

Viral Hepatitis: A Review

Ahmed Mayet, Pharm.D

Assistant Professor; KSU

Introduction

■ Hepatitis A and E

- Fecal-oral transmission

■ Hepatitis B and C

- Blood and percutaneous transmission

Definition of Acute and Chronic Hepatitis

■ Acute hepatitis

- Sign and symptoms last less than 6 months and resolve

■ Chronic hepatitis

- Hepatocellular necrosis for more than 6 months or more beyond the one set of acute illness

Important features of HAV, HBV, HCV, HDV, & HEV

	HAV	HBV	HCV	HDV	HEV
Virus	HAV	HBV	HCV	HDV	HEV
Family	Picornavir- us	Hepadnaviru s	Flaviviru s	Satellite	Calciviru s
Size (nm)	27	42	30-60	40	32
Genome	RNA	DNA	RNA	RNA	RNA
Incubation (Wks)	2-4	4-20	2-26	6-9	3-8
Transmission	Fecal-oral, Cont. food & water	Parental, Sexual, Perinatal	Parental Sexual (?)	Parental Sexual (?)	Fecal-oral
Acute mortality %	0.2	0.2-1	0.2	2-20	0.2
Chronicity	No	2-7%	50-70%	2-70%	No
HCC	No	Yes	Yes	Yes	No



Hepatitis A Virus

HAV

Case

- Mr. X is father of five children. One of his child is four years old and attending a pre-school where most of the pupils are of the same age. The school principle informed him that some of the pupils are having hepatitis A in his school. He wants to protect him and his wife from Hepatitis A infection. Next day they went to clinic to test their hepatitis A status. Mr. X is tested positive for Hepatitis A anti-IgG antibody while his wife Mrs. X is tested negative for Hepatitis A anti-IgG and IgM antibody. His son is tested positive for Hepatitis A anti-IgM antibody

Case

- Is Mr. X infected with Hepatitis A virus currently and he may take immunoglobulin for Hepatitis A infection to protect him from full blown hepatitis

or

- Mr. X is infected with Hepatitis A virus currently and he may take vaccination for Hepatitis A infection to protect him from full blown hepatitis

- Can we say that Mrs. X is not infected with Hepatitis A virus and she does not need to take HAV IgG and vaccination both immediately?
- What shall we do with her?

Case

- What will you advise to his father for his four year old son?
- What about rest of the children should do?

Hepatitis A

- Self limiting, mild and unrecognized
- No human asymptomatic carrier
- No chronicity
- Preventable either by vaccination or IG
- Children age 5-14 years → highest incidence and in lower socioeconomic groups
- Fulminant is rare 0.1-1.0%

Risk Factors

- Close contact with HAV
- Day care center
- Recent traveling history
- Raw shell-fish ingestion

Clinical Manifestations

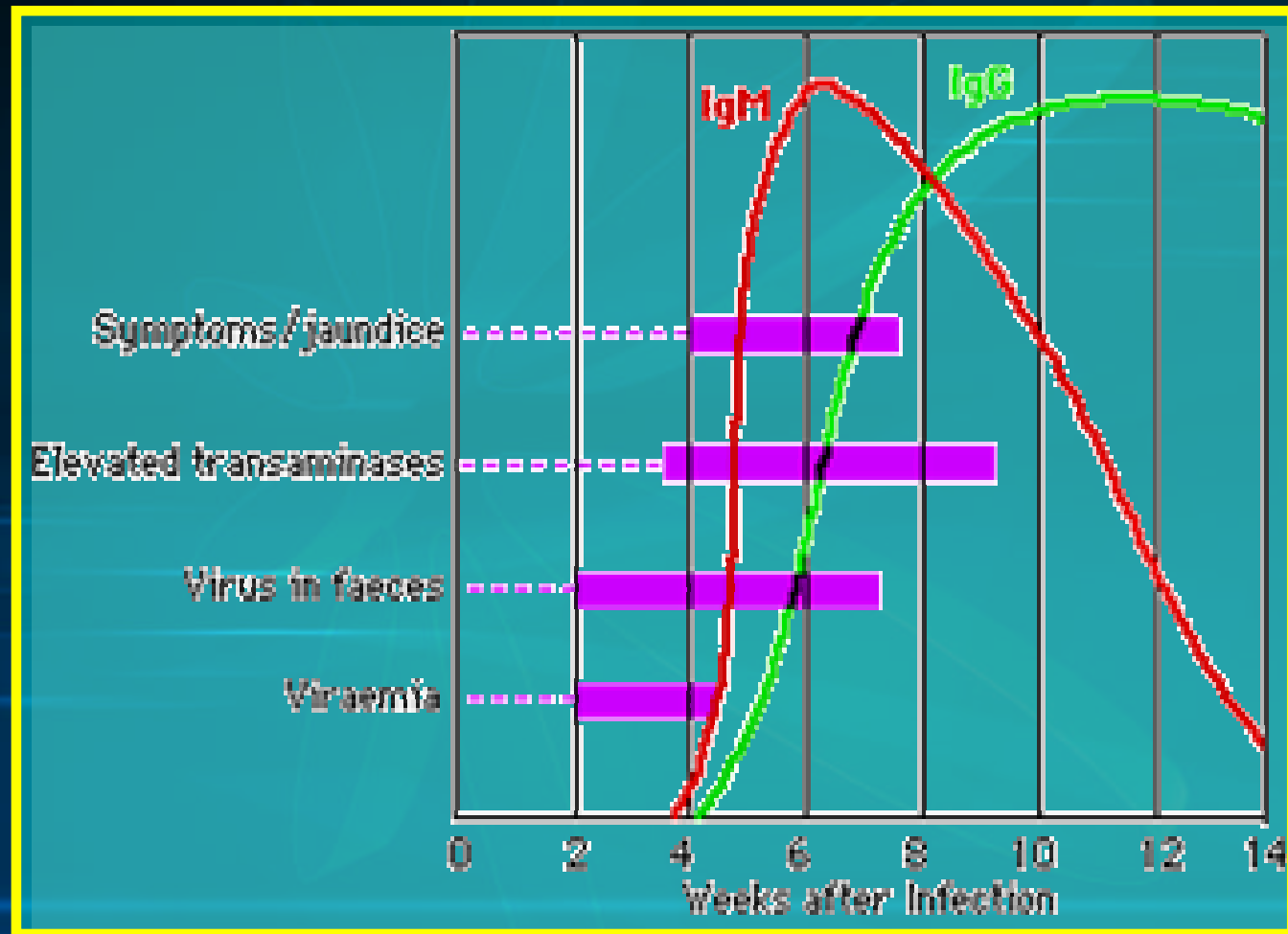
- Symptoms present within 1-2 wks before the onset of jaundice
- Symptoms include fatigue, weakness, anorexia, nausea, vomiting, & abdominal pain
- Prodromal phase ALT > AST peak occur before the onset of jaundice
- Serum bilirubin rarely > 10 mg/dl

Diagnosis

- Two classes of anti-HAV are detectable: IgM & IgG.
- Detection of IgM consistent with acute HAV infection.
- IgG appears early in the convalescent phase and in individual with past exposure give a life long immunity

Hepatitis A.

Hepatitis A



Prevention

- **Passive immunization**, temporary protective antibody in the form of IgG is administered
- **Active immunization**, a vaccine is administered to induce the production of protective antibody
- **Prophylaxis**, can be administered before exposure (pre-exposure prophylaxis) or after exposure (post-exposure prophylaxis)

Pre & Post-Exposure Prophylaxis

- 0.02 ml/kg and 0.06 ml/kg of IgG administered I.M gives protection for < 3 and < 5 months respectively
- Vaccination by at least 1 month before exposure to HAV don't require IgG → protective antibody titers are achieved in > 95% of pts 1 month after vaccination
- IgG giving within 2 weeks of exposure to HAV is up to 90% effective in preventing acute HAV infection

Precautions

- IgG may interfere with the response to live attenuated vaccines like MMR and varicella vaccines when administered as either individual or combination vaccines
- MMR and varicella vaccines should be delayed for at least 3 months after administering IgG for HAV prophylaxis
- IgG should not be given within 2 weeks after the administering MMR or varicella vaccine

Vaccines

- Havrix (GSK) and Vaqta (Merck)
- Havrix contains a preservative (2-Phenoxyethanol)
- Vaqta is preservative free
- The immune response to each preparation has been rapid and complete with $> 94\%$ in 1 month after vaccination, second dose 100% protection

Pre-Exposure Prophylaxis

Doses Table: Recommended of Hepatitis A Vaccines

Product	Age (years)	Dose	Volume (ml) IM	Schedule (months)
Havrix	2-18	720 EL.U.	0.5	0,6-12
	> 18	1440 EL.U.	1.0	0,6-12
Vaqta	2-17	25U	0.5	0,6-18
	>17	50U	1.0	0,6

Hepatitis A..

ACIP recommends vaccination

- Travellers to high endemic area
- Children living in communities with high rates of hepatitis A infection and periodic hepatitis A outbreaks. (higher socioeconomic groups)
- Homosexual
- IV drug users
- Occupational risk for hepatitis A (e.g., health care workers)
- People with clotting factor disorders.
- People with chronic liver disease who are at an increased risk for HAV

Case

- Mr. X is father of five children. One of his child is four years old and attending a pre-school where most of the pupils are of the same age. The school principle informed him that some of the pupils are having hepatitis A in his school. He wants to protect him and his wife from Hepatitis A infection. Next day they went to clinic to test their hepatitis A status. Mr. X is tested **positive** for Hepatitis A **anti-IgG** antibody while his wife Mrs. X is tested **negative** for Hepatitis A **anti-IgG** and **IgM** antibody. His son is tested **positive** for Hepatitis A **anti-IgM** antibody.

Case

- Is Mr. X infected with Hepatitis A virus currently and he may take immunoglobulin for Hepatitis A infection to protect him from full blown hepatitis.
- or
- Mr. X is infected with Hepatitis A virus currently and he may take vaccination for Hepatitis A infection to protect him from full blown hepatitis

- Can we say that Mrs. X is not infected with Hepatitis A virus and she does not need to take HAV IgG and vaccination both immediately?
- What shall we do with her?

Case

- What will you advise to his father for his four year old son?
- What about rest of the children should do?

Case

- Khalid is a pharmacy student who is planning to leave to Sudan next week to do voluntary work for a year. His serology test is positive for IgG anti-HAV and negative for IgM anti-HAV. He wants to get prophylactic treatment before leaving the country and asks you for your recommendation. What will you recommend?
 - a. start hepatitis A vaccine 1440 ELU now
 - b. immunoglobulin 0.02 ml/kg now
 - c. immunoglobulin 0.06 ml/kg now
 - d. does not need any treatment

- All of the following individual should be vaccinated against hepatitis A except one statement is incorrect. Mark the incorrect one:
 - a. travelers to high endemic area
 - b. military personnel
 - c. employees of child care center
 - d. children who live in poor countries



Hepatitis B Virus

HBV

Case

- Zara is a 25-year-old woman who was recently diagnosed with hepatitis B while undergoing a physical examination for employment. She is otherwise healthy except for a history of depression. Social history is insignificant. Her family history is significant for mother with hepatitis B. Her grandmother died of (HCC). She lives with her brother and sister, neither of whom have been immunized against hepatitis B .Laboratory values are significant for an elevated an AST 73 units/L and an **ALT of 78 units/L**. Her hepatitis serology are positive for HAV IgG, **HBsAg, anti-HBe**, and anti-HBc IgG; **negative for HBeAg**; HBVDNA concentration of **800,000 IU/ml**; and undetectable HCVRNA. Her other laboratory values are within normal limits. A liver biopsy performed 2 weeks ago revealed chronic hepatitis B (CHB) with **minimal fibrosis**.

Case

1. What is the most likely mode of transmission in her?
2. Does Zara need treatment? Why?
3. What is the best regimen for her?
4. Why you have chosen this regimen?
5. What is the best prophylaxis regimen for Zara's brother and sister?

Case

- Zara mother has the following serology and laboratory values: HBsAg-positive, anti- HBe-positive, ALT of 43 units/L, HBVDNA of less than 2,000IU/ml, and a liver biopsy with no inflammation or fibrosis.
6. What is the best regimen for Zara's mother?
 7. If Zara develops YMDD mutation while on lamivudine, what shall we do?

Hepatitis B

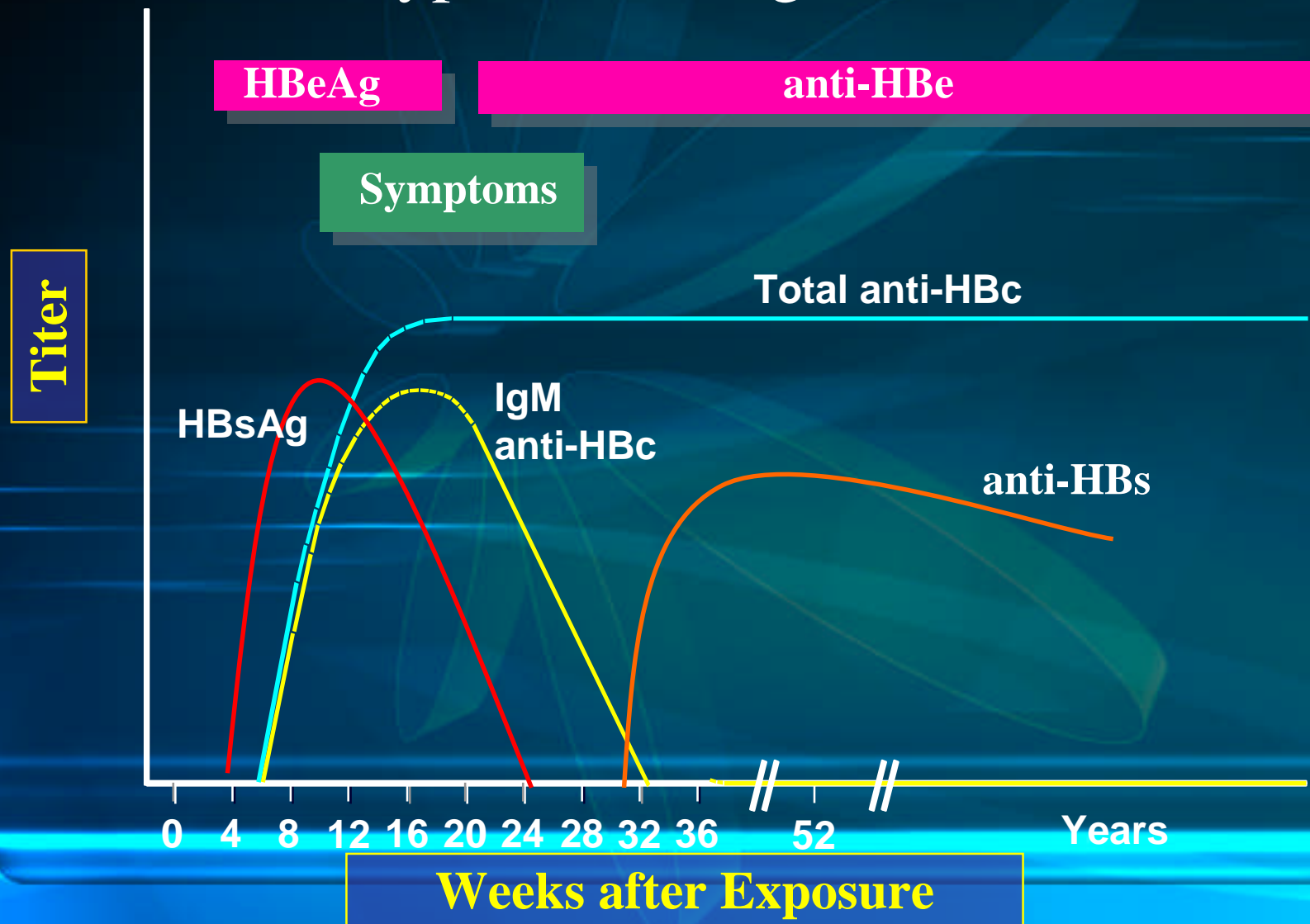
- HBV is responsible for 1-14% of CLD and more likely to develop in infants compared to adults
- Common cause for primary HCC
- It is preventable disease
- Parenterally transmitted
- Heterosexuals contact (42%)

Hepatitis B

- The HBsAg **is essential for maintaining the HBV life cycle**
- HBeAg is a secreted product of the nucleocapsid core & **its presence means viral replication**

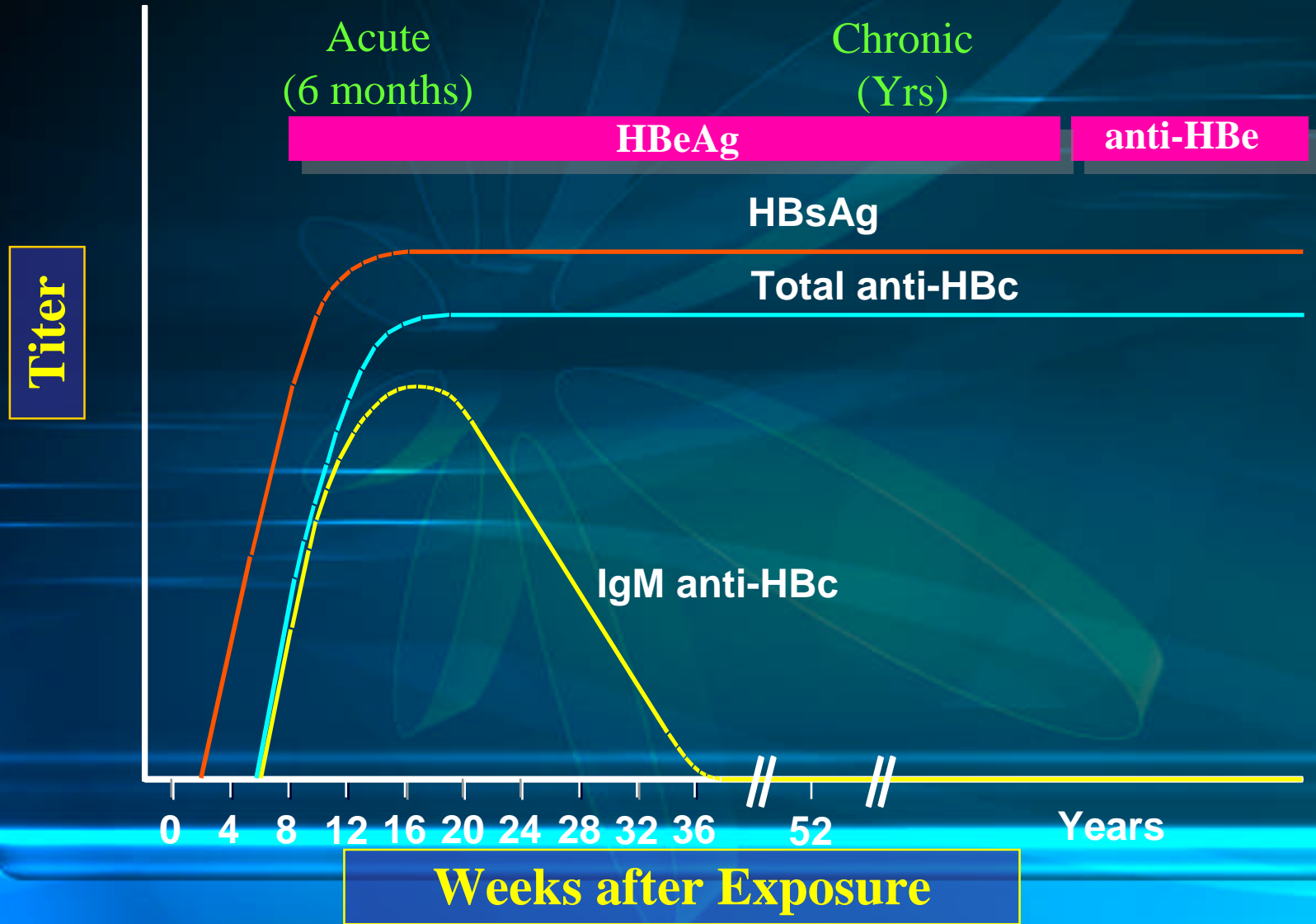
Acute HBV Infection with Recovery

Typical Serologic Course



Progression to Chronic HBV Infection

Typical Serologic Course



Hepatitis B.. Definitions and Diagnostic Criteria

Diagnostic Criteria

Definitions

Chronic hepatitis B

Chronic necro-inflammatory disease of the liver caused by persistent HBV infection

1. HBsAg positive > 6 months
 2. Serum HBV DNA > 10^5 copies/ml (20,000 IU/ml)
 3. Persistent or intermittent elevation of ALT/AST levels
 4. Liver biopsy showing chronic hepatitis (necroinflammatory \geq score 4)
-

Hepatitis B.. Definitions and Diagnostic Criteria

Diagnostic Criteria

Definitions

Chronic hepatitis B

-
- a. HBeAg-positive chronic hepatitis B  HBeAg positive, anti-HBe negative
- b. HBeAg-negative chronic hepatitis B  HBeAg negative, anti-HBe positive
-

Hepatitis B.. Definitions and Diagnostic Criteria

Diagnostic Criteria

Definitions

Inactive HBsAg carrier state

Persistent HBV infection of the liver without significant ongoing necroinflammatory disease

1. HBsAg positive > 6 months
 2. HBeAg negative, anti-HBe positive
 3. Serum HBV DNA < 20,000 IU/ml
 4. Persistently normal ALT/AST levels
 5. Liver biopsy showing absence of significant hepatitis (necroinflammatory score < 4)
-

Hepatitis B.. Definitions and Diagnostic Criteria

Diagnostic Criteria

Definitions

Resolved hepatitis B

Previous HBV infection without further virological, biochemical, or histological evidence of active virus infection or disease

1. Previous known history of acute or chronic hepatitis B with the presence of anti-HBs
 2. HBsAg negative
 3. Undetectable serum HBV DNA
 4. Normal ALT levels
-

Guide to Immunoprophylaxis After Exposure

Type of Exposure	Immunoprophylaxis
Perinatal	Vaccination + HBIG
Sexual	Vaccination ± HBIG
Household contact	
Chronic carrier	Vaccination
Acute case, known exposure	HBIG ± vaccination
Inadvertent (percutaneous/per mucosal)	Vaccination ± HBIG

Hepatitis B..

Recommended vaccines dosage & schedule

Vaccine	Age group	Dose	Volume	# Doses	Schedule
Enerix-B (Glaxo-SmithKlin)	0–19 years	10 μ g	0.5 ml	3	Infants: birth, 1–4, 6–18 mos. of age Alternative for older children: 0, 1–2, 4 mos.
	20 years & older	20 μ g	1.0 ml	3	0, 1, 6 mos.

Note For adult dialysis patients, the Enerix-B dose required is 40 μ g/2.0ml (use the adult 20 μ g/ml formulation) on a schedule of 0, 1, 2, and 6 months

Hepatitis B..

Recommended vaccines dosage & schedule

Vaccine	Age group	Dose	Volume	# Doses	Schedule
Recombivax HB (Merck & Co.)	0–19 years	5 μ g	0.5 ml	3	Infants: birth, 1–4, 6–18 mos. of age Alternative for older children: 0, 1–2, 4 mos.
	20 years & older	10 μ g	1.0 ml	3	0, 1, 6 mos.

Note For adult dialysis patients, the Recombivax HB, a special formulation for dialysis patients is available. The dose is 40 μ g/1.0ml and it is given on a schedule of 0, 1, and 6 months

Hepatitis B.. Combinations using HAV and/or HBV

Vaccine	Age group	Antigens used	Volume	# Doses	Schedule
Comvax (Merck & Co.)	6 weeks thru 4 yrs.	Recombivax HB (5 μ g) + PedvaxHib	0.5 ml	3	2, 4, 12–15 mos. of age
Pediarix (Glaxo-SmithKlin)	6 weeks thru 6 yrs.	Engerix-B (10 μ g), Infanrix (DTaP), and IPV	0.5 ml	3	2, 4, 6 mos. of age
Twinrix (Glaxo-SmithKlin)	18 years & older	Havrix (720 EI.U.) + Engerix-B (20 μ g)	1.0 ml	3	0, 1, 6 mos.

Diagnostic Markers

- **Typical markers to diagnosis chronic HBV are:**

1. Serology: HBsAg HBeAg anti-HBc
2. Virology: non-amplified hybridization assays (limit of quantification of 10^5 – 10^6 copies/ml)

Note: Polymerase Chain Reaction (PCR) assays have lower limit of detection (as low as 6-100 IU/ml)

3. Biochemistry: ALT
4. Histology: staging (necroinflammatory) and grading (fibrosis)

Primary Aims of Treatment

1. Reduce the HBV DNA level and maintain it at the lowest possible levels
2. Seroconversion (loss of HBeAg and Gain of HBe antibody)
3. ALT level normalization
4. Loss of HBsAg (resolution)
5. Histological improvement

Patients Stratum

- **This algorithm include the following Patients:**

1. HBeAg-Positive Patients
2. HbeAg-Negative Patients
3. Lamivudine-Resistant Patients
4. Patients with Cirrhosis
5. Patients Co-infected with HIV-HBV
6. Patients Co-infected HCV-HBV
7. Chemotherapy Patients
8. Pregnancy
9. Transplants

Approved HBV Therapies

- **Five approved treatments for chronic HBV the US:**

1. IFN alfa-2b or 2a
2. Lamivudine (Epivir-HBV)[®]
3. Adefovir Dipivoxil
4. Entecavir
5. Pegylated INF alfa-2a or 2b

HBV Treatment Strategies

1. HBeAg-Positive Patients

HBsAg-Positive Patients

HBsAg
Status

HBV
DNA

ALT

Treatment Strategy



Positive

< 20000
UI/ml

Normal

No treatment

Monitor every 6–12 mo

Consider therapy in patients with
known significant

histological disease, even if low-level
replication

HBeAg-Positive Patients

HBeAg
Status



Positive

HBV
DNA



≥ 20000
IU/ml

ALT



Normal

Treatment Strategy



Consider biopsy; treat if disease
Low rate of HBeAg seroconversion
for IFN, lamivudine, adefovir
If treated, entecavir or adefovir
preferred (more potent HBV
Suppressive agents with fewer
side effects)

HBeAg-Positive Patients

HBeAg
Status

HBV
DNA

ALT

Treatment Strategy



Positive

≥ 20000

Elevated

Adefovir, lamivudine, or IFN are first-line options

If “high” HBV DNA, adefovir or lamivudine preferred

Peginterferon α -2A and Lamivudine

Treated for 48 wks, assessed wk 24 of after treatment	PEGASYS 180 ug/wk + Placebo (n=271)	PEGASYS 180 ug/wk + Lamivudine 100mg/d (n=271)	Lamivudine 100mg/d (n=272)

Peginterferon α -2a monotherapy is as effective as combination with lamivudine and more effective than lamivudine monotherapy in HBeAg-positive chronic HBV

HBV DNA <100,000 copies/ml (P=0.012)* (P=0.003)*

* Compared with Lamivudine therapy

Peginterferon α -2A and Lamivudine

Treated for 48 wks, assessed wk 24 of after treatment	PEGASYS 180 ug/wk + Placebo (n=271)	PEGASYS 180 ug/wk + Lamivudine 100mg/d (n=271)	Lamivudine 100mg/d (n=272)

Peginterferon α -2a monotherapy and in combination with lamivudine is more effective than lamivudine monotherapy in HBeAg-positive chronic HBV

ALT normalization	41% (P=0.002)*	39% (P=0.006)*	28%
-------------------	-------------------	-------------------	-----

* Compared with Lamivudine therapy

Lamivudine

- Lamivudine (100mg po od)
- HBeAg seroconversion 17% 27% 40% 47% 50% at 1,2,3,4,5yrs
- Longer the treatment better the response
- High pretreatment ALT level the best predictor of response to lamivudine treatment
- Seroconversion are durable after a median follow-up of 37 months

Lamivudine

- Longer the treatment higher the MYDD mutation
- 14-32% 1yr, 69% 5yrs and ALT bounce back to pretreatment level and rapid decompensation.
- Well tolerated
- HBsAg conversion is rare (no sufficient data)
- Excellent safety profile
- Reasonable price (SR 300/month)
- Continue lamivudine atleast 6 months post seroconversion

Adefovir

- 46% loss HBeAg; 23% seroconversion (52 weeks)
- No resistance mutation after 52 weeks of treatment
- HBsAg loss is rare (no sufficient data)
- Safety profile as similar to placebo
- Cost SR 2,000 /month
- Durability of response after adefovir is no available

Hepatitis B.. Duration of Therapy and Monitoring

- Monitor lamivudine for resistance
- Treatment then should be continued for additional 6 months after HBeAg seroconversion .
- Patient who fails to seroconvert (HBeAg+) should be treated indefinitely*
- Patient who experience relapse should be retreated
- Adefovir should be considered if patients who were intially treated with Lamivudine

HBV Treatment Strategies

2. HBeAg-Negative Patients

HBeAg-Negative Patients

- Therapy end-point is difficult to assess because HBeAg seroconversion can not be determine
- HBV DNA suppression and ALT level normalization are the only measures of response to therapy
- HBeAg negative patients tend to have lower serum HBV DNA than HBeAg positive patient, but may still have considerable disease

HBeAg-Negative Patients

HBeAg Status	HBV DNA	ALT	Treatment Strategy
Negative	< 2000 IU/ml	Normal	No treatment Monitor every 6–12 months Consider therapy in patients with known significant histological disease, replication

HBeAg-Negative Patients

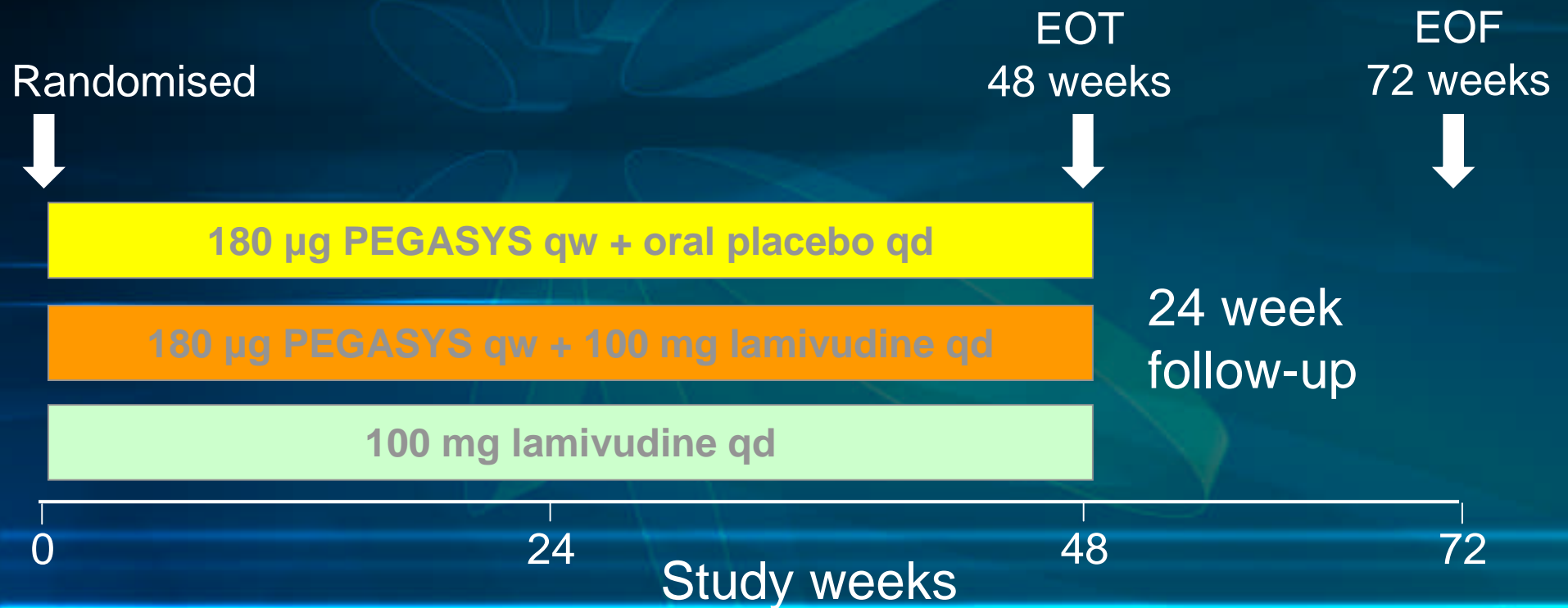
HBeAg Status	HBV DNA	ALT	Treatment Strategy
Negative	≥ 2000 IU/ml	Normal	Consider biopsy; treat if disease Low "efficacy" for lamivudine, IFN, adefovir

HBeAg-Negative Patients

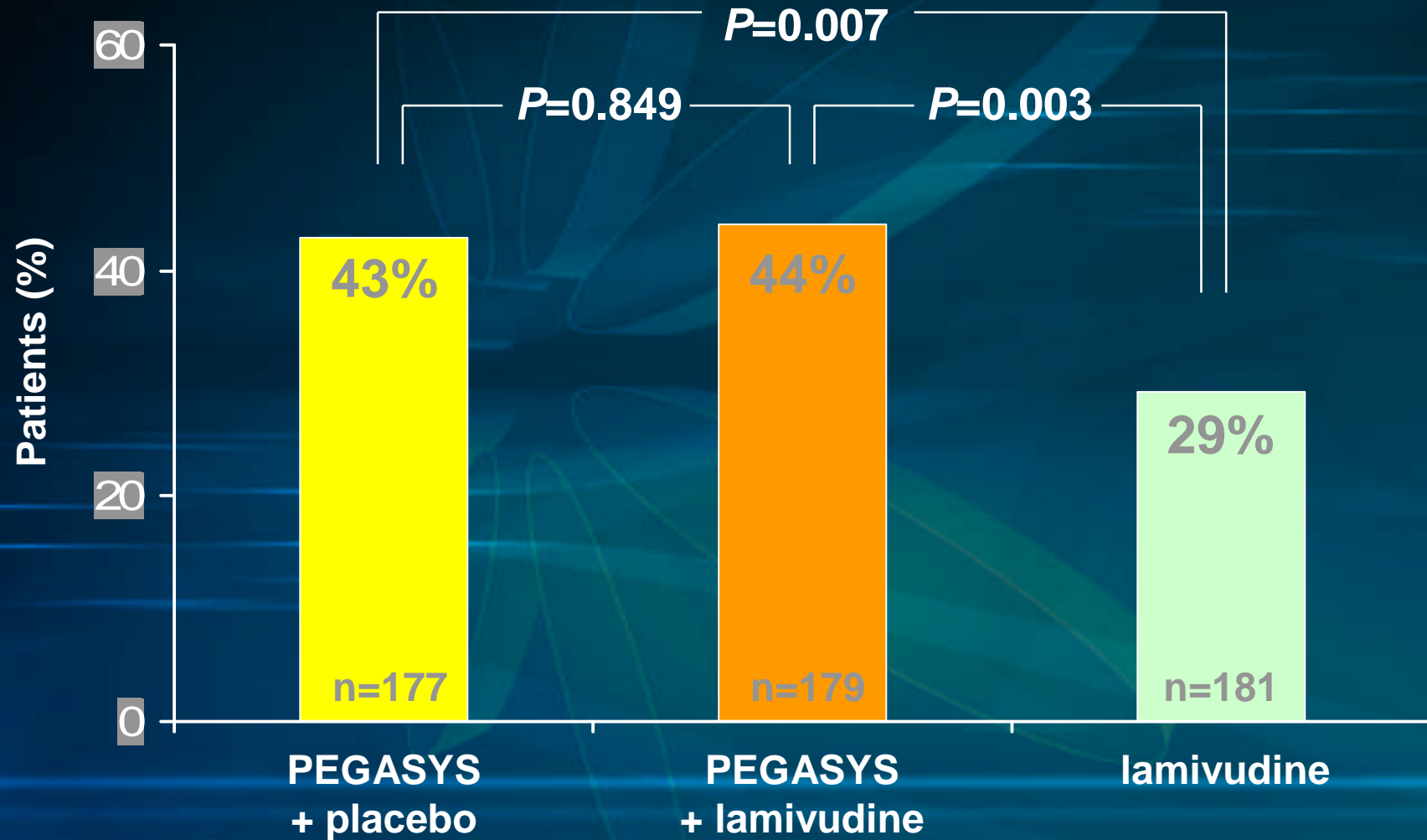
HBeAg Status	HBV DNA	ALT	Treatment Strategy
Negative	≥2000 IU/ml	Elevated	Adefovir, lamivudine, entecavir or IFN are first-line options Long-term treatment required Adefovir preferred (low rate of resistance)

Study Design

- Patients with HBeAg-negative CHB were randomised using a 1:1:1 ratio (n=537)



Co-primary Endpoint - HBV DNA Response* 24 Weeks After End of Treatment (Week 72)



* HBV DNA response defined as <20,000 cp/mL

Duration of Therapy and Monitoring

- Duration of therapy for IFN remains unclear
- Longer treatment duration (12 months) with INF appears more beneficial in terms of sustained virological response
- Lamivudine and adefovir need to be administered for long term
- Adefovir preferred over Lamivudine due to YMDD mutants

HBV Treatment Strategies

3. Patients with Cirrhosis

Patients with Cirrhosis

HBeAg Status	HBV DNA	Cirrhosis	Treatment Strategy
↓	↓	↓	↓
Positive or Negative	< 2000 IU/ml	Compensated	May choose to treat or observe Adefovir or entecavir or lamivudine Adefovir or lamivudine are first- line options

Patients with Cirrhosis

HBeAg Status	HBV DNA	Cirrhosis	Treatment Strategy
Positive or Negative	≥ 2000 UL/ml	Compensated	Long-term treatment required Adefovir preferred (low rate of resistance) Combination adefovir plus lamivudine has theoretical advantage because of low likelihood of resistance to either virus

Patients with Cirrhosis

HBeAg Status	HBV DNA	Cirrhosis	Treatment Strategy
↓	↓	↓	↓
Positive or Negative	≥ 200 IU/ml	De- compensated	Adefovir, entecavir or lamivudine are first-line options Long-term treatment required Adefovir preferred (low rate of resistance)

HBV Treatment Strategies

4. Patients with Co-Infections

Hepatitis B..

HIV-HBV Co-infected Patients

- About 10% HIV- are co-infected with HBV
- Mortality 14-fold greater than either virus alone
- Do not treat HBV infection first in co-infected patient
- Resistant is high reaching 90% at 4 years lamivudine

HIV-HBV Co-infected Patients

- Adefovir 10 mg/day is effective in lamivudine- resistant HBV
- Tenofovir is effective against both HIV and HBV
- Entecavir has no effect on HIV, does not promote HIV viral resistance to the drug no effect on CD4 or HIV viral load
- If patient not requires HAART in near future or are on HAART no include drug active against HBV, then use INF or adefovir or entecavir

Hepatitis B.. **HCV-*HBV* Co-infected Patients**

- Patients with *HBV* DNA levels $\geq 10^3$ copies/ml (200 IU/ml) and undetectable *HCV* RNA should be treated for *HBV* infection
- Low *HBV* DNA levels and detectable *HCV* RNA should be treated for 3 months with peginterferon and ribavirin in standard doses
- If *HBV* DNA does not begin to respond or levels increase on therapy lamivudine or adefovir can be added

HBV Treatment Strategies

5. Pregnant Patients

Pregnancy

- Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of HBV; a multicentre, randomized, double-blind, placebo-controlled study

Endpoint (Infants at Wk 52)	LAM+VAC+HBIg N=56	PLA+VAC+HBIg N=59	<i>p</i> - value
HBsAg +ve	10 (18%)	23 (39%)	0.014
HBsAb +ve	47 (84%)	36 (61%)	0.008
HBV DNA +ve ³	11 (20%)	27 (46%)	0.003

LAM, 100mg OD from wk 32 ± 2 wks of gestation until 4 wks postpartum; HBIg, 200IU, single dose within 24 hrs of birth; VAC 0.5ml dose within 24hours of birth

Case

- Zara is a 25-year-old woman who was recently diagnosed with hepatitis B while undergoing a physical examination for employment. She is otherwise healthy except for a history of depression. Social history is insignificant. Her family history is significant for mother with hepatitis B. Her grandmother died of (HCC). She lives with her brother and sister, neither of whom have been immunized against hepatitis B .Laboratory values are significant for an elevated an AST 73 units/L and an **ALT of 78 units/L**. Her hepatitis serology are positive for HAV IgG, **HBsAg**, **anti-HBe**, and anti-HBc IgG; **negative for HBeAg**; HBVDNA concentration of **800,000 IU/ml**; and undetectable HCVRNA. Her other laboratory values are within normal limits. A liver biopsy performed 2 weeks ago revealed chronic hepatitis B (CHB) with **minimal fibrosis**

Case

1. What is the most likely mode of transmission in her?
2. Does Zara need treatment? Why?
3. What is the best regimen for her?
4. Why you have chosen this regimen?
5. What is the best prophylaxis regimen for Zara's brother and sister?

- Zara mother has the following serology and laboratory values: HBsAg-positive, anti- HBe-positive, ALT of 43 units/L, HBVDNA of less than 2,000IU/ml, and a liver biopsy with no inflammation or fibrosis.
6. What is the best regimen for Zara's mother?
 7. If Zara develops YMDD mutation while on lamivudine, what shall we do?



Hepatitis C Virus

HCV

Case

- Ramzi (BMI 33) is a 50-year-old black male with hepatitis C. He was treated in 2000 with (IFN)-a2b (Intron A) 3 mU 3 times/week for 48 weeks, but he did not benefit from treatment. He was IV drug user in his teens. Lab values include an HCVRNA level of 500,000 IU/ml, ALT of 74 units/L, AST of 53 units/L, total bilirubin of 1.1 mg/dl, and albumin of 3.5 g/dl. He has genotype 4 disease. A liver biopsy in 2000 revealed mild disease with moderate fibrosis. For the past 6 months, he has been retreated with PEG-IFN-2a (Pegasys) 180 mcg/ml with ribavirin 600 mg BID. He had an undetectable HCVRNA level at week 12 of therapy. At this time, his LFTs are normal; however, he does have an abnormal complete blood cell count panel: WBC = 2400 cells/mm³, ANC = 900 cells/mm³, Hgb = 8.9 g/dl, Hct = 26.6 %, and Plt= 50,000 cells/mm³. He complains of fatigue and tired.

1. Should he be treated for HCV infection?
2. Is he receiving an appropriate drug regimen?
3. How long does he need to be treated?
4. Does he need dose adjustment?
5. Would he be a good responder?

6. What is sustain responder?
7. What response rate would you expect?
8. How do we access response? (3 parameters)
9. For HCV genotype 2 or 3, what is the treatment duration and response rate expected?
10. When is a good time to access an earlier response?

Prevalence

- 170 million people are infected with Hepatitis virus worldwide
- Global seroprevalence is around 3%
- 1.1% in Northern America to 20% in Egypt*
- HCV Prevalence among Saudi's is estimated to be between 1-3% **

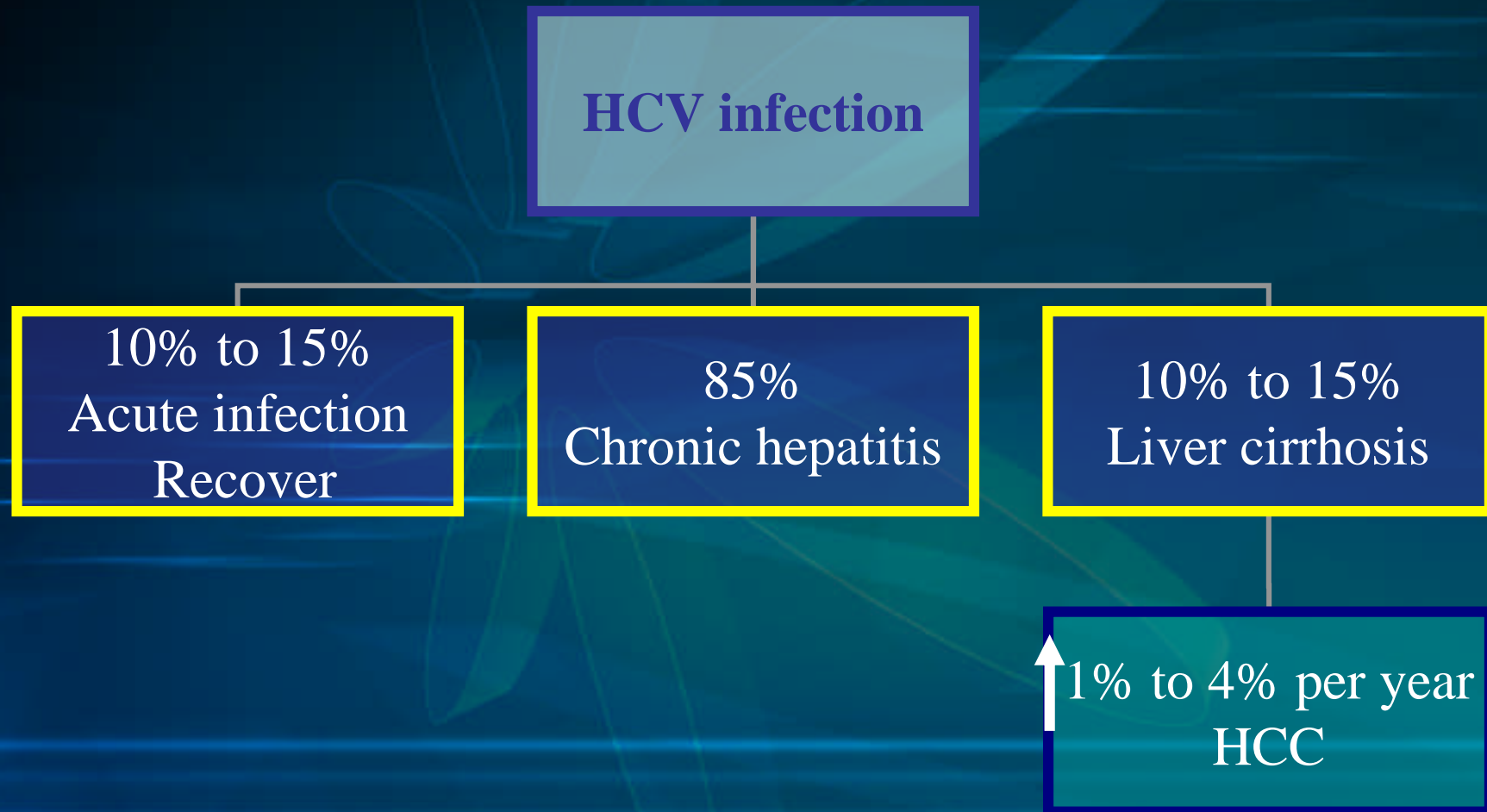
Genotypes

- Six Genotypes 1-6 and subtype 1a,1b,2a,2b
- Type 1 is common in USA (75%)
- In Saudi Arabia
 - ◆ Genotype 4 prevalence: 62%
 - ◆ Genotype 1 prevalence: 24%
 - ◆ Genotype 2 and 3 prevalence: 13.4%

Risk Factors

- IV drug abuser (most common)
- Accidental needle sticks (2%)
- Multiple sex partners (5%)
- Vertical transmission (5%)

Progression of Infection



Serology Testing

Enzyme immunoassay
(high false positive)

Positive

RIBA for
Anti HCV

PCR HCV
Qualitative
Or
Quantitative

Primary Prevention

1. Screening and testing

- ✓ Blood and Blood products
- ✓ Plasma
- ✓ Organ
- ✓ Tissue
- ✓ Semen donors

2. Instruments Sterilization

3. Education and Counseling

Hepatitis C.. **Treatment Goal: NIH Recommendation**

1. Virologic (HCV RNA concentration)

- ✓ undetectable (>100 copies/ml)

2. Biochemical

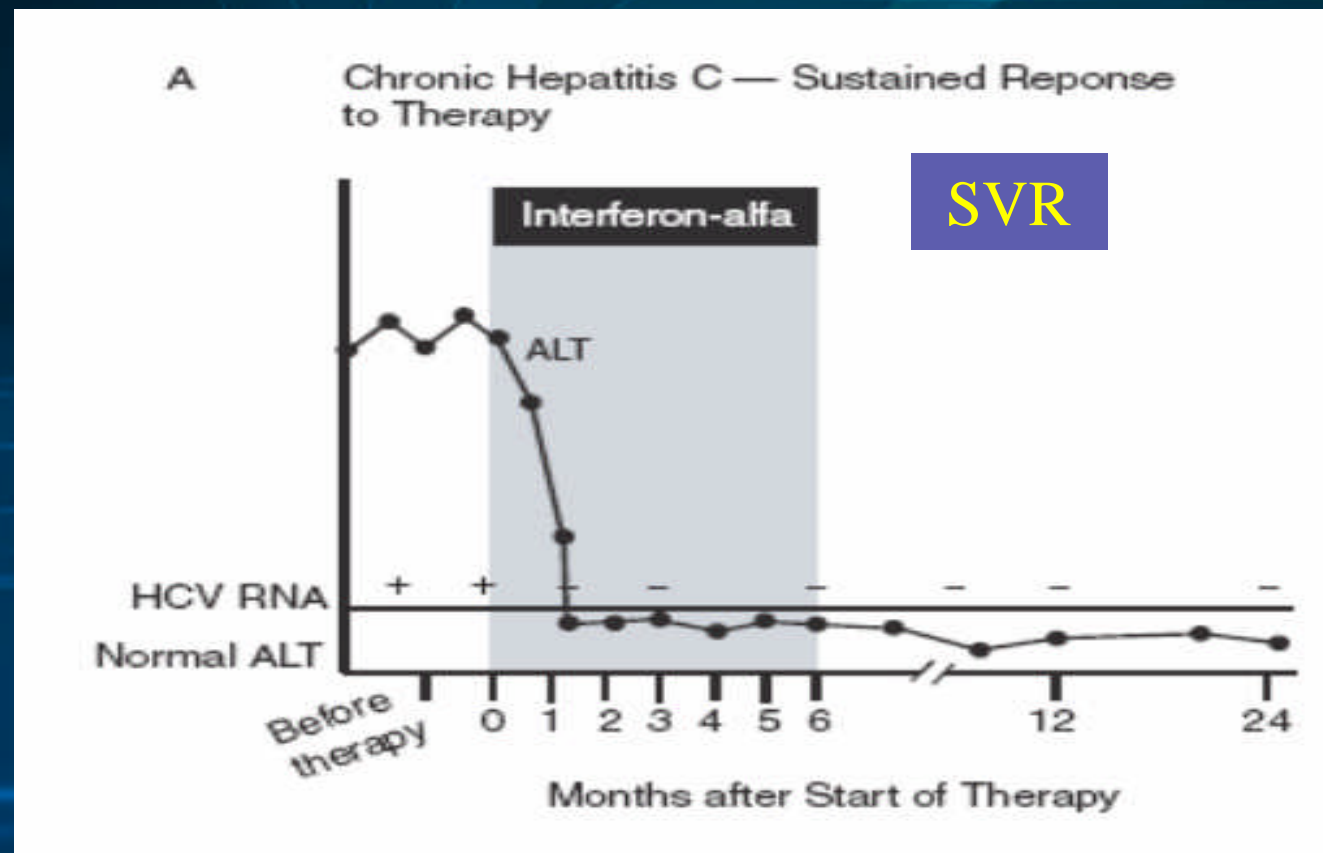
- ✓ Normalization of Alt

3. Histological (Liver Biopsy)

- ✓ 2 points decrease in inflammation (grading)
- ✓ 1 point decrease in fibrosis (staging)

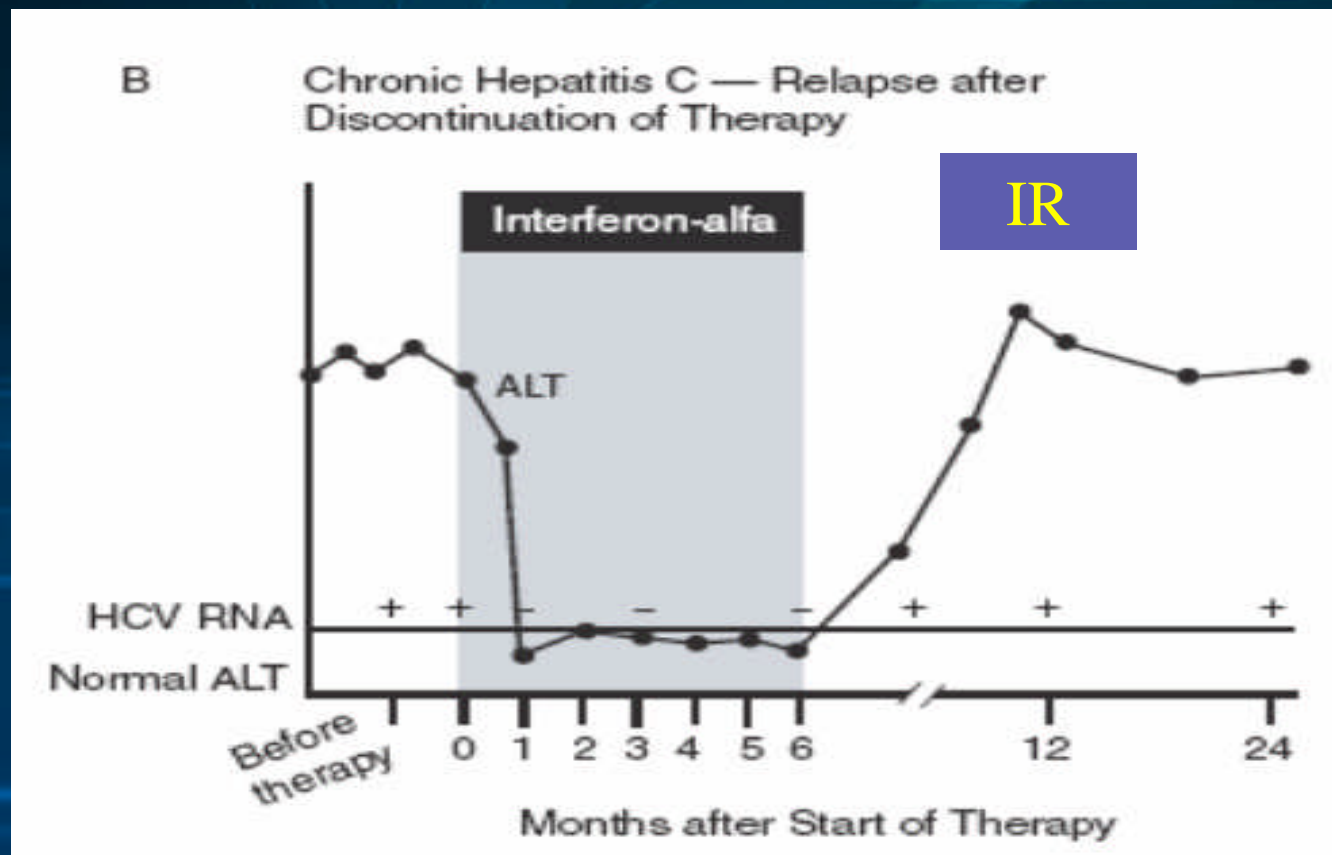
Hepatitis C.. Definition of Treatment Responses

- SVR = Sustained Virological Response



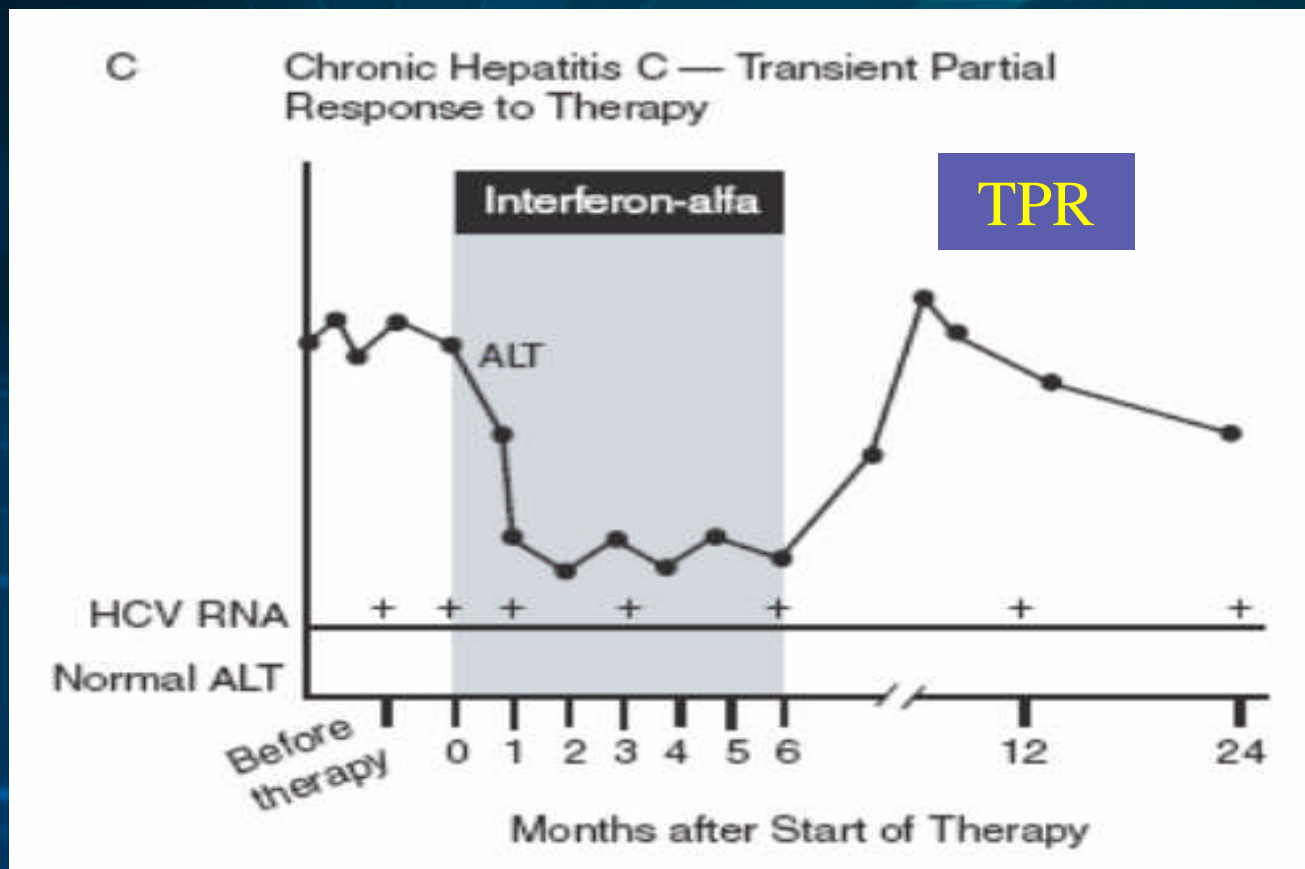
Hepatitis C.. Definition of Treatment Responses

- IR = Intermediate Response



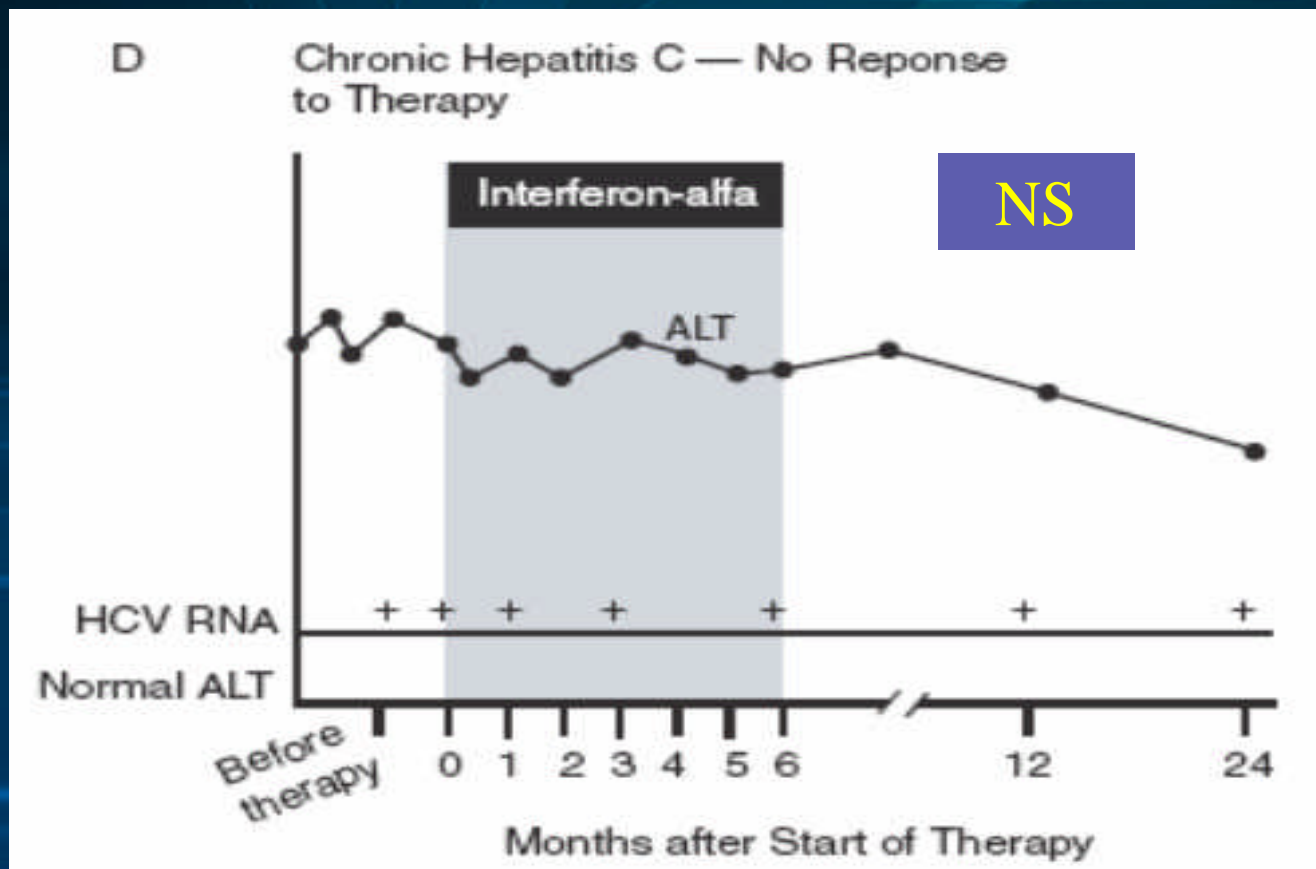
Hepatitis C.. Definition of Treatment Responses

- TPR = Transient Partial Response



Hepatitis C.. Definition of Treatment Responses

- NS = No Response



Why Does HCV Treatment Fail?

Host factors

- Race
- Age
- Gender
- Fibrosis
- Body weight
- Insulin resistance
- Active substance abuse
- Concomitant disease

Virus

- Genotype
- Viral load

Reasons for treatment failure

Treatment

- Poor adherence to therapy
- Side effects
- Use of a less than effective regimen

Favorable SVR Responder

- Low HCV RNA load prior to Rx
- Low BMI
- Genotype 2 and 3 (75% to 85% response rate)
- Female gender
- Young age

Poor Responder

- Genotype 1 (40% to 50%)
- Genotype 4 (50%)
- African American
- Male gender
- Old age
- Cirrhosis and bridging fibrosis

Drugs

- Before 1998 only Interferon α 2a or 2b 3 mU 3 times/wk for 48 weeks with SVR of 12% to 16% (genotype nonspecific)
- 1998 to 2001 Interferon α 2a or 2b plus Ribavirin for 48 wks SVR of 35% to 45% (genotype nonspecific)
- After 2002 INH recommendation is Peginterferon α 2a or 2b plus Ribavirin 48 wks SVR 55% genotype nonspecific and in genotype 2 and 3 up to 75% to 85% and genotype 1 is 40% to 50%

Hepatitis C..

Pegasys[®] (Peginterferon Alfa-2a)

- Adult Dose:
 - ✓ Combination therapy with ribavirin: 180 mcg once/wk with 1000- 1200mg ribavirin
- Duration of therapy based on genotype:
 - ✓ Genotype 1,4: Treat for 48 wks
 - ✓ Genotype 2,3: Treat for 24 wks

Hepatitis C.. **Pegasys[®] (Peginterferon Alfa-2a)**

- Based on hematologic parameters:
 - ✓ **ANC <750/mm³: 135 mcg/wk.**
 - ✓ **ANC <500/mm³: Suspend therapy until >1000/mm³ , then restart at 90 mcg/wk and monitor**
 - ✓ **Platelet count <50,000/mm³: 90 mcg/wk**
 - ✓ **Platelet count <25,000/mm³: D/C therapy**

Ribavirin (Dose)

- In combination with interferon alfa-2b:
 - ✓ <75 kg: 400 mg AM, then 600 mg PM
 - ✓ >75 kg: 600 mg AM, then 600 mg PM

Dosage Adjustment

- Patient without cardiac history:
 - ✓ Hgb <10 g/dL: Dec. to 600 mg/day
 - ✓ Hgb <8.5 g/dL: Permanently D/C Tx

Hepatitis C.

Despite increasing SVR rates,
treatment may be unsuccessful

Genotype 1 accounts for 60% of HCV infections worldwide¹

Genotype 1: 48 weeks of therapy with
PEGASYS[®] plus Ribavirin

SVR^{2,3}

Low viral load

65%

High viral load

47%

Genotype 2 or 3: 24 weeks of therapy with
PEGASYS[®] plus Ribavirin

Low viral load

85–86%

High viral load

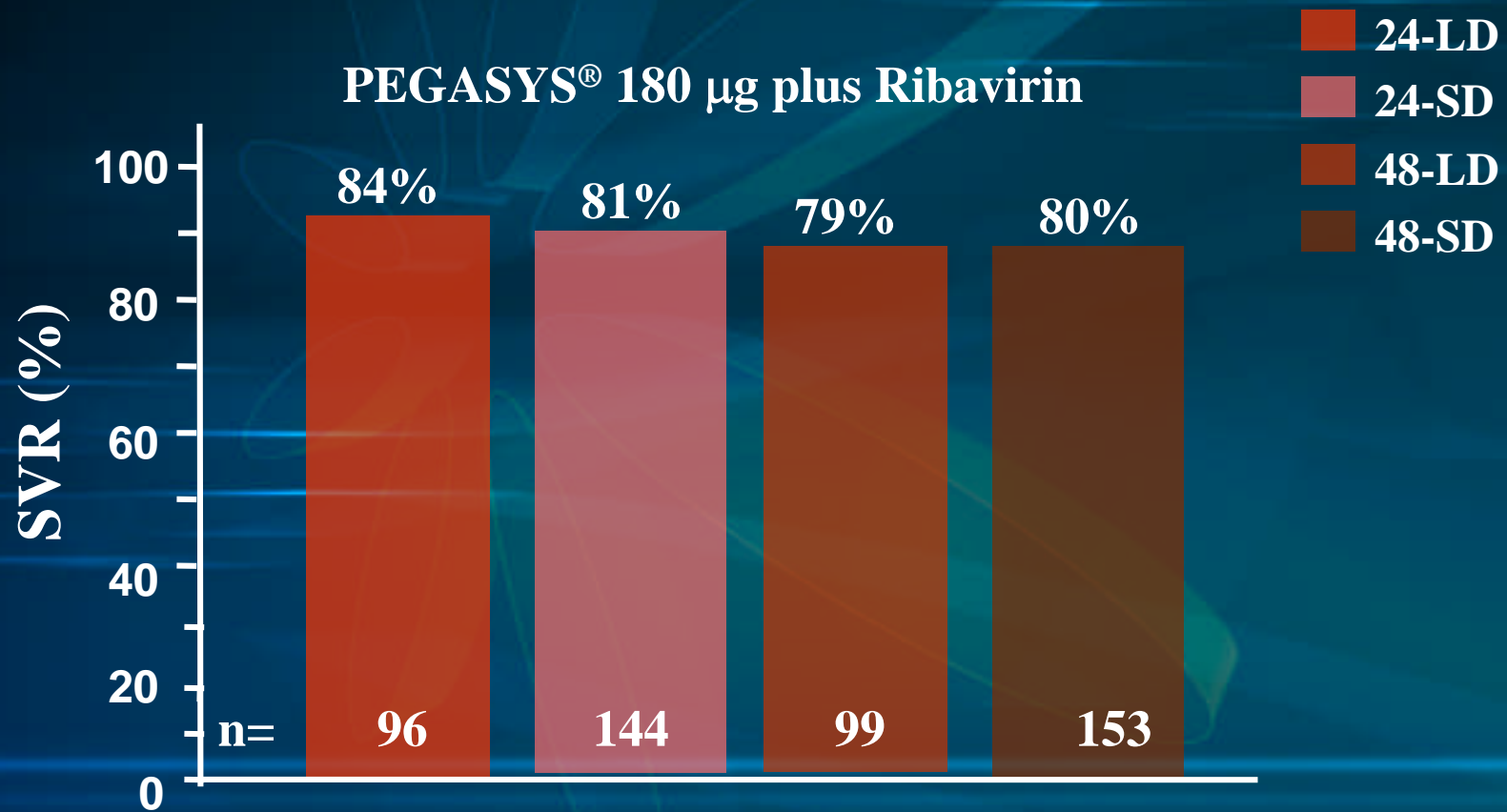
73–84%

1. World Health Organization. www.who.int/csr/disease/hepatitis/whocdesrlyo2003/en/index2

2. Hadziyannis S, et al. Ann Intern Med 2004; 140: 346; 3. Shiffman M, et al. 41st EASL 2006; Abstract 734

Treatment Duration: Genotype 2/3

- Treatment duration for genotype 2/3 can be reduced to 24 weeks

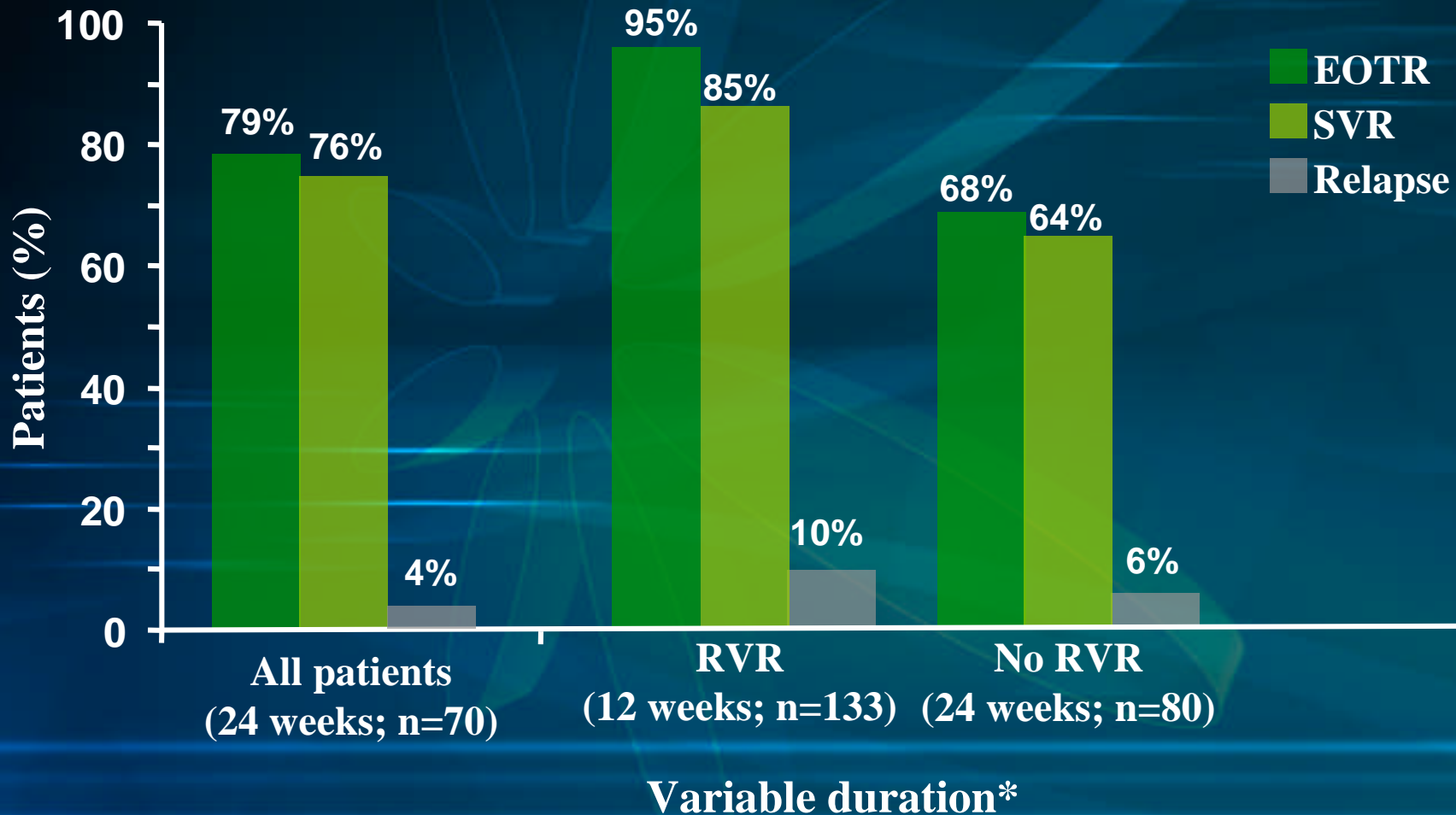


LD = RBV 800 mg/day

SD = RBV 1000–1200 mg/day

Hepatitis C.. High rates of SVR with a shorter duration in patients with a RVR (genotype 2 and 3)

- Pegylated interferon alfa-2b (12KD) 1.0 mcg/kg plus RBV 1-1.2 g



Mangia A, et al. N Engl J Med 2005; 352: 2609

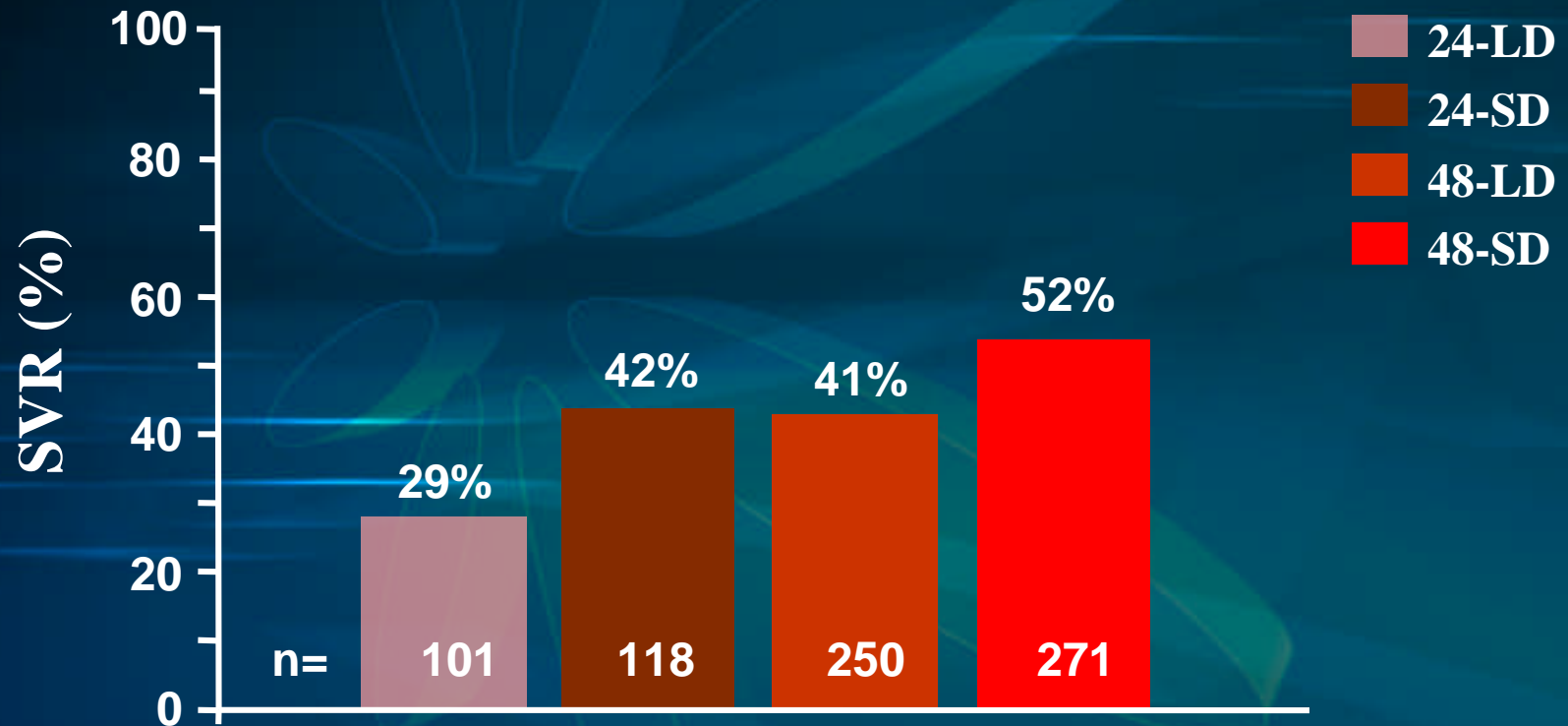
RVR = undetectable HCV RNA at week 4 (**50 IU/ml**)

* Patients with a RVR received 12 weeks; those without a RVR received 24 weeks

Hepatitis C..

Genotype 1: 48 weeks is the current standard

PEGASYS[®] 180 µg plus Ribavirin



LD = RBV 800 mg/day

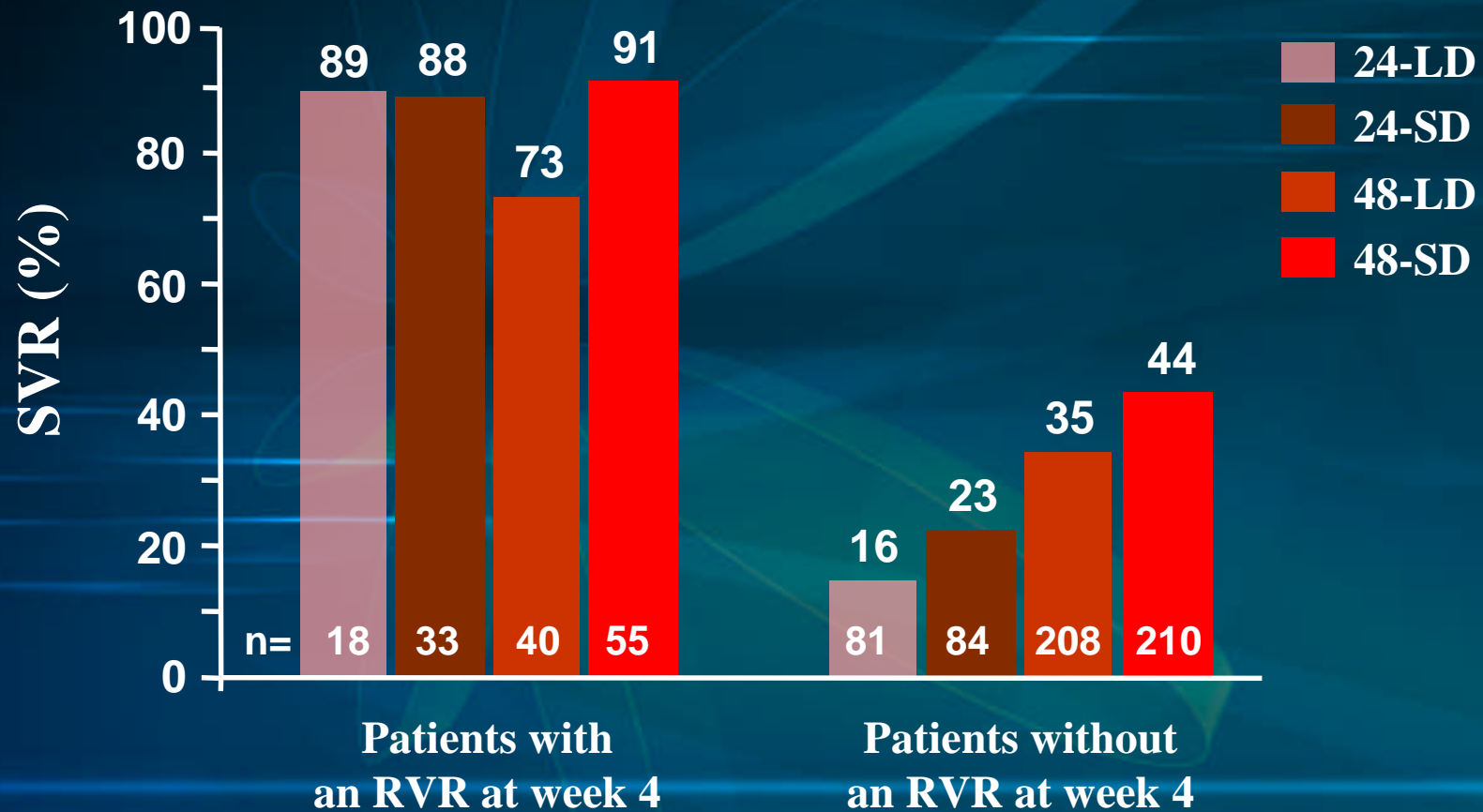
SD = RBV 1000–1200 mg/day

Hadziyannis S, et al. Ann Intern Med 2004; 140: 346

Hepatitis C.

RVR is a strong predictor of SVR in patients with genotype 1

PEGASYS® 180 µg plus Ribavirin



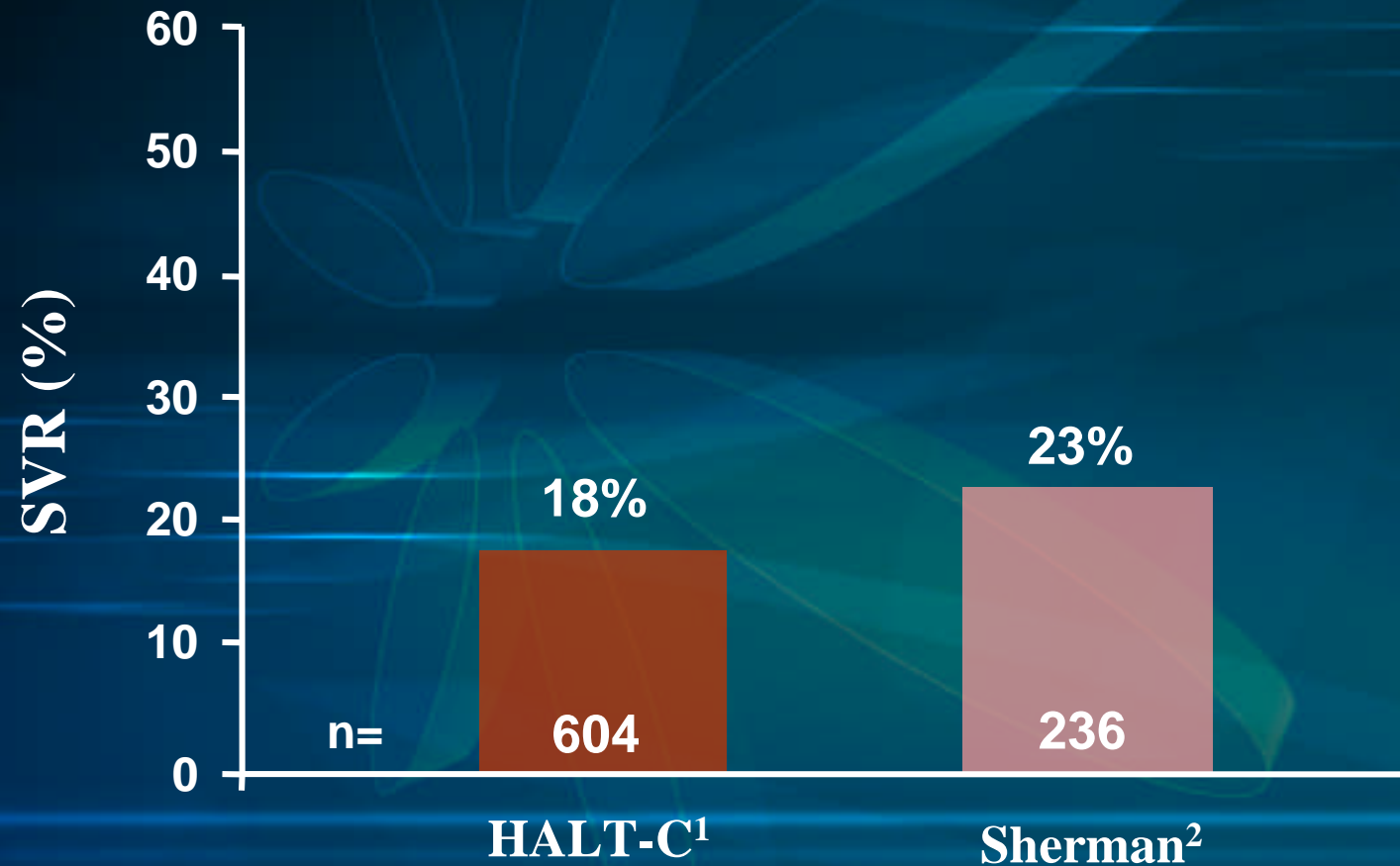
LD = RBV 800 mg/day; SD = RBV 1000–1200 mg/day;
RVR = HCV RNA <50 IU/mL at week 4

Jensen D, et al. 56th AASLD 2005; Abstract 1155

Hepatitis C..

Retreatment of conventional IFN non-responders with PEGASYS

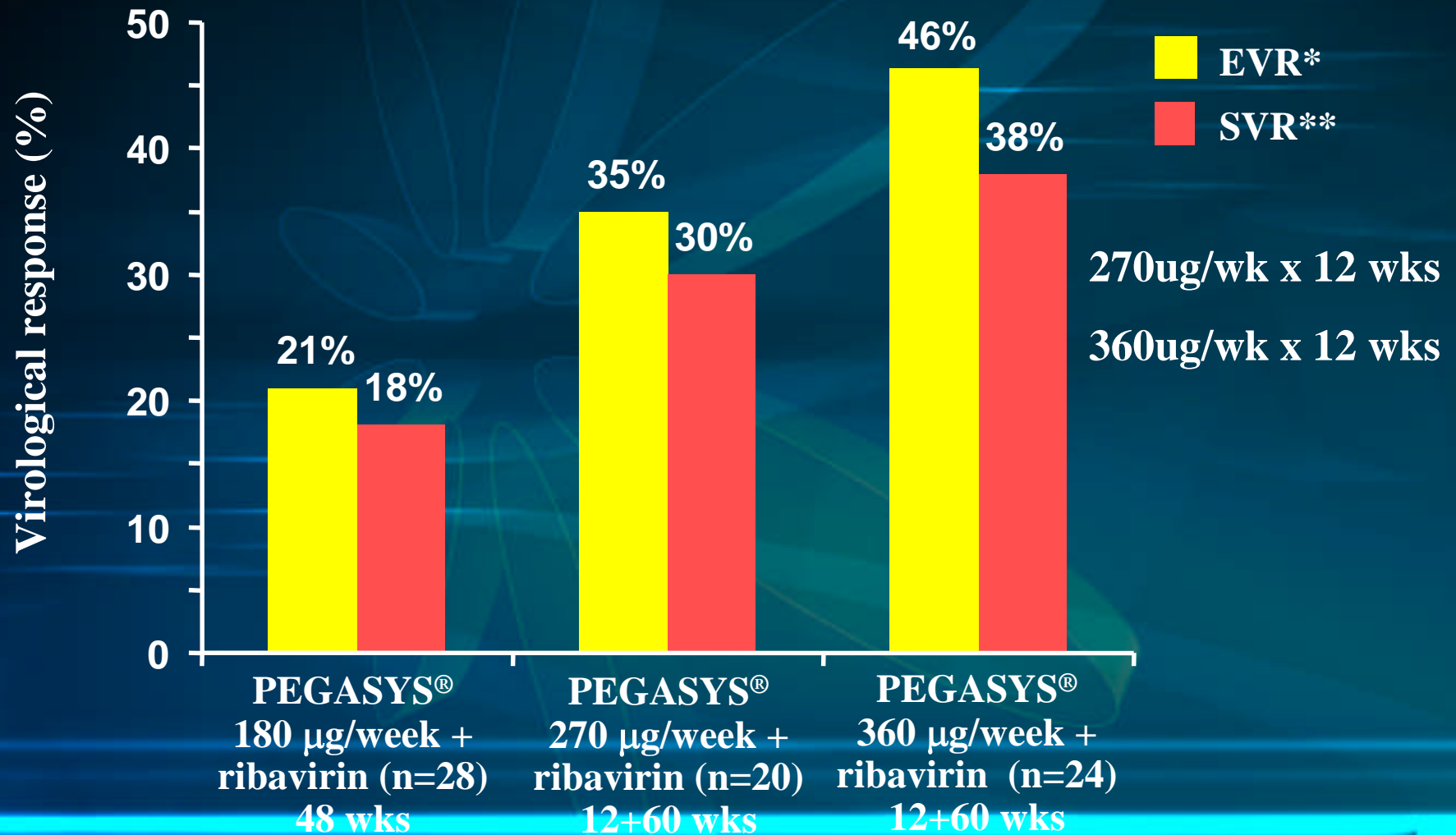
PEGASYS® 180 µg plus Ribavirin for 24 or 48 weeks



1. Shiffman M, et al. Gastroenterology 2004; 126: 1015

2. Sherman M, et al. 40th EASL 2005; Abstract 603

Hepatitis C.. Spanish high-dose induction pilot trial: (re-treatment of non-responders)



* EVR: HCV RNA <50 IU/mL at week 12

** SVR: HCV RNA <50 IU/mL 24 weeks post-treatment

Diago M, et al. 55th AASLD 2004; Abstract 522

Hepatitis C.. Comparing with earlier studies on Genotype 4 VRS

Type of INF	Our study	Shobokshi Et al* KSA	Hassan et al* Kuwait N = 44	Esmat et al* Egypt
Peg-INF Ribavirin SVR (72wk)	42.9%	50% Fix dose Ribavirin 800mg	61% Weight-base Ribavirin dose 1000-1200mg	40% Weight-based Ribavirin dose 800-1000mg
Reg-INF Ribavirin SVR (72wk)	32.3%	30% Fix dose Ribavirin 800mg		39% Ribavirin dose Weight-based 800-1000mg

Important Notes

- Anemia is a common side effect that begins soon after the initiation of peginterferon/*ribavirin* in the treatment of hepatitis C virus (HCV) infection
- Negative impact QOL and is the most common reason for reducing the dose and temporarily or permanently discontinuing *ribavirin*
- Dose modifications have been shown to reduce the efficacy of treatment

Important Notes

- *Erythropoietin* can improve anemia caused by peginterferon and *ribavirin* therapy and is more effective than dose reduction at improving QOL during treatment
- A new *ribavirin* analog, viramidine, is expected to be associated with a lower incidence of anemia and, if proven effective, may eventually be substituted for *ribavirin*

Case

- Ramzi (BMI 33) is a 50-year-old black male with hepatitis C. He was treated in 2000 with (IFN)-a2b (Intron A) 3 mU 3 times/week for 48 weeks, but he did not benefit from treatment. He was IV drug user in his teens. Lab values include an HCVRNA level of 500,000 IU/ml, ALT of 74 units/L, AST of 53 units/L, total bilirubin of 1.1 mg/dl, and albumin of 3.5 g/dl. He has genotype 4 disease. A liver biopsy in 2000 revealed mild disease with moderate fibrosis. For the past 6 months, he has been retreated with PEG-IFN-2a (Pegasys) 180 mcg/ml with ribavirin 600 mg BID. He had an undetectable HCVRNA level at week 12 of therapy. At this time, his LFTs are normal; however, he does have an abnormal complete blood cell count panel: WBC = 2400 cells/mm³, ANC = 900 cells/mm³, Hgb = 8.9 g/dl, Hct = 26.6 %, and Plt= 50,000 cells/mm³. He complains of fatigue and tired.

1. Should he be treated for HCV infection?
2. Is he receiving an appropriate drug regimen?
3. How long does he need to be treated?
4. Does he need dose adjustment?
5. Would he be a good responder?

6. What is sustain responder?
7. What response rate would you expect?
8. How do we access response? (3 parameters)
9. For HCV genotype 2 or 3, what is the treatment duration and response rate expected?
10. When is a good time to access an earlier response?