

# Viral Hepatitis

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# Viruses that cause Hepatitis in Humans

- Hepatitis A
- Hepatitis B
- Hepatitis C
- Hepatitis D
- Hepatitis E
- Coxsackie
- Echovirus
- Yellow fever
- Rubella
- Junin virus
- Machupo virus
- Lassa virus
- Rift Valley virus
- Marburg virus
- Ebola virus
- Measles virus
- Human adenovirus
- CMV
- EBV
- HSV
- Varicella-Zoster

# Hepatitis A

# Hepatitis A

- Hepatovirus from Picornavirus family.
- 27-32 nm, linear, (+) sense, simple stranded RNA.
- Reservoir: human only
- Acquisition: fecal-oral; concentrated in oysters.  
Contaminated water or food, men having sex with men, blood during short viremic phase.
- Non-cytopathic; immune mediated injury by lymphocytes

# Hepatitis A

## Sero-Prevalence

- *Poor sanitation countries:*
  - near 100 % by age 5.
- *Good sanitation countries (USA) :*
  - 10 % by age 14;
  - 37 % in adults.

# Hepatitis A

## Clinical Features

- **Incubation:** 2-4 (up to 6) weeks
- Children < 2 year: 80% anicteric & asymptomatic
- Children > 2 y and adults: 80% icteric & symptomatic
- **Symptoms:** Fatigue (90%), anorexia (85%), jaundice (80%), nausea (75%), low fever (65%), headache, abdominal pain and myalgias.
- **Duration:** usually < 8 weeks



# Hepatitis A

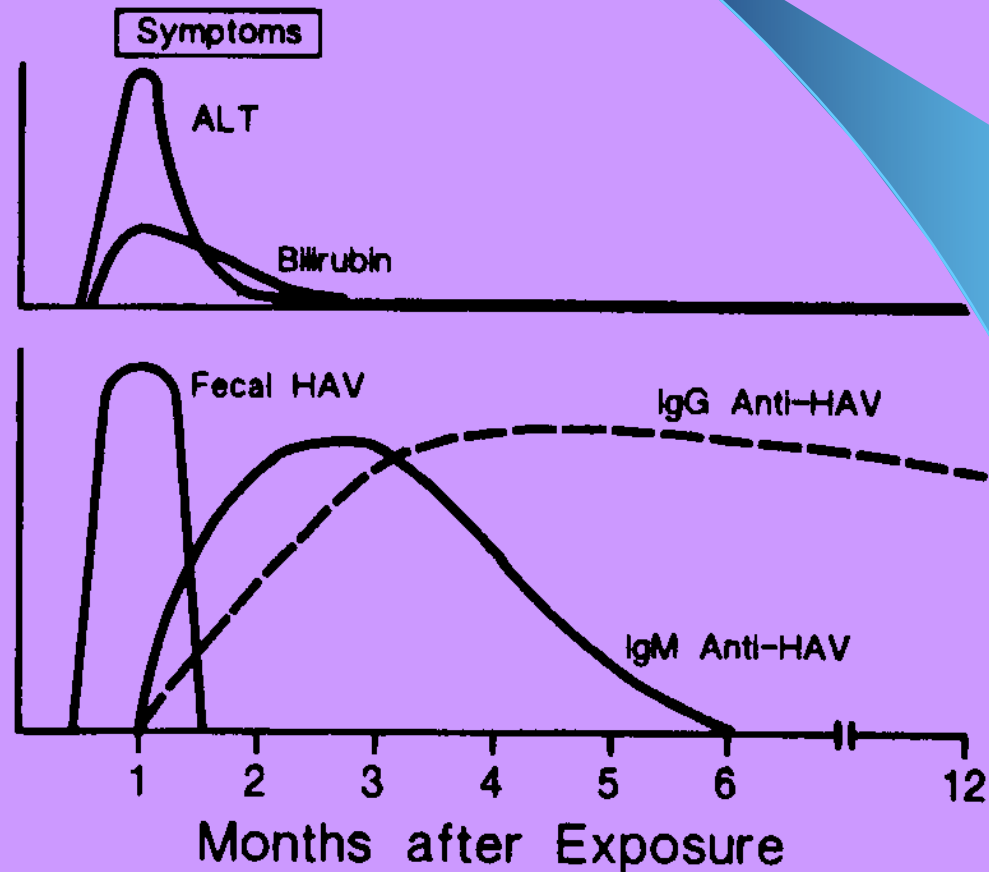
## Atypical Manifestations

- **Relapsing hepatitis:** less than 10%; 2 or more bouts of elevated enzymes.
- **Cholestatic hepatitis:** Severe and prolonged jaundice > 10 weeks. Is rare.
- **Fulminant Hepatitis:** very rare but lethal in 50%.
- **Extrahepatic:** renal failure, red blood cell aplasia, hemolysis, pancreatitis, neurologic disease.
- **Mortality:** Not increased by pregnancy.
  - a) younger than 49 = 0.3%;
  - b) older than 49 = 1.8%.



# Hepatitis A

## HEPATITIS A



# Hepatitis A

## Vaccination Recommendation

- Children in areas with rate  $>20/100000$
- High risk: traveler to endemic area, men having sex with men, illegal drug users, person with clotting factor disorder, researcher working with HAV.
- Chronic liver disease: HBV, HCV
- During community outbreaks.
- **Immunogenicity:**  $> 70\%$  within 2-4 weeks after 1<sup>st</sup> dose, and 94-99% after second dose.

# Hepatitis A

## Post-Exposure Management

- Post-exposure prophylaxis can be done:
  - with Intramuscular “Immune Serum Globulin” (ISG) within 14 days from exposure at 0.06 mL/kg (69-89% effective and lasting 12-20 weeks) or
  - with Inactivated Vaccine given also within 14 days post-exposure.
- Response to vaccine is less robust:
  - before age 1 (due to circulating maternal antibodies), and
  - after age 40.
- Inactivated Vaccine is the preferred approach from age 1 to 40.
- Immune serum globulin is preferred in all other groups unless contraindicated due to IgA deficiency or hypersensitivity to ISG.

# Hepatitis E

# Hepatitis E

- 27-30 nm non-enveloped, single-stranded, positive-sense RNA Hepevirus.
- There are 4-6 genotypes.
  - 1: India, China, Pakistan;
  - 2: Mexico;
  - 3: USA, France, Japan.
  - 4: China, Japan
  - There is an avian and a rat HEV variant.
- Acquisition:
  - Waterborne, fecal-oral, by organ meat ingestion, or by contact with animals. In USA swine is a common source.
  - Rare person-person (1.5% intra-familial).
  - Increased risk in homosexual men.

# Hepatitis E

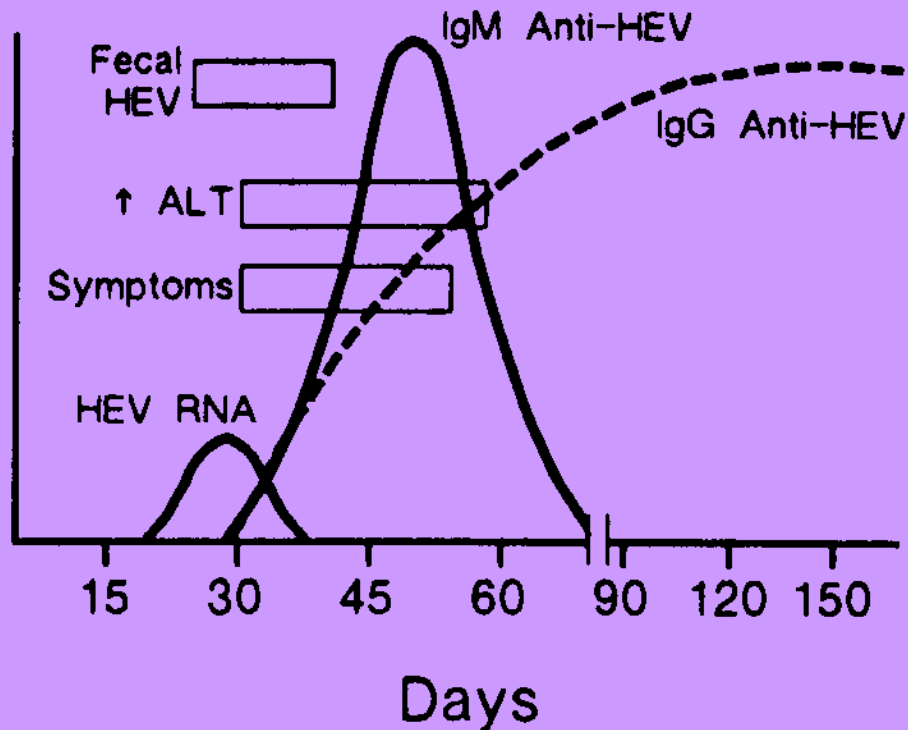
- **Types:** Sporadic, epidemic & endemic acute hepatitis. Rare chronic hepatitis.
  - **Sporadic:** traveler to endemic areas, pet owners, organ meat eaters, male homosexuals, military service (Midwest USA).
  - **Epidemic:** after heavy rain and flooding in areas with poor sanitation (India, China Latin America, Africa)
  - **Endemic:** In areas where asymptomatic infection occurs at early age, like in Egypt
  - **Chronic hepatitis:** in immunosuppressed patients, with progressive liver damage and cirrhosis (worse with Tacrolimus than with CSA).
- **Reservoir:** human, pig, sheep, cattle, rat,...
- **Prevention:** there is an experimental recombinant vaccine.

# Hepatitis E

- **Incubation:** 2-10 weeks.
- **Prodrome:** 2 weeks of malaise, mild chills & fever, transitory macular rash.
- **Symptoms & Signs:** jaundice, nausea, vomiting, anorexia, aversion to food & smoking, abdominal pain, clay-color stool. Hepatomegaly in 65-80%; symptoms usually for 4 weeks.
- **Mortality:**
  - 0.1-0.6%; 15-25% during pregnancy in the epidemic form in India.
  - Mortality in pregnancy is low in Egypt and other endemic areas.
- **Diagnosis:**
  - Anti HEV-IgM last only 3 months, and is not always present in acute infection;
  - Anti-HEV IgG lasts for years;
  - HEV can be found by PCR in stool, serum, and bile.
- **Treatment:** Peg-IFN and Ribavirin have effect in chronic HEV.

# HEV Infection

## Sequence of Events





# Hepatitis B

# Hepatitis B

- 42 nm, partially double-stranded circular DNA virus.
- 350 million carriers world-wide; causes 250000 deaths a year.
- 1.25 million carriers in USA.(0.5 %); > 8% in Alaskan Eskimos.
- New infections: decreasing in frequency
  - 260,000/y in 1980's;
  - now 73,000/y
- Greatest decline among children & adolescents (vaccine effect).

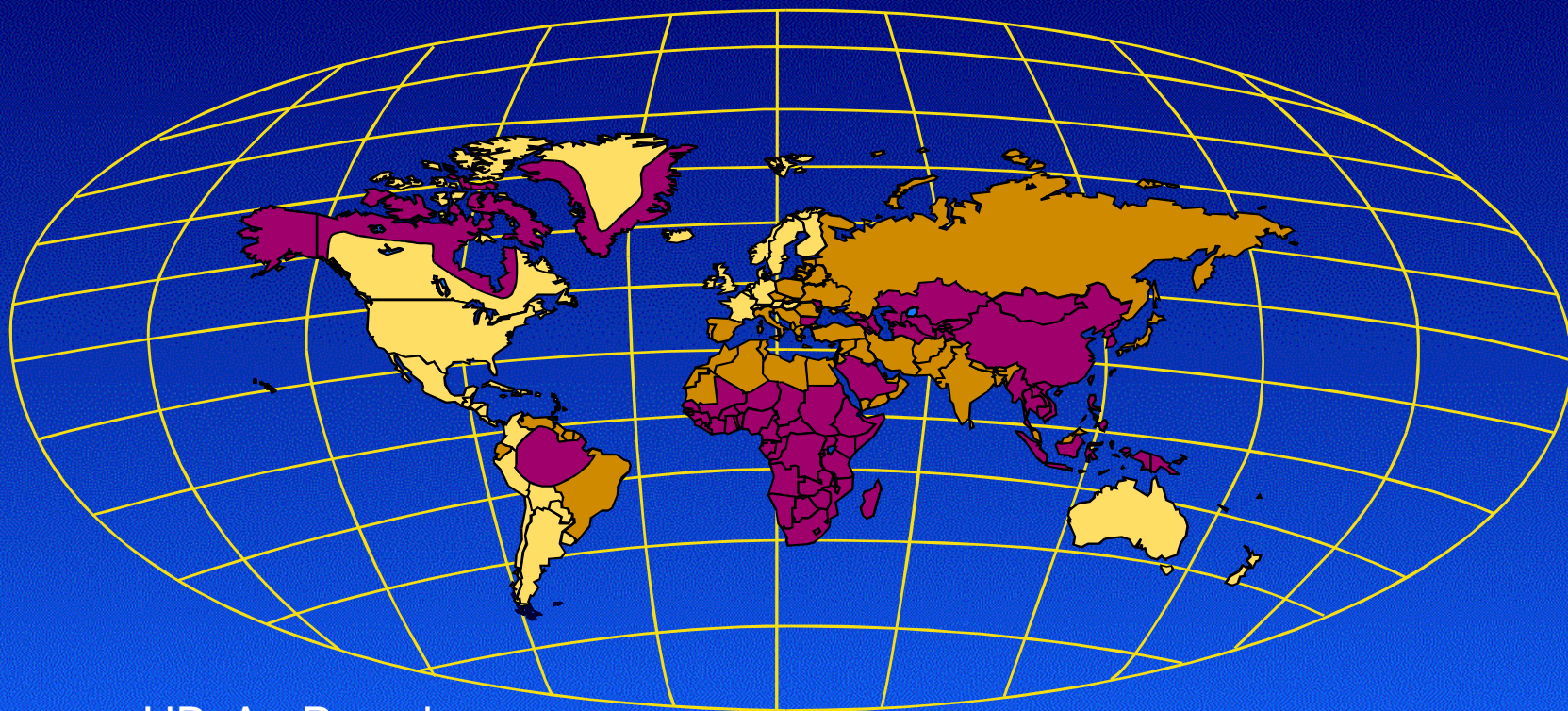
# Hepatitis B

- 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

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HBsAg Prevalence



Low < 2%



Intermediate 2-8%



High > 8%

Source: World Health Organization / Centers for Disease Control and Prevention.

# 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, ...

# 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 ( $\leq 4\%$ ).
- 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.

# HBV & Pregnancy

- If mother has HBV-DNA  $< 10^8$  IU/ml:
  - neonatal immuno-prophylaxis [HBIG + HBV immunization] prevents transmission in 95%.
- Cesarean section decreases vertical transmission rate, but:
  - is not indicated because [HBIG + HBV immunization] is very effective.
- If mother is “highly infectious” with HBV-DNA  $> 10^8$  IU/mL
  - risk of HBV transmission is 30-40% despite [HBIG + HBV immunization]



# HBV & Pregnancy

- 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.
- 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.

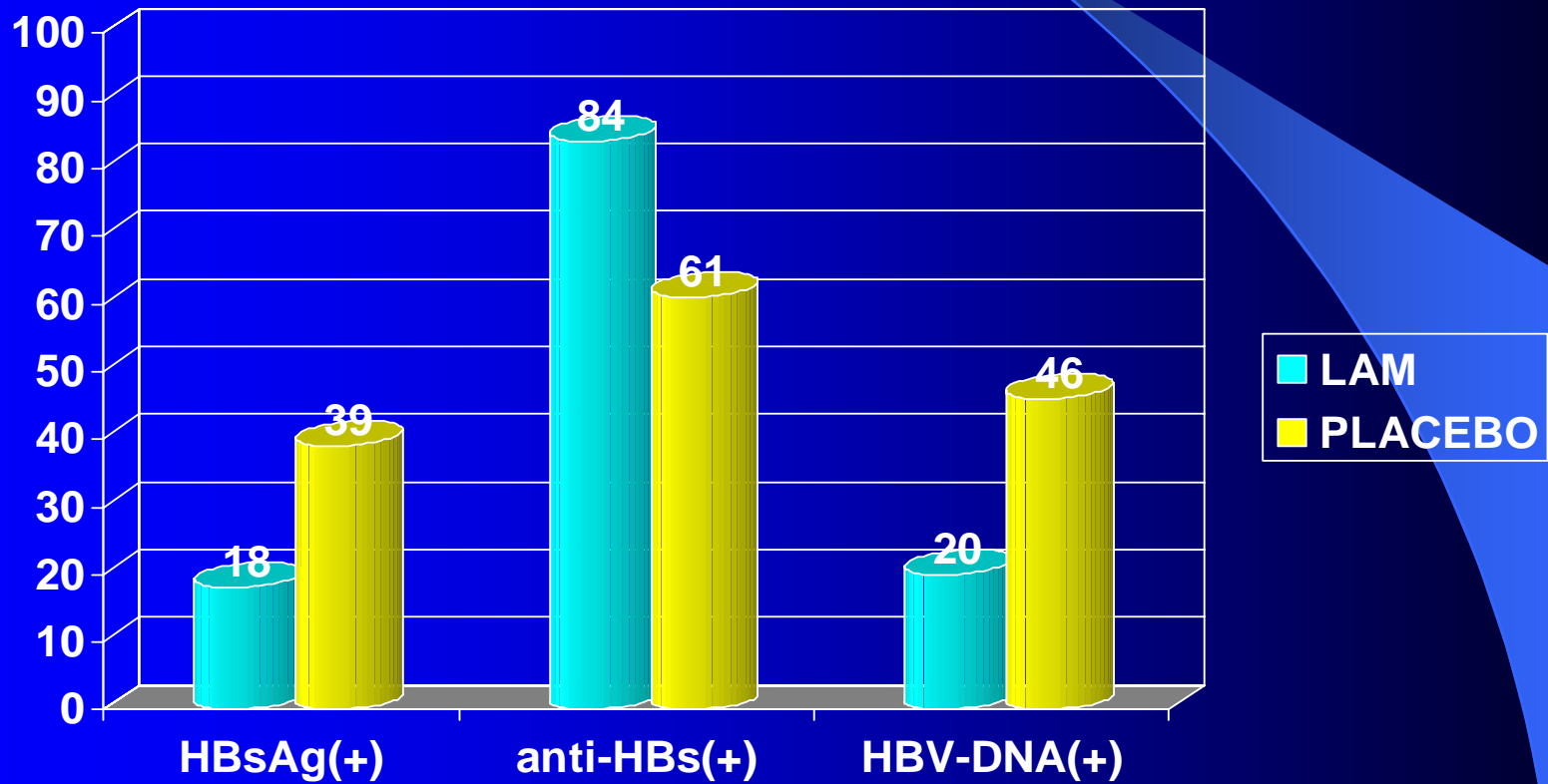
# Effect of Lamivudine on HBV Vertical Transmission from Highly Infectious Mothers

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



# CONCLUSION

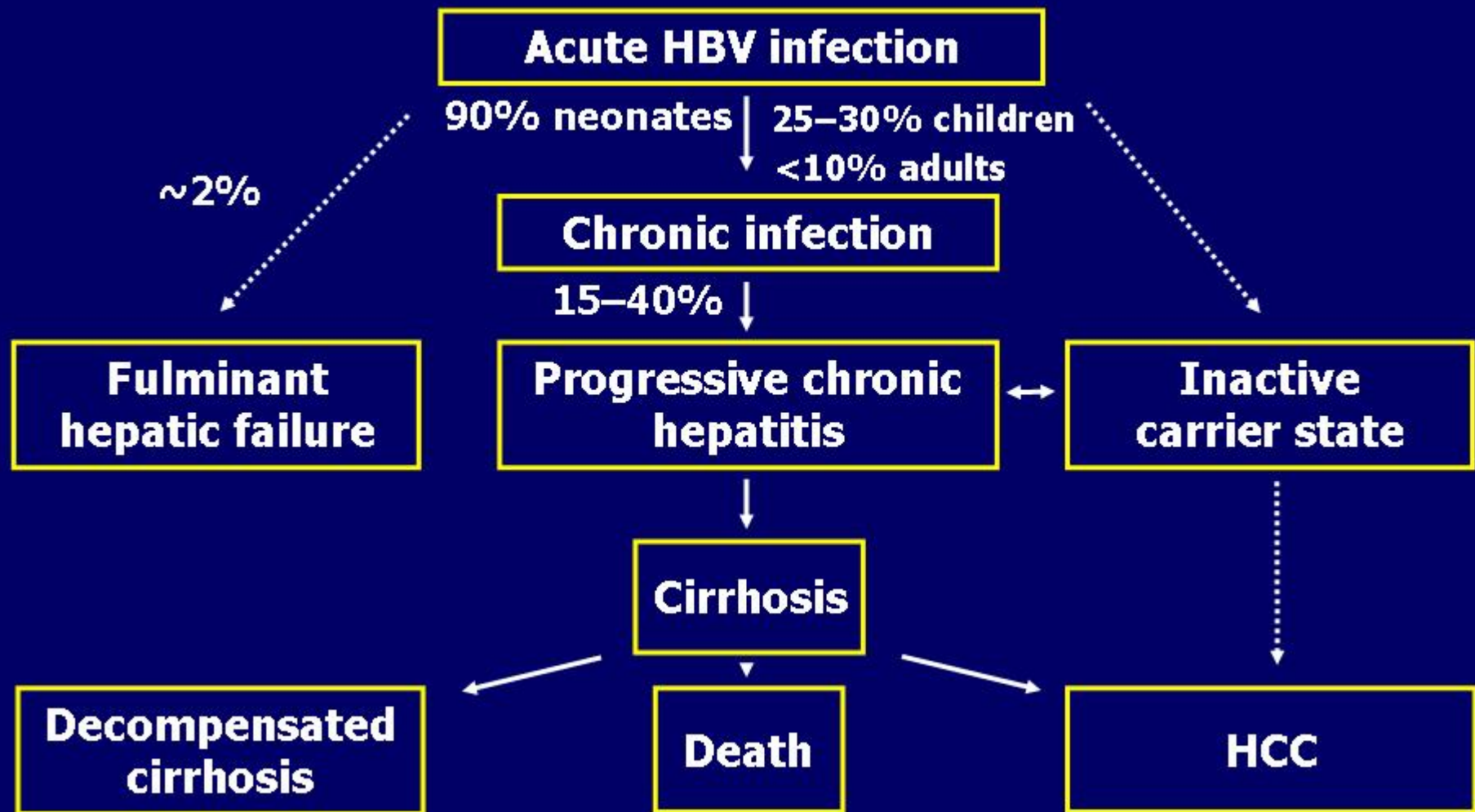
Abstr # 246

- 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.

The background is a solid blue color with a subtle gradient. A thin, light blue curved line starts from the top left and arcs across the upper half of the slide. On the right side, there is a darker blue triangular shape pointing towards the center.

# Hepatitis B in the General Population

# Spectrum of Disease



# 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 3<sup>rd</sup> dose)
  - Infants from HBsAg(+) mother (at age 9-15 months)
  - Hemodialysis patients (1 month post 3<sup>rd</sup> dose, and then yearly).
  - Sexual partner of HBsAg(+) persons (1 month after 3<sup>rd</sup> dose)



# 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.

# 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 20000 IU/mL to allow performance of exposure-prone procedures.

# 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  $\leq 5.08$  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  $\geq 1$  million IU/mL)

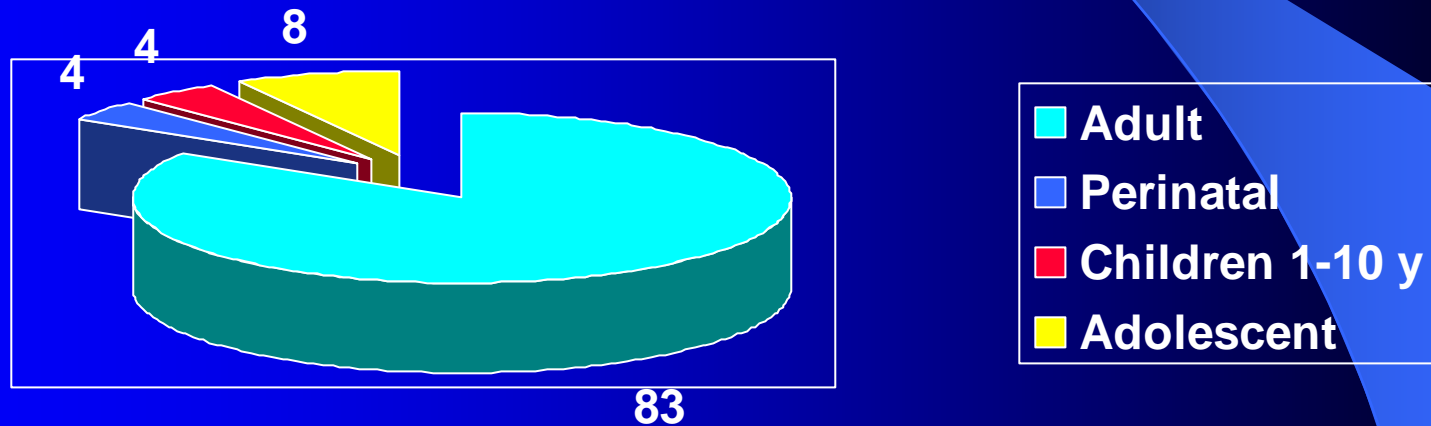
- **Evolution to Chronicity:**

- a) Infants: 90%,
- b) Children 1-5: 25-50% (**30%**) ,
- c) Adults & older children: 5%

- **Treatment:**

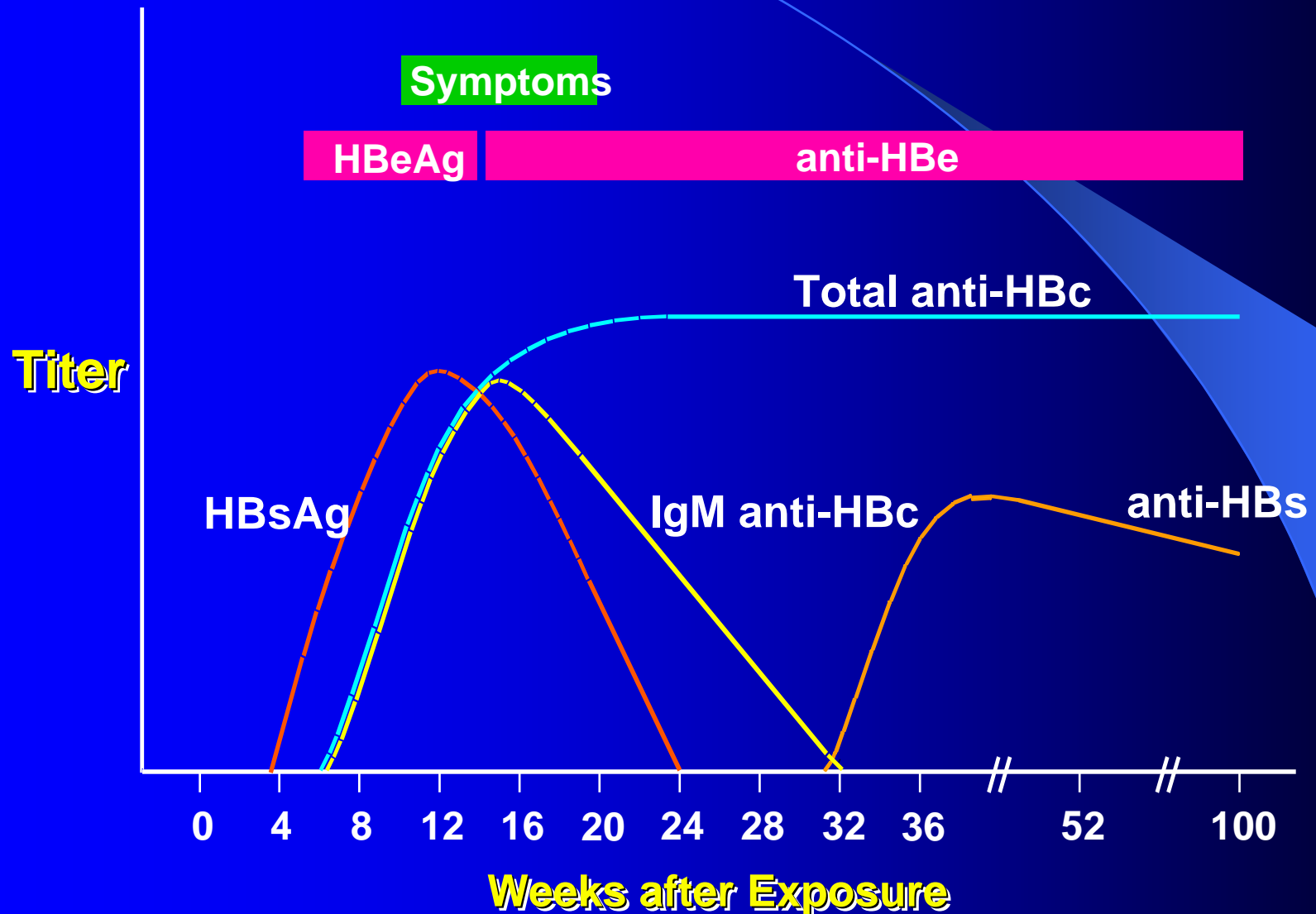
- Supportive;
- Anti-virals in “protracted hepatitis”, or failure to regenerate/sub-massive necrosis.

# Age of Acquisition of Acute Hepatitis B 1989 estimates



# Acute Hepatitis B Virus Infection with Recovery

## Typical Serologic Course



# Chronic HBV



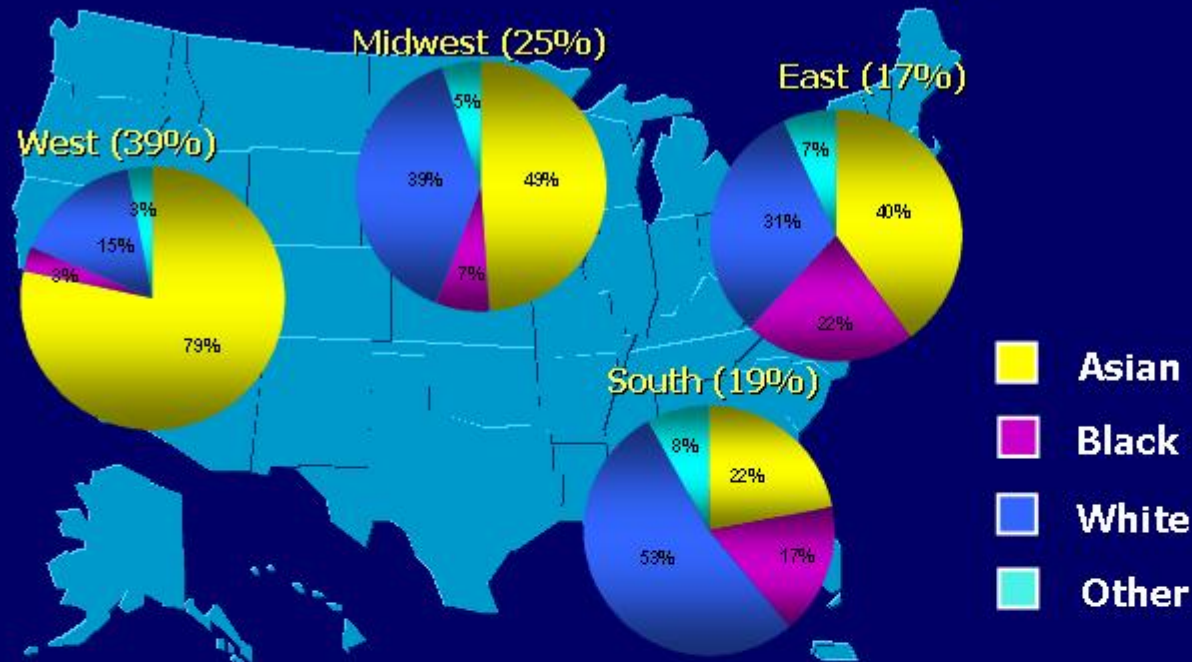
# Chronic Hepatitis B

- 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 cryoglobulinemia, IgA nephropathy, papular acrodermatitis.

# Chronic Hepatitis B

- 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
- Death from chronic HBV liver disease
  - 15-25% of chronically infected
- USA yearly mortality from HBV
  - 5000 per year

# Chronicity of HBV



In a survey of 17 liver centers across the US, approximately 56% of HBV carriers were of Asian descent

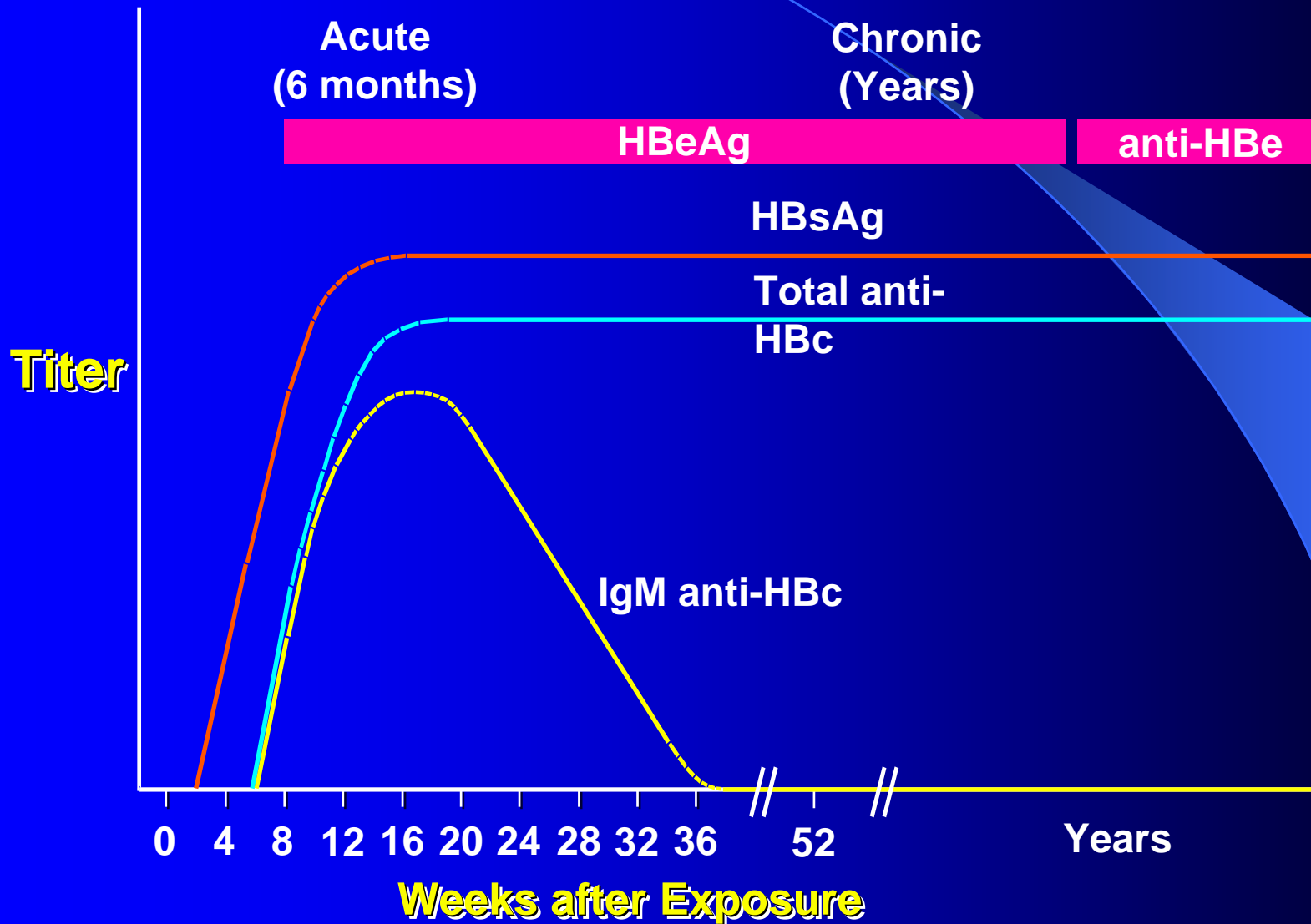
## Patient Type

## Mode Transmission

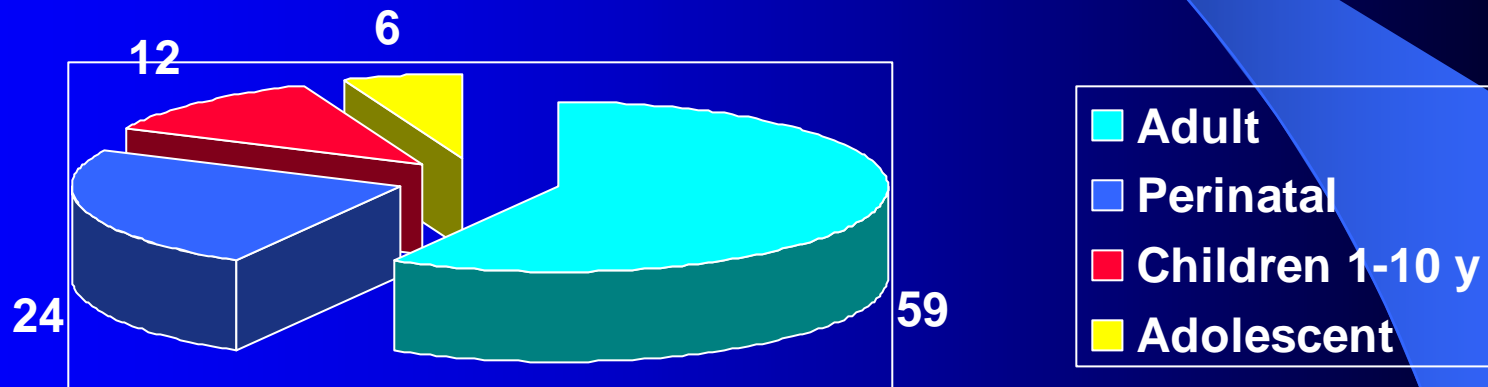
## Percent Developing Chronic HBV

- |                       |   |                        |   |          |
|-----------------------|---|------------------------|---|----------|
| • U.S.-born           | → | • Sexual, Parenteral   | → | • 2-10%  |
| • Foreign-born (Asia) | → | • Perinatal (vertical) | → | • 80-90% |

**Acute  
(6 months)**



# Age of Acquisition of Chronic Hepatitis B 1989 estimates



# HBV Genotypes

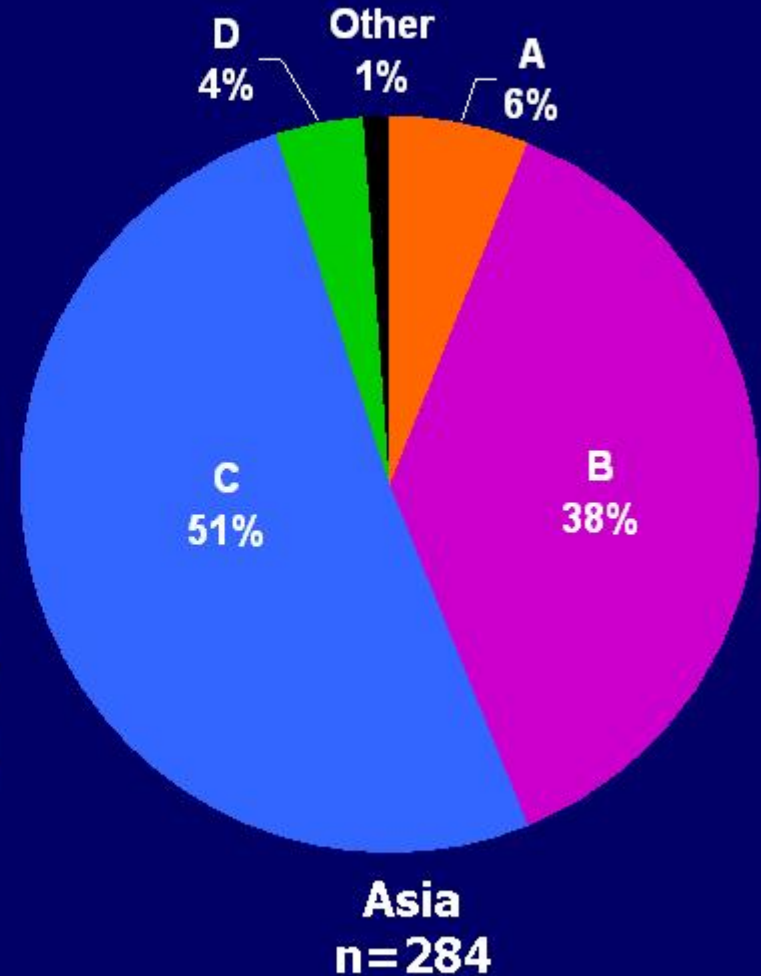
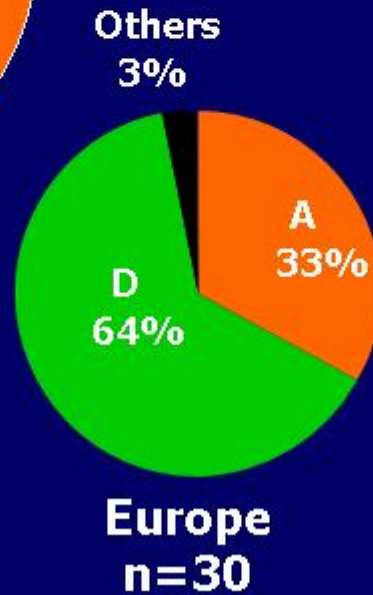
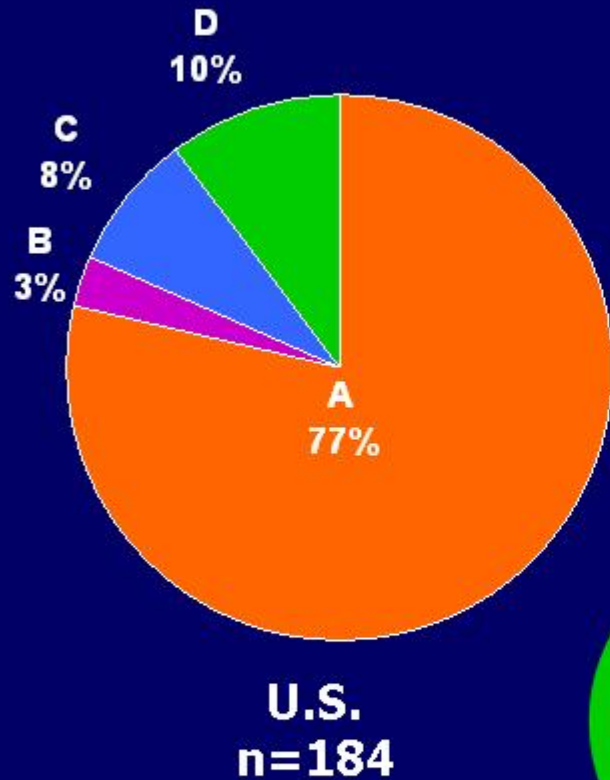
Test genotype with: INNO-LiPA HBV Genotyping

Genotype	Areas of prominence
A	North West Europe, USA, Central Africa
B	Taiwan, Japan, Indonesia, China, Vietnam
C	East Asia, Taiwan, Korea, China, Japan, Vietnam
D	Mediterranean area, India
E	West Africa
F	Central and South America
G	France, USA



# HBV Genotypes and Place of Birth

Test genotype with: INNO-LiPA HBV Genotyping



# 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

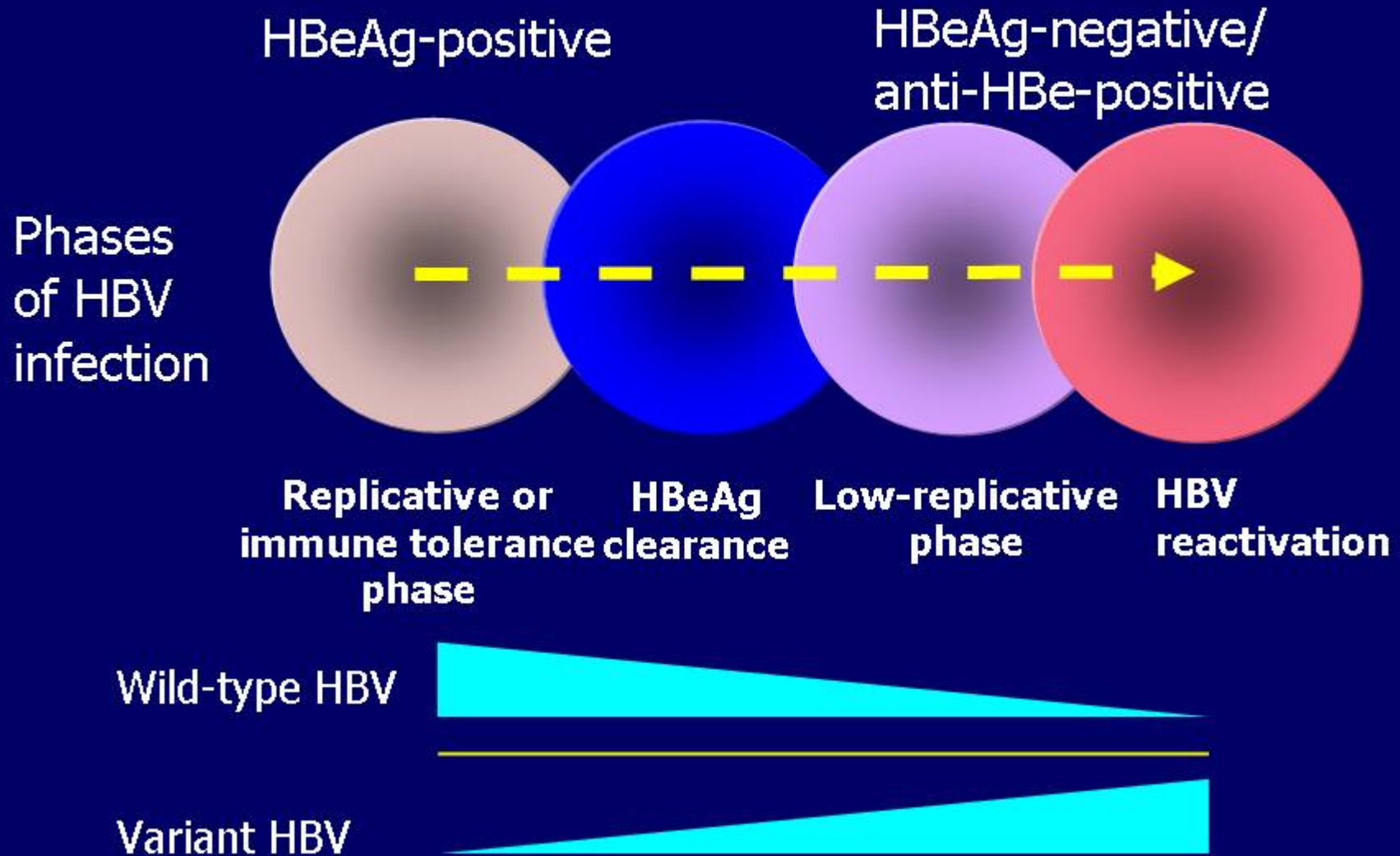


# Prognostic Factors For Progression To Cirrhosis

<b>Factors</b>	<b>P-value</b>
<b>Older age</b>	<b>.0001</b>
<b>HBV-DNA persistence</b>	<b>.0001</b>
<b>Virus genotype C</b>	<b>.001</b>
<b>Recurrent acute flares</b>	<b>.001</b>
<b>Histologic Staging</b>	<b>.0002</b>
<b>Alcohol consumption</b>	<b>.001</b>
<b>HCV, HDV co-infection</b>	<b>.001</b>
<b>HIV co-infection</b>	<b>.02</b>

# Development of Pre-Core and Core-promoter Mutants

# Natural History of HBV: Development of HBeAg-negative CHB



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

## **HBeAg (+)**

- **High HBV DNA**
- **HBeAg produced**
- **Less difficult to treat**
- **Slower rate of progression to liver disease**
- **Natural resolution over time (8-10%)**
- **Clinical outcome measures: HBV DNA, ALT, "e" & "s" seroconversion**

## **HBeAg (-)**

- **Lower HBV DNA**
- **No HBeAg produced**
- **Difficult to treat**
- **Fast rate of progression to liver disease**
- **No natural resolution over time**
- **Clinical outcome measures: HBV DNA, ALT normalization**



# 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<sup>1</sup>
  - **up to 90% in Mediterranean regions**
  - **~30–55% in Asia Pacific**
  - **~30–50% in Northern Europe**
  - **up to 40% in the United States**
- Prevalence of HBeAg-negative CHB is increasing worldwide<sup>2</sup>

<sup>1</sup>Hadziyannis SJ, Vassilopoulos D. *Hepatology*. 2001;34(4 Pt 1):617-624.

<sup>2</sup>Funk et al. *J Viral Hepat*. 2002.

# 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.**

# Testing for HB Pre-core & Core-Promoter Mutant

- 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  $\leq 30$  U/L, females  $\leq 19$  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 =  $2.86 \times 10^5$  copies/ml )



# **States of Chronic Hepatitis B**

**Inactive Carrier**

**Immunotolerant**

**Immunoactive**

**Occult Hepatitis B**

# 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 ( $\text{ALT} > 1\text{-}2 \times \text{the ULN}$ ) and
  - 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 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(+):** **20000 IU/mL**
  - **Mutant HBeAg(-):** **2000 IU/mL**

# Viral Load and ALT Thresholds to Consider Treatment

- When a patient is HBeAg(-) and has an HBV-DNA  $> 2000$  IU/mL but less than 20000 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)
  - **AGE 40 or OLDER**: In patients older than 40, liver damage may occur with viral load  $> 2000$  U/L even in absence of ALT elevation, hence liver biopsy is recommended on them to directly assess presence or absence of liver injury.

# Chronic Hepatitis B states

- Inactive Carrier state
  - *Normal ALT and*
    - **HBe(+) or “Wild-type”:**  
HBV-DNA < 20000 IU/mL,
    - **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 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 Bx if older than 40;
  - otherwise observe (immunotolerant state).



# Chronic Hepatitis B states

- Immunotolerant state
- *Normal ALT and*
  - **HBe(+) or Wild-type:**  
HBV-DNA > 20000 IU/mL,
  - **Mutant-HBe(-):**  
HBV-DNA > 2000 IU/mL
  - *NOTE: Consider Liver Bx in older than 40 years & HBV-DNA > 2000 IU/mL ( $10^4$  copies/mL), (May be immunoactive)*

# 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  $\geq$  40: consider liver Bx to assess histologic activity and decide about treatment

# Chronic Hepatitis B states

- **Immunoactive state**
- *Elevated ALT ( $> ULN$ )*
  - **HBe(+) or Wild-type:**  
HBV-DNA  $> 20000$  IU/mL
  - **Mutant-HBe(-):**  
HBV-DNA  $> 2000$  IU/mL
- *Treat*

# 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

# Occult Hepatitis B

- **Management:**

- a) Test donated blood for HBV-DNA in highly endemic areas.
- b) Test for HBsAg & anti HBc before immunosuppression;
  - if HBsAg(+), investigate and treat accordingly;
  - if only HBc(+), give pre-immunosuppression prophylaxis with Lamivudine or other anti-HBV drug, and monitor while on immunosuppressive therapy 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
- **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  
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 <  $12 \times 10^6$  IU/mL (200 pg/mL, or  $57 \times 10^6$  copies/mL)

- **Peg-IFN:**

- non-cirrhotic, and
- HBV-DNA <  $3.6 \times 10^9$  IU/mL ( $6.36 \times 10^4$  pg/mL, or  $18.2 \times 10^9$  copies/mL),
- ALT > 1 x ULN

# 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 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:**
  - Only use Peg-IFN, or Adefovir, unless the anti-HBV drug is being use as part of HAART.
  - Use of other HBV drugs, as monotherapy, may facilitate HIV resistance.

# 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 < 60 IU/mL (complete response)
- **Mutant-HBe(-):** Convert to “inactive carrier state” with:
  - HBV-DNA < 2000 IU/mL
  - ideally < 60 IU/mL (complete response)
- **Cirrhotic:** Convert to:
  - HBV-DNA < 2000 IU/mL
  - ideally < 60 IU/mL (complete response)



# Chronic HBV Therapy Points to Keep in Mind

- Sustained loss of HBeAg requires:
  - to continue Lamivudine, Adefovir, Entecavir, Telbivudine, or Tenofovir for at least 6 months after confirmation of the loss of HBeAg and development of anti-Hbe.
  - the confirmation of seroconversion is done by a second test 1-3 months post-seroconversion.
- Long therapy with oral agents increases frequency of drug-resistance.
- If patients were HBe(-) pre-treatment, therapy will be life-long or until patient loses HBsAg.



# 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  $> 2000$  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.**

# 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

- **Complete On-therapy Response:**
  - HBV-DNA < 60 IU/mL
- **Sustained Virological Response:**
  - Persistence of clinical response 6 months after end-of-therapy, to a predefined goal (like HBV-DNA < 2000 IU/mL in HBeAg(-) or < 20000 IU/mL in HBeAg(+)).
- **Commercial Test for Drug Resistance:**
  - Inno-LiPA HBV DR v2 (Lamivudine, Telbuvudine, Emtricitabine and Adefovir)

# Drug Cross-Resistance Profile

(reverse transcriptase mutations)

Zoulim F et al. J of Hepatology 2008;48: S2-S19

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
<b>Wild</b>	<b>S</b>	<b>S</b>	<b>S</b>	<b>S</b>	<b>S</b>
<b>M204I</b>	<b>R</b>	<b>R</b>	<b>R</b>	<b>S</b>	<b>S</b>
<b>L180M + M204V</b>	<b>R</b>	<b>R</b>	<b>I</b>	<b>S</b>	<b>S</b>
<b>A181T/V</b>	<b>I</b>	<b>S</b>	<b>S</b>	<b>R</b>	<b>S</b>
<b>N236T</b>	<b>S</b>	<b>S</b>	<b>S</b>	<b>R</b>	<b>I</b>
<b>I169T + V173L + M250V</b>	<b>R</b>	<b>R</b>	<b>R</b>	<b>S</b>	<b>S</b>
<b>T184G + S202I/G</b>	<b>R</b>	<b>R</b>	<b>R</b>	<b>S</b>	<b>S</b>
<b>I233V</b>				Resistance ?	
<b>A194T</b>					Resistance ?

# Treatment Options for Antiviral Resistance

<b>Resistance to</b>	<b>Rescue Therapy</b>
<b>Lamivudine or Telbivudine</b>	<b>Add:</b> Adefovir, or Tenofovir, or <b>Switch to:</b> Tenofovir + Emtricitabine (Truvada)
<b>Adefovir</b>	<b>Add:</b> Lamivudine, or Entecavir, or <b>Switch to:</b> Tenofovir + Emtricitabine (Truvada)
<b>Entecavir</b>	<b>Add:</b> Adefovir, or Tenofovir
<b>Multidrug</b>	?

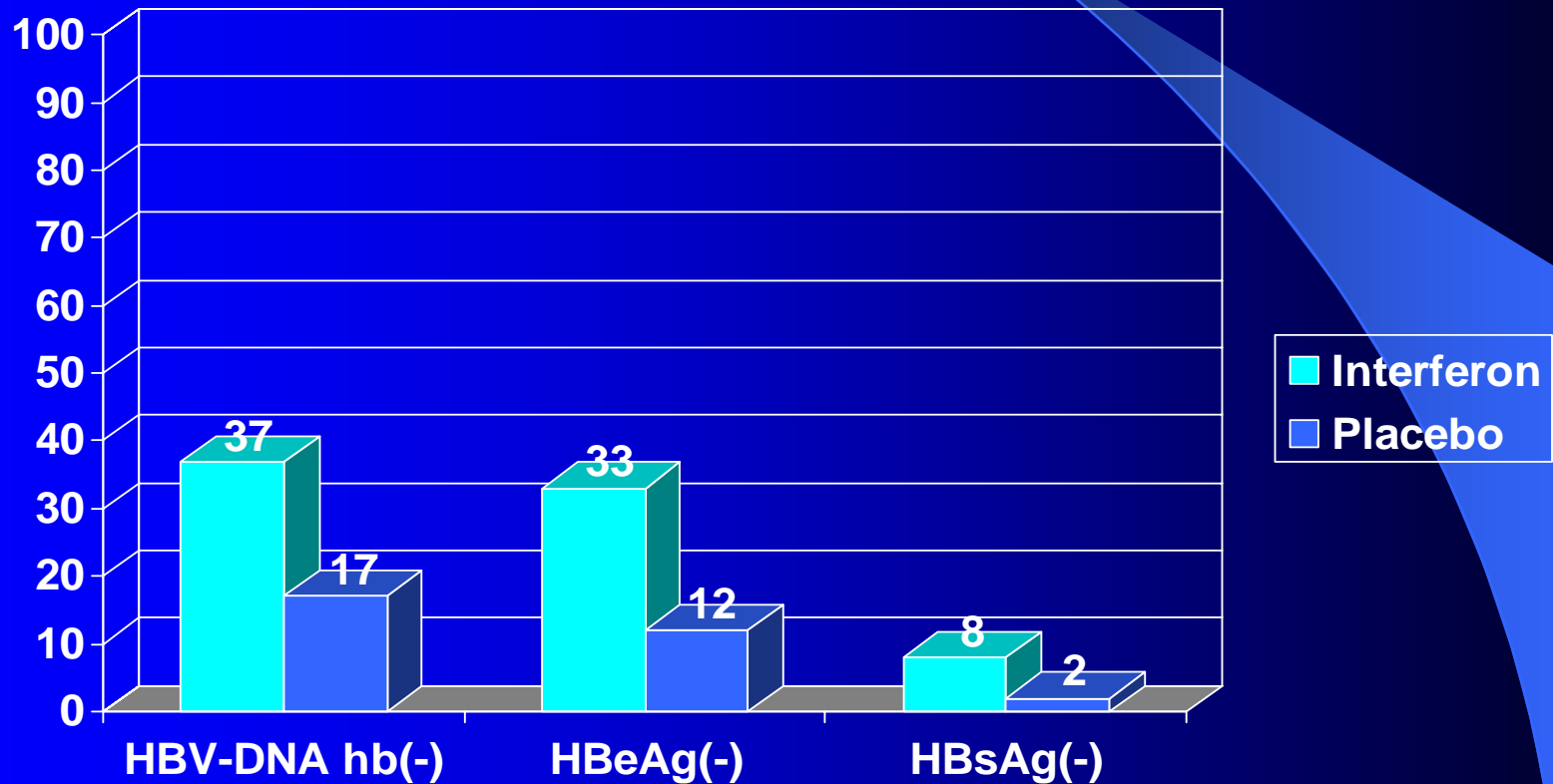
# Regular Interferon

# 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 <  $12 \times 10^6$  IU/mL ( $57 \times 10^6$  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(+)

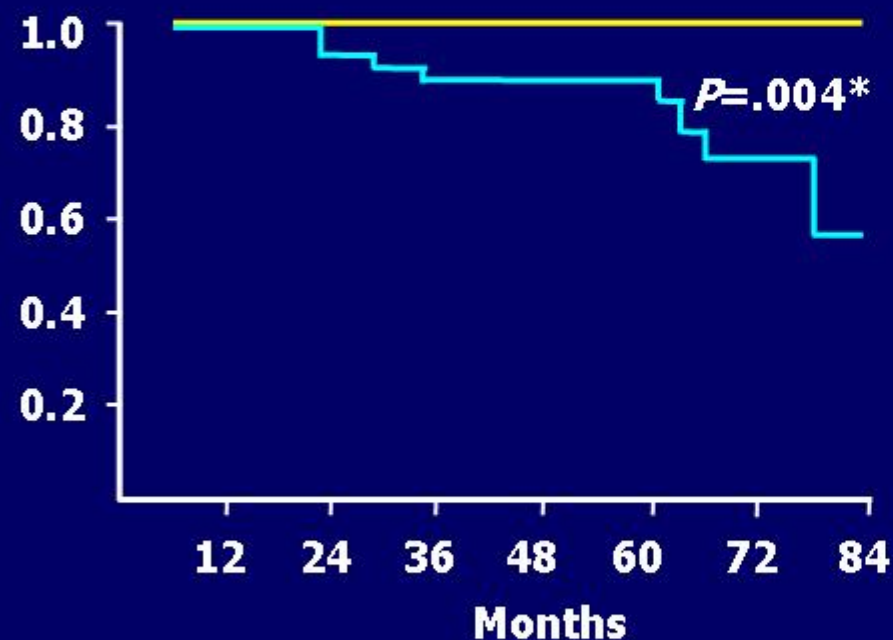
Wong D et al. Ann Intern Med 1993; 119:312-323



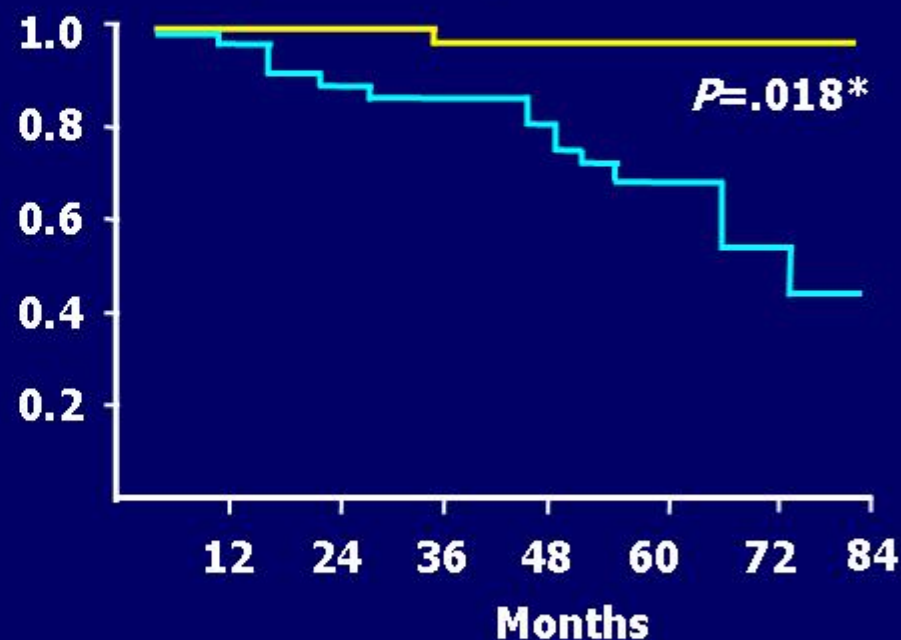


# Survival After HBeAg Clearance in HBeAg-positive CHB

Proportion of patients surviving



Proportion of patients free of  
hepatic complications



— IFN $\alpha$ -treated WITH HBeAg clearance  
— IFN $\alpha$ -treated WITHOUT HBeAg clearance

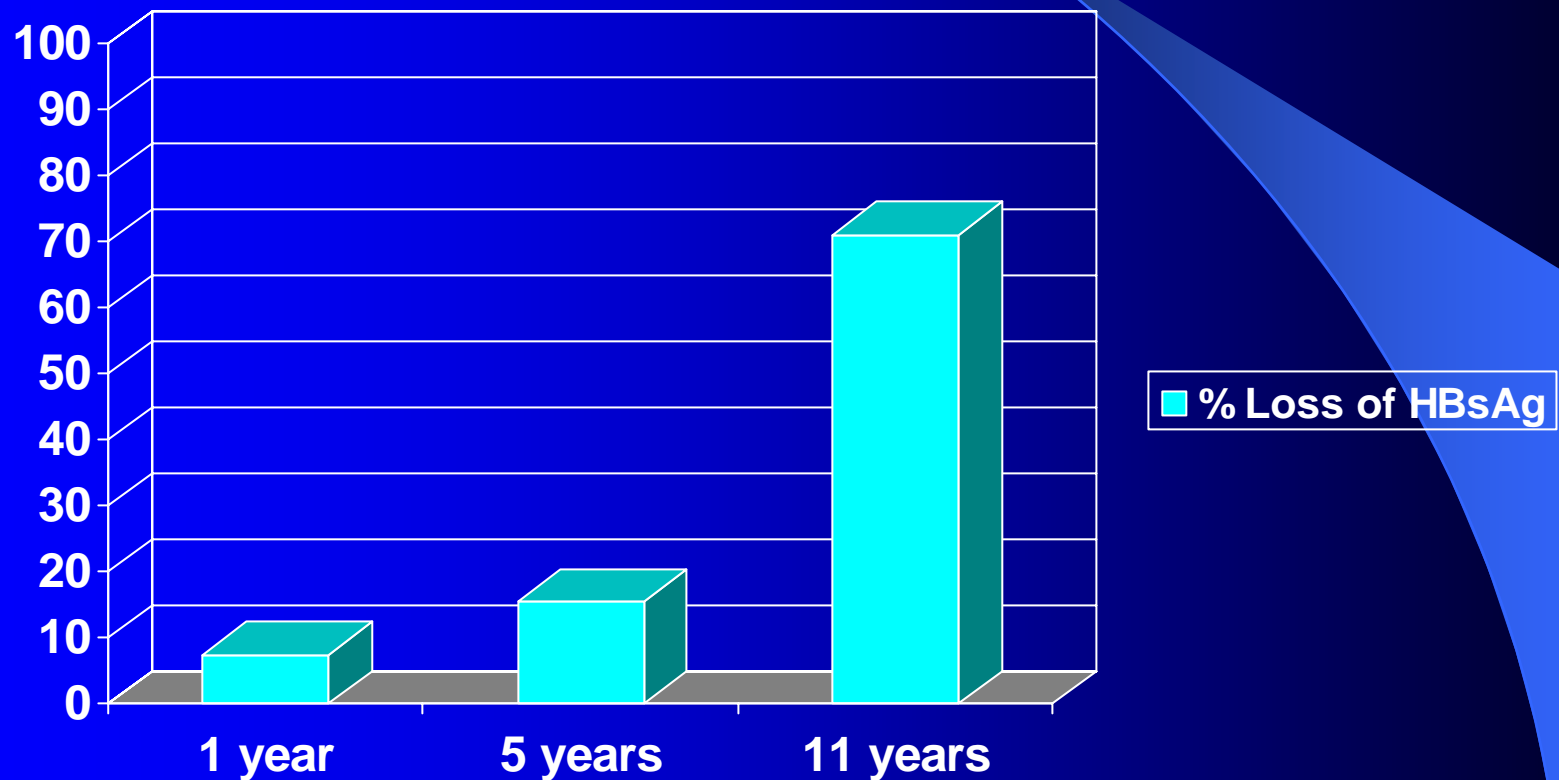
\*According to the proportional hazards model

Niederau C et al. *N Eng J Med*. 1996.

# Long term F/U of Interferon Responders

## Loss of HBsAg (Europeans & Americans)

Gut 2000;46:715-718, Am J Gastroenterol 1998;93:896-900, Gastroenterology 1997;113:1660-1667



# Pegylated Interferons

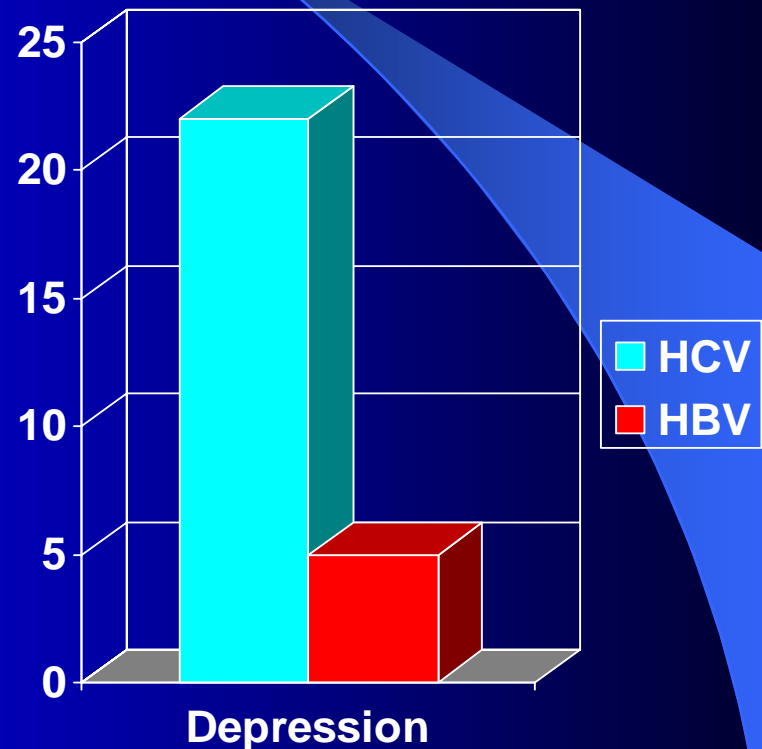
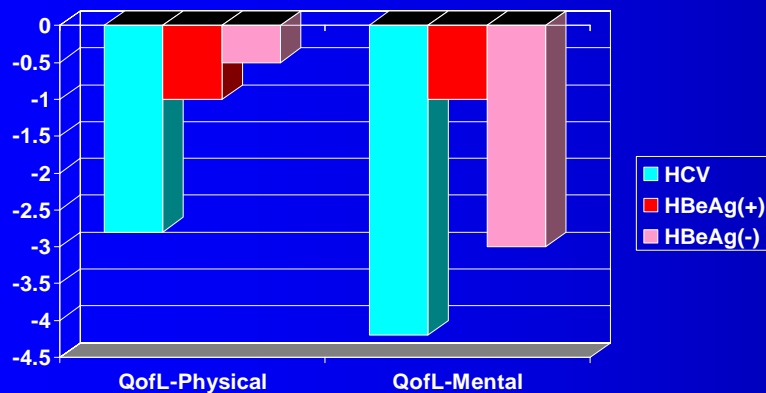
# Tolerability of Pegasys in Chronic HBV vs. HCV

Marcellin et al. AASLD Abstr.# 1158, 2004

- 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



# 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**

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

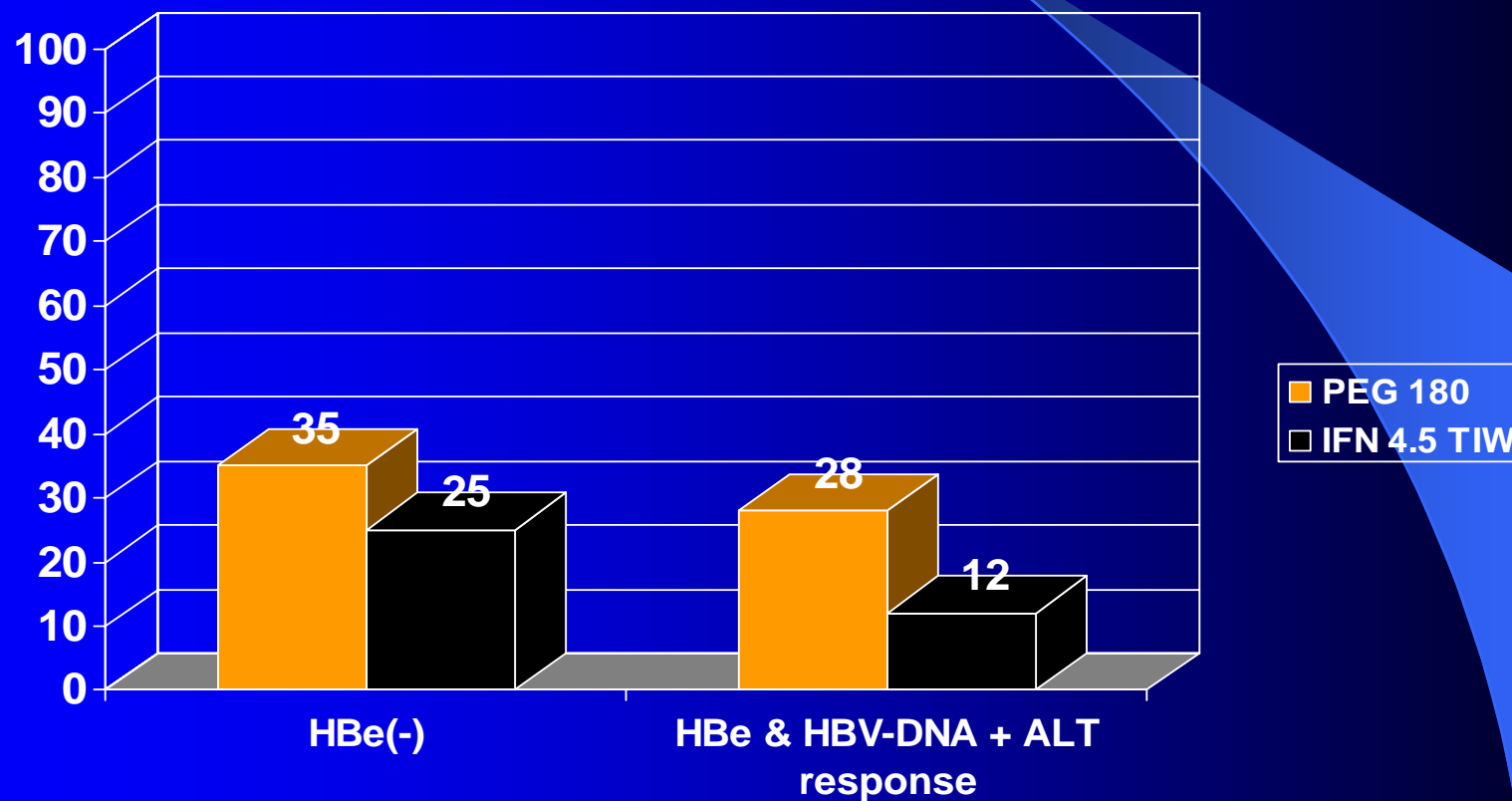
# Peg-Interferon in HBeAg(+)



# Pegasys 180 x 24 wks in HBe(+)

## Week 48 (SVR ?) Data

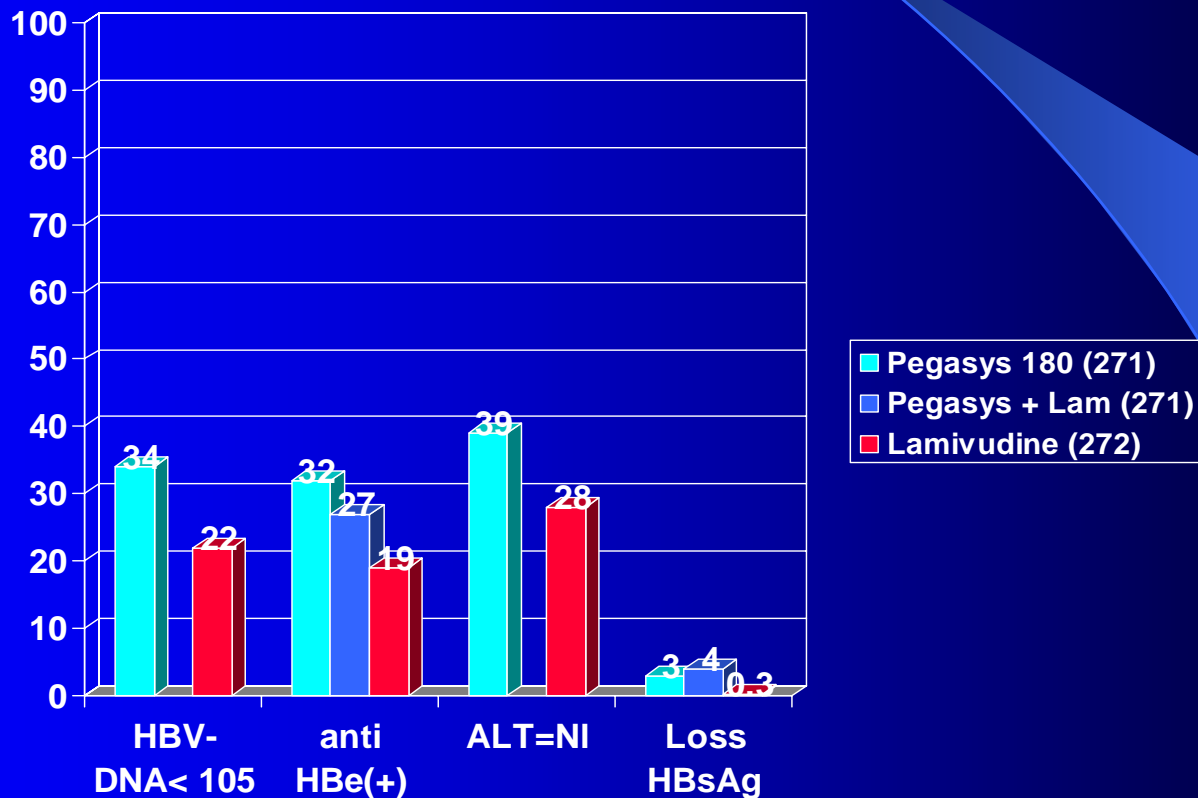
Cooksley W et al. J Viral Hepat 2003, 10:298-305



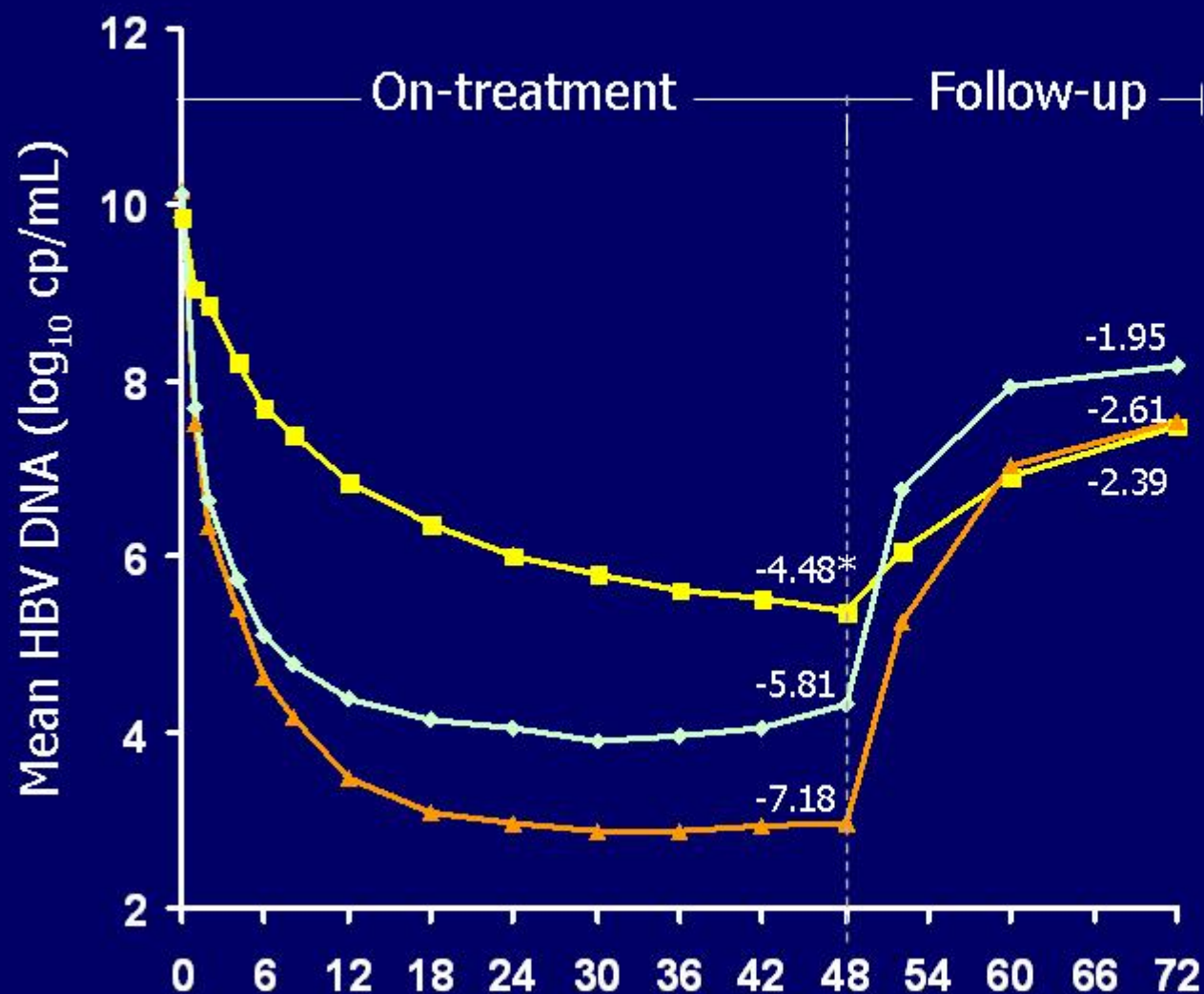
# Pegasys 180 x 48 wks in HBe(+)

## Week 72 (SVR ?) Data

Lau G et al. Hepatology 2004; 40:171A



# HBV DNA Levels Over Time



■ **PEGASYS®  
+ placebo**

**HBeAg seroconversion**  
EOT=27%; EOF=32%

▲ **PEGASYS®  
+ lamivudine**

**HBeAg seroconversion**  
EOT=24%; EOF=27%

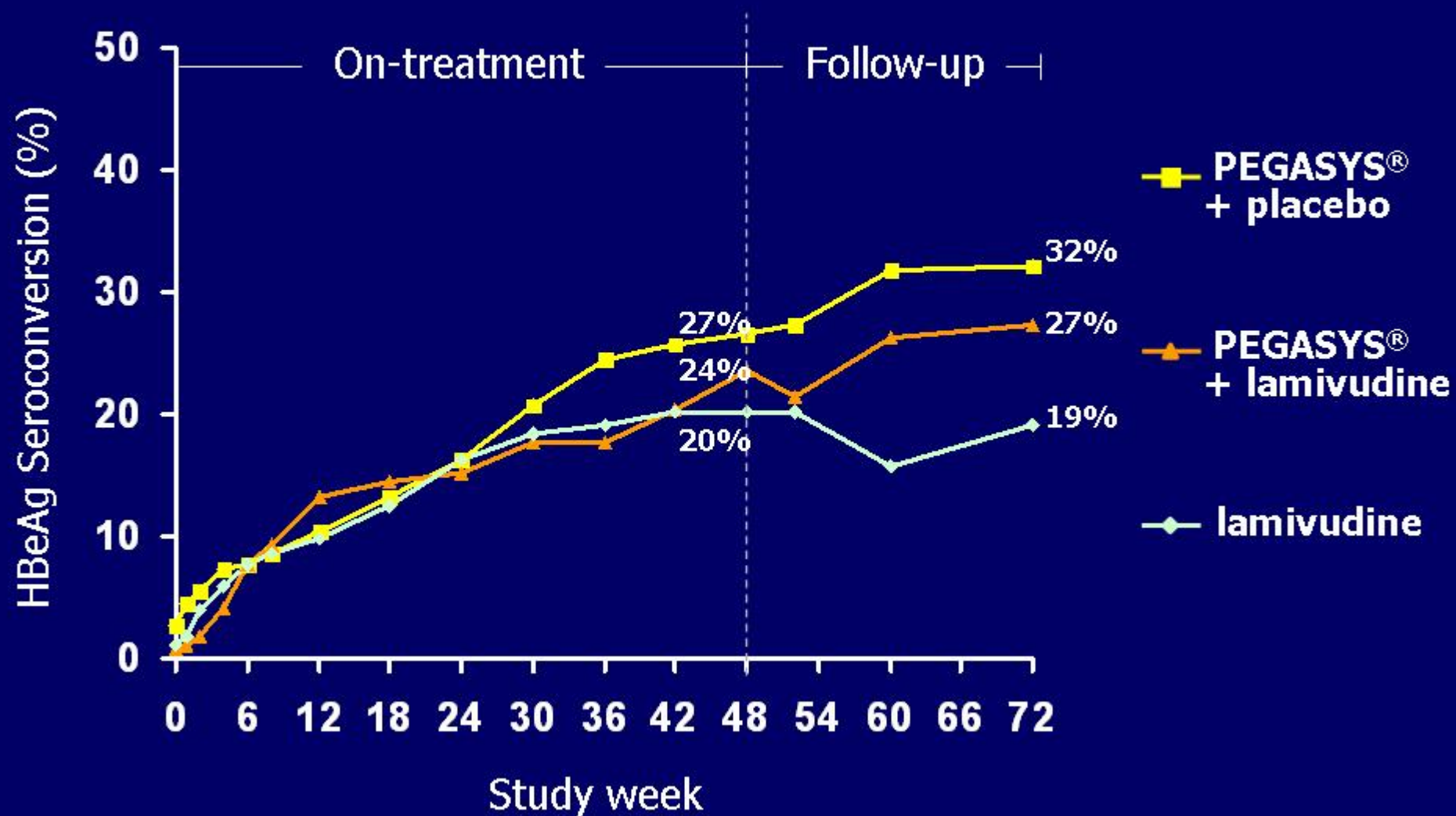
◆ **lamivudine**

**HBeAg seroconversion**  
EOT=20%; EOF=19%

\* all numbers shown are log<sub>10</sub> reduction from baseline

Lau et al. AASLD. 2004.

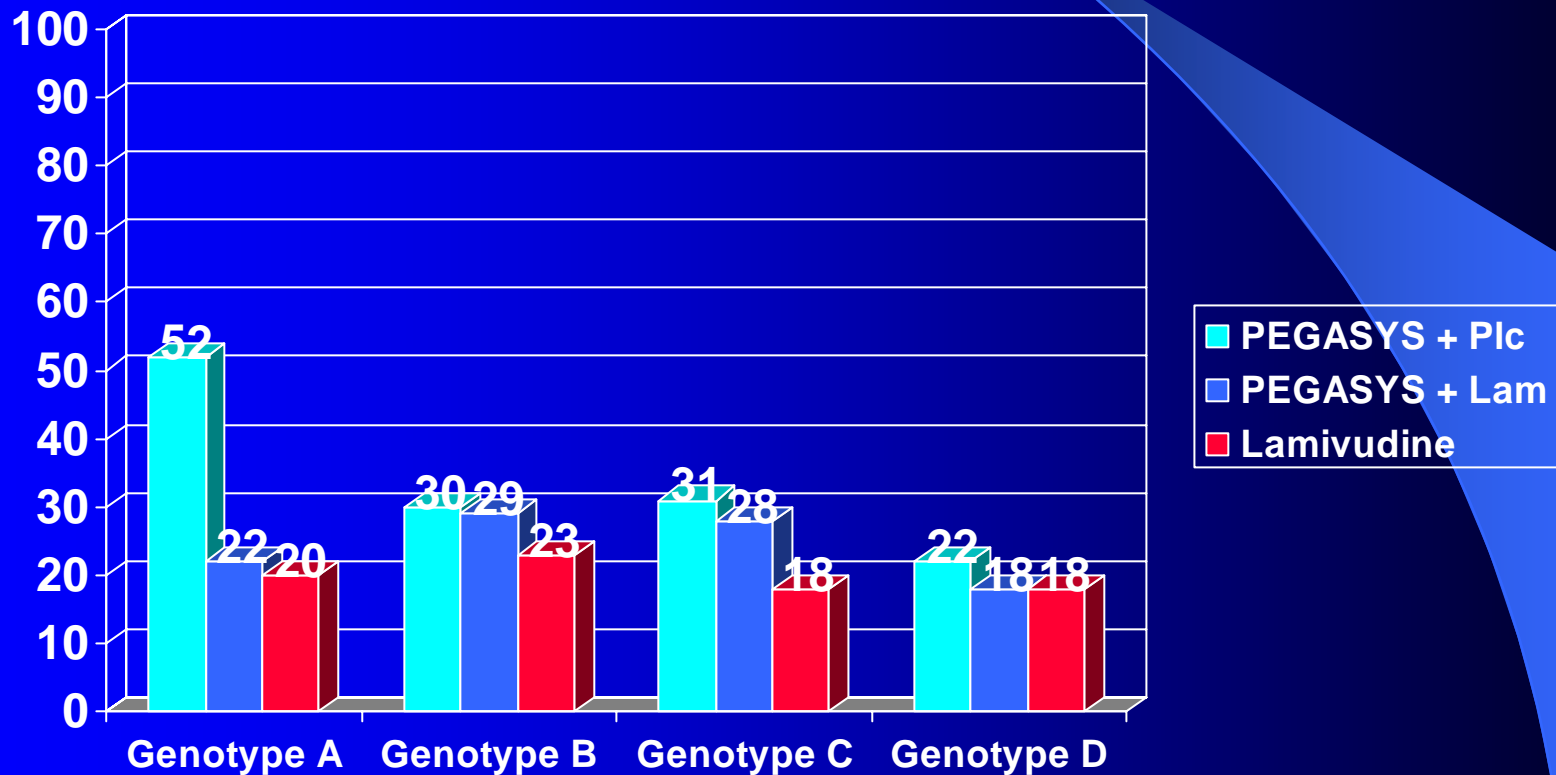
# HBeAg Seroconversion Rates Over Time



# Effect of HBV Genotype

## HBe Seroconversion 24 wks after EOT

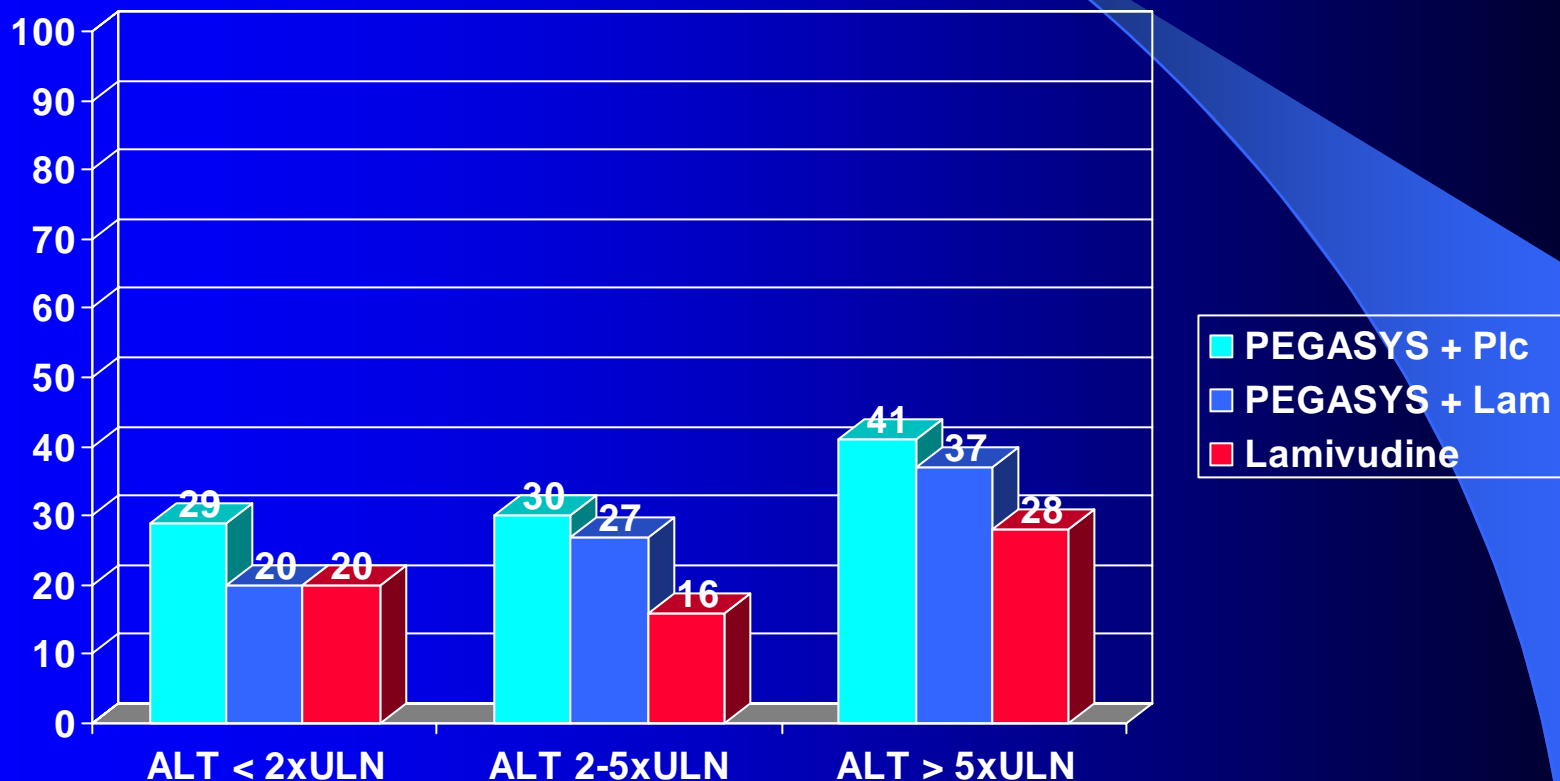
Cooksley W et al. EASL 2005



# Effect of Pre-Treatment ALT

## HBe Seroconversion 24 wks after EOT

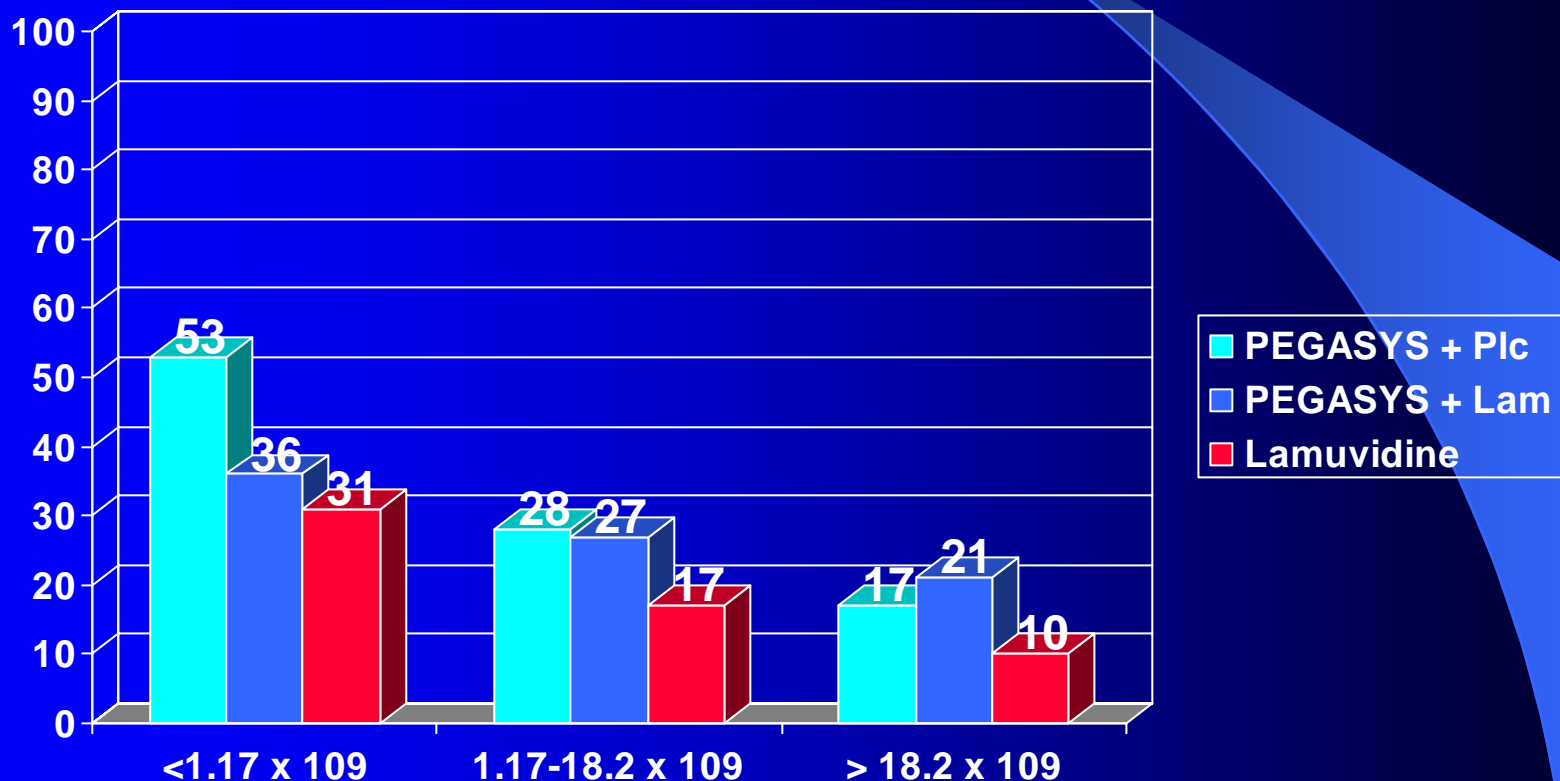
Cooksley W et al. EASL 2005



# Effect of Baseline HBV-DNA

## HBe Seroconversion 24 wks after EOT

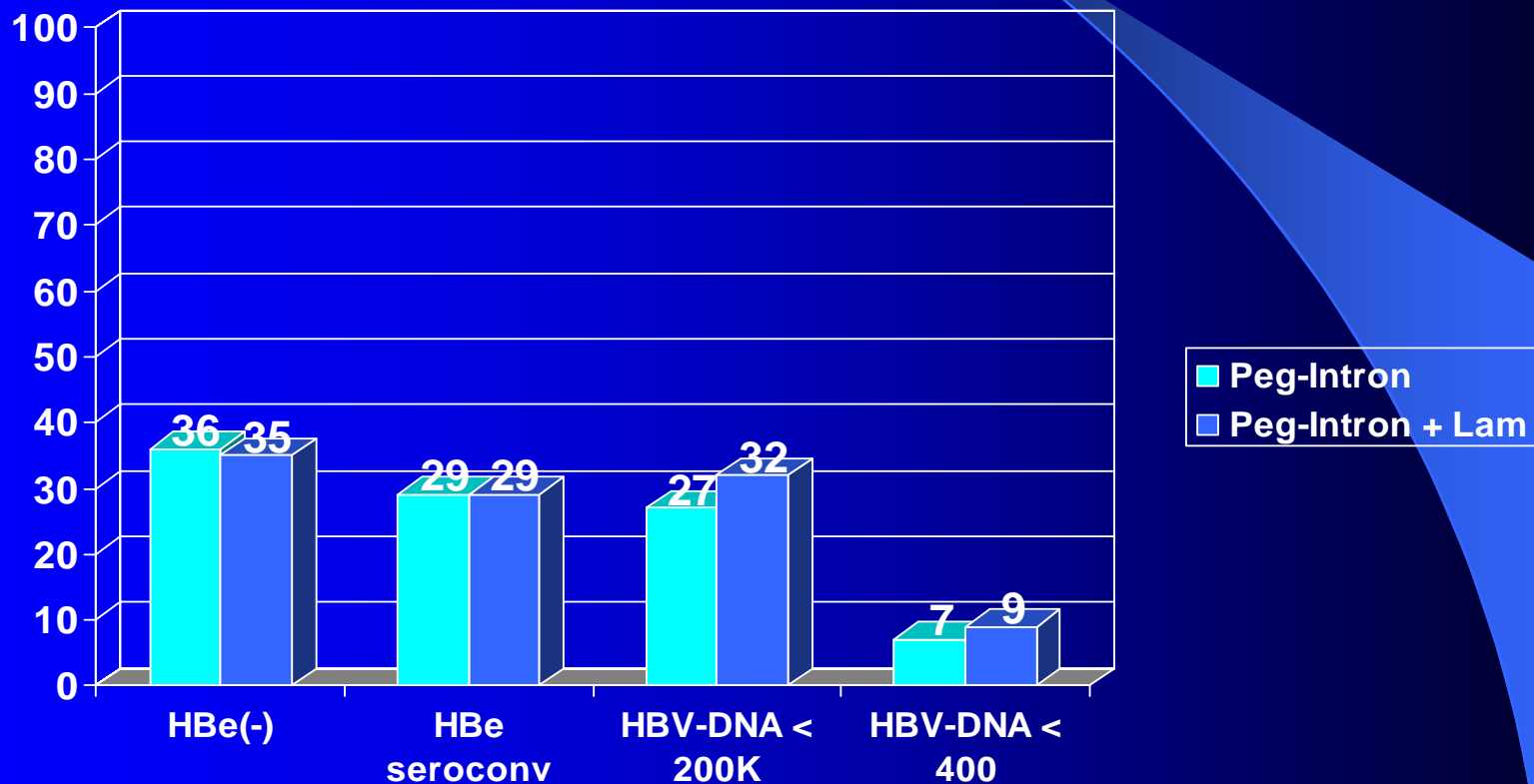
Cooksley W et al. EASL 2005



# Peg-Intron 100x 32w + 50x20w in HBe(+)

## Week 78 Data

Janssen et al. Lancet 2005;365:123-129





# CONCLUSIONS

## Peg-IFN in HBeAg(+) Chronic HBV

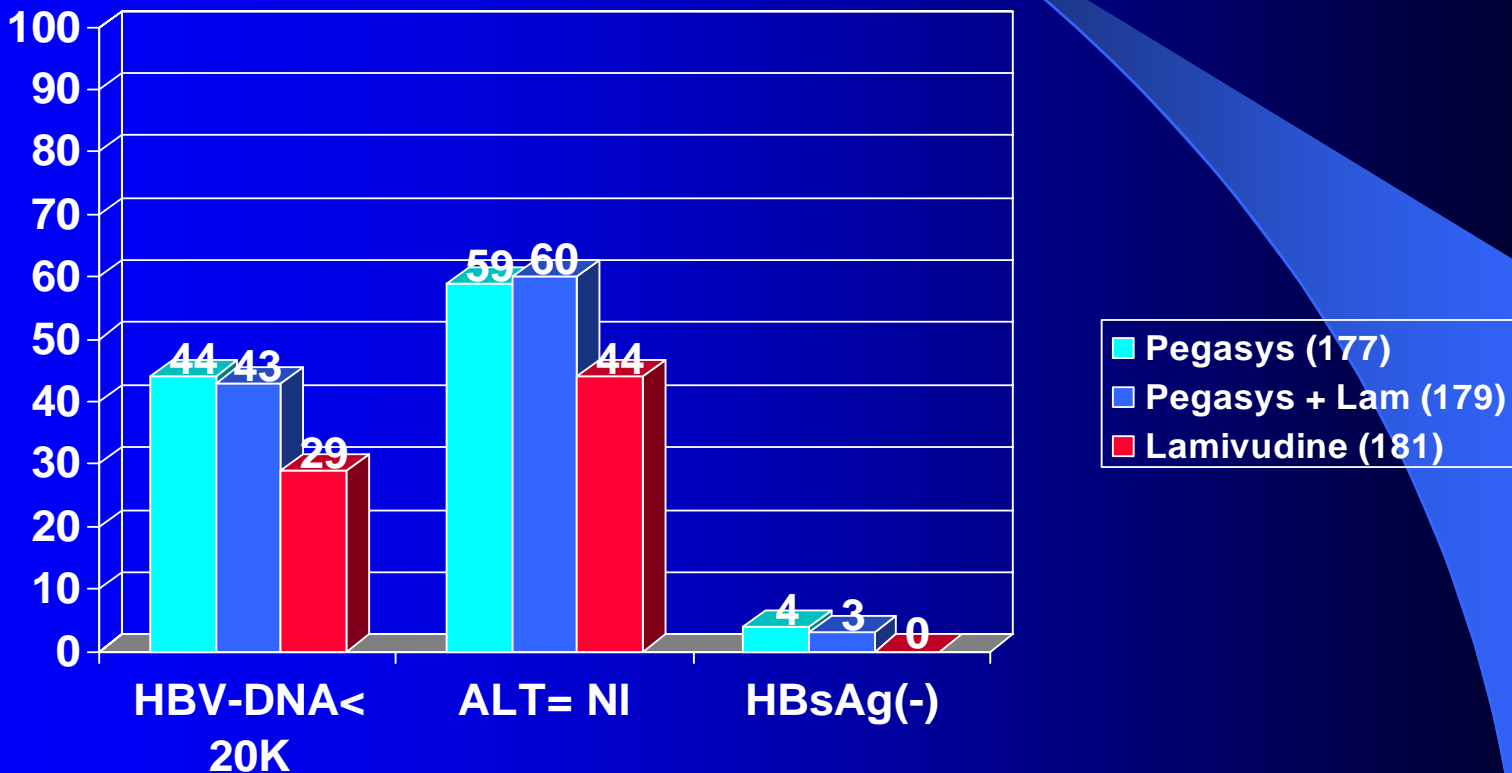
- One third of chronic HBeAg(+) infected patients achieve sustained seroconversion
- Loss of HBsAg occurs in 3 to 4% in the first year. Additional HBsAg loss is expected in long-term follow up.
- Genotypes A, B, and C respond better than genotype D
- Test genotype with: INNO-LiPA HBV Genotyping
- Viral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

# Peg-Interferon in HBeAg(-)

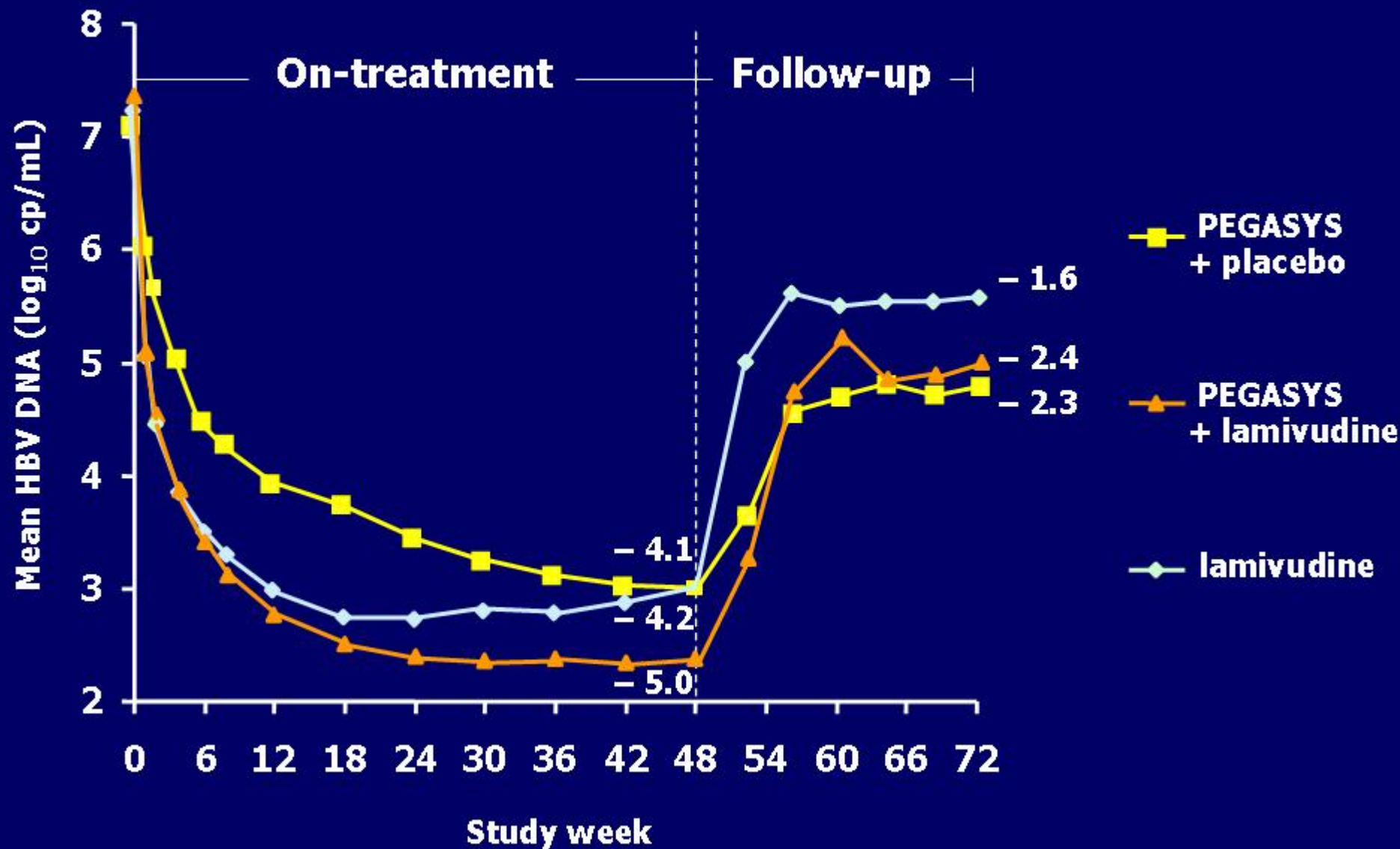
# Pegasys 180 x 48 wks in HBe(-)

## Week 72 Data

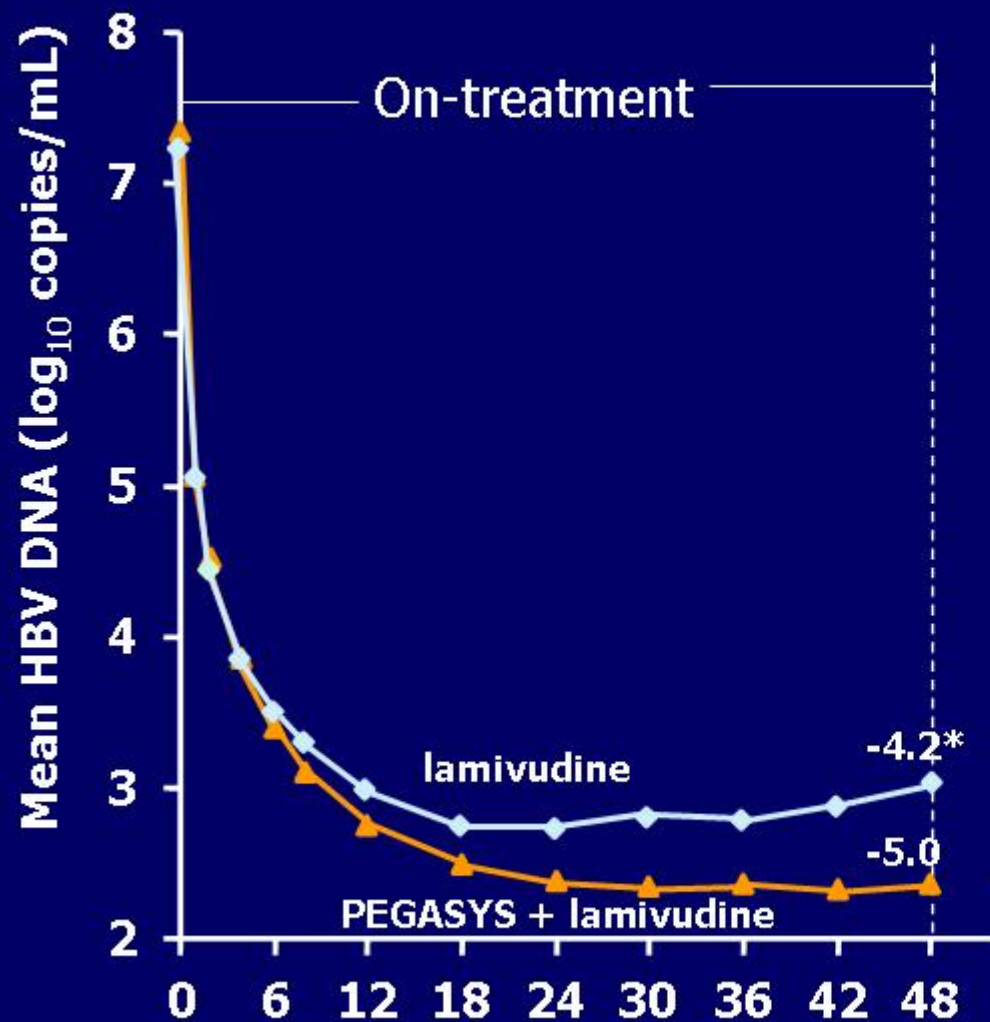
Marcellin P et al. N Engl J Med 2004;351:1206-17



# HBV DNA Levels Over Time



# On-therapy HBV DNA Suppression and LAM Resistance



YMDD mutation development  
at end of treatment



32/179 = 18%



1/173 = <1%

$P < .001$

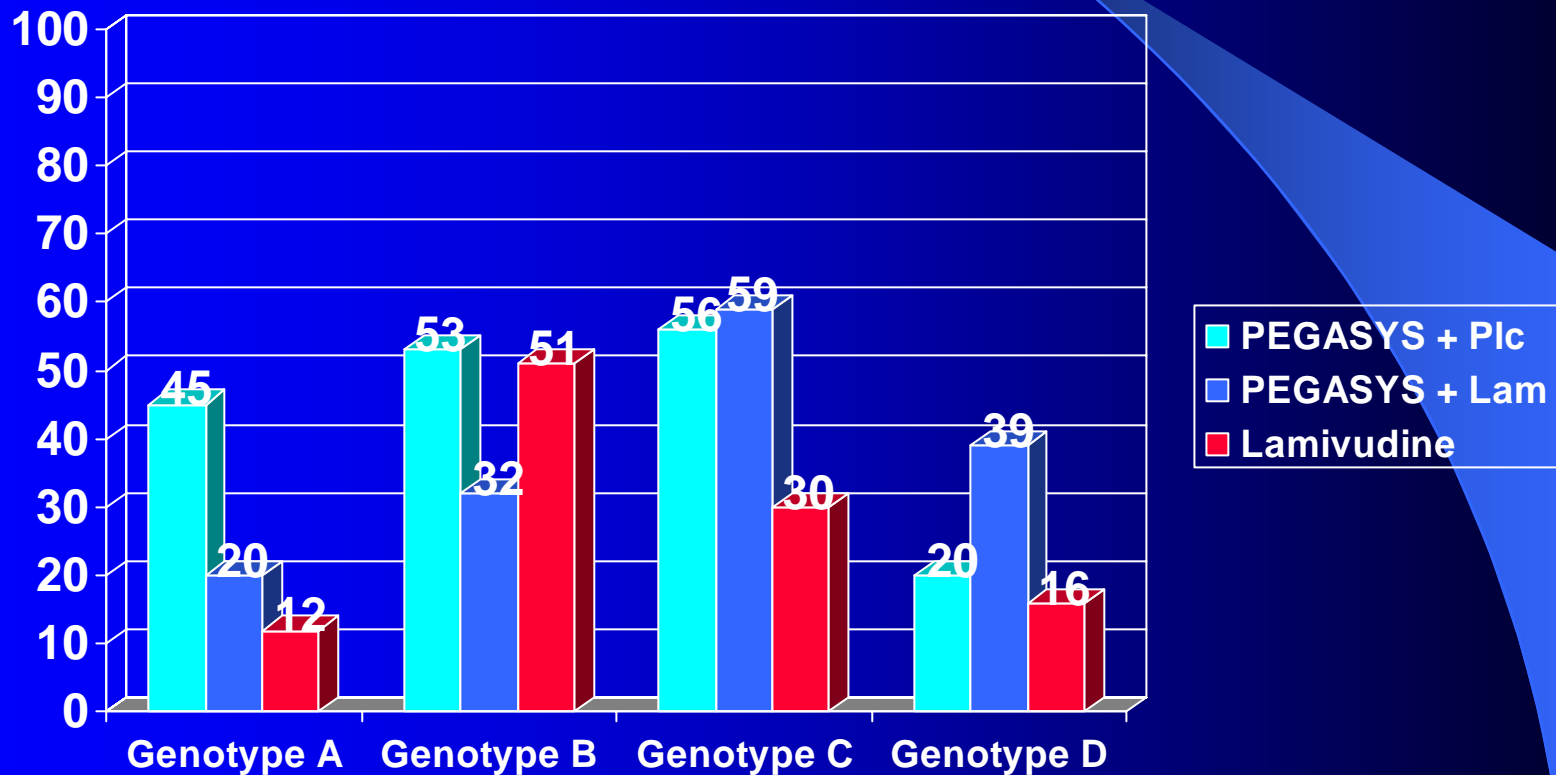
\* All numbers shown are log<sub>10</sub> reduction from baseline.

Marcellin et al. *NEJM*. 2004;351:1206-17.

# 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 a2a in HBeAg(-) Patients

Rijckborst V et al. Hepatology 2010;52:454-461

- 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.

## Change from Baseline to Wk 12

HBsAg decline	HBV-DNA drop $\geq$ 2 log	Recommendation	SR Rate
No	No	STOP	0%
No	Yes	Continue	24%
Yes	No	Continue	25%
Yes	Yes	Continue	39%



# 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

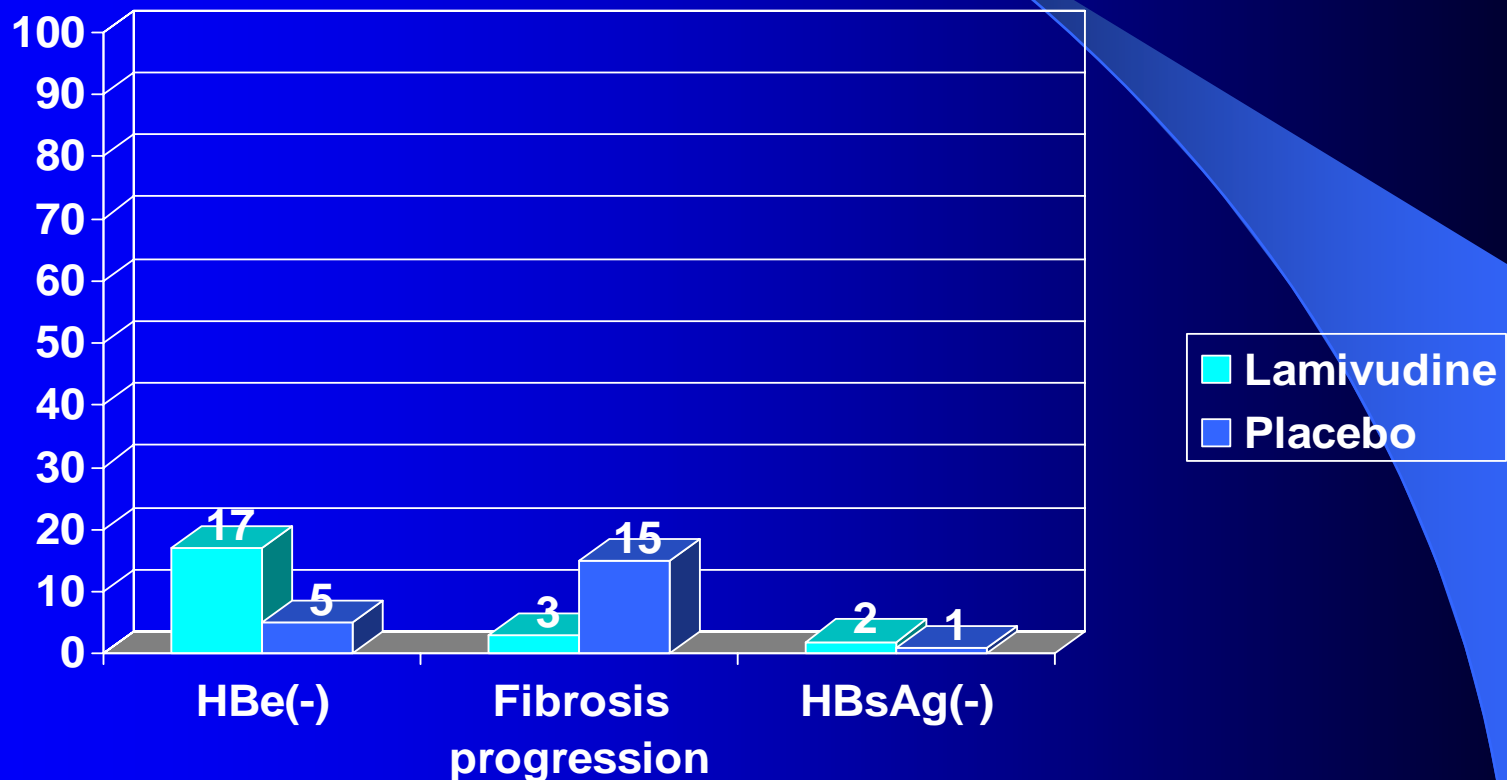


Lamivudine

# Lamivudine x 48 wks in HBe(+)

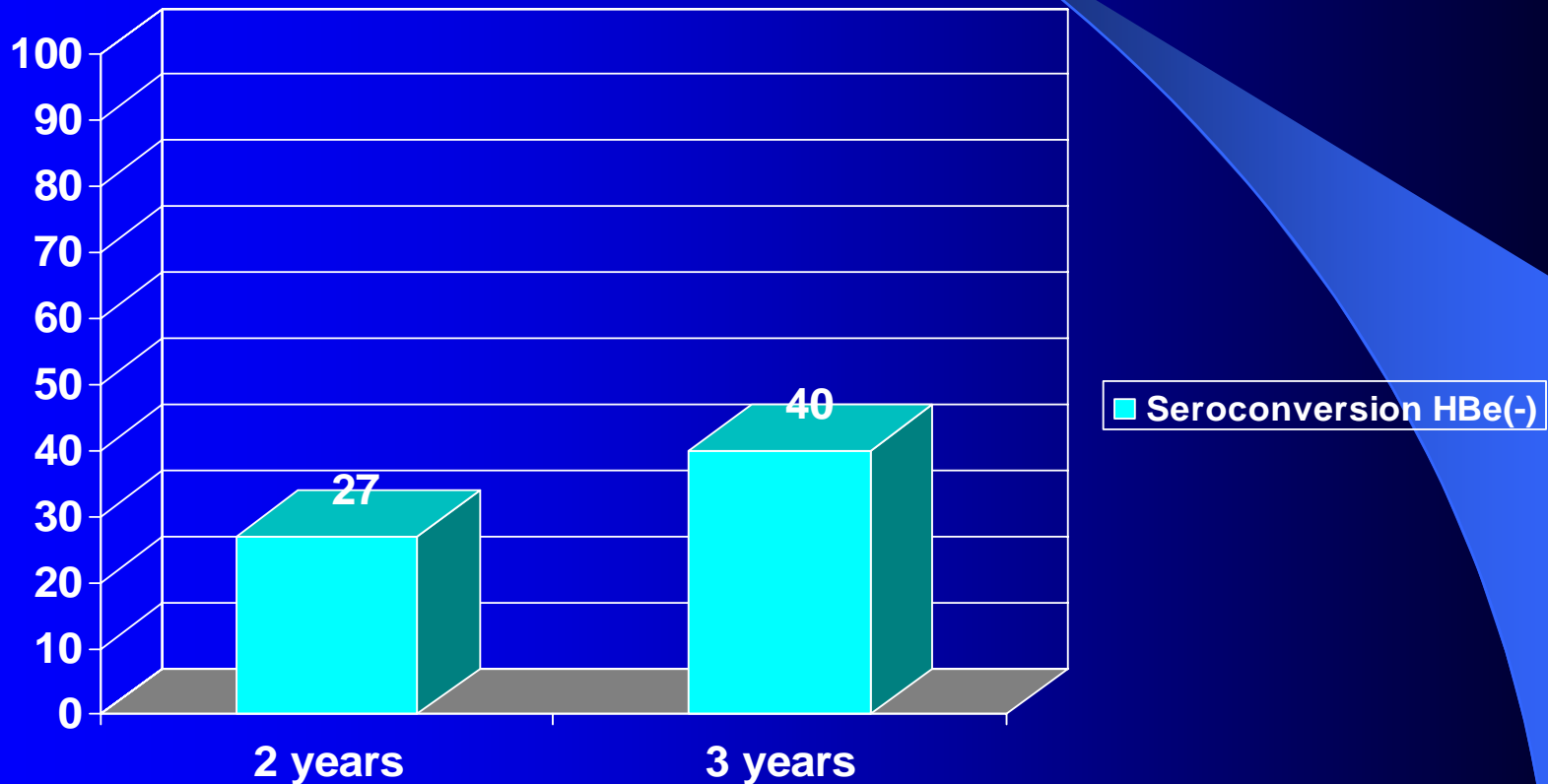
Diengstag J et al. N Engl J Med 1999;341:1256-63

Lai G et al. N Engl J Med 1998;339:61-68

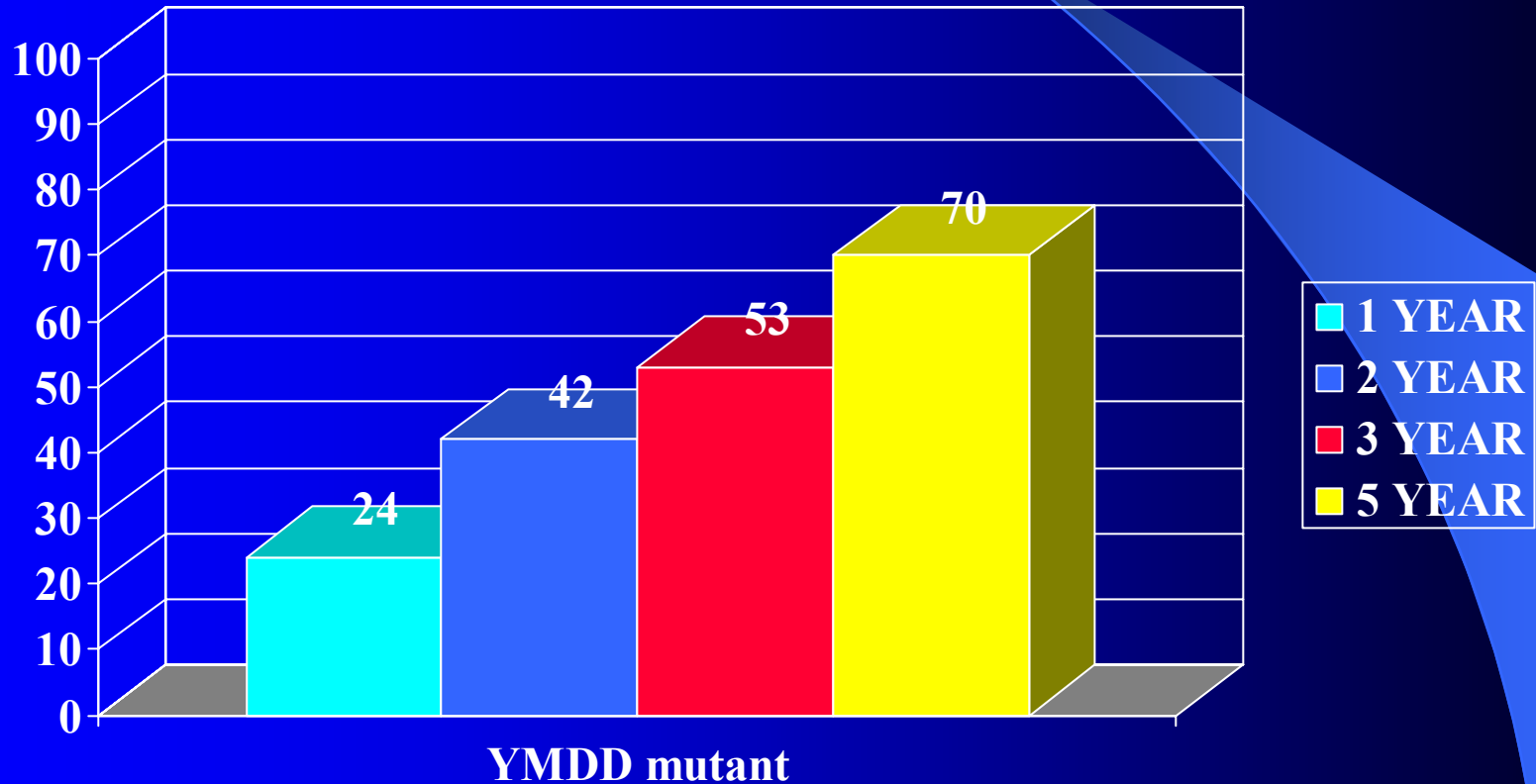


# Lamivudine in HBe(+) x 3 y

Leung N et al. Hepatology 2001;33:1527-32



# Lamivudine Resistance YMDD mutants



# 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

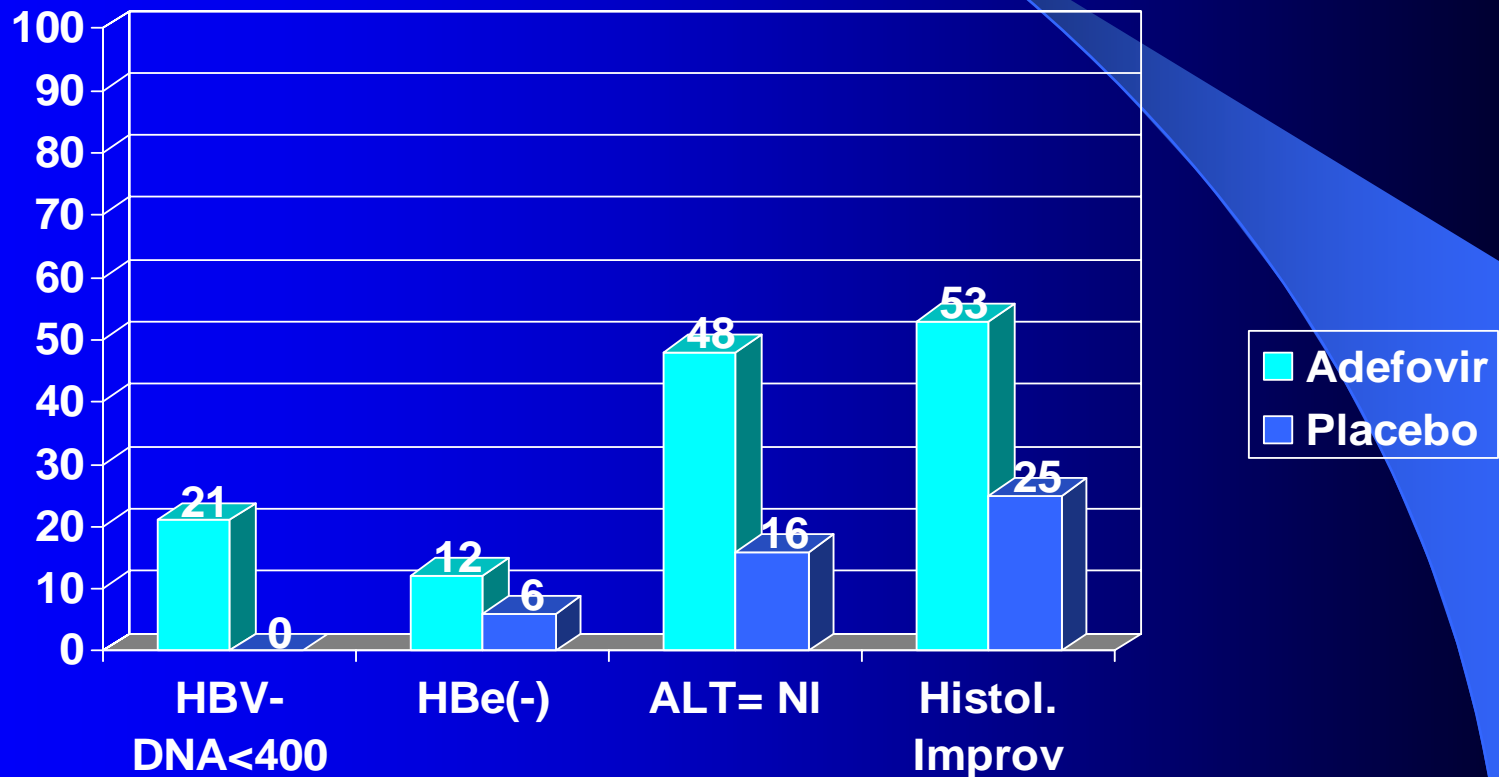
- Oral adenosine nucleotide analog.
- Moderately active in wild, HBe(-), and YMDD mutant.
- Good choice for HBe(-) mutant, and as second drug for YMDD mutant, and as monotherapy in HIV co-infection.
- Decreases levels of intrahepatic cccDNA.
- Used together with Peg-IFN, increases rate of HBe seroconversion 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

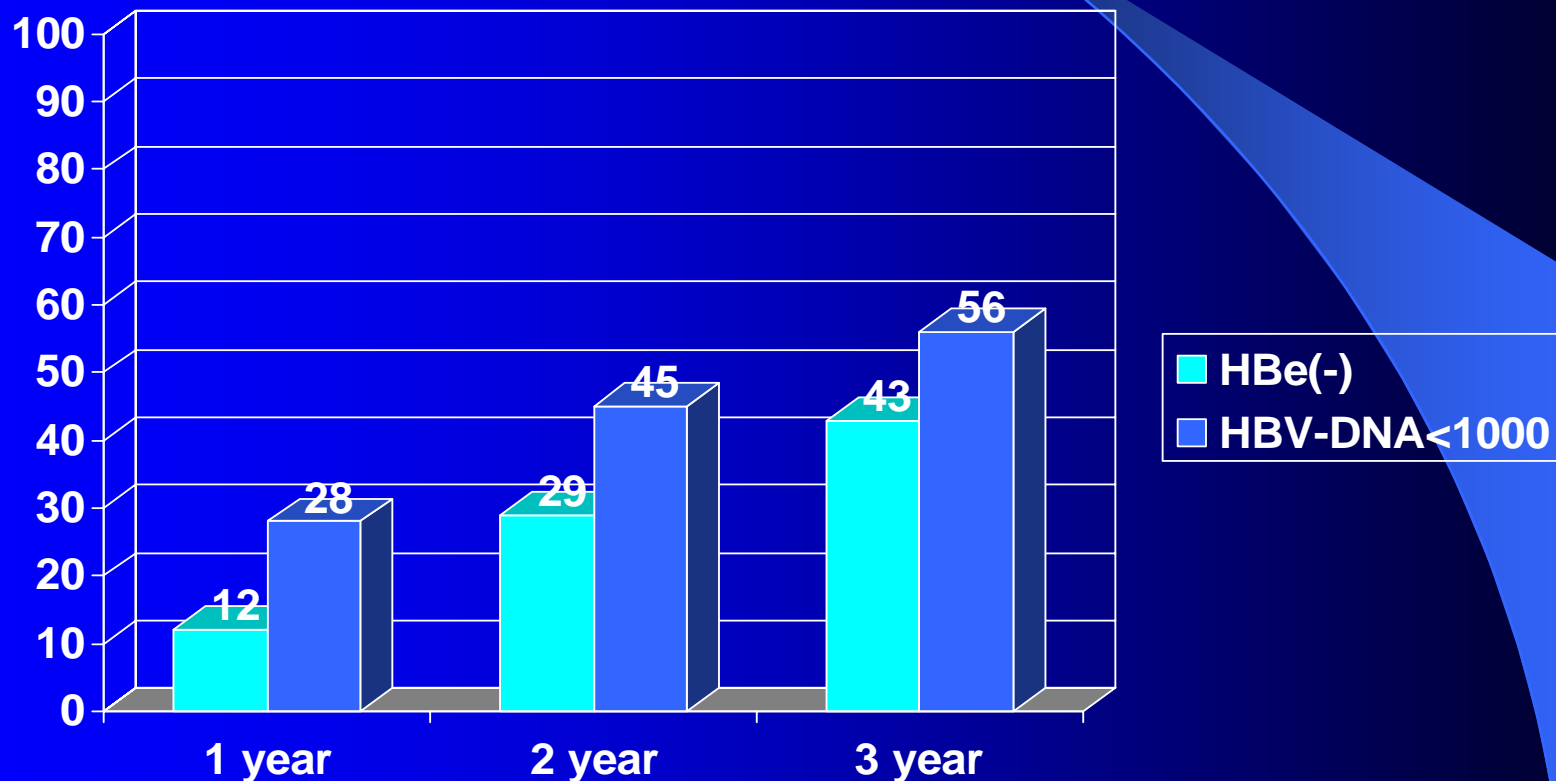
# Adefovir x 48 wks in HBe(+)

Marcellin P et al. N Engl J Med 2003;348:808-816



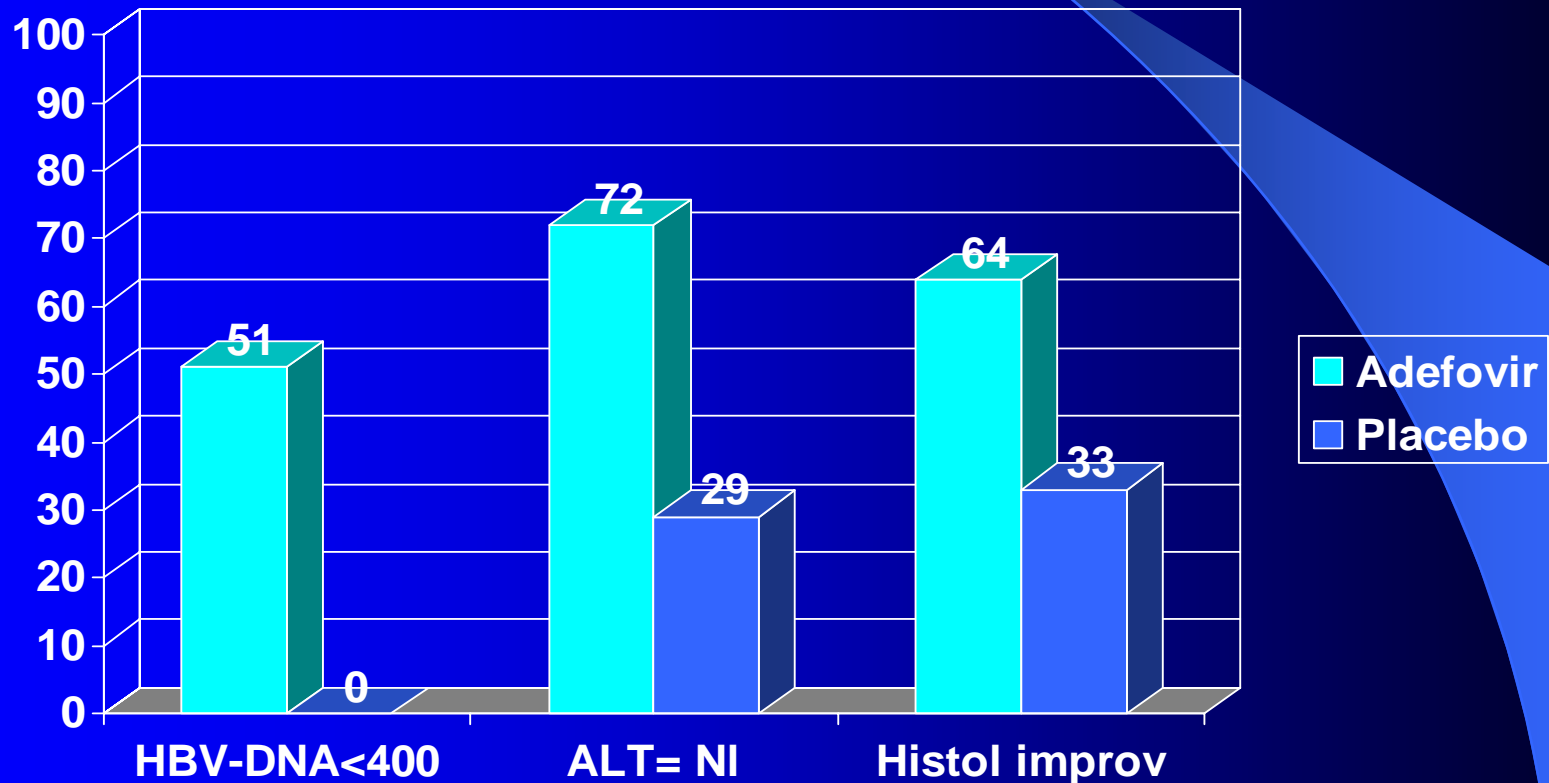
# Adefovir x 3 y in HBe(+)

Marcellin P et al. AASLD Abst 1135, 2004

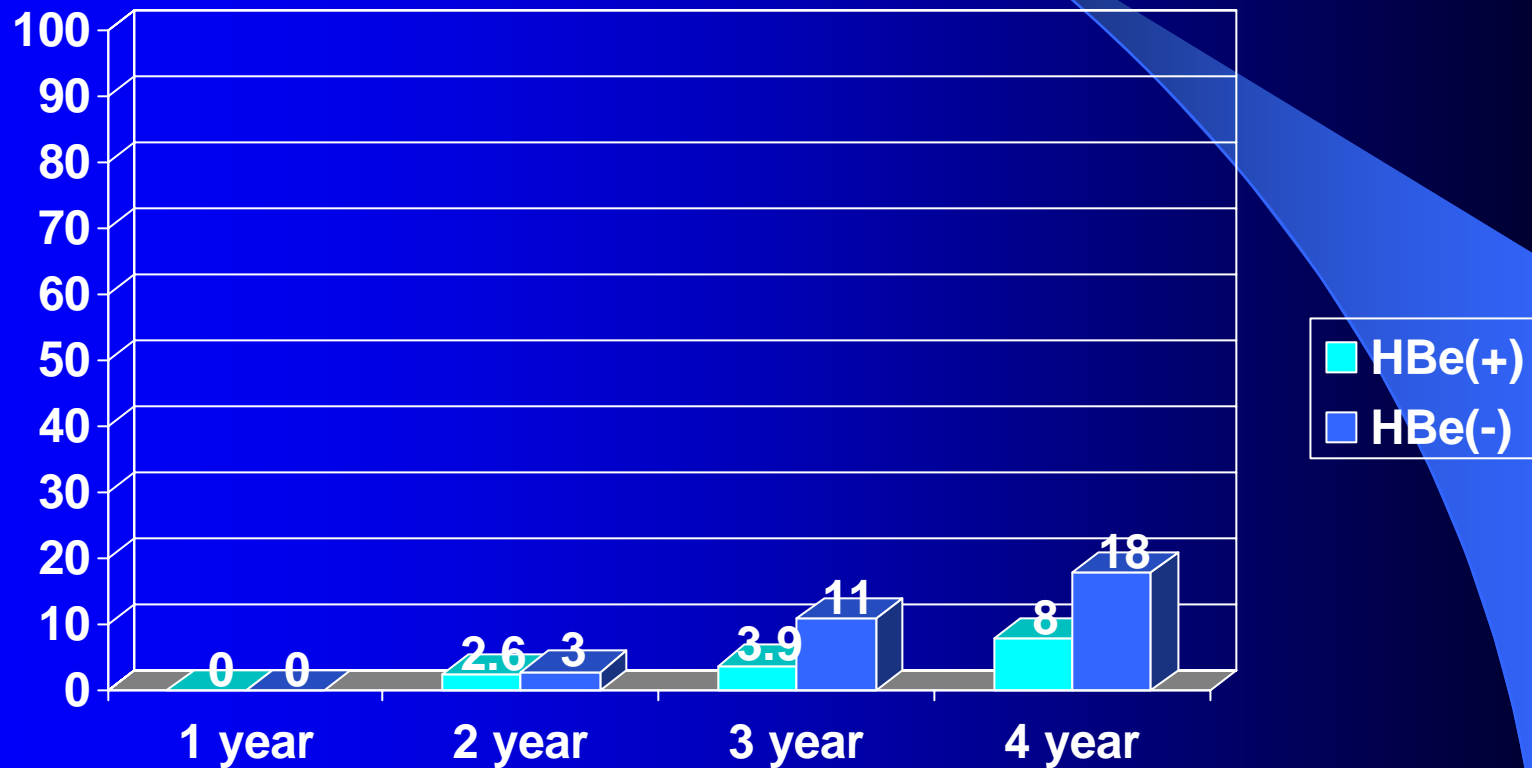


# Adefovir x 48 wks in HBe(-)

Hadziyannis S et al. N Engl J Med 2003; 348:800-807

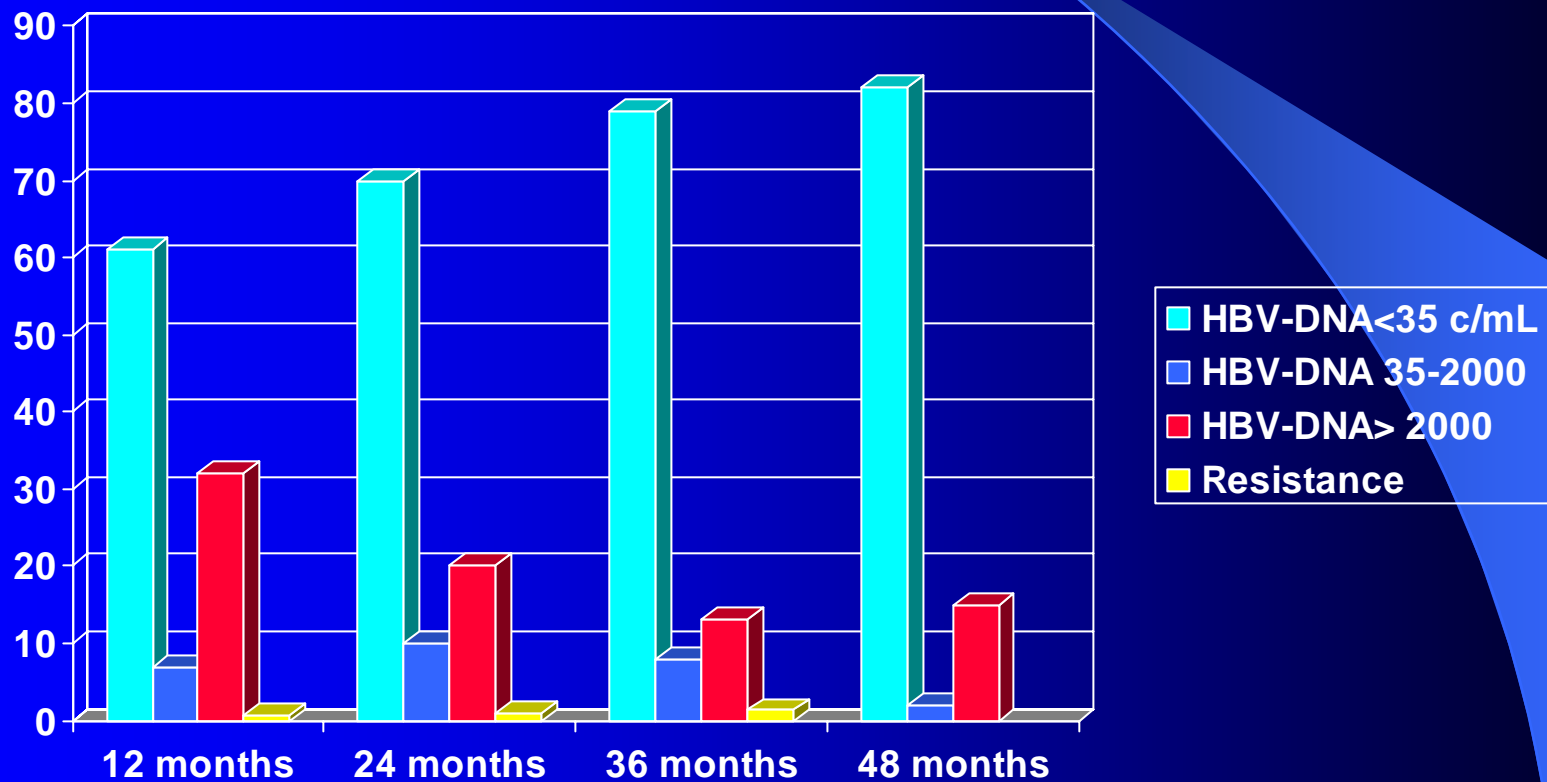


# Adefovir Resistant Mutants (%)



# Adefovir + Lamivudine in Lam-Resistant HBV

Gastroenterology 2007;133:1445-1451

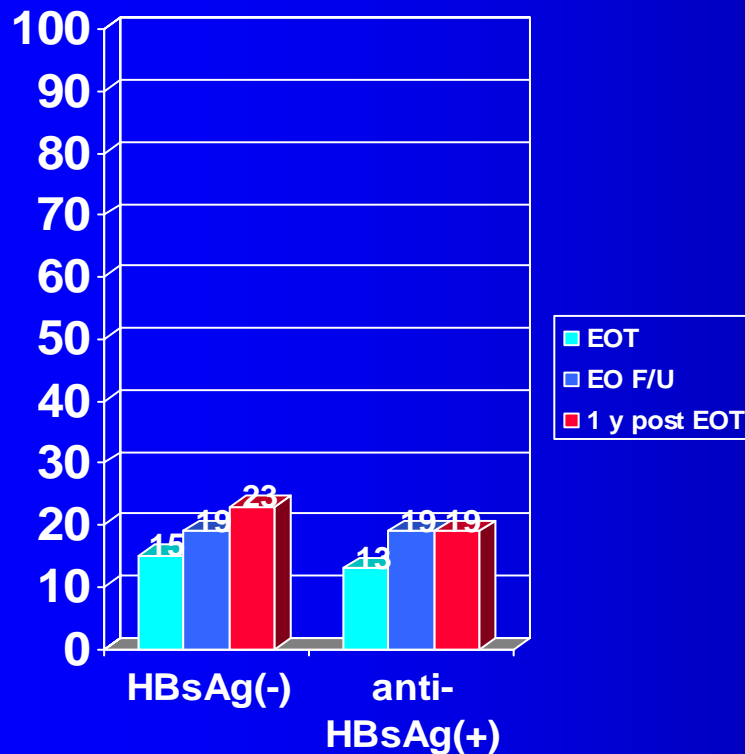


**High rate of HBsAg loss and HBsAg seroconversion in chronic hepatitis B patients on combination therapy with Peginterferon alfa-2a (Pegasys®) and Adefovir (Hepsera®): HBsAg titer predicts HBsAg loss or seroconversion. (Abstr LB 14)**

- **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 Lamivudine
- Resistance to Adefovir is relatively low, but is higher in HBeAg(-) mutant.
- When Adefovir is 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.

The background of the slide features a large, sweeping arc that transitions from a deep blue on the left to a lighter, medium blue on the right. The word "Entecavir" is centered within this arc.

Entecavir

# Entecavir

- Oral deoxyguanine 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 discontinued when Entecavir is initiated.

# Entecavir

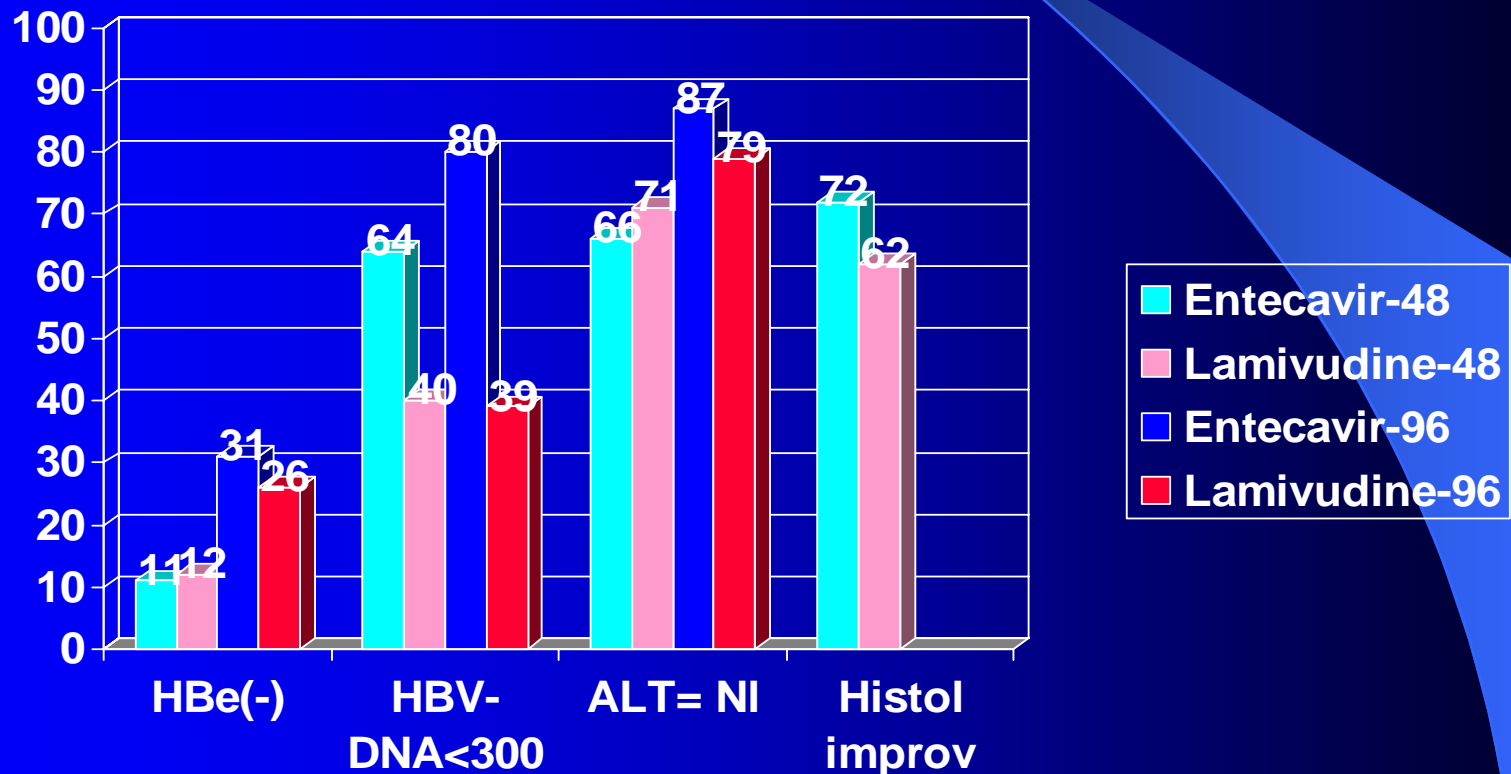
- **Side effects:** headache, fatigue, nausea
- **Viral Response after 1 y therapy:**
  - HBe(+)=82%,
  - HBe(-)=48%
- **Resistance:**
  - YMDD mutant (Lamivudine resistant): 7% @ 1 y, 26% @ 3y, & > 50% @ 5y.
  - In Naïve: 1.2% @ 5 y.
  - Resistance to Lamivudine increases risk of resistance to Entecavir,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

# Adjustment of Adult Entecavir dose by Creatinine Clearance

	Naive	Lam Resistant
$\geq 50$ mL/min	0.5 mg/day	1 mg/day
30-39 mL/min	0.25 mg/day	0.5 mg/day
10-29 mL/min	0.15 mg/day	0.3 mg/day
< 10mL/min, Hemodialysis, Peritoneodialysis	0.05 mg/day	0.1 mg/day

# Entecavir x 48 & 96 wks in HBe(+)

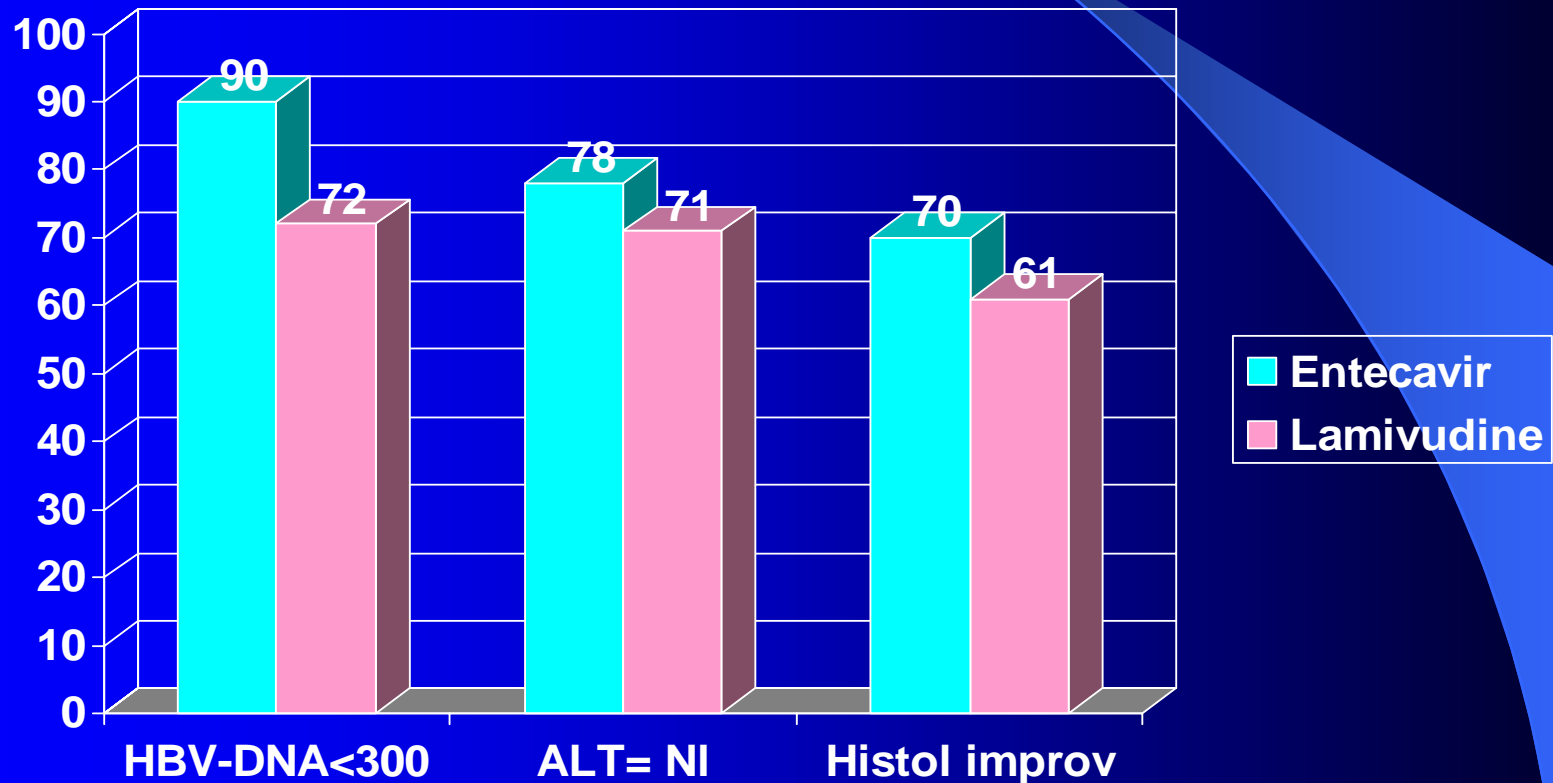
Gastroenterology 2007;133:1437-1444



1 of 354 patients developed Entecavir resistance & 13 had virologic breakthrough

# Entecavir x 48 wks in HBe(-)

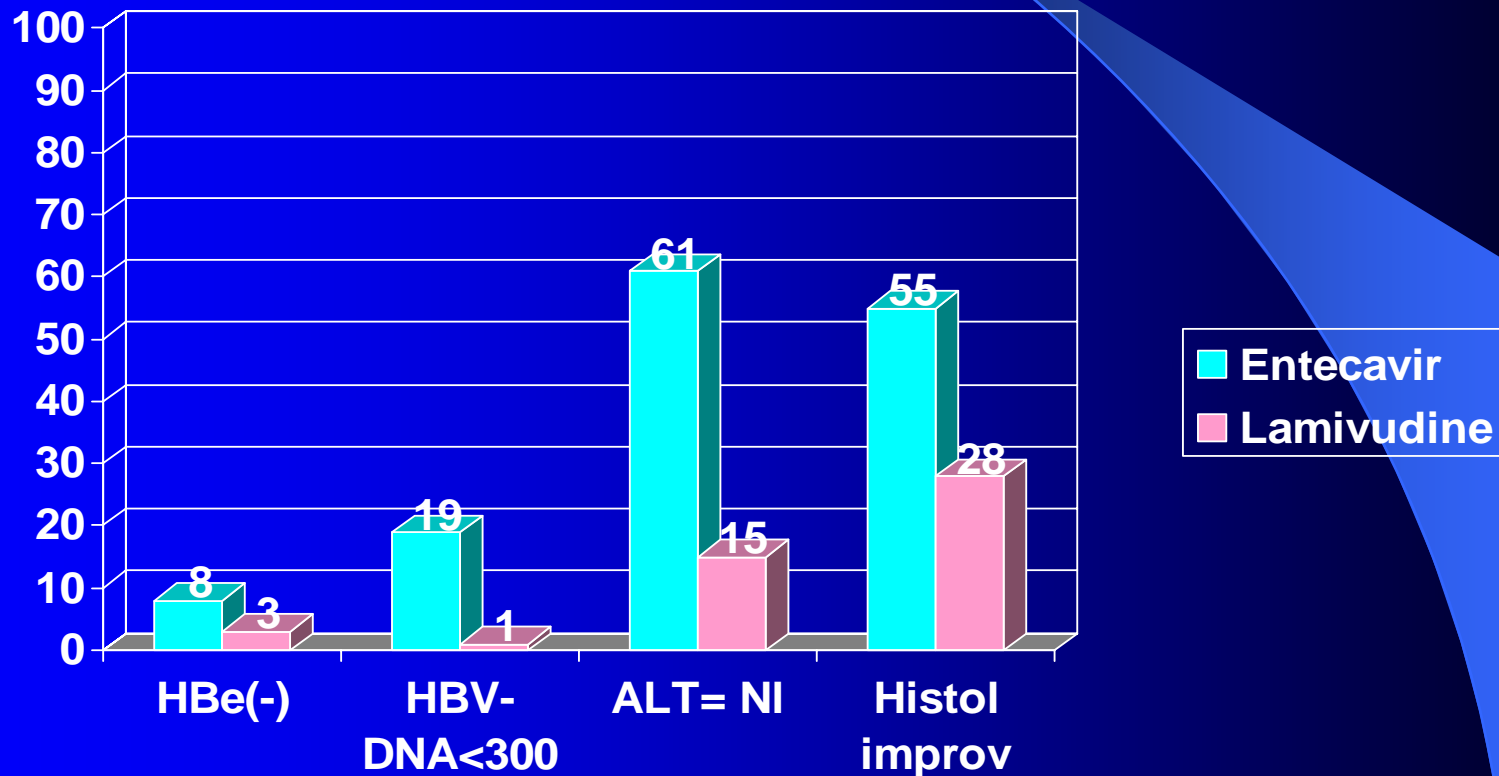
Bristol-Myers Squibb package insert





# Entecavir x 48 wks in YMDD mutant

Bristol-Myers Squibb package insert



# 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

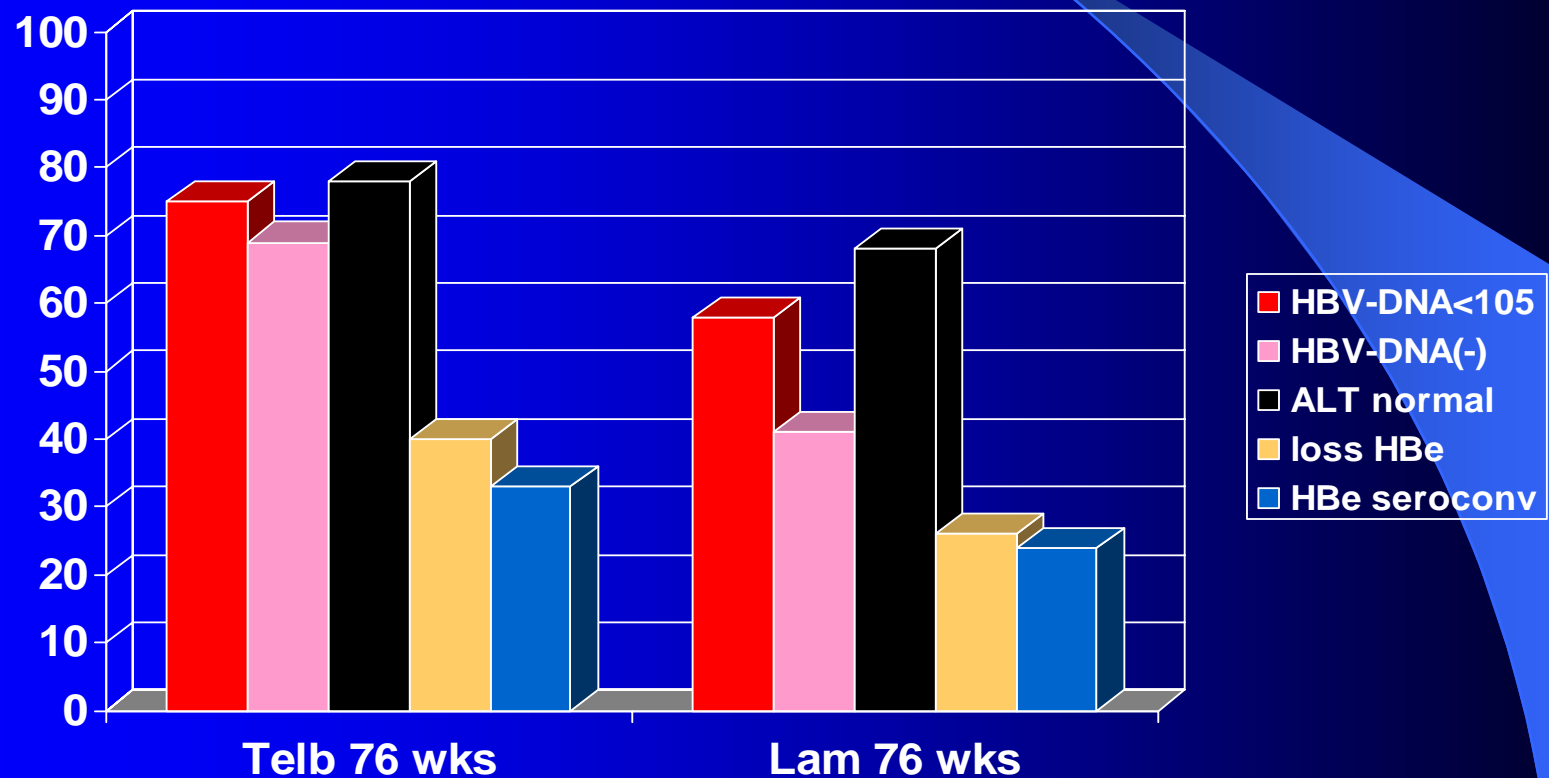
- $\geq 50$  mL/min 600 mg/day
- 30-49 mL/min 400 mg/day
- 10-29 mL/min 200 mg/day
- Hemodialysis 200 mg after each dialysis

# 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
- **1<sup>st</sup> end-point:** HBV-DNA <  $10^5$  + [normal ALT or loss HBeAg]
- **2<sup>nd</sup> 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

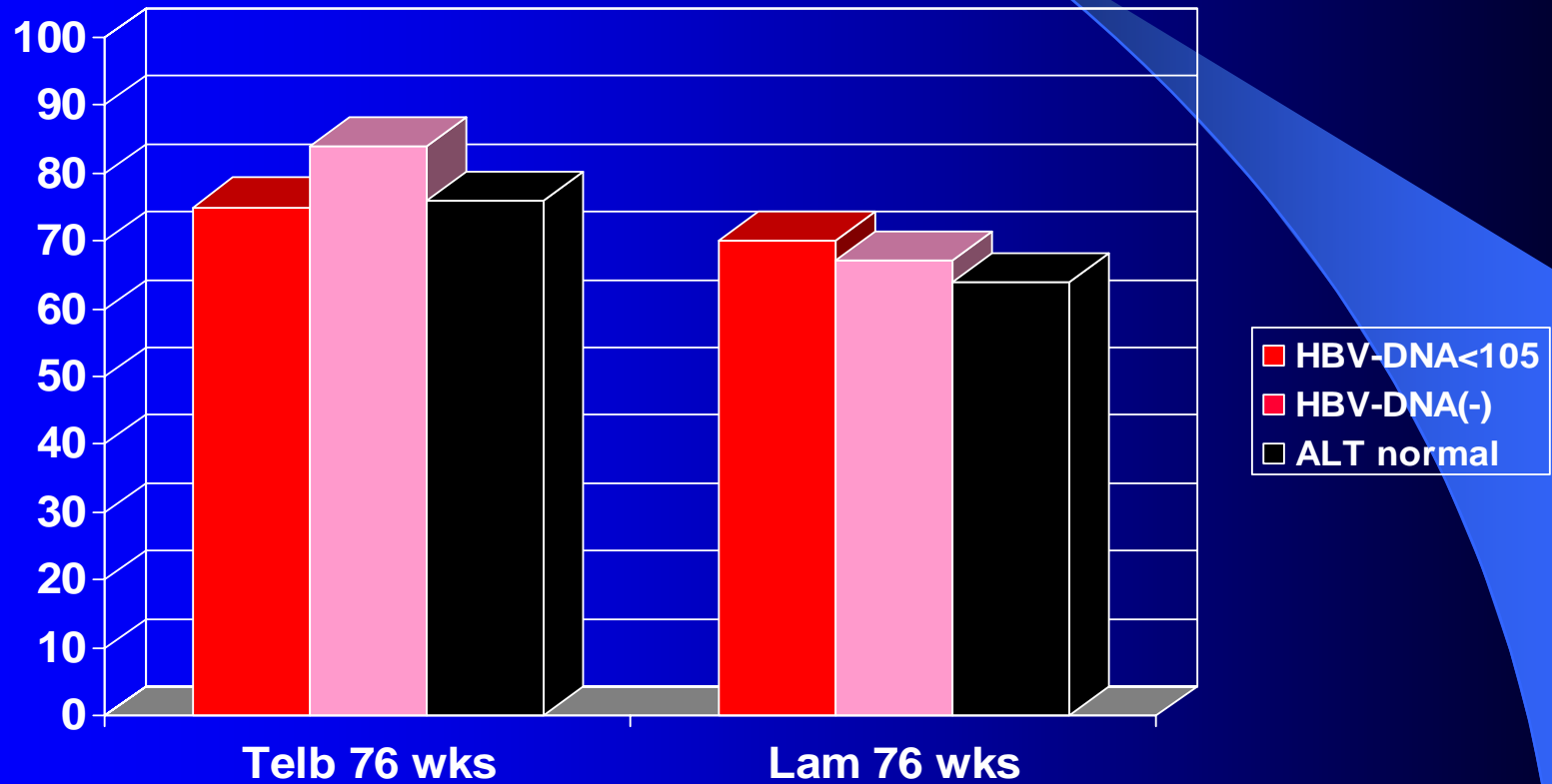
## Telbivudine (LdT) vs Lamivudine in Chronic HBV – Phase III GLOBE Study

### 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

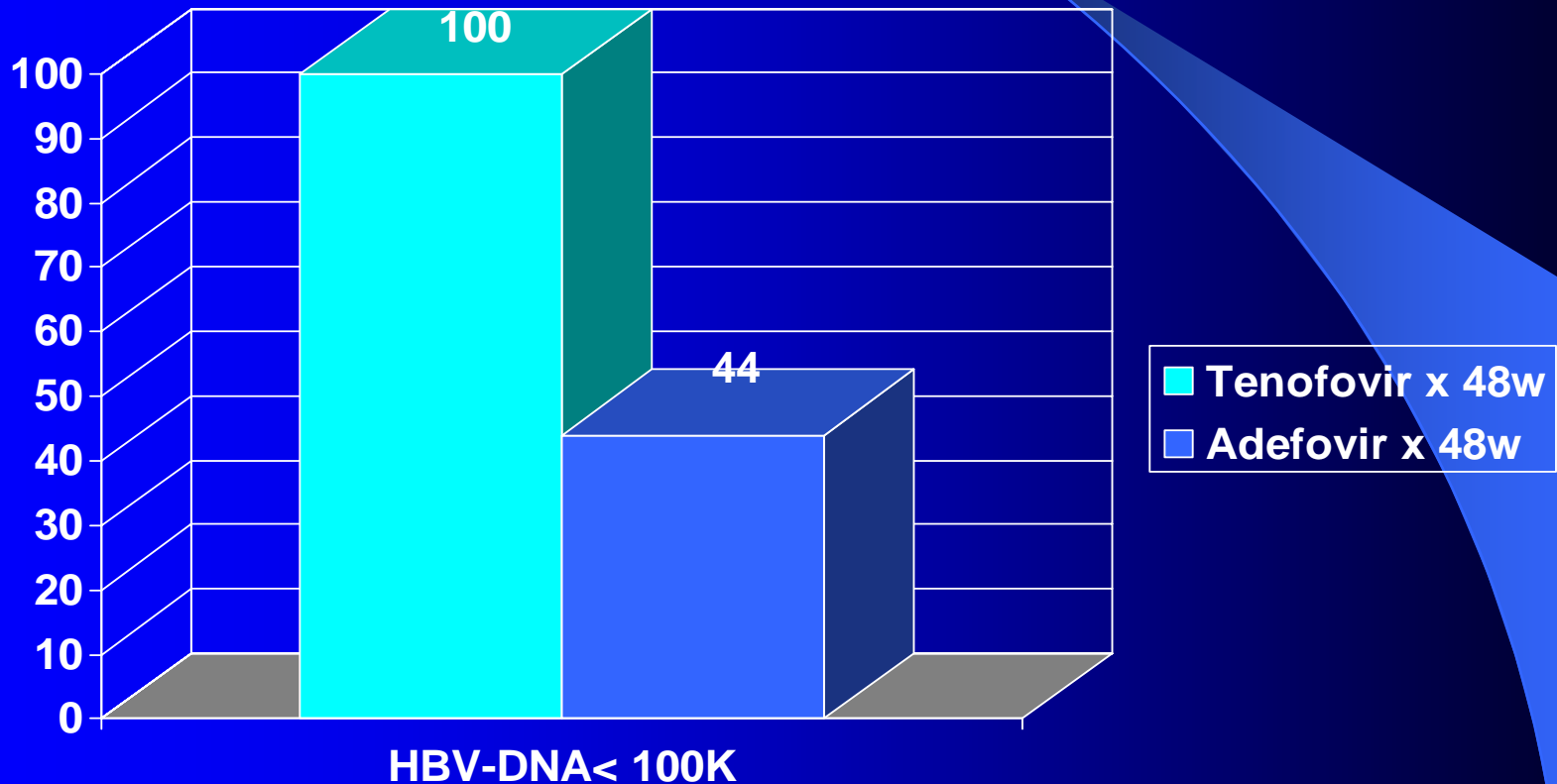
- **log drop HBV-DNA at week 24:**  
Telbivudine = 6.3, Adefovir = 4.97
- **HBV-DNA < 300 copies/mL @ wk 24:**  
Telbivudine = 38.6%, Adefovir = 12.4%
- **Loss of HBeAg:**  
Telbivudine = 16%, Adefovir = 10%
- **Normalization of ALT:**  
No difference.

# 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

von Bommel et al. Hepatology 2004; 40:1421-1425



# Comparison of Entecavir & Tenofovir

Lok A. Hepatology 2010; 52(2):743-747

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

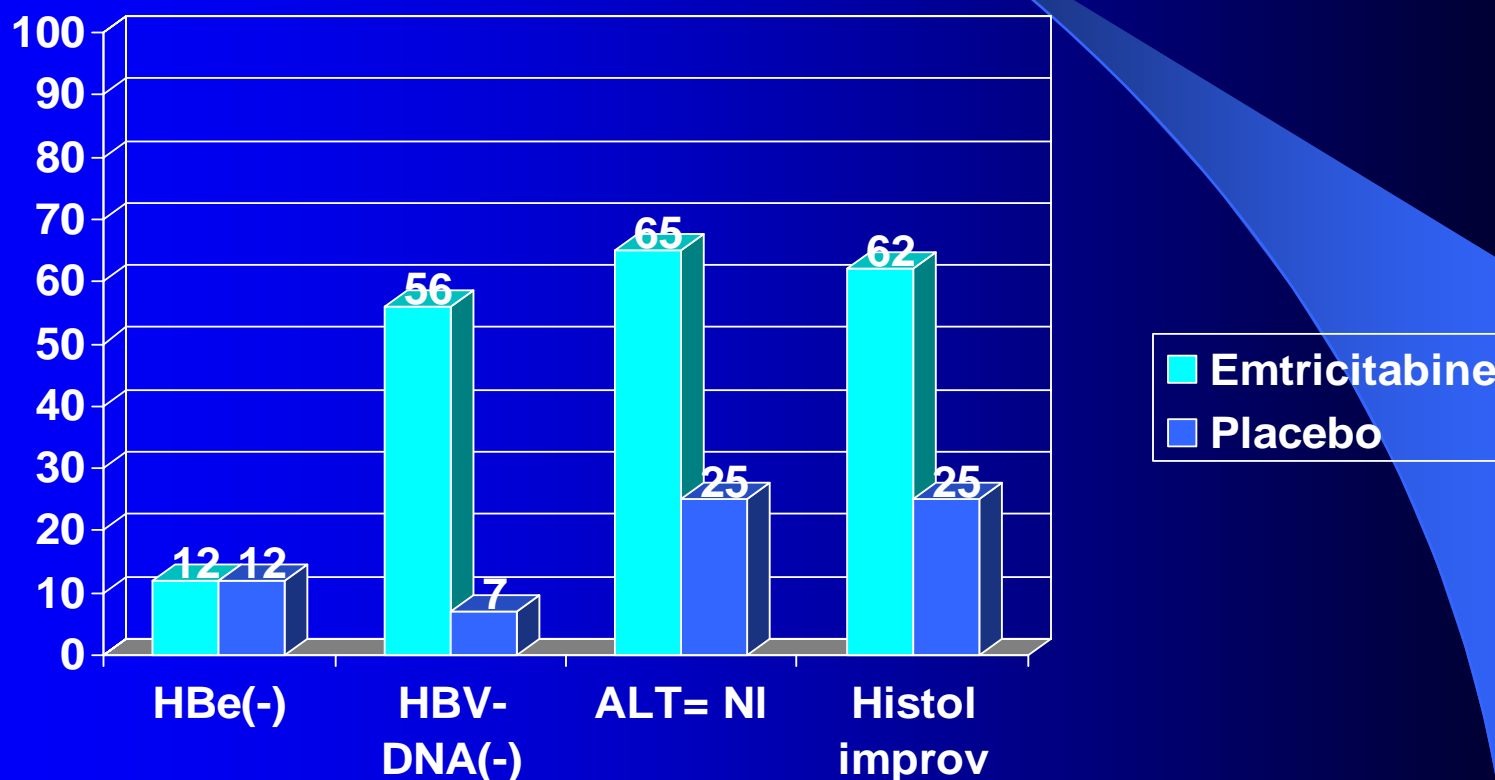
# Other Oral Agents

# 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

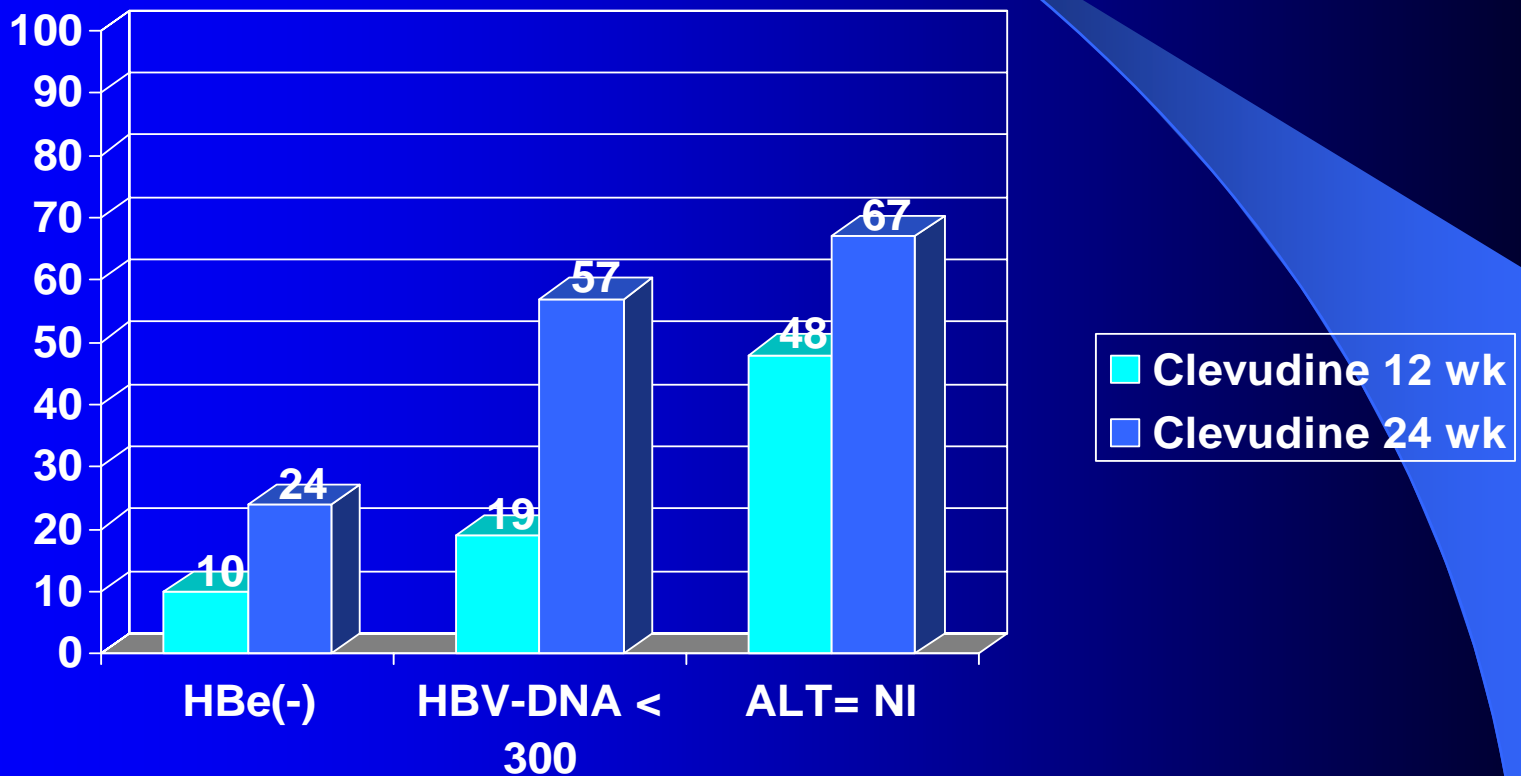


# Clevudine

- 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(+)

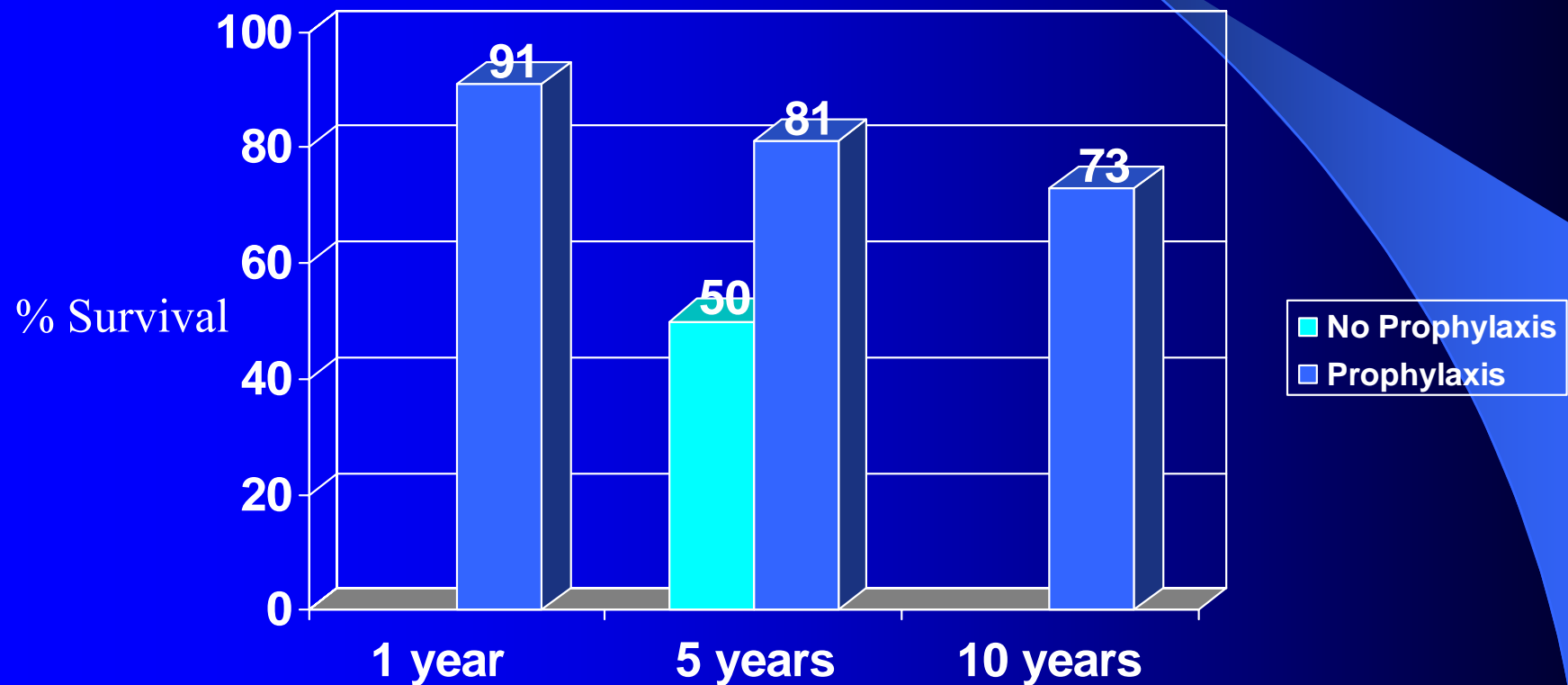


# HBV prevention Post-OLTx

HBsAg(+) Recipient

# Benefits of HBIG Prophylaxis

## HBsAg(+) Recipients



# 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.



# UofL Protocol: HBsAg (+) Liver Transplant Recipient

Recipient's viral load	Anhepatic Phase	First week	Thereafter	Monitoring
HBV-DNA > 2000 IU/mL	HBIG 10000 IU, IV	HBIG 10000 IU, qd IV, x 6 days  Adefovir+Lamivudine, or Entecavir, or Tenofovir, <b><u>for life</u></b>	HBIG 936 IU (3 mL Nabi-HB), IM on day 7, and q month for life  Adefovir+Lamivudine, or Entecavir, or Tenofovir <b><u>for life</u></b>	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
HBV-DNA ≤ 2000 IU/mL	HBIG 936 IU (3 mL Nabi-HB), IM	HBIG 936 IU (3 mL Nabi-HB), qd IM, x 7 days  Adefovir+Lamivudine, or Entecavir, or Tenofovir, <b><u>for life</u></b>	HBIG 936 IU (3mL Nabi-HB), q month IM. Immunize after 1 year, and if anti-HBs response > 100 IU/L, d/c HBIG  Adefovir+Lamivudine, or Entecavir, or Tenofovir <b><u>for life</u></b>	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life

**Anti-HBc(+) organ  
given to HBsAg(-) Recipients**

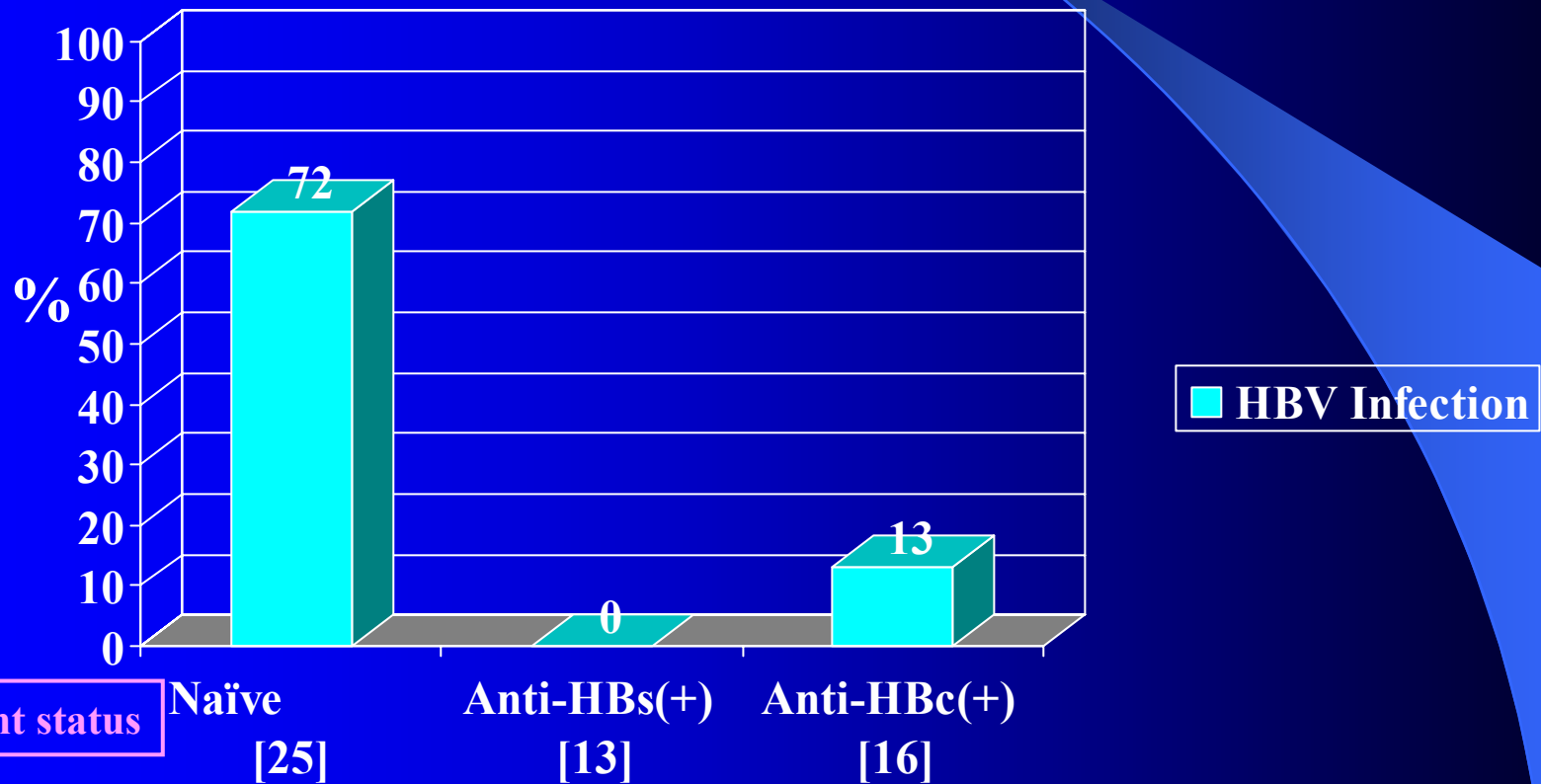
# Anti-HBc(+) organ donors

## 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



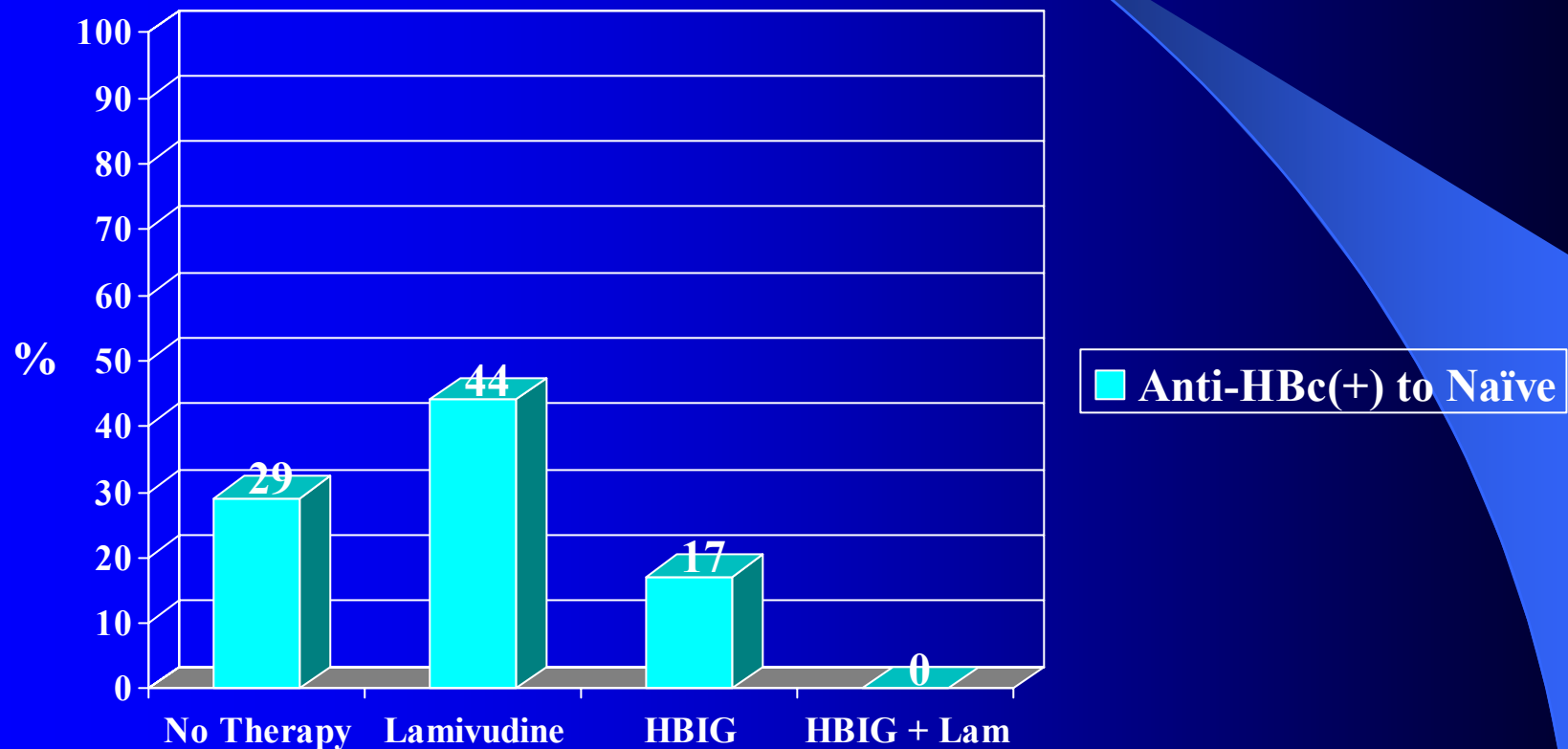
No HBV prophylaxis was given

# Anti-HBc(+) Donor To Naïve Recipient

## Effect of Prophylaxis

### UCLA Experience

Ghobrial RM ; Transplant Hepatology CAQ Course - 2006



# 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.

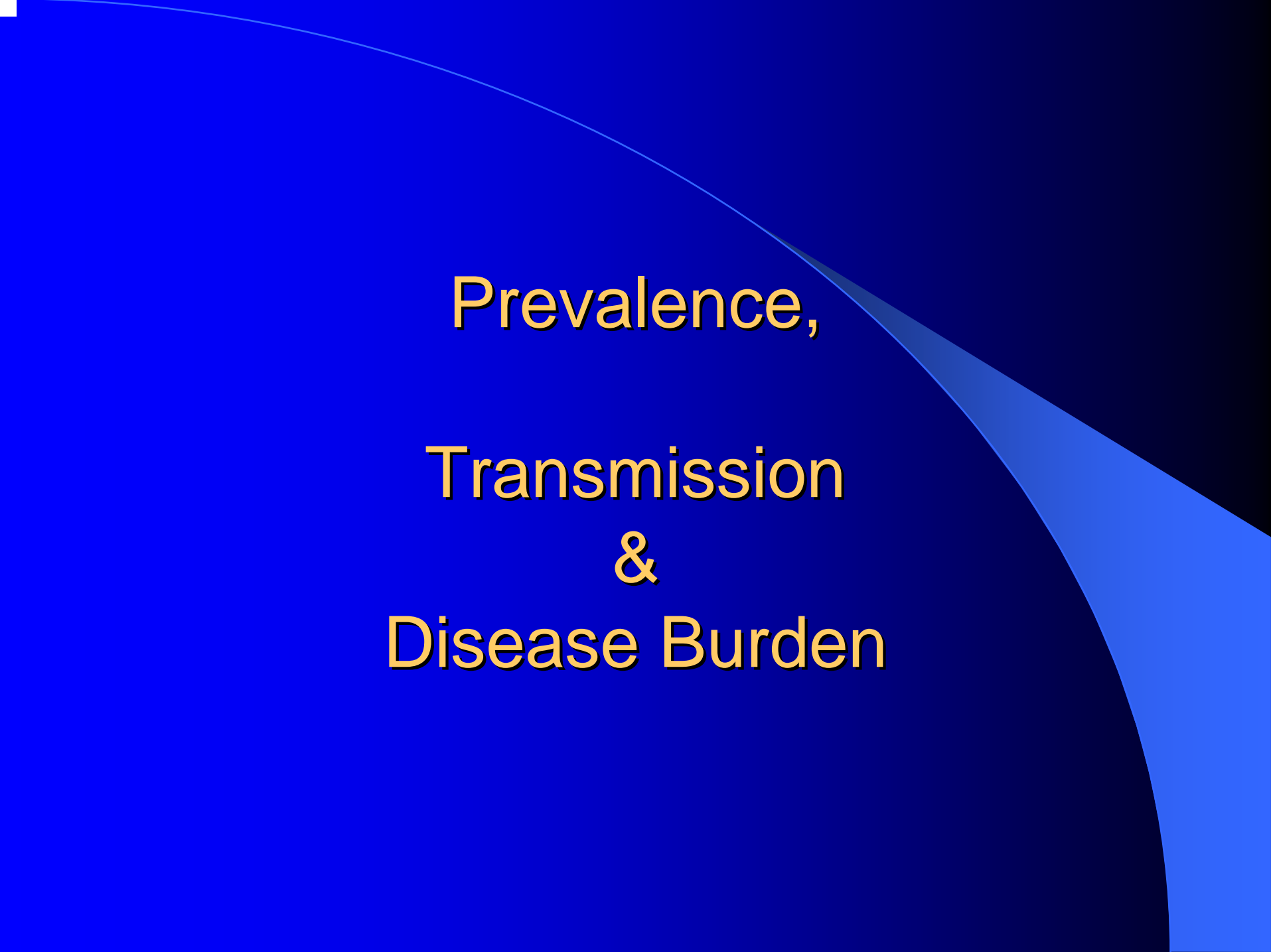
# UofL Protocol: Anti-HBc(+) organ given to HBsAg(-) Recipient

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

# Hepatitis C

# Hepatitis C

- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus.
- Six genotypes and > 100 subtypes.
- 170 million infected worldwide;
- 4 million in USA (1.8%); 38,000 new infections/year.

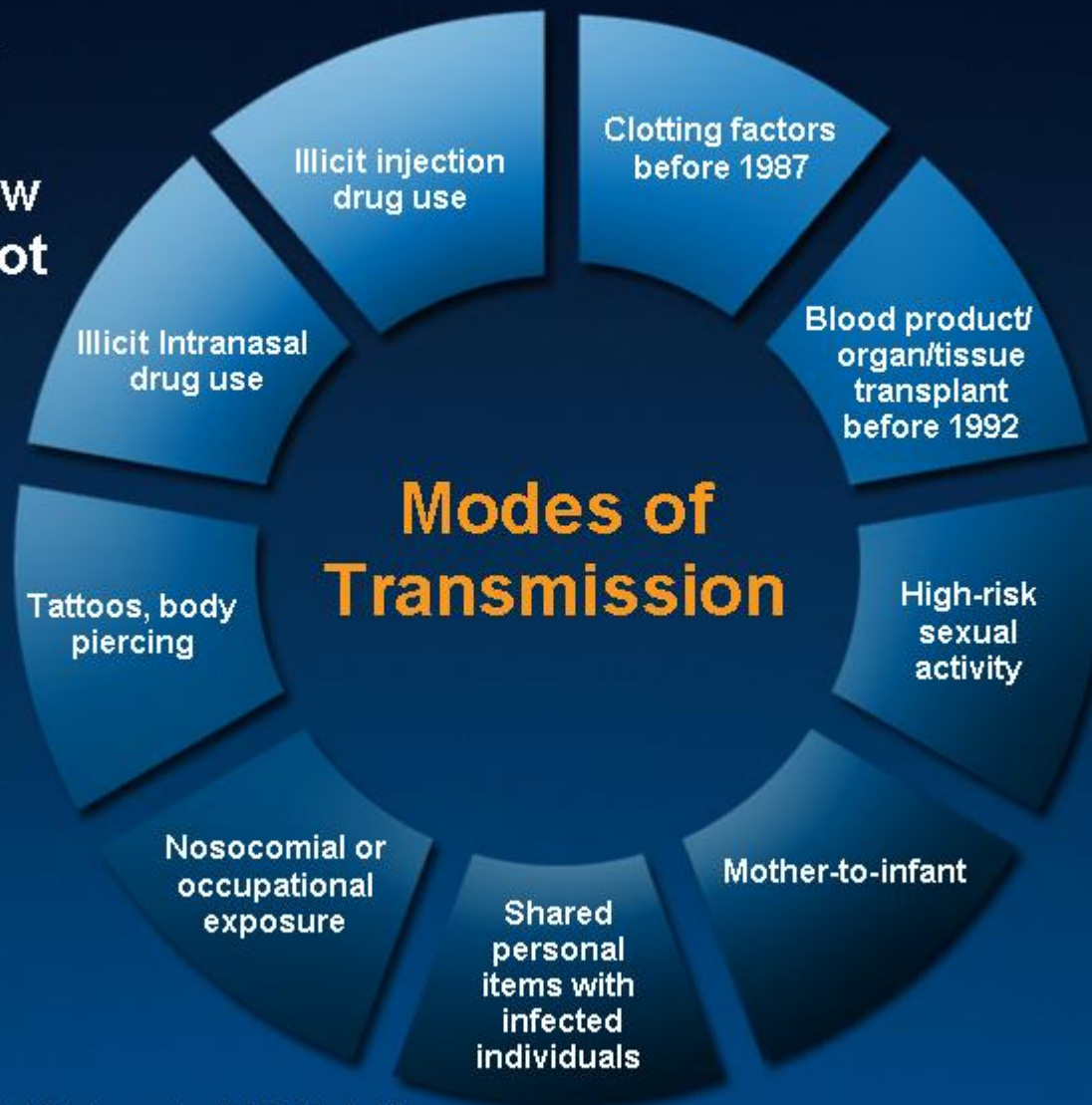


# Prevalence, Transmission & Disease Burden



# Transmission of HCV

**~ 30% of  
patients  
do not know  
how they got  
HCV**



# Hepatitis C Disease Burden: US

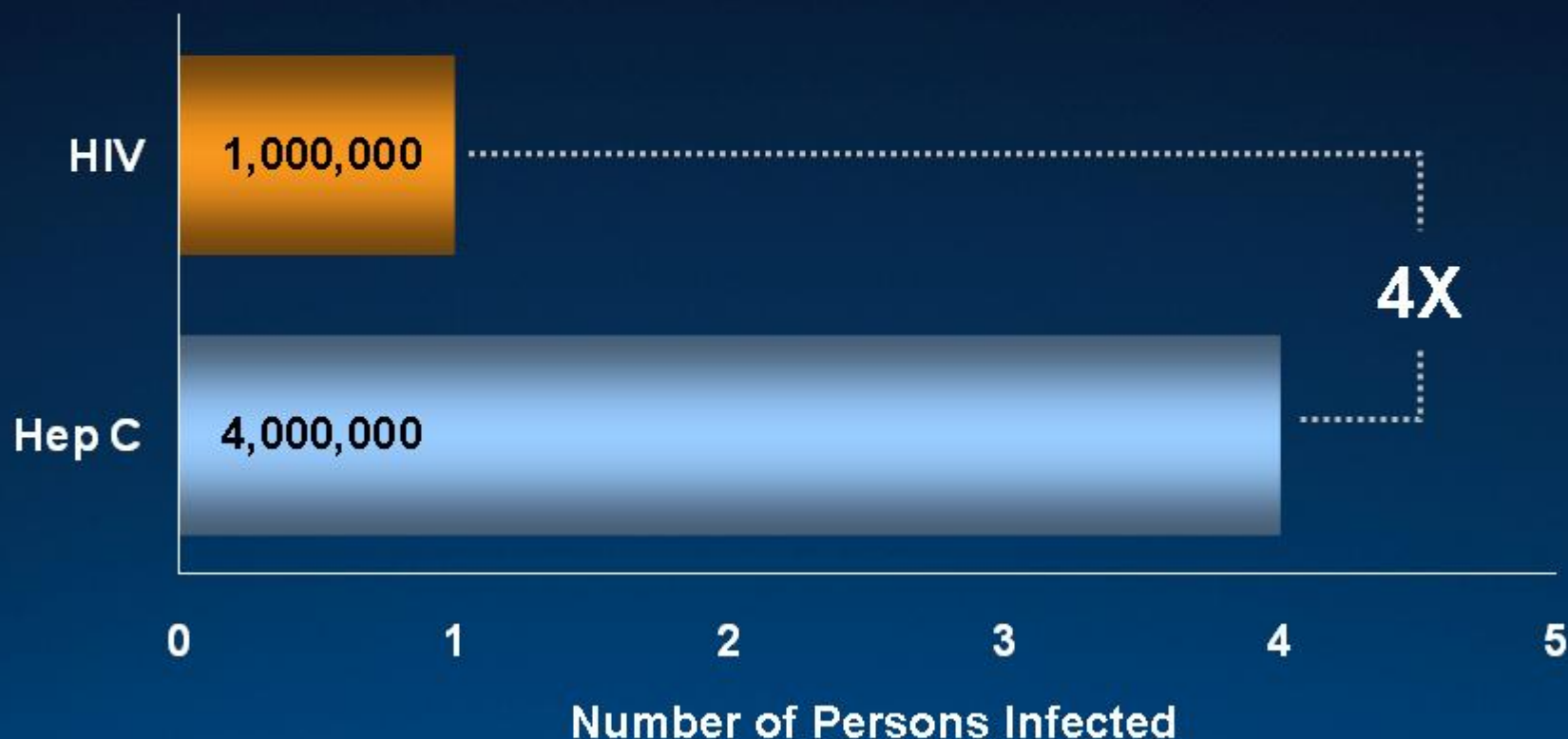
- Hepatitis C is the most common chronic blood-borne viral infection in the US<sup>1</sup>
  - ~ 1/2 of cirrhotic patients<sup>2</sup>
  - ~ 1/3 of HCC patients<sup>3</sup>
  - #1 reason for liver transplants<sup>4</sup>
  - #1 cause of death in HIV patients<sup>5,6</sup>

**It is estimated that 4 million Americans are infected with HCV<sup>7</sup>**

1. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 2. NDDIC, 2006. Available at <http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc/>; 3. NIH. *NIH Consensus State Sci Statements*. 2002;19:1-46; 4. CDC Hepatitis Fact Sheet. <http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm>. Updated December 8, 2006; 5. Bica I et al. *Clin Infect Dis*. 2001;32:492-497; 6. Salmon-Ceron D et al. *J Hepatol* 2005;42:700-805; 7. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

# Prevalence of Hepatitis C

- Hepatitis C is 4 times more prevalent than HIV<sup>1,2</sup>

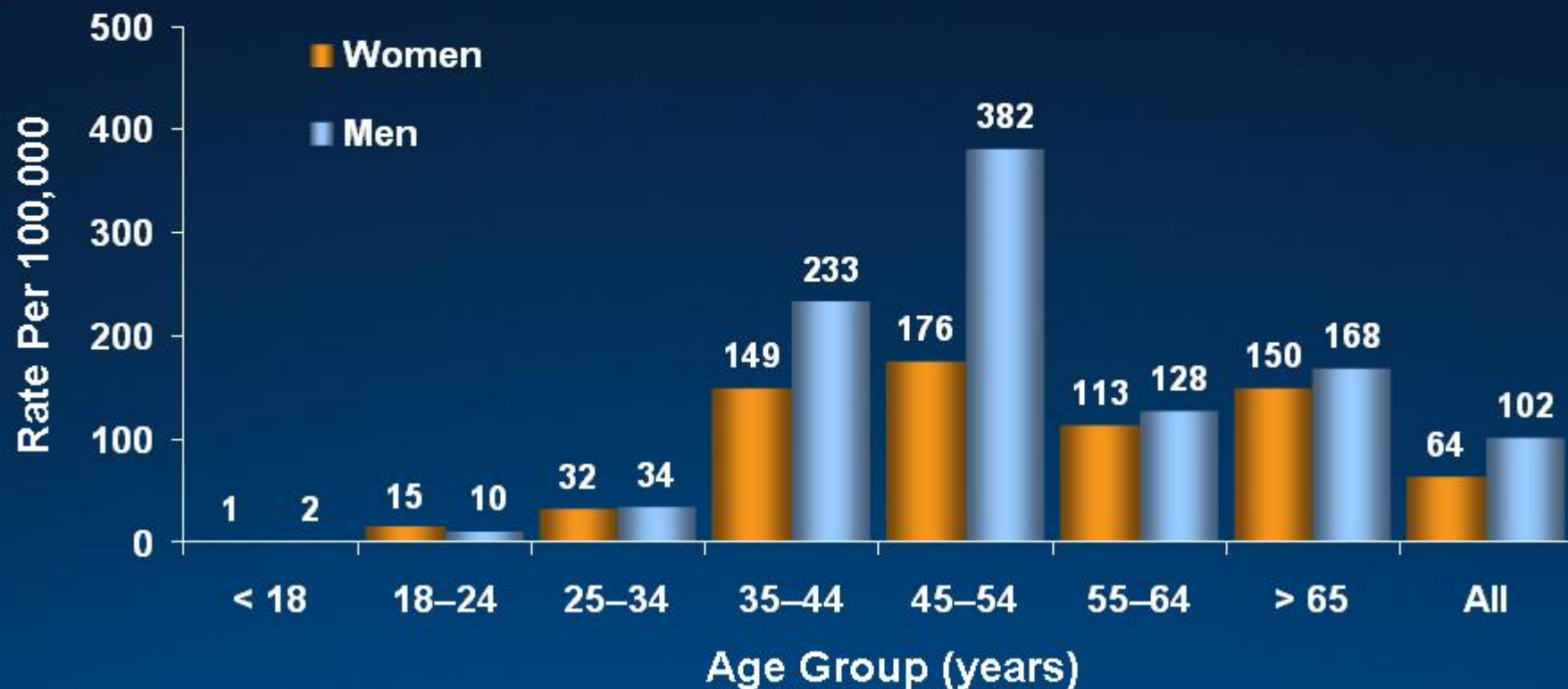


1. NIAID HIV/AIDS fact sheet, 2007. Available at: [www.niaid.nih.gov/factsheets/hivinf.htm](http://www.niaid.nih.gov/factsheets/hivinf.htm); 2. Edlin B, et al. Presented at AASLD 2005, November 11-15, 2005; San Francisco, CA. Oral Presentation #44.



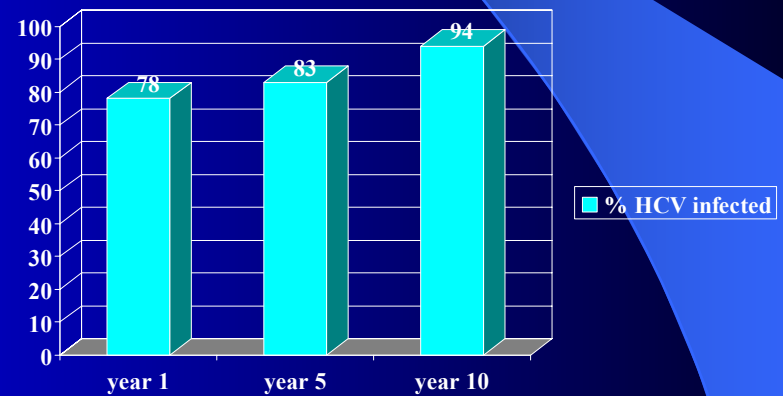
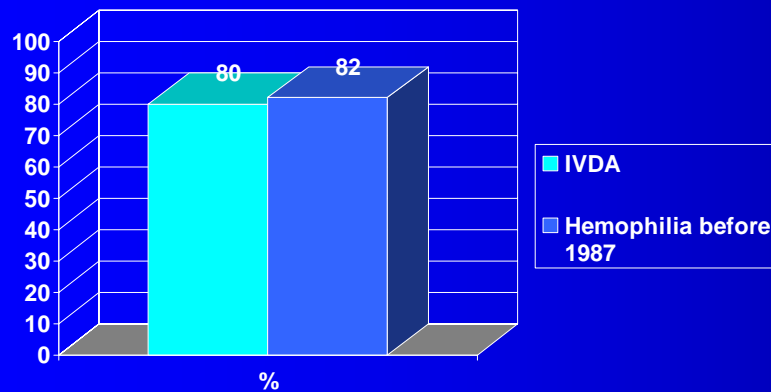
# Prevalence of Hepatitis C by Age and Sex

Retrospective review of claims from 1997–1999 in US  
Health Plan with 3.9 million members

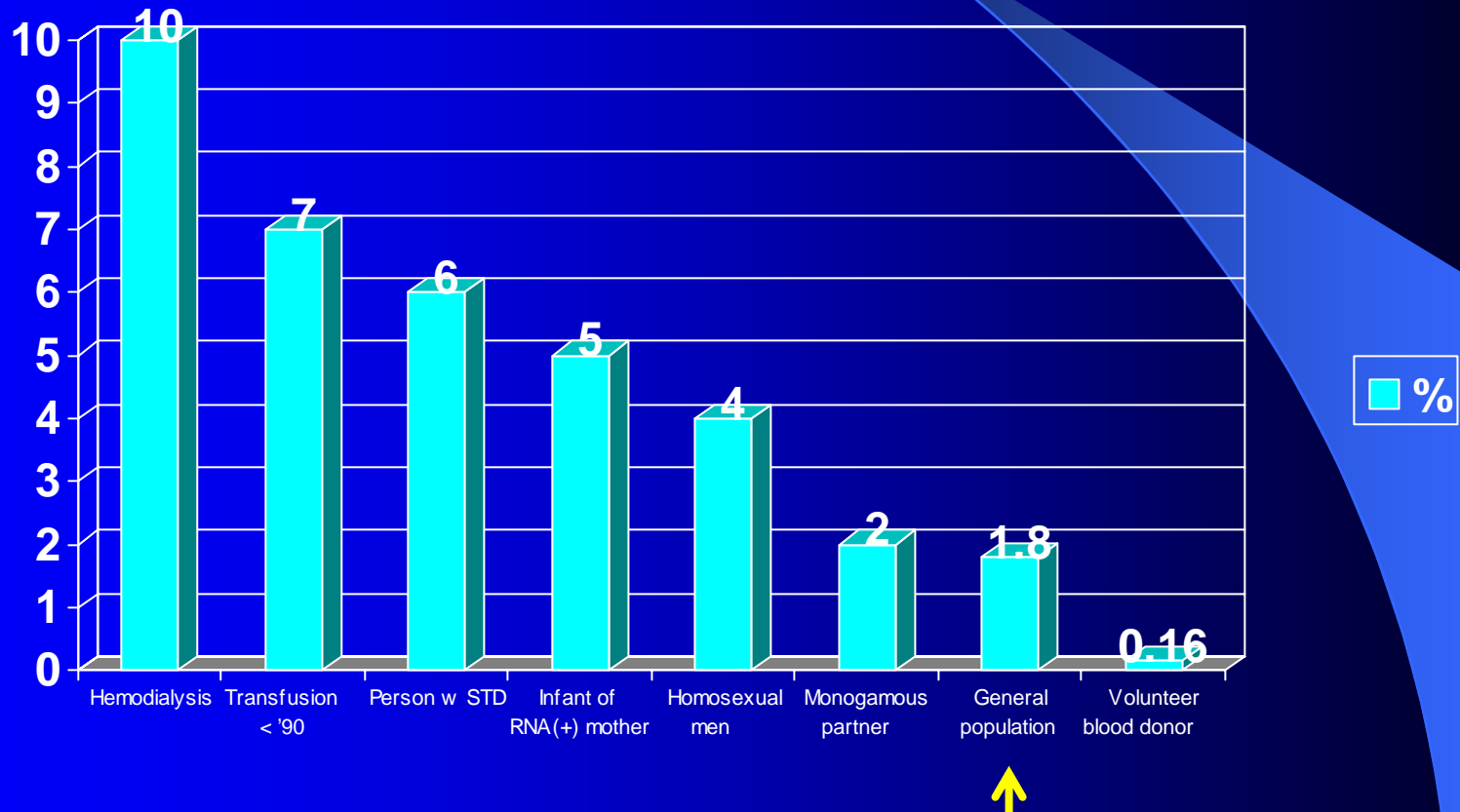


# Extremely High HCV Prevalence

## Risk of HCV in IVDA



# HCV Prevalence in Other Groups



# HCV Prevalence Hemodialysis Patients

● Egypt	general= 18.1%	HD= 80%
● Moldavia	4.9%	75%
● Bulgaria	1.1%	66%
● Saudi Arabia	1.8%	57%
● Turkey	1.5%	31%
● Italy	0.5%	22%
● France	1.1%	16%
● Belgium	0.9%	9%
● <b>USA</b>	<b>1.8%</b>	<b>9%</b>
● Netherlands	0.1%	3%

# HCV Transmission Dialysis Unit

- Sharing medications (heparin)
- Poor hand washing / not changing gloves
- Reuse of dialyzer after disinfection (rare)
- Internal contamination of HD machine (very rare)
- ***Must use “Universal Precautions”;***  
*consider room, machine & staff separation  
and separate dialyzer disinfection-room*



# Source and Risk HCV infection in ESRD

<i>SOURCE</i>	<i>Degree of RISK</i>
Breakdown of “Universal Precautions” in Dialysis Unit	Very High
Contaminated HD equipment	High
Blood Tx before 1992	Moderate
Peritoneal Dialysis	Low
Blood Tx after 1992	Very low
Illicit drug use	As general population

# Vertical Transmission of HCV

(Obstet Gynecol Surv 2006; 61:666-72)

- Risk if mother anti-HCV(+) is approximately 2%;
  - If mother is HCV-RNA (+), risk is 4-5%.
  - Scalp electrodes increase risk of transmission.
- Up to 30% of infected neonates may have acquired HCV “in utero” (Arch Dis Child Fetal Neonatal Ed 2005;90:F156-60)
- In HCV/HIV co-infection the risk is higher (15-18%) but HAART may decrease the risk.
- There is no association between vertical transmission of HCV, gestational age at delivery, nor chorioamnionitis.
- Data are conflicting about duration of ruptured membranes and risk of HCV transmission (increased after 6 h ?)

# Vertical Transmission of HCV Cesarean Section vs Vaginal Delivery

- The “Cochrane Pregnancy and Childbirth Group’s Trial Register”, and the “Cochrane Central Register of Controlled Trials” were analyzed until April 2006.
- No randomised controlled trials were found (Cochrane Database Syst Rev 2006; Oct 18).
- Systematic review of observational studies (subject to biases) or RCT’s are needed.

# Vertical Transmission of HCV

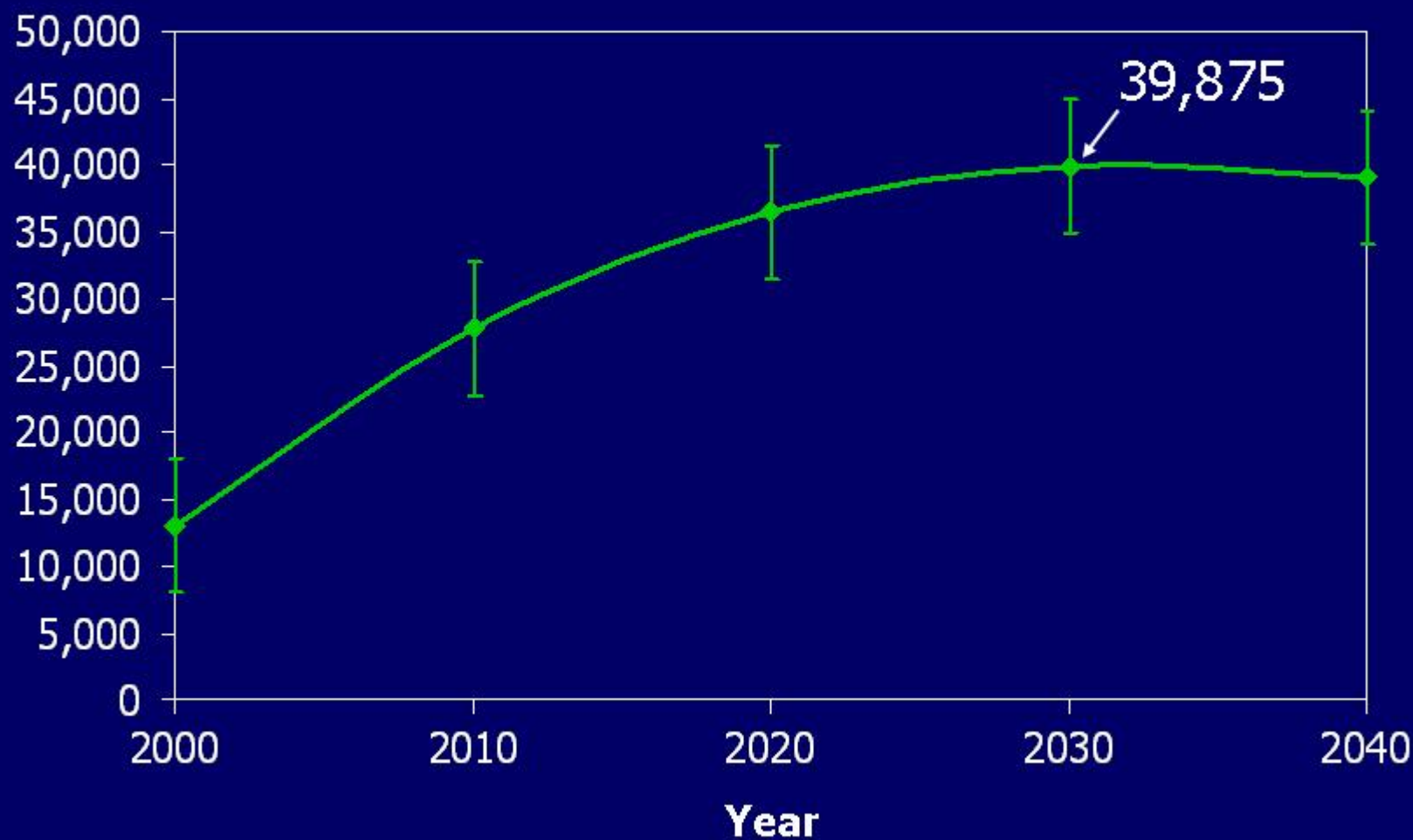
(Obstet Gynecol Surv 2006; 61:666-72)

- **In HCV(+)/HIV(-) mothers:**
  - Route of delivery does not influence vertical transmission.
  - There is no need to discourage breast feeding.
- **In HCV(+)/HIV(+) mothers:**
  - Mode of delivery should be based in HIV status.
  - Breast feeding should be discouraged.

# Measures to Avoid Transmission of HCV

- HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound in order to prevent contact of their blood with others
- Persons should be counseled to stop using illicit drugs. Those who continue to inject drugs should be counseled to avoid reusing or sharing syringes, needles, water, cotton or other paraphernalia; to clean the injection site with a new alcohol swab; and to dispose of syringes and needles after one use in a safe, puncture-proof container
- HCV-infected persons should be advised to not donate blood, body organs, other tissue or semen
- HCV-infected persons should be counseled that the risk of sexual transmission is low, and that the infection itself is not a reason to change sexual practices ( i.e., those in long-term relationships need not start using barrier precautions and others should always practice “safer” sex)

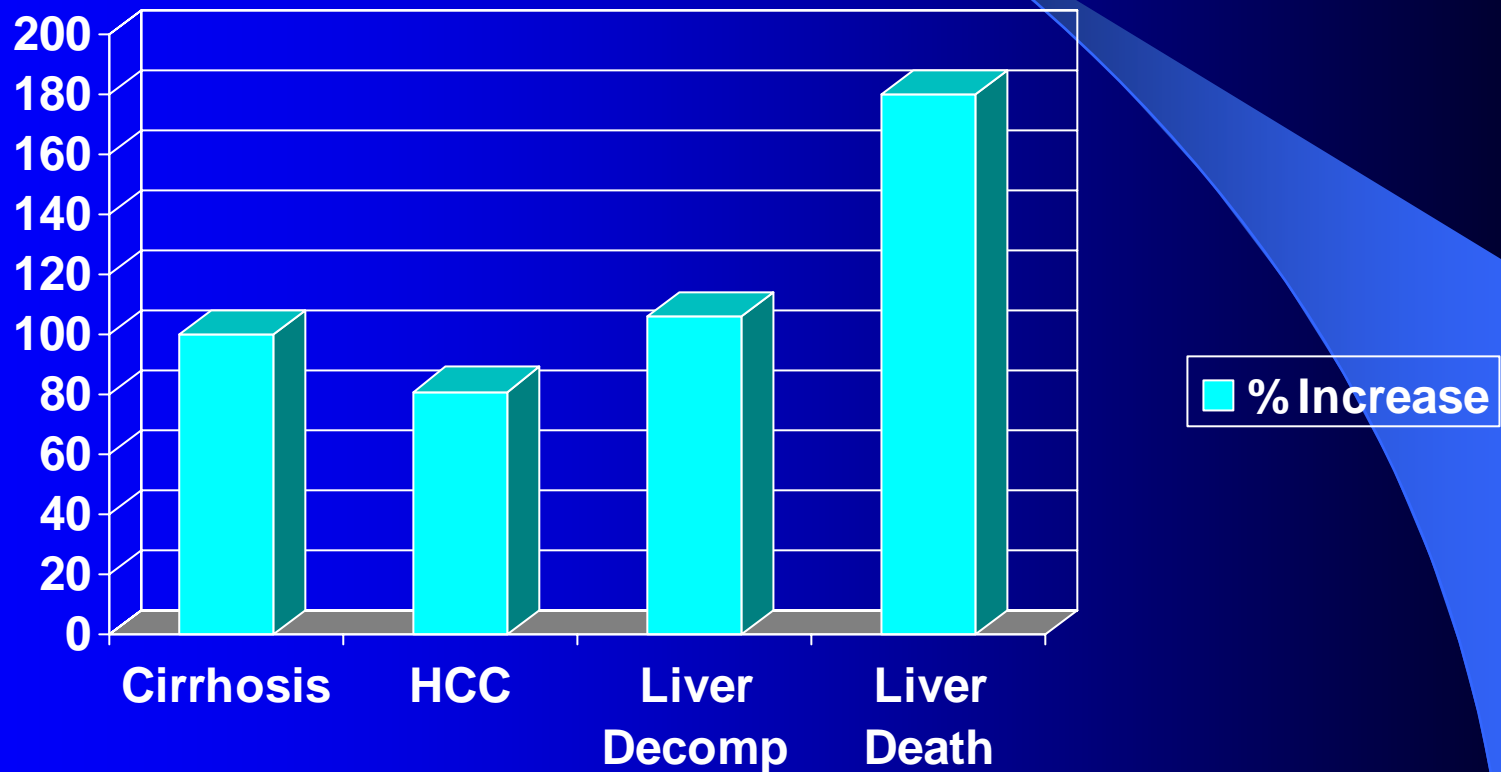
# Projected HCV Mortality



Adapted from Davis et al. *Liver Transpl.* 2003;9:331-338.

# Future Disease Burden: Estimated Increases from 2000-2020

(Davis GL Liver Transpl 2003;9:331-338)



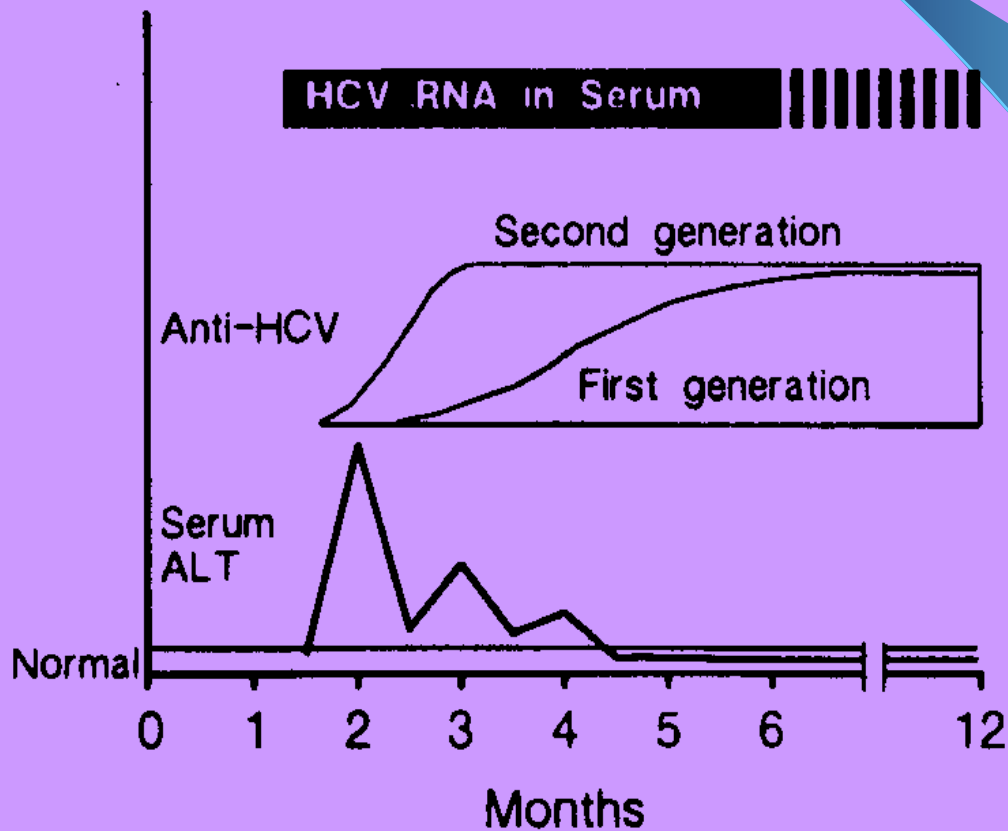
# Acute HCV



# Acute HCV

- **Incubation:** 2-26 weeks (usually 7-8)
- **Symptoms:** in < 30%, mild & last < 1month;
  - Usually: anorexia, arthralgia, myalgia, fatigue;
  - Rarely: jaundice, fever, or skin rash.
  - Extremely rare: FHF.
- **DX:** HCV-RNA (+) days to weeks after acquisition ; anti-HCV (+) in 6 weeks.
- **Spontaneous HCV clearance:** (within 12 weeks in adults)
  - Children < 2 y.o. & young women = 45%;
  - Others = 23%

# Acute Hepatitis C Virus



# Acute HCV Treatment

- If still HCV-RNA(+) 3 months after inoculation, spontaneous clearance is rare.
- Best regimen is unknown:
  - starting 3 months after inoculation, IFN 5 MU QD x 4 wks + 3 MU TIW x 20 wks gave 98% clearance;
  - the mildest & shortest effective therapy is unknown.
- Patients should be abstinent from alcohol (impairs treatment response) and drugs (anti-HCV is not protective against re-infection).

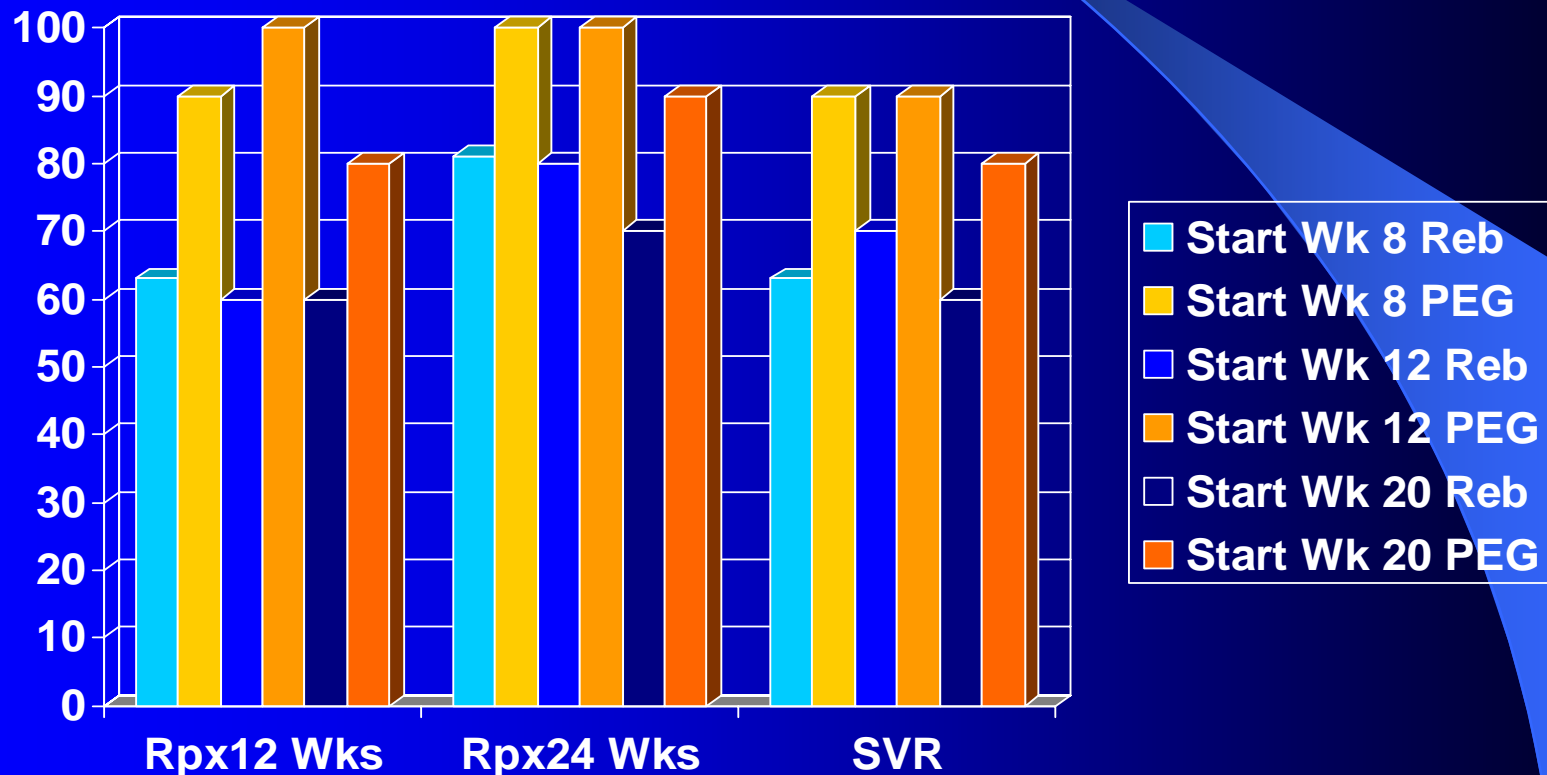
# Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

Kamal et al Abst # 37 AASLD, 2004

- 68 pts with Acute hepatitis C;  
7 had spontaneous clearance.
- Treatment started at (time from acquisition):
  - A) Wk 8 (21),
  - B) Wk 12 (20),
  - C) Wk 20 (20)
- Rebetron vs Pegasys x 12 wks; if HCV-RNA still (+) at wk 12, treated 12 more wks.

# Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

Kamal et al Abst # 37 AASLD, 2004

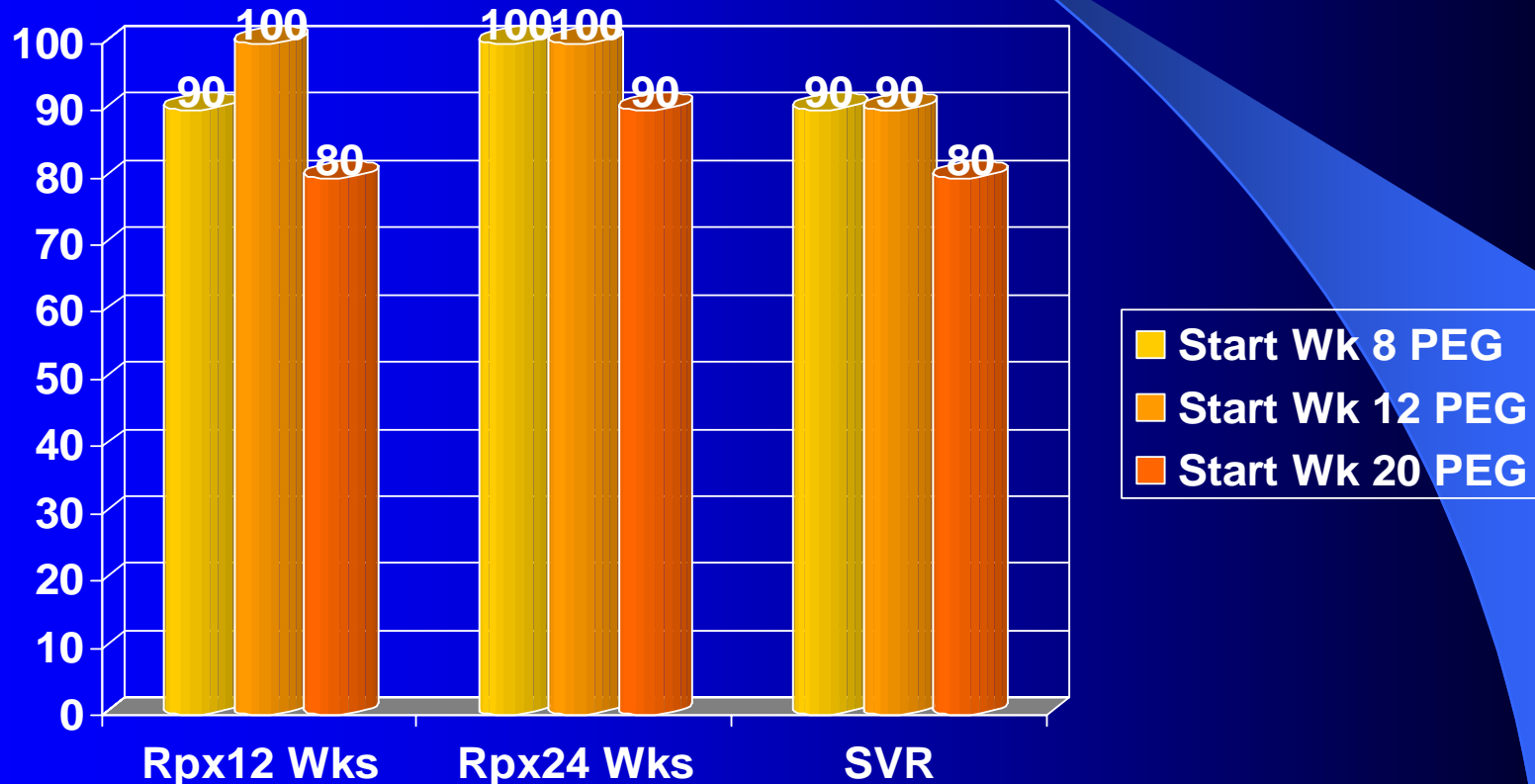


**BLUE = Rebetron**

**ORANGE = Pegasys**

# Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

Kamal et al Abst # 37 AASLD, 2004



# Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

Kamal et al Abst # 37 AASLD, 2004

- Starting therapy at week 12 gave best results with SVR of 90%.
- Pegasys 180 mcg/week monotherapy x 12 weeks, was superior to Rebetron treatment x 12 weeks, in all groups.

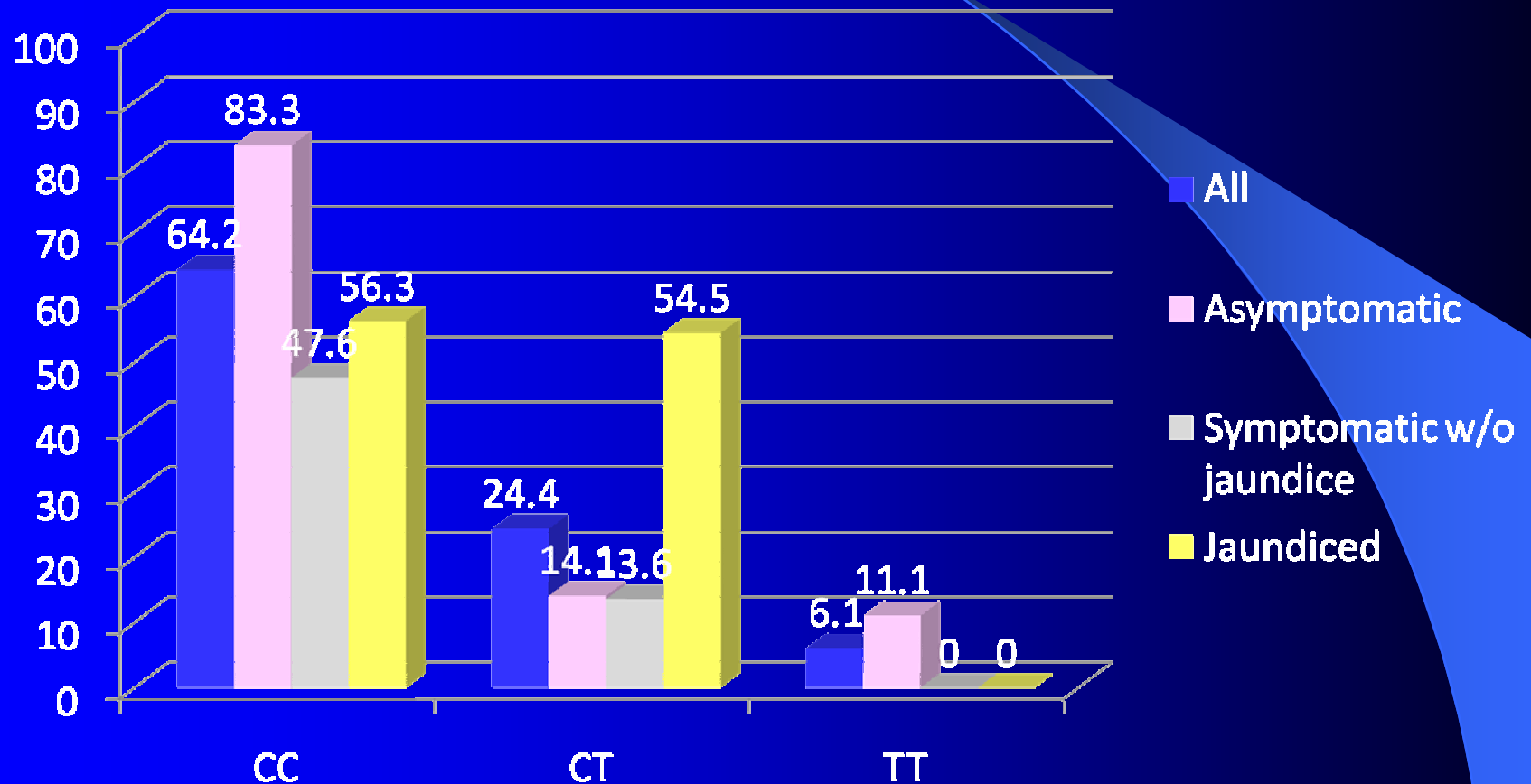
# Practical Approach to Treat Acute HCV

- Wait for 12 weeks from time of acquisition to see if spontaneous clearance occurs.
- Spontaneous clearance is more likely if patient is:
  - IL28B (rs12979860) CC regardless of symptoms or jaundice, or
  - IL28B CT and jaundiced.
- In absence of spontaneous clearance, treat with Peg-IFN + RBV (may improve outcome) for:
  - 3 months if HCV-RNA (-) at 4 weeks;
  - otherwise treat longer.



# Spontaneous HCV Clearance in Acute HCV in 136 Young Women (25+/-4 y/o) by IL28B Genotype

Gastroenterology 2020;139:1586-1592



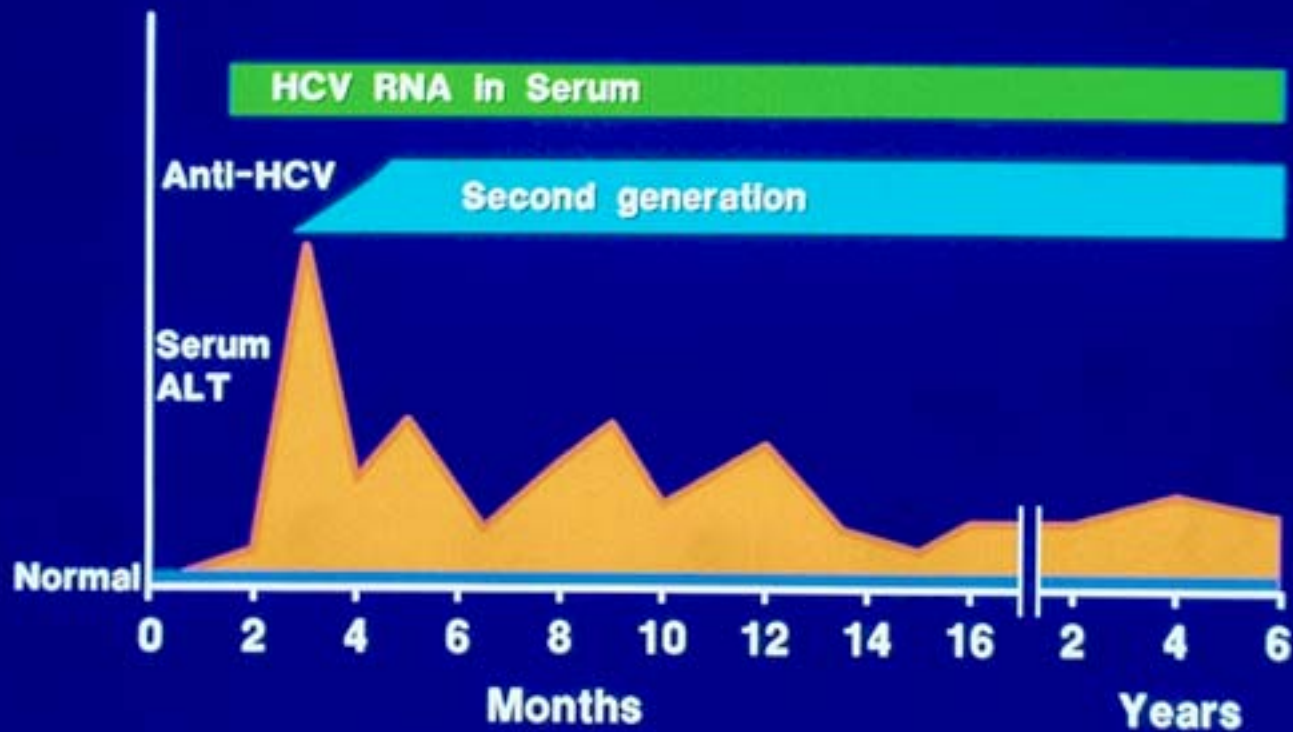
# Chronic HCV

# Chronic HCV

- Most are asymptomatic; 6% symptomatic before diagnosis.
- **Symptoms:** fatigue, RUQ discomfort, anorexia, nausea, itching, arthralgia, myalgia.
- **Extrahepatic:** mixed cryoglobulinemia, purpura, mononeuritis multiplex, PCT, membranoproliferative glomerulonephritis, xerostomy, low-grade B-cell lymphoma, corneal ulcers and idiopathic pulmonary fibrosis, lichen planus.

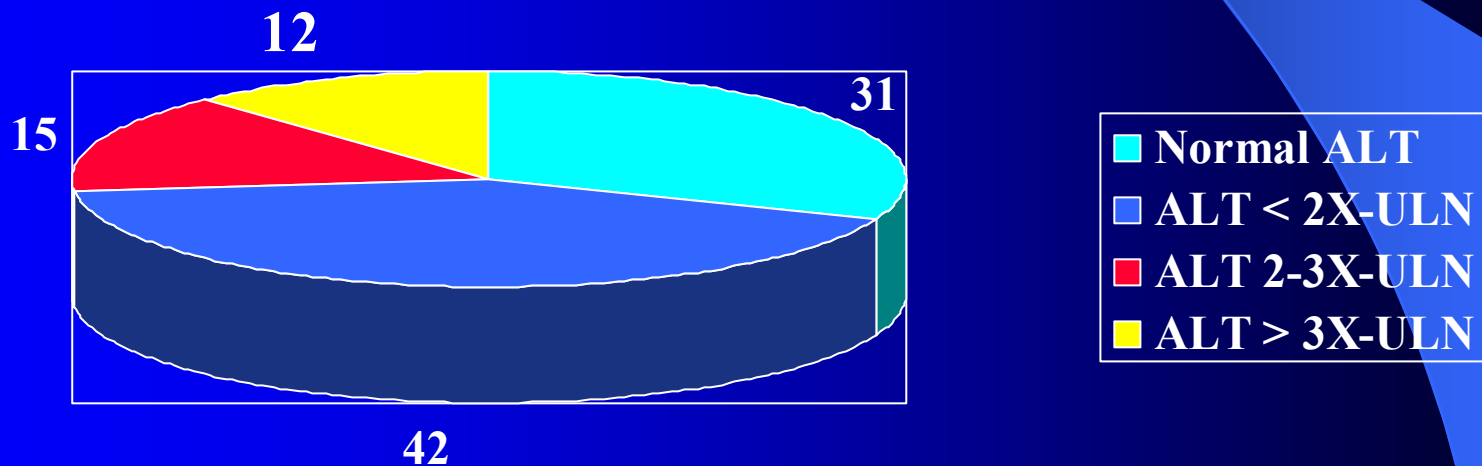
## HEPATITIS C VIRUS

### Chronic Hepatitis



# Pattern of ALT Elevation in Chronic HCV

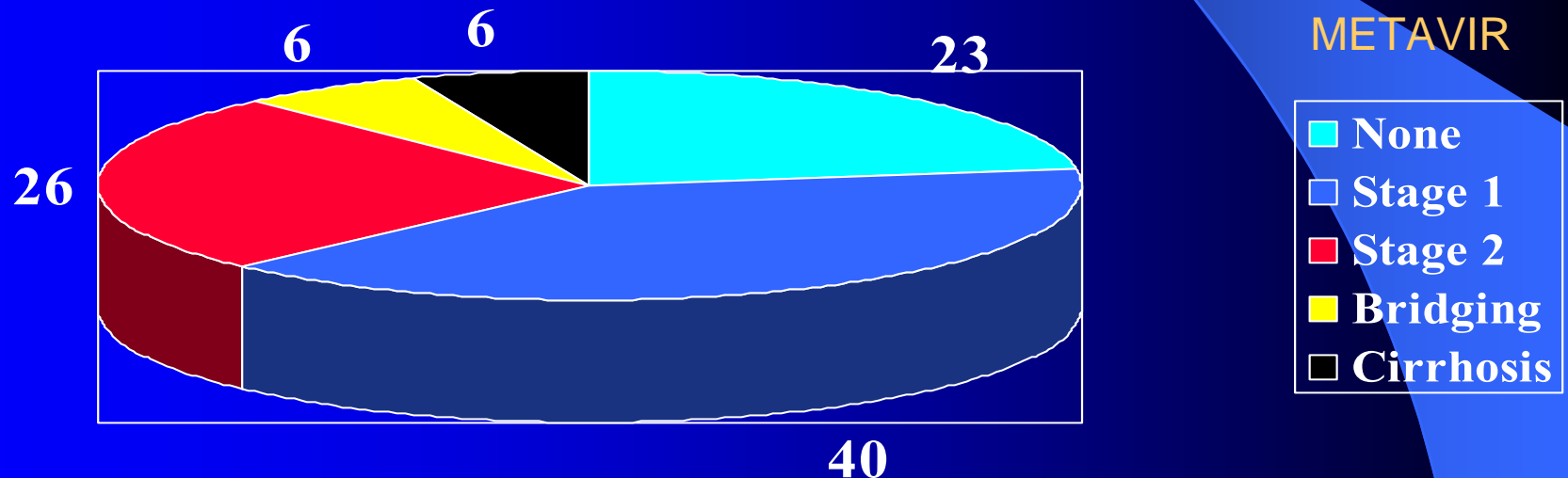
Pattern of ALT Elevation



# Degree of Fibrosis in Chronic HCV With Normal ALT

(Schiffman et al. J Infect Dis. 2000; 182:1595-1601)

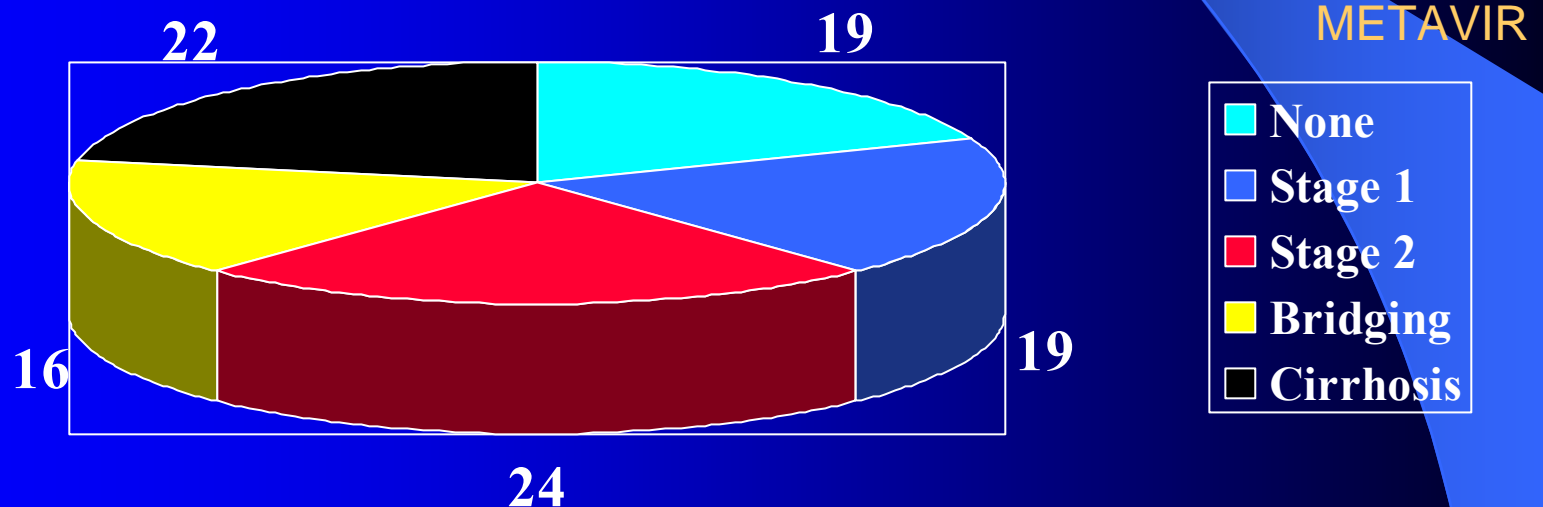
## Degree of Fibrosis



**38% qualify for therapy (METAVIR  $\geq 2$ )**

# Degree of Fibrosis in Chronic HCV With Elevated ALT

Degree of Fibrosis

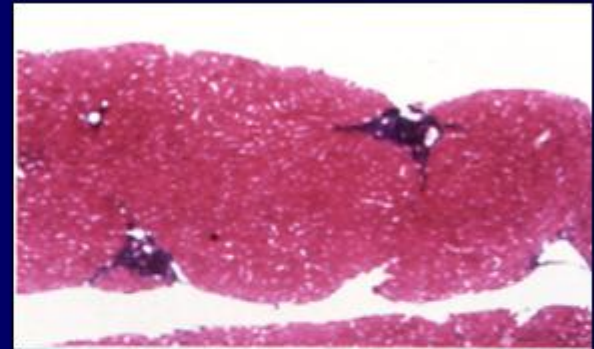


68% qualify for therapy (METAVIR  $\geq 2$ )

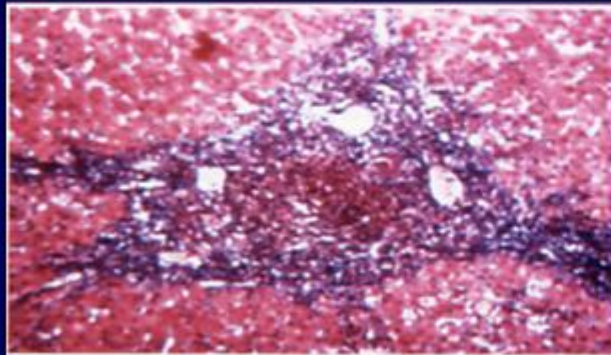
# Histologic Progression of HCV on Biopsy



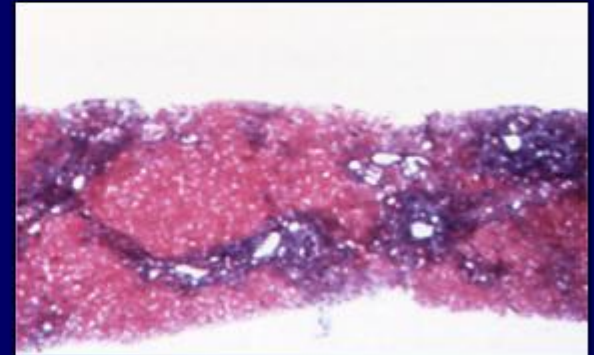
**Normal**



**Mild Chronic Hepatitis**



**Moderate Chronic Hepatitis**



**Cirrhosis**

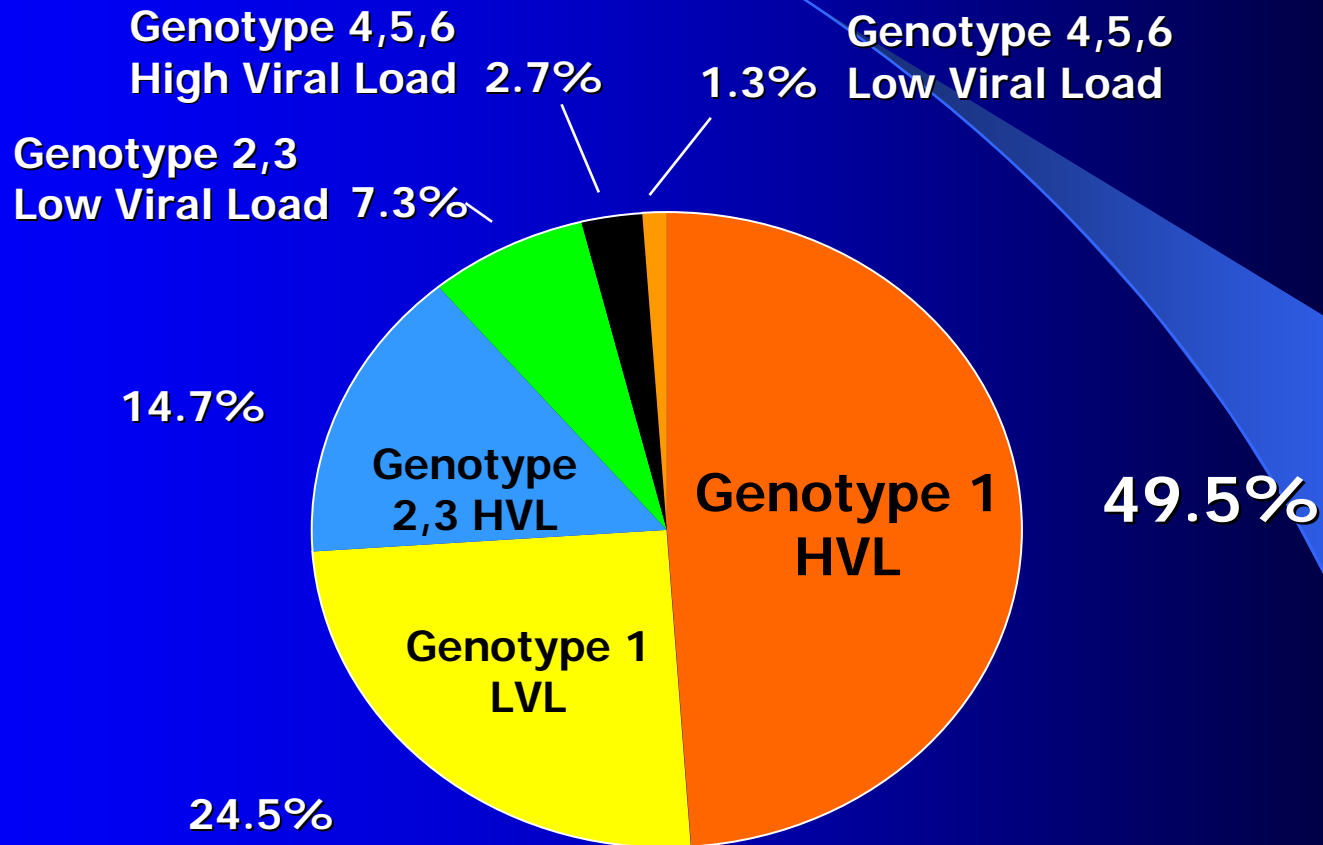


# Relation of “Fibrosis Stage” to “Mean Area of Fibrosis” by Imaging Analysis

Bedossa P et al. Hepatology 2003;38;1449-1457

Metavir Stage	Mean Area of Fibrosis (range)
F0	2 (0.7-2.7)
F1	3.4 (2.7-4.6)
F2	5.8 (4.6-10.2)
F3	14.7 (10.2-19.9)
F4	25.1(19.9-30.2)

# Genotype and Viral Load in US Patients





Hepatitis C

**Diagnostic Tests**

# Diagnostic Tests for HCV

<b>EIA (enzyme immunoassay)</b>	Recommended screening test for HCV <ul style="list-style-type: none"><li>– Tests for antibodies against infection</li><li>– 98.8–100% sensitivity</li></ul>
<b>Qualitative HCV RNA</b>	Recommended to confirm HCV diagnosis <ul style="list-style-type: none"><li>– May be more sensitive than quantitative test</li></ul>
<b>Quantitative HCV RNA</b>	Obtain viral load and confirm HCV diagnosis <ul style="list-style-type: none"><li>– May be less sensitive than qualitative test</li></ul>
<b>Genotype</b>	Used to determine HCV genotype after confirmation of diagnosis
<b>Liver biopsy</b>	May be used by specialist to determine extent of liver fibrosis and guide treatment decisions

# Markers of Viral Hepatitis C:

## ***Anti-HCV***

- Usually ELISA-3
- False (+) in low prevalence population without risk factors (40%) and hypergammaglobulinemia
- Rare false (-) [HIV(+), hemodialysis, transplant]
- Acute HCV turns (+) at week 4 in 74%; 98% at week 20. (*average “window” is 8-12 weeks*)

# Markers of Viral Hepatitis C:

## ***Anti-HCV, continued***

- Not a protective antibody
- May remain (+) up to 10 years post-acute infection
- **Almost all patients with chronic HCV are anti-HCV (+)**

# Markers of HCV infection:

## **HCV-RNA Quantitation**

- Uses Real-time PCR, Transcription mediated amplification (TMA), or TaqMan
- Appears 1-2 weeks after infection
- In perinatal infection:
  - 70% (+) @ 3 months; many clear spontaneously.
  - Better test @ 18 months if anti-HCV is (+).
- **Variations of up to 0.5 log (3-fold) have no clinical meaning.**

# Markers of Viral Hepatitis C:

## ***HCV-RNA Quantitation***

- Fall of  $< 2$ -log at week 12 of therapy predicts lack of response (PEG-interferon + Ribavirin)
- Fall  $> 2$ -log at week 12 of therapy predict SVR in 68% [90% if PCR(-) & 26% if PCR(+)]
- Low viral load ( $\leq 400,000$  IU/ml) respond better to therapy than High viral load (HVL);
- HVL patients respond similarly independently of how high is the load.
- Infrequent false (+) or false (-)



# Quantitative HCV-RNA ASSAYS

	Conversion Factor IU/mL	Dynamic Range IU/mL	FDA Approved
Amplicor HCV Monitor	0.9 copies/mL	600-500,000	Yes
COBAS Amplicor HCV Monitor V2	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3 Assay (bDNA)	5.2 copies/mL	615-7'700,000	Yes
LCX HCV RNA- Quantitative Assay	3.8 copies/mL	25-2'630,000	No
SuperQuant	3.4 copies/mL	30-1'470,000	No
COBAS Taqman HCV Test		43-69'000,000	Yes
Abbott RealTime		12-100'000,000	No

# HCV in ESRD

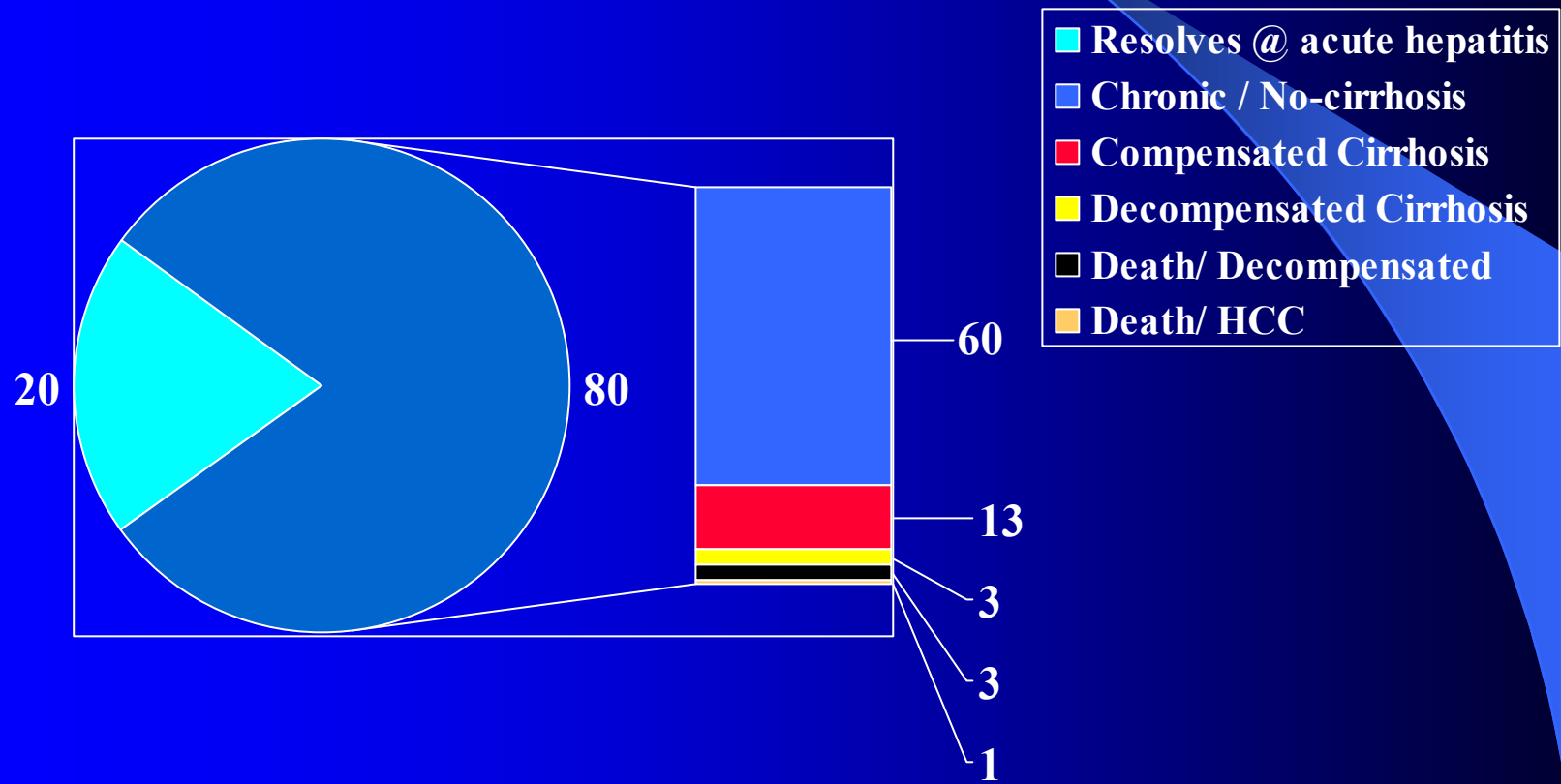
## Problems with Diagnosis

- False (-) anti-HCV by ELISA-2 = 2.60 %
- False (-) anti-HCV by ELISA-3 = 0.23 %
- Delayed sero-conversion ( $>7$  mo) and short-lived elevation of ALT after acute infection.
- ALT frequently normal in chronic HCV (+) patients with ESRD and/or in hemodialysis
- Heparin in dialysis interferes with PCR
- Hemodialysis decreases HCV-RNA load.

The background is a solid blue gradient. A thin, light blue curved line starts from the top left and arcs across the upper half of the image. On the right side, there is a darker blue triangular shape pointing towards the center.

# ***Immunocompetent Host Natural History***

# Outcome of HCV 25-30 year Follow-up



# Factors Associated With Disease Progression

Associated with disease progression <sup>1</sup>	Not Associated with disease progression <sup>1</sup>
Alcohol consumption	Alanine aminotransferase level
<div> <div>30 g/day for males</div> <div>20 g/day for females</div> <div> } ~2 drinks/day </div> </div>	Viral load
	Transmission mode
Disease acquisition at >40 years	Genotype
Male gender	
Coinfection: HIV or HBV <sup>2</sup>	
Immunosuppression <sup>2</sup>	

<sup>1</sup>Poynard et al. *Lancet*. 1997;349:825-832.

<sup>2</sup>NIH. *NIH Consensus State Sci Statements*. 2002;19(3):1-46.

# Histological Scoring of Fibrosis

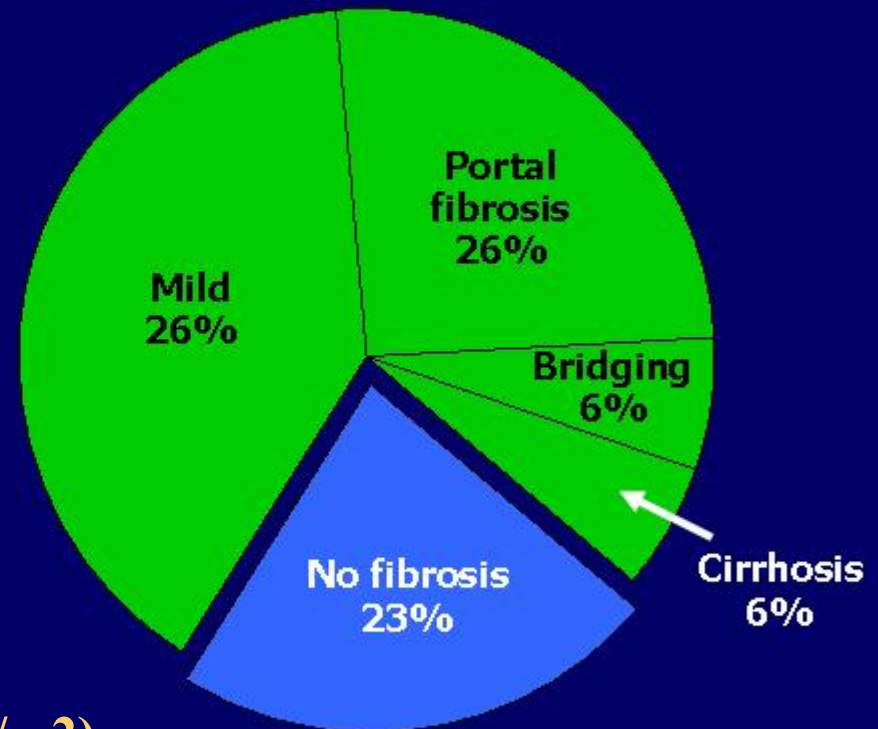
Description	Modified HAI (Ishak)	HAI (Knodel)	Batts-Ludwig, Scheuer, or IASL	METAVIR
None	0	0	0	0
Mild-Portal fibrosis (some p. areas)	1	1	1	1
Moderate-Periportal Fibrosis (most p. areas, or occasional portal-portal septa)	2	3	2	2
<i>Severe-Bridging fibrosis (few / occasional bridges, any portal-central)</i>	<b>3</b>	<b>3</b>	<b>3</b>	<b>2</b>
Severe-Bridging fibrosis (many portal-central bridges)	<b>4</b>	<b>3</b>	<b>3</b>	<b>3</b>
Incomplete cirrhosis	<b>5</b>	<b>4</b>	<b>4</b>	<b>4</b>
Cirrhosis	<b>6</b>	<b>4</b>	<b>4</b>	<b>4</b>

Treat METAVIR  $\geq 2$ , or Ishak/Batts-Ludwig/Scheuer/Knodell  $\geq 3$

# HCV Disease Progression in Patients With Normal ALT

Despite 'persistently normal' ALT levels, >75% have some degree of liver damage on biopsy, with 32% having portal and bridging fibrosis

**38% qualify for therapy (METAVIR  $\geq 2$ )**

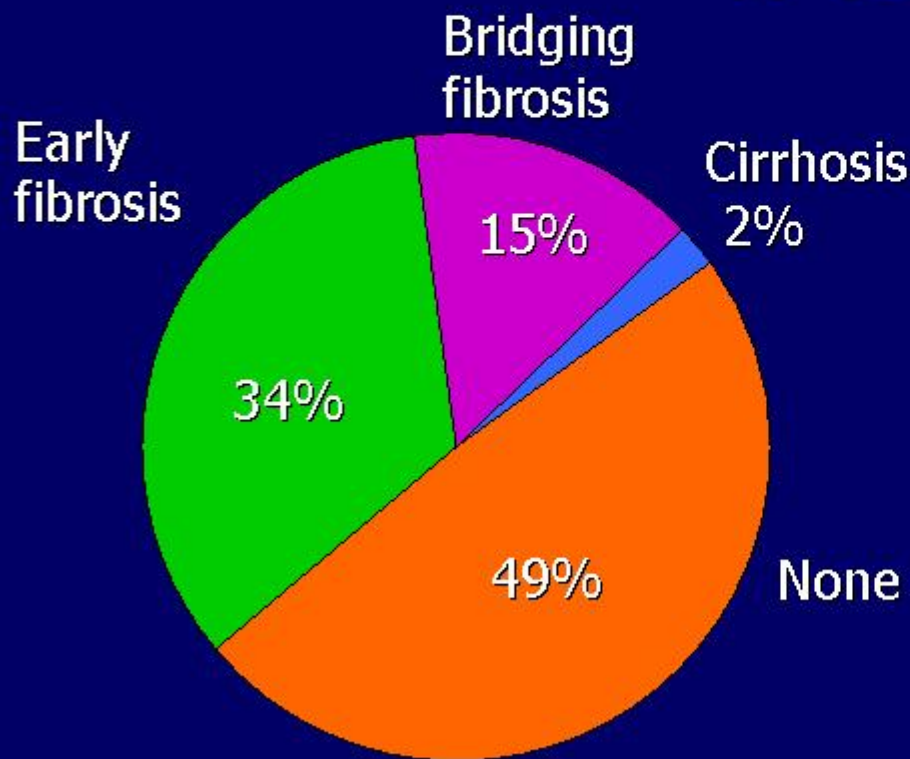


Normal ALT



# Liver Fibrosis After 17 Years of Infection in Nonalcoholic Young Women

**N=363**

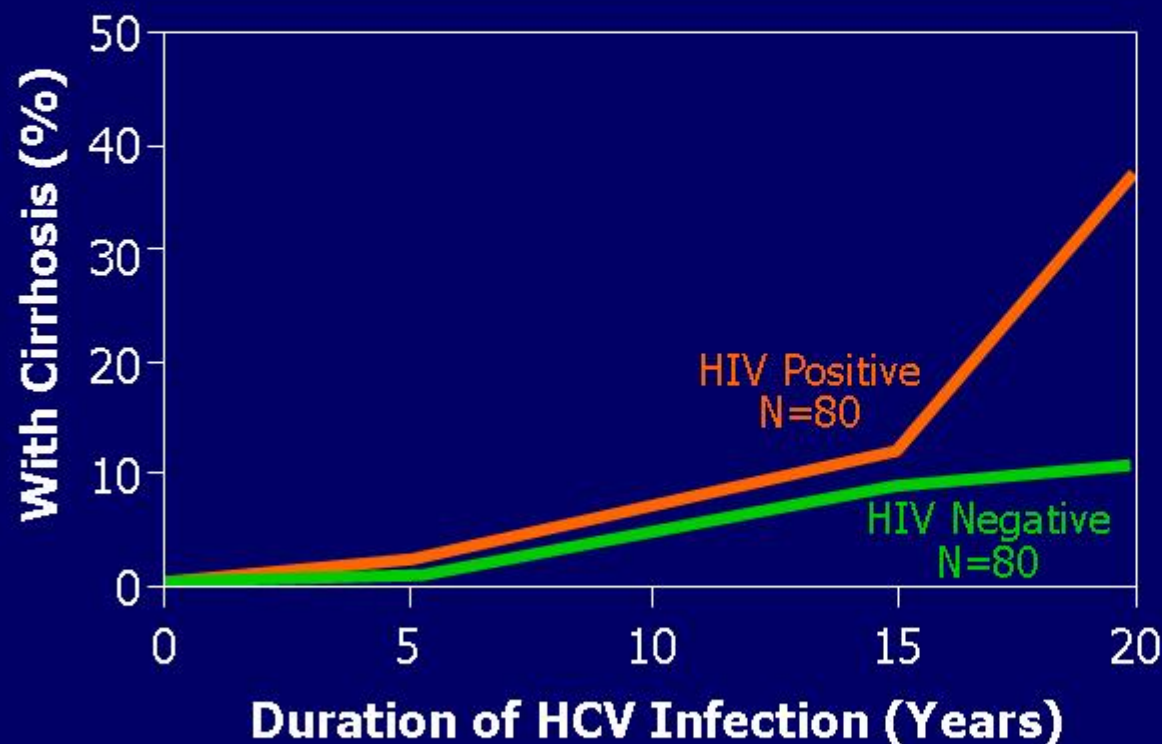


- Young women at infection
- Nonalcoholic
- Not immunosuppressed
- Not coinfectd
  - HIV or HBV



# Profile of Patients at Higher Risk for Disease Progression

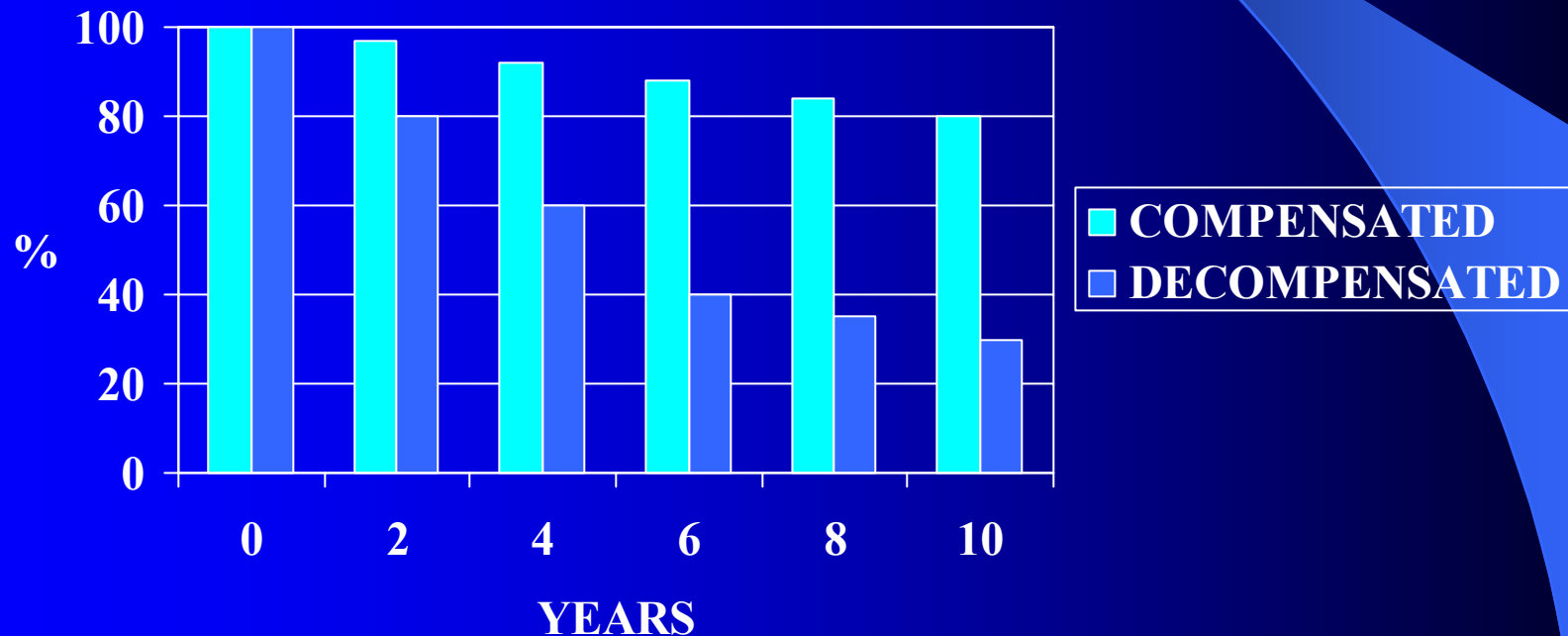
**N=160**



- 73% male overall
- Coinfected with HIV
- Immunocompromised
- Alcohol abuse

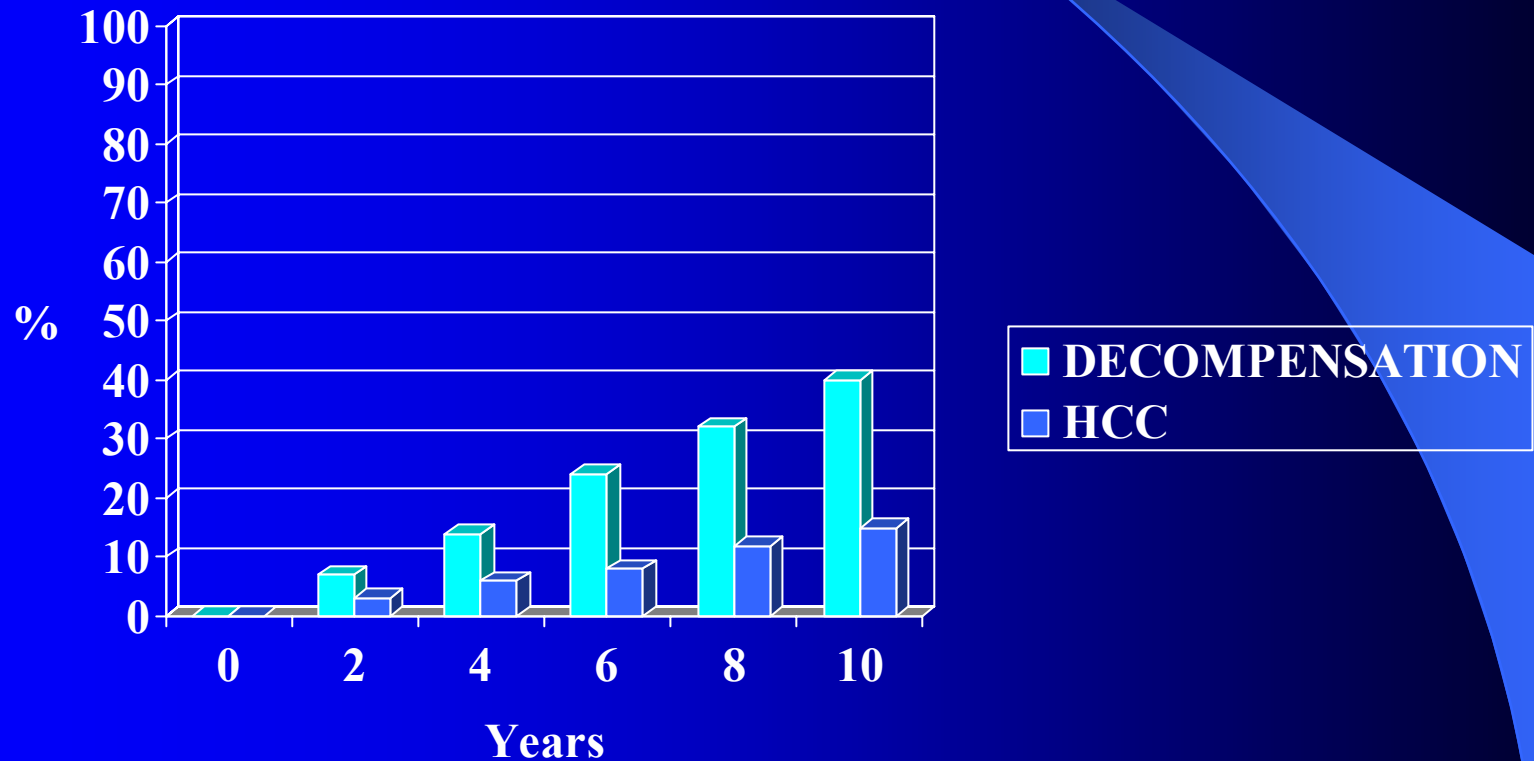
# HCV Cirrhosis Survival

## SURVIVAL IN CIRRHOSIS



# HCV Cirrhosis

## Decompensation & Hepatocellular CA



# Chronic HCV in ESRD

## Natural History

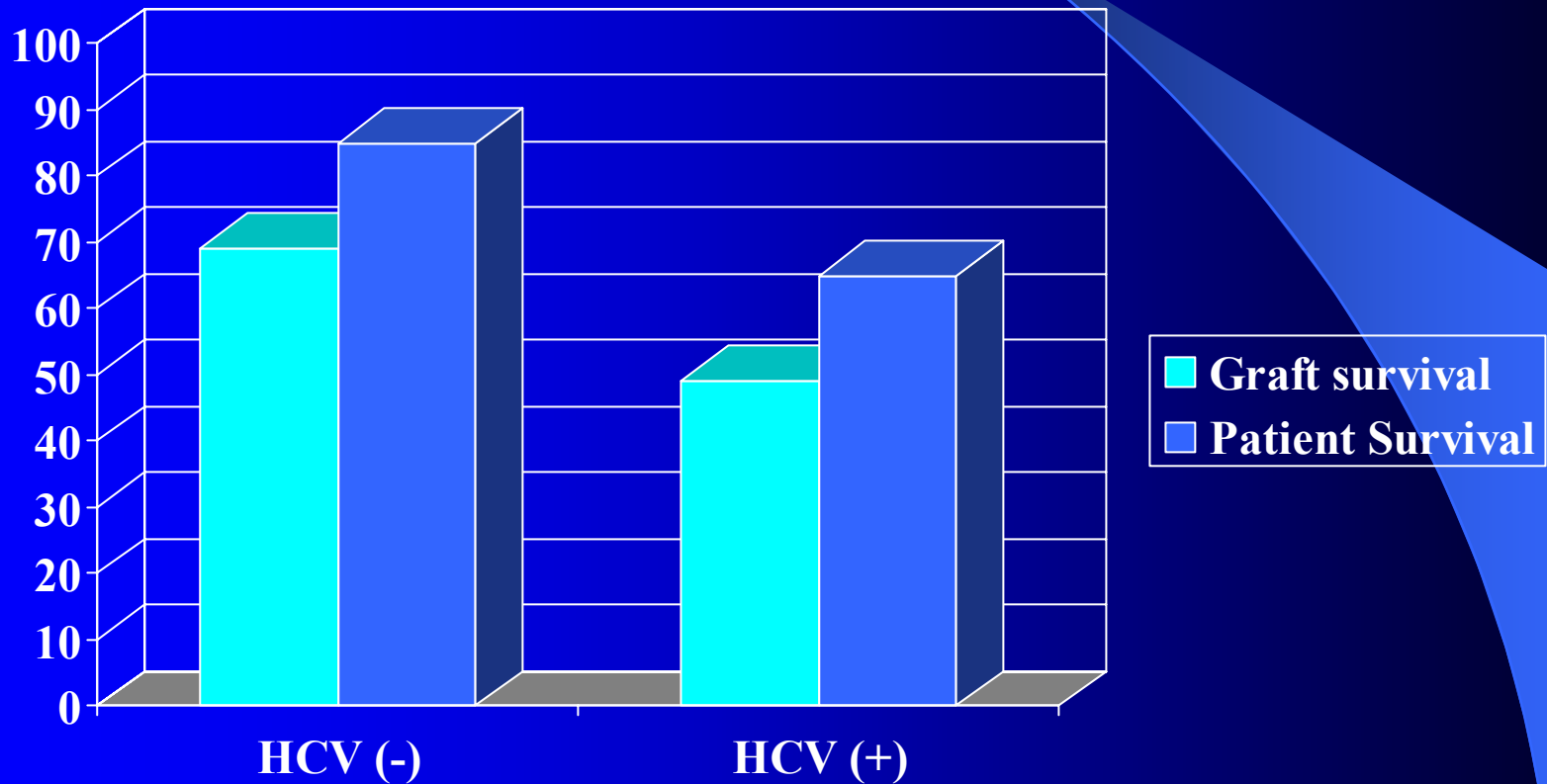
# Chronic HCV in ESRD

## Natural History

- Indolent & asymptomatic; normal liver enzymes
- Advanced fibrosis (F3-F4) in 22-32%
- Death rate 35% higher in HCV cirrhosis
- Risk of Liver Ca 50% higher in HCV (+)
- Mortality of HCV (+) kidney Tx is 40% higher than HCV (-) kidney Tx.
- Mortality of HCV (+) who receive kidney Tx is 50% lower than those who continue in hemodialysis.

# HCV in Renal Tx

## Natural History (10 years)



# HCV in Renal Transplant

- Survival: same 5-year but lower @ 10-years
- Survival better than if continue on HD
- Liver damage accelerated by Azathioprine and anti-lymphocyte globulin
- Higher risk of membranous and membranoproliferative glomerulonephritis.
- Decreased renal graft function

Immunocompromised Host

HCV Recurrence Post Liver  
Transplant

**Natural History**



# Post-OLTx HCV Recurrence

- Infection occurs during graft reperfusion.
- Negative-strand HCV-RNA (replication) as early as 48h post-LTx.
- 25% have HCV core Ag in hepatocyte 10 d post-LTx, & > 90% @ 3 months post-LTx
- Pre-LTx HCV-RNA level may be reached by day 4.
- Peak titers reached at 1-3 mo post-Tx.
- 1-y post-LTX, HCV-RNA level are 10-100X pre-LTx
- Failure to develop a HCV-specific MHC-complex class II-restricted CD4<sup>+</sup> T-cell response contributes to graft-injury.

# Post-OLTx HCV Recurrence

- Risk of death (hazard ratio 1.23) & of graft-loss (hazard ratio 1.3) is higher in HCV(+) than in HCV(-), at 1, 3, & 5 years.
- Fibrosis progression in HCV:
  - LTx = 0.3-0.8 stage/y vs
  - Immunocompetent = 0.1-0.2 stage/year.
- Median time to cirrhosis:
  - LTx = 10y;
  - Immunocompetent = 20-40 y.

# Post-OLTx HCV Recurrence

- Cirrhosis:
  - 6-23% in 3-4 y,
  - 30% by 5 y.
- Risk of decompensation:
  - 1y = 42% ( < 5% immunocompetent) &
  - 3y = 62% ( < 20% in Immunocompetent)
- Approximately 10-25% of post-LTx HCV-liver disease will need re-Tx or will be dead within initial 5 years.

# Risk Factors Associated to Severity of Recurrence

- **Recipient related**

- **Female gender:** lower survival
- **Age:** lower survival
- **Non-white race:** lower survival, more severe
- **Severity of illness:** lower survival
- *Hepatitis B co-infection:* *controversial*

- **Donor Related**

- **Age > 65:** lower survival, more severe
- *HLA-mismatch* *controversial*
- *Living donor:* *controversial*
- *Donor-liver fat:* *controversial*
- *Genetic factors:* *controversial*

# Risk Factors Associated to Severity of Recurrence

- **Virological**

- **Pre-LTx viral load (>1M copies):** more severe
- **Early post-LTx load:** more severe
- **CMV infection (+ g-1a):** more severe
- **HIV co-infection:** more severe
- *Genotype 1b:* controversial
- *Quasispecies:* controversial

- **Other**

- **Time to recurrence:** more severe
- **Steroid bolus, OKT3:** more severe
- **Short time to recurrence:** more severe
- *Cold ischemia time:* controversial

# Post-OLTx HCV Recurrence

## Factors That Affect Outcome

- Pre-OLTx HCV-RNA > 600000 IU (1 M copies)
- Advanced Donor Age (increase 1%/y after age 25; poor if > 65 y)
- Treatment of ACR
- High-average daily steroid dose
- T-cell depleting therapy
- CMV disease
- Non-caucasian recipient
- Year of OLTx (?); (worse in recent years)

# Acute Post-OLTx HCV Recurrence

- Mild to moderate ALT/AST elevation
- **Total bilirubin < 6 mg/dL**
- Liver Bx in HCV recurrence: mononuclear lobular infiltrate, variable hepatocyte necrosis, and fatty infiltration;(Il-2, IFN-gamma, and TNF dominate).
- Liver Bx in Acute Cellular Rejection: endothelitis, severe bile duct damage, and *mixed-cell* infiltrate;(Il-4 & Il-10 gene expression dominate).
- Portal lymphocytic infiltrate and lymphocyte aggregates are seen in both HCV & ACR.

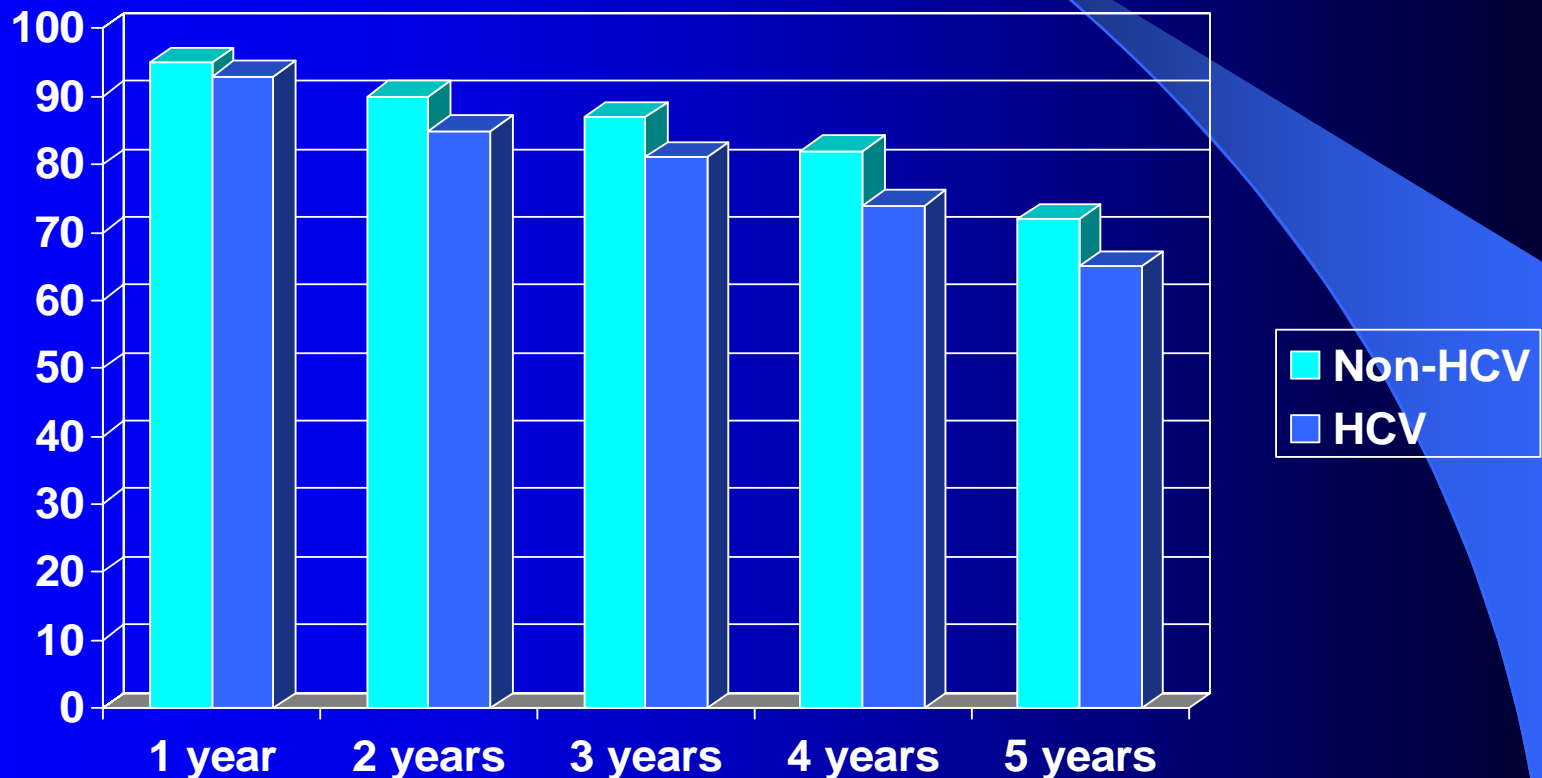
# Chronic HCV Recurrence

- There is portal-portal bridging fibrosis and portal & lobular infiltration; variable degrees of hepatocyte necrosis.
- Progressive, non-specific Th<sup>1</sup> inflammatory response.



# Survival After Liver Transplantation

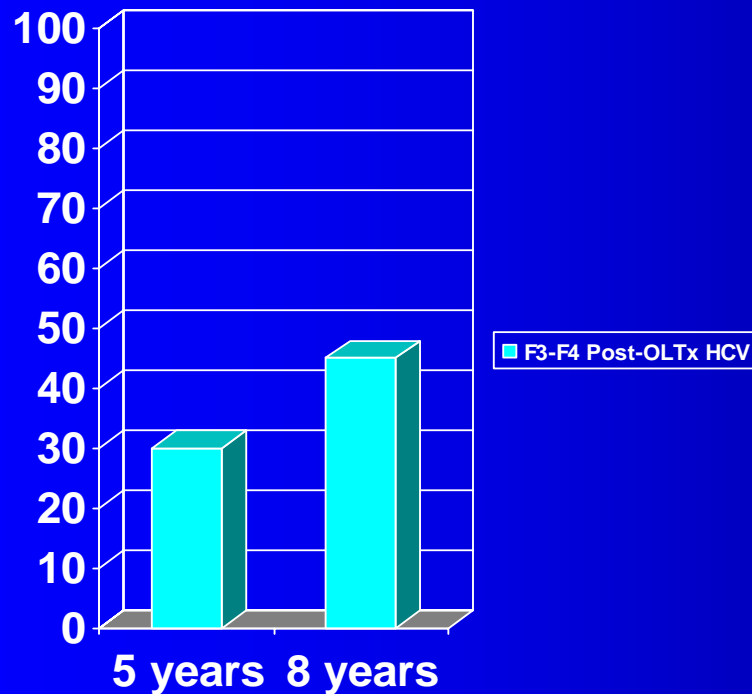
UNOS (1992-98) Gastroenterol 2002;122:889-896



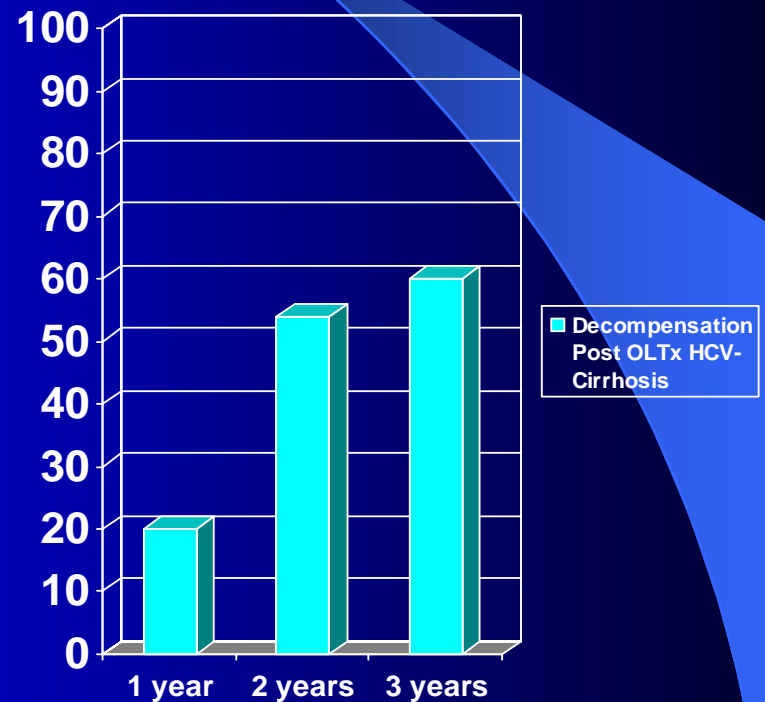
# Progression to F3-F4 Fibrosis and to Decompensated Cirrhosis Post OLTx HCV

Berenguer et al J. Hepatol 2000;32:673-684 & Hepatology 2000;32:852-858

## All patients

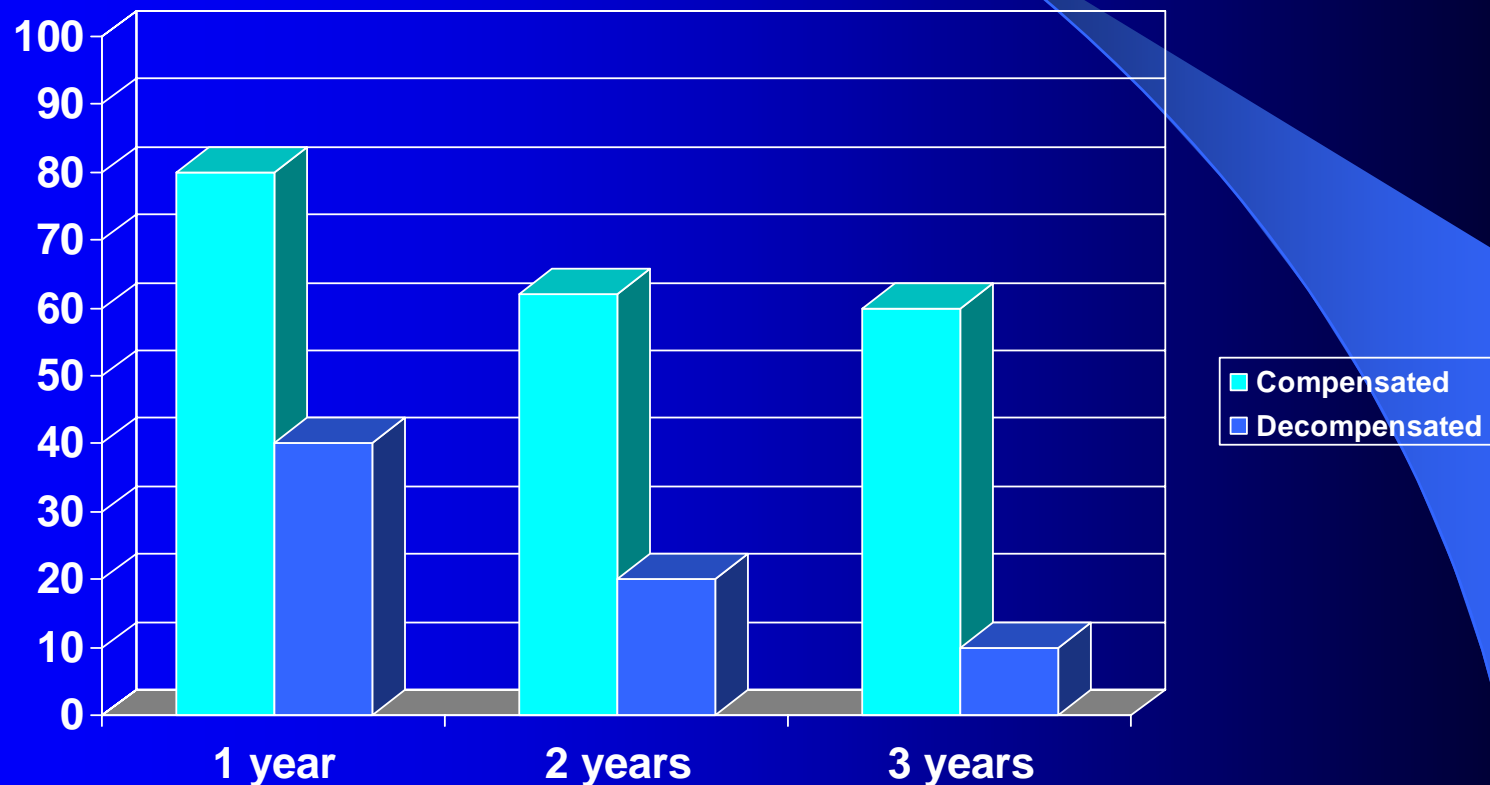


## Cirrhotics



# Survival in Post-OLTx HCV-Cirrhosis

Berenguer et al. Hepatology 2000;32:852-858



# Fibrosing Cholestatic Hepatitis C

- **Bilirubin > 6 mg/dL without biliary or vascular complications.**
- **ALT & AST elevated 2-5X; alk. phosph. > 500 U/L & GGT > 1000 U/L**
- **Very high serum & intrahepatic HCV-RNA**
- **Begins about 1 mo post LTx; liver failure in 3-6 months.**
- **Liver Bx: severe perivenular hepatocyte ballooning, intrahepatic cholestasis, pericellular & portal fibrosis, ductular proliferation, and paucity of inflammation.**
- **Probably due to high immunosuppression; stable quasispecies;  $T_H2 > T_H1$  cytokine response; direct cytotoxic injury.**

# Predictors of Poor Outcome in HCV Re-Transplantation

- Bilirubin  $> 10$  mg/dL
- Creatinine  $> 2$  mg/dL
- Creatinine clearance  $< 40$  mL/min
- Recipient  $> 55$  years
- Cirrhosis  $< 1$  year post-LTx
- Donor  $> 40$  years

# Chronic Hepatitis C

## Treatment

# Characteristics of Persons for Whom Therapy Is Widely Accepted

- Age 18 years or older, and
- HCV RNA positive in serum, and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and
- Compensated liver disease (total serum bilirubin 1.5 g/dL; INR 1.5; serum albumin 3.4, platelet count 75,000 mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and
- Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm<sup>3</sup> and serum creatinine 1.5 mg/dL, and
- Willing to be treated and to adhere to treatment requirements, and
- No contraindications

# Characteristics of Persons for Whom Therapy Is Currently Contraindicated

- **Major uncontrolled depressive illness**
- **Solid organ transplant (renal, heart, or lung)**
- **Autoimmune hepatitis or other autoimmune condition known to be exacerbated by peginterferon and ribavirin**
- **Untreated thyroid disease**
- **Pregnant or unwilling to comply with adequate contraception**
- **Severe concurrent medical disease such as severe hypertension, heart failure, significant coronary heart disease, poorly controlled diabetes, chronic obstructive pulmonary disease**
- **Age less than 2 years**
- **Known hypersensitivity to drugs used to treat HCV**



# Characteristics of Persons for Whom Therapy Should Be Individualized

- Failed prior treatment (non-responder and relapsers) either interferon with or without ribavirin or peginterferon monotherapy
- Current users of illicit drugs or alcohol but willing to participate in a substance abuse program (such as a methadone program) or alcohol support program. Candidates should be abstinent for a minimum period of 6 months
- Liver biopsy evidence of either no or mild fibrosis
- Acute hepatitis C
- Coinfection with HIV
- Under 18 years of age
- Chronic renal disease (either requiring or not requiring hemodialysis)
- Decompensated cirrhosis
- Liver transplant recipients

# Histological Scoring of Fibrosis

Description	Modified HAI (Ishak)	HAI (Knodel)	Batts-Ludwig, Scheuer, or IASL	METAVIR
None	0	0	0	0
Mild-Portal fibrosis (some p. areas)	1	1	1	1
Moderate-Periportal Fibrosis (most p. areas, or occasional portal-portal septa)	2	3	2	2
<b><i>Severe-Bridging fibrosis (few / occasional bridges, any portal-central)</i></b>	<b>3</b>	<b>3</b>	<b>3</b>	<b>2</b>
Severe-Bridging fibrosis (many portal-central bridges)	4	3	3	3
Incomplete cirrhosis	5	4	4	4
Cirrhosis	6	4	4	4

Treat METAVIR  $\geq 2$ , or Ishak/Batts-Ludwig/Scheuer/Knodel  $\geq 3$

# Early Parameters of Response

# Prediction of SVR (Naïve)

## PEG-Interferons + Ribavirin

HCV-RNA Status @ 12 wk	<i>% Non- Responders</i>	<i>% SVR</i>
HCV-RNA (-)	10	90
HCV-RNA (+) & drop > 2 log	74	26
HCV-RNA (+) & drop < 2 log	98.4	1.6

# Type of Treatment Response

Time to HCV-RNA < 50 IU/mL (-)

	4 weeks	12 weeks	24 weeks
<b>RVR</b>	<b>(-)</b>	<b>(-)</b>	<b>(-)</b>
<b>cEVR</b>	<b>(+)</b>	<b>(-)</b>	<b>(-)</b>
<b>pEVR</b> Slow Responder	<b>(+)</b>	<b>&gt; 2 log drop</b> <b>(+)</b>	<b>(-)</b>
<b>pEVR</b> Partial Responder	<b>(+)</b>	<b>&gt; 2 log drop</b> <b>(+)</b>	<b>(+)</b>
<b>Null Responder</b>	<b>(+)</b>	<b>&lt; 1 log drop</b>	<b>&lt; 2 log drop</b>

No Responder

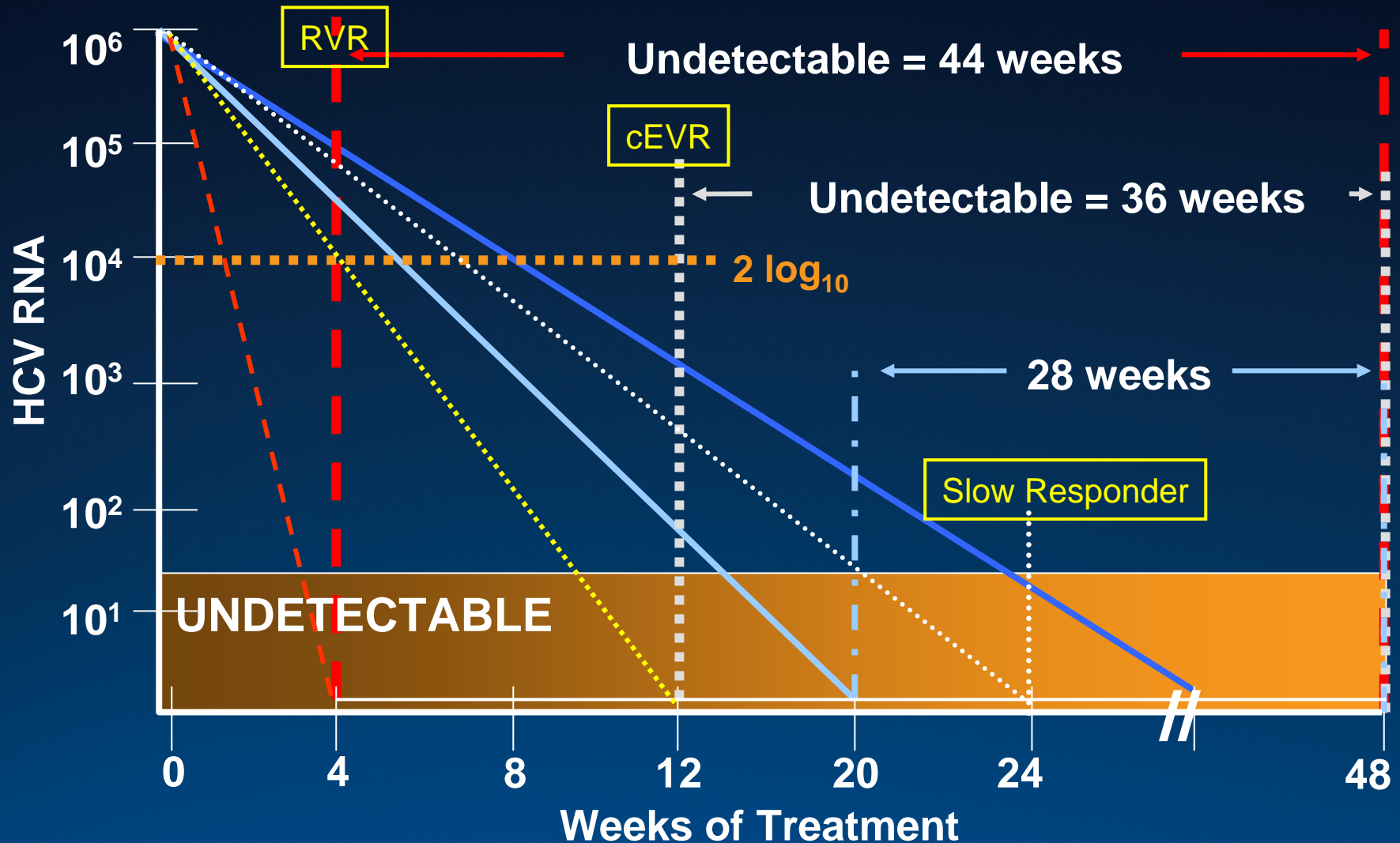
No Responder

**Breakthrough:** from (-) to (+) during treatment

**Relapse:** from (-) to (+) after treatment

**Non-Responder:** HCV-RNA (+) @ week 24

# Rate of Viral Decline Determines Period of HCV RNA Negativity

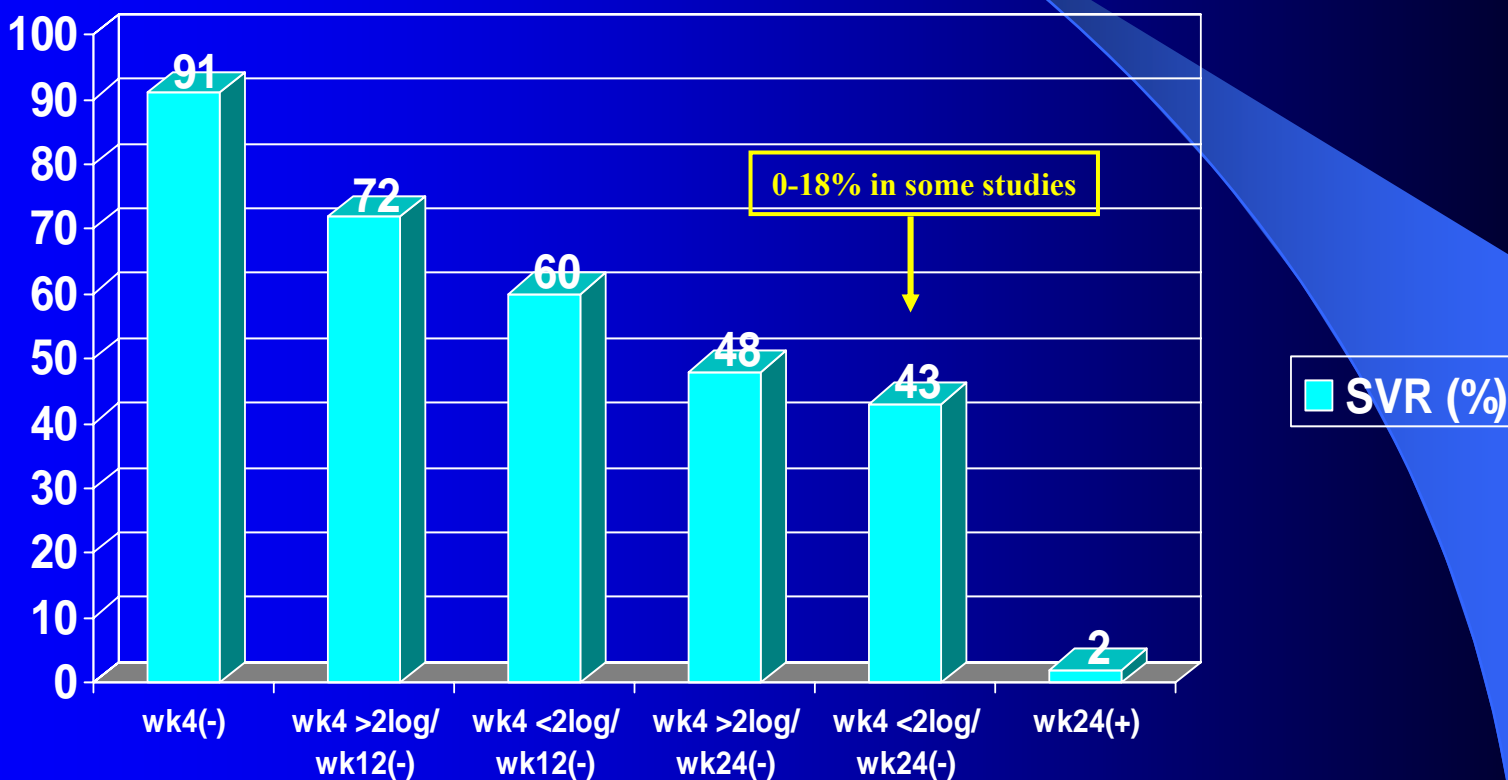


Darling JM, et al. *Clin Liver Dis*. 2006;10:835-850.

Adapted from <http://www.hepatitis.va.gov/vahep?page=prtop04-wp-03>. Accessed January 4, 2008.

# Predicting SVR by HCV-RNA fall

## Peg-IFN alpha 2a + RBV



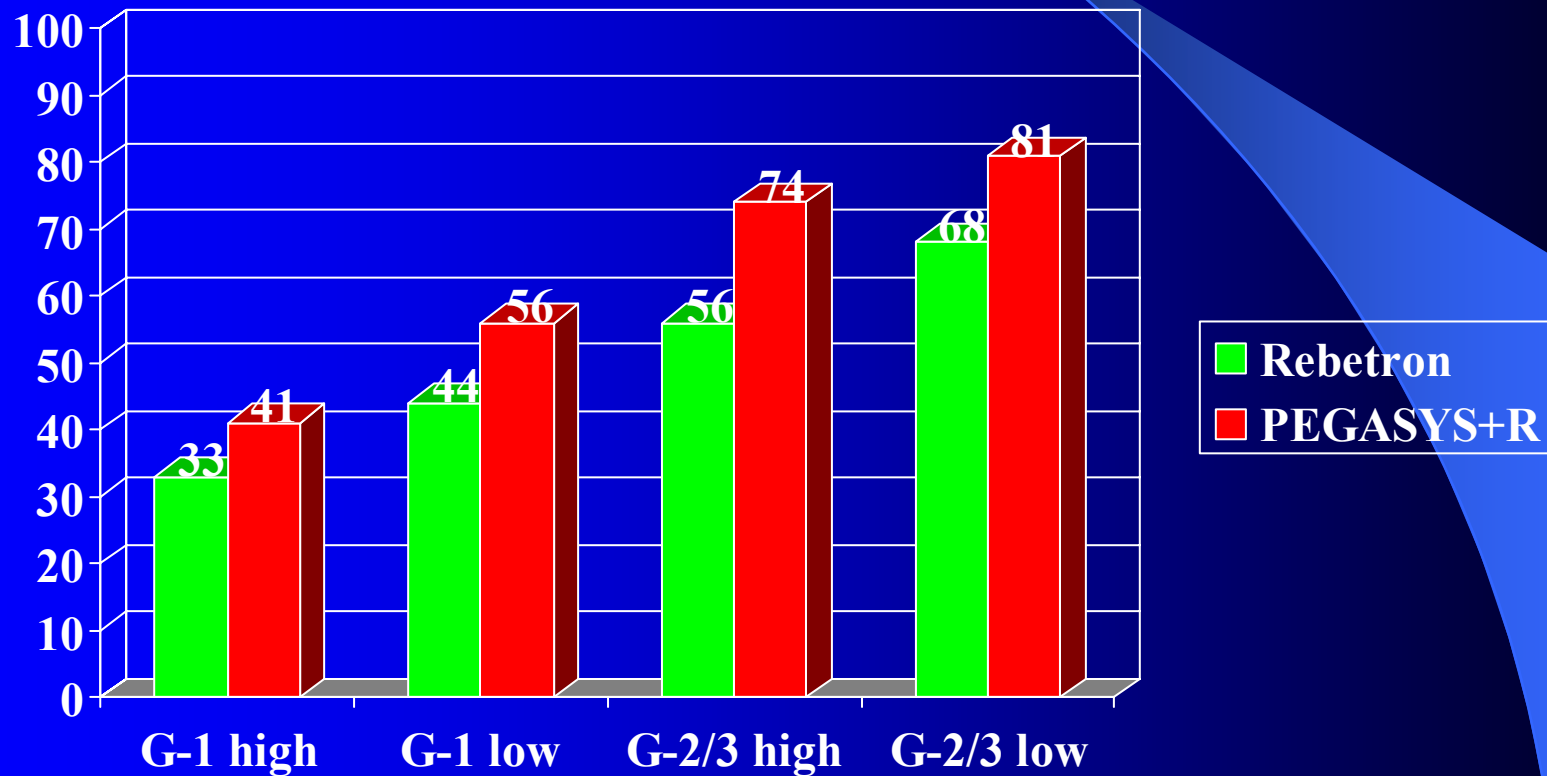
Ferenci P, et al. J Hepatol 2005; 43:425-433 (Retrospective analysis)

# Peg-Interferon/RBV vs Interferon/RBV



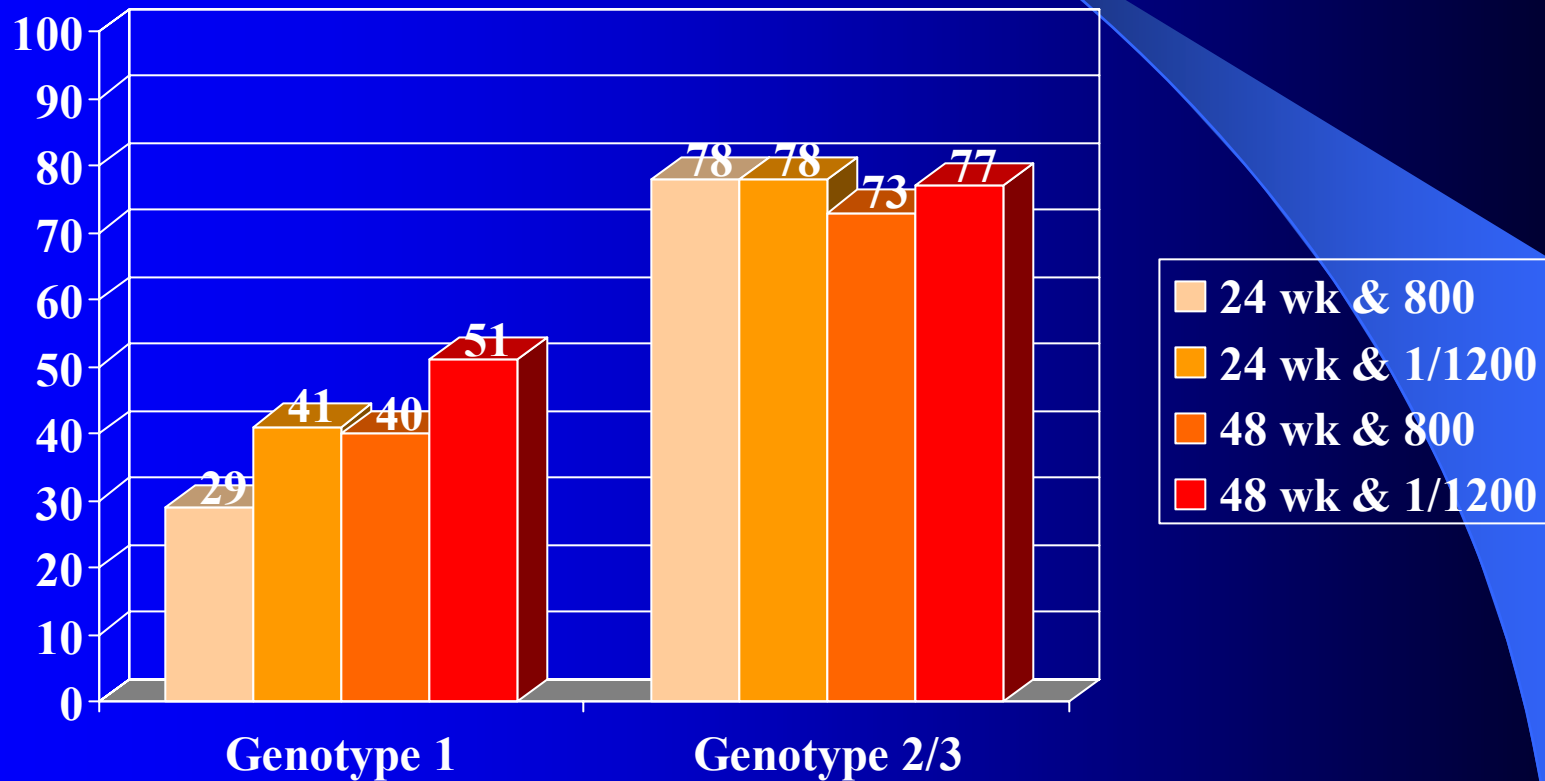
# PEGASYS + Ribavirin 1-1200

## Genotype & Viral Load on *SVR*

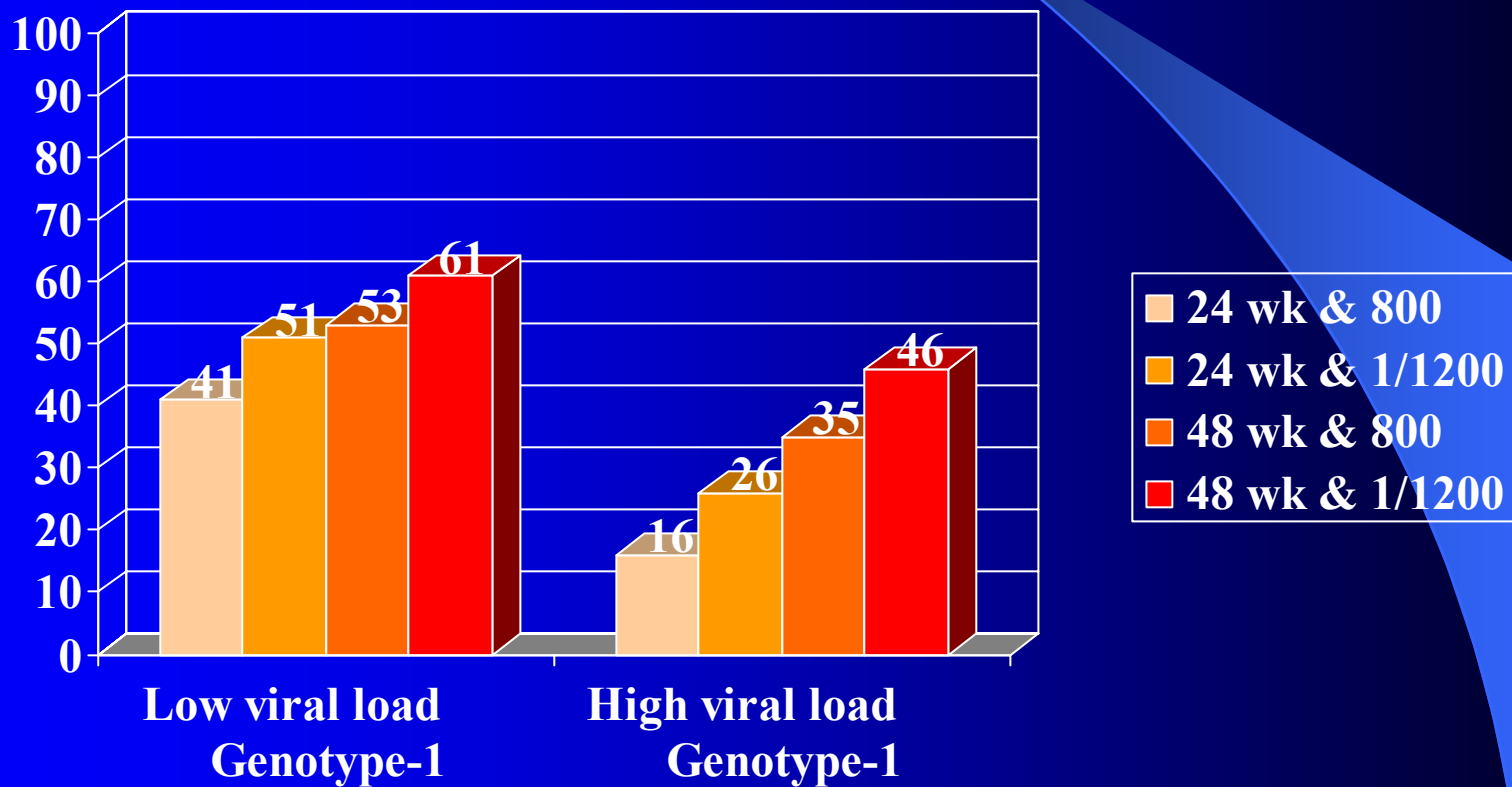


# PEGASYS + Ribavirin

## Sustained Virologic Response

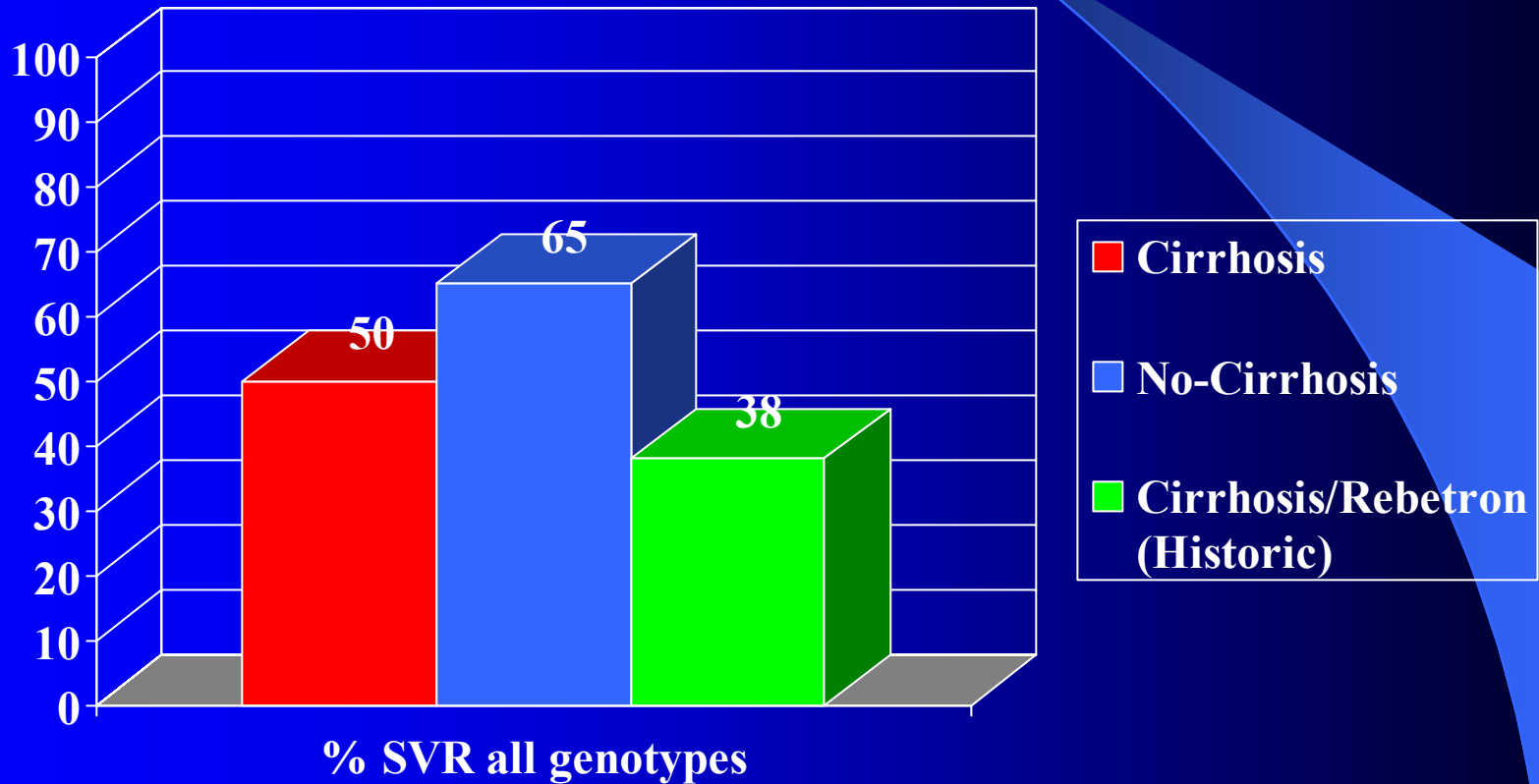


# Genotype-1 chronic HCV SVR by Treatment Regimen



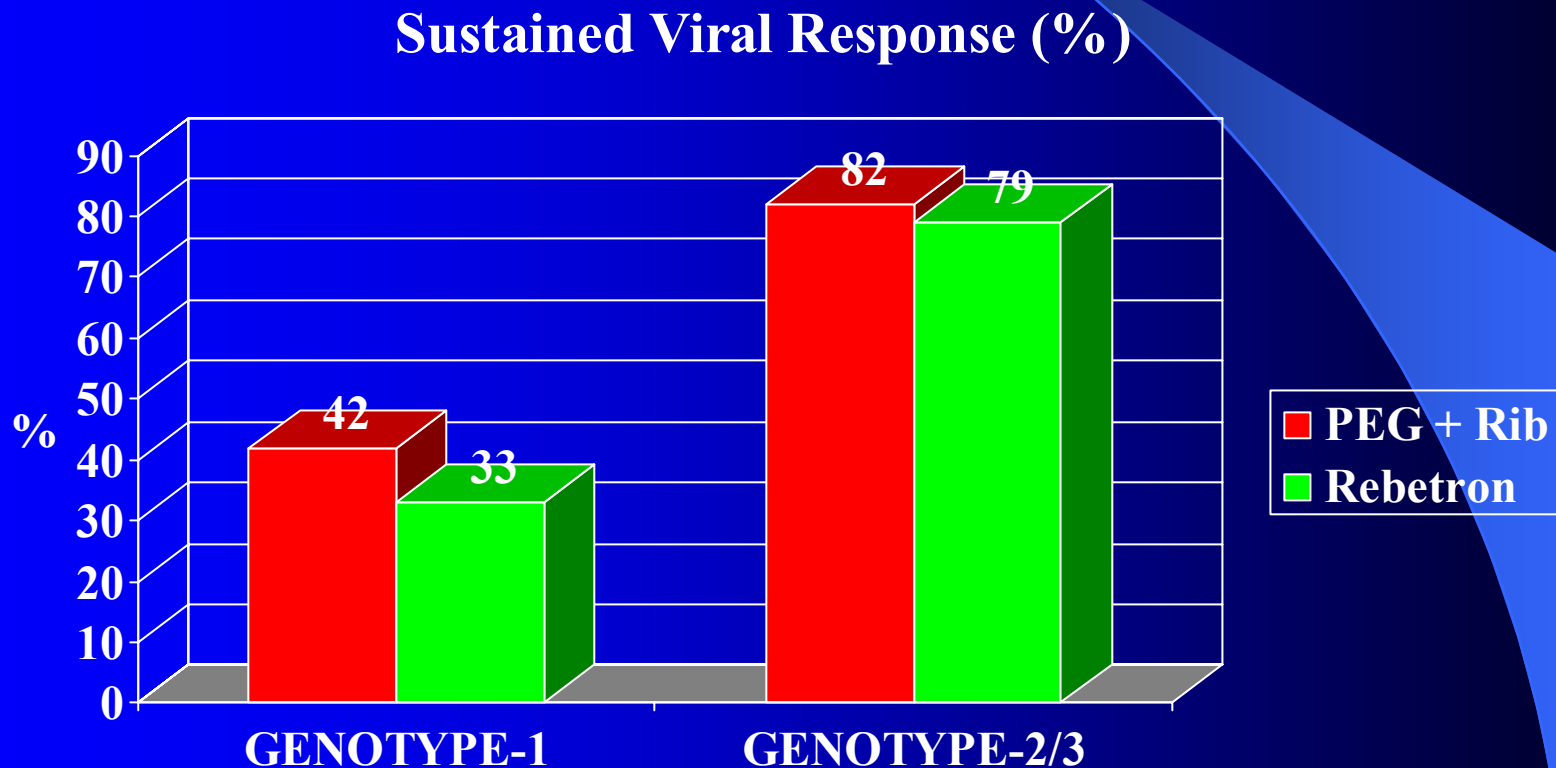
# HCV Cirrhosis vs No-Cirrhosis

## Pegasys + Ribavirin 1/1200 x 48 wks



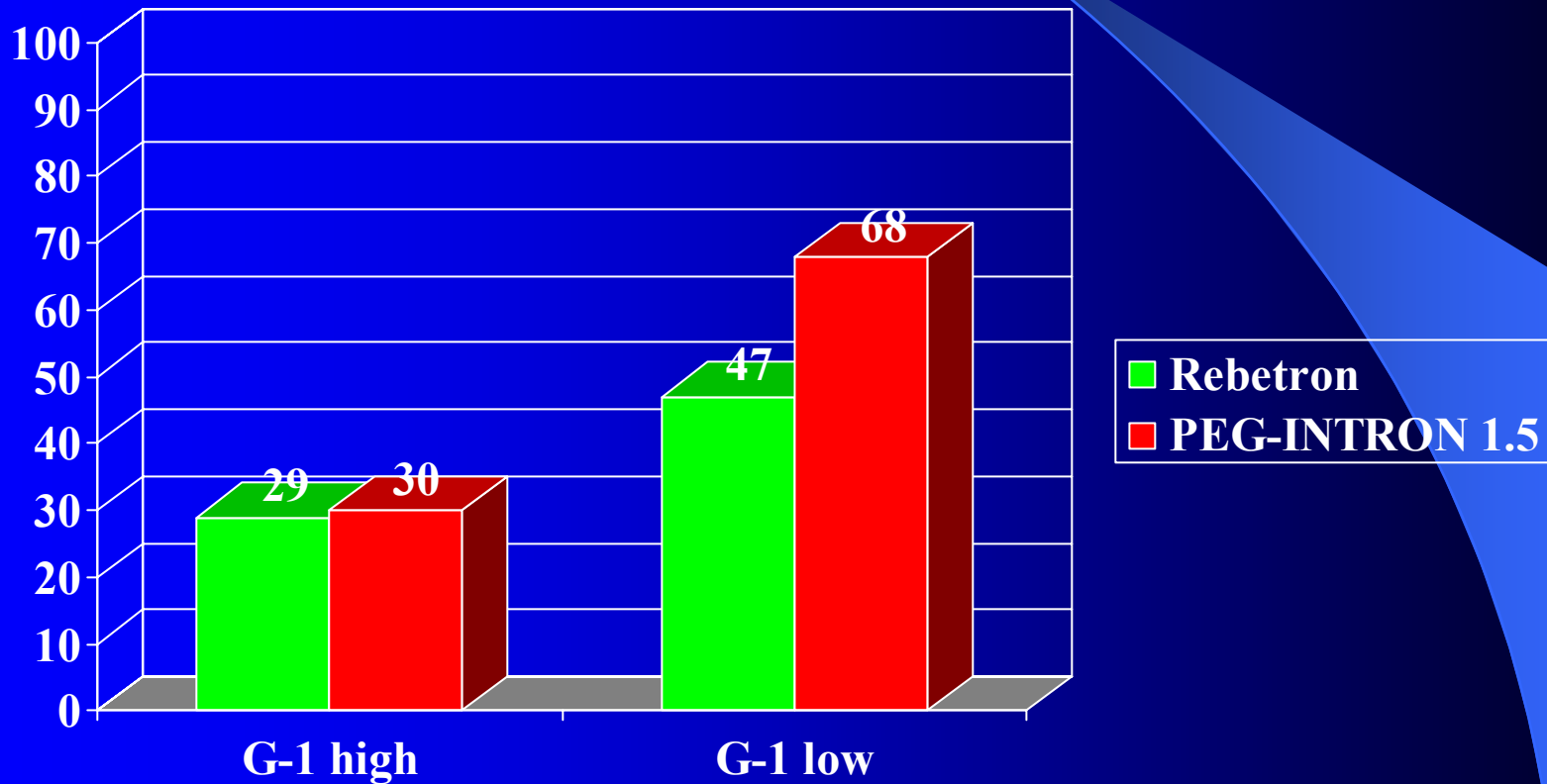
# PEG-INTRON + Ribavirin 800

## SVR Genotype-1 vs G-2/3 Naïve



# PEG-INTRON + Ribavirin 800

## Effect of Viral load in Genotype-1



**Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4)  
predicts SVR in genotype-1, with Pegasys + RBV x 24 wks**

Jensen D et al. AASLD 2005, Abstr

- Retrospective analysis of a randomized, multinational, phase III trial (Hadziyannis).
- 216 patients with HCV g-1 were randomized to 24 wks of therapy; F3/F4 in 23%;
- 99 received 800 mg RBV, and 117 received 1-1200 mg RBV.

**Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4)  
predicts SVR in genotype-1, with Pegasys + RBV x 24 wks**

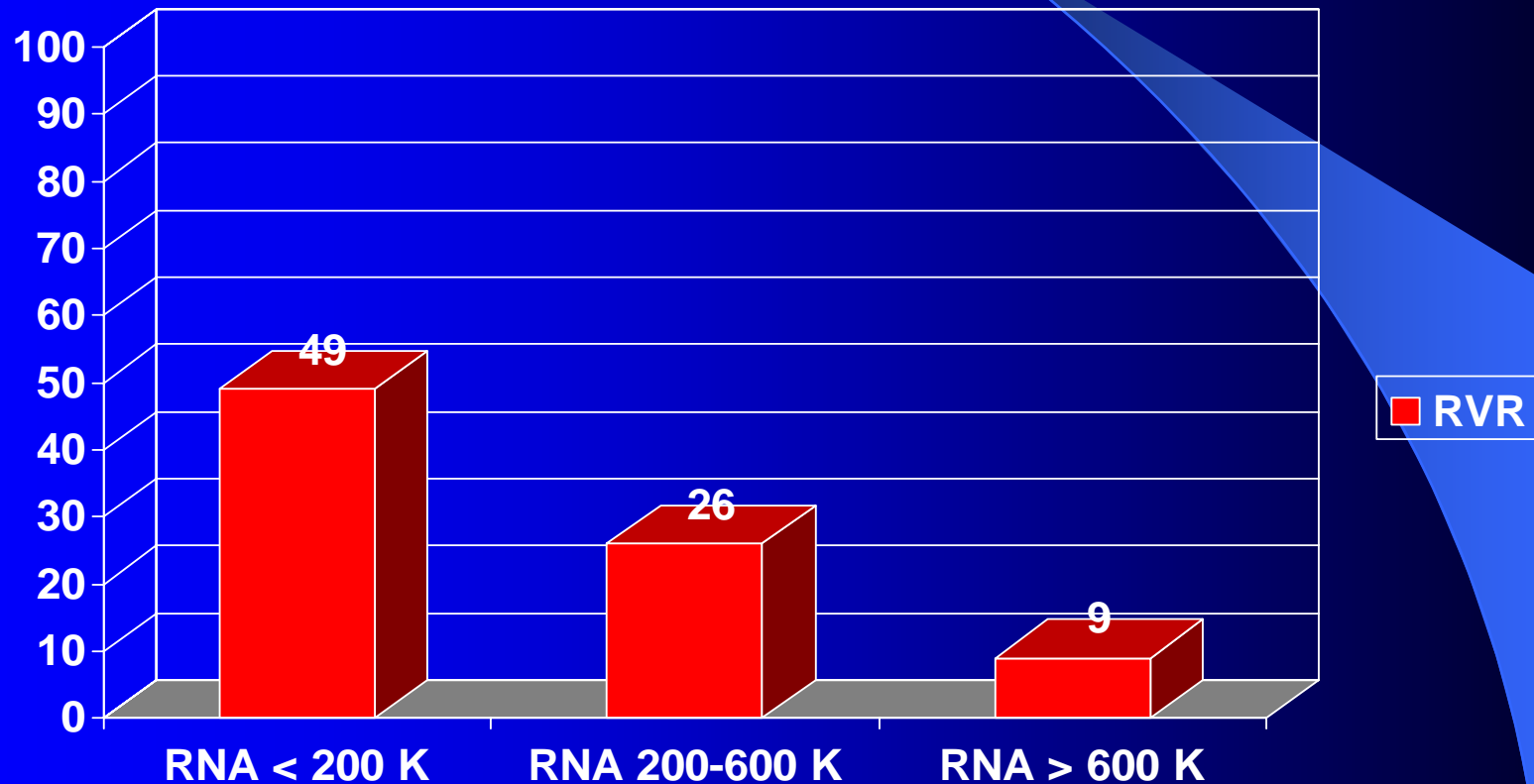
## **RESULTS**

- 51 patients (24%) had RVR (HCV-RNA < 50 IU/mL @ wk 4):
  - 18% of g-1a &
  - 28% of g-1b.
- RVR was:
  - 18.2% with 800 RBV &
  - 28.2% with 1-1200 RBV;
- 20% of F3/F4 patients had RVR.



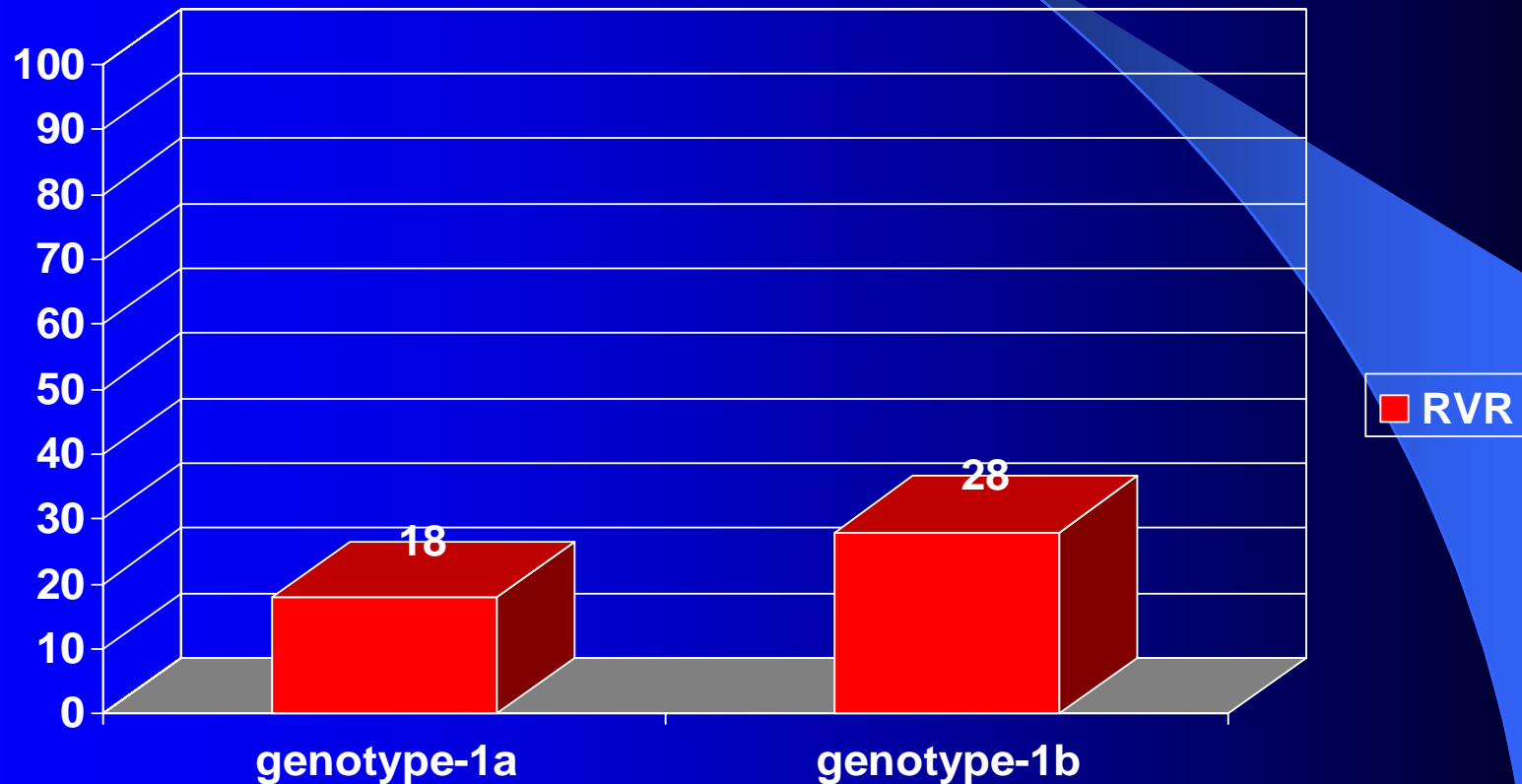
Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4)  
predicts SVR in genotype-1, with Pegasys + RBV x 24 wks

## RVR by Baseline Viral Load



Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4)  
predicts SVR in genotype-1, with Pegasys + RBV x 24 wks

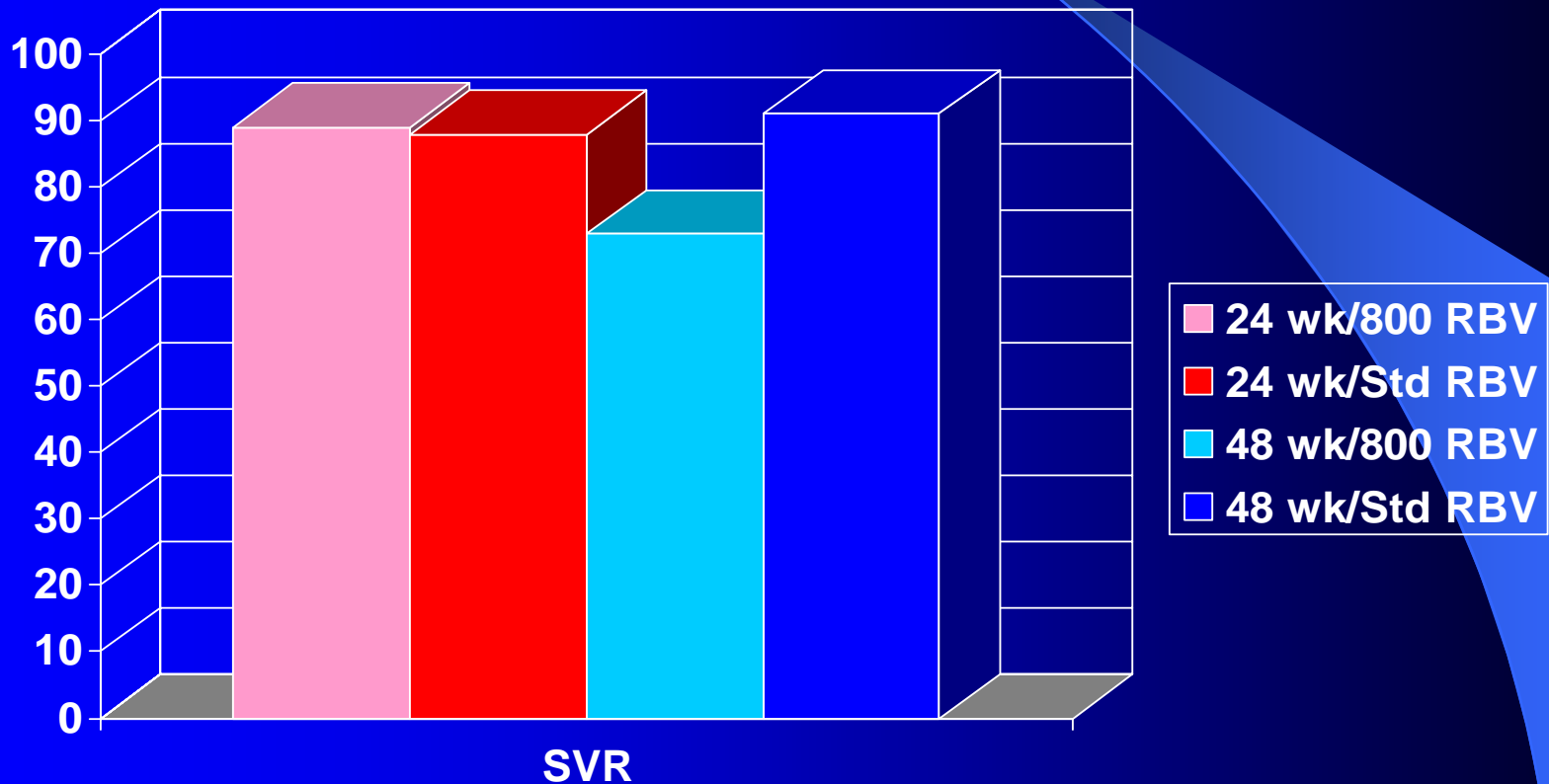
## RVR by genotype-1 a vs b



Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4) predicts  
SVR in genotype-1, with Pegasys + RBV x 24 wks

Jensen D et al. AASLD 2005, Abstr

## SVR of RVR-patients, by type of therapy



Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4)  
predicts SVR in genotype-1, with Pegasys + RBV x 24 wks

## **CONCLUSION**

- Patients with genotype-1 chronic HCV who are HCV-RNA (-) at week 4 of therapy, have the same SVR with 24 or 48 weeks of therapy, and with either 800 or 1-1200 mg RBV.
- Genotype-1 patients with lowest (<200K) baseline viral load are more likely to have a Rapid Virological Response (49%); those with loads of 200K-600K, have a 26% rate of RVR.
- RVR is more common with genotype-1b (28%) than with genotype-1a (18%).

The background is a solid blue gradient. A thin, light blue curved line starts from the top left and arcs across the upper half of the image. On the right side, there is a darker blue curved shape that overlaps the main blue area.

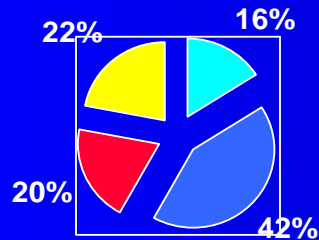
Rapidity of Response and SVR

# Rapidity of Response by Genotype

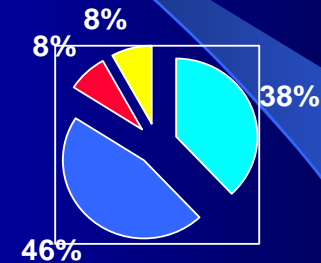
Fried MW, EASL 2008; Abstr #7

**Genotype-1**  
N: 569

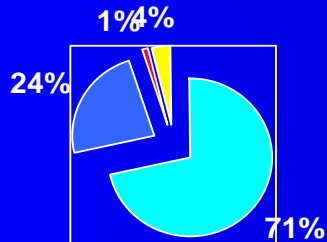
**PEG 180**  
**RBV 1000-1200**  
**48 wks**



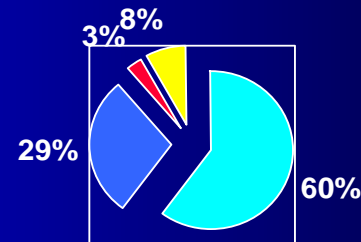
**Genotype-4**  
N: 24



**PEG 180**  
**RBV 800**  
**24 wks**



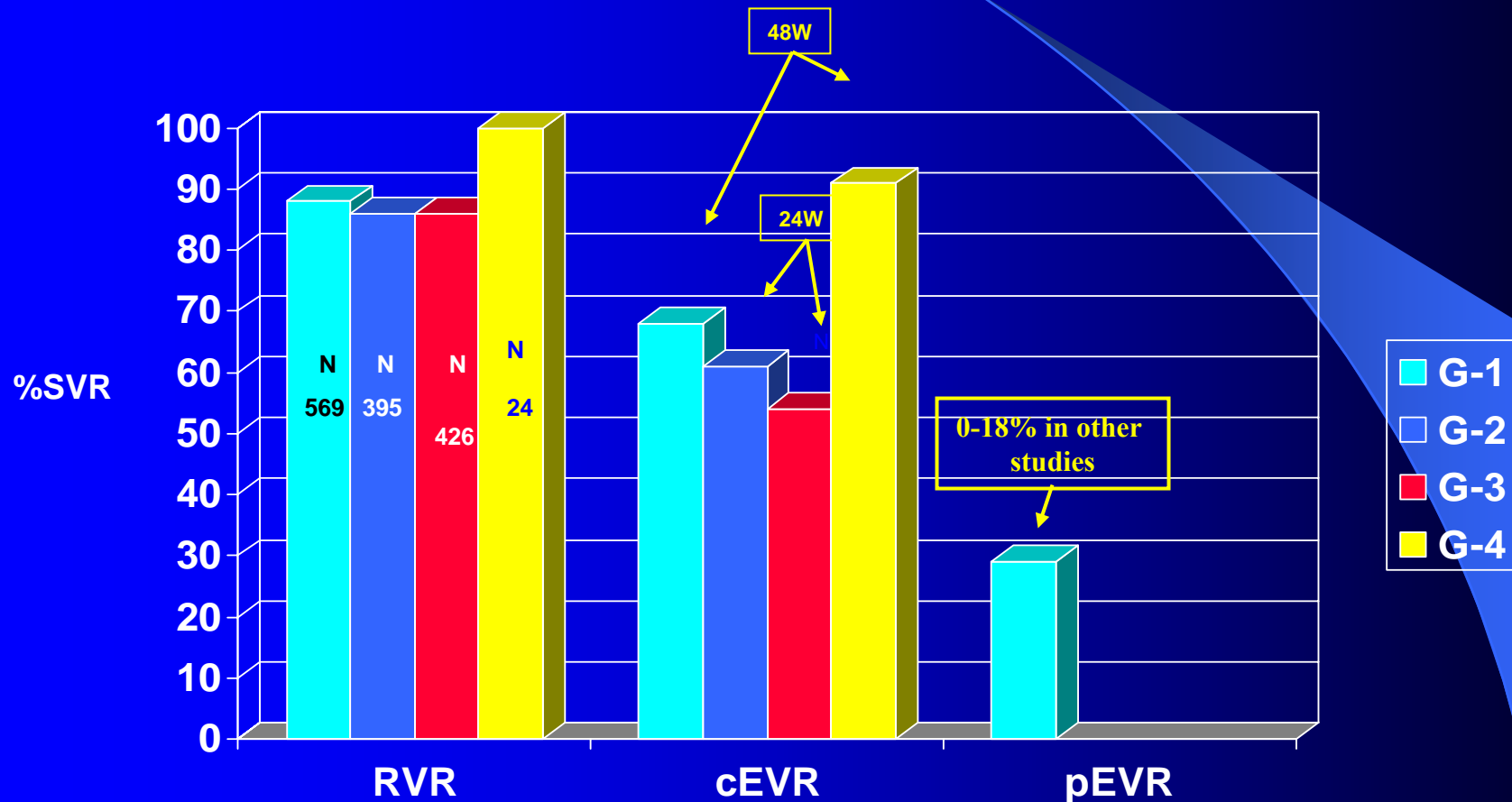
**Genotype-2**  
N: 395



**Genotype-3**  
N: 426

# SVR by Response Type & Genotype

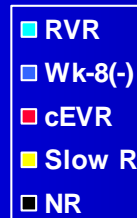
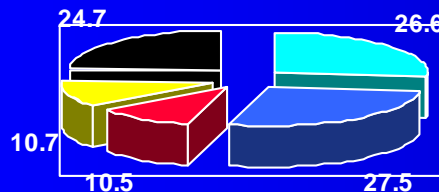
Fried MW, EASL 2008; Abstr #7



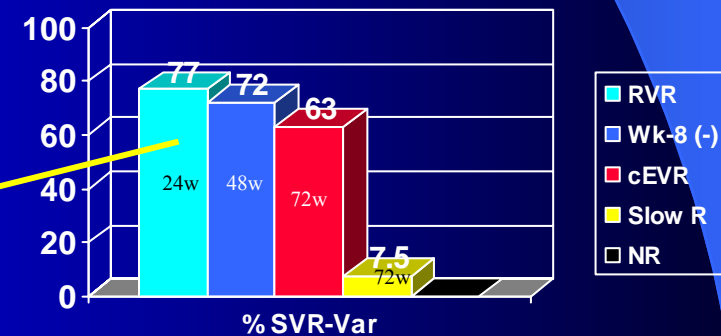
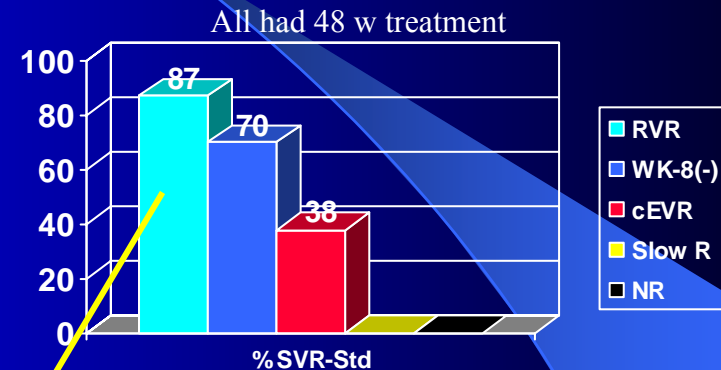
# Individualized Treatment Duration in HCV G-1

Mangia A et al. Hepatology 2008;47:43-50

646 HCV G-1 patients  
Peg-IFNa or b + RBV 1-1200



85% SVR if Baseline  
HCV-RNA < 400K IU

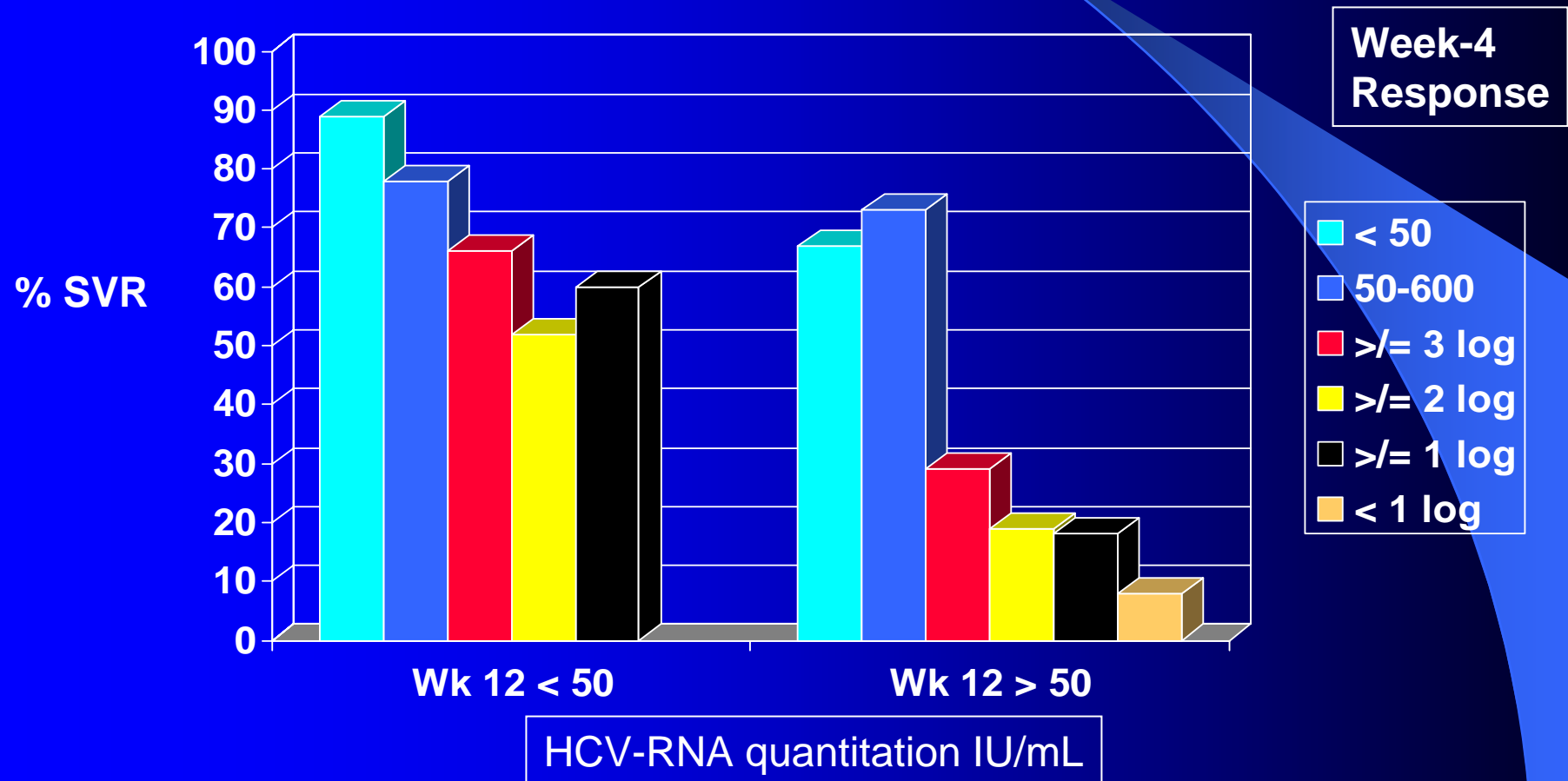


Unclear why SVR in cEVR treated x 48w was 68% in Fried's & 38% in Mangia's Study



# HCV g-1 Refined SVR Prediction by virologic response at weeks 4 & 12 (AASLD 2008: Abstr 1853)

558 patients with HCV G-1: Peg 180 + RBV 1-1200 x 48 w



# Conclusion from Data

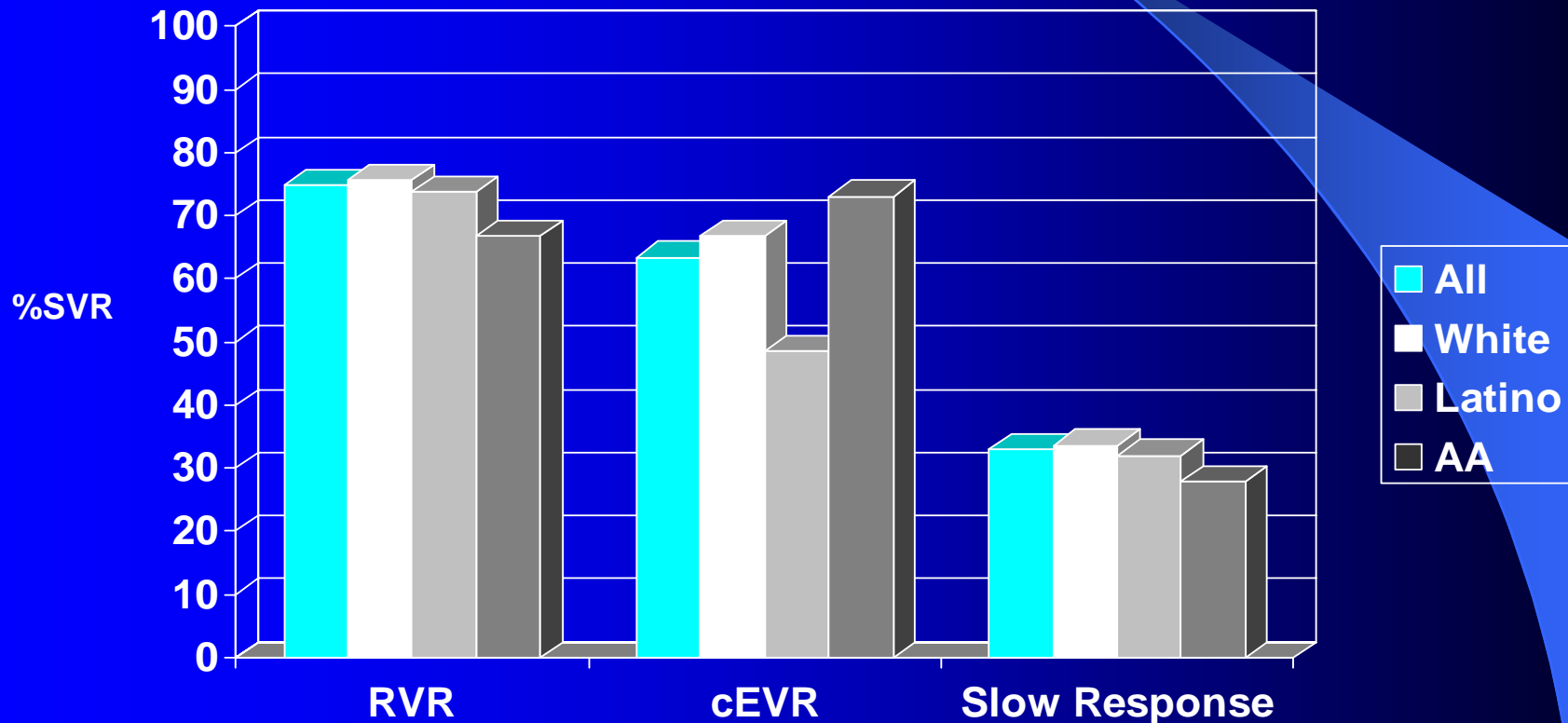
- Patients who at week 12 of PEG/RBV have HCV-RNA  $> 600$  IU/mL should be considered for Treatment Modification.
- Proposed Treatment Modification Options:
  - Change to daily Interferon alfacon-1 @ 15 mcg/d + RBV for 48 more weeks (total 60 wk) if tolerating therapy well (preferred option)
  - Continue PEG/RBV for 72 weeks total (if tolerating only fair).

Effect of RVR, cEVR, & slow response  
in SVR  
among

Different Ethnicities,  
Baseline Viral Load and  
Degree of Fibrosis

# Type of Response, Ethnicity and SVR in G-1

Shiffman ML. ESLD 2008; Poster 835

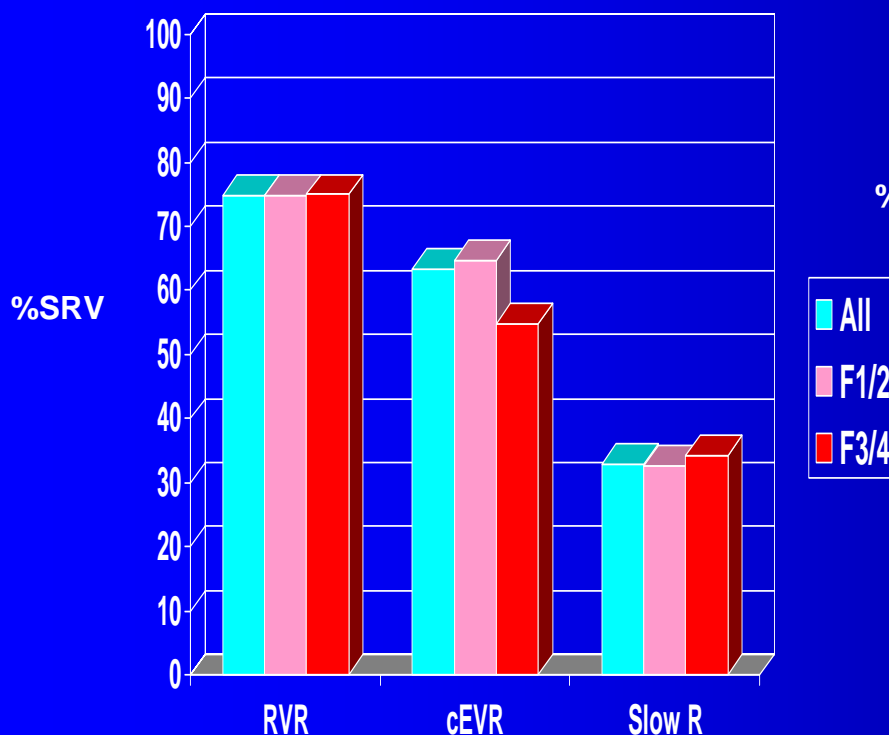


1243 pts G-1 infection (Fried, Hadziyannis, Virahep-C, LATINO studies)

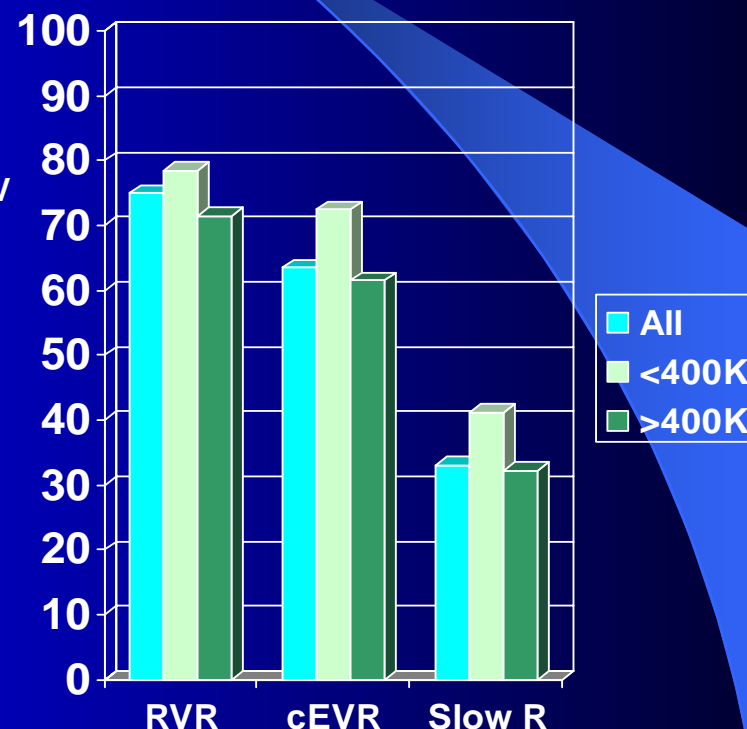
# Effect of Fibrosis & Viral Load in G-1 SVR

Shiffman ML. ESLD 2008; Poster 835

SVR by Response-Type & Fibrosis



SVR by Response-Type & Viral-Load

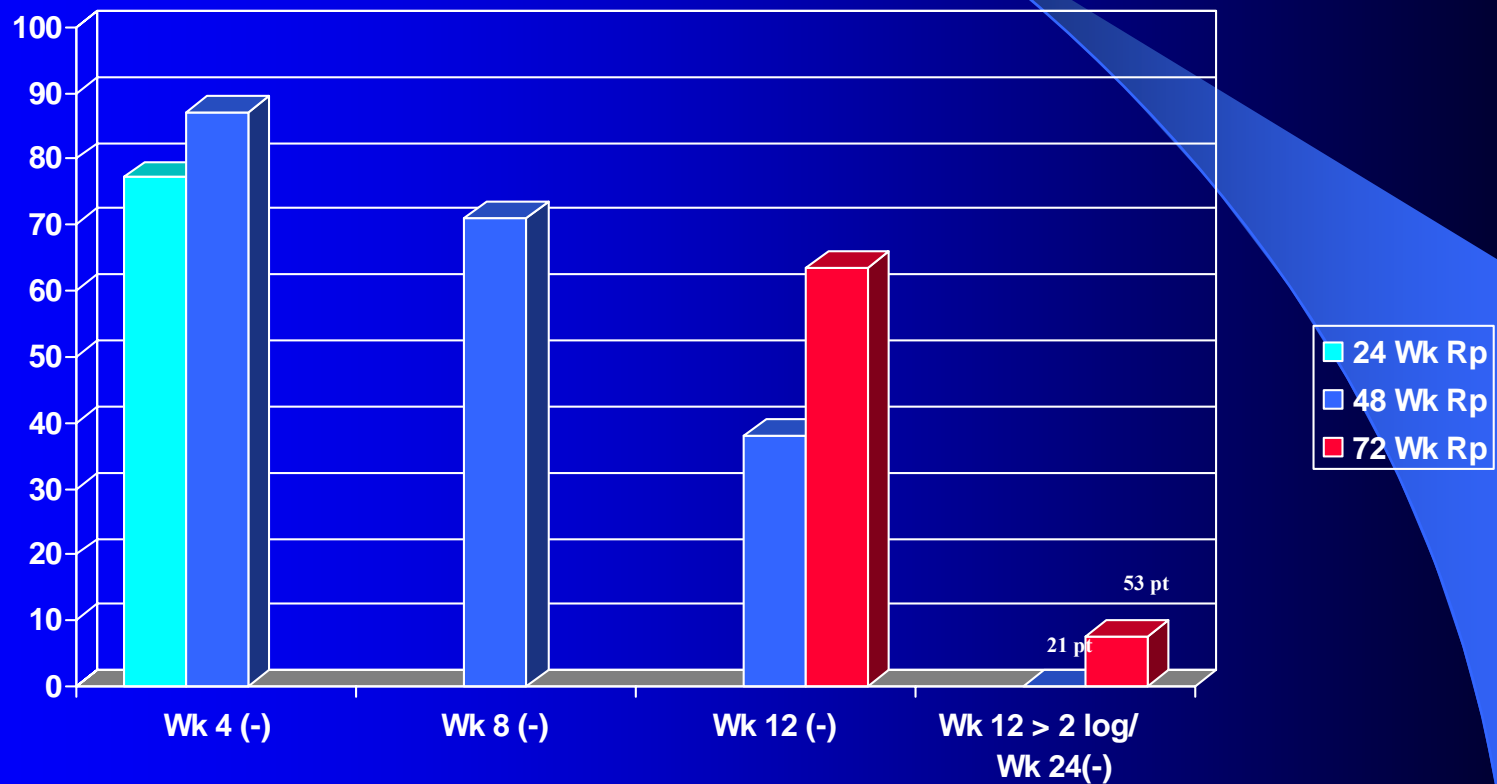


1243 pts G-1 infection (Fried, Hadziyannis, Virahep-C, LATINO studies)

# Effect of Treatment Prolongation

# SVR in HCV G-1 by time to HCV-RNA(-) & Length of Therapy Peg-IFN alfa 2 a or b + RBV 1000-1200

Mangia et al Hepatology 2008; 47:43-50

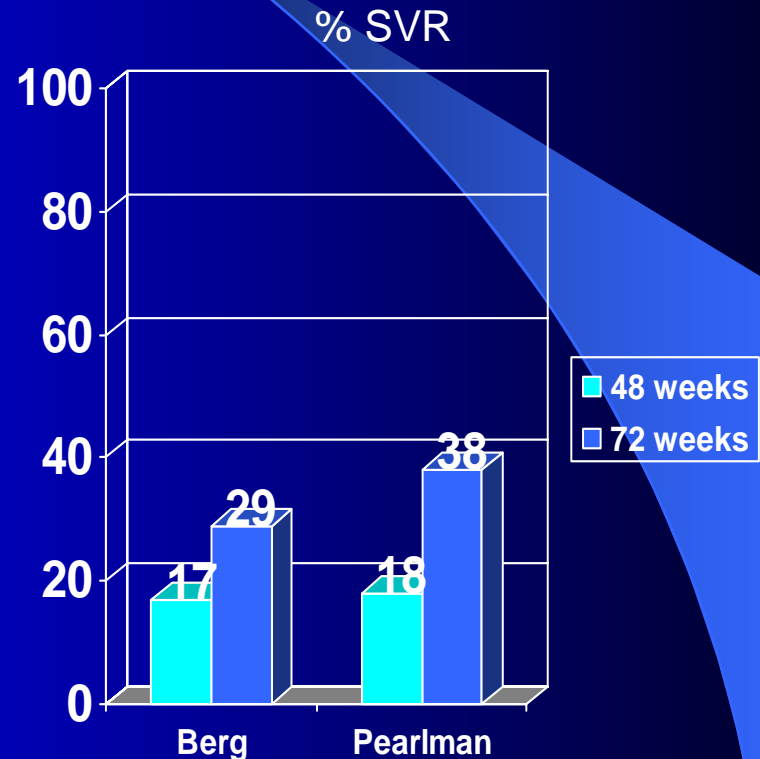


Prospective Randomized Study (Mean BMI 27)

# Prolonged Therapy in HCV g-1

## Slow Responders [ $> 2$ log drop but (+) at week 12]

- Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, et al. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 2006;130:1086-1097. (retrospective analysis; 100 (48 w) vs 106 (72 w) pts; RBV dose 800 mg/d)
- Pearlman BL, Ehleben C, Saif S. Treatment extension to 72 weeks of peginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. HEPATOLOGY 2007;46:1688-1694. (prospective, randomized, Peg 1.5/kg, RBV 800-1400, 49 (48 w) vs 52 (72 w) pts; no growth factors)





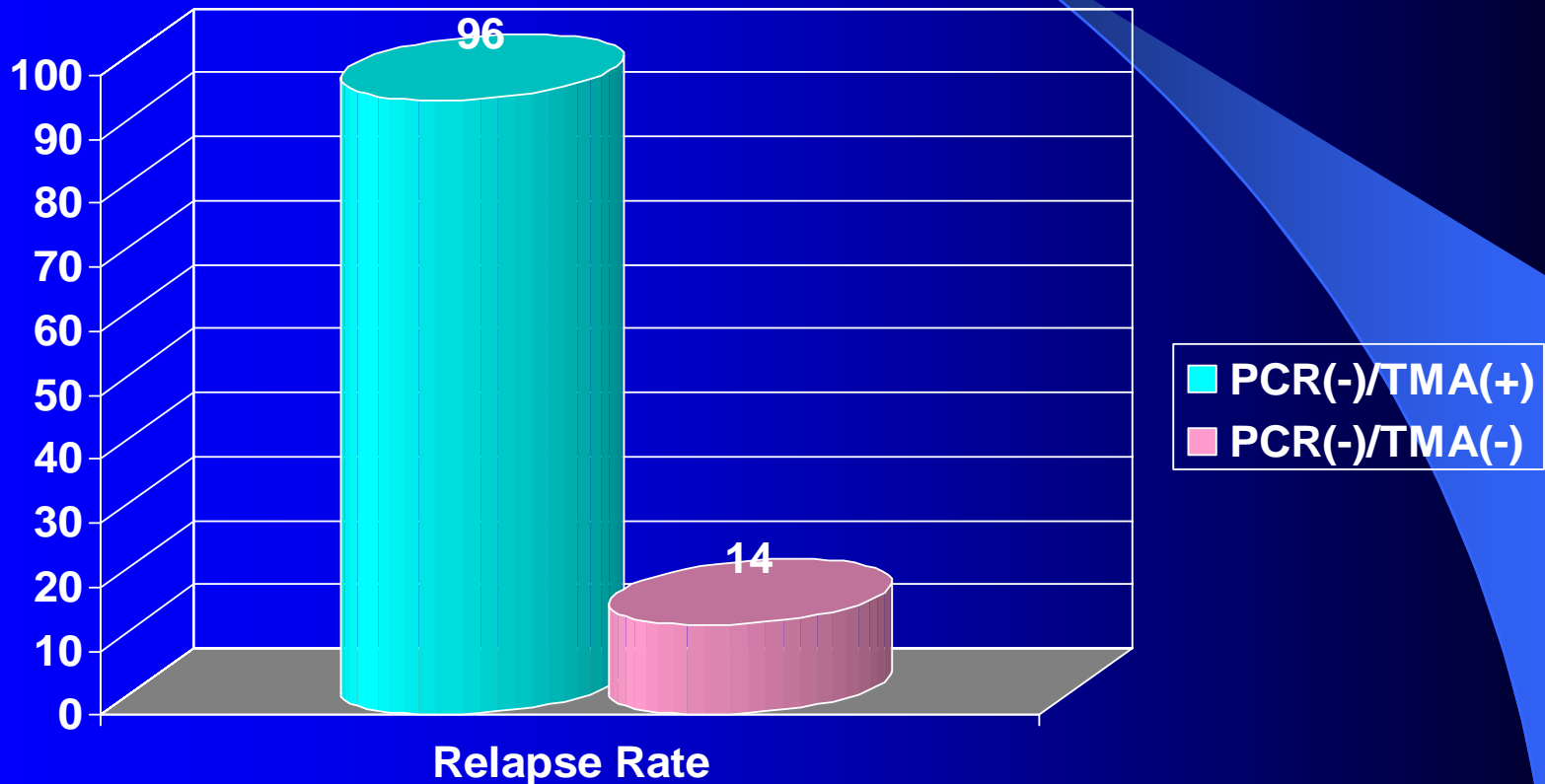
# “Minimal Residual Viremia” @ EOT predicts post-treatment HCV relapse

Gerotto et al Abstr. AASLD # 40, 2004

- 135 patients treated with Peg-IFN + RBV who passed the “12 & 24 wk rule”.
- HCV-RNA during month 11 of therapy by:
  - A) PCR (LDL 50-100 IU/mL), (Cobas-Roche) and
  - B) Qual TMA (LDL 9.6 IU/mL) (Versant-Bayer)

# “Minimal Residual Viremia” @ EOT predicts post-treatment HCV relapse

Gerotto et al Abstr. AASLD # 40, 2004



# Conclusion

Abstr # 40

- Positive HCV-RNA by highly sensitive assay (10 IU/mL) near EOT, predicts HCV relapse.
- Only 14% of patients who were HCV-RNA (-) by a highly sensitive assay near EOT, will had viral relapse.

# Parameters for Dose-Reductions

# Dose Reduction or Discontinuation

HEMATOLOGIC THRESHOLD	DOSE MODIFICATION
ANC 500-750	Reduce Peg-IFN; ? Neupogen
ANC < 500	D/C Peg-IFN
Platelets 25K to 50 K	Reduce Peg-IFN
Platelets < 25 K	D/C Peg-IFN
Hemoglobin =/< 10	Reduce Ribavirin; ? Epo
Hemoglobin =/< 8.5	D/C Ribavirin

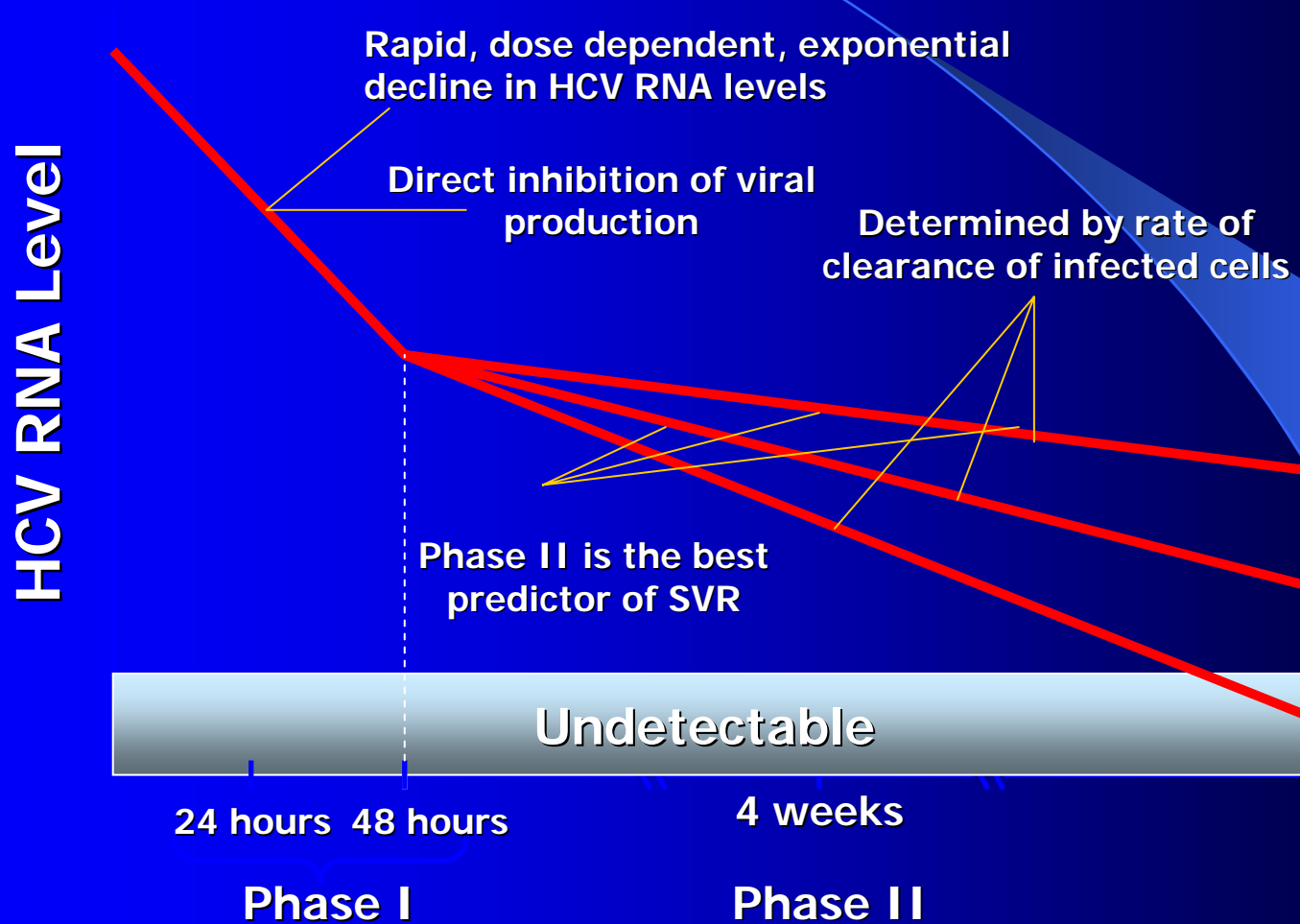
RBV dose  
High & Constant

# **Suggested RBV dose by Creatinine Clearance**

Kamar N et al. Am J Kidney Dis. 2004;43:140-146 &  
Bruchfeld A et al. Drug Monit. 2002;24:701-708

<b>Creatinine Clearance (Cockcroft-Gault)</b>	<b>120 mL/ min</b>	<b>100 mL/ min</b>	<b>80 mL/ min</b>	<b>60 mL/ min</b>	<b>40 mL/ min</b>	<b>20 mL/ min</b>
<b>RBV (mg/day)</b>	<b>1400</b>	<b>1200</b>	<b>1000</b>	<b>800</b>	<b>600</b>	<b>400</b>

# Biphasic Model of Viral Load Reduction on IFN





# Effect of Ribavirin in HCV

## Phase-I Kinetics

Pawlotsky et al. Gastroenterol 2004;126:703-714

- RBV monotherapy causes moderate & transitory decline of HCV-RNA in first 48-72 h in 50% of patients (Phase 1 effect)
- Patients with higher RBV half-life and levels, got the benefits: Is it better to start on day 1 with high dose ?
- Combination with daily or TIW IFN does not affect serum RBV levels.

# Effect of Ribavirin in HCV Phase II & III Kinetics

Pawlotsky et al. Gastroenterol 2004;126:703-714

- RBV partially prevents HCV-RNA rebound before next IFN dose (important in TIW Interferon).
- RBV does not affect the second phase of viral decline.
- RBV accelerates the third phase HCV-RNA decay when given with Peg-Interferons (Herrmann et al. Hepatology 2003;37:1351-1358); in high doses decreases the relapse rate (Shiffman M et al AASLD 2005, abstr 55)

# Effect of timing for RBV dose reduction in genotype-1 HCV

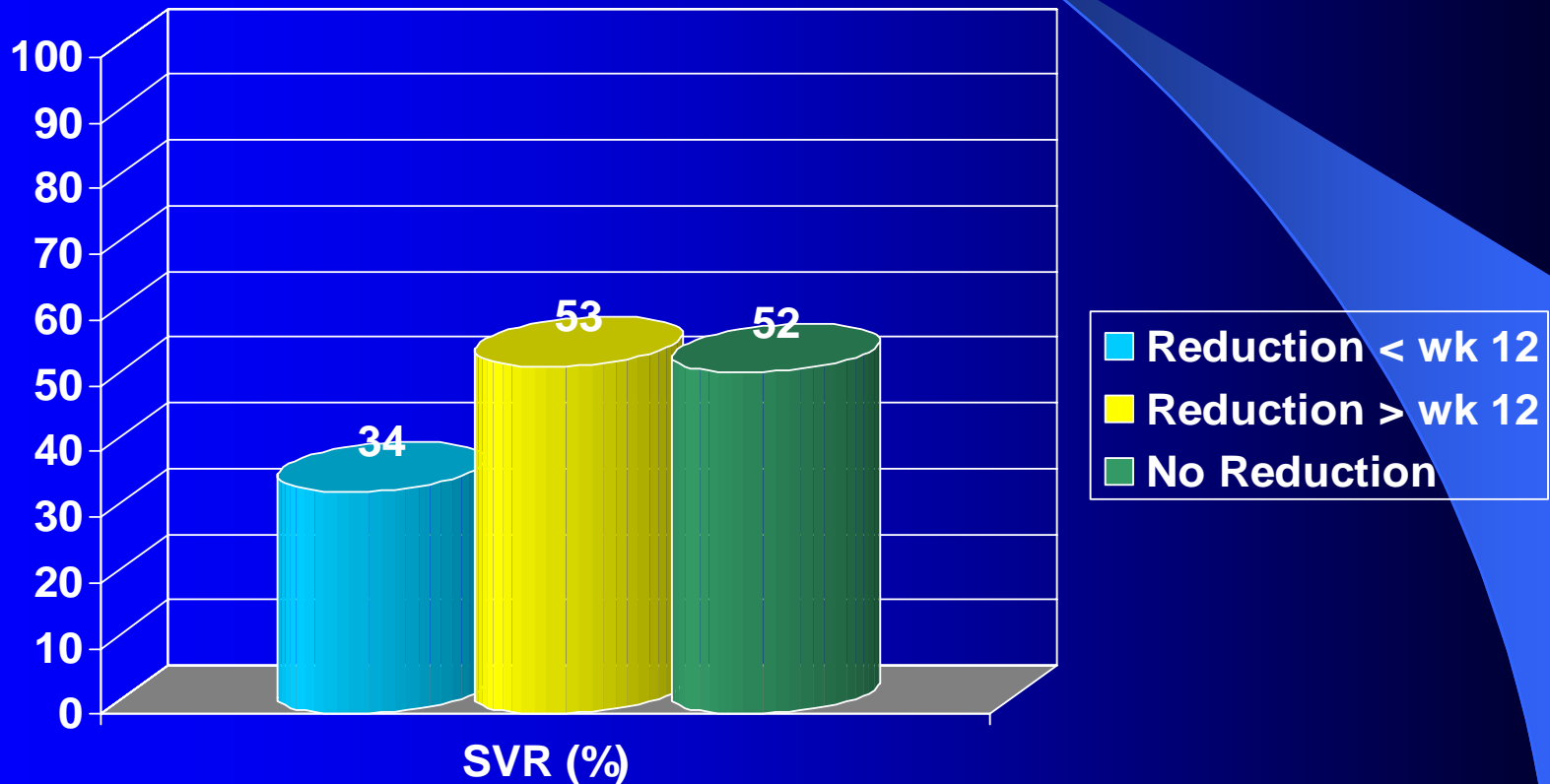
Lee et al. Abstr # 394, AASLD 2004

- 569 pts with g-1 chronic HCV on Pegasys 180 + RBV 1-1200 mg
- Analysis of SVR depending on timing for reduction of RBV dose.
- All groups continued Peg-IFN at similar level: 93-98% of intended dose

Effect of timing for RBV dose reduction in genotype-1 HCV

# SVR by Time of RBV-Reduction

Lee et al. Abstr # 394, AASLD 2004



# CONCLUSION

Abstr # 394

- In patients without dose reductions of Peg-Interferon:  
**Reductions in RBV dose during the initial 12 weeks of therapy has a negative effect in EVR and SVR.**

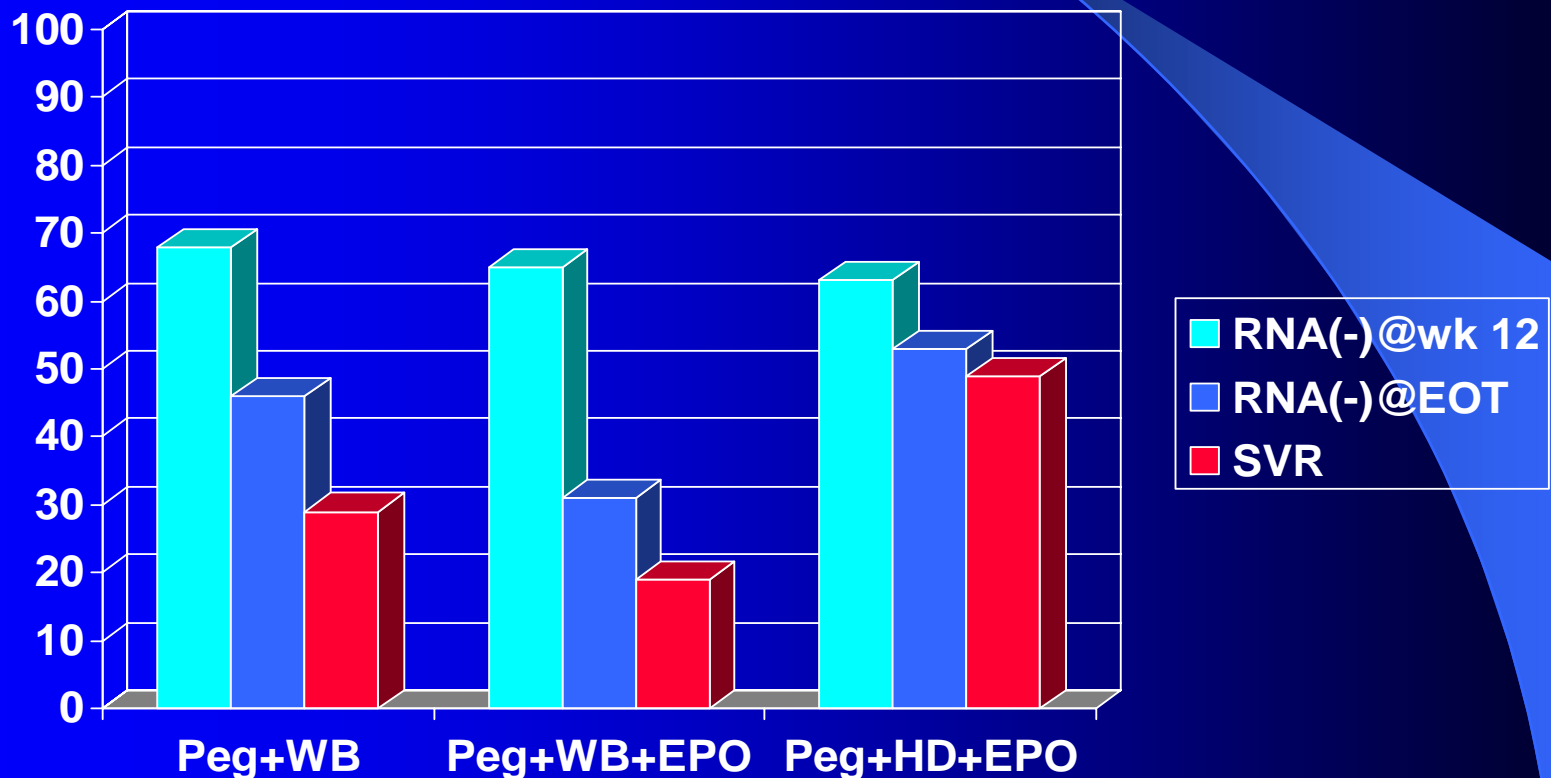
# **Peg-Intron + {[WB-RBV] vs [WB-RBV/EPO] vs [HD-RBV/EPO]} in HCV g-1 naïve**

**Shiffman M et al AASLD 2005, abstr 55**

- 150 HCV g-1, naïve, in prospective, single-center study.
- Peg-Intron 1.5 mcg/kg-week +
  - A) WB-RBV 800-1400 (13.3/kg)
  - B) WB-RBV 800-1400 (13.3/kg) + 10-60K EPO
  - C) HD-RBV 1000-1600 (15.2/kg) + 10-60K EPO
- RBV dose decreased for Hb < 10
- Mean age=48, male=60%, AfrAm=34%,  
mean weight=82.4 kg(49-149), cirrhosis=6%, log  
HCV-RNA 5.5+/-0.32

# Peg-Intron + {[WB-RBV] vs [WB-RBV/EPO] vs [HD-RBV/EPO]} in HCV g-1 naïve

Shiffman M et al AASLD 2005, abstr 55



# **Peg-Intron + {[WB-RBV] vs [WB-RBV/EPO] vs [HD-RBV/EPO]} in HCV g-1 naïve**

**Shiffman M et al AASLD 2005, abstr 55**

	<b>Peg+WB</b>	<b>Peg+WB+ EPO</b>	<b>Peg+HD+ EPO</b>
<b>Max Hb decline (gm/dl)</b>	4.1+/-1.7	3.6+/-1.8	3.8+/-1.5
<b>Mean RBV dose (md/d)</b>	1027+/-167	1088+/-157	1227+/-171
<b>% RBV dose reduction</b>	36	13	27



# CONCLUSION

- Significant increase in SVR can be achieved in HCV-g-1 patients with higher doses of RBV (15.2/kg) along with EPO, to limit dose reduction.

# Ribavirin and Teratogenicity

- Patients should be informed that Ribavirin is teratogenic.
- Ribavirin should not be started unless a pre-treatment pregnancy test has been negative.
- Women of childbearing potential and all males should use 2 methods of contraception during treatment and for 6 months after therapy.
- If pregnancy occurs, they should be advised of the significant teratogenic risk to the fetus.
- Physicians are strongly encouraged to report any pregnancy in a patient or partner, during treatment or 6 months after treatment to: **Ribavirin Pregnancy Registry @ 1-800-593-2214**

# Importance of Maintaining Peg-Interferon Dose

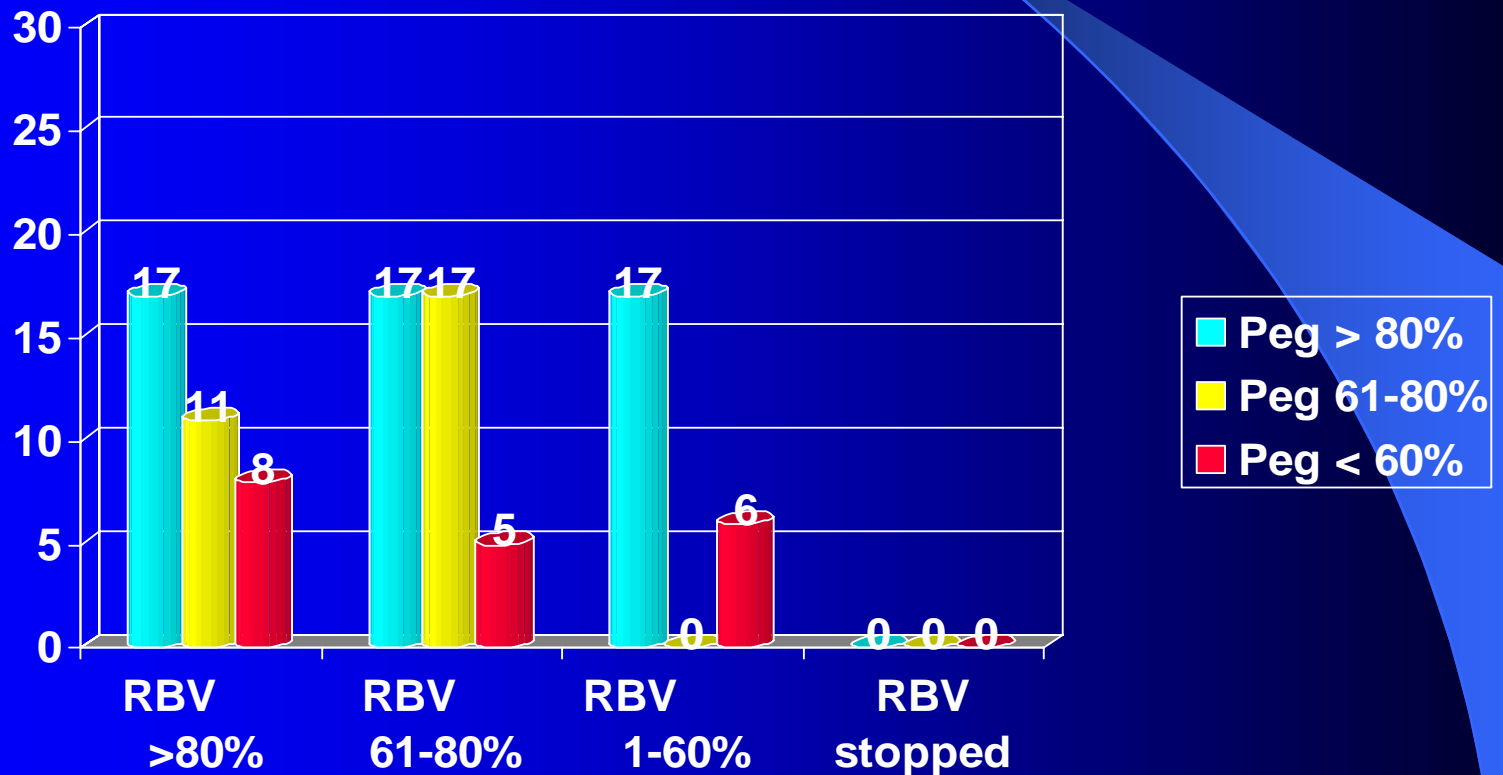
# Effect of Pegasys & RBV dose in G-1 Ifn/Rebetron-NR with advanced fibrosis

Shiffman et al. AASLD Abstr # 349, 2004

- Subgroup analysis of SVR in genotype-1, HALT-C trial patients.
- Doses calculated as “% of target” of Pegasys 180 mcg & RBV 1000-1200 mg depending on weight.
- Analysis of doses from week 1 to 20.

# SVR by Dose Maintained at week 20

Shiffman et al. AASLD Abstr # 349, 2004



# CONCLUSION

Abstr # 349

- In patients with advanced fibrosis (F3/4), non-responders to IFN or IFN/RBV, the best SVR (17%) was observed in patients receiving  $> 80\%$  of their Pegasys during the initial 20 weeks of therapy.
- The RBV dose only affected the outcome if it was discontinued.

# Boceprevir in Chronic HCV

# SPRINT-1 Study Design

Week 4

Week 28

Week 48

Control

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 800-1400 mg for 48 wks

24 wks  
Follow-up

N=104

Lead-in  
Strategy

Peg-IFN $\alpha$ 2b  
+ RBV  
800-1400 mg

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg +  
RBV 800-1400mg +  
Boceprevir 800 mg TID for 24 wks

44 wks  
Follow-up

N=103

Peg-IFN $\alpha$ 2b  
+ RBV  
800-1400 mg

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 800-1400 mg  
+ Boceprevir 800 mg TID for 44 wks

24 wks  
Follow-up

N=103

No  
Lead-in  
Strategy

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 800-1400 mg  
+ Boceprevir 800 mg TID for 28 wks

44 wks  
Follow-up

N=107

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 800-1400 mg  
+ Boceprevir 800 mg TID for 48 wks

24 wks  
Follow-up

N=103

Low  
Dose  
RBV  
Strategy

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 800-1400 mg  
+ Boceprevir 800 mg TID for 48 wks

24 wks  
Follow-up

N=16

Peg-IFN $\alpha$ 2b 1.5  $\mu$ g/kg + RBV 400-1000 mg  
+ Boceprevir 800 mg TID for 48 wks

24 wks  
Follow-up

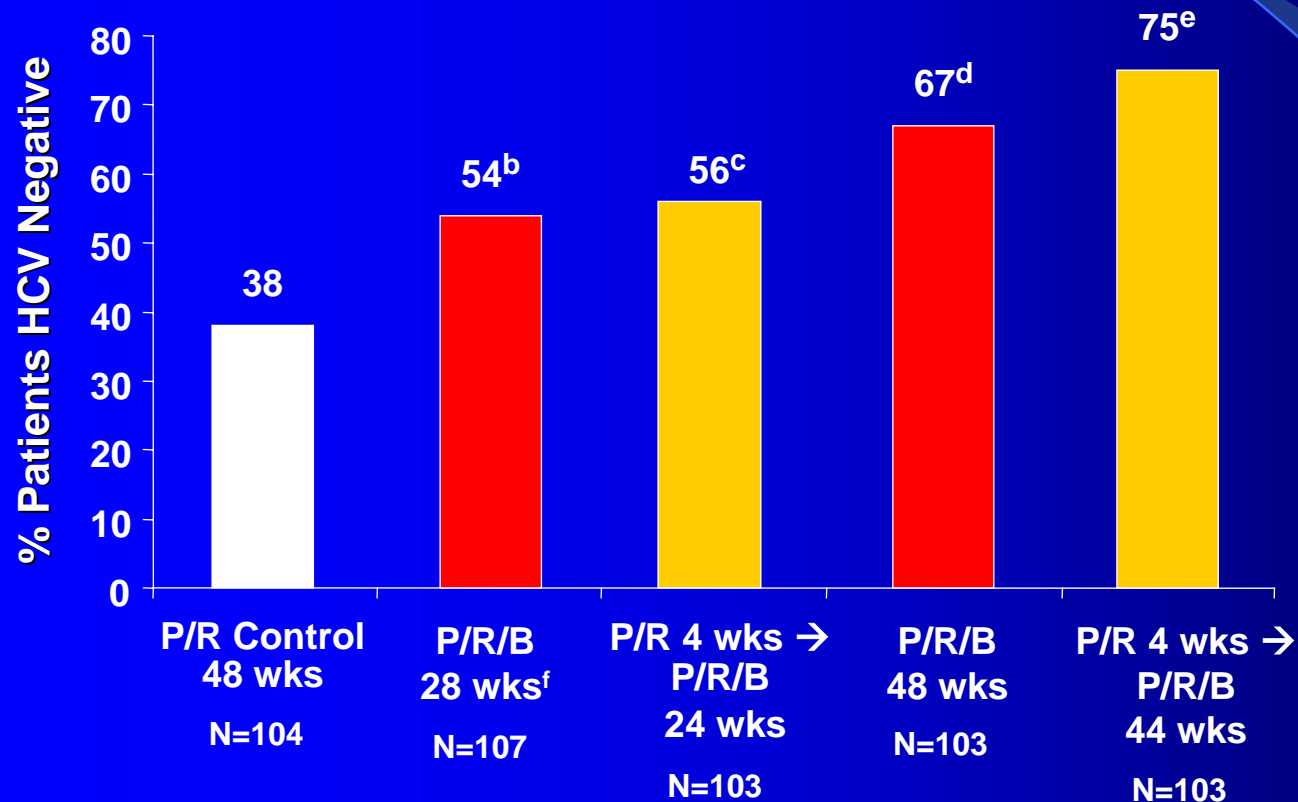
N=59

<sup>a</sup>Part two consisted of 75 patients in 10 US sites, 1:4 randomization.

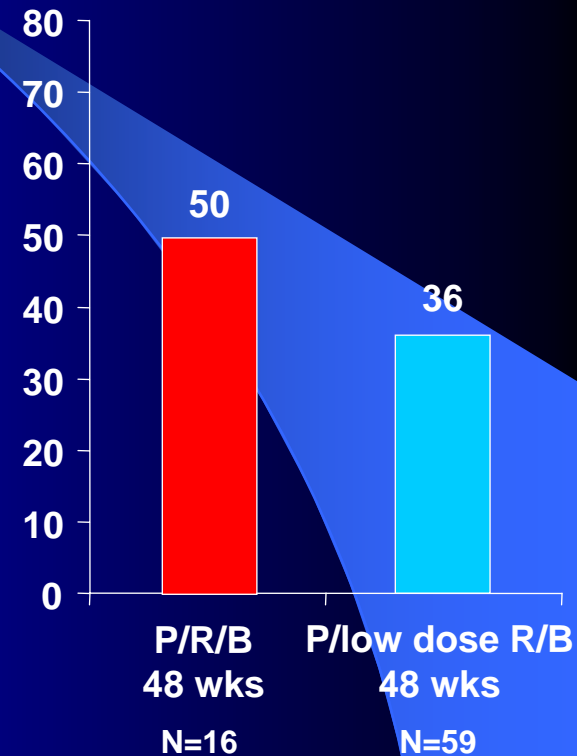


# Sustained Virologic Response<sup>a</sup>

## Part 1



## Part 2

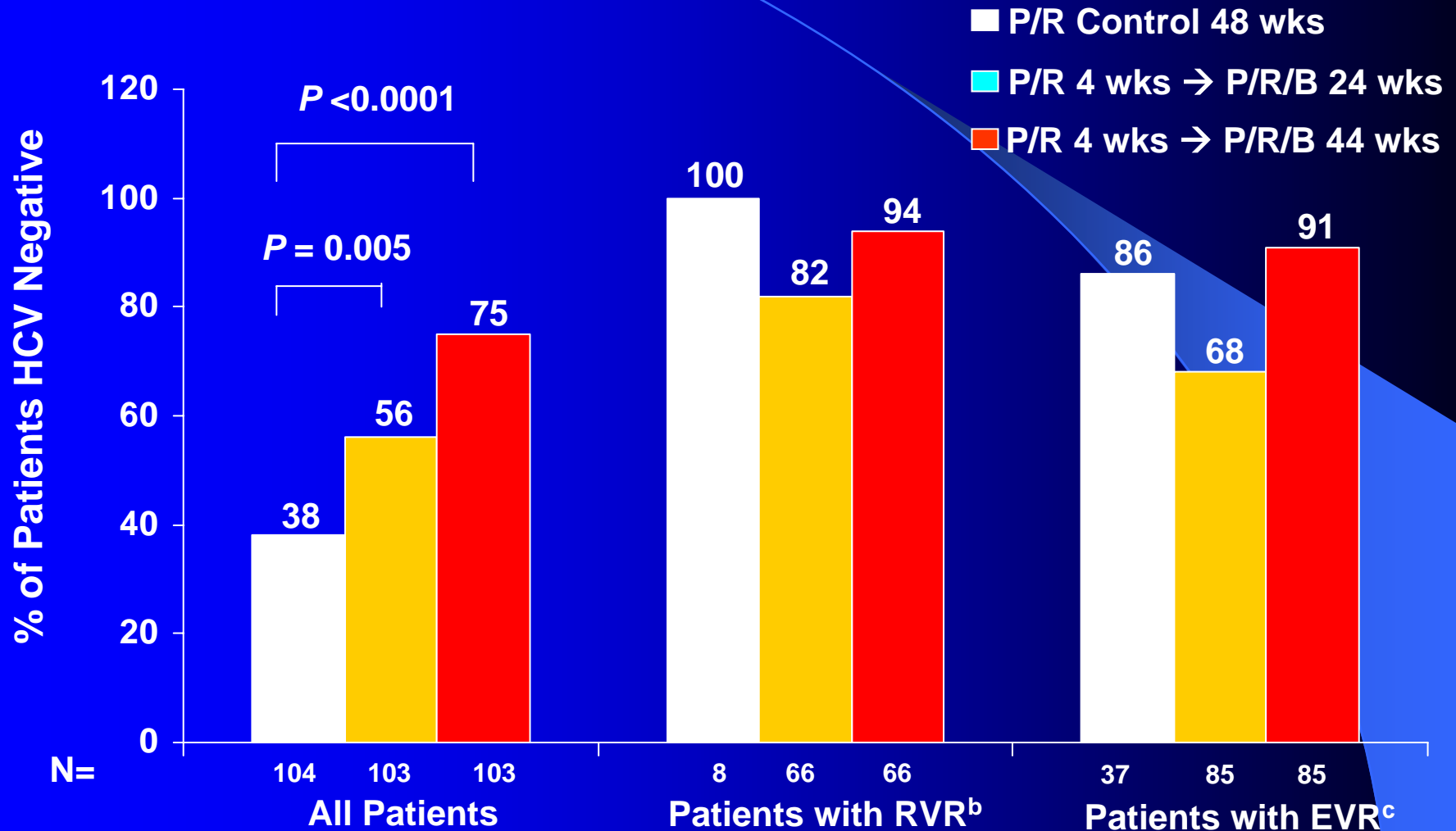


<sup>a</sup>Roche COBAS TaqMan LLD <15 IU/mL; <sup>b</sup> $P = 0.013$ ; <sup>c</sup> $P = 0.005$ ; <sup>d</sup> $P < 0.0001$ ; <sup>e</sup> $P < 0.0001$  compared to P/R Control;

<sup>f</sup>1 late relapser after follow-up week 24, not included in SVR.

# Predictability of SVR: RVR and EVR

SVR<sup>a</sup> by time to first PCR-negative HCV RNA



<sup>a</sup>Roche COBAS TaqMan LLD <15 IU/mL; <sup>b</sup>RVR: undetectable HCV-RNA on or before 4 wks of boceprevir treatment; undetectable HCV-RNA on or on before 4 weeks for P/R control <sup>c</sup>EVR: undetectable HCV-RNA on or before 12 wks of boceprevir treatment; undetectable HCV-RNA on or before 12 weeks for P/R control

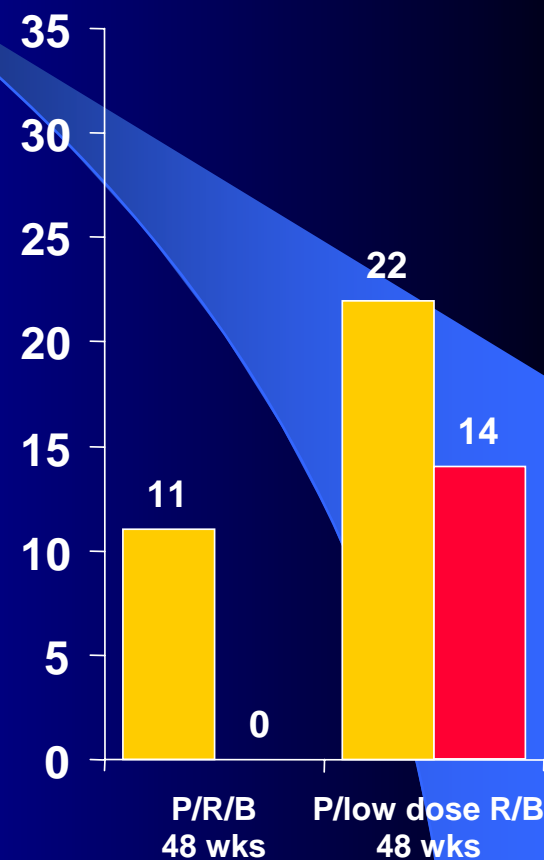
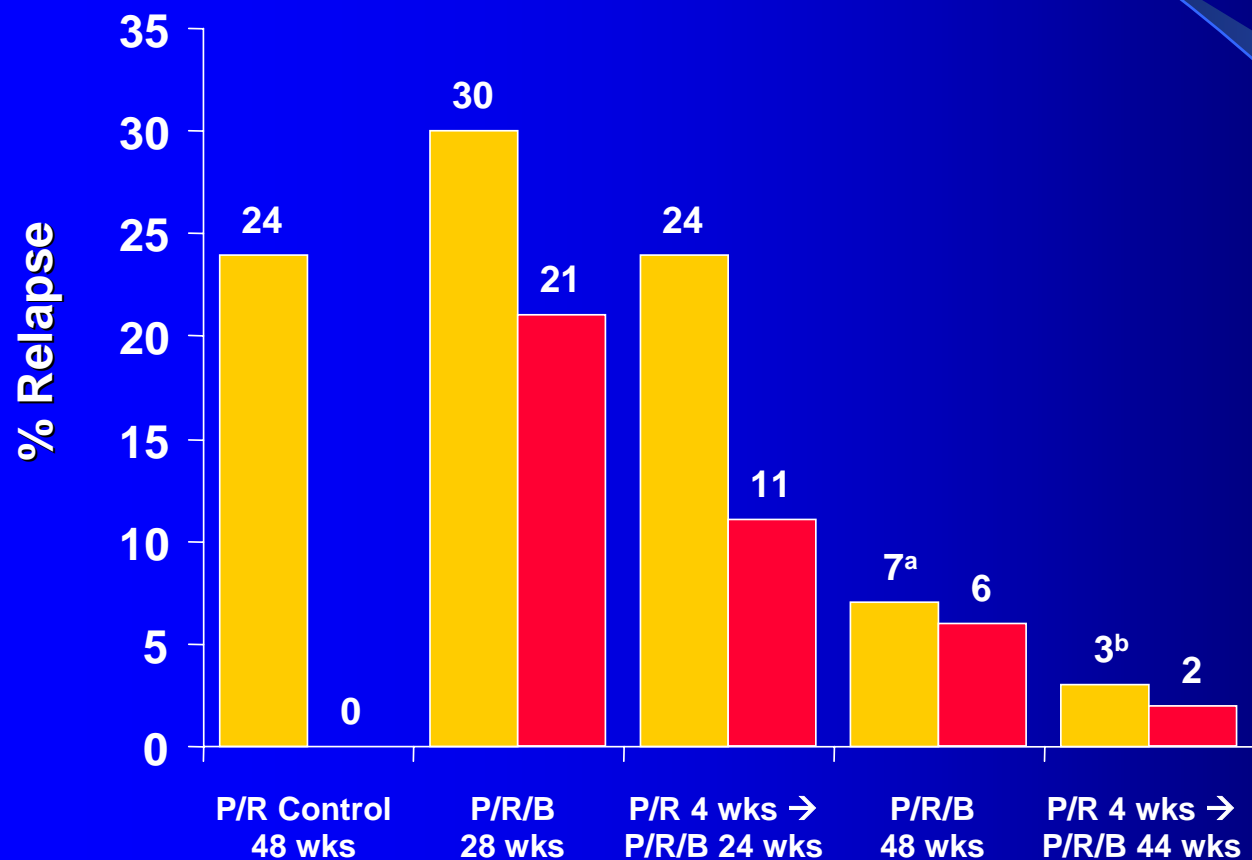
# Overall Relapse and Relationship to RVR

## Part 1

## Part 2

■ Relapse overall

■ Relapse in RVR pts



<sup>a</sup> $P = 0.0079$ ; <sup>b</sup> $P = 0.0002$  compared to P/R Control.

# Summary

- Boceprevir significantly improves SVR
  - Boceprevir with SOC for 48 weeks nearly doubles SVR
  - Week 4 P/R response, RVR, and EVR all show promise for response guided therapy
  - Anemia appears to be a surrogate for response
  - Full dose RBV required
- Safety
  - Boceprevir is well-tolerated for up to 48 weeks
  - No boceprevir-defining toxicity responsible for treatment discontinuation
  - Boceprevir is associated with ~1 g/dL incremental hemoglobin decrease
  - Anemia management with EPO is associated with increased completion rates

# Special Groups

# Non-Responders to PEG/RBV

# Daily IFN alfacon-1 + RBV 1-1200 in PEG/RBV Non-Responders any genotype (DIRECT Trial)

Bacon et al. Hepatology 2009; 49:1938-1846

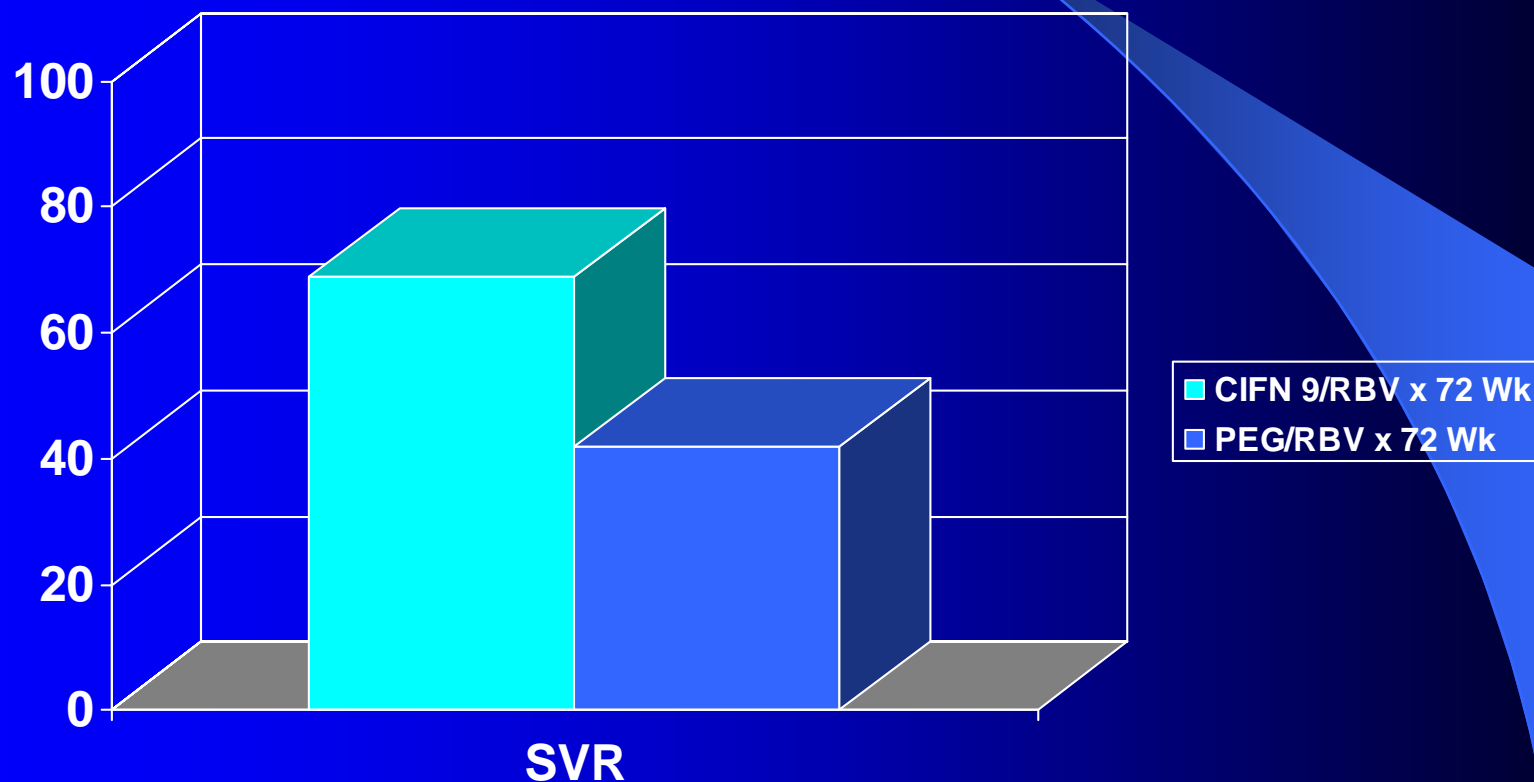
- Best Candidates:
  - Only patients with  $\geq 1$  log drop in HCV-RNA benefit from therapy. Specially true in cirrhotic patients.
  - Patients F0-F3 who had  $> 2$  log HCV-RNA drop @ Wk 12 in PEG/RBV had SVR of 31% with 15 mcg/d.
  - Patients with Non-1 genotype had SVR of 48%.
- Overall response: 6.9% with 9 mcg/d, and 10.7% with 15 mcg/d.
- If patients had cEVR (HCV-RNA(-) @ Wk 12), SVR was 81% for 9 mcg/d and 63% for 15 mcg/d.
- In Slow responders ( $> 2$  log drop @ Wk 12, HCV-RNA(-) @ Wk 24), SVR was 12% with 9 mcg/d and 35% with 15 mcg/d.

# Relapsers to PEG/RBV



# Daily IFN-alfacon/RBV vs PEG/RBV x 72 Wks in G-1 PEG/RBV Relapsers

Kaiser et al. Hepatology 2007; 46(4 suppl 1):819A. Abstr



N = 120 patients in the prospective study.

# Indolent B-Cell Non-Hodgkin Lymphoma

# Treatment of HCV-related Indolent B-Cell Non-Hodgkin Lymphoma

- Indolent NHL has reasonable long-term survival of several years.
- Usually not curable with conventional therapy.
- Indolent HCV-related NHL treatable with Peg-IFN/RBV:
  - Follicular (stage I & II)
  - Plasmacytoid
  - Marginal Zone (Splenic, Nodal, or Extra-nodal)
- Up to 80% of those with SVR have a sustained hematological response.
- Non-Responders to Peg-IFN/RBV: Rituximab + CHOP

# Ann-Arbor Classification of NHL

Stage I	Involvement of a single lymph node region (I), or a single extralymphatic organ or site (IE)
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II), or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement.

**A:** no systemic symptoms;

**B:** unexplained fever, night sweats, or weight loss > 10% during 6 months before diagnosis

# HCV-related Mixed (IgG/IgM) Cryoglobulinemia

# HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Type II mixed: 95% of patients have HCV infection.
- Some cases of type-III mixed cryoglobulinemia are also HCV-related.
- Palpable purpura, skin necrosis in exposed areas, hepatosplenomegaly, hypocomplementemia C3, C4, C1q ( $C4 < C3$ ), & IgM kappa Rheumatoid Factor.
- Renal disease: hematuria, proteinuria (nephritic range), hypertension (80%), moderate renal insufficiency (50%).
- HCV-containing immune complexes cause the renal disease.

# HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Plasmapheresis: one plasma volume TIW replaced with warmed 5% albumin x 2-3 weeks. Indicated for:
  - Progressive renal failure
  - Distal necrosis requiring amputation
  - Advanced neuropathy.
- Peg-Ifn + RBV: Not appropriate when plasmapheresis is needed (but can be used 2-4 months after plasmapheresis)
  - SVR is 40-50%.
  - Decreases cryoglobulin levels.
  - Improves vasculitis, skin rash and arthritis/arthralgia, proteinuria.
  - Polyneuropathy & renal function do not reliably improve.
  - Treatment may be preceded by Plasmapheresis, and/or Rituximab
  - Cryoglobulinemia may persist or recur even after SVR.

# HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Rituximab: When other options not indicated. Once a week IV for 4 weeks.
  - Improves vasculitis, skin rash, indolent B-cell NHL, arthralgia, MPGN, arthritis/arthralgia.
  - HCV-RNA increases 2-fold.



# HCV-Related Renal Disease

# HCV-Related Renal Disease

## Peg-IFN + RBV Treatment

- **Mixed Cryoglobulinemia** (good data; treat)
- **Membranoproliferative Glomerulonephritis**, even without detectable cryoglobulins (good data; treat)
- **Membranous Nephropathy** (conflicting data; consider treatment)
- **Crescentic Glomerulonephritis** associated to the previous three disorders (good data; treat with Plasmapheresis followed by Rituximab; 2-4 months later Peg-IFN/RBV).
- Give ACE inhibitor or ARB to control proteinuria y blood pressure.
- Uncommon (no good data available):
  - Focal Segmental Glomerular Sclerosis
  - Proliferative Glomerulonephritis
  - Fibrillary Glomerulopathy
  - Immunotactoid Glomerulopathy
  - Post-transplant Thrombotic Microangiopathy

# Treatment of Chronic HCV in ESRD on Dialysis

# HCV in ESRD & post-KTx Treatment

- Risk of Interferon use post-KTx is high: 15-64% vascular rejection / tubulo-interstitial lesion.(not recommended)
- Difficult to use Ribavirin in ESRD b/o toxicity (dose is 150-300 mg/d) ; severe hemolysis.
- Lower efficacy of Interferon (18-27% SVR) in ESRD.
- Dose: PEG-Intron 1 mcg/kg/week; PEGASYS 135-180 mcg/week.
- Erythropoietin is usually needed

# Peg-IFN-a2a in ESRD

## Pharmacokinetics

- Peg-Ifn-a2a is not significantly cleared by dialysis (hemodialysis or peritoneodialysis).
- In a 12 weeks study, Peg-Ifn-a2a 135 or 180 mcg once weekly gave safe and constant concentration on patients with ESRD on hemodialysis.
- The dose of 135 mcg/wk in ESRD gives levels similar to those of patients with normal renal function receiving 180 mcg/wk (13000 pg/mL).
- Safety of 135 vs 180 mcg per week in ESRD is similar.

# Peg-Ifn-a2a Monotherapy in ESRD (hemo- or peritoneo- dialysis)

Author	Treatment	Result
Kokoglu (J Gastroenterol Hepatol 2006;21:575-580)	Rp(12): Peg 135 x 48w C(13): no therapy	Rp: EOT(-) 84%, <b>SVR 75%</b> C: EOT(-) 8%, SVR 8%
Sporea (World J Gastroenterol 2006;12(26):4191-4194)	Rp(10): Peg 180 x 48w	SVR: <b>ITT 30%</b> , PP 50%
Chan (Nephrology 2007;12:11-17)	Rp(6): Peg 135 x 48 w	EOT(-) 83%, <b>SVR 33%</b>
Teta (Nephrol Dial Transplant 2005;20:991-993)	Rp(3): Peg 90-180 x 24-48 w	<b>SVR 66%</b>
Peck-Radosavljevic (EASLD Abstr. April 2007)	Rp(38): Peg 135 x 48 w Rp(43): peg 90 x 48 w	Interim wk 24: HCV-RNA(-) 58% vs 49%
Ionita-Radu (EASLD Abstr. April 2007)	Rp(29): Peg 135	<b>SVR 41%</b>

# Peg-Inf-a2a + RBV in ESRD (hemo- or peritoneo- dialysis)

Author	Treatment	Result
Rendina (Journal of Hepatology 2007:768-774)	Rp(35): Peg 135/RBV 200qd x 48 w(g-1) or 24 w (g-no-1)+EPO C(35): no therapy	Rp: <b>SVR 97%</b> (93% g-1, 100% g-non-1)
Hakim (DDW Abstr. May 2006)	Rp(20): Peg 135/RBV 200 TIW x 48 w	Interim 12 w: HCV-RNA(-) 45%
Deltenre (AASLD Abstr. Oct 2006)	Rp(14): Peg 180/RBV 800 per w x 24-48 w + EPO	EOT(-): 79%, <b>SVR 63%</b>
Carriero (AASLD Abstr. Oct 2006)	Rp(15): Peg 135-180/RBV 200 qd x 4-76 w + EPO	<b>SVR 31%</b>
Bruchfeld (J Viral Hepatitis 2006;13:316-321)	Rp(2): Peg 135/RBV 1400-2000 mg per w + EPO	<b>SVR 100%</b>

# Treatment According to Stages of Chronic Kidney Diseases

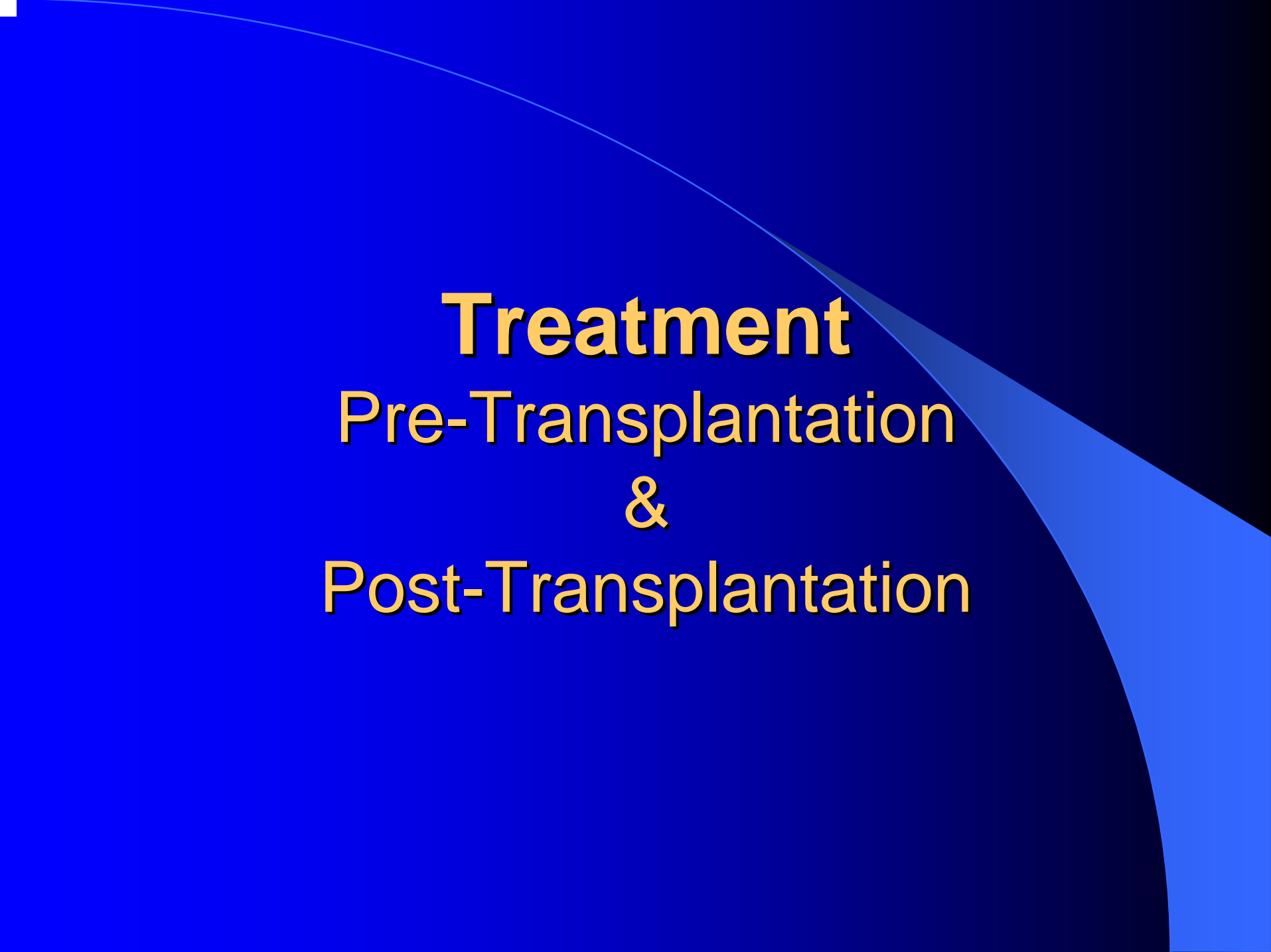
Stage	Description	GFR (ml min <sup>-1</sup> 1.73 m <sup>2</sup> )	Recommended Treatment
1.	Kidney damage with normal or increased GFR	90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	15	B
5D.	Dialysis (hemo-or peritoneal)		C

**A:** Routine combination therapy according to viral genotype.

**B:** Peginterferon alfa-2b, 1 mcg/kg subcutaneously once weekly, or Peginterferon alfa-2a, 135 mcg subcutaneously once weekly plus Ribavirin, 200-800 mg/day in two divided doses starting with low dose and increasing gradually

**C:** Controversial: Standard interferon (2a or 2b) 3mU three times weekly, or Pegylated interferon alfa-2b, 1 mcg/kg/week, or Pegylated interferon alfa-2a, 135 mcg/week ♦ Ribavirin in markedly reduced daily dose.



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# **Treatment**

## **Pre-Transplantation**

### **&**

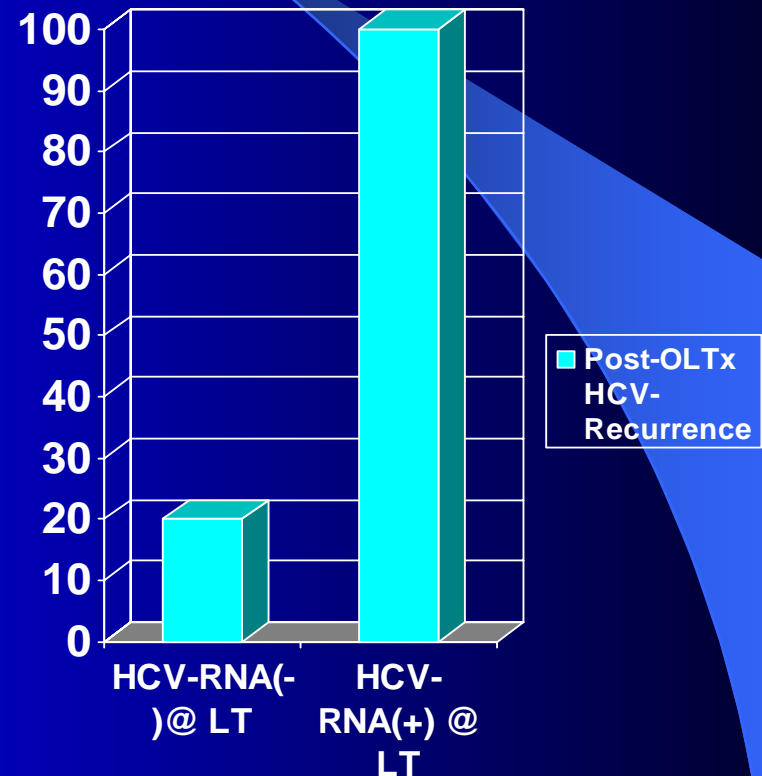
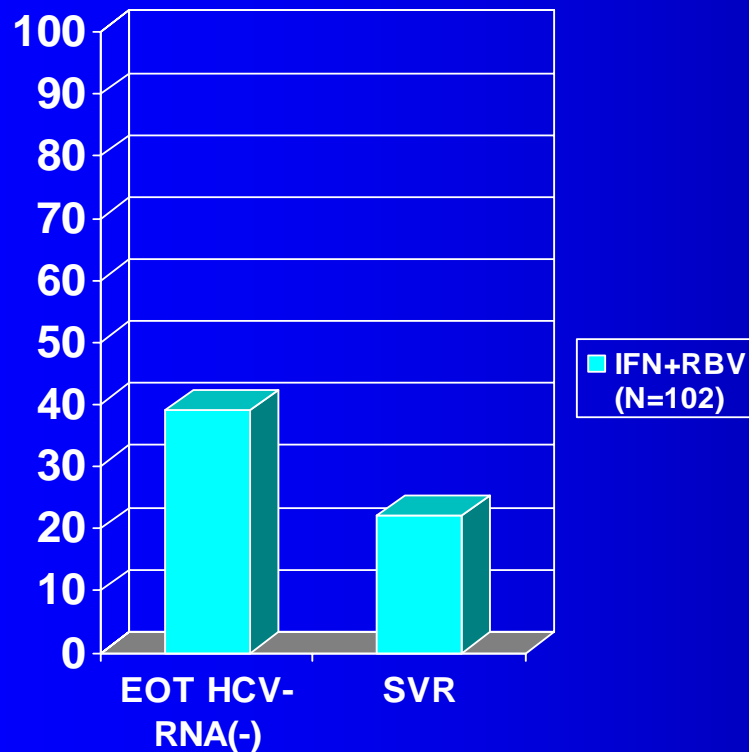
## **Post-Transplantation**

# Pre-LTx Treatment Candidates

- **Best Candidates:**
  - Child-Turcotte score  $\leq 7$
  - MELD  $\leq 18$
- **Best response:**
  - genotype 2 & 3 (47% SVR) vs g-1 (13% SVR)
- Patients with Child-Turcotte 8 to 10, or MELD 18 to 24 are controversial. They benefit from antibiotic prophylaxis during therapy (Norfloxacin).
- **Patients with Child-Turcotte  $\geq 11$ , or MELD  $\geq 25$  are not treatment candidates.**

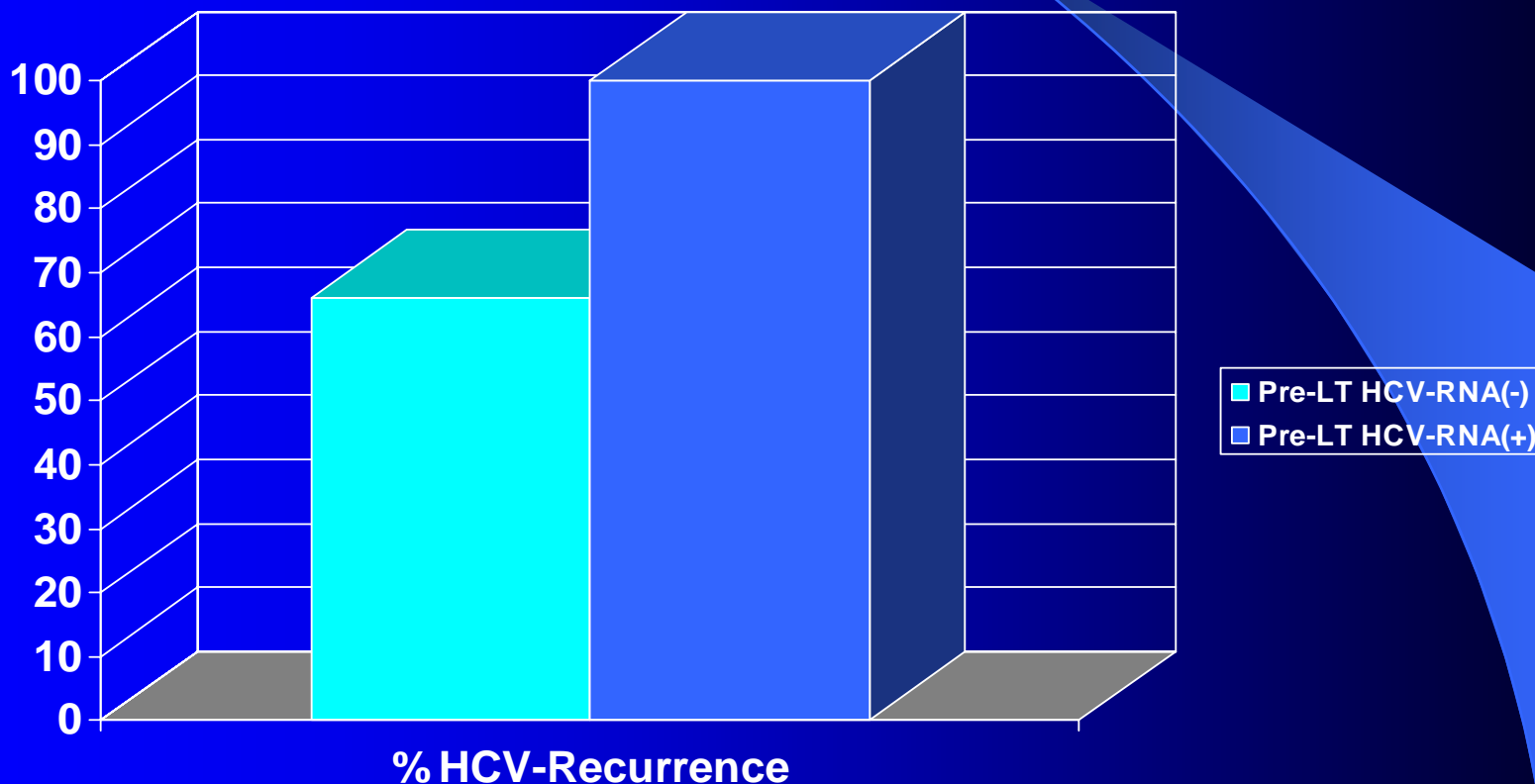
# Effect of pre-LT Therapy on Post-OLTx Outcome in Cirrhotics listed for LT

Everson et al. Rev. Gastrointest Disord 2004;4 Suppl 1:S31-38



# Post OLTx HCV-Recurrence in Listed Cirrhotics Treated with Daily IFN Monotherapy

Thomas et al. Liver Transpl 2003;9:905-915



# Treatment of Recurrent HCV

## Preemptive

- Starts therapy shortly post LTx.
- Treatment is poorly tolerated.
- Discontinuation rate: 33%
- Reported SVR: 10-25%

# Treatment of Recurrent HCV

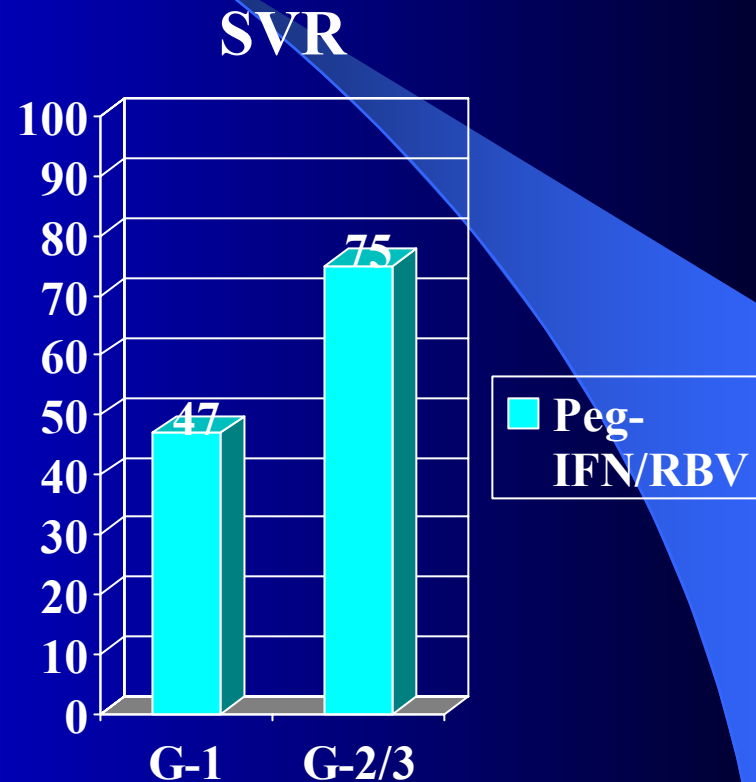
## After METAVIR Stage 2 (occasional bridging)

- Interferon or RBV monotherapy have not improved fibrosis nor induced SVR.
- With Peg-IFN + RBV, SVR has been 26-45%
- 60% of patients with SVR improve histology; 20 % remain stable.
- 30-60% require RBV dose reduction;
- 30% need discontinuation of therapy.
- There is no increase in rate of Acute nor Chronic Rejection if adequate levels of anti-rejection therapy are kept.
- Anti-rejection drug levels frequently fall as liver improves during therapy; check levels and modify dose as needed.

# Peg-IFN + RBV for HCV Recurrence in OLTx Recipients

Berenguer M et al. Liver Transpl 12:1067-1076, 2006

- 36 patients
- Median time OLTx-Rp = 513 d
- Cirrhosis 15%,  
cholestatic HCV 9%
- 88% off steroids
- Premature D/C 40%
- ADEs 57%
- Rejection 14%
- EPO increased SVR
- HCV-RNA drop  $< 2$  log @ 12 wks = non-response



# 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 HBV)
- **Prophylaxis:** HBV vaccination.

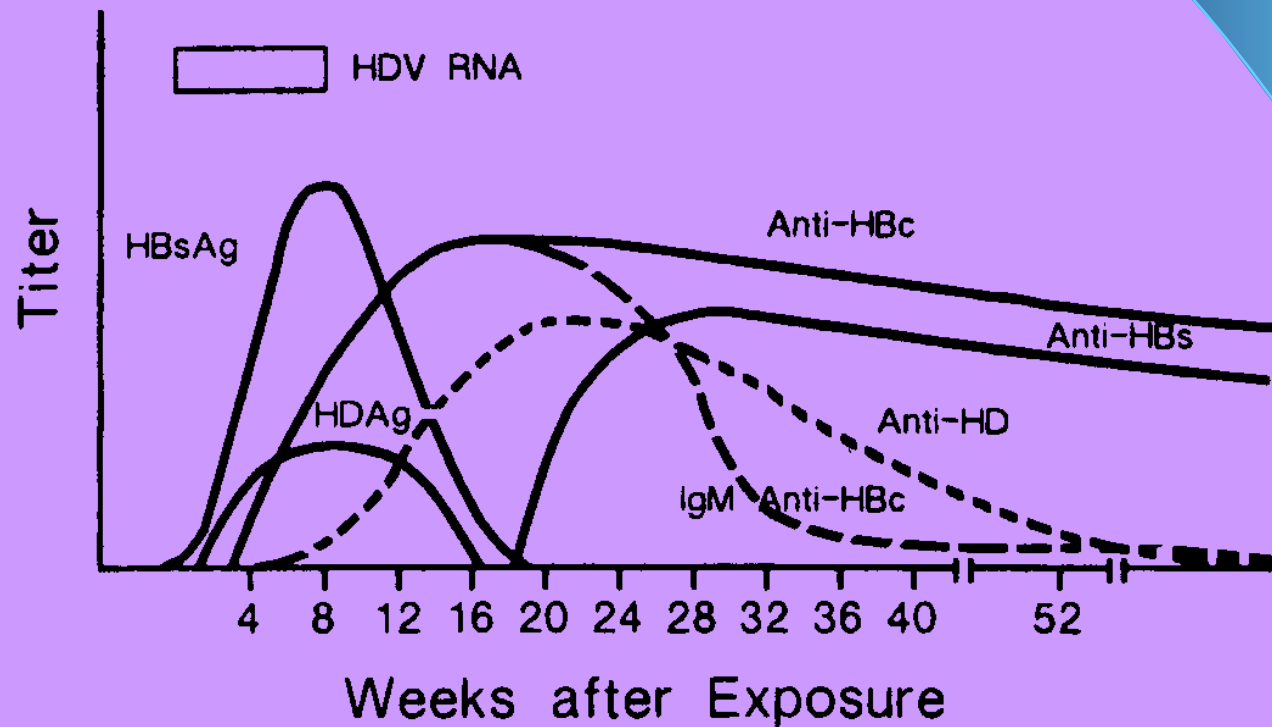
# HDV Co-Infection

- 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 Coinfection with HBV

HDV

## Coinfection with HBV



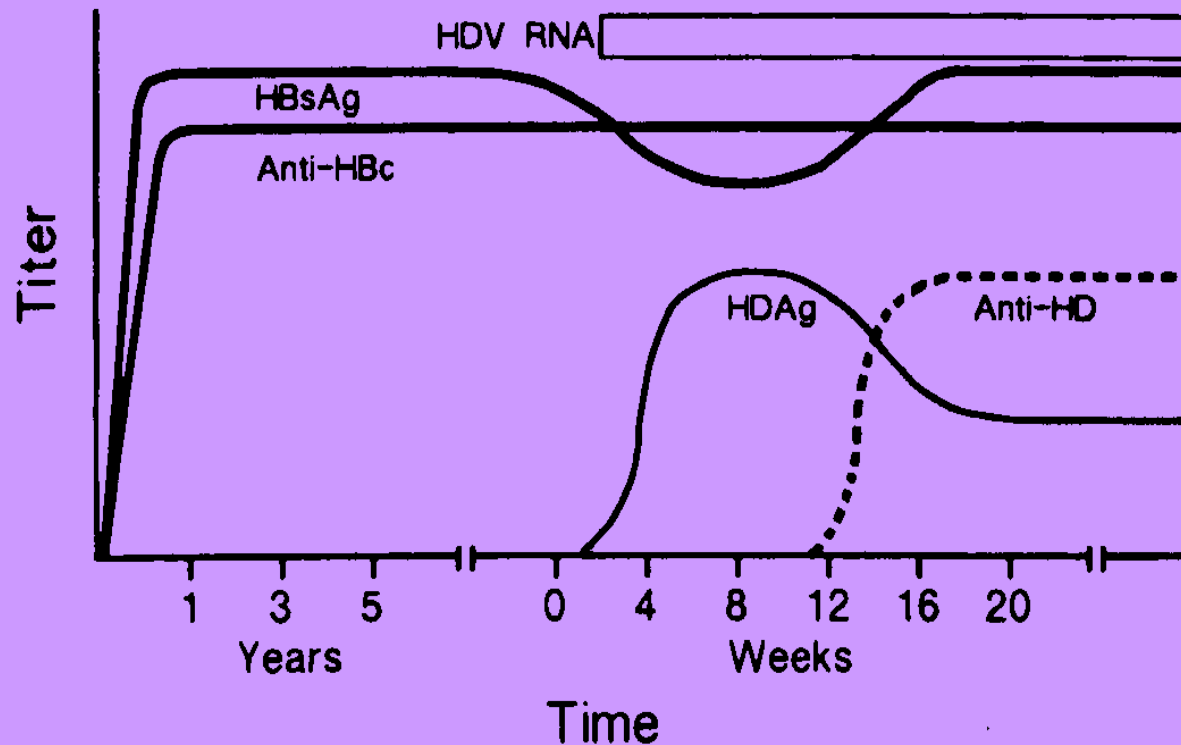
# HDV Super-Infection

- 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(+).

# Chronic Hepatitis D

**HDV**

Persistent Infection after  
Superinfection of HBV Carrier



# 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 %

**QUESTIONS ?**

# Basic Principles of Viral Kinetics

## Phase I (Early Phase)

- Early decline (*24-48 hours*) in HCV RNA
- Represents effects generally associated with a drug's *ability to block virion production and release*
- Drug efficacy ( $\epsilon$ ) is measured during Phase I
- Measured in % and/or  $\log_{10}$  decline
  - 90% = 1 log decline
  - 99% = 2 log decline
  - 99.9% = 3 log decline
- Low efficacy (<90% or <1.0 log decline)
  - Predictive of non-SVR
  - Interferon “resistance” (?); IFN with early peak will give better “phase I” decline.
- Time to decline may also be predictive of drug efficacy



# Basic Principles of Viral Kinetics

## Phase II (Late Phase)

- Delayed decline in HCV-RNA (3-28 days)
- Reflective of
  - *Cell death by cytotoxic or NK cells*
  - *Non-cytopathic clearance of virus from cells by cytokines*
- Greater degrees of patient variability (calculated by the slope to “undetectable” level)
  - Rapid decline (<30days) => ++++ response
  - Medium decline (30-90 days) => +++ response
  - Slow decline (30 -180 days) => +/- response
  - Initial response then rebound => no response
  - Flat decline => no response
- Rate of decline to “undetectable” in first 28 days is predictive of response with IFN monotherapy
- Questionable predictive value in immunocompromised patients

# Basic Principles of Viral Kinetics

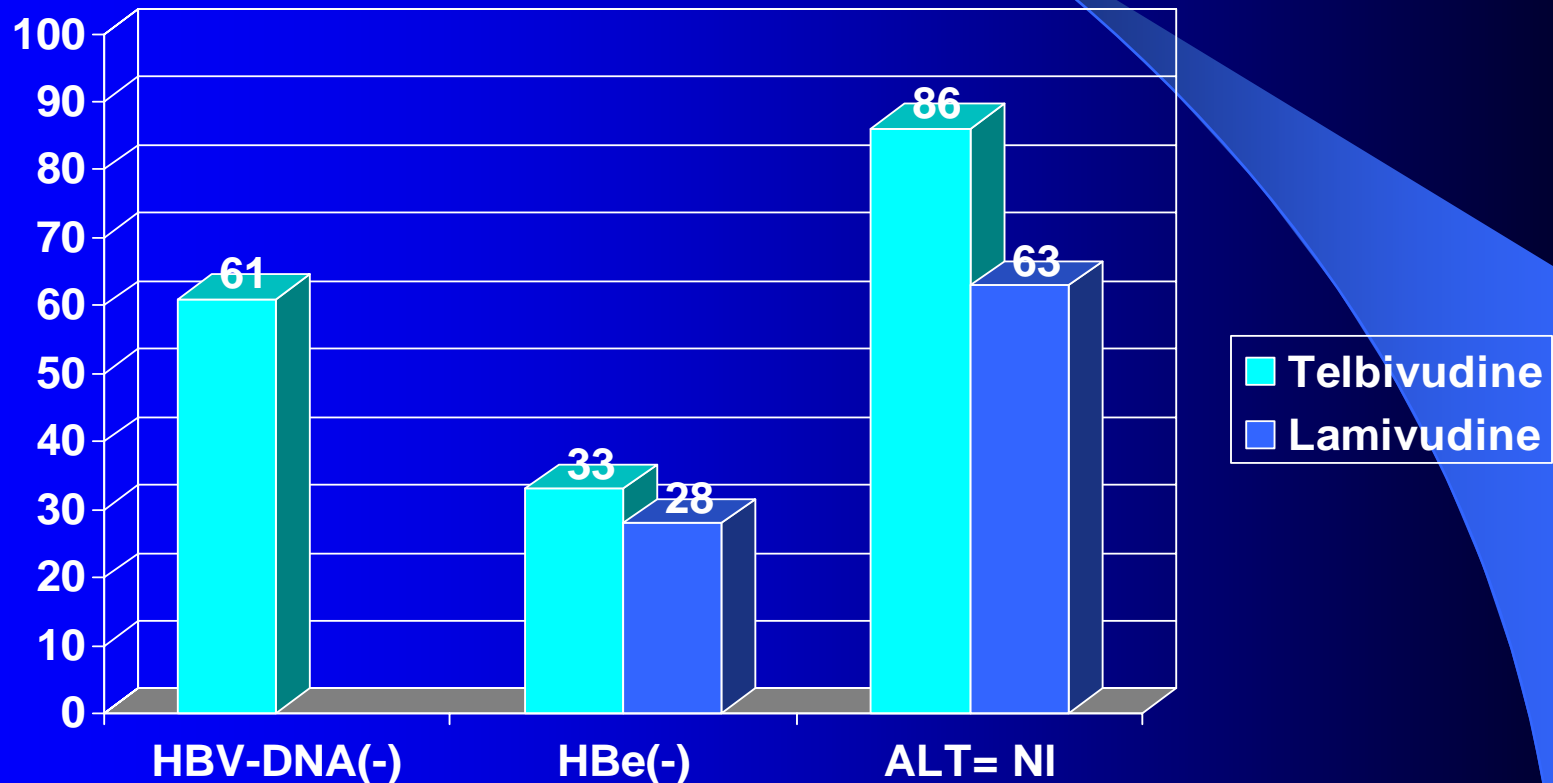
## Phase III (Delayed Phase)

- Triphasic pattern best reported in combination therapy studies
- Late decline (28 - ?? days)
- Represents *continued immune clearance of HCV infected hepatocytes*
- Has been noted with IFN and IFN/RBV combinations but felt to be predominantly associated with RBV
- Important for:
  - Determination of EVR
  - Reduction in relapse?
- Degree of Phase I decline **and** viral rebound are important in determining effectiveness of Phase II and III for viral elimination (lower starting point).



# Telbivudine x 52 wks in HBe(+)

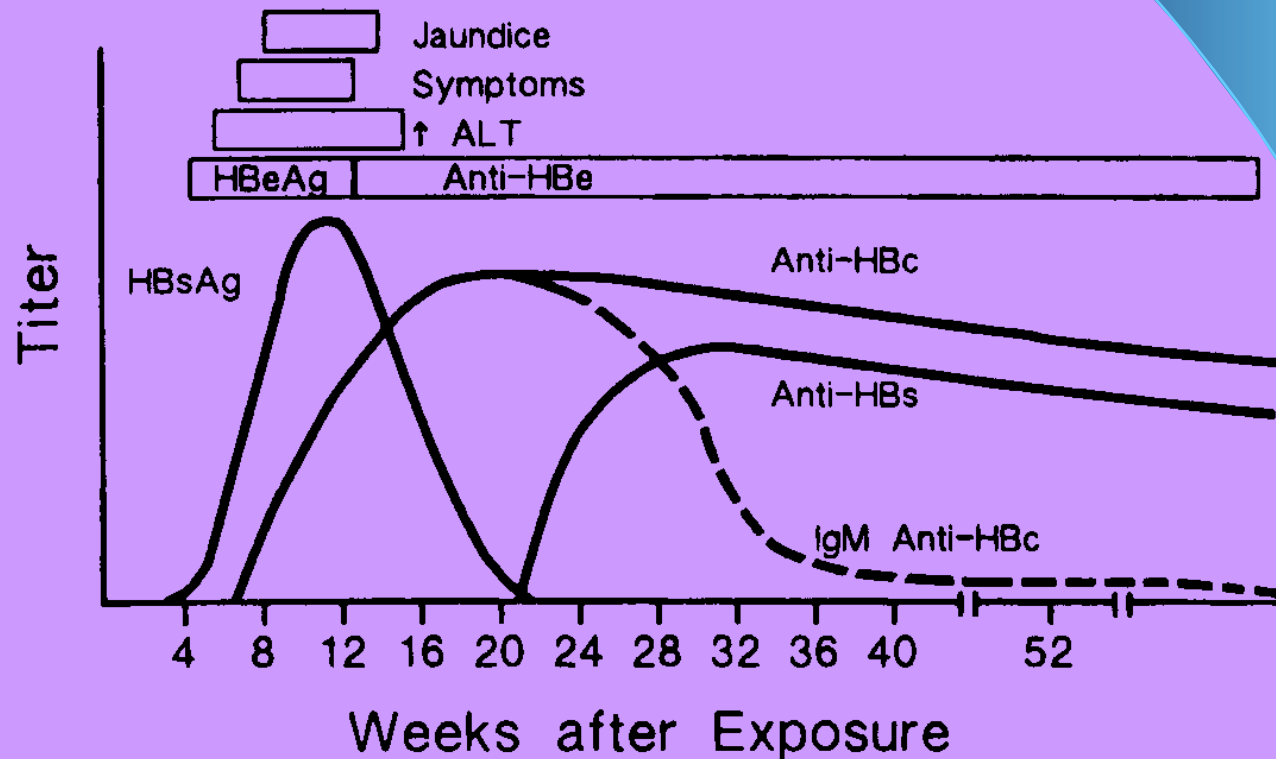
Han S et al. EASL 2004, Abstr# 42



# Acute HBV Infection

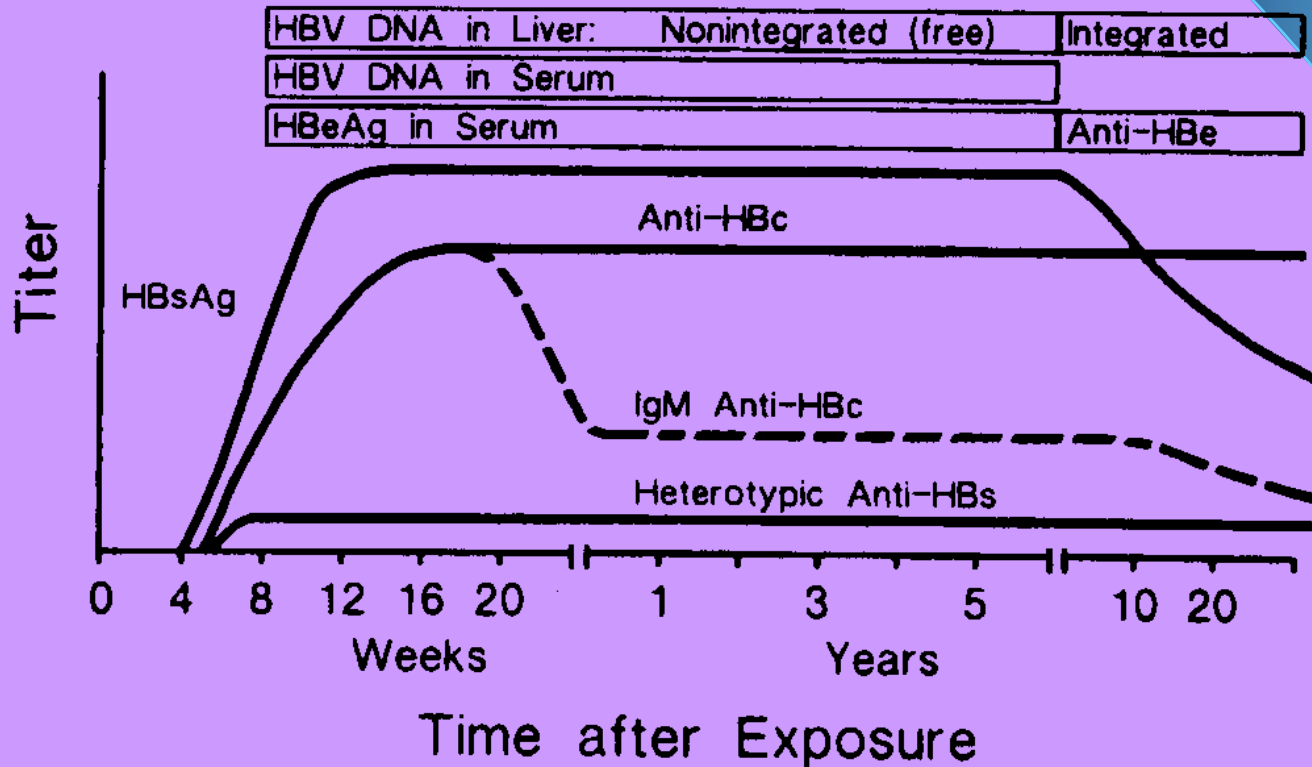
## ACUTE HBV INFECTION

### Sequence of Events

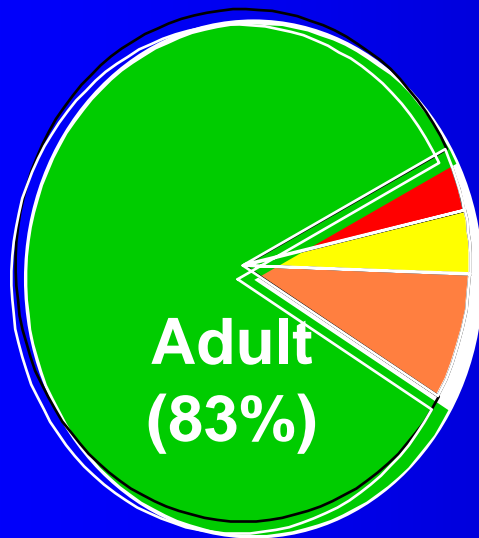


# Chronic HBV Infection

## Sequence of Events

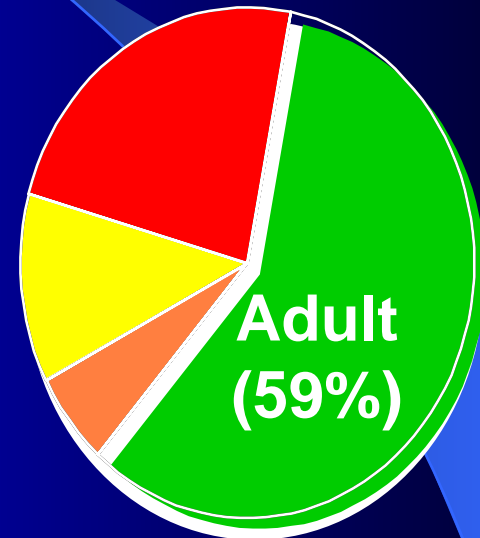


# Age at Acquisition of Acute and Chronic HBV Infection: United States, 1989 Estimates



Acute HBV Infections

(4%) Perinatal (24%)  
(4%) Children (12%)  
(1-10 yrs)  
(8%) Adolescent (6%)



Chronic HBV Infections

# Prevalence of HCV

● GROUP	%
● Hemophilia <'87	82
● IVDA	80
● Hemodialysis	10
● Transfusion < '90	7
● Person w STD	6

● GROUP	%
● Infant of RNA(+) mother	5
● Homosexual men	4
● Monogamous partner	2
● General population	1.8
● Volunteer blood donor	.16



# Risk of HCV in IVDU (% infected)

