



# Therapies for Hepatitis B and C

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## Goals of Therapy

- Eradicate circulating virus
- Prevent histologic progression of disease
- Delay or prevent complications of cirrhosis

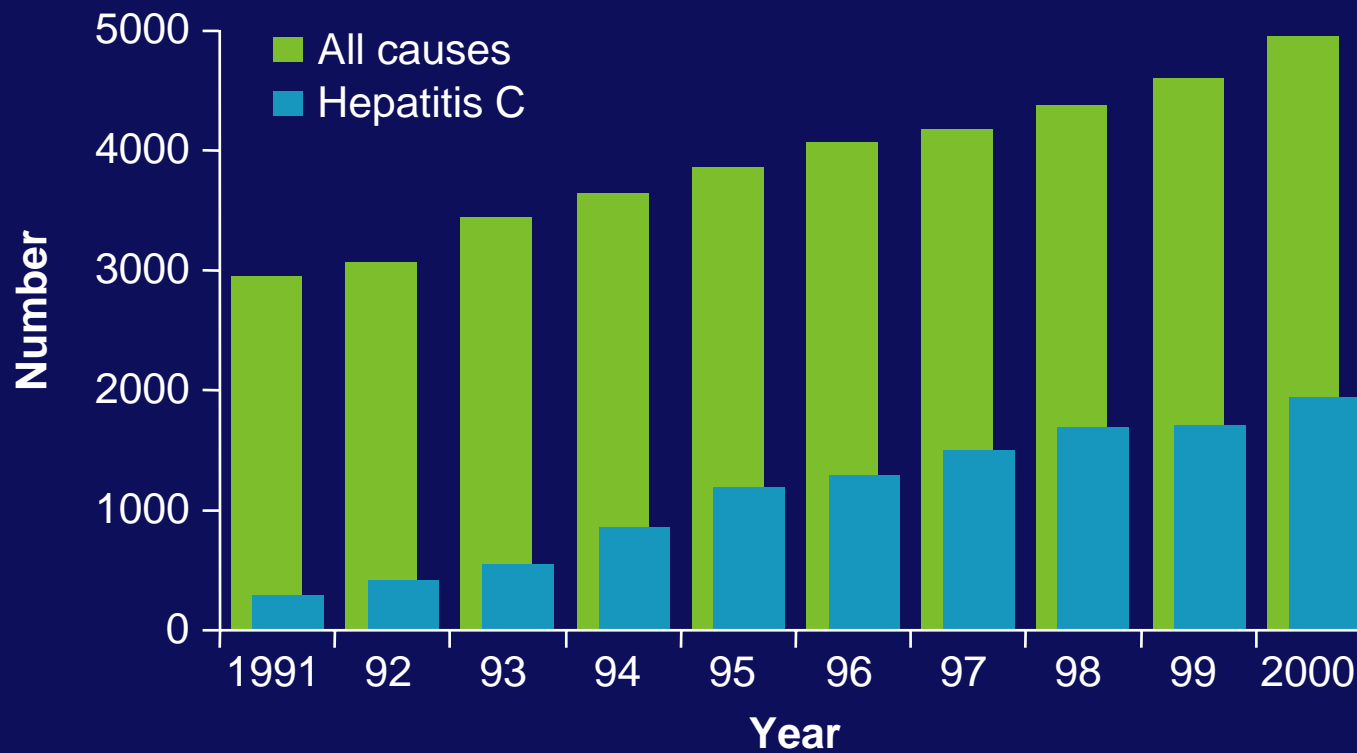
## Patient Selection: Key Questions

- Does the patient need treatment?
- What is the likelihood of eradicating circulating virus?
- Can the patient tolerate the side effects of therapy?
- Can the patient be expected to comply with treatment?

# Themes

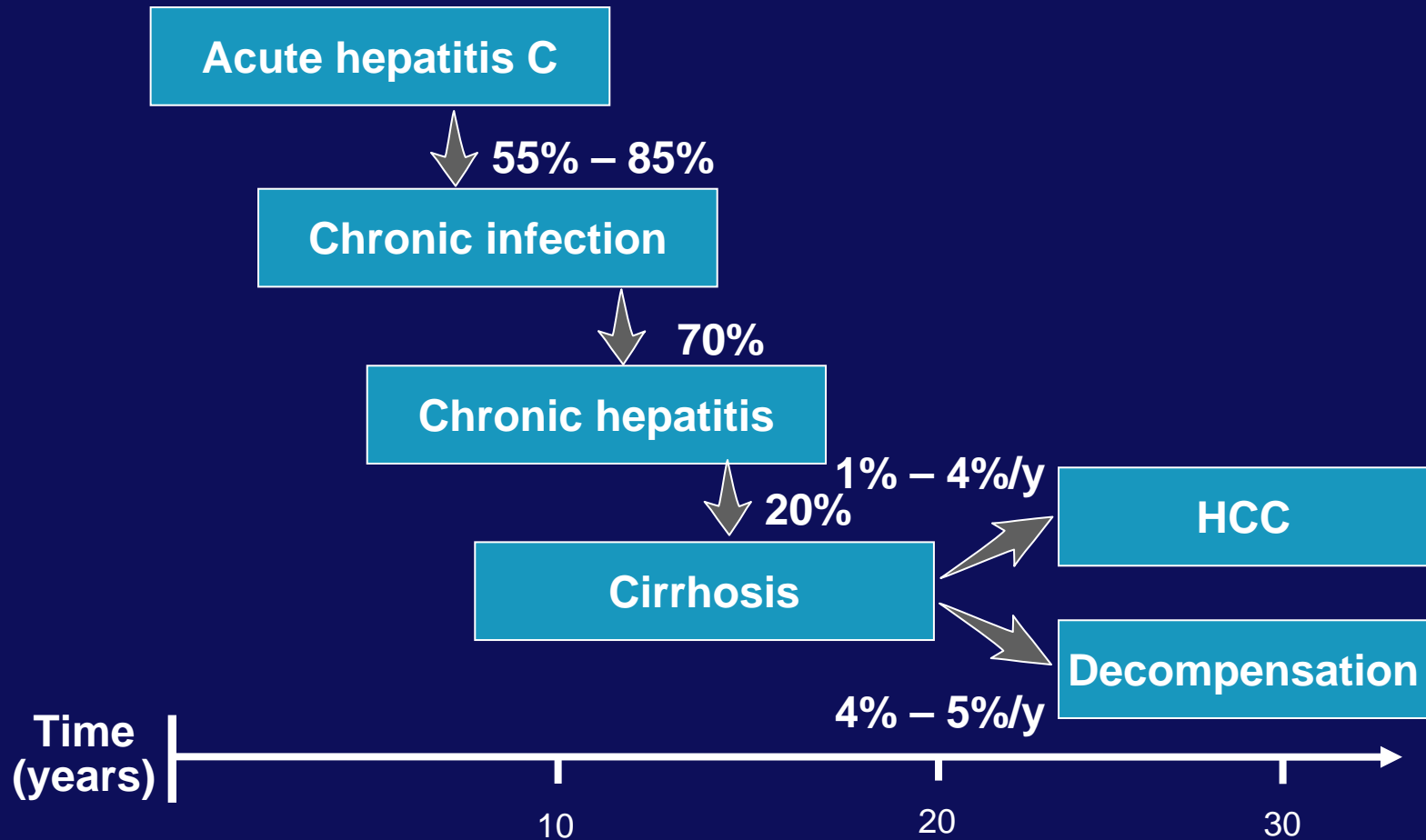
- Natural history of chronic hepatitis C
- Current status of treatment: hepatitis C
- Natural history of chronic hepatitis B
- Current status of treatment: hepatitis B

# Liver Transplantation in the United States



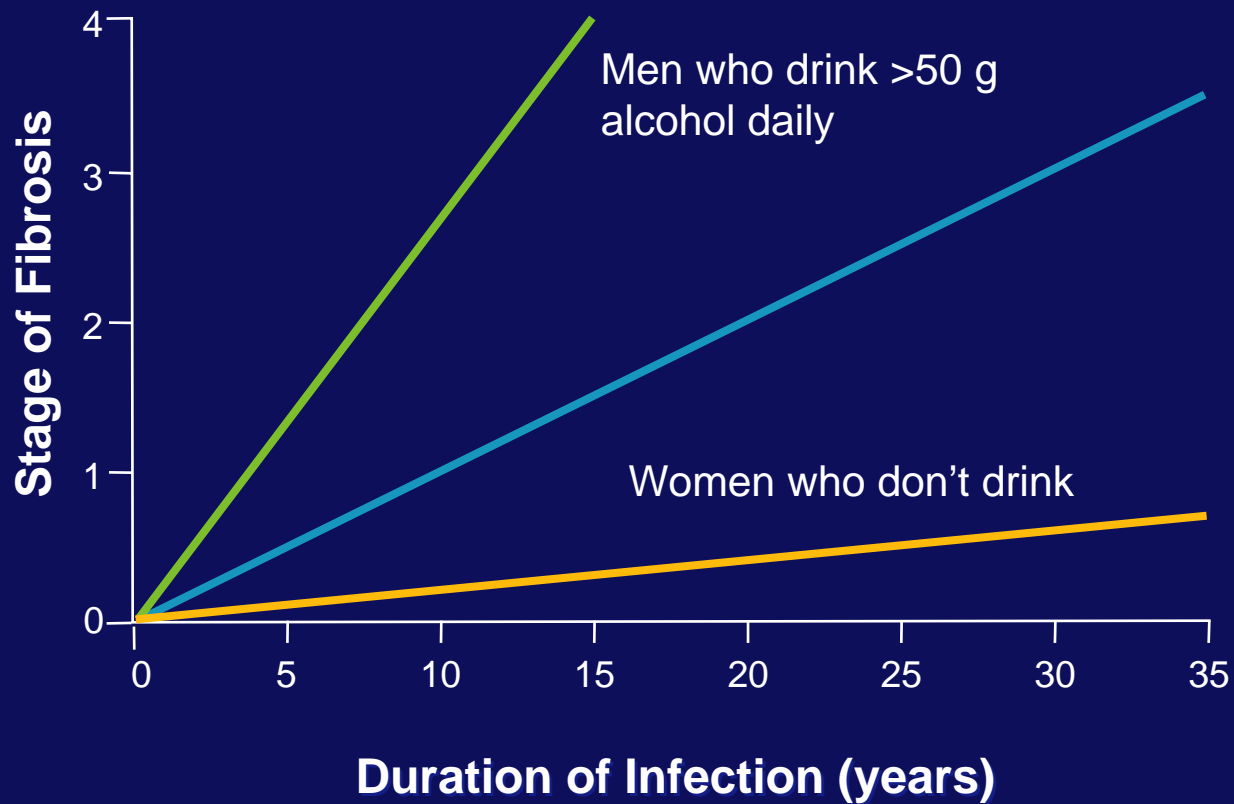
United Network for Organ Sharing (UNOS).

# Outcome Following Hepatitis C Infection



HCC = hepatocellular carcinoma.

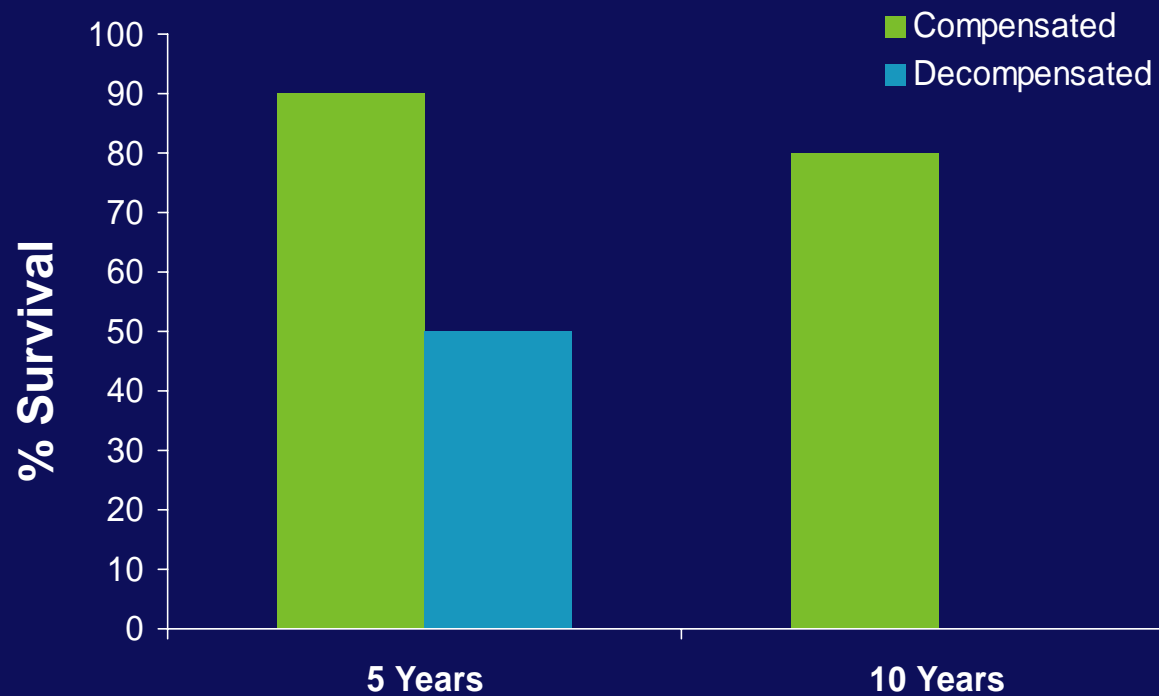
# Fibrosis Rate Varies Among Individuals



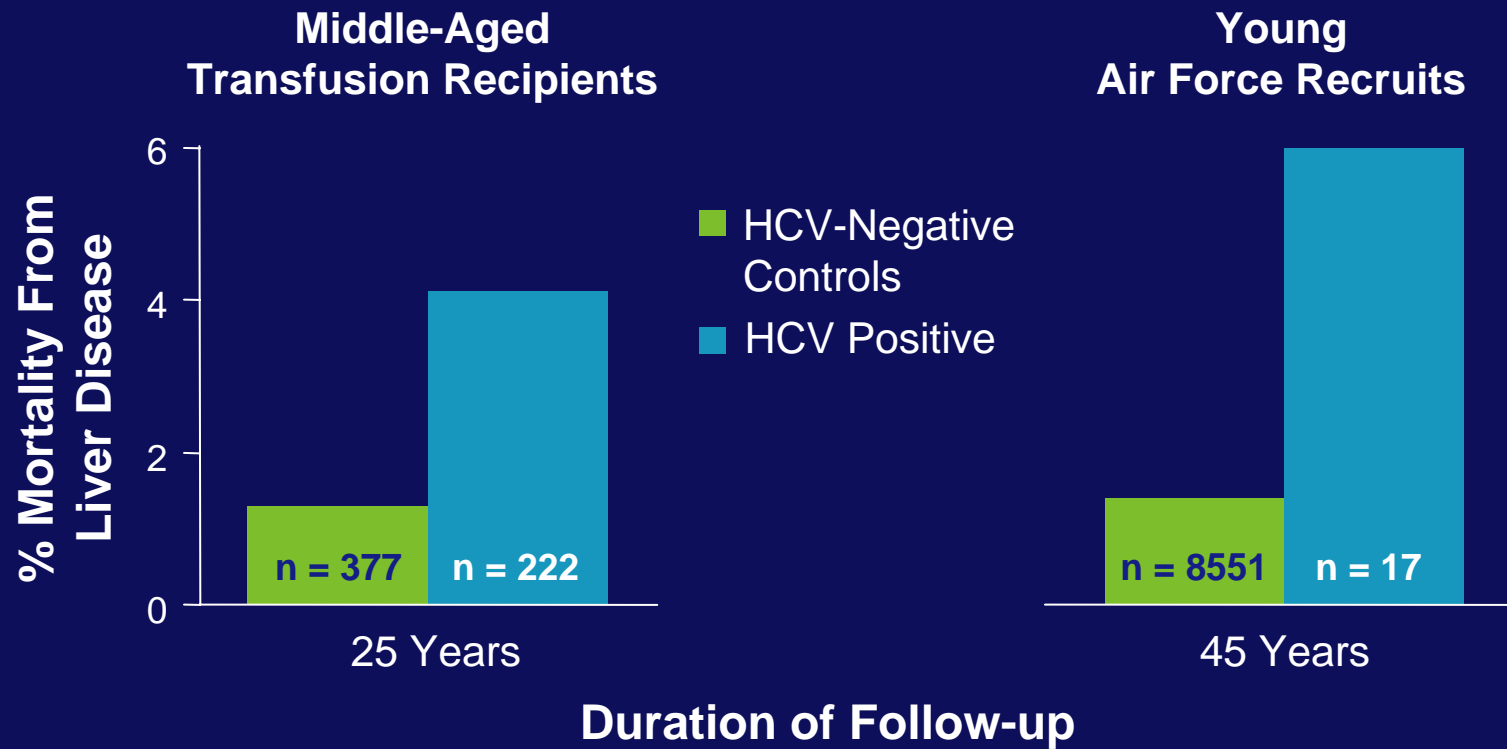
# Variable Disease Progression

- Factors associated with increased disease progression
  - Older age at time of infection
  - Male gender
  - Alcohol abuse
- Factors **not** associated with increased disease progression
  - Genotype
  - Viral load

# Survival After Diagnosis of Cirrhosis



# Liver-Related Mortality in Chronic Infection



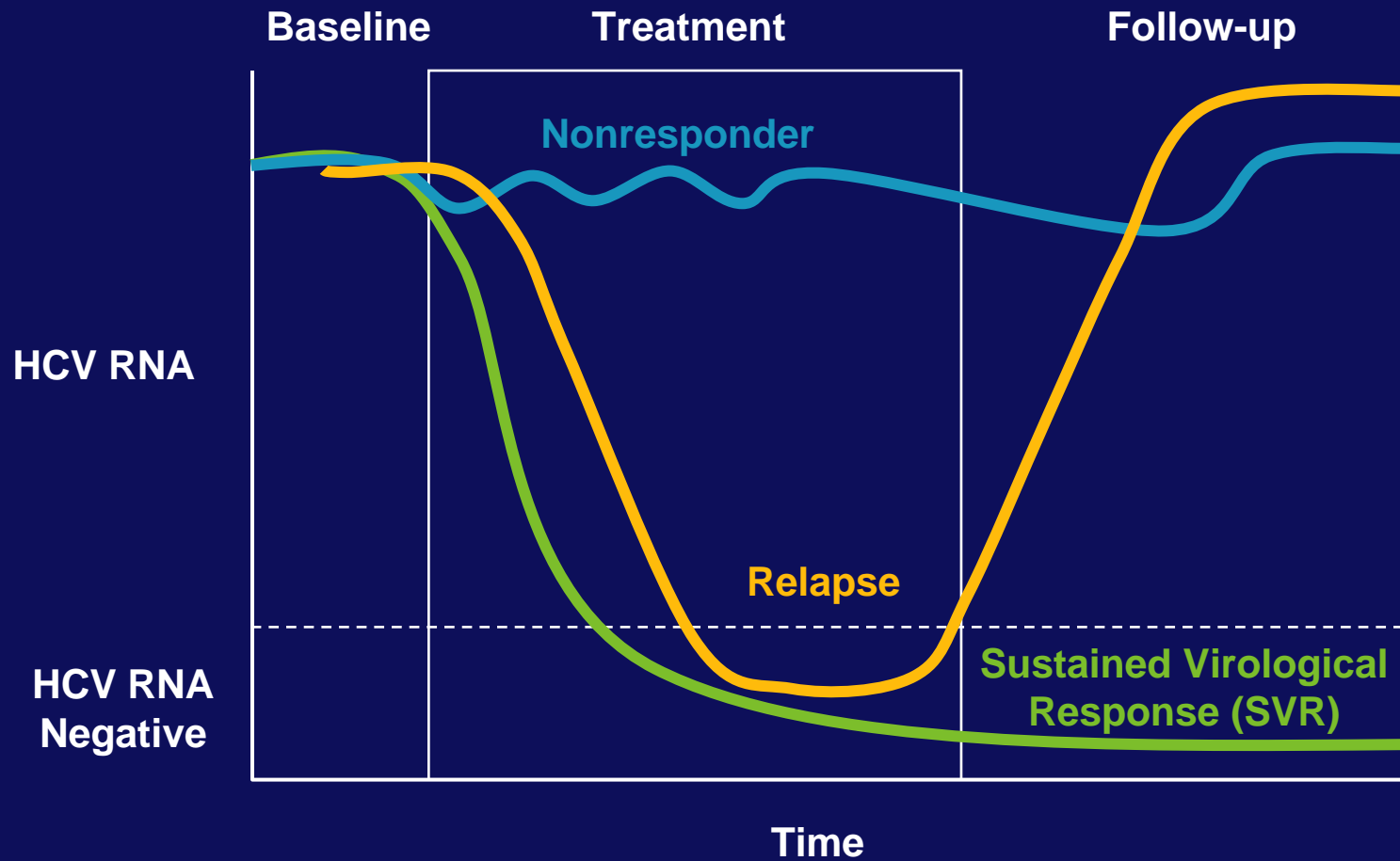
HCV = hepatitis C virus.

Seeff LB, et al. *Ann Intern Med.* 2000;132:105-111.  
Seeff LB, et al. *Hepatology.* 2001;33:455-463.

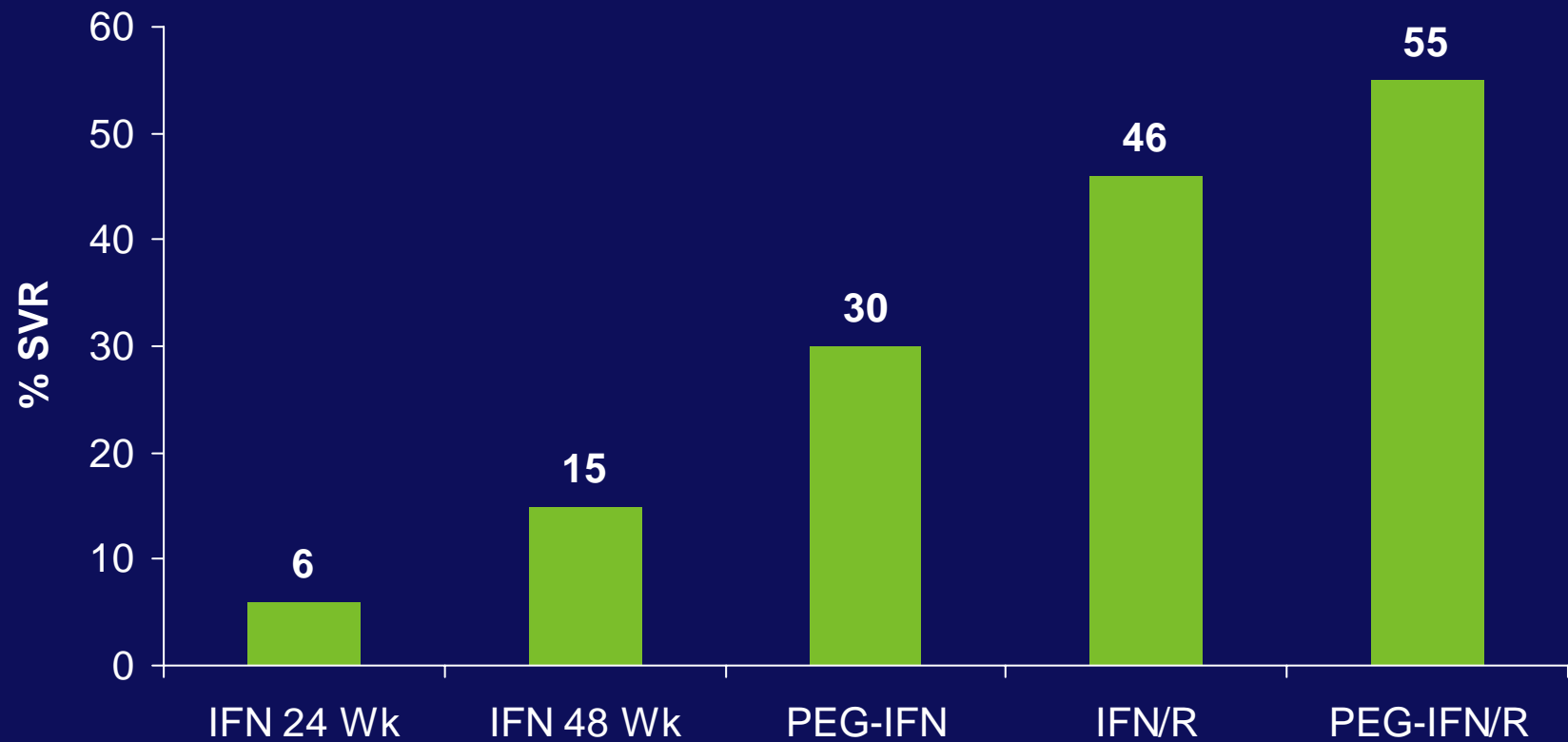
# Themes

- Natural history of chronic hepatitis C
- Current status of antiviral therapy: hepatitis C
- Natural history of chronic hepatitis B
- Current status of antiviral therapy: hepatitis B

# Patterns of Response to Therapy



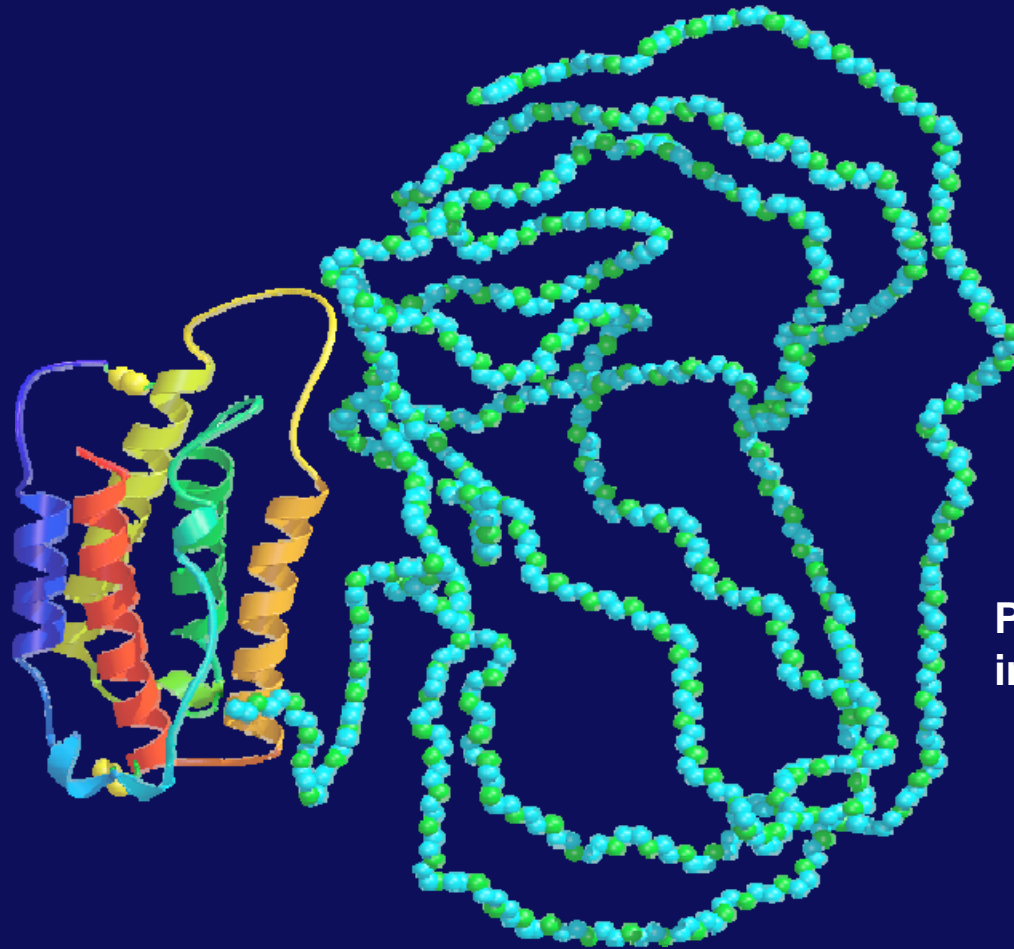
# Progress in Treatment



IFN = interferon; PEG-IFN = pegylated interferon; R = ribavirin.

# Pegylated Interferon

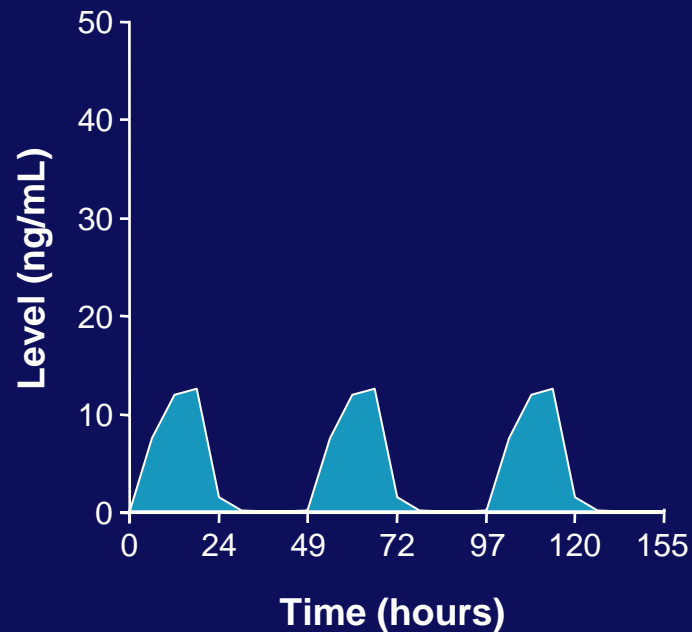
Interferon



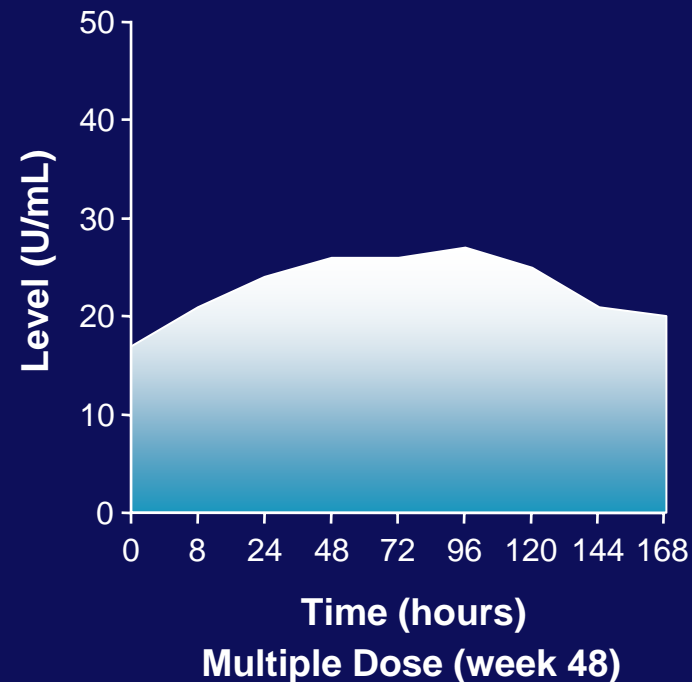
Pegylated  
interferon

# Pharmacokinetics of Pegylated Interferon Alfa-2a Compared With Standard Interferon Alfa-2a

**IFN alfa-2a**  
**IFN TIW Dosing**



**PEG-IFN alfa-2a**  
**Weekly Dosing**

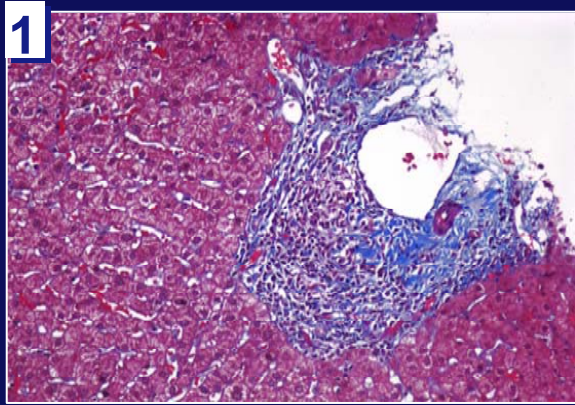


# Patient Selection: Key Questions

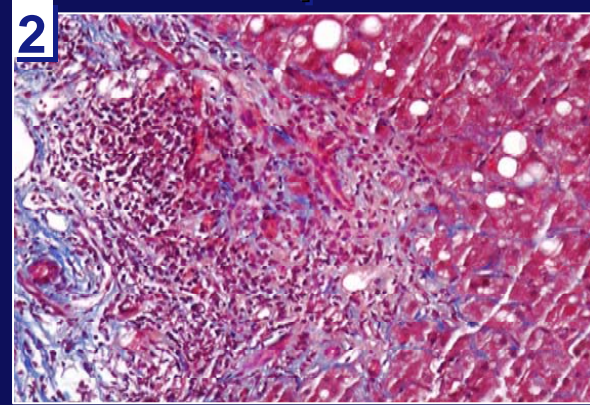
- Does the patient need treatment?

# Stages of Fibrosis in Chronic Hepatitis

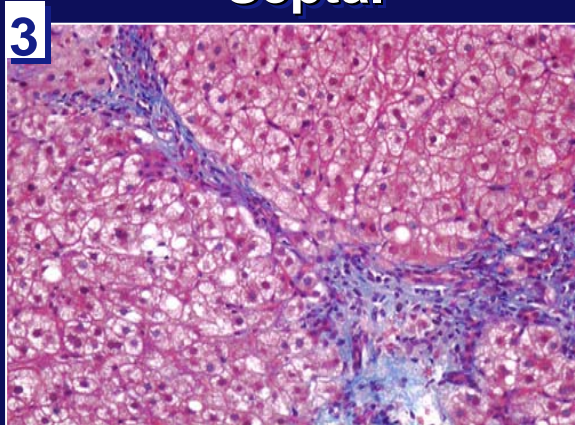
Portal



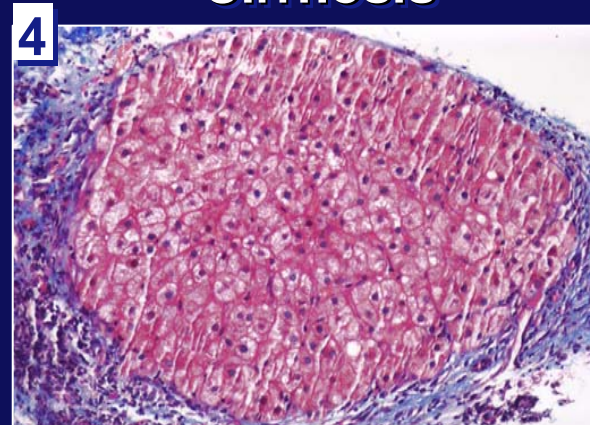
Periportal



Septal



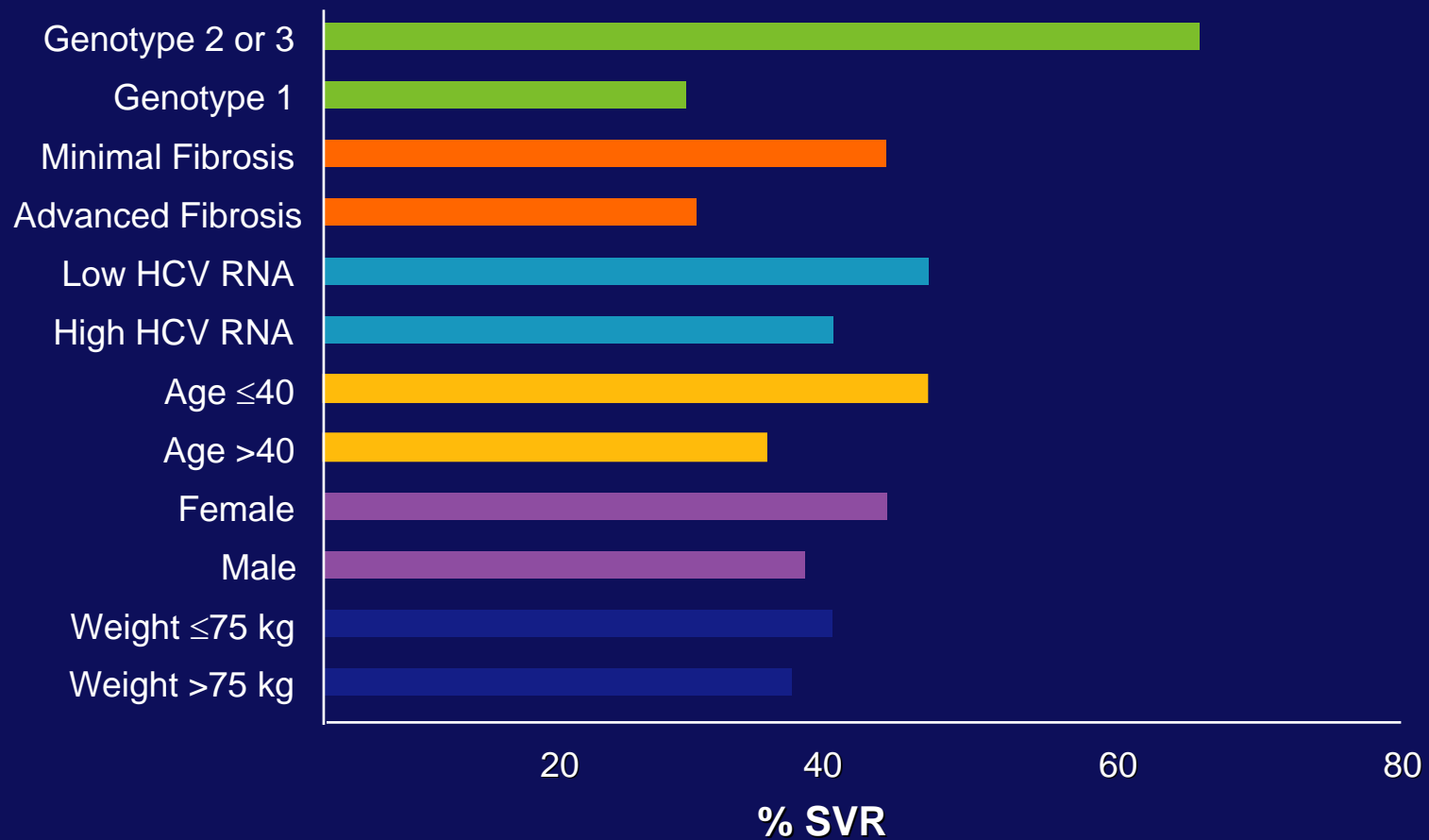
Cirrhosis



## Patient Selection: Key Questions

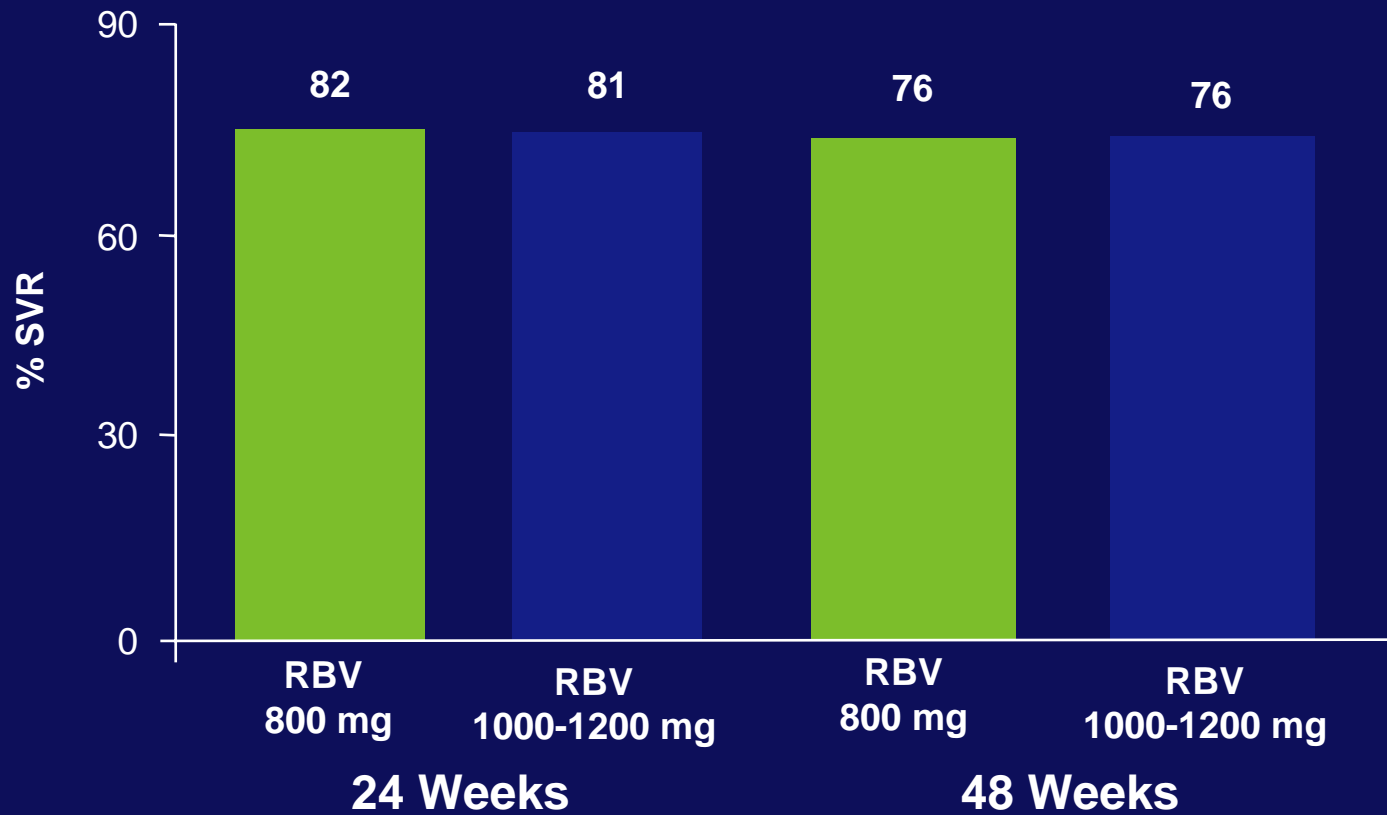
- Does the patient need treatment?
- What is the likelihood of eradicating circulating virus?
- Can the patient tolerate the side effects of therapy?
- Can the patient be expected to comply with treatment?

# Genotype Is the Most Important Predictor of Response to Treatment

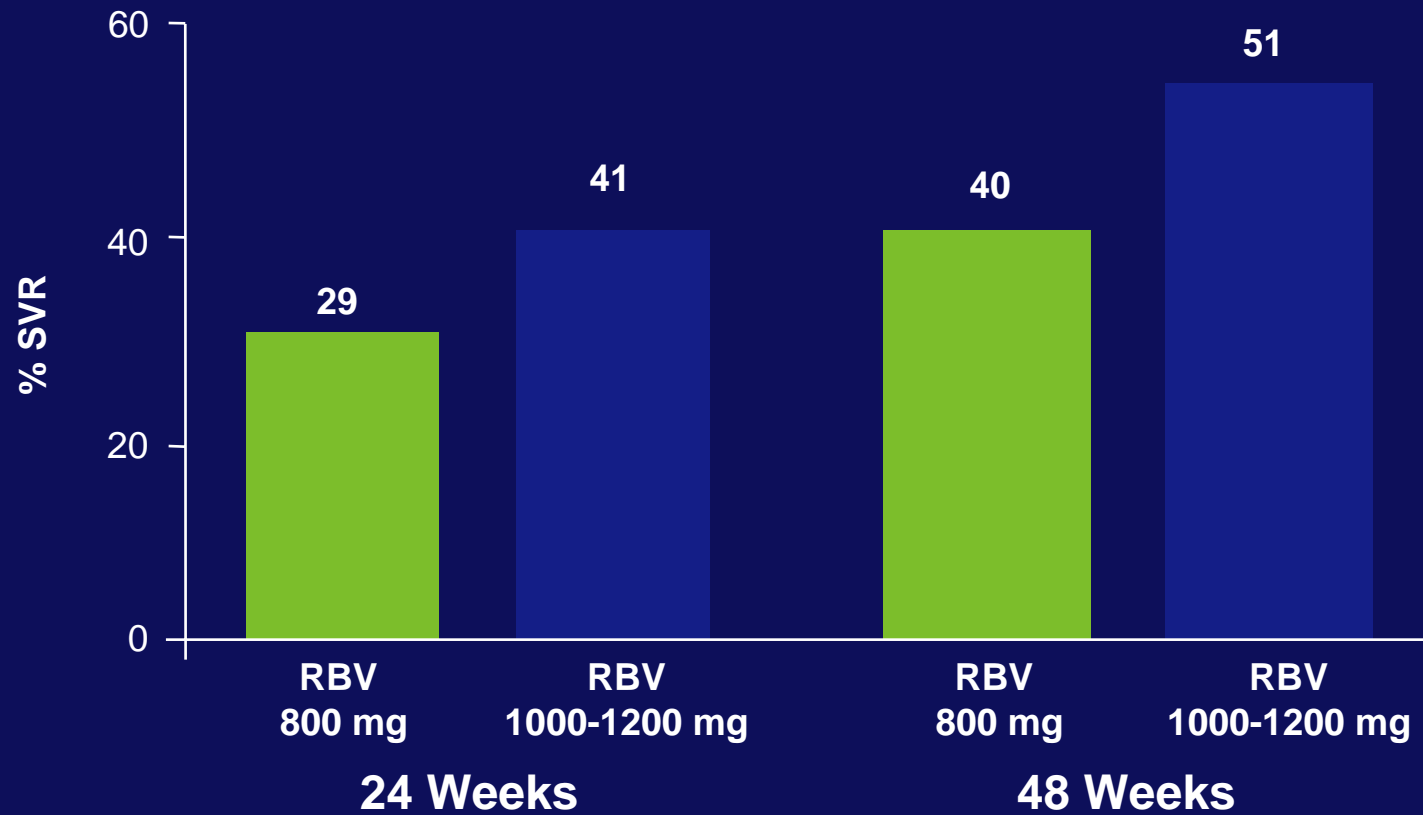


McHutchison JG, Poynard T. *Semin Liver Dis.* 1999;19(Suppl 1):57-65.

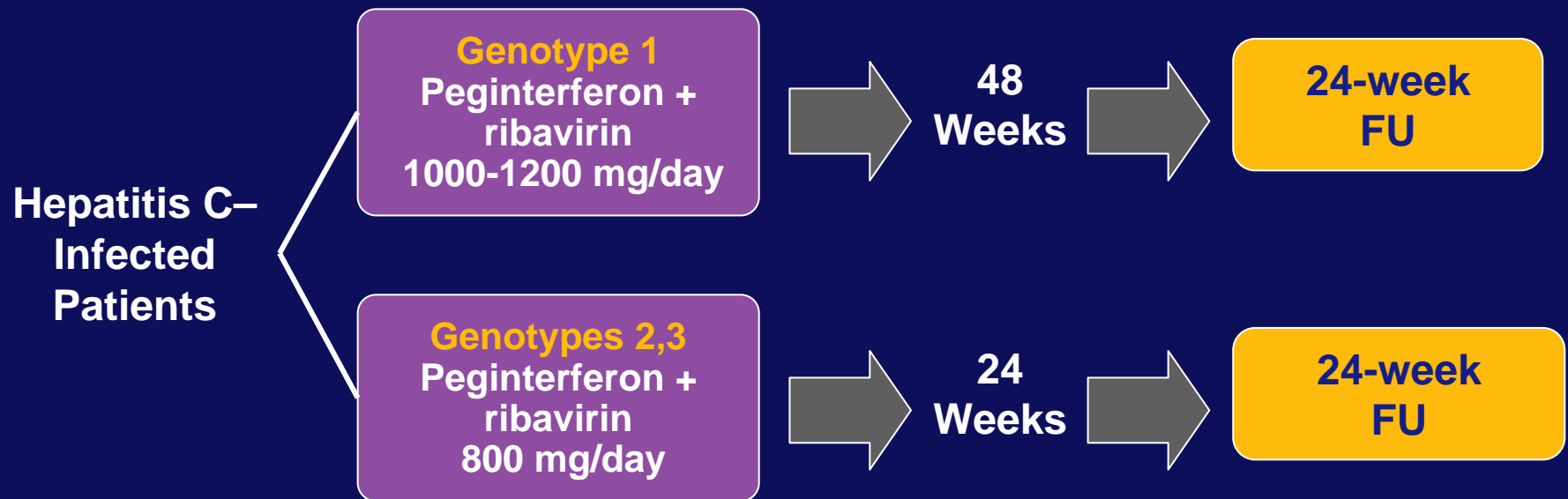
# Pegylated Interferon + Ribavirin: Genotype 2 and 3 Infections



# Pegylated Interferon + Ribavirin: Genotype 1 Infection

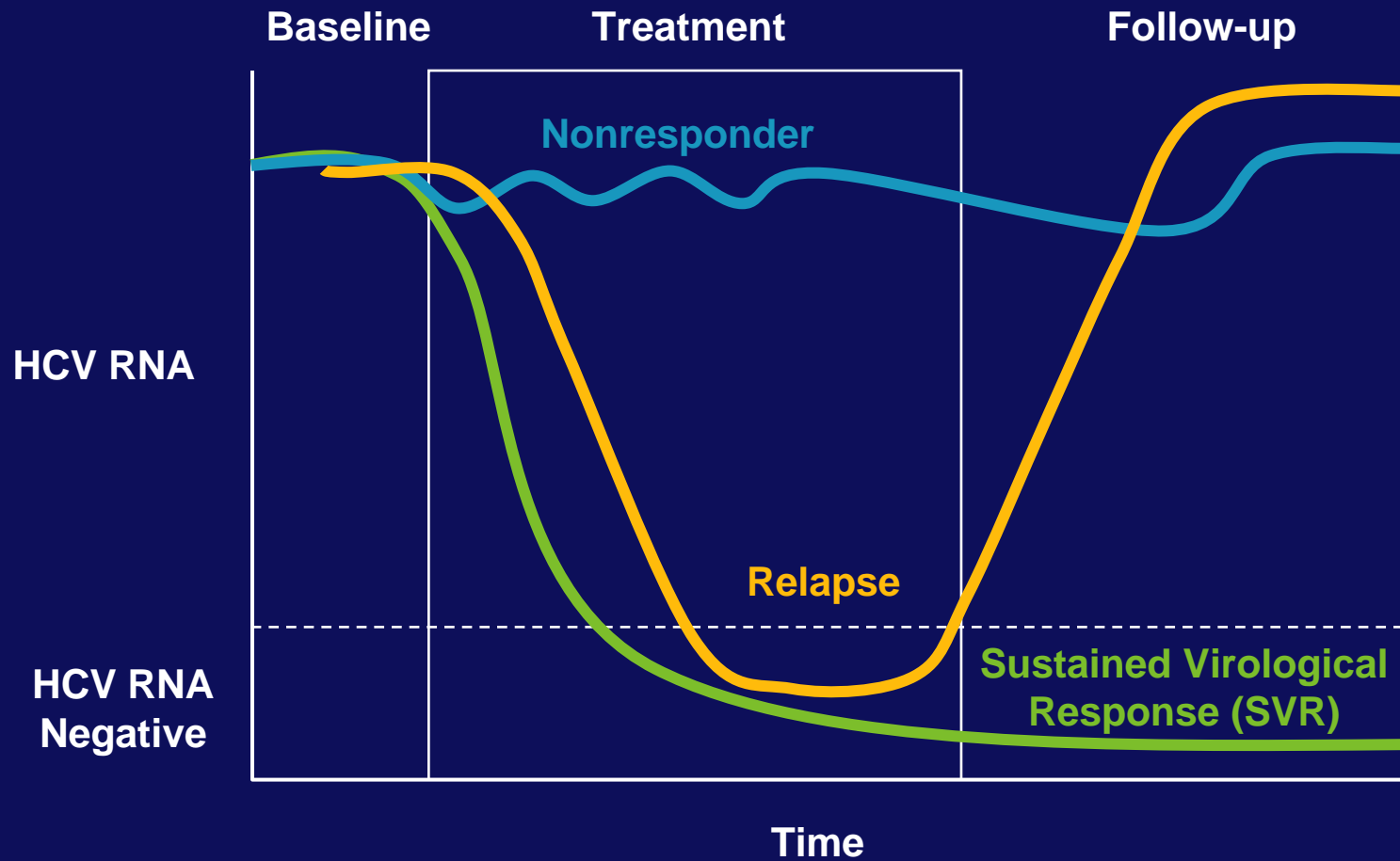


# Pegylated Interferon + Ribavirin: Current Treatment Paradigm



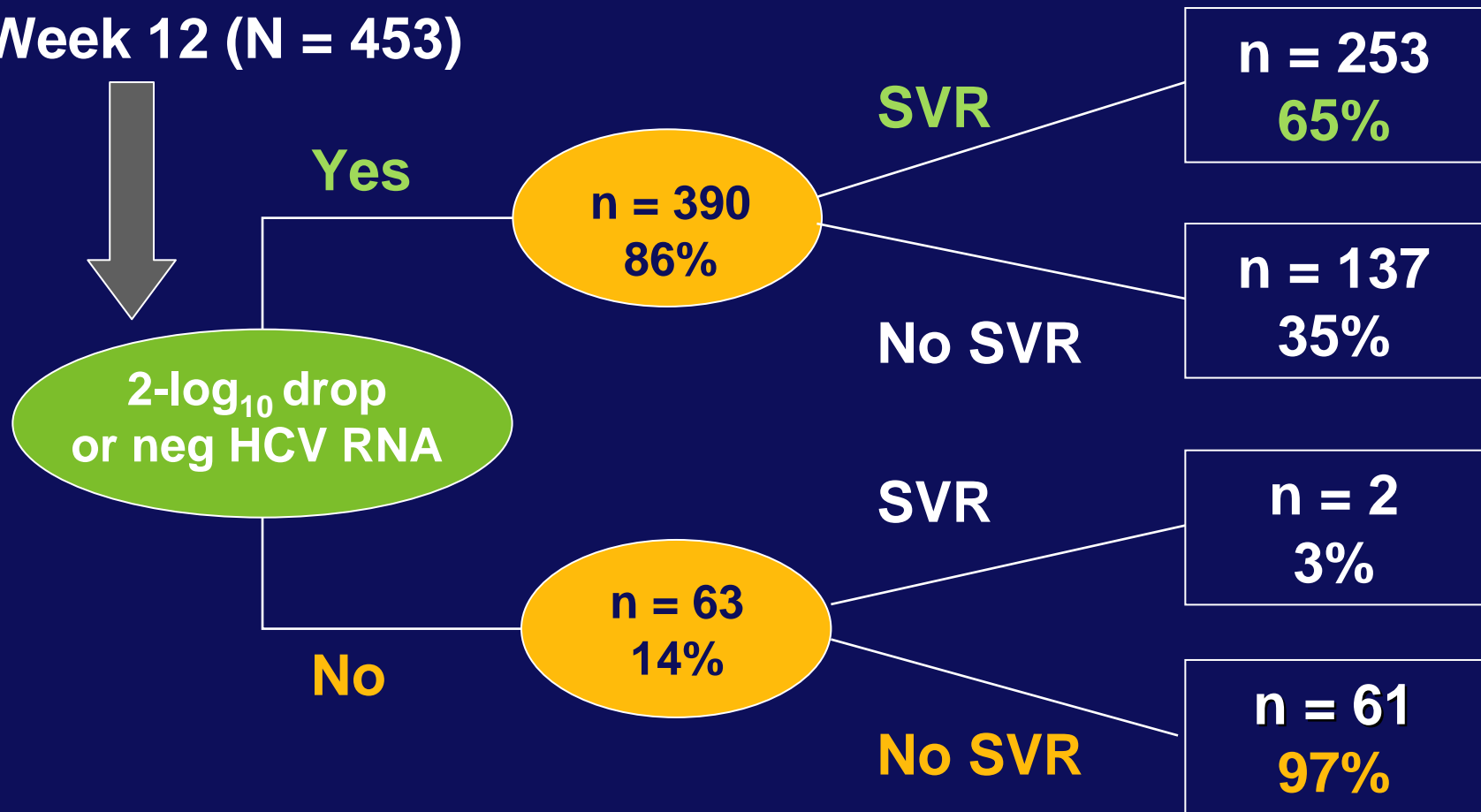
FU = follow-up.

# Patterns of Response to Therapy

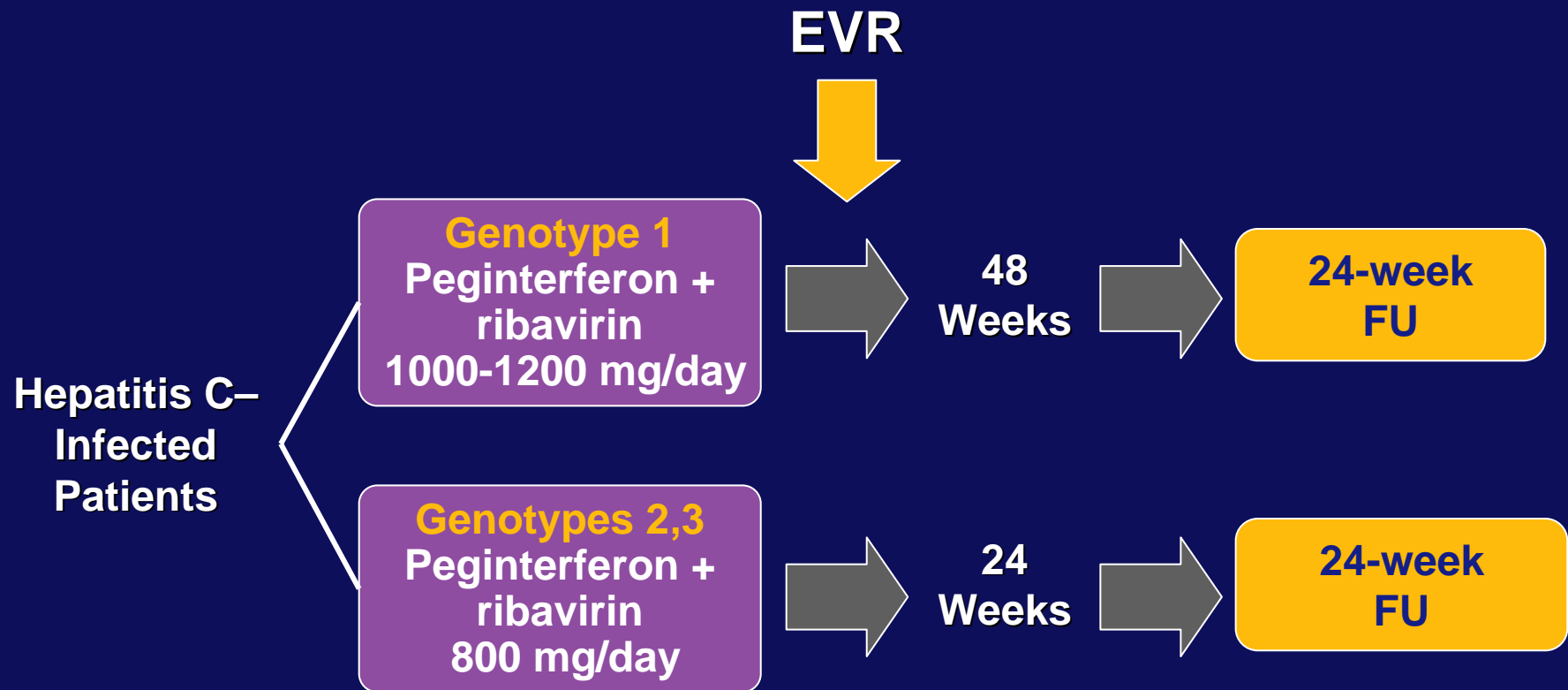


# Pegylated Interferon Alfa-2a + Ribavirin: Early Virological Response (EVR)

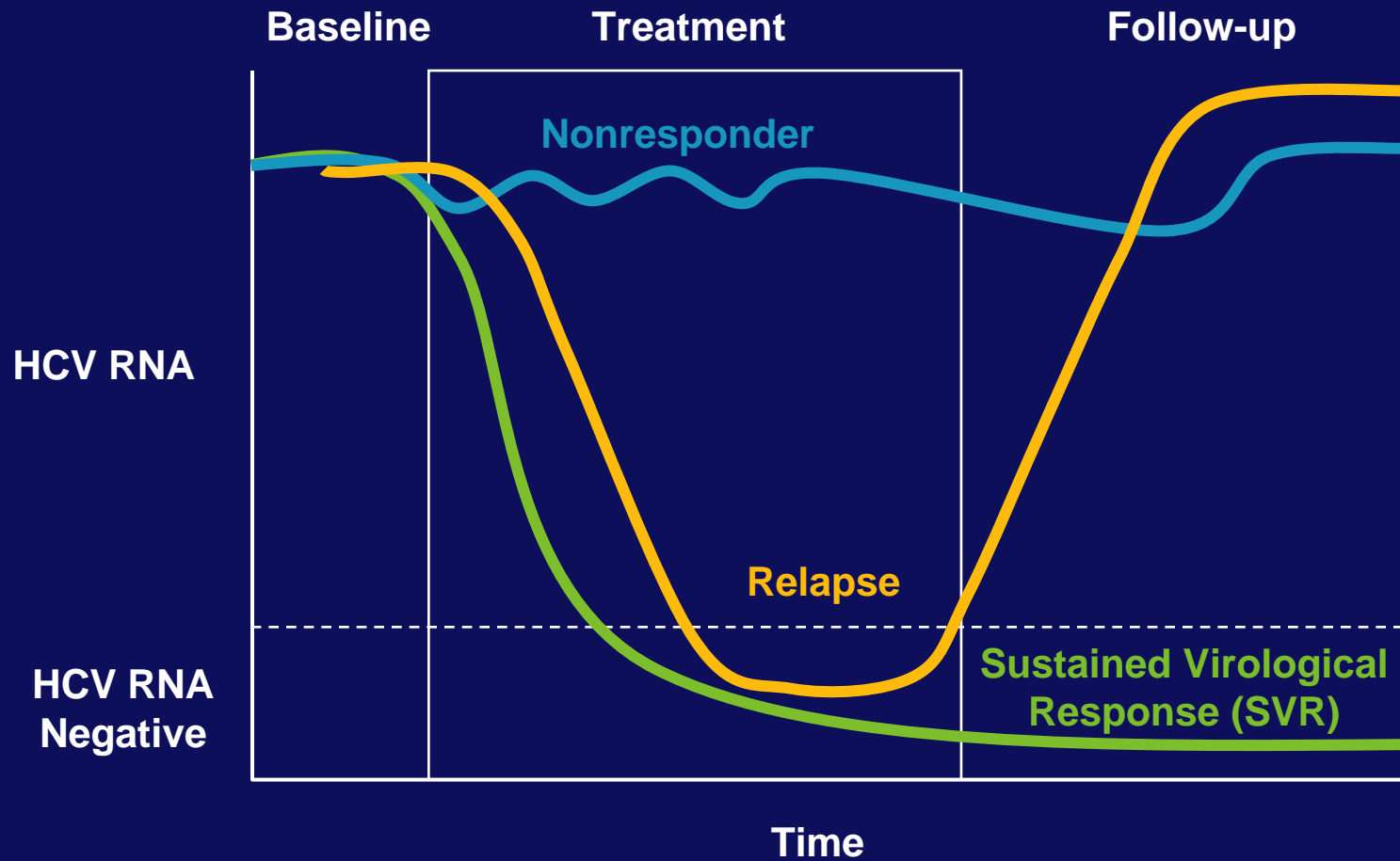
Week 12 (N = 453)



# Pegylated Interferon + Ribavirin: Current Treatment Paradigm



# Patterns of Response to Therapy



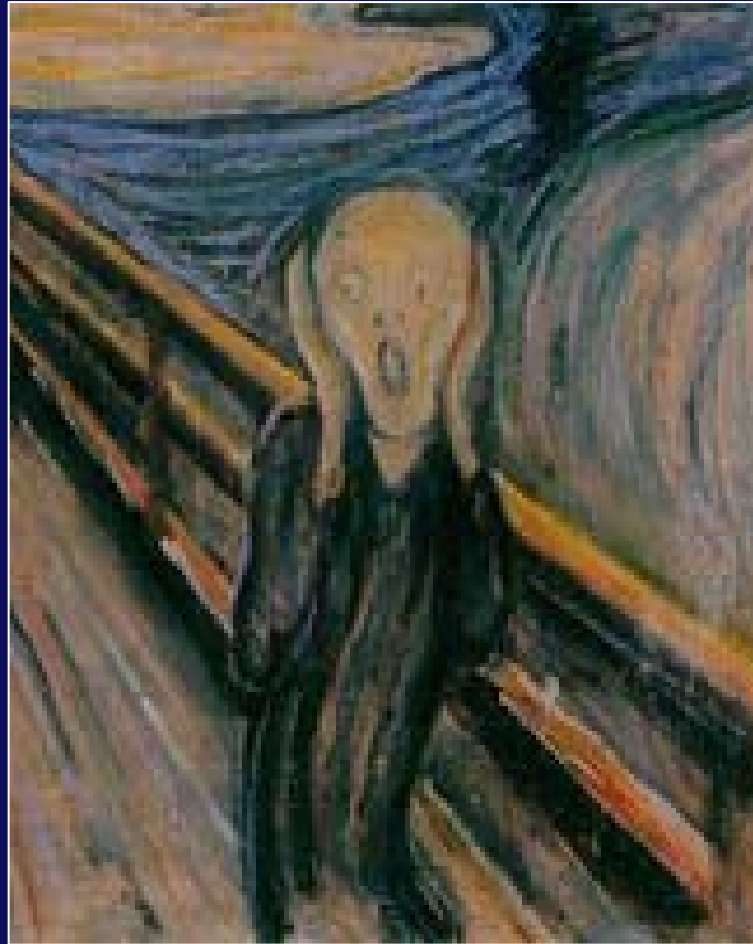
## Patient Selection: Key Questions

- Does the patient need treatment?
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# Interferon Therapy: Common Side Effects

- Flu-like symptoms
- Injection-site reactions
- Myalgias and arthralgias
- Nausea, anorexia and weight loss
- Neuropsychiatric side effects (mania, depression, insomnia)
- Bone marrow suppression
- Thyroid dysfunction
- Exacerbation of autoimmune disorders

# Self-Report of Patient on Interferon Therapy

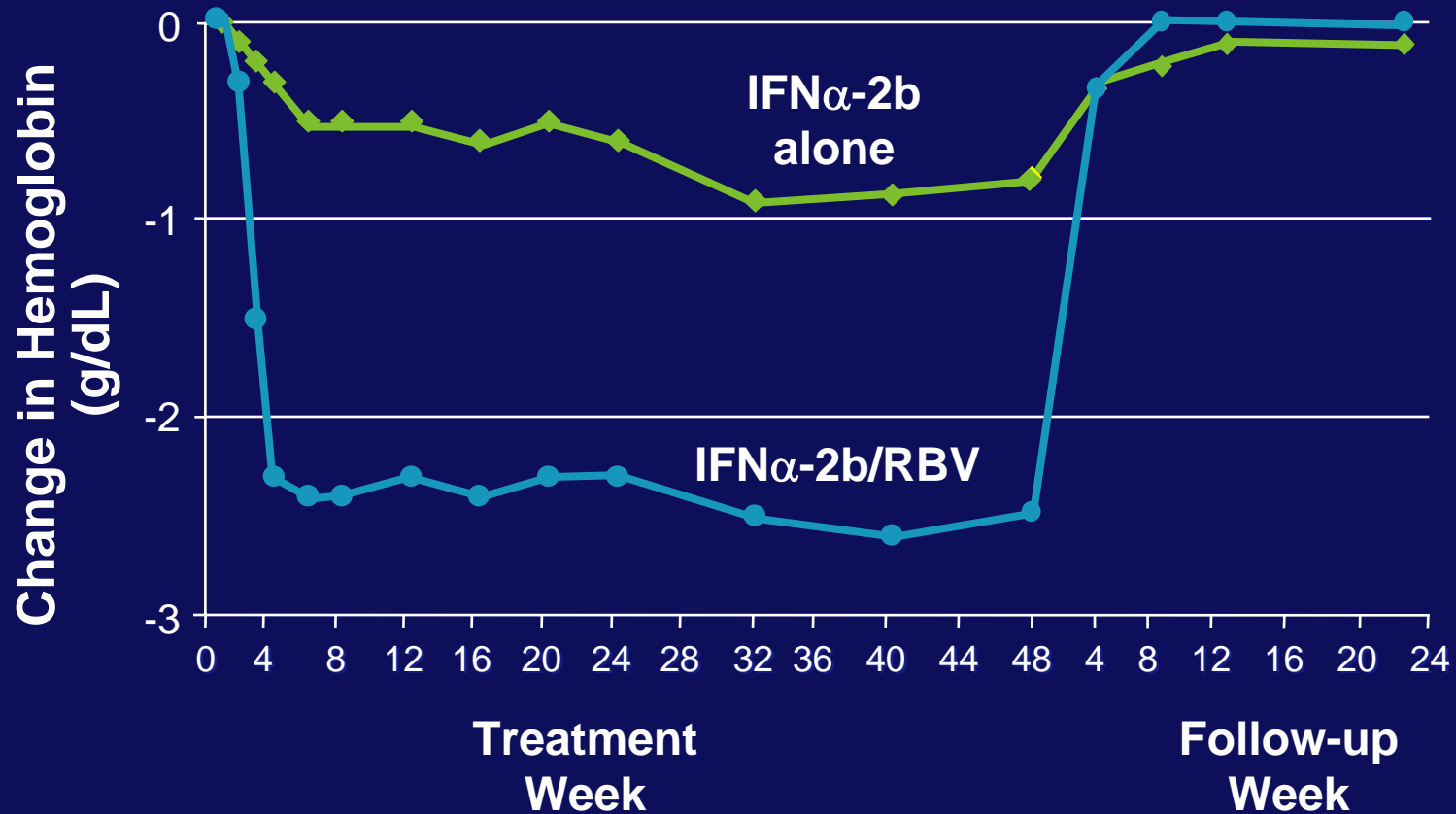


Edvard Munch (1863-1944)

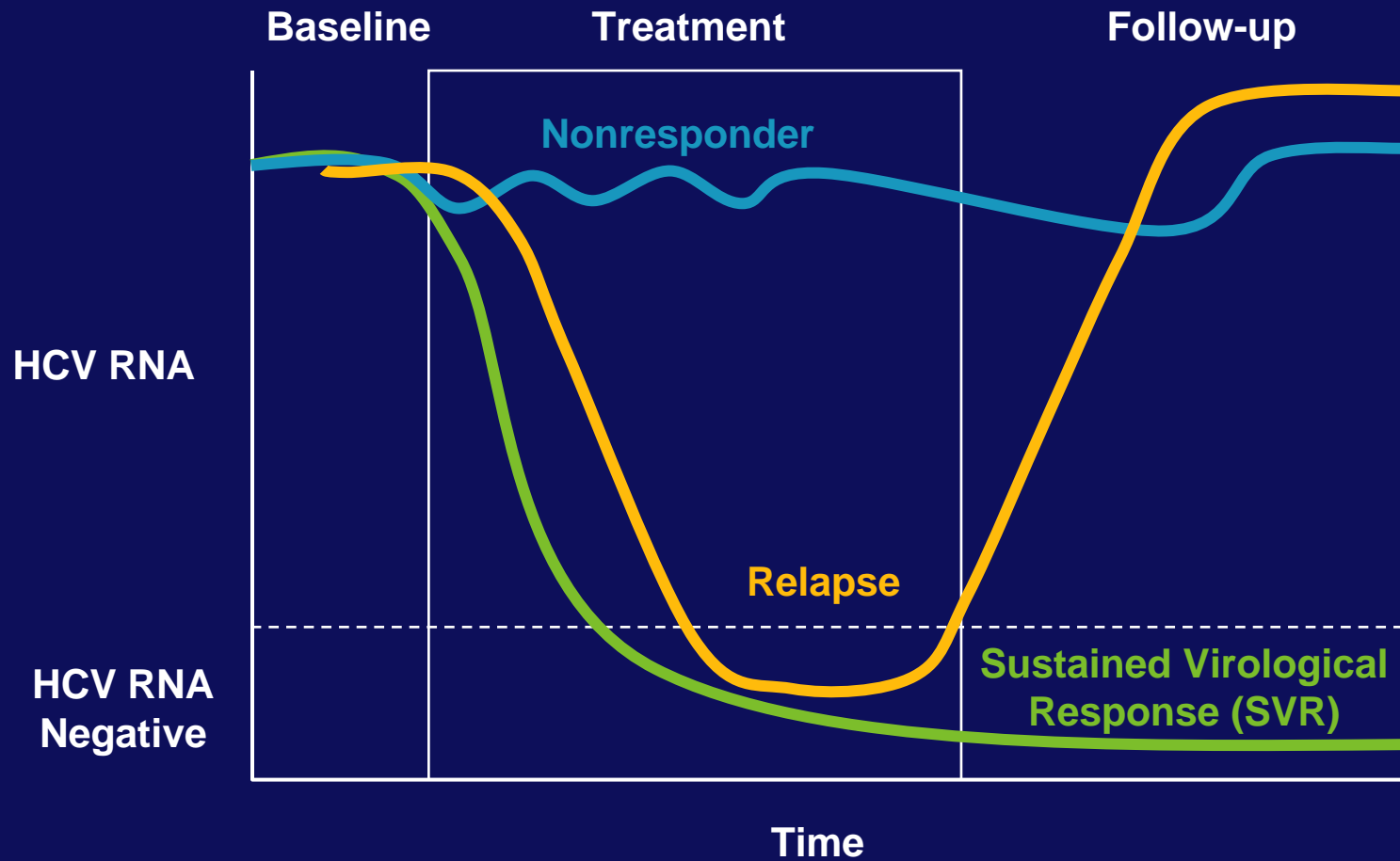
# Ribavirin Therapy: Major Side Effects

- Teratogenic
- Hemolytic anemia
- Skin rash
- Cough
- Insomnia
- Fatigue

# Hemolytic Anemia Associated With Ribavirin Therapy



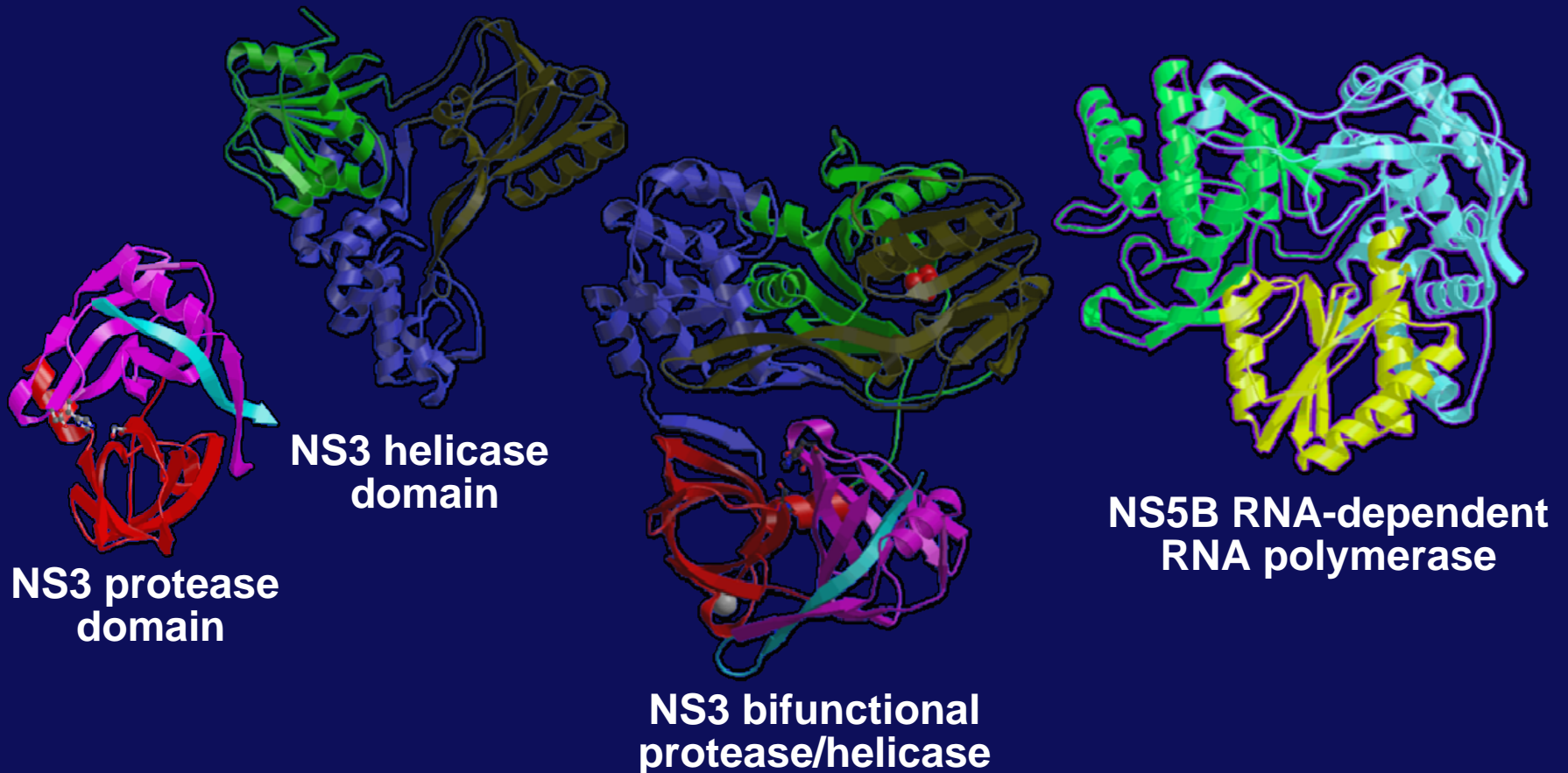
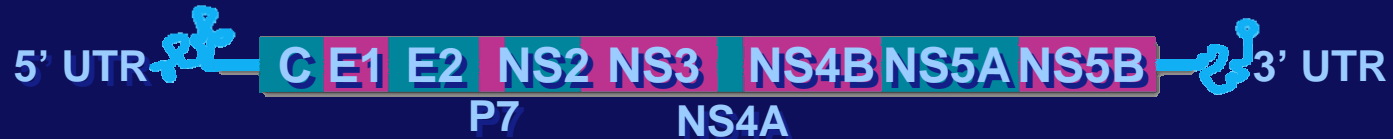
# Patterns of Response to Therapy



## Current Clinical Challenges

- Nonresponders to initial therapy
- Patients with HCV/HIV coinfection
- African-American patients
- Patients with decompensated cirrhosis
- Patients with renal failure
- Patients with recurrent disease after transplantation
- Patients who cannot tolerate interferon or ribavirin therapy

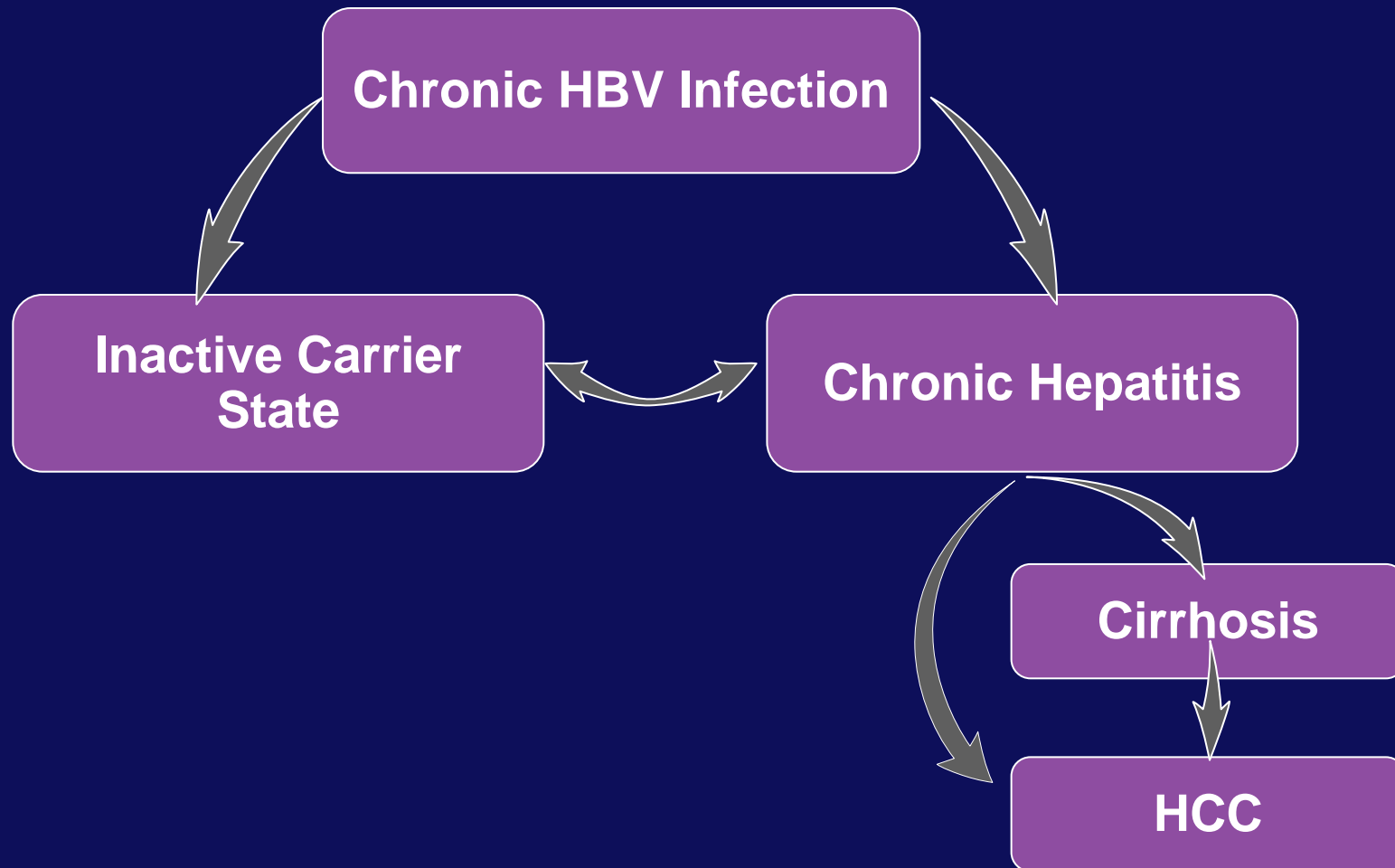
# HCV-Specific Enzymes as Targets for Future Therapy



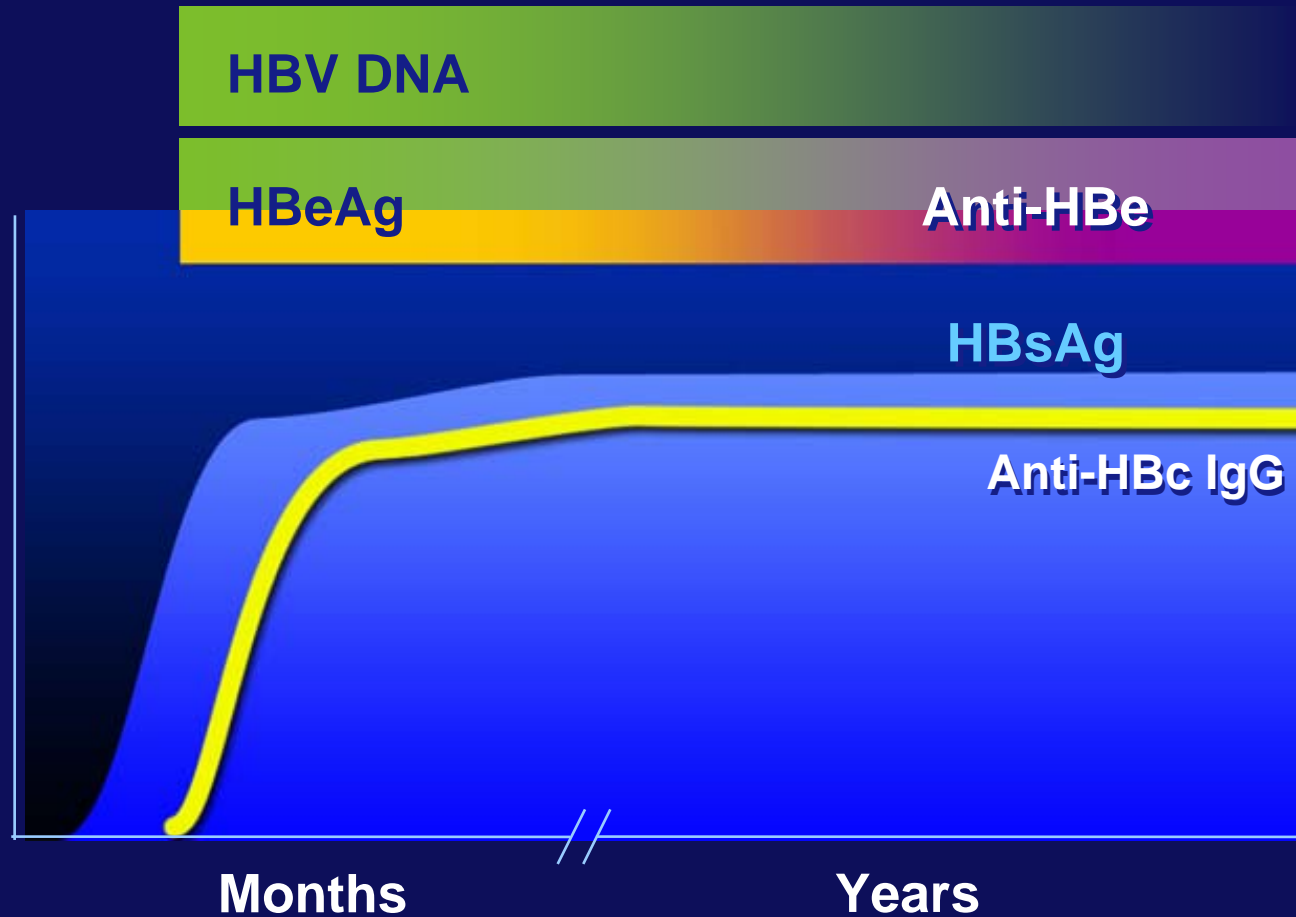
# Themes

- Natural history of chronic hepatitis C
- Current status of treatment: hepatitis C
- Natural history of chronic hepatitis B
- Current status of treatment: hepatitis B

# Clinical Outcome of Chronic Hepatitis B

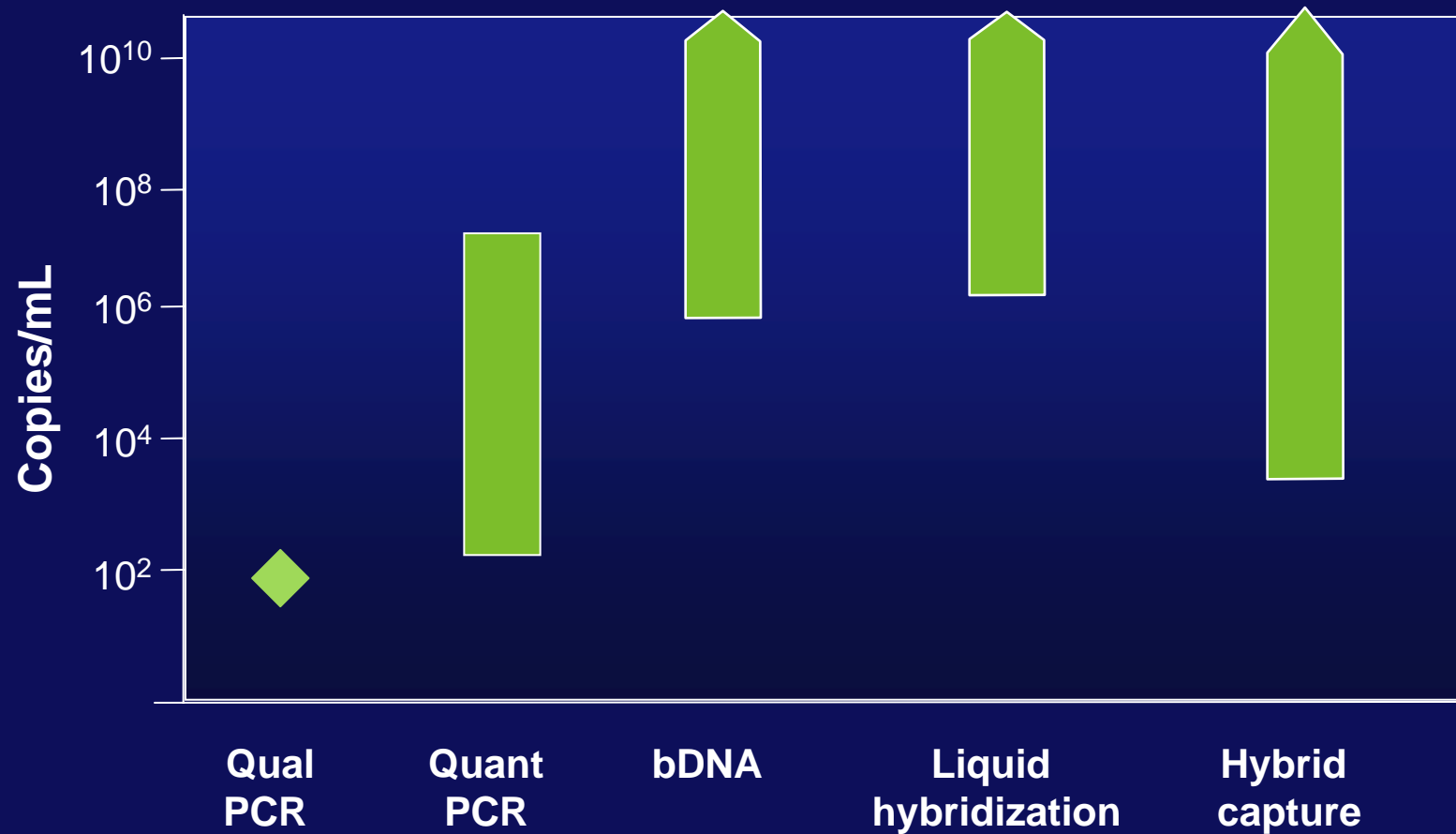


# Chronic HBV Infection



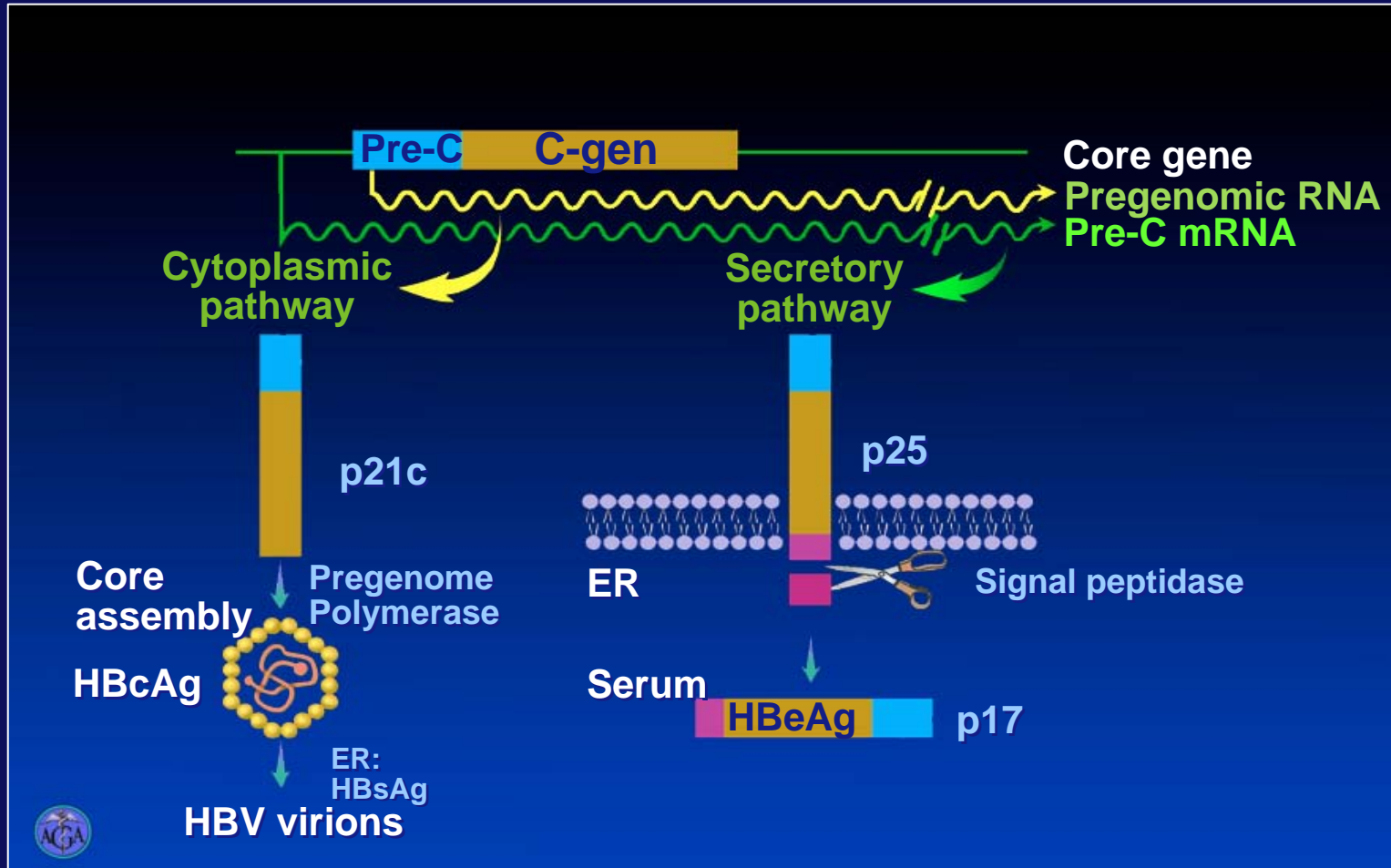
HBV = hepatitis B virus; HBe = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; Anti-HBc IgG = anti-hepatitis B core immunoglobulin G.

# Serum HBV DNA Assays



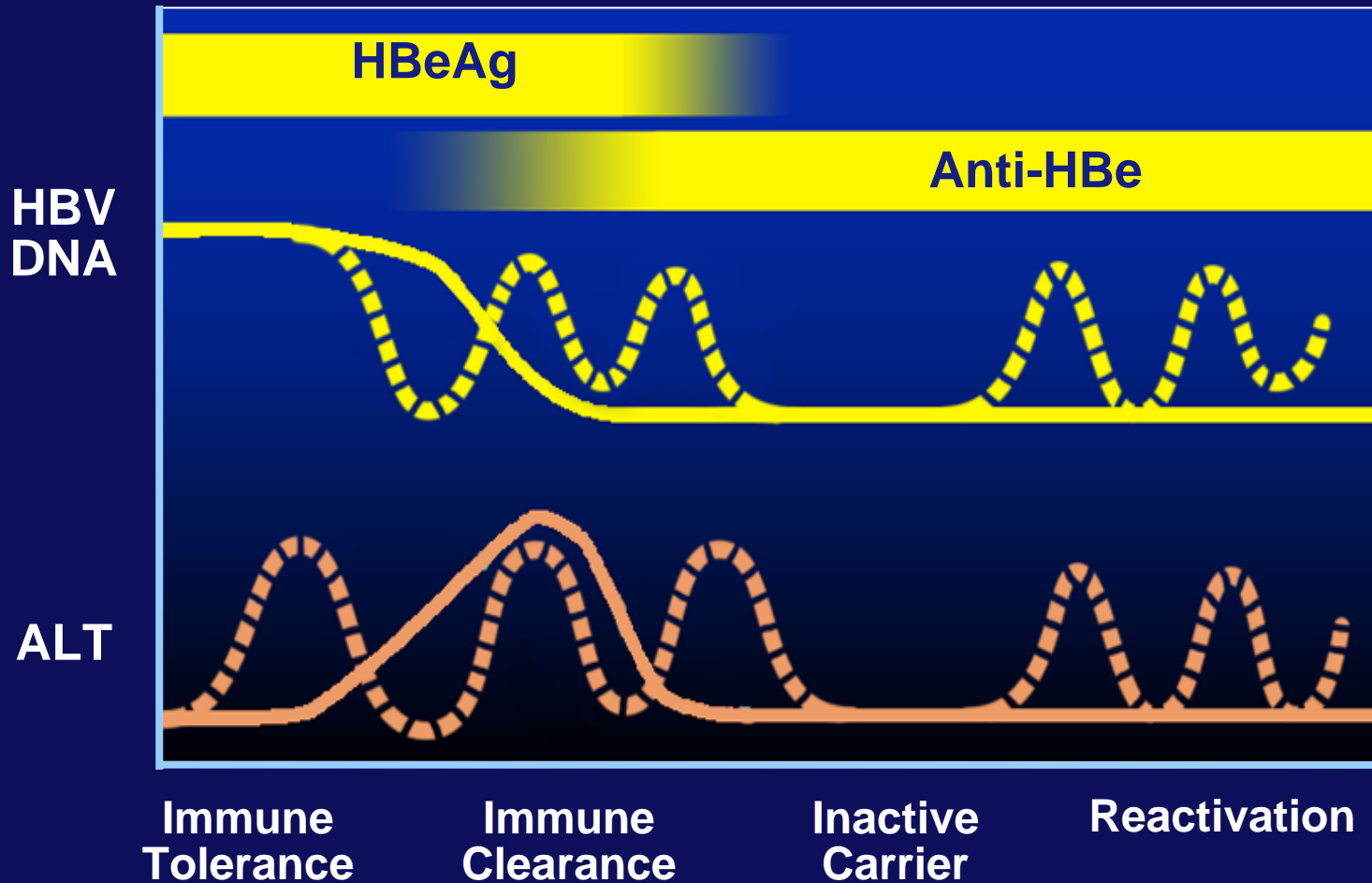
PCR = polymerase chain reaction.

# Hepatitis B Virus: HBeAg and HBcAg



ER = endoplasmic reticulum.

# Natural Course of Chronic HBV Infection



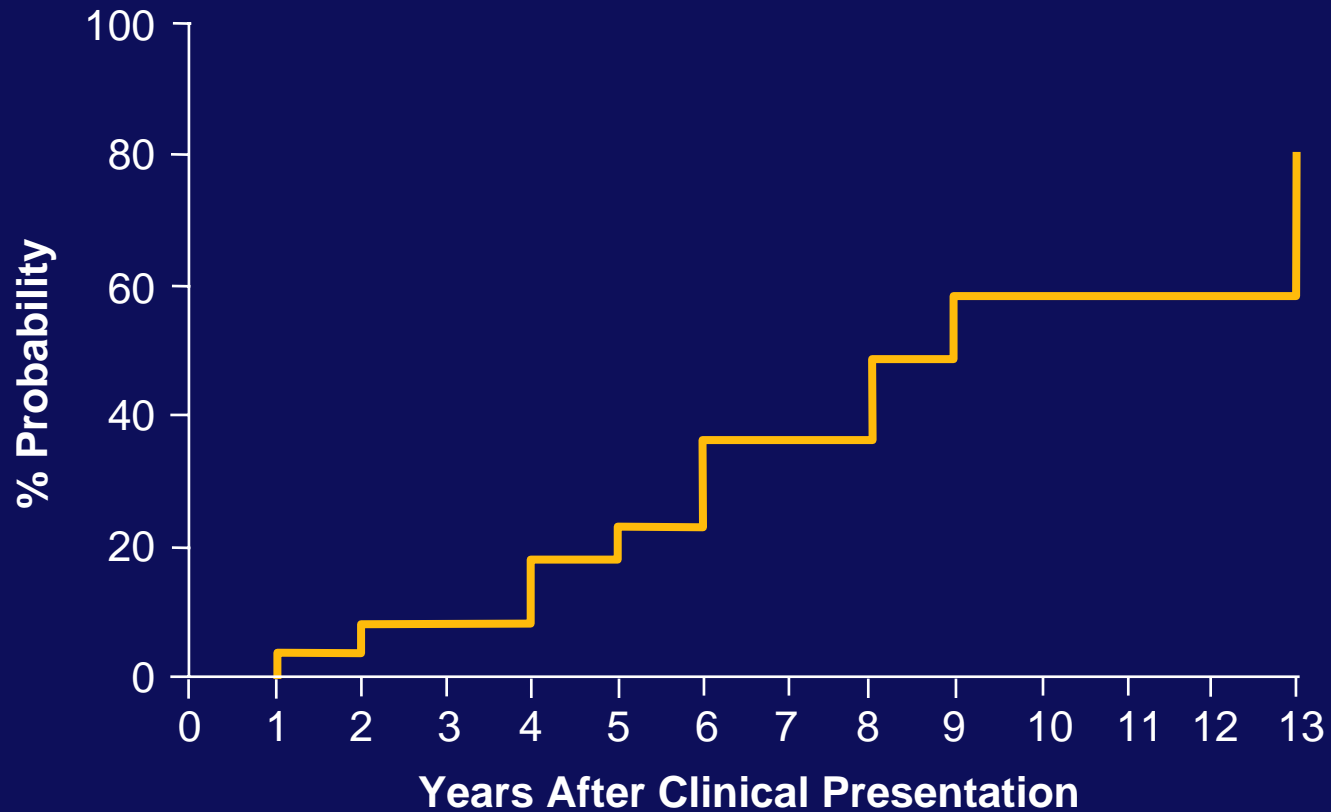
ALT = alanine aminotransferase.

# Stages of Chronic HBV Infection

	Immune tolerance	HBeAg+ hepatitis	Inactive carrier	HBeAg- hepatitis
HBsAg	+	+	+	+
Anti-HBs	-	-	-	-
Anti-HBc	+	+	+	+
HBeAg	+	+	-	-
Anti-HBe	-	-	+	+
HBV DNA	+++++	+++	+/-	++
ALT	-	+++	-	++
cccDNA	+	+	+	+

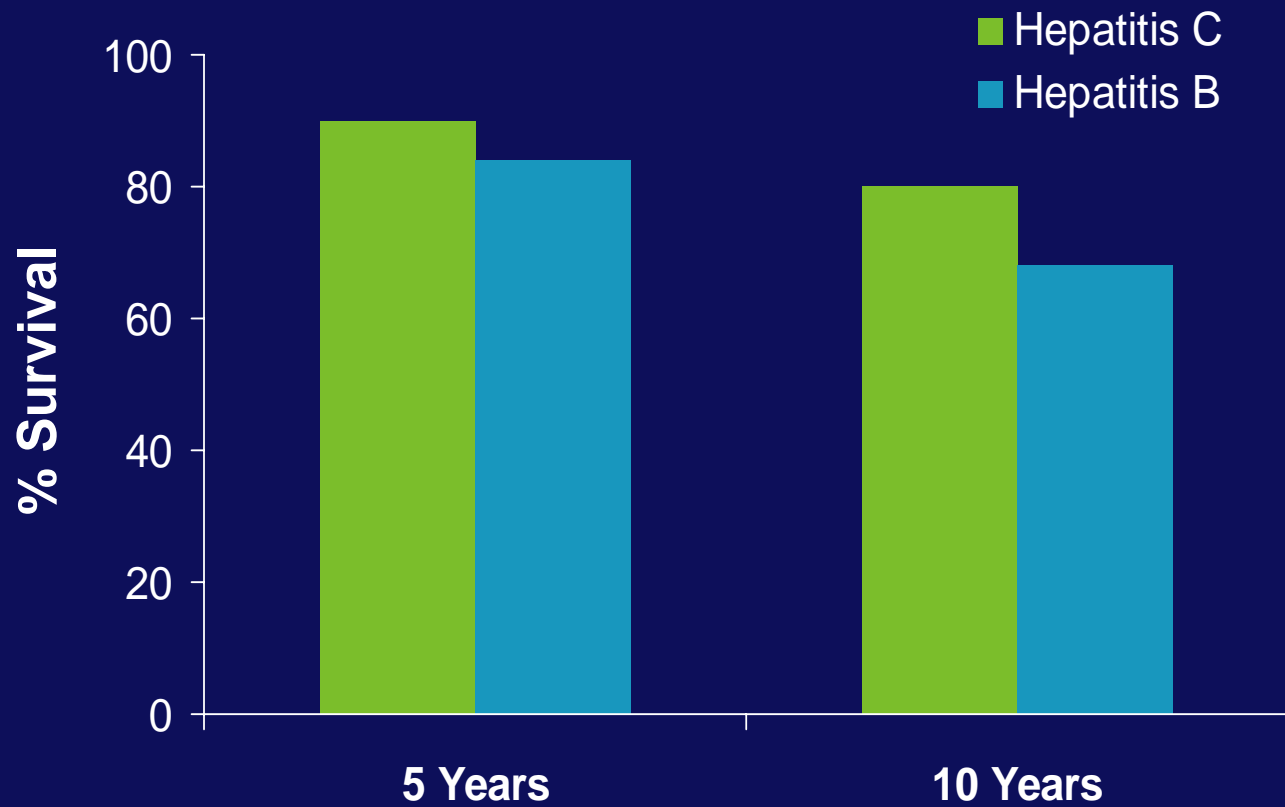
cccDNA = covalently closed circular DNA.

# Overall Risk of Progression to Cirrhosis



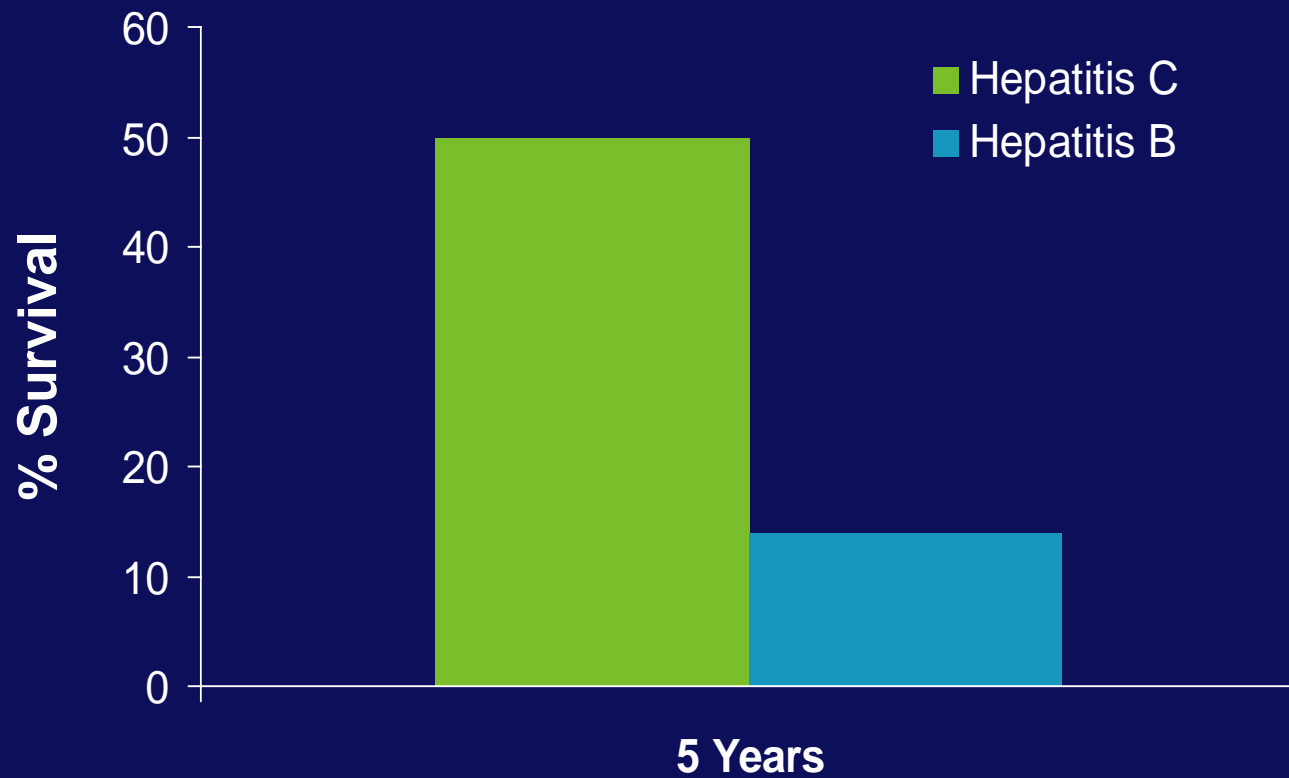
Fattovich G. *Gut*. 1991;32:294-298.

# Survival With Compensated Cirrhosis



Fattovich G, et al. *Gastroenterology*. 1997;112:463-472.  
Realdi G, et al. *J Hepatol*. 1994;21:656-666.

# Survival With Decompensated Cirrhosis



Fattovich G, et al. *Gastroenterology*. 1997;112:463-472.  
Fattovich G, et al. *Hepatology*. 1995;21:77-82.

# Predictors of Survival in Patients With Cirrhosis

- Biochemical remission of disease
- HBeAg clearance
- HBV DNA clearance

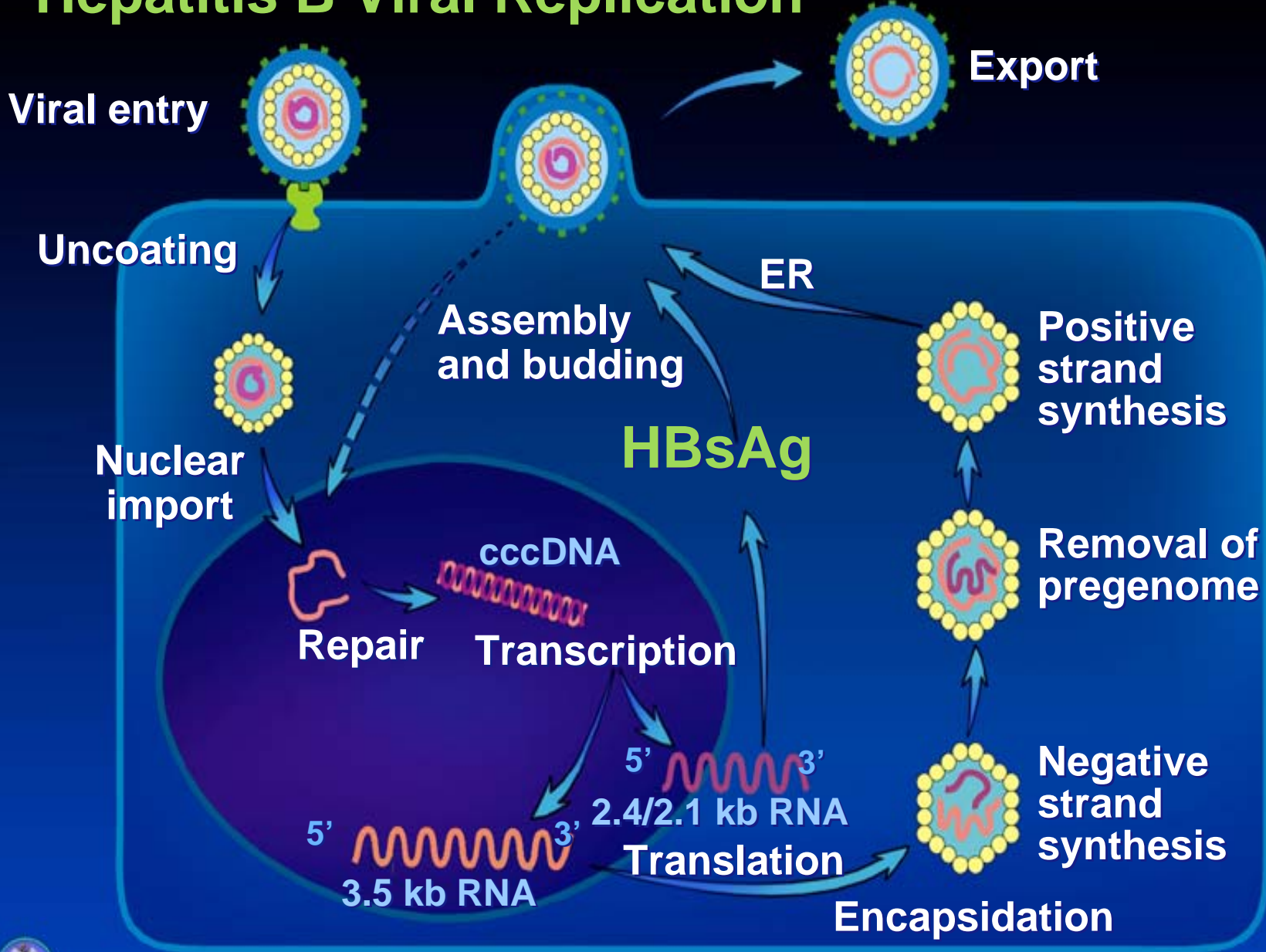
# Themes

- Natural history of chronic hepatitis C
- Current status of treatment: hepatitis C
- Natural history of chronic hepatitis B
- **Current status of treatment: hepatitis B**

# Goals of Therapy

- Sustained suppression of HBV replication
  - HBV DNA undetectable in serum
  - HBeAg to HBeAb seroconversion
  - HBsAg to anti-HBs seroconversion
- Remission of liver disease
  - Normalization of serum ALT levels
  - Improvement in liver histology
- Improvement in clinical outcome
  - Prevention of liver failure and HCC
  - Increased survival

# Hepatitis B Viral Replication



# Nucleos(t)ide Analogues

## Lamivudine

Infectious  
HBV virion

Partly  
double-  
stranded  
DNA

DNA pol

RT

HBsAg  
envelopes

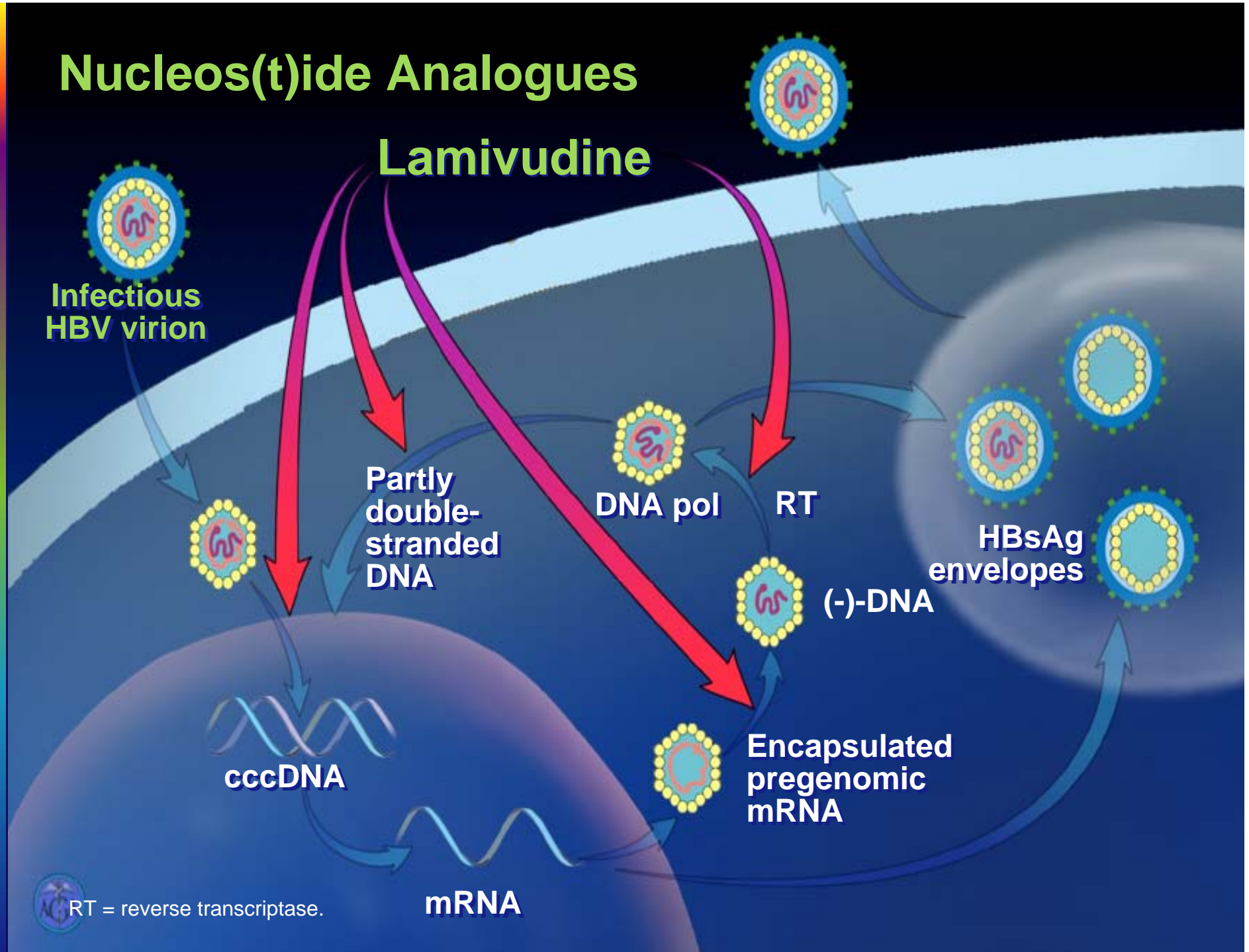
(-)-DNA

cccDNA

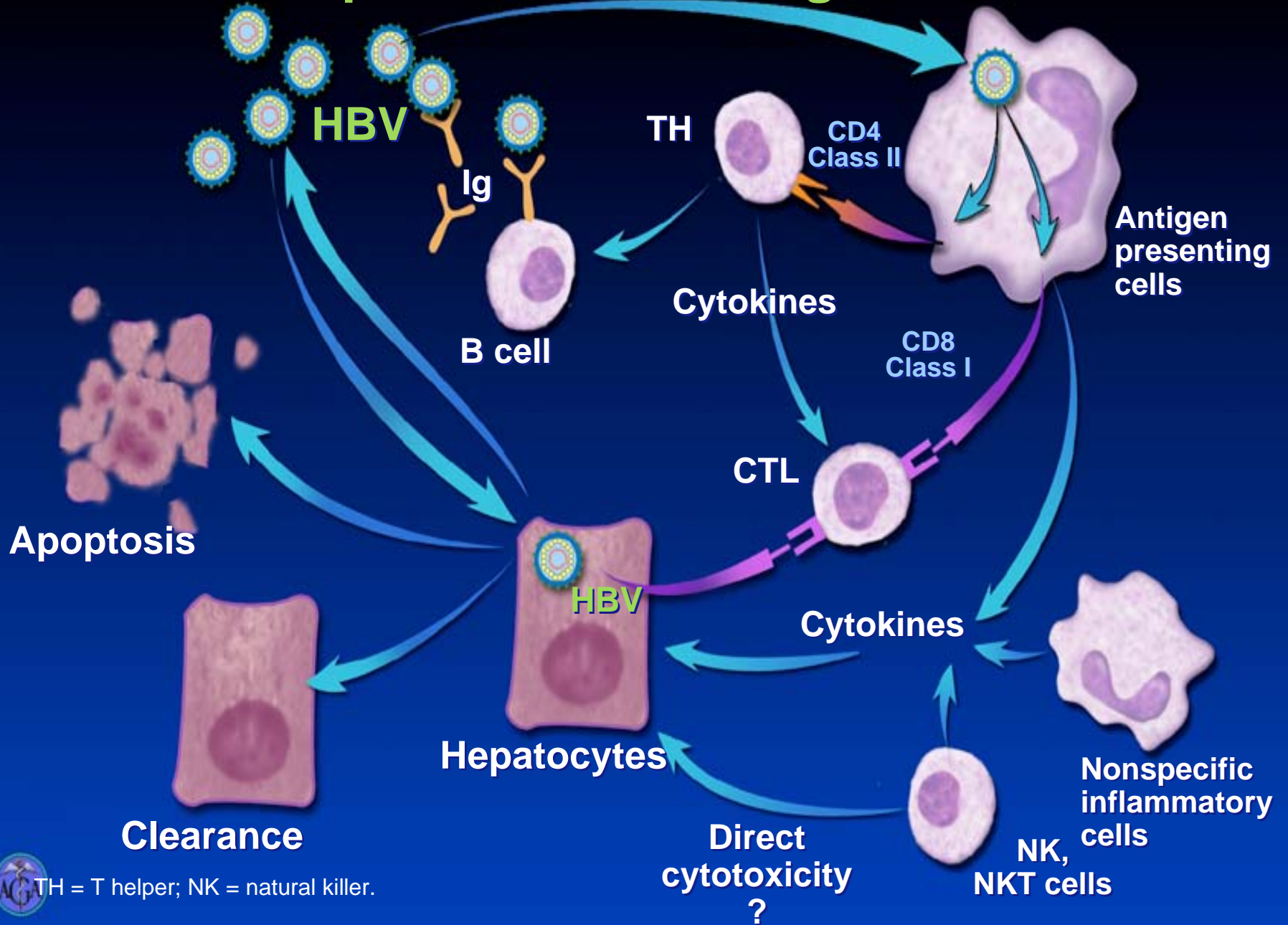
Encapsulated  
pregenomic  
mRNA

mRNA

RT = reverse transcriptase.



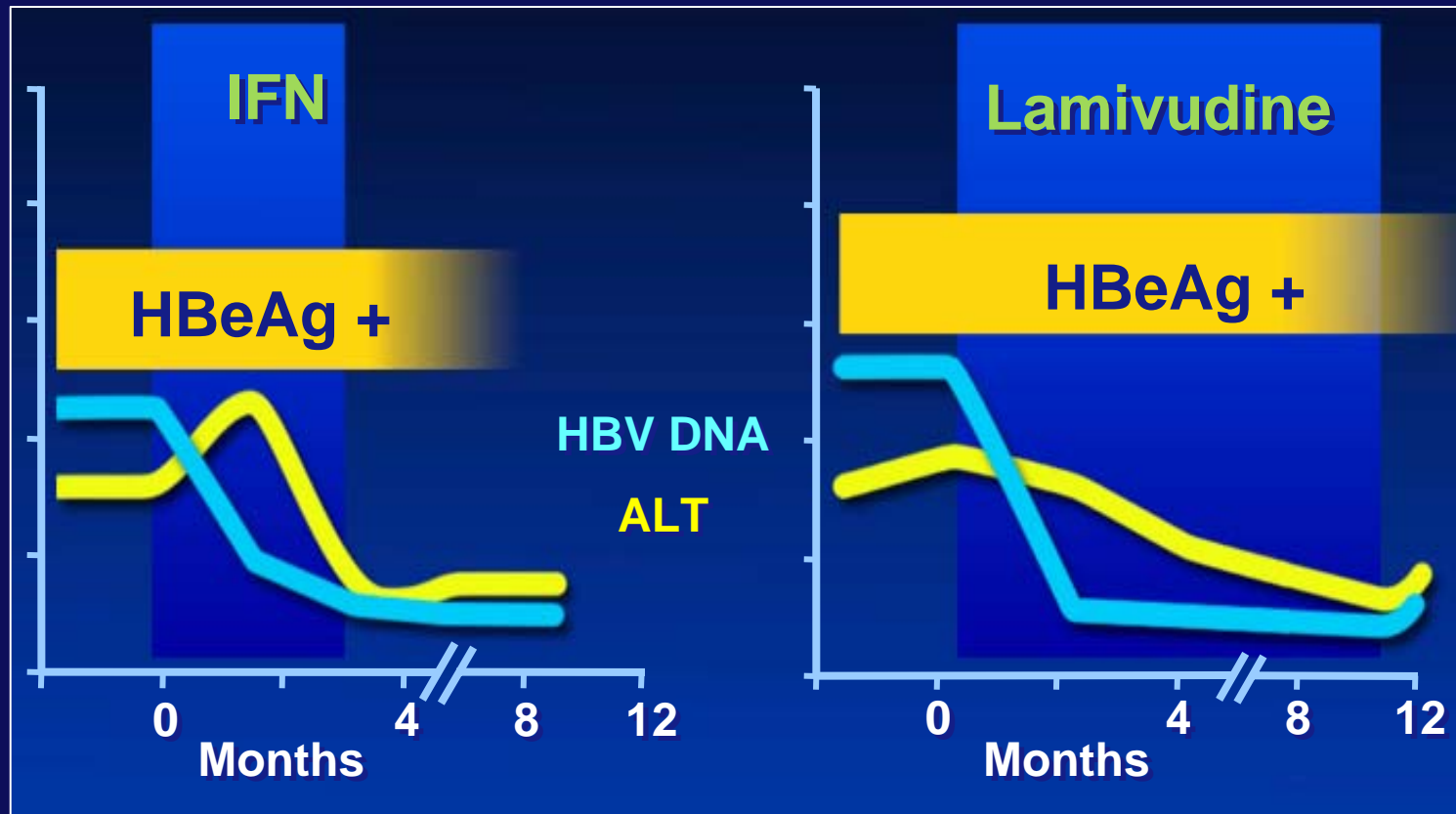
# Immune Responses and Pathogenesis



# FDA-Approved Therapies for Chronic HBV

FDA-Approved Therapies for Chronic HBV	
Interferons	Nucleos(t)ide Analogues
Interferon alfa-2b	Lamivudine
Pegylated interferon alfa-2a	Adefovir
	Entecavir

# Comparison of Treatments for Chronic HBeAg+ Hepatitis B



# Interferon Therapy

- Advantages

- Finite duration of treatment
- Higher HBeAg seroconversion rates
- More durable responses after discontinuing therapy
- HBsAg may clear years after HBeAg seroconversion

- Disadvantages

- Injection therapy
- Multiple side effects, although incidence of depression is much lower than in patients with chronic hepatitis C
- “Flare” can result in liver failure in patients with severe disease
- Cannot be used in patients with decompensated cirrhosis

# Nucleoside/Nucleotide Analogue Therapy

- Advantages

- Oral medication
- Few side effects
- More rapid clearance of HBV DNA
- Effective and safe in patients with decompensated cirrhosis

- Disadvantages

- Antiviral effect lost after discontinuation of treatment
- Indefinite period of treatment
- Cost-effectiveness unknown
- Severe exacerbations of liver disease after discontinuing therapy
- Resistant mutants

# Indications for Treatment

- Chronic HBV infection: HBsAg+ >6 months
- Evidence of viral replication: elevated HBV DNA level
- Evidence of liver damage: ALT >2x ULN and/or chronic hepatitis on liver biopsy

HBeAg+ patients:

- HBV DNA >10<sup>5</sup> copies/mL

HBeAg- patients:

- HBV DNA >10<sup>5</sup> copies/mL

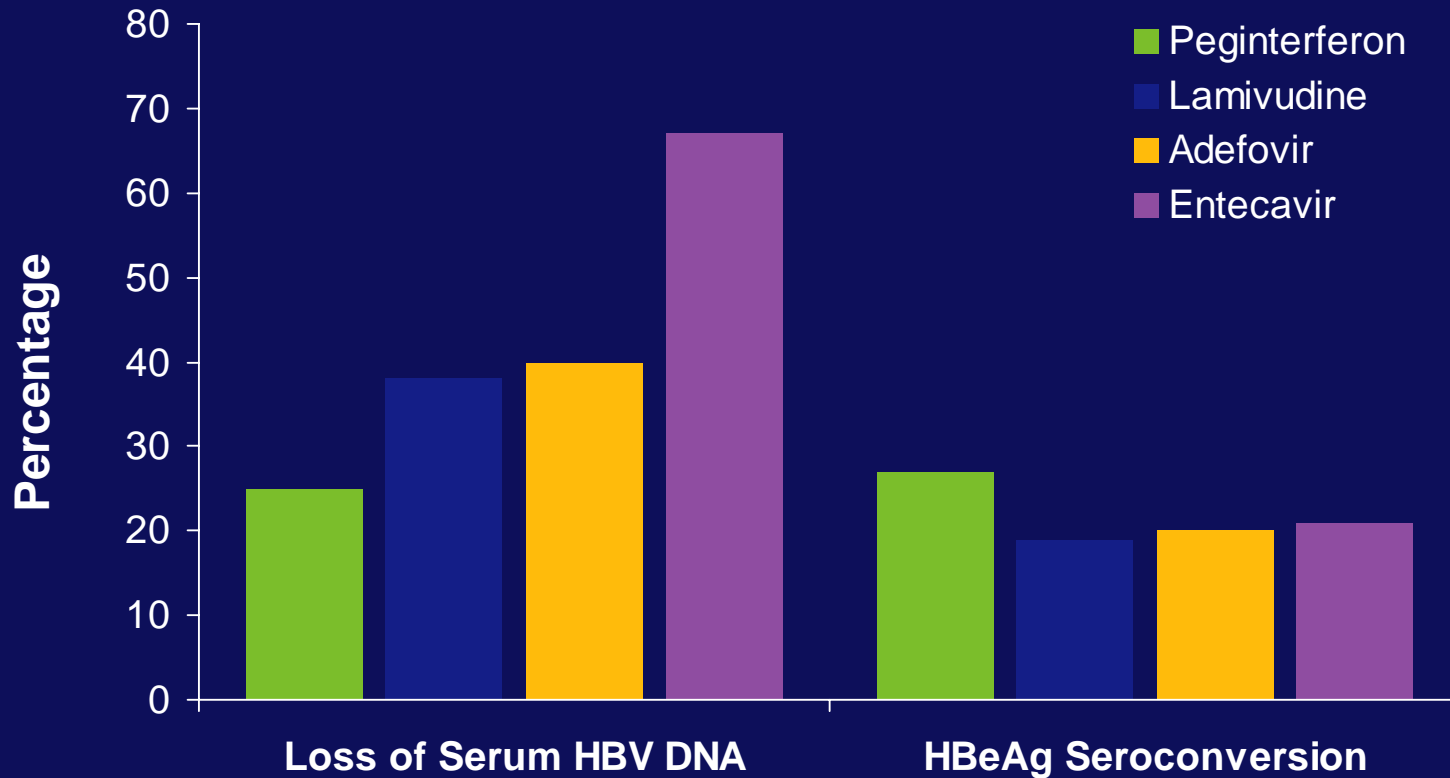
ULN = upper limit of normal.

From the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines.  
Lok ASF, McMahon BJ. *Hepatology*. 2004;39:857-861.

# Predictors of Response in HBeAg+ Patients

- High serum ALT level
- Low serum HBV DNA level
- Adult-acquired infection
- Active liver histology

# Serologic Responses to 48 Weeks of Treatment in HBeAg+ Patients



# HBeAg- Chronic Hepatitis B

## Clinical characteristics

- Disease progression often insidious
- HBV DNA levels generally lower than in HBeAg+ patients
- Durability of response less than in HBeAg+ patients

## Predictors of response to antiviral therapy

- Duration of treatment
- Early ALT normalization

## Factors not predictive of therapeutic response

- HBV DNA level
- ALT level
- Gender
- Histologic activity or severity of liver damage

# Stages of Chronic HBV Infection

	Immune tolerance	HBeAg+ hepatitis	Inactive carrier	HBeAg- hepatitis
HBsAg	+	+	+	+
Anti-HBs	-	-	-	-
Anti-HBc	+	+	+	+
HBeAg	+	+	-	-
Anti-HBe	-	-	+	+
HBV DNA	++++	+++	+/-	++
ALT	-	+++	-	++
cccDNA	+	+	+	+

cccDNA = covalently closed circular DNA.

# Recommendations for Treatment

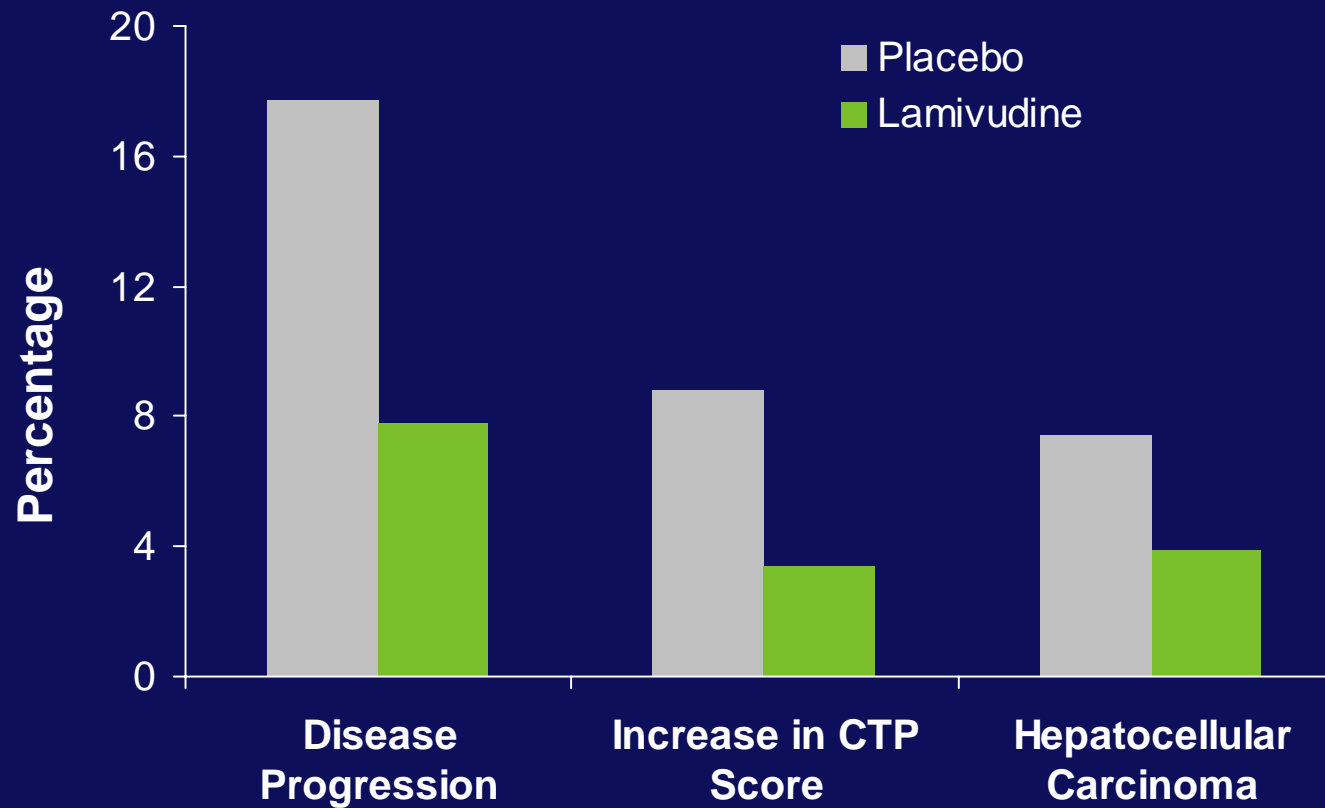
HBeAg	HBV DNA	ALT	Treatment Strategy
+	$>10^5$	$\leq 2 \times \text{ULN}$	Low efficacy, observe
-	$<10^5$	$\leq 2 \times \text{ULN}$	No treatment required
+	$>10^5$	$\geq 2 \times \text{ULN}$	Interferon, lamivudine or adefovir as primary therapy
-	$>10^5$	$\geq 2 \times \text{ULN}$	Interferon, lamivudine or adefovir, prolonged therapy*
$\pm$	$>10^5$	Cirrhosis	Lamivudine or adefovir, refer to transplant center
$\pm$	$<10^5$	Cirrhosis	Observe, refer for transplant*

\*Levels of HBV DNA controversial.

Lok ASF, McMahon BJ. *Hepatology*. 2004;39:857-861.

Keefe EB, et al. *Clin Gastroenterol Hepatol*. 2004;2:87-106.

# Lamivudine for Patients With Chronic Hepatitis B and Advanced Liver Disease



CTP = Child-Turcotte-Pugh.

Liaw Y-F, et al. *N Engl J Med.* 2004;351:1521-1531.

# Comparison of Major HBV Treatments

	Interferon	Lamivudine	Adefovir
<b>Pros</b>	<ul style="list-style-type: none"> <li>■ Finite duration of therapy</li> <li>■ Durable response post-treatment</li> <li>■ Resistant mutants not reported</li> </ul>	<ul style="list-style-type: none"> <li>■ Oral</li> <li>■ Negligible side effects</li> </ul>	<ul style="list-style-type: none"> <li>■ Oral</li> <li>■ Effective against lamivudine-resistant mutants</li> <li>■ Resistant mutants uncommon</li> </ul>
<b>Cons</b>	<ul style="list-style-type: none"> <li>■ Injection</li> <li>■ Frequent side effects</li> </ul>	<ul style="list-style-type: none"> <li>■ Long/indefinite duration of therapy</li> <li>■ Resistant mutants</li> </ul>	<ul style="list-style-type: none"> <li>■ Long/indefinite duration of therapy</li> <li>■ Long-term renal toxicity</li> </ul>

# Treatment Summary

## ■ Hepatitis C

- Peginterferons + ribavirin are the current standard of care
- Histologic stage is most important determinant of need for therapy
- Genotype is the best predictor of response to therapy
- Compliance with optimal doses of medication is crucial to outcome

## ■ Hepatitis B

- Interferon versus nucleoside/nucleotide analogue therapy
- Patients with active disease have the best responses to treatment
- Interferon: durable responses versus side effects
- Nucleos(t)ide analogues: tolerability versus need for prolonged therapy
- Clearance of HBV and HBeAg seroconversion has major impact on survival in patients with advanced disease