

# **Treatment of Chronic Hepatitis B: When to Start and When to Stop?**

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# Goals of HBV Treatment

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- **Suppress HBV replication – persistent virus suppression is necessary for continued clinical benefit**
- **Stop ongoing necroinflammation**
- **Prevent progression to cirrhosis, liver failure, and hepatocellular carcinoma**

# Assessment of Response

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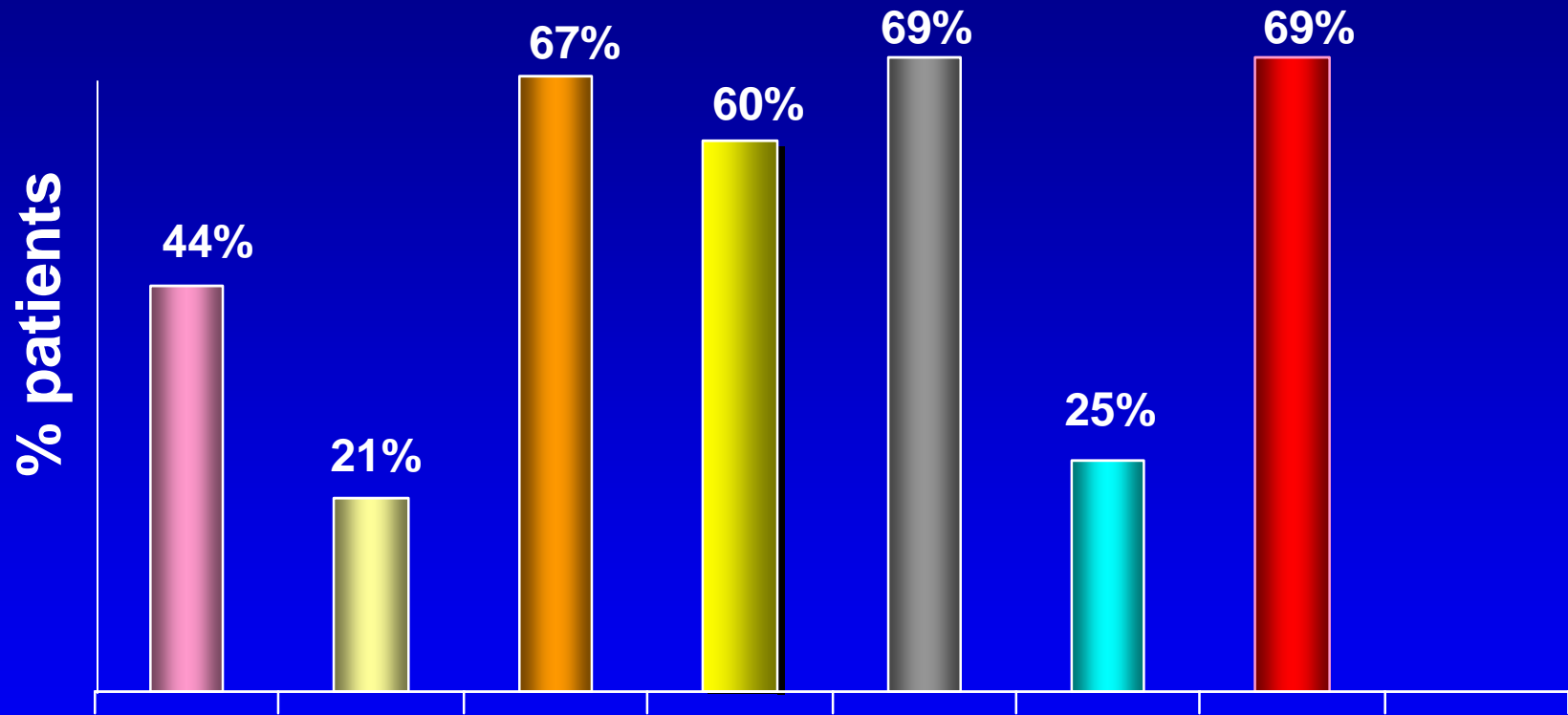
- **Virologic**
  - Serum HBV DNA: log decrease, undetectable
  - HBeAg seroconversion: HBeAg + → -, anti-HBe - → +
  - HBsAg seroconversion: HBsAg + → -, anti-HBs - → +
- **Biochemical**
  - AST / ALT: decrease, normalize
- **Histologic**
  - Inflammation and fibrosis: decrease

## **Approved HBV Treatments**

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- **Interferon alpha – standard and pegylated**
- **Lamivudine**
- **Adefovir**
- **Entecavir**
- **Telbivudine**
- **Tenofovir**

# Virologic Response in HBeAg+ patients (undetectable HBV DNA by PCR at week 48-52)



LAM

ADV

ETV

LdT

TDF

Peg  
IFN

Peg  
IFN +  
LAM

LAM = lamivudine, ADV = adefovir,  
ETV = entecavir, LdT = telbivudine, TDF = tenofovir,  
Peg IFN = pegylated interferon

# Therapy of Chronic Hepatitis B in 2008

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- **Multiple treatment options**
  - 5 oral therapies and 2 formulations of interferon
- **Potent antiviral activity**
  - Up to 6 log reduction in HBV DNA after 48-52 week treatment
  - Virus suppression associated with biochemical, histological, and clinical improvement (decreased rate of disease progression)
- **Excellent safety**
  - Frequency and severity of adverse events of oral therapies similar to placebo

# Limitations of HBV Treatments

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- **Current treatments suppress but not eradicate HBV → long durations, frequently life-long treatment needed to maintain virus suppression**
  - Risk of drug resistance
  - Unknown long-term safety
  - High costs

# Who Should be Treated?

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- **Not a question of whom to treat but when: treat now or monitor and treat later when indicated**
- **All HBV carriers are potential treatment candidates**
- **A patient who is not a treatment candidate now can be a treatment candidate in the future**
  - **Changes in HBV replication status and/or activity/stage of liver disease**
  - **Availability of new and better treatments**

# When to Start Treatment?

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## Benefits

Likelihood of  
- adverse outcome  
- long-lasting response



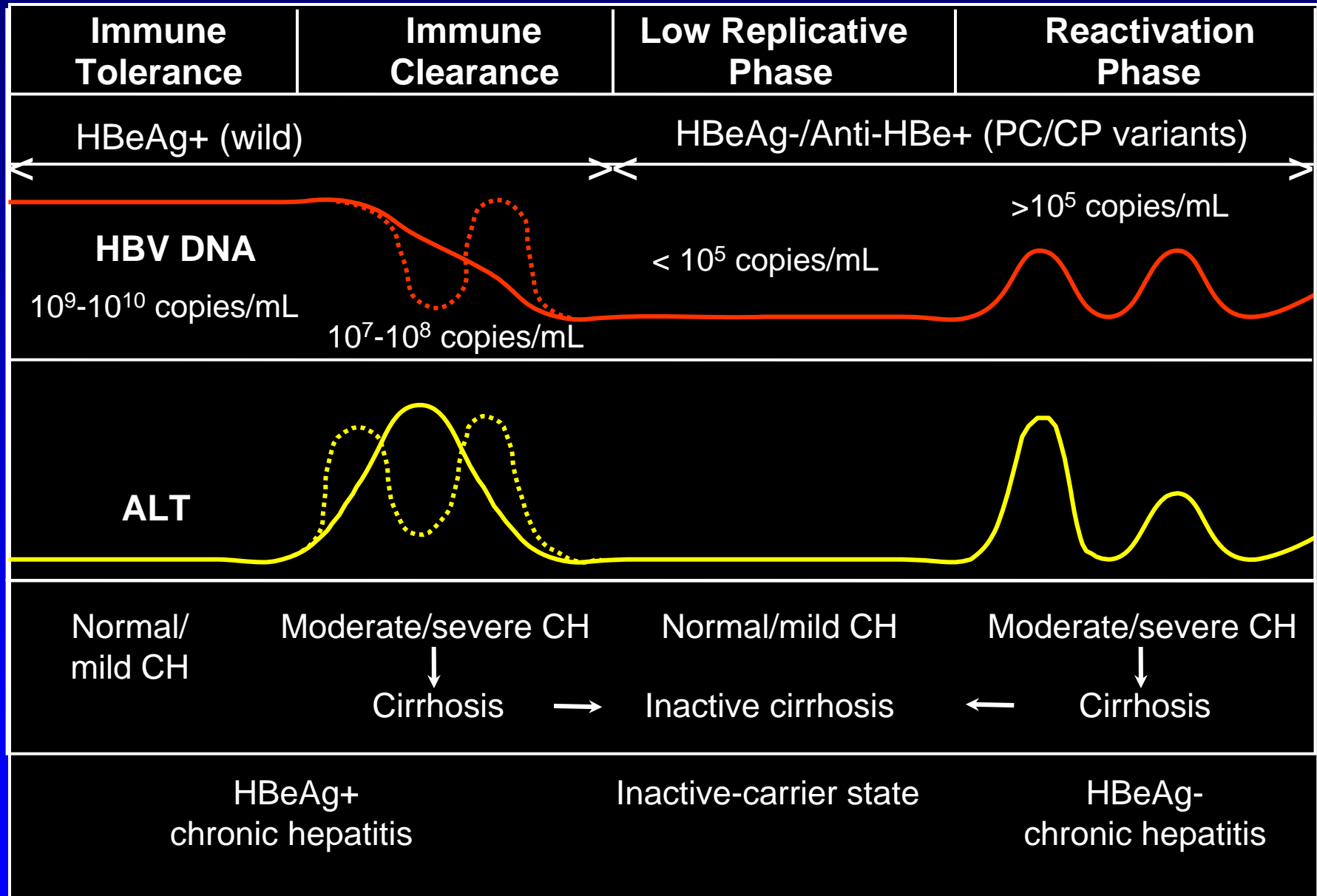
Patient's age  
and preference  
Costs

## Risks

Side effects  
Drug resistance

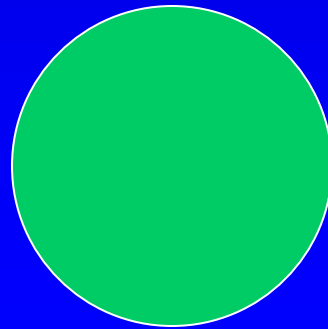
Likelihood of adverse outcome without treatment  
Activity and stage of liver disease at presentation  
Risk of cirrhosis / HCC in the next 10-20 yrs  
Likelihood of long-term benefit with treatment

# Stages of Chronic HBV Infection



PC, precore; CP, core promoter; CH, chronic hepatitis

**Clear cut cases in which treatment  
should be initiated**



# **Case 1 – Severe hepatitis flare in a patient with chronic HBV infection**

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## **Rationale for recommending treatment**

- **ALT flares associated with increase in bilirubin or INR may progress to liver failure**
- **Case series have reported improved survival compared to untreated historical controls**

## **Case 2 – Compensated cirrhosis and high HBV DNA**

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### **Rationale for recommending treatment**

- **Virus suppression has been shown to prevent disease progression (liver failure, liver cancer) in patients with advanced fibrosis / cirrhosis and high serum HBV DNA or HBeAg+**

## **Case 3 – HBeAg+ chronic hepatitis**

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- **M/38**
- **HBeAg+, HBV DNA 315 million IU/mL**
- **ALT 98 U/L (repeat tests over 4 months: ALT remained 2-3 x ULN)**

**Treatment may be deferred for 3-6 months if compensated to determine if spontaneous HBeAg seroconversion will occur**

**– Liver biopsy optional**

## Case 4 – HBeAg- chronic hepatitis

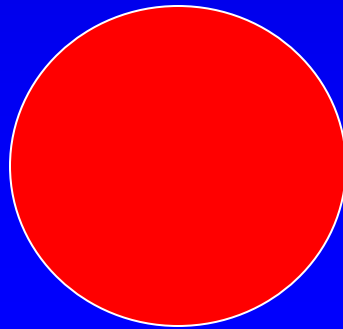
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- F/62, ALT 83 U/L (101 and 92 on repeat)
- HBeAg-, HBV DNA 69,000 IU/mL (53,000 on repeat)
- Biopsy: moderate inflammation, bridging fibrosis

**Treatment recommended because: age 62, advanced fibrosis, ALT >2 x normal**

- Spontaneous sustained remission extremely rare

# Cases in which treatment can be deferred



## Case 5 – Inactive HBV Carrier

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- F/38, asymptomatic
- HBeAg-, HBV DNA 50 IU/mL
- ALT 20 U/L
- Repeat labs on 3 occasions similar results

### Rationale for not recommending treatment at this time

- Favorable prognosis if patient remains in inactive carrier state during follow-up
- Continued monitoring required

## Case 6 – Immune tolerant, <30 years

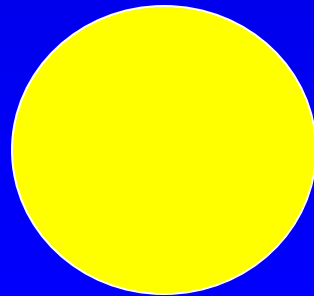
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- F/25
- HBeAg+, HBV DNA 724 million IU/mL, ALT 18 U/L
- Mother and brother also HBsAg+

### Rationale for not recommending treatment at this time

- Likelihood of significant liver injury at this stage is low
- Short- and mid- term prognosis favorable
- Possibility of spontaneous HBeAg seroconversion and subsequent remission
- Low rate of HBeAg seroconversion even with treatment
- Additional consideration if patient plans to be pregnant in the next few years

# **Cases in Which Treatment Decision Should be Individualized**



## Case 7 – Immune tolerant, >40 years

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- M/45
- ALT 29 U/L, repeat test 6 months later: 24 U/L
- HBeAg+, HBV DNA 54 million IU/mL
- Repeat labs on 3 occasions similar

### Factors to consider in treatment decision

- Persistently high HBV DNA (years / decades) and HBeAg positive x >40 years is associated with increased risk of cirrhosis and HCC
- Liver biopsy may help in determining urgency of treatment

# What are the Indications to Start Treatment?

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## AASLD Practice Guidelines 2007

- Evidence of liver disease – abnormal ALT ( $>2x$  ULN) in the presence of high serum HBV DNA ( $>20,000$  IU/mL)
  - Lower threshold if
    - Older age
    - Active inflammation or advanced fibrosis on biopsy
    - Clinical evidence of cirrhosis
- Borderline ALT or HBV DNA – monitor, if persistent, consider biopsy
- Others – monitor, treat later when indication arises or more effective treatment available

# When to Stop / Modify Treatment?

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- **Predetermined duration regardless of patient response**
- **Achievement of therapeutic endpoint**
- **Treatment failure**
  - **Primary: inadequate initial response**
  - **Secondary: drug resistance**
- **Unacceptable adverse events**
- **Patient request**
- **Pregnancy?**
- **Never?**

# When to Stop Interferon Treatment?

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- **Finite duration: 12 months**
  - Immunomodulatory effects may persist after cessation of treatment
  - Need for parenteral administration, side effects, and high costs

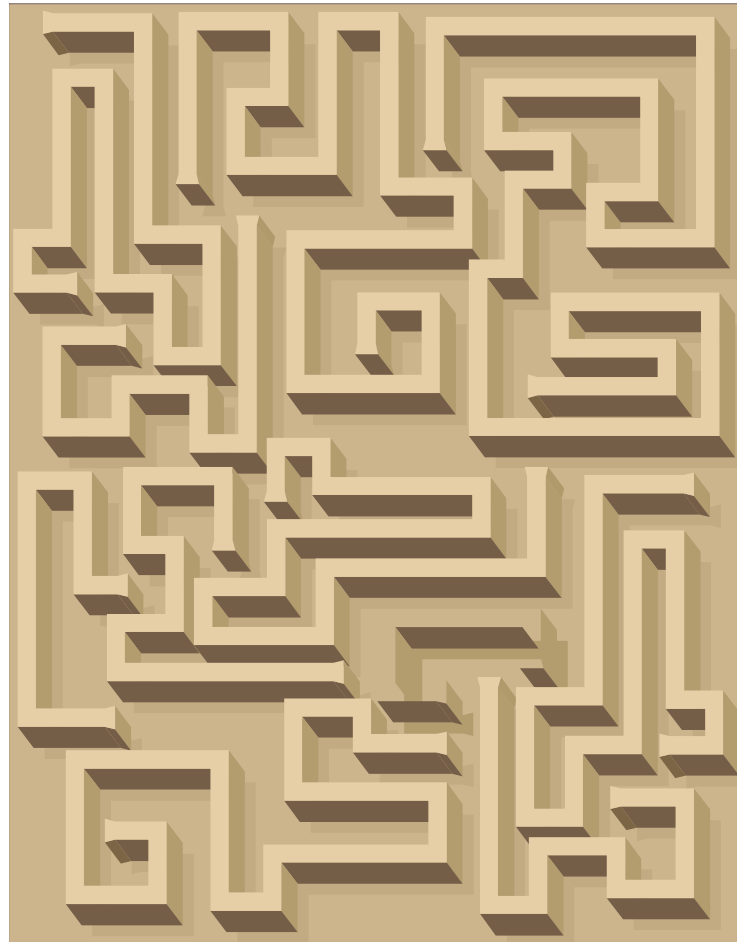
## **What Should be the Therapeutic Endpoint for Nucleos/tide Therapies?**

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- **Ideally, viral suppression (to undetectable by sensitive PCR) that can be sustained after treatment is discontinued**
- **HBeAg+ patients: HBeAg seroconversion – ~50% after 5 yr treatment, add 6-12 months consolidation treatment**
- **HBeAg- patients: endpoint unclear, many years or life-long**
- **Patients with cirrhosis: life-long?**

# The Maze of Hepatitis B Treatments

**Where  
to start**



**Which  
direction  
to go**

**How to  
get out**

**Think carefully and make sure you know how to  
navigate your way around before entering this maze**