stain weakly positive, HBCAg stain weakly positive
- Virology: HBsAg+
  - HBeAg-
  - HBeAb+
  - HBVDNA titre 1.5 – 2.2 x 10^6 cpm

**Options: case 2 CN**

- Do nothing and transplant later
- Interferon
- Lamivudine
- Adefovir

**Concerns for future:**
- HCC development
- Liver failure

**Case 2 CN**

- Treatment with lamivudine was associated with an initial decline in HBV DNA titers to undetectable levels by PCR assay and normalization of serum aminotransferases
Hepatitis B Disease Progression

- Acute infection
- Chronic infection
- Cirrhosis
- Liver Cancer (HCC)
- Death

- 60% of chronic HBV-infected individuals
- <10% of infected immunocompetent adults progress to chronic disease
- <5% of infected immunocompetent adults progress to chronic disease

Liver Cancer (HCC)

Liver Transplantation

Cirrhosis

Liver Failure ( Decompensation)

Chronic HBV is the 6th leading cause of liver transplantation in the US

5-Year Survival in Chronic Hepatitis B


Importance of HBeAg and HBsAg seroconversion

Study of HBV progression and HCC in 11,893 Taiwanese men

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBeAg</th>
<th>ALT</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>neg</td>
<td>normal</td>
<td>1</td>
</tr>
<tr>
<td>Neg</td>
<td>neg</td>
<td>elevated</td>
<td>5.4</td>
</tr>
<tr>
<td>Pos</td>
<td>neg</td>
<td>normal</td>
<td>10.3</td>
</tr>
<tr>
<td>Pos</td>
<td>neg</td>
<td>elevated</td>
<td>29.3</td>
</tr>
<tr>
<td>Pos</td>
<td>pos</td>
<td>normal</td>
<td>61.3</td>
</tr>
<tr>
<td>Pos</td>
<td>pos</td>
<td>elevated</td>
<td>109</td>
</tr>
</tbody>
</table>

Yang et al, NEJM 2002

HBV and Risk of HCC

HBsAg(+), HBeAg(+) (RR = 60.2)

HBsAg(+), HBeAg(-) (RR = 9.6)

Percent cumulative incidence

Year

Clinical outcome after HBeAg seroconversion

- 283 Taiwanese, at least 12 months post seroconversion
- Prospective study
- FU 1-18 yrs, median 9yr
- 67% sustained remission
- 33% ALT > 2X ULN
- 4.2% HBeAg reversion
- 8% developed cirrhosis
- 2.2% developed HCC

Hsu et al, Hepato 2002;35:1522

HCC

HBV DNA Associated With Increased Risk of HCC and Cirrhosis

- **REVEAL**: Long-term follow-up of untreated HBsAg positive individuals in Taiwan

Baseline HBV DNA (copies/mL)

<table>
<thead>
<tr>
<th>Baseline HBV DNA (copies/mL)</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10^4</td>
<td>2.0 x 10^3</td>
</tr>
<tr>
<td>10^4 to &lt; 10^5</td>
<td>4.0 x 10^3</td>
</tr>
<tr>
<td>≥ 10^5</td>
<td>6.0 x 10^3</td>
</tr>
<tr>
<td>≥ 10^6</td>
<td>8.0 x 10^3</td>
</tr>
<tr>
<td>≥ 10^7</td>
<td>1.0 x 10^4</td>
</tr>
<tr>
<td>≥ 10^8</td>
<td>1.2 x 10^4</td>
</tr>
</tbody>
</table>

Cumulative Incidence of HCC at Year 13 Follow-up (N = 3653)

- Men: 1475
- Women: 352

Cumulative Incidence of Cirrhosis at Year 13 Follow-up (N = 3582)

- Men: 1475
- Women: 352


Who should be treated?

- Chronic infection with significant activity
  - Prevention of cirrhosis
- Chronic infection with cirrhosis
  - Prevention of HCC
  - Prevention of decompensation
- Chronic infection with low activity?
  - Health care workers
  - Immunosuppressed patients

Decision to treat

- Based on a number of parameters:
  - ALT level
  - HBVDNA level
  - HBeAg status
  - Liver biopsy
  - Previous treatments
  - Compensated disease
  - "clinical experience"

Predictors of response

- **Negative parameters**
  - Male gender
  - HIV co-infection
  - Normal ALT
  - High HBVDNA levels

- **Positive parameters**:
  - High ALT level
  - Low HBVDNA level
  - Genotype (A and B)
  - ALT flare during IFN rx

Rate of HBeAg seroconversion can be predicted by pre-tx ALT

<table>
<thead>
<tr>
<th></th>
<th>LAM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT normal</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>ALT 1-2 ULN</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>ALT 2-5 ULN</td>
<td>21%</td>
<td>11%</td>
</tr>
<tr>
<td>ALT &gt; 5 ULN</td>
<td>47%</td>
<td>14%</td>
</tr>
</tbody>
</table>

Penillo et al, Hepatology 1999
Key factors in considering treatment options

- Efficacy
- Safety
- Resistance
- Convenience

Treatment of HBV 2012

- Ideal candidate:
  - High potency
  - High genetic barrier to resistance
  - Oral agent

Lamivudine in HBeAg+ infection: rate of HBe-Seroconversion

Lamivudine vs Placebo

Lamivudine-induced HBeAg seroconversion is less durable than that induced by IFNα

Cumulative rate of relapse in patients who had achieved HBeAg seroconversion by end of treatment
LAM resistance over time

<table>
<thead>
<tr>
<th>Years of lamivudine</th>
<th>% Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>38%</td>
</tr>
<tr>
<td>3</td>
<td>53%</td>
</tr>
<tr>
<td>4</td>
<td>66%</td>
</tr>
</tbody>
</table>

Lamivudine Resistance: clinical significance

- Associated with:
  - Rebound in HBV DNA
  - Increase in serum ALT levels
  - Reversion of histological improvement
  - Disease progression
  - Acute exacerbations (severe flares)
  - In special cases severe courses with very high replication

- Limits utility of lamivudine

Prototypic HBV Polymerase Mutations Associated with Lamivudine Resistance

<table>
<thead>
<tr>
<th>Terminal protein</th>
<th>Spacer</th>
<th>Pol/RT</th>
<th>RNaseH</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>B</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>183</td>
<td>354</td>
<td>552*</td>
<td>694</td>
</tr>
</tbody>
</table>

Lamivudine: L528M (L180M) M552V (M204V/I)

* M552V & M552I (M204V/I) frequently observed as double mutations with L528M (L180M)

Relationship between early HBVDNA suppression and LAM resistance

<table>
<thead>
<tr>
<th>Serum HBVDNA level at 6 months (c/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
</tr>
<tr>
<td>8%</td>
</tr>
<tr>
<td>&lt; 3log10</td>
</tr>
<tr>
<td>13%</td>
</tr>
<tr>
<td>&lt; 4log10</td>
</tr>
<tr>
<td>32%</td>
</tr>
<tr>
<td>&gt; 4log10</td>
</tr>
<tr>
<td>64%</td>
</tr>
</tbody>
</table>

Yuen et al, Hepatol 2001; 34:785

Case 3: JO

- 16 yr old Nigerian boy, adopted by Irish family
- GP detects HBsAg+, refers to liver OPD Jan 2002
- Virology: HBsAg+, HBeAg-, HBeAb+, HCVAb-
- Liver profile: AST 40, ALT 45, Bili 11
- aFP normal, liver US normal
- Diagnosis: non-replicating carrier of HBV

- Routine clinic visit October 2002
- LFTS: bili 21, AST 1315, ALT 1727
- Virology: HBsAg+, HBeAg-, HBeAb-
- All other viruses negative
- Diagnosis?????
The Diff dx of acute hepatitis in HBV carrier is as follows:

- Drugs and toxins eg. Paracetamol, Chinese CAM
- Alcohol
- Reactivation of HBV in a non-R, ie “flare”
- Exacerbation LFTs HBV at time of seroconversion to anti-HBV status
- Superinfection with other viruses, eg. HCV, HAV, HDV, HIV

**HBVDNA titre 25,839,900 cpm** (Digene assay)

- Inhouse PCR: mutation at position 1896 PRECORE mutation

- Liver biopsy: stage 3 fibrosis, moderate activity

- Archived sample from Jan 2002: HBVDNA +

**Precore mutation:**

- \(G_{1896}A\) mutation creates a premature stop codon which abolishes production of HBeAg
- Commonly found in Med basin (genotype D)
- Rarely found in USA, NW Europe (genotype A)

- \(A_{1762}T\) and \(G_{1764}A\) core promoter mutations
- Also reduce production of HBeAg

**Lamivudine: Summary**

**Advantages**

- Oral administration
- Few side effects
- Safe in advanced disease (decompensated cirrhosis, transplantation)
- Reduced disease progression vs placebo in patients with advanced disease

**Disadvantages**

- Low sustained response rate
- Indefinite treatment duration/maintenance therapy
- Lamivudine-resistant YMDD mutations
- Post-treatment potentially life-threatening ALT flares

**Case 2 CN**

- Treatment with lamivudine was associated with an initial decline in HBV DNA titers to undetectable levels by PCR assay and normalization of serum aminotransferases

- However, after 18 months of treatment, a flare in serum aminotransferases is noted with increasing levels of HBV DNA

- HBeAg remains negative.
Breakthrough infection with Lamivudine-resistant mutants

- Differentiate from HBeAg seroconversion
- Specific testing can be performed to confirm resistant mutants
- Add adefovir 10 mg daily (while continuing lamivudine).
- Resistance to adefovir occurs rarely in patients with lamivudine resistance who continue to take lamivudine concurrently with adefovir.
- Adefovir is preferred to entecavir because mutations to entecavir develop in patients with pre-existing lamivudine-resistant mutations

Regression of Fibrosis with ADV

Patient from 5-year cohort

Virological response to ADV in LAM resistant patients

Cumulative Incidence of Genotypic Resistance

Entecavir

- Guanosine analogue
- Inhibits all three HBV polymerase functions
  - Priming
  - DNA-dependent synthesis
  - Reverse transcription
- Phase II studies
  - Double blind RCT (ETV 0.1 and 0.5mg vs LAM 100mg) for 24 weeks reported superiority of ETV over LAM
  - Well tolerated

Relationship between HBVDNA suppression and ADF resistance

Entecavir

- Guanosine analogue
- Inhibits all three HBV polymerase functions
  - Priming
  - DNA-dependent synthesis
  - Reverse transcription
- Phase II studies
  - Double blind RCT (ETV 0.1 and 0.5mg vs LAM 100mg) for 24 weeks reported superiority of ETV over LAM
  - Well tolerated
Entecavir

- Longterm safety excellent
- Rescue therapy in pre-treated chronic HBV
- Decompensated liver disease
- Superior to ADF in decompensated disease
- Suppresses HBV after transplantation

Keating GM Drugs 2011;71(18):2511
Manns M et al. Expert Opin Drug saf 2012; Jan 11th
Fung J et al. Gastroenterol 2011;141A:1212
Liu YF et al. Hepatol 2011;54(1):91

Entecavir in HBeAg positive CHB

<table>
<thead>
<tr>
<th></th>
<th>Entecavir</th>
<th>Lamivudine</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EOT)</td>
<td>(EOT)</td>
<td></td>
</tr>
<tr>
<td>48 weeks</td>
<td>0.5 mg qd</td>
<td>100 mg qd</td>
</tr>
<tr>
<td>(n=354)</td>
<td>(n=355)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Entecavir</th>
<th>Lamivudine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg seroconversion</td>
<td>21%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Undetectable HBV DNA*</td>
<td>69%</td>
<td>38%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histological improvement (primary endpoint)</td>
<td>72%</td>
<td>62%</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

*<400 cp/mL

Entecavir in HBeAg negative CHB

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<td>(EOT)</td>
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</tr>
<tr>
<td>48 weeks</td>
<td>0.5 mg qd</td>
<td>100 mg qd</td>
</tr>
<tr>
<td>(n=325)</td>
<td>(n=313)</td>
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<tr>
<th>Parameter</th>
<th>Entecavir</th>
<th>Lamivudine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite endpoint*</td>
<td>84%</td>
<td>78%</td>
<td>0.04</td>
</tr>
<tr>
<td>Undetectable HBV DNA*</td>
<td>91%</td>
<td>73%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Histological improvement</td>
<td>70%</td>
<td>61%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*<0.7 MEq/mL by bDNA and ALT <1.25 x ULN

Lai et al, NEJM 2006;354:1011

Entecavir in LAM resistant patients

- ETV activity against LAM R HBV is 6-10 fold lower compared to wildtype

- Phase III study of LAM resistance patients:
  - Received ETV 1mg (not 0.5mg)
  - 60% patients had detectable HBV DNA at 2yrs
  - ETV mutations noted: 4% at yr 1, 12% at yr 2

Sherman et al, Gastro 2006;130:2039

Combination Therapy

What have we learned from HIV treatment?
Rationale for combination therapy

- More rapid and profound suppression of virus
- Improved sustained response rate
- Reduced risk of resistant strains emerging

HBV treatment – current strategy

- Monotherapy: selection of Entecavir, Tenofovir, or PegIFN 2α

The challenge:
which drugs to use
how (associated, sequentially, staggered)
how-long

Ayoub W, Kellis GJ. Antivir Ther 2011;16(10):1145.