
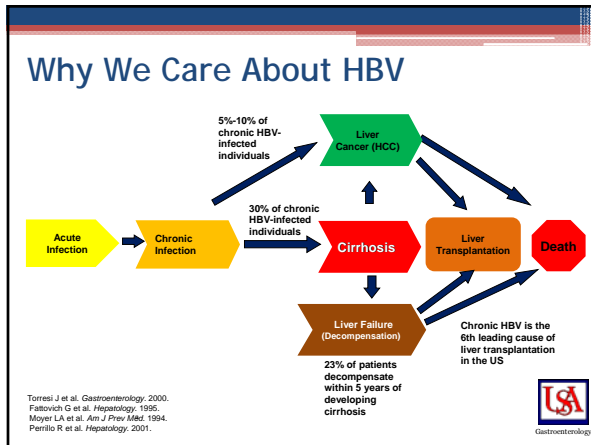


Hepatitis B: Why We Care and How To Treat

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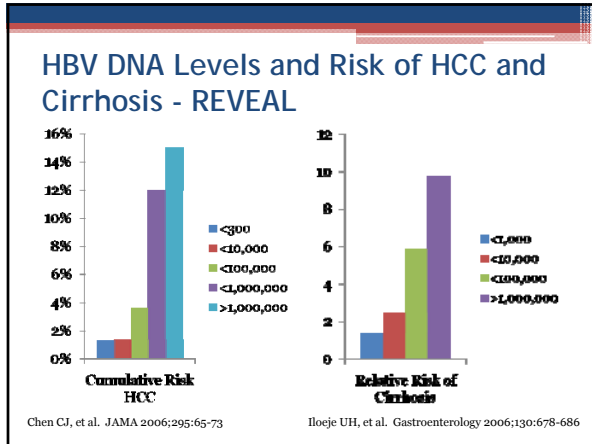
Importance of HBV-DNA Levels in the Natural History of HBV

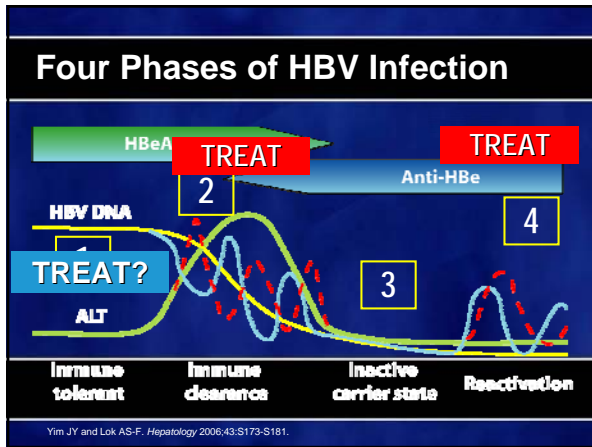
- **The REVEAL Study**
 - 3653 patients, HBV (+)
 - 13 year follow up
 - HBV-DNA level determined at entry and correlated with incidence of HCC and cirrhosis at 13 years
- **Study population**
 - Male – 62%
 - Age \geq 40 years – 67%
 - HBeAg negative – 85%

Chen CJ, et al. JAMA 2006;295:65-73
Iloeje UH, et al. Gastroenterology 2006;130:678-686



Hepatitis B: Why We Care and How to Treat





The "Immune Tolerant" Patient

- Profile**
 - Perinatal acquisition of infection
 - Young (<40 years)


Response to therapy?
Higher risk of developing resistance?

- Most will develop active disease
 - Mean age 30.7 years¹
 - No liver damage while immune tolerant

1. Andreati T, et al. Clin Gastroenterol Hepatol 2007;5:636-641
2. Hui CK, et al. Hepatology 2007;46:395-401

Approach to the HBV Patient

The question is not **WHO** to treat, but rather **WHEN** to treat




Deciding When to Treat

- **2 Elements**
 - **Liver inflammation**
 - **Elevated viral load**
- **Modifiers that increase risk of progression**

Host Factors	Virus Factors	Environmental Factors
Age >40 [*]	High levels of HBV-DNA [*]	Concurrent infection
Male [*]	Genotype (C>D) [*]	Alcohol use [*]
Immune status	HBV variant (core promoter)	Diabetes mellitus [‡]
Family history HCC [*]		Obesity [‡]

^{*} Supported by strong evidence. [‡] Further studies needed




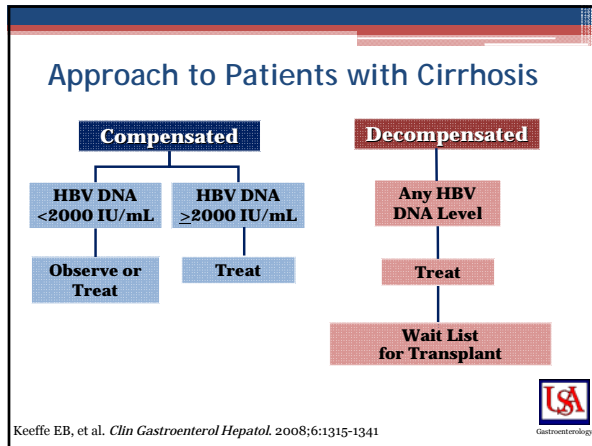
Treatment Algorithm

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    graph TD
      A[HBsAg Positive] --> B[HBV DNA >20,000 IU/mL]
      C[HBsAg Negative] --> D[HBV DNA >2,000 IU/mL]
      B --> E[ALT Evaluation]
      D --> E
      E --> F[Elevated ALT]
      E --> G[Normal ALT]
      F --> H[Treat]
      G --> I[Monitor]
      G --> J[Liver Biopsy]
      I --> E
      J --> K[Abnormal Histology]
      K --> H
  
```

Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341





- ## FDA-Approved Treatment Options
- **Interferons**
 - Interferon alfa-2b
 - Peginterferon alfa-2a
 - **Nucleosides / Nucleotides**
 - Lamivudine
 - Adefovir dipivoxil
 - Entecavir
 - Telbivudine
 - Tenofovir

Recommendations for First-Line Therapy

HBeAg Positive or Negative Chronic HBV

Preferred	Alternative	Not Preferred
Tenofovir	Adefovir	Lamivudine
Entecavir	Telbivudine	
Peginterferon alfa-2a		


Keeffe EB, et al. *Clin Gastroenterol Hepatol* 2008;6:1315-1341
Lok AS, McMahon BJ. *Hepatology* 2009;50:661-662

Interferon for Hepatitis B

Pros	Cons
<ul style="list-style-type: none">• Defined duration of therapy (16-52 weeks)• Highest HBV DNA levels• No drug-resistant mutants	<ul style="list-style-type: none">• Relatively contraindicated in decompensated cirrhosis• Use with caution in cirrhotics

1. Early prediction of response
2. Combination therapy


Cooksley WG. Sem Liv Dis 2004;24(Suppl 1):45-53



New Data on Interferon for HBV

- **HBV DNA levels <2,000 IU at week 8 of therapy predict sustained response¹**
 - Sensitivity 89%, NPP 92%
- **HBeAg (-) disease - HBsAg cleared in 9% with DNA <400 at EOT²**
 - If HBV-DNA negative 3 years after EOT, 44% cleared HBsAg
- **3-year follow of of HBeAg (+) interferon responders³**
 - 81% remained HBeAg (-), 30% lost HBsAg


1. Moucari R, et al. Hepatology 2009;49:1151-1157
2. Marellin F, et al. Gastroenterology 2009;136:2169-79
3. Buster EH, et al. Gastroenterology 2008;135:459-467

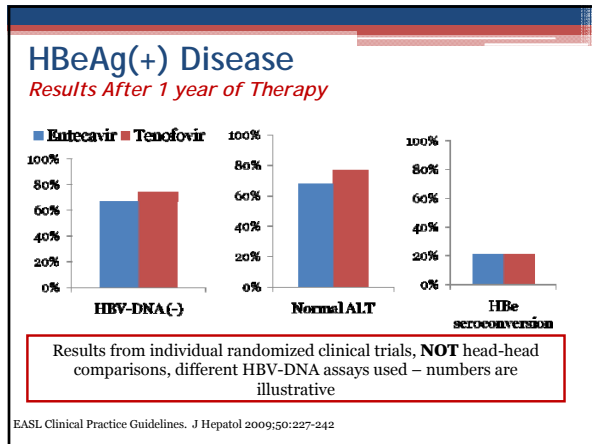


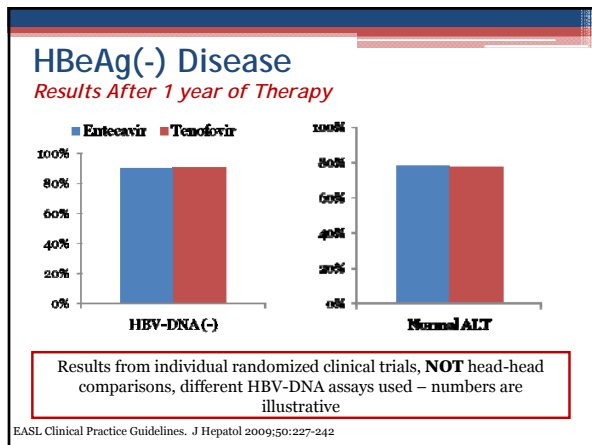
Oral Therapy for HBV

Preferred	Alternative
Tenofovir	Adefovir
Entecavir	Telbivudine

Keeffe EB, et al. Clin Gastroenterol Hepatol 2008;6:1315-1341
Lok AS, McMahon J. Hepatology 2009;50:661-662







Antiviral Therapy Selection

Entecavir	Tenofovir
<ul style="list-style-type: none"> ~1% resistance at 5 years Not ideal in lamivudine experienced patients Effective in adefovir resistance Effective in adefovir partial response Take on empty stomach Pregnancy class C No concern for renal toxicity 	<ul style="list-style-type: none"> No resistance at 2 years Effective in lamivudine resistance Not ideal in adefovir resistance Effective in adefovir partial response No food effect Pregnancy class B Renal toxicity noted in HIV patients


When to Stop Therapy

- Interferon therapy
 - 4 to 12 months
- HBeAg (-) disease
 - Treat indefinitely or until HBsAg (-) / HBsAb (+)
- Cirrhosis
 - Treat indefinitely
- HBeAg (+) disease
 - Treat for 6-12 months after HBeAg seroconversion and HBV-DNA not detectable
- **Controversy:**
 - Treat all until HBsAg (-) / HBsAb (+) ????



Special Circumstances


Immunosuppression HIV-Coinfection



HBV is Always Hiding Somewhere...

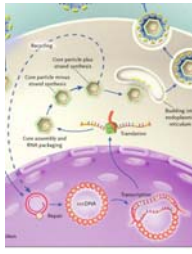
- Immunosuppression allows viral reactivation
 - Chemotherapy, anti-TNF therapy, immunomodulators, corticosteroids
- **2008 CDC recommendation:**
 - “Screen all persons needing immunosuppressive therapy including chemotherapy, and immunosuppression for rheumatologic or GI disorders”

CDC. MMWR 2008;57(No. RR-8):9-10
Lok AS, McMahon J. Hepatology 2009;50:661-662



Immunosuppression and HBV Reactivation

- At risk
 - HBsAG (+)**, any HBV-DNA level
 - HBsAG (+)**, negative HBV-DNA
 - HBsAG (-), HBcAB (+)** patients, neg HBV-DNA
 - Prior HBV Infection
 - Risk present even if HBsAb (+) as well




RISK

cccDNA remains in the nucleus

Mindikoglu AL, et al. Clin Gastroenterol Hepatol 2006;4:1076-1081

Recommendations

- Screen all patients about to undergo immune suppression
 - HBsAg, HBcAb (total)
 - If positive for either, measure HBV-DNA
- Start antiviral therapy if HBsAg or HBV-DNA positive
 - 2 weeks before and at least for 6-12 months after
- If HBsAG (-), HBcAb (+), HBV-DNA (-)
 - Treat with antiviral therapy¹ **OR**
 - Monitor HBV-DNA periodically during immune suppression²




¹Meeting Report. J Clin Virol 2008;41:243-254
²Vassiliadis T, et al. Am J Hematol 2005;80:197-203

HBV-HIV Co-infection

You can't treat HBV only!

- All HBV patients **must** be tested for HIV at diagnosis and **before** starting therapy
- Most HBV drugs are active against HIV
 - Treating HBV with monotherapy leads to prompt HIV multi-drug resistance**



McMahon MA, et al. NEJM 2007;356:2614-21

Treatment of HBV in HIV patients

3 Options

- 1. Standard of Care:** Start tenofovir-based HAART regimen¹
 - HBV infection is an indication for HAART in HIV co-infection
- 2. Treat HBV with pegylated interferon monotherapy**
- 3. Treat HBV with adefovir 10mg and telbivudine combo**
 - Improves potency and minimizes emergence of resistance, no studies.

¹www.aidsinfo.nih.gov/ContentFiles/AdultAdolescentGL.pdf
Matthews GV, et al. Hepatology 2008;48:1062-1069



Five Take Home Points

Approach to the patient with chronic HBV

1. All patients are candidates for therapy – the question is **WHEN** to treat
 - a. viremia, b. inflammation, c. prognostic factors
2. Preferred therapeutic options:
 - Tenofovir, entecavir or pegylated interferon
3. Duration of therapy
 - Determined by choice of therapy, e-antigen status, and severity of disease
4. Before initiating immunosuppression, all patients should be tested for
 - HBsAg, HBcAb (total), ± HBV-DNA
5. All HBsAg (+) patients must be tested for HIV