Hepatitis C Update

Luis S. Marsano, MD
Professor of Medicine
Director of Clinical and Transplant Hepatology
University of Louisville & Louisville VAMC

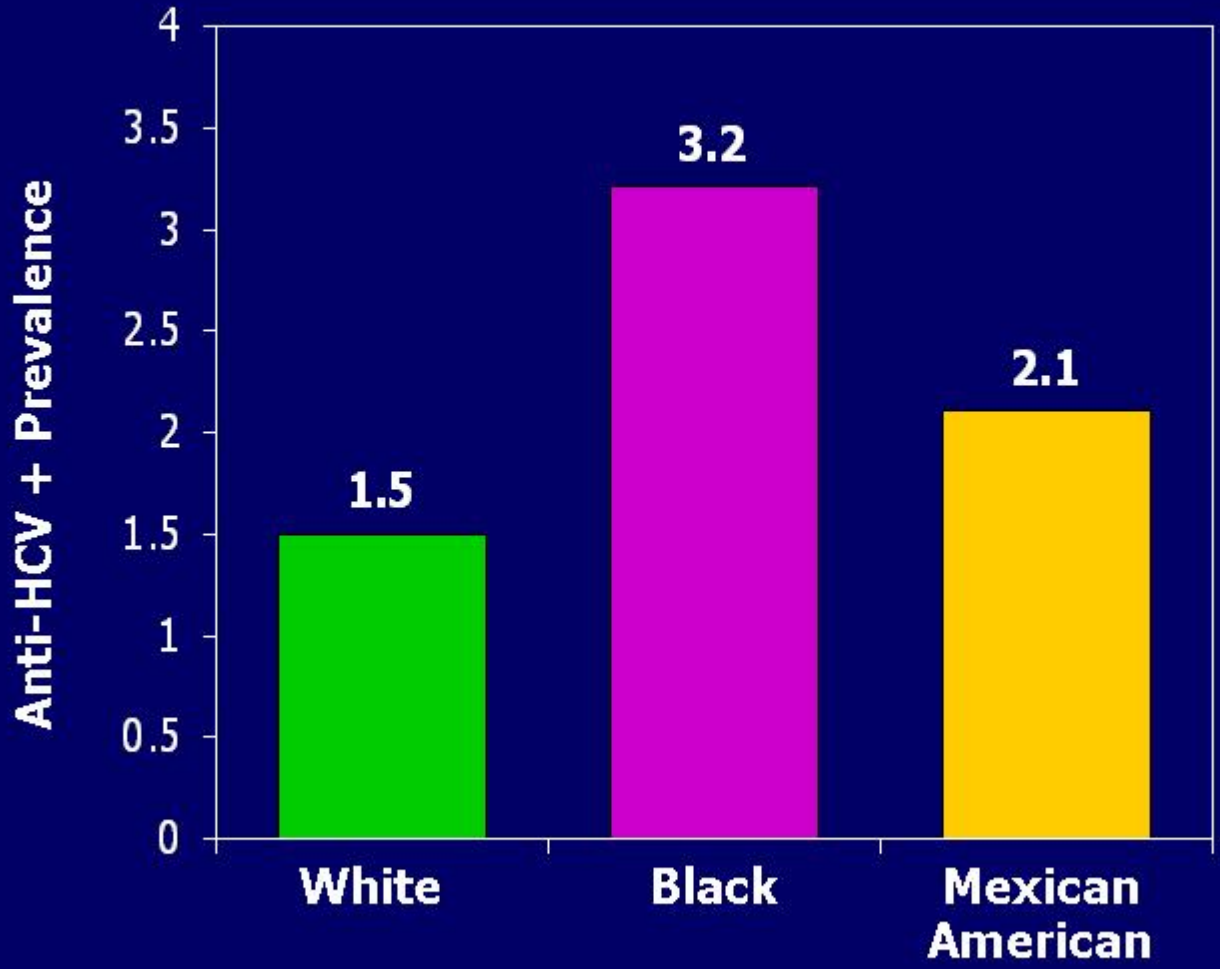
Objectives

- To understand prevalence & risk factors for HCV infection
- To recognize groups of patients who need to be screened for HCV
- To understand repercussions of HCV to society and individual patients
- To understand treatment options.

Hepatitis C

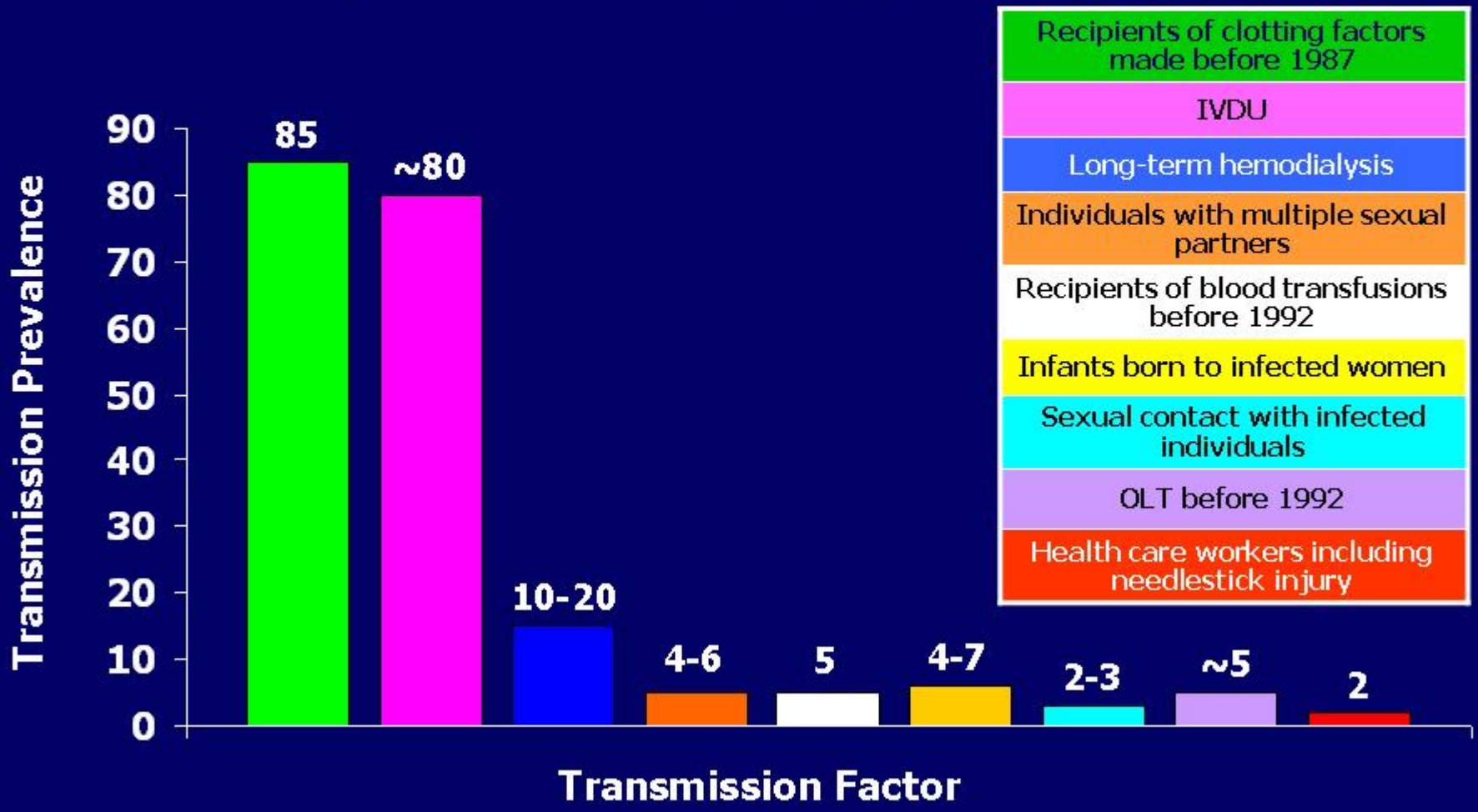
- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus.
  Six genotypes and > 100 subtypes.
- 170 million infected worldwide; 4 million in USA (1.8%); due to “uncounted populations”, CDC estimates true number is 7 million infected.
- 38,000 new infections/year.
- Highest prevalence in 30 to 54 year-olds.

US Prevalence by Race/Ethnicity



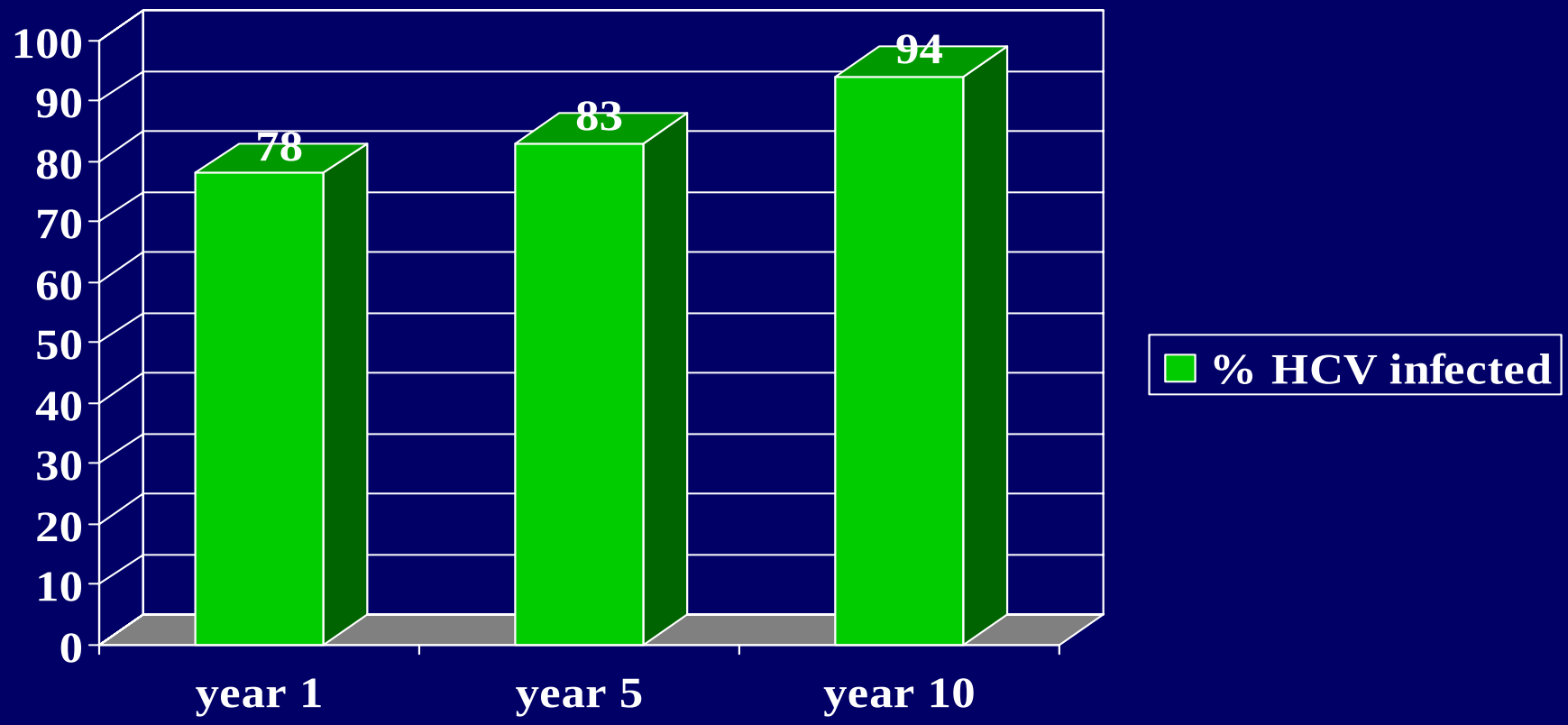
Adapted from Alter et al. *N Engl J Med.* 1999;341(8):556-562.

Estimated Average Prevalence of HCV Infection in US



CDC. *MMWR*. 1998;47(RR-19):1-39.

Risk of HCV in IVDU
(% infected)



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%
• ***USA***		***1.8%***		***9%***
• ***Peru***		***0.8%***		***60-84%***
• 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

SOURCE	*Degree of RISK*
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)

- In HCV(+)/HIV(-):
  - transmission risk is approximately 2%;
  - if mother is HCV-RNA (+), risk is 4-5%,
  - route of delivery does not influence vertical transmission,
  - scalp electrodes increase risk of transmission,
  - no need to discourage breast feeding.
- Up to 30% of infected neonates may have acquired HCV "in utero" (Arch Dis Child Fetal Neonatal Ed 2005;90:F156-60)
- Data are conflicting about duration of ruptured membranes and risk of HCV transmission (increased after 6 h ?)

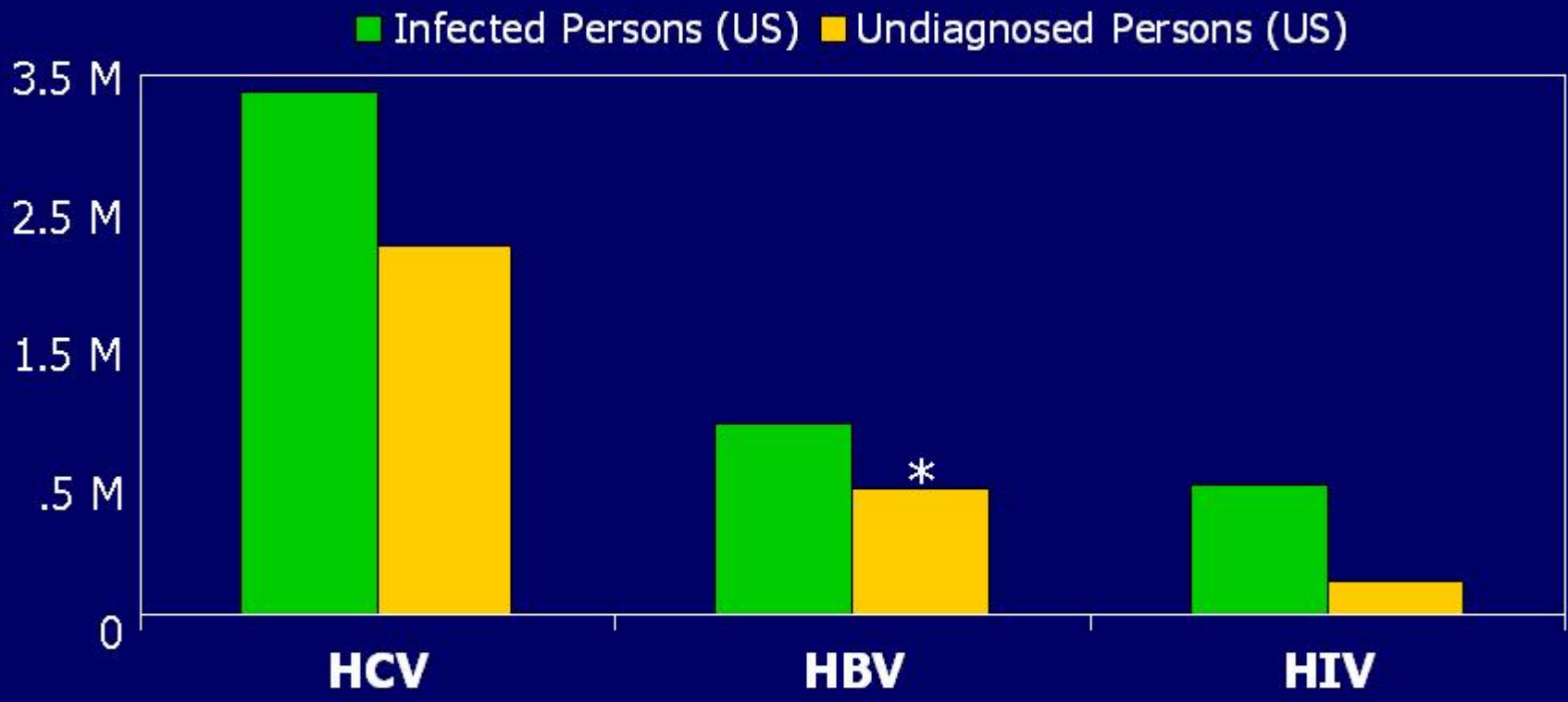
Vertical Transmission of HCV

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

- No association between vertical transmission of HCV and
  - gestational age at delivery, nor
  - presence of chorioamnionitis.
- In HCV/HIV co-infection:
  - transmission risk is higher (15-18%),
  - mode of delivery should be based in HIV status,
  - HAART may decrease transmission risk,
  - breast feeding should be discouraged.

Identifying the Patients

HCV, HBV, and HIV: Prevalence vs Undiagnosed Cases



*Extrapolated from small population study.

1. American Liver Foundation. *Hepatitis C Factsheet*. Available at: www.liverfoundation.org. Accessed March 14, 2005.
2. NIAID. *HIV/AIDS Statistics*. Available at: www.niaid.nih.gov.
3. Lok et al. *Hepatology*. 2004;39:1-5.
4. Thompson et al. *J Cancer Educ*. 2002;17(4):222-226.

2004 AASLD Practice Guidelines: Who Should Be Tested

- Persons who have injected illicit drugs in the recent or remote past, including those who have injected only once and do not consider themselves drug users
- Persons with conditions associated with high prevalence of infection
  - Persons with HIV
  - Hemophiliacs who received clotting factor concentrates prior to 1987
  - Persons who ever received hemodialysis
  - Persons with unexplained ALT elevations

Strader et al. *Hepatology*. 2004;39:1147-1171.

2004 AASLD Practice Guidelines: Who Should Be Tested

- Prior recipients of transfusions or organ transplants including:
  - Persons notified that they received blood from an HCV+ donor
  - Persons who received transfusions prior to 1992
  - Persons who received organ transplants prior to 1992
- Children born to HCV+ mothers
  - Should not be tested until at least 18 months of age due to viral clearance of HCV
- Health care/emergency/public healthcare personnel who have had a needle-stick injury or mucosal exposure to HCV+ blood
- Current sexual partners of HCV-infected persons
  - Although prevalence of infection is low, a negative test in the partner provides reassurance, making testing of sexual partners beneficial in clinical practice

Strader et al. *Hepatology*. 2004;39:1147-1171.

Clinical & Sub-clinical Hepatitis C

Clinical Manifestations of HCV Infection

Acute infection	Majority asymptomatic but jaundice may occur
Chronic infection	No symptoms or fatigue, depression, abdominal discomfort, others
Advanced chronic infection	Portal hypertension with ascites, encephalopathy, gastrointestinal bleeding, jaundice and decompensation

CDC. *MMWR*. 1998;47(RR-19):1-38.

Acute HCV

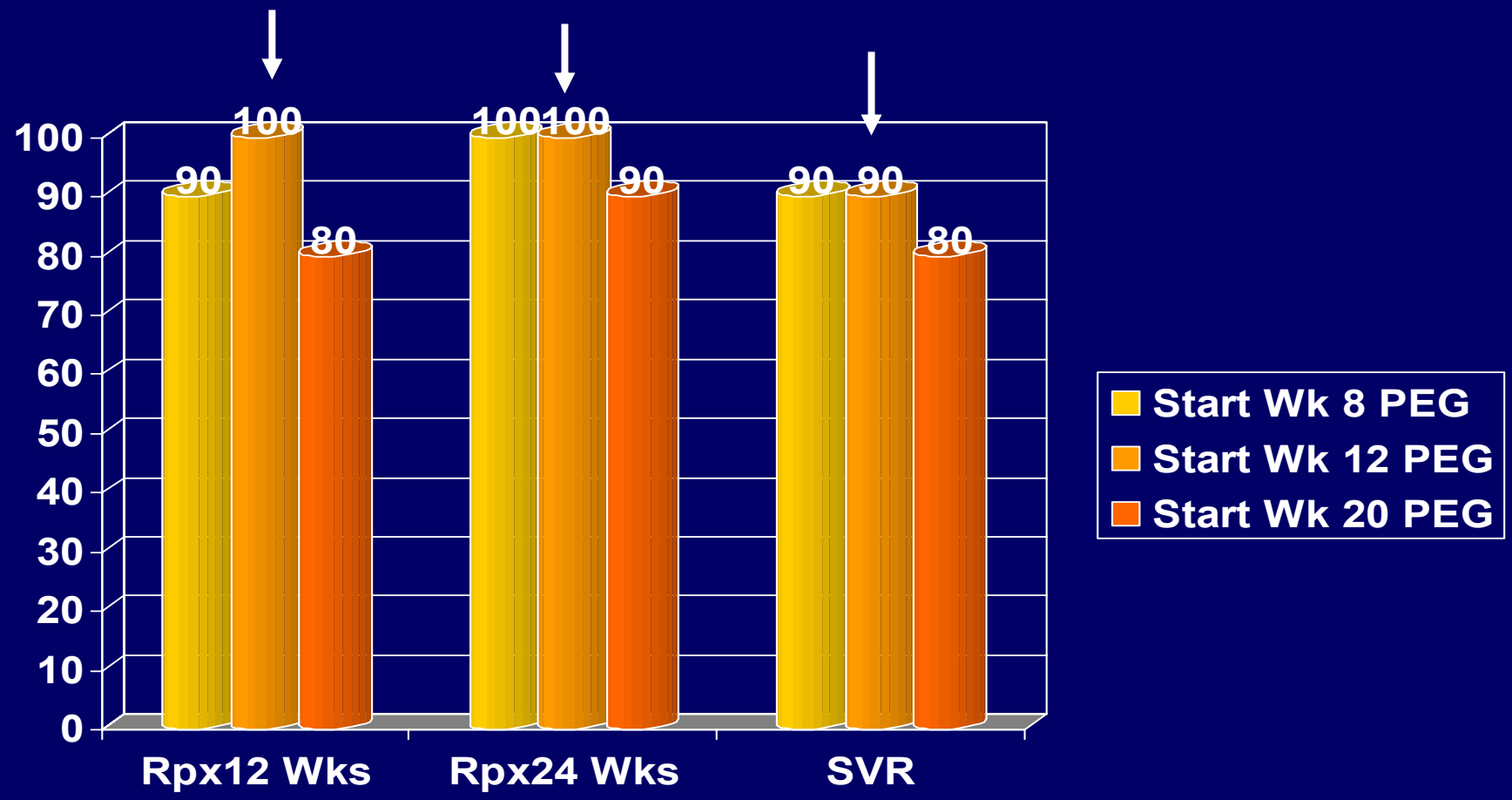
- **Incubation**: 2-26 weeks (usually 7-8)
- **Symptoms:** present in < 30%, mild & < 1month:
  - Common: anorexia, arthralgia, myalgia, fatigue;
  - Rare: jaundice, fever or skin rash.
  - Extremely rare: FHF.
- **DX**: HCV-RNA (+) days to weeks after acquisition ; anti-HCV (+) in 4 weeks (74%).
- **Spontaneous HCV clearance**:
  - Children < 2 y.o. & young women = 45%;
  - Others = 23%

Acute HCV Treatment

- If 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 and drugs (anti-HCV is not protective).

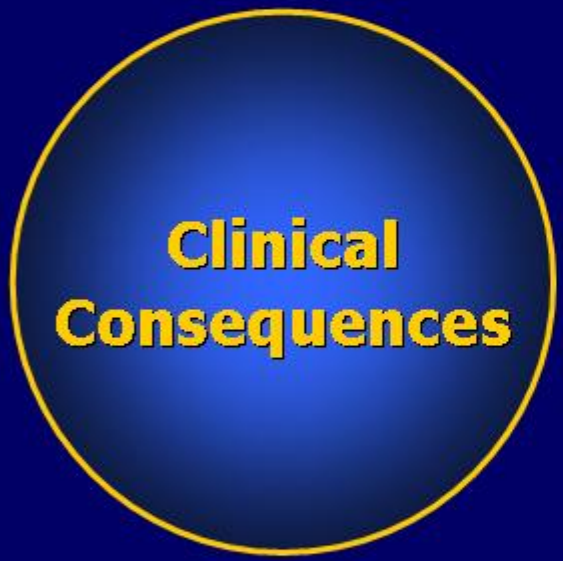
Treatment of Acute HCV @ 8,12, & 20 wks, Peg-IFN alpha 2a vs IFN+RBV x 12 wks

Kamal et al Abst # 37 AASLD, 2004



Chronic Hepatitis C

Impact of HCV Infection: Clinical Consequences



- Chronic hepatitis
- Hepatic fibrosis
- Cirrhosis
- Hepatocellular carcinoma
- End-stage liver disease necessitating liver transplantation
- Extrahepatic manifestations

Hoofnagle. *Hepatology*. 1997;26(suppl 1):15S-20S.

Extrahepatic Manifestations Associated With HCV

Hematologic
- Mixed cryoglobulinemia[1]
- Aplastic anemia[2]
- Thrombocytopenia[2]
- Non-Hodgkin's b-cell lymphoma[2]

Dermatologic
- Porphyria cutanea tarda[1]
- Lichen planus[2]
- Cutaneous necrotizing vasculitis[2]

Renal
- Glomerulonephritis[1]
- Nephrotic syndrome[2]

Endocrine
- Hypothyroidism[2]
- Diabetes mellitus[2]

Ocular
- Corneal ulcer[2]
- Uveitis[2]

Vascular
- Necrotizing vasculitis[2]
- Polyarteritis nodosa[2]

Neuromuscular[2]
- Weakness/myalgia
- Peripheral neuropathy
- Arthritis/arthralgia

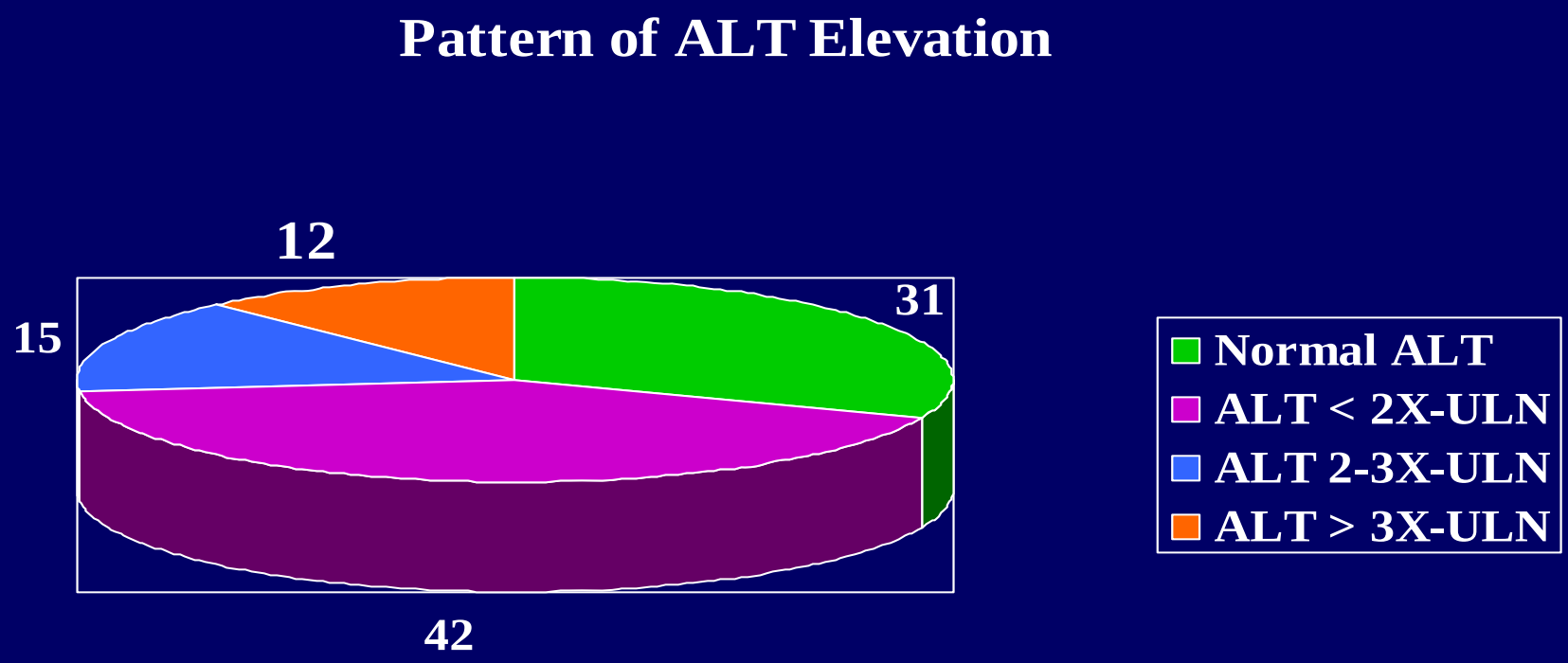
Autoimmune Phenomena[2]
- CREST syndrome

Neuropsychiatric
- Depression[1]

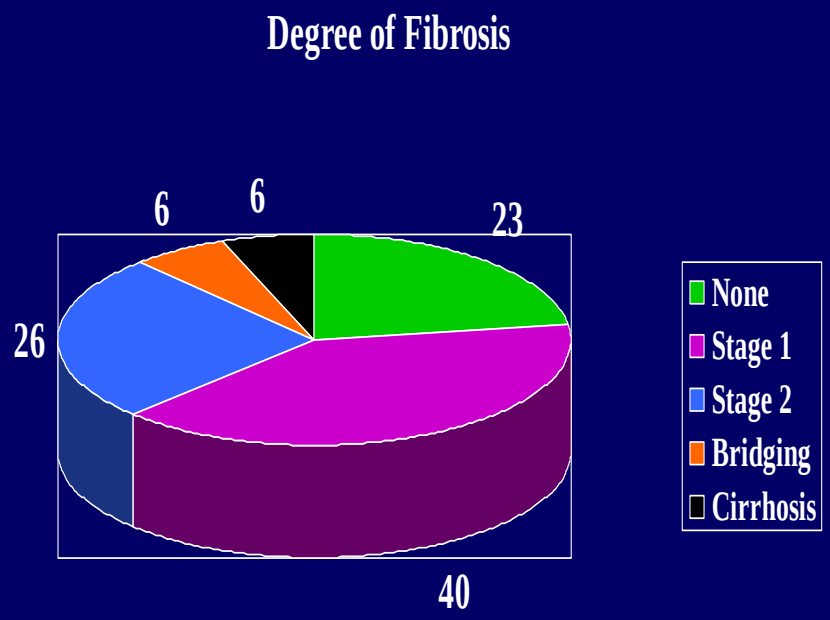
[1]NIH. *NIH Consens State Sci Statements*. 2002;19(3):1-46.
[2]Sene et al. *Metab Brain Dis*. 2004;19(3-4):357-381.

Diagnostic Tests

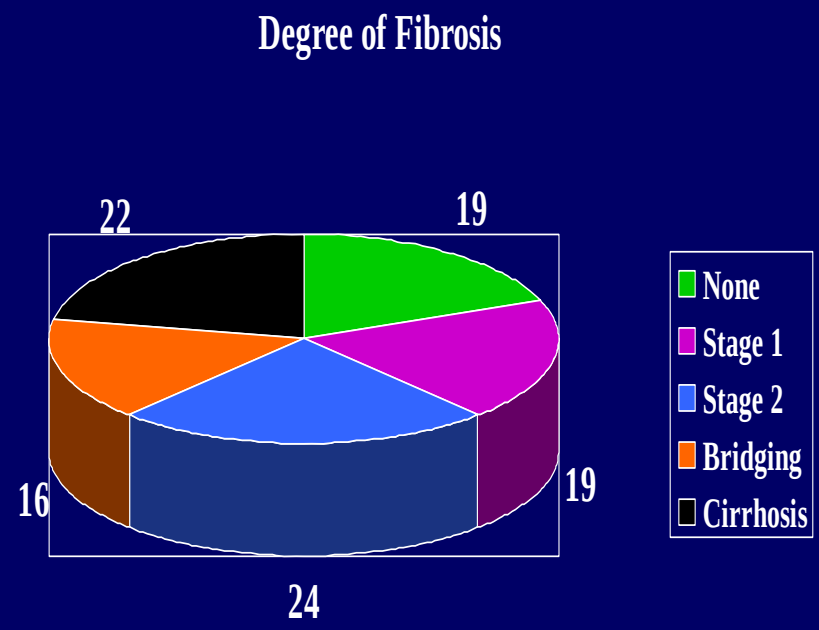
Pattern of ALT Elevation in Chronic HCV



Degree of Fibrosis in Chronic HCV



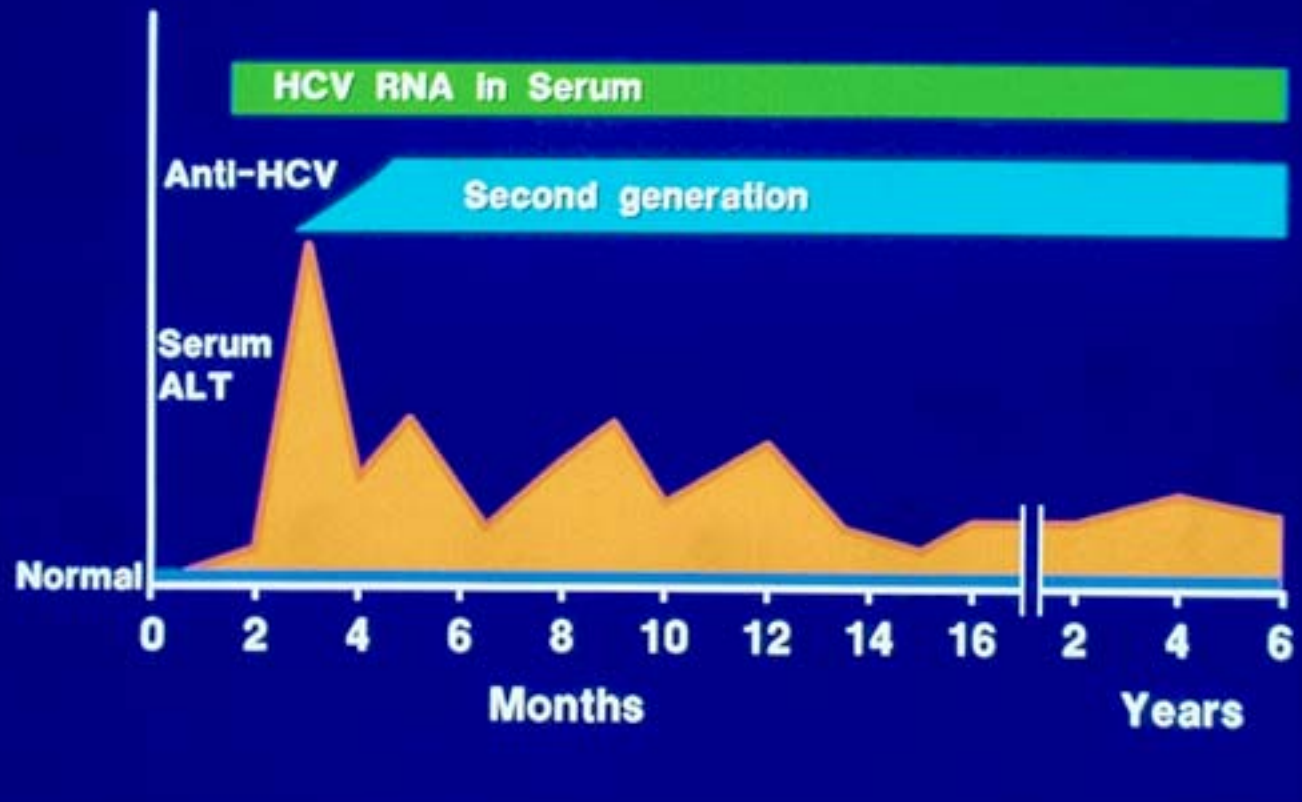
Normal ALT



Elevated ALT

HEPATITIS C VIRUS

Chronic Hepatitis



Markers of Viral Hepatitis C:
Anti-HCV

- Usually ELISA-3
- In patients with risk factors, almost all (+) are “true positives”
- False (+) frequent in low prevalence population without risk factors (40%) and hypergammaglobulinemia
- Rare false (-) [HIV(+), hemodialysis, transplant]

Markers of Viral Hepatitis C: ***Anti-HCV**, continued*

- Acute HCV: anti-HCV turns (+) in
  - 74% at week 4;
  - 98% at week 20.
    (average "window" is 8 weeks)
- 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

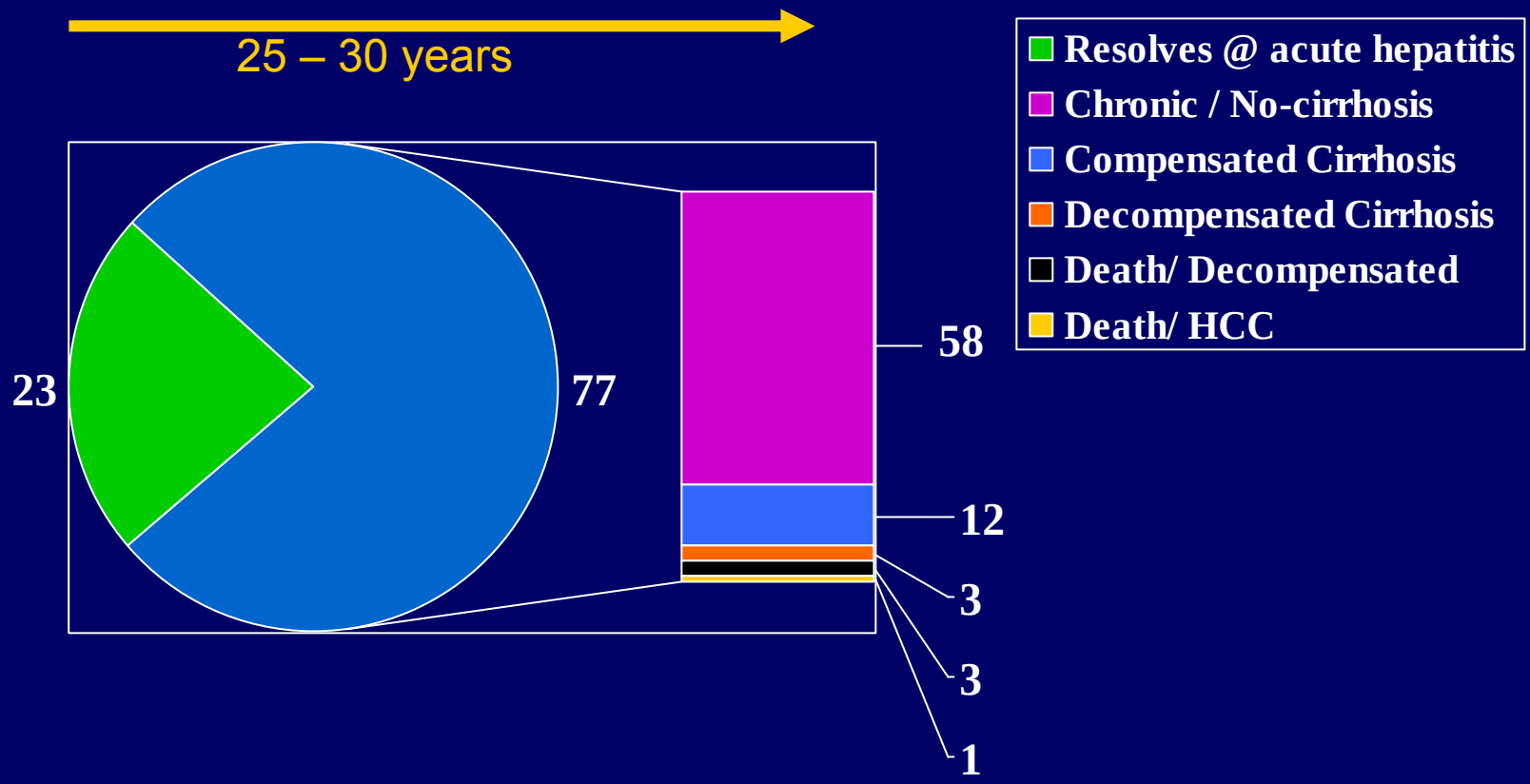
- Uses Real-time PCR, Transcription mediated amplification (TMA), or TaqMan
- **Positive test confirms current infection.**
- Appears 1-2 weeks after infection
- In perinatal infection 70% (+) @ 3 months; many clear spontaneously. Better test @ 18 months if anti-HCV is (+).
- **Variations of up to 0.5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

Markers of Viral Hepatitis C:
HCV-RNA Quantitation

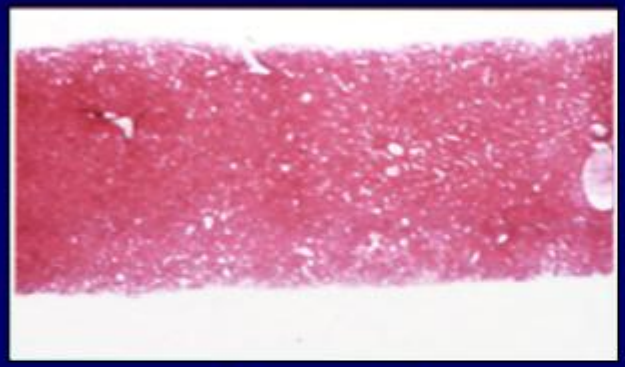
- Fall of < 2-log at week 12 of therapy predicts lack of response (PEG-interferon + Ribavirin)
- Low viral load ($\leq$ 400,000 IU/ml) respond better to therapy
- Infrequent false (+) or false (-)
- **Viral load does not correlate with severity of disease**.

Natural History

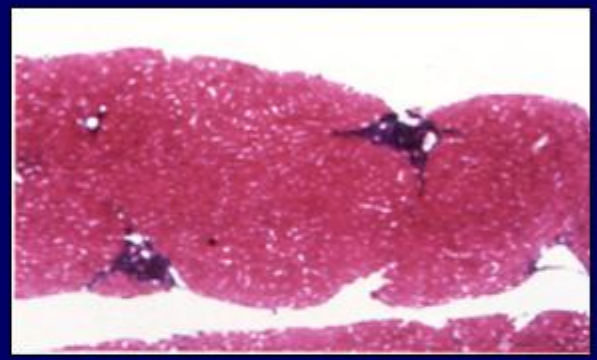
Outcome of HCV
25-30 year Follow-up



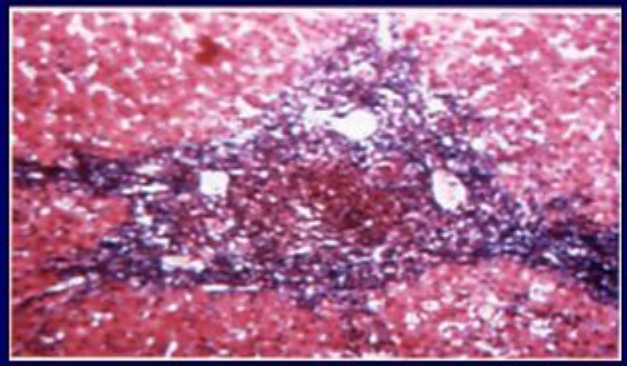
Histologic Progression of HCV on Biopsy



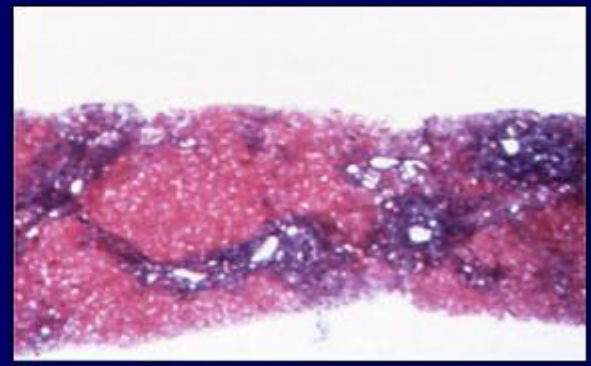
Normal



Mild Chronic Hepatitis



Moderate Chronic Hepatitis



Cirrhosis

Slide Courtesy of Bennett, MD.

Factors Associated With Disease Progression

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

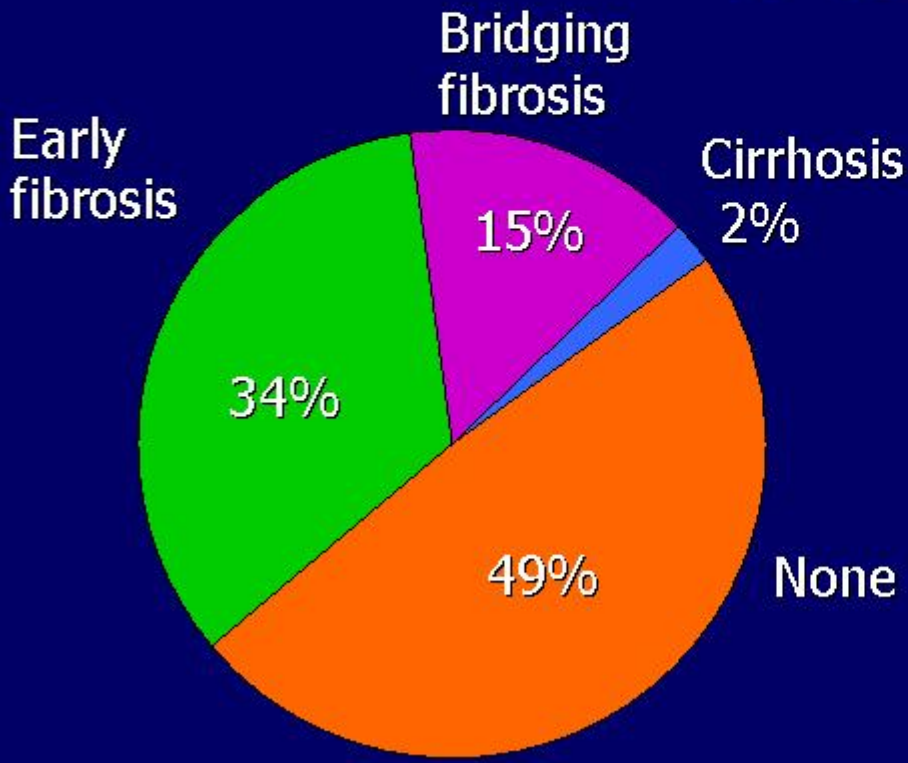
***(1 drink = 12 oz beer = 1.5 oz liquor = 5 oz wine = 13.3g)**

[1]Poynard et al. *Lancet.* 1997;349:825-832.

[2]NIH. *NIH Consens State Sci Statements.* 2002;19(3):1-46.

Liver Fibrosis After 17 Years of Infection in Nonalcoholic Young Women

N=363

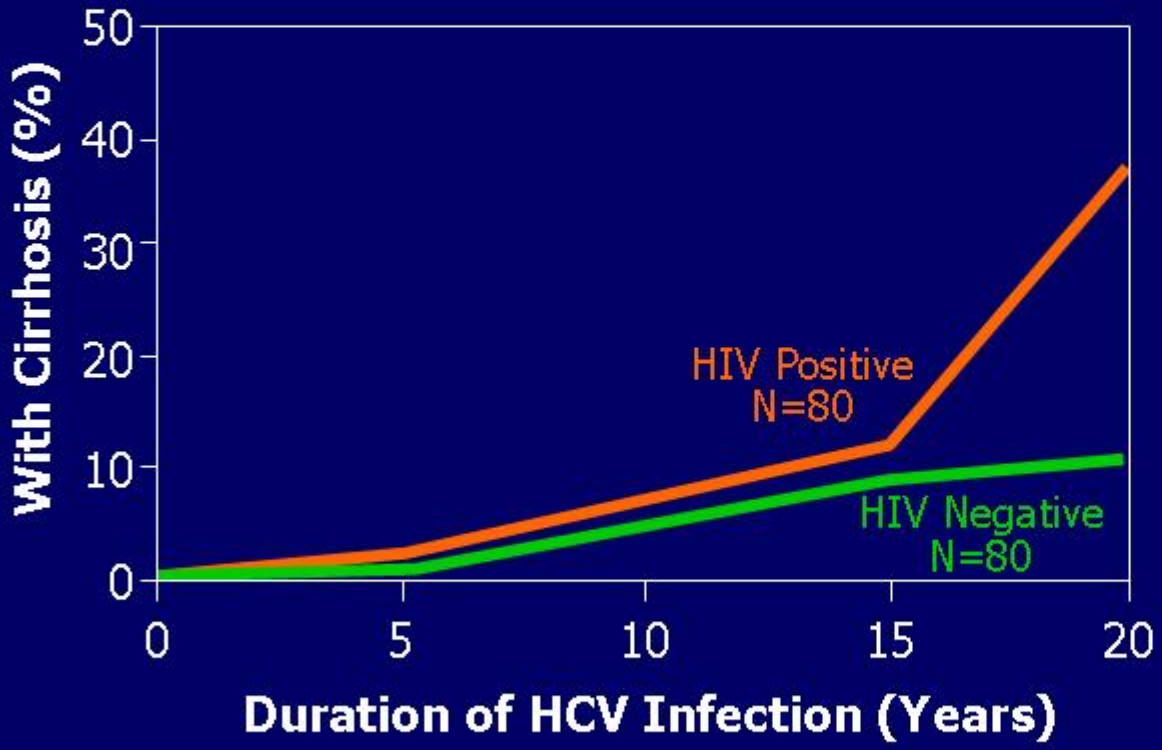


- Young women at infection
- Nonalcoholic
- Not immunosuppressed
- Not coinfected
  - HIV or HBV

Kenny-Walsh et al. *N Engl J Med.* 1999;340:1228-1233.

Profile of Patients at Higher Risk for Disease Progression

N=160

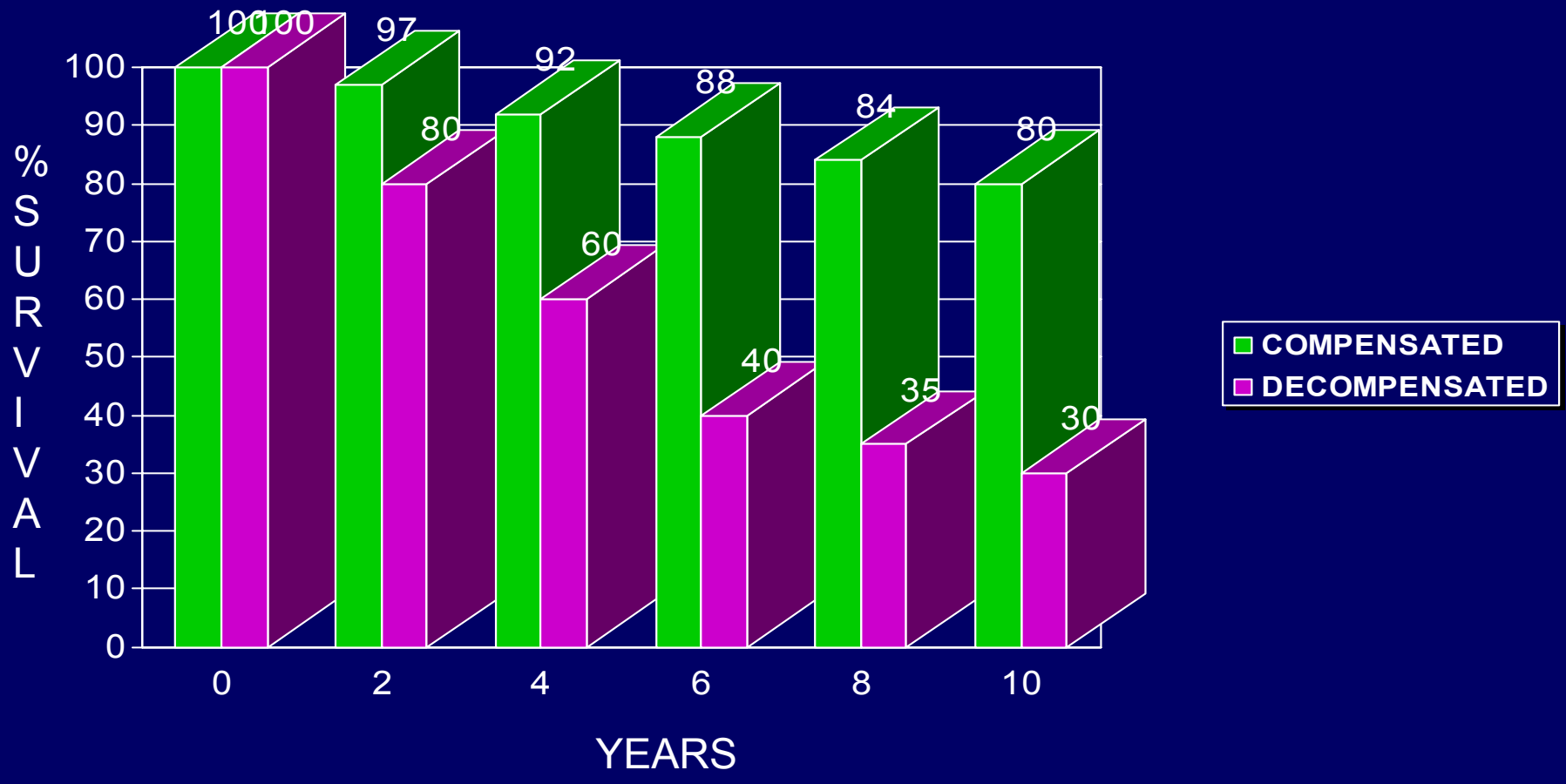


- 73% male overall
- Coinfected with HIV
- Immunocompromised
- Alcohol abuse

Adapted from Di Martino et al. *Hepatology.* 2001;34(6):1193-1199.

HCV Cirrhosis Survival

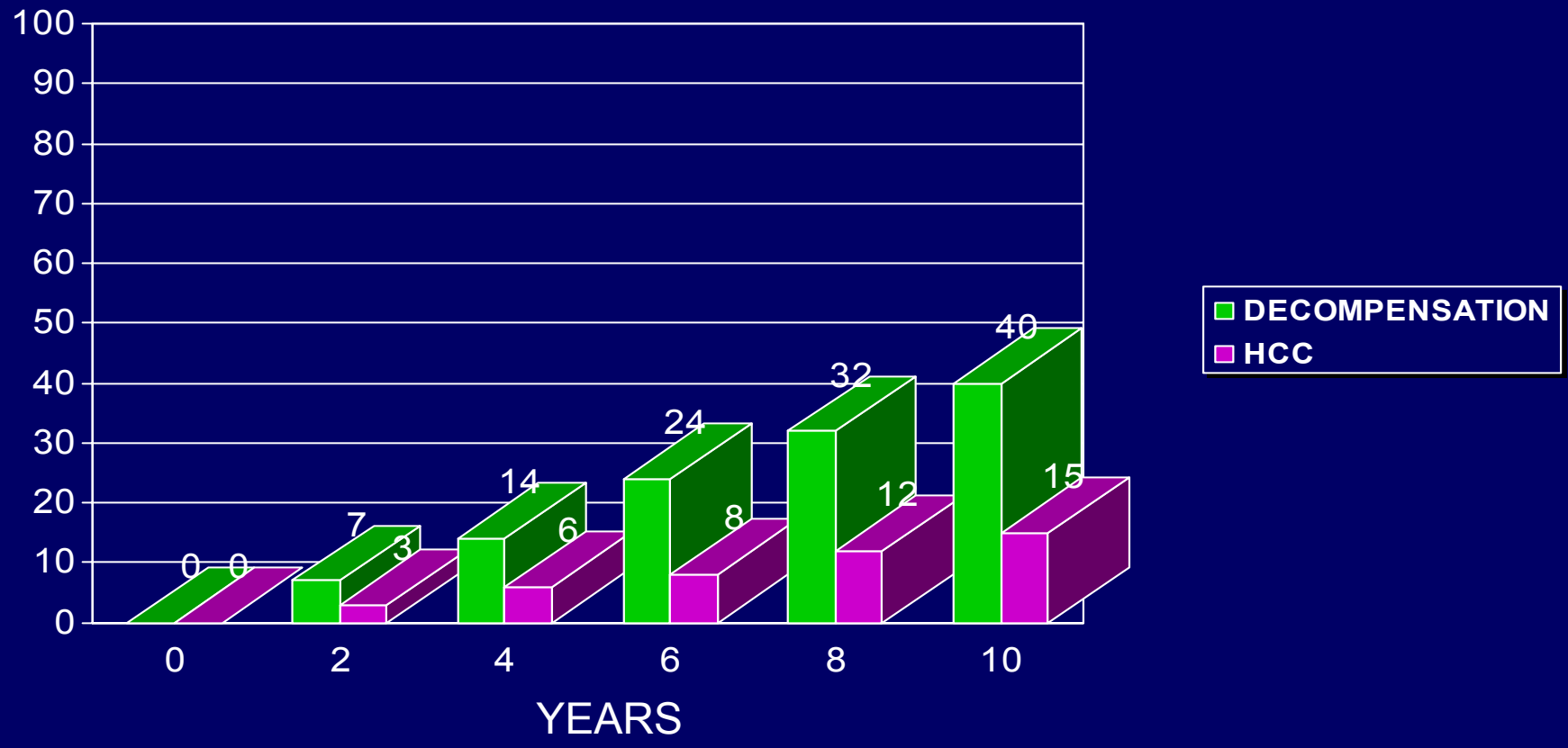
(Fattovich G, et al. Gastroenterology 1997; 112:463-472)



HCV Cirrhosis

Decompensation & Hepatocellular CA

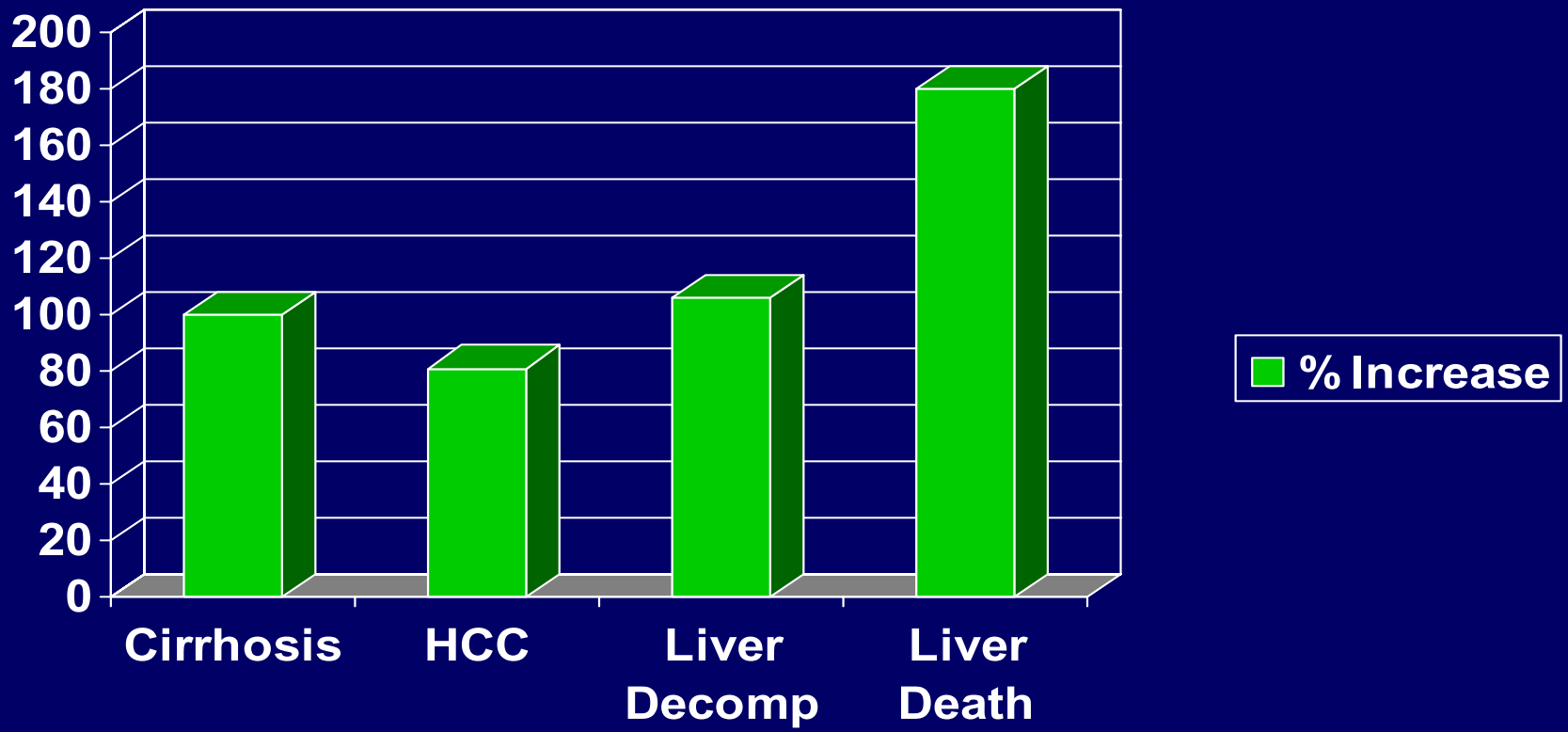
(Fattovich G, et al. Gastroenterology 1997; 112:463-472)



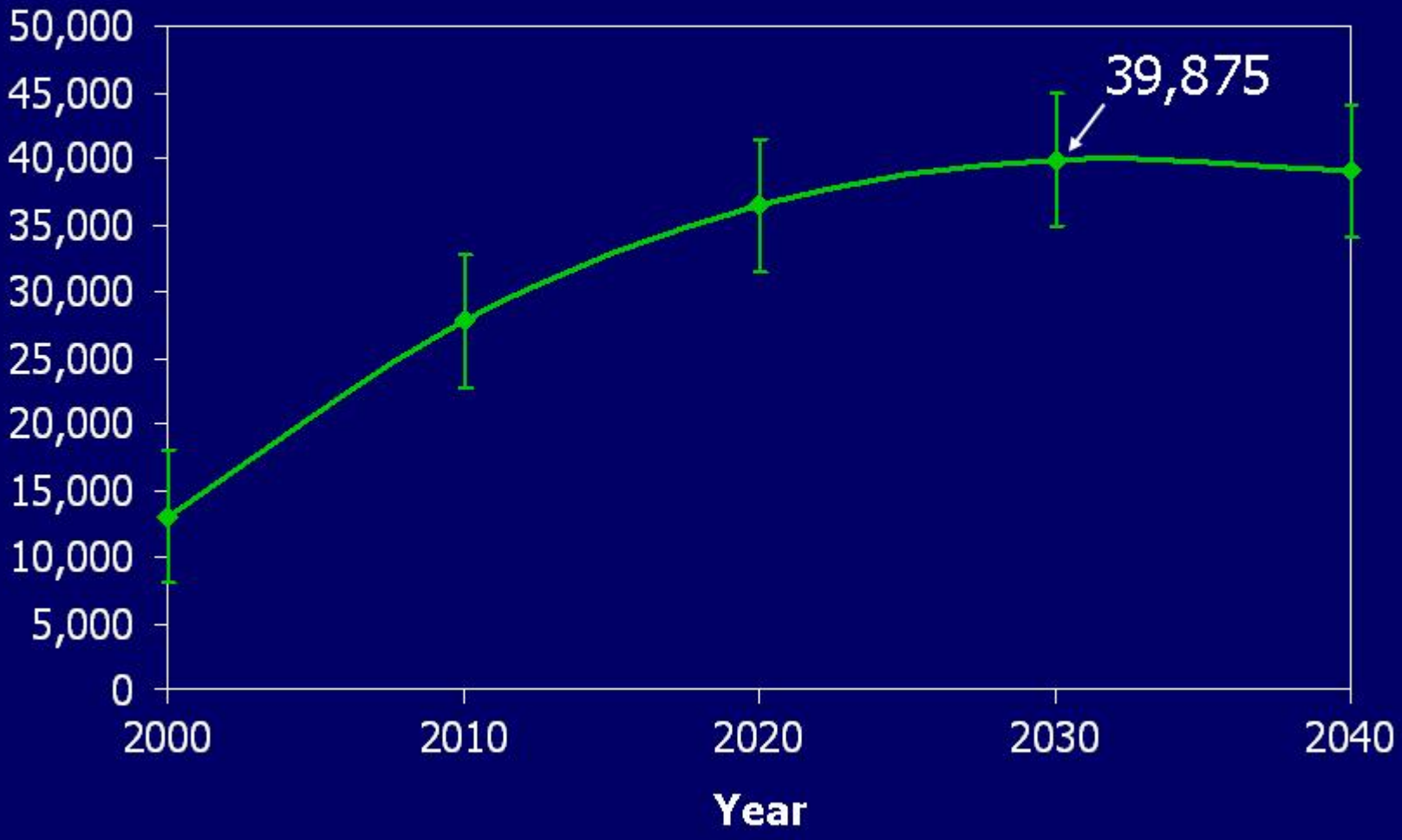
Effects of HCV in Society

Future Disease Burden:
Estimated Increases from 2000-2020

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



Projected HCV Mortality



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

Treatment

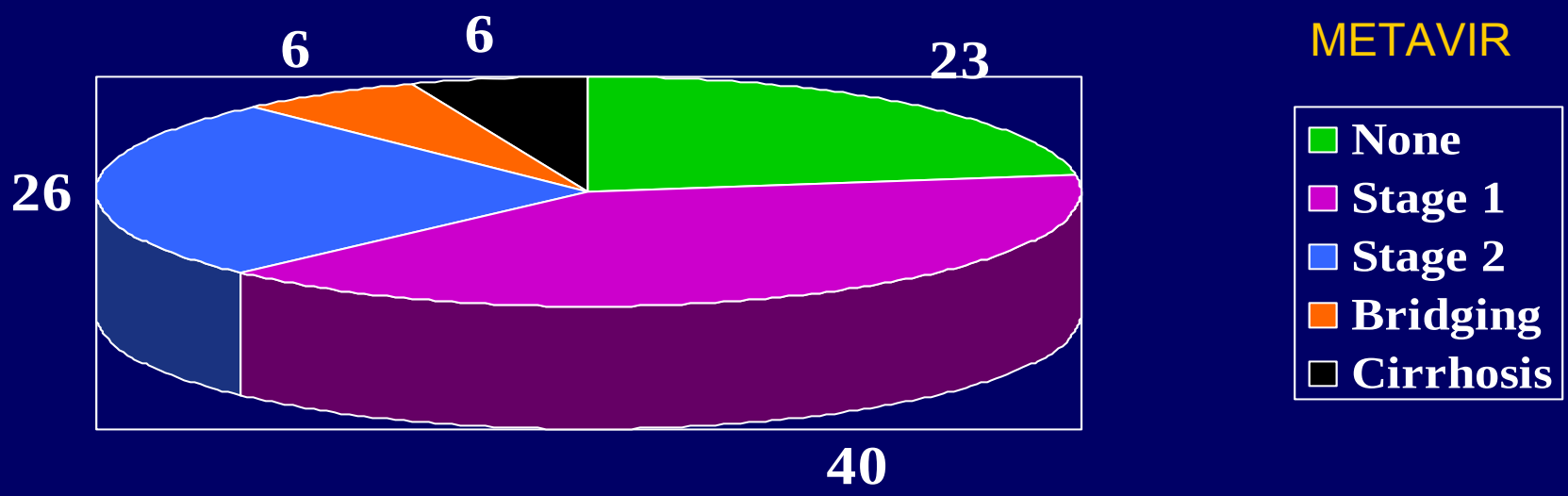
Histologic Scoring of Fibrosis

FIBROSIS	METAVIR or Knodell	Ishak
None	0	0
Portal fibrosis (some p. areas)	1	1
Portal Fibrosis (most p. areas)	1	2
Bridging fibrosis (occasional)	***2***	***3***
Bridging fibrosis (marked)	**3**	**4**
Incomplete cirrhosis	**4**	**5**
Cirrhosis	**4**	**6**

Treat METAVIR/Knodell =/> 2, or Ishak =/> 3

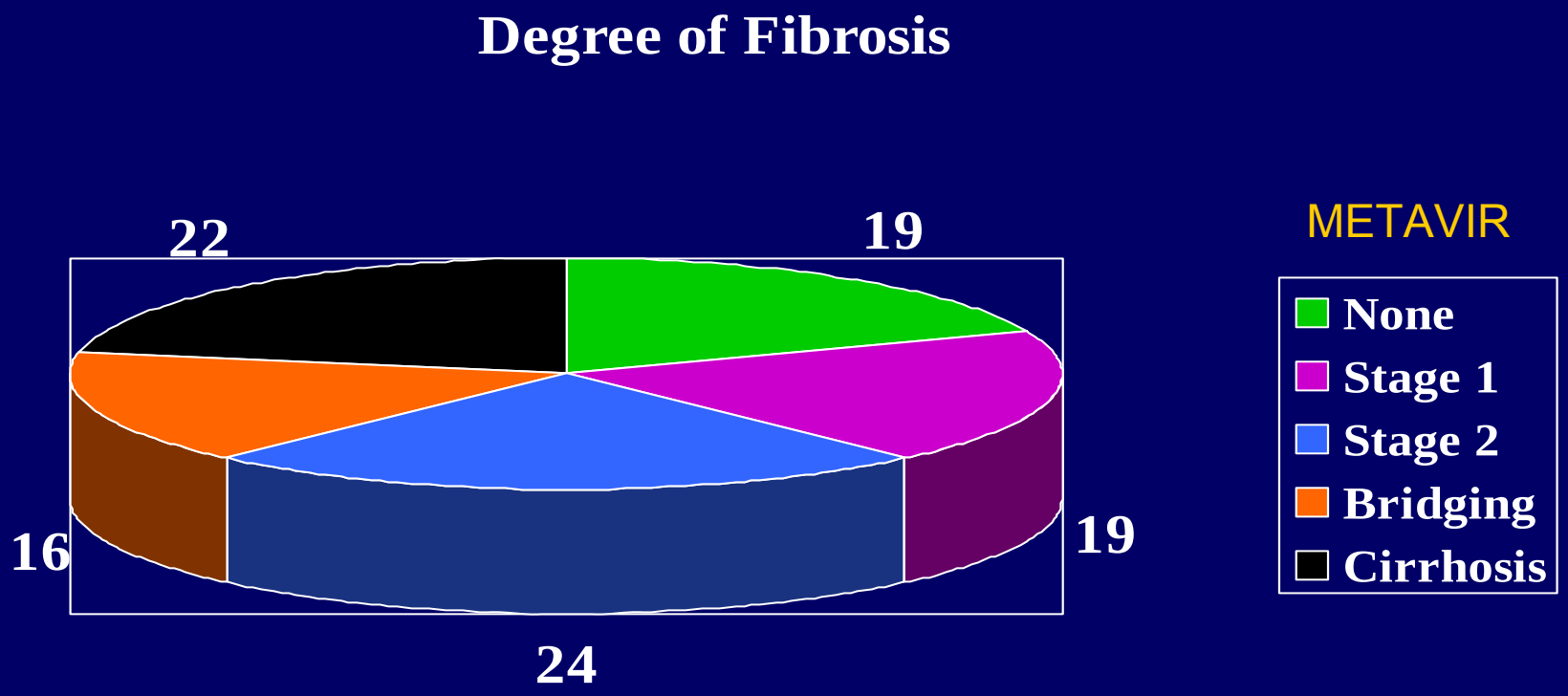
Degree of Fibrosis in Chronic HCV With Normal ALT

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



38% qualify for therapy (METAVIR >/= 2)

Degree of Fibrosis in Chronic HCV With Elevated ALT

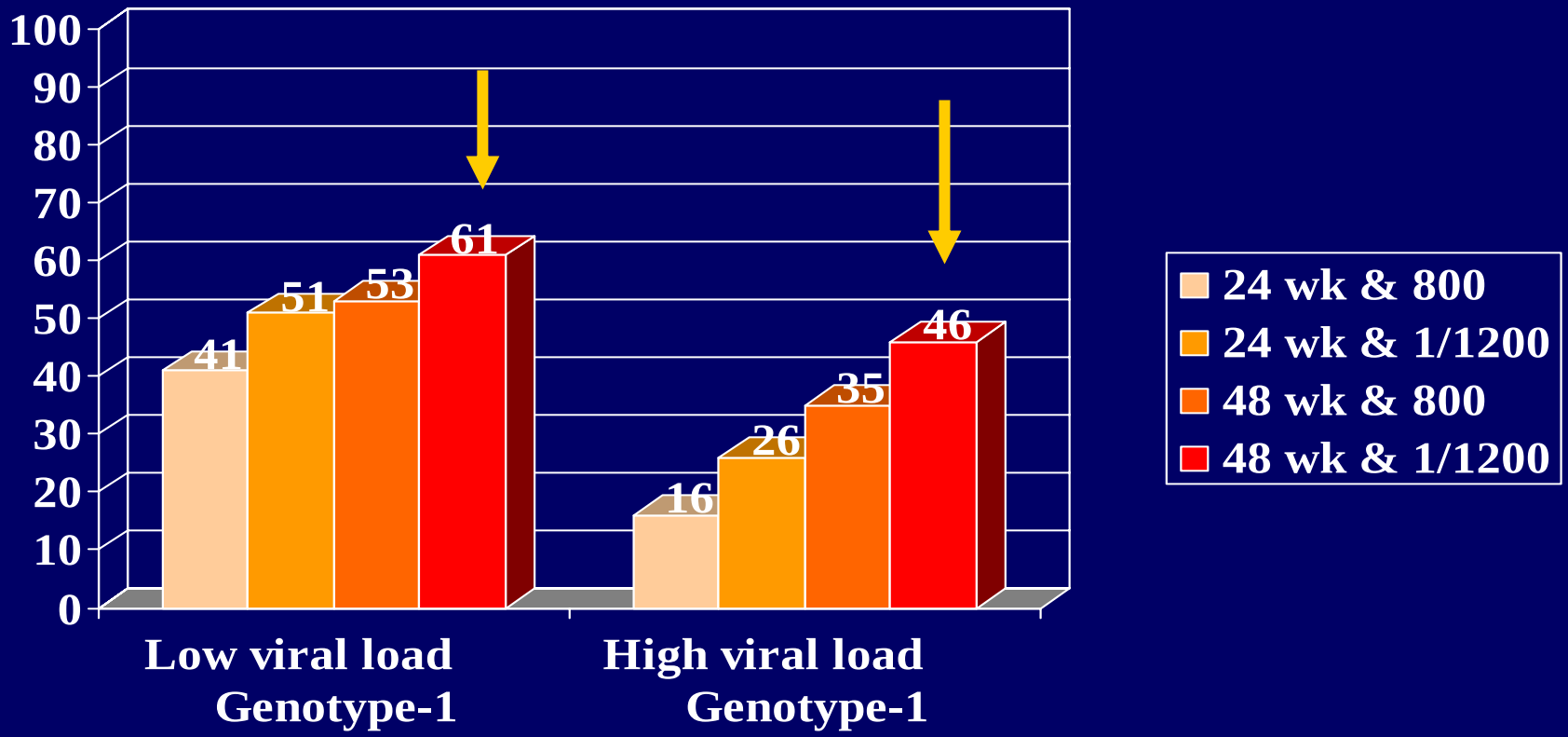


68% qualify for therapy (METAVIR >/= 2)

STANDARD TREATMENT

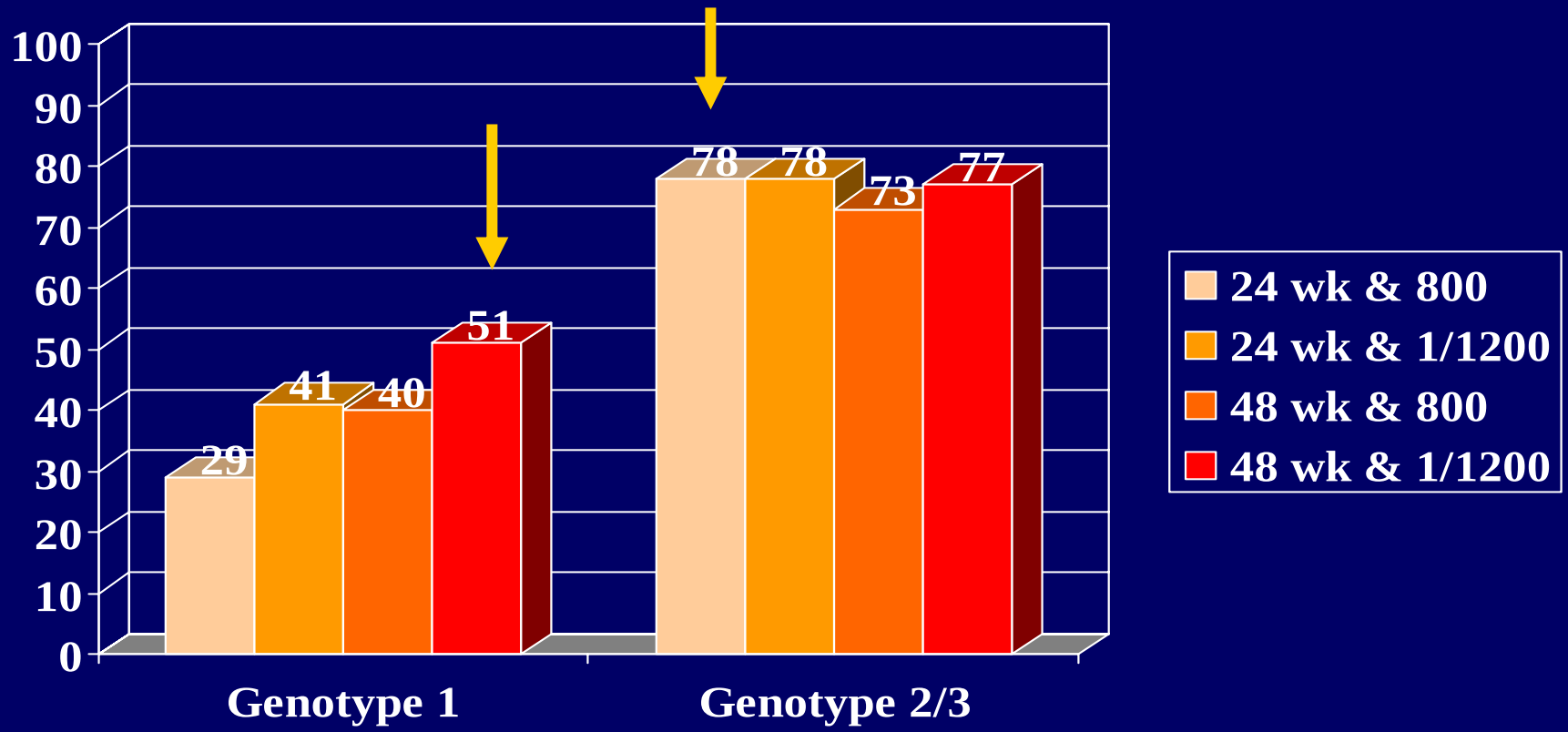
- Peg-Interferon dose
  - Alpha-2a 180 mcg per week SQ
  - Alpha-2b 1.5 mcg per kg per week SQ
- Ribavirin dose
  - Genotypes 1,4,5, and 6
    - Less than 75 kg 1000 mg per day, divided BID
    - More than 75 kg 1200 mg per day, divided BID
  - Genotypes 2 and 3 800 mg per day divided BID

Genotype-1 **chronic HCV** SVR **by Treatment Regimen**

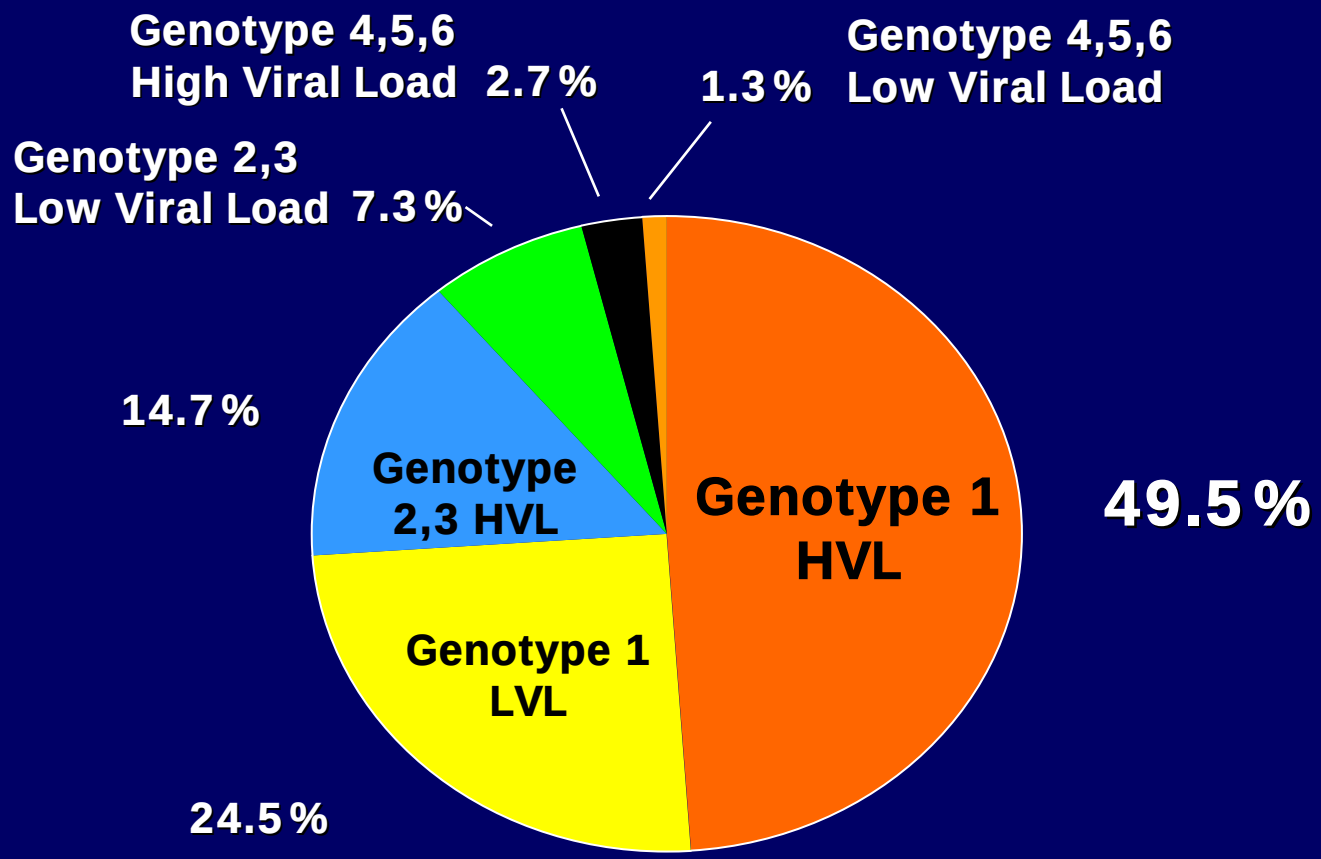


PEG-IFN alpha 2a + Ribavirin

Sustained Virologic Response



Genotype and Viral Load in US Patients



Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

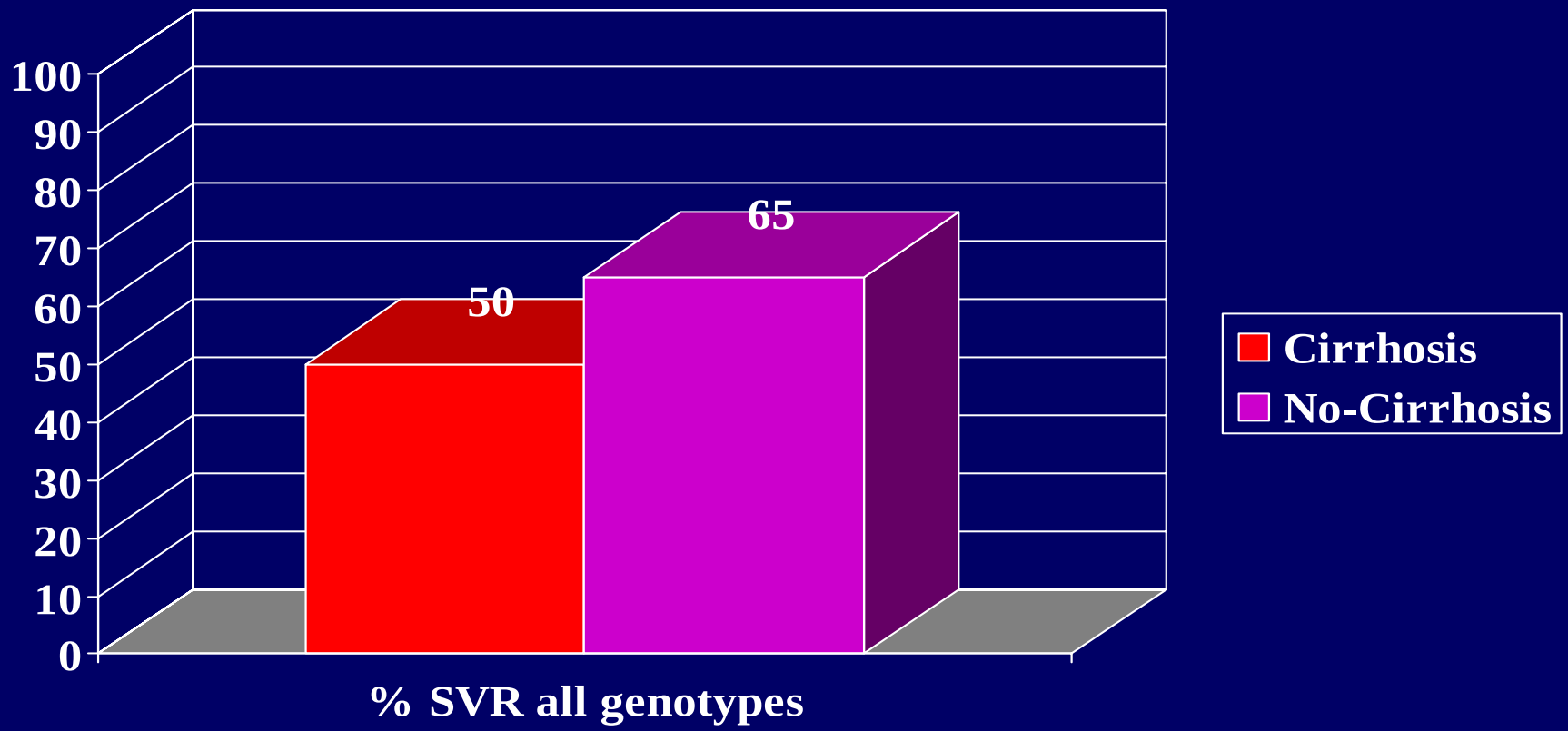
Dose Reduction or Discontinuation AASLD

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

Effect of Fibrosis

HCV Cirrhosis vs No-Cirrhosis

Peg-Ifn alpha 2a + Ribavirin 1/1200 x 48 wks



Patients with pre-cirrhosis & cirrhosis (F3/F4) will remain at risk of HCC even if they eliminate the infection (SVR); they should be under HCC surveillance.

Classification of Treatment Response
By time to be HCV-RNA negative

Type of Treatment Response

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

	4 weeks	12 weeks	24 weeks
RVR	**(-)**	(-)	(-)
cEVR	(+)	**(-)**	(-)
pEVR Slow Responder	(+)	**> 2 log drop**	**(-)**
pEVR Partial Responder	(+)	**> 2 log drop**	**(+)**
Null Responder	(+)	**< 1 log drop**	

No Responder

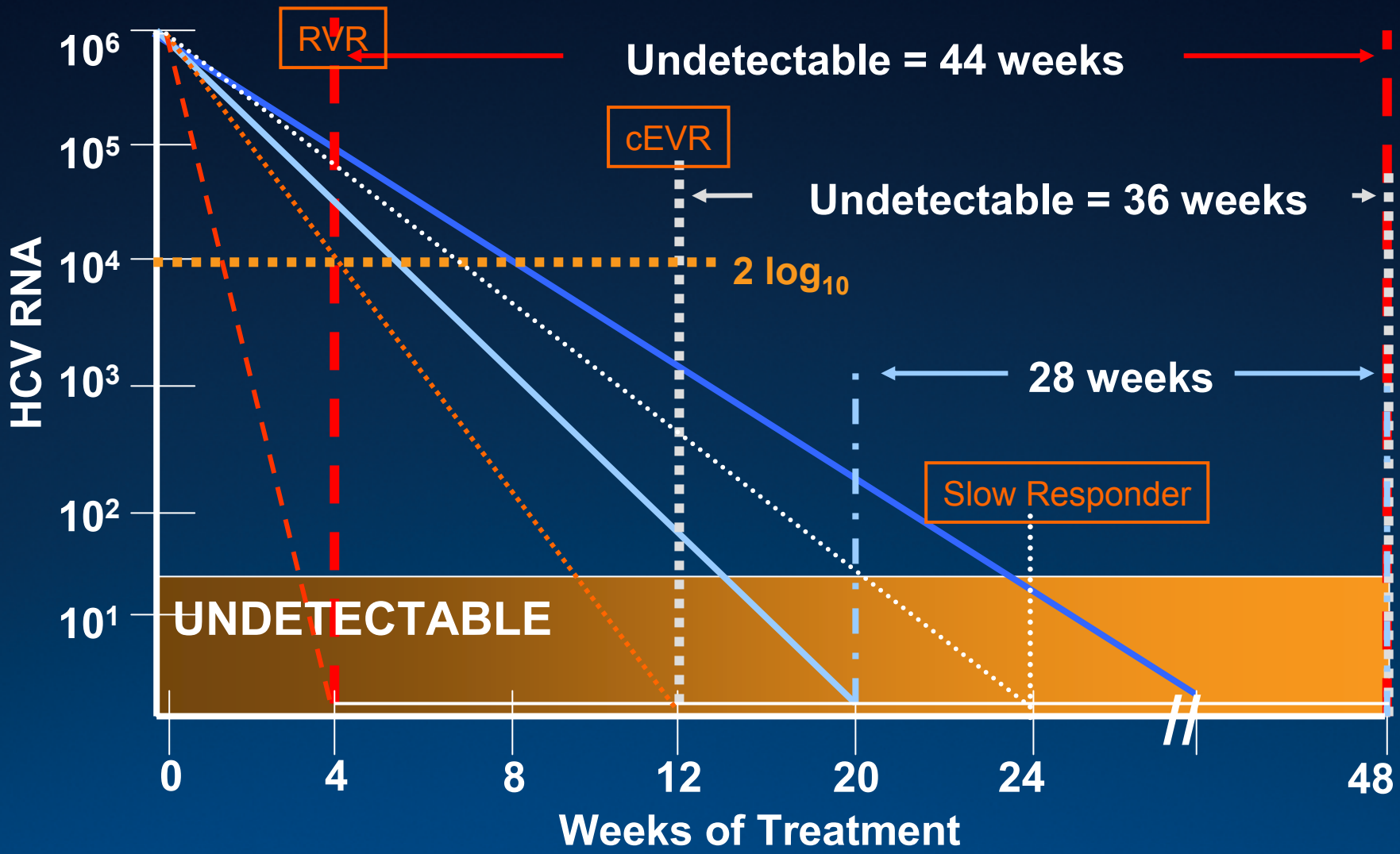
No Responder

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

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

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

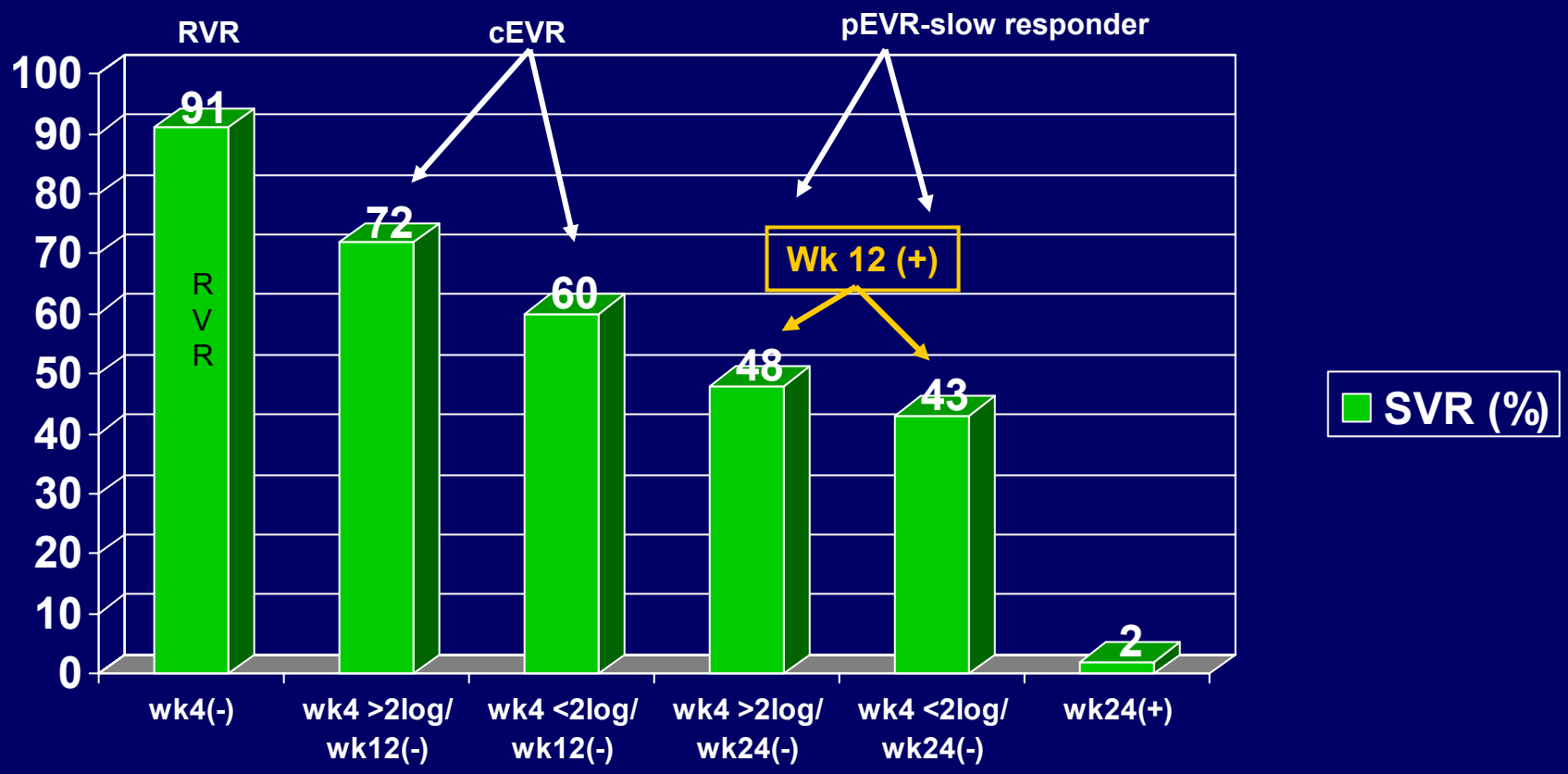
Rate of Viral Decline Determines Period of HCV RNA Negativity



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.

Predictors of Response to Therapy

Predicting SVR by HCV-RNA fall
Peg-IFN alpha 2a + RBV



Ferenci P, et al. J Hepatol 2005; 43:425-433

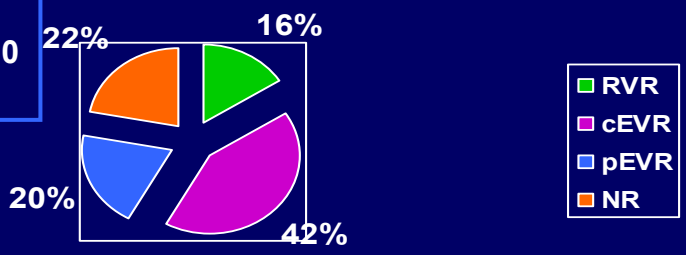
Effect of RVR & cEVR in SVR among Different HCV Genotypes

Rapidity of Response by Genotype

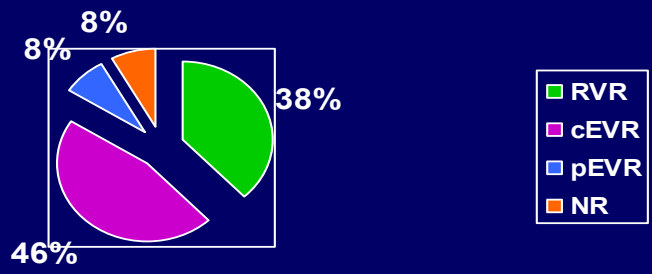
Fried MW, EASL 2008; Abstr #7

Genotype-1
N: 569

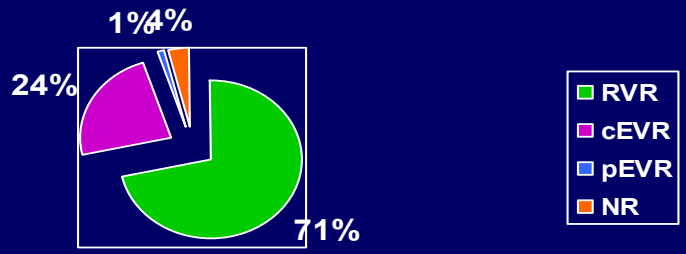
PEG-Ifn 180
RBV 1000-1200
48 wks



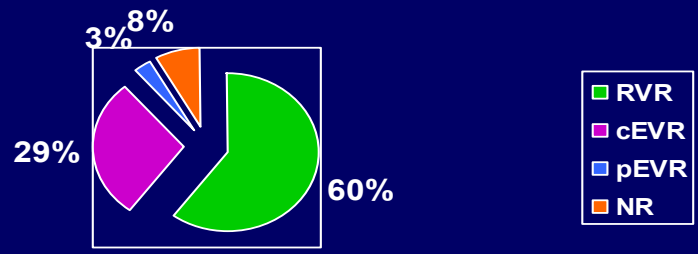
Genotype-4
N: 24



PEG-Ifn 180
RBV 800
24 wks



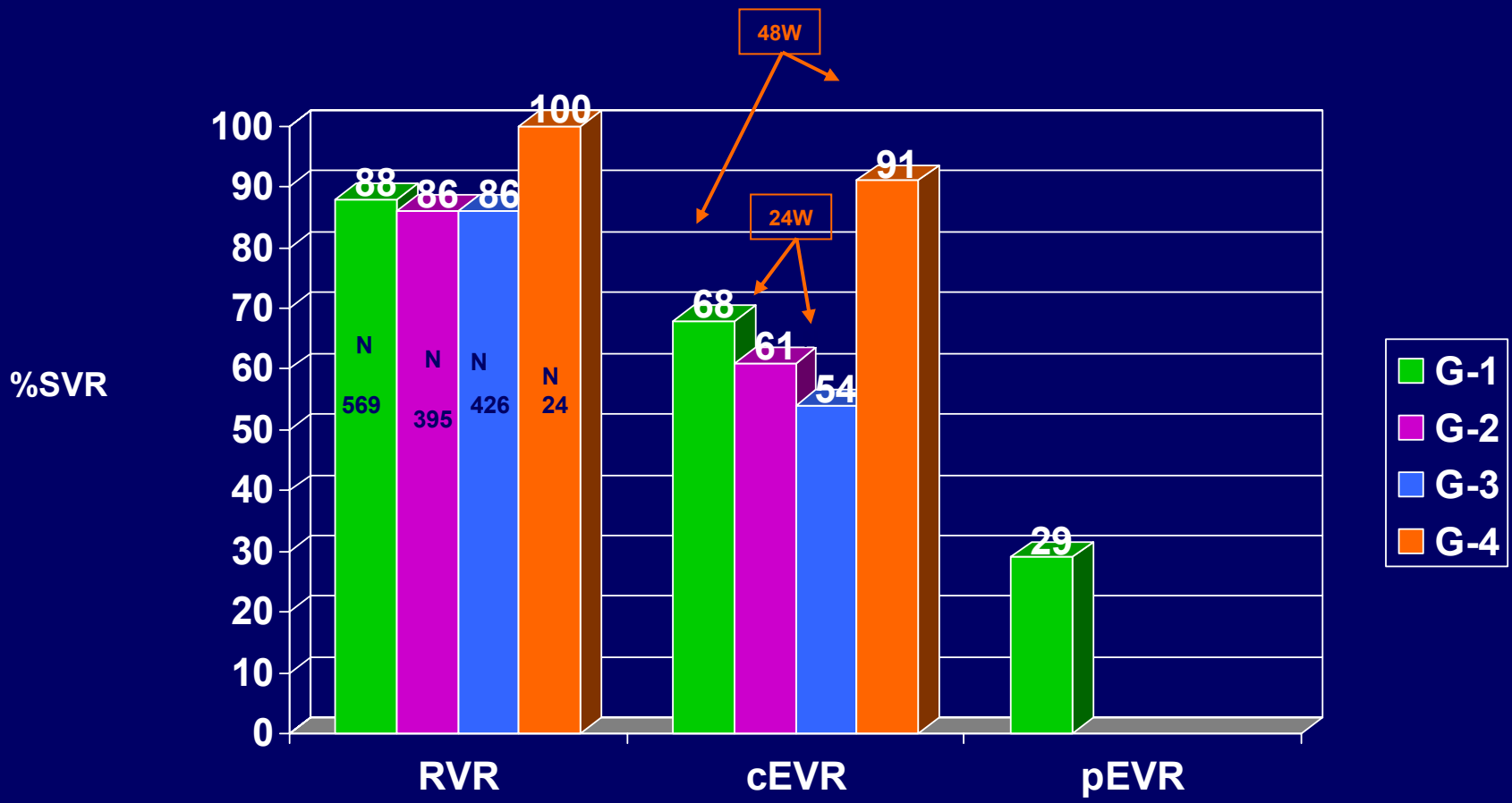
Genotype-2
N: 395



Genotype-3
N: 426

SVR by Response Type & Genotype

Fried MW, EASL 2008; Abstr #7



RVR Important Predictor of SVR: Conclusion

Subanalysis of 3 Phase III trials

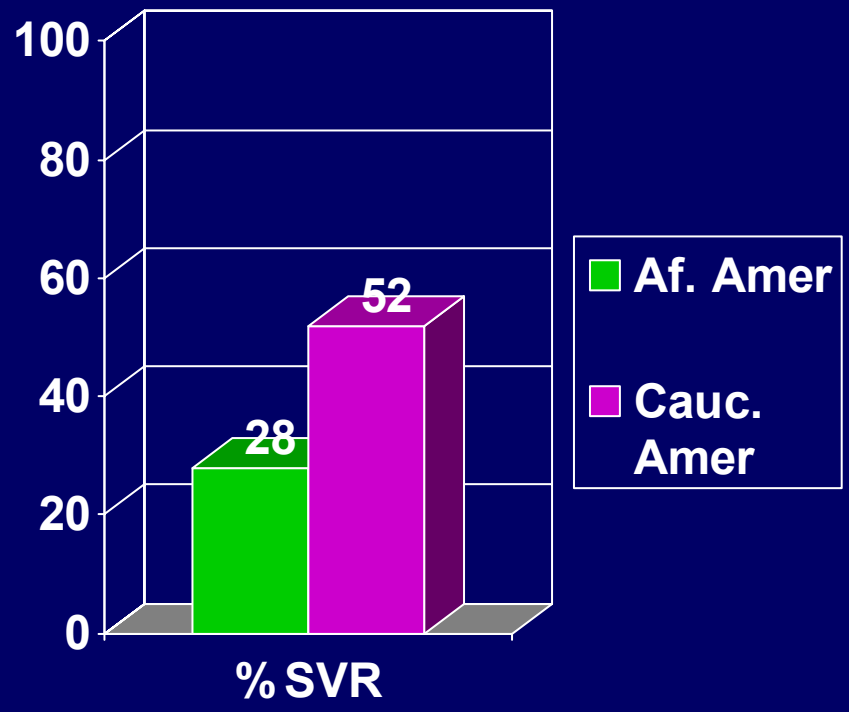
- Patients achieving RVR at week 4 have a high probability of SVR (> 86%) regardless of HCV genotype
- RVR is a better predictor of SVR than other pre-treatment factors including genotype
- This information may allow treatment to be tailored to the individual, regardless of genotype

Fried MW, et al. Presented at EASL 2008. April 23-27, 2008; Milan, Italy. Abstract #7.

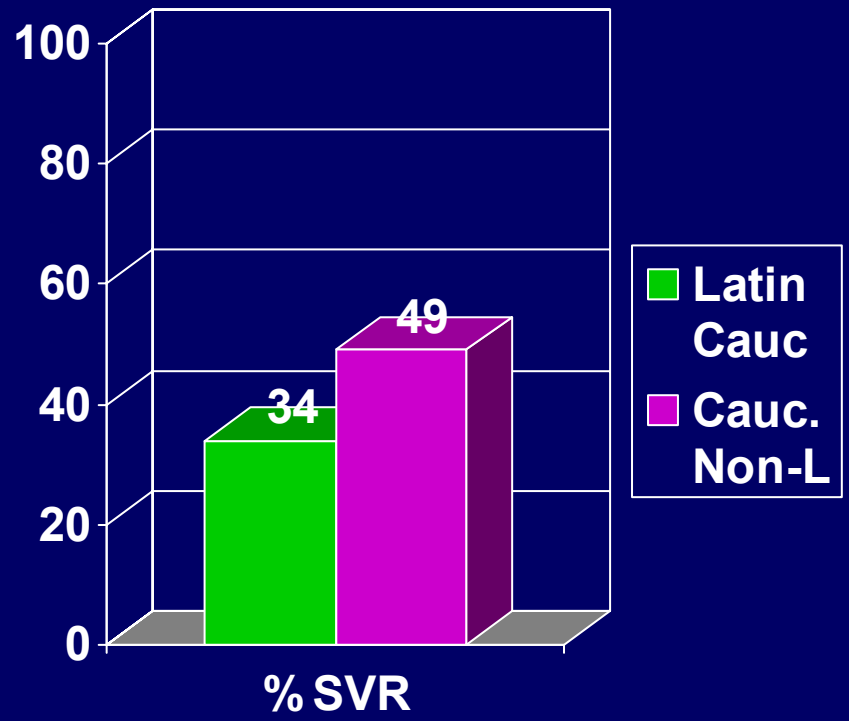
Effect of Ethnicity

Effect of Ethnicity in SVR – Genotype 1

Virahep C Study



Latino Study



Virahep-C Trial: *Baseline Characteristics*

Characteristic	AA (n = 196)	CA (n = 205)	*P* value
% Male	65	65	0.99
Median Age (years)	49.0	48.0	0.08
Median BMI (kg/m^2)	29.3	27.6	0.0003
% History of Diabetes	15	4	0.0004
% History of Hypertension	43	21	< 0.0001
Median ALT (IU/L)	59	74	< 0.0001
Median Hemoglobin (g/dL)	14.3	15.0	< 0.0001
Median WBC (10^3 cells/mm^3)	5.8	6.2	0.08
Median Platelet Count (10^3 cells/mm^3)	214.5	207.0	0.11

Conjeevaram HS, et al. *Gastroenterology*. 2006;131:470-477.

LATINO Study: *Baseline Characteristics*

	Latinos	Non-Latinos
Age ≤ 40 years	27.9%	16.3%
BMI		
> 27 kg/m^2	65.1%	50.7%
> 30 kg/m^2	40.1%	25%
ALT > 3x ULN	24.5%	16.7%
Cirrhotic	13.4%	9.7%

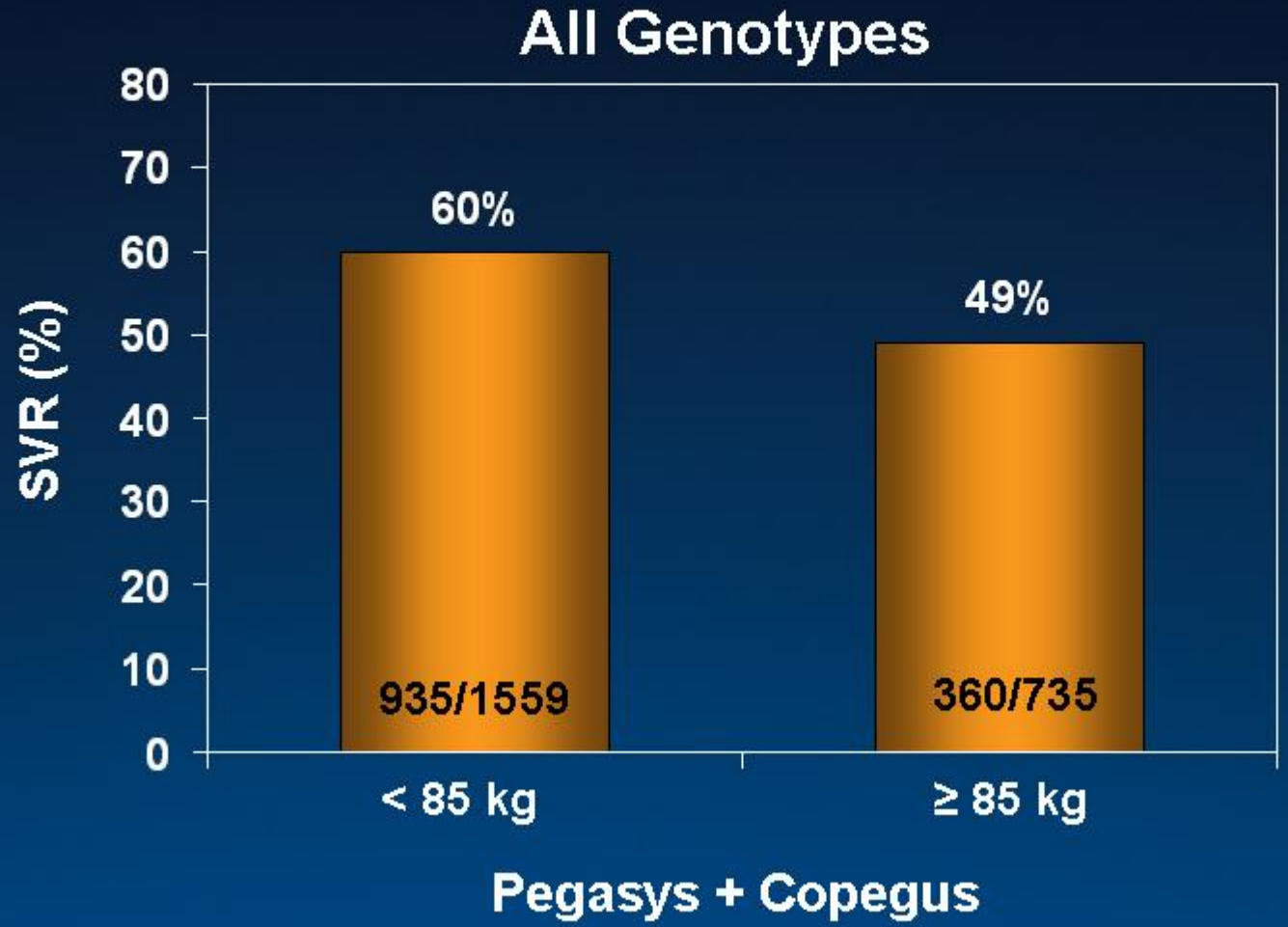
Other baseline characteristics were similar

Rodriguez-Torres M, et al. Presented at EASL 2008. April 23-27, 2008; Milan, Italy. Poster #2553.

Effect of Weight, Steatosis & Insulin Resistance

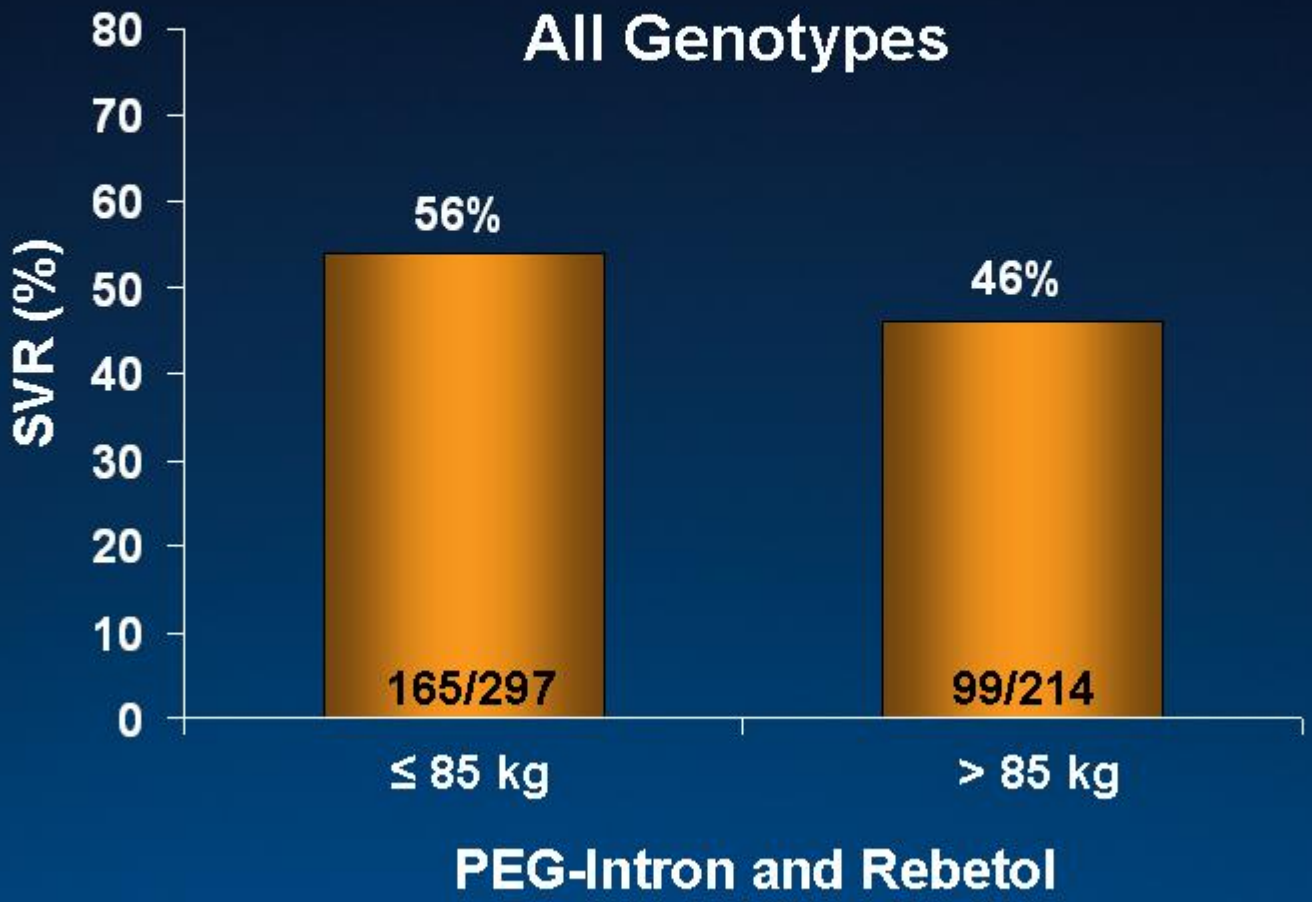
EFFECT OF BODY WEIGHT

SVR Rates in Lighter vs Heavier Patients: Pegasys



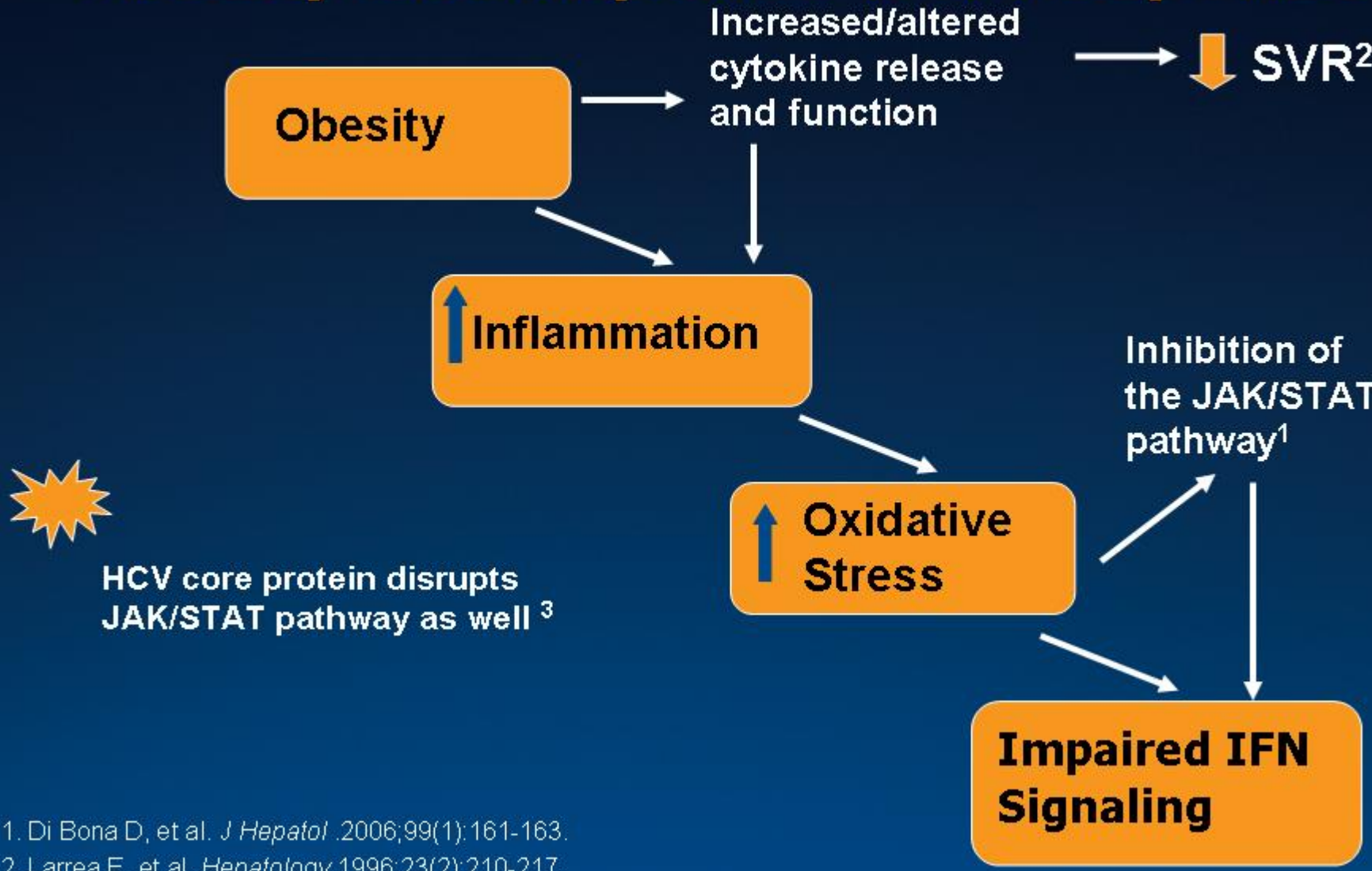
Pegasys (Peginterferon alfa-2a) [package insert]. Hoffmann-La Roche Inc. Nutley, NJ.
FDA Briefing Paper. Pegasys. November 14, 2002. htpp://www.fda.gov/ohrms/dockets/ac/02/transcripts/3909T1.pdf

SVR Rates in Lighter vs Heavier Patients: PEG-Intron



Adapted from FDA Antiviral Drugs Advisory Committee Proceedings. Peginterferon alfa-2b. December 12, 2001. http://www.fda.gov/ohrms/dockets/ac/01/briefing/3819b1_03_FDA-Clinical%20review.PDF

Obesity and Impaired IFN Response



1. Di Bona D, et al. *J Hepatol* .2006;99(1):161-163.
2. Larrea E, et al. *Hepatology*.1996;23(2):210-217.
3. Lin W. *Gastroenterology*. 2005;128:1034-1041.

EFFECT OF STEATOSIS

Proposed Mechanisms for Co-Existent HCV and Steatosis

HCV
- Genotype 3
- Insulin Resistance

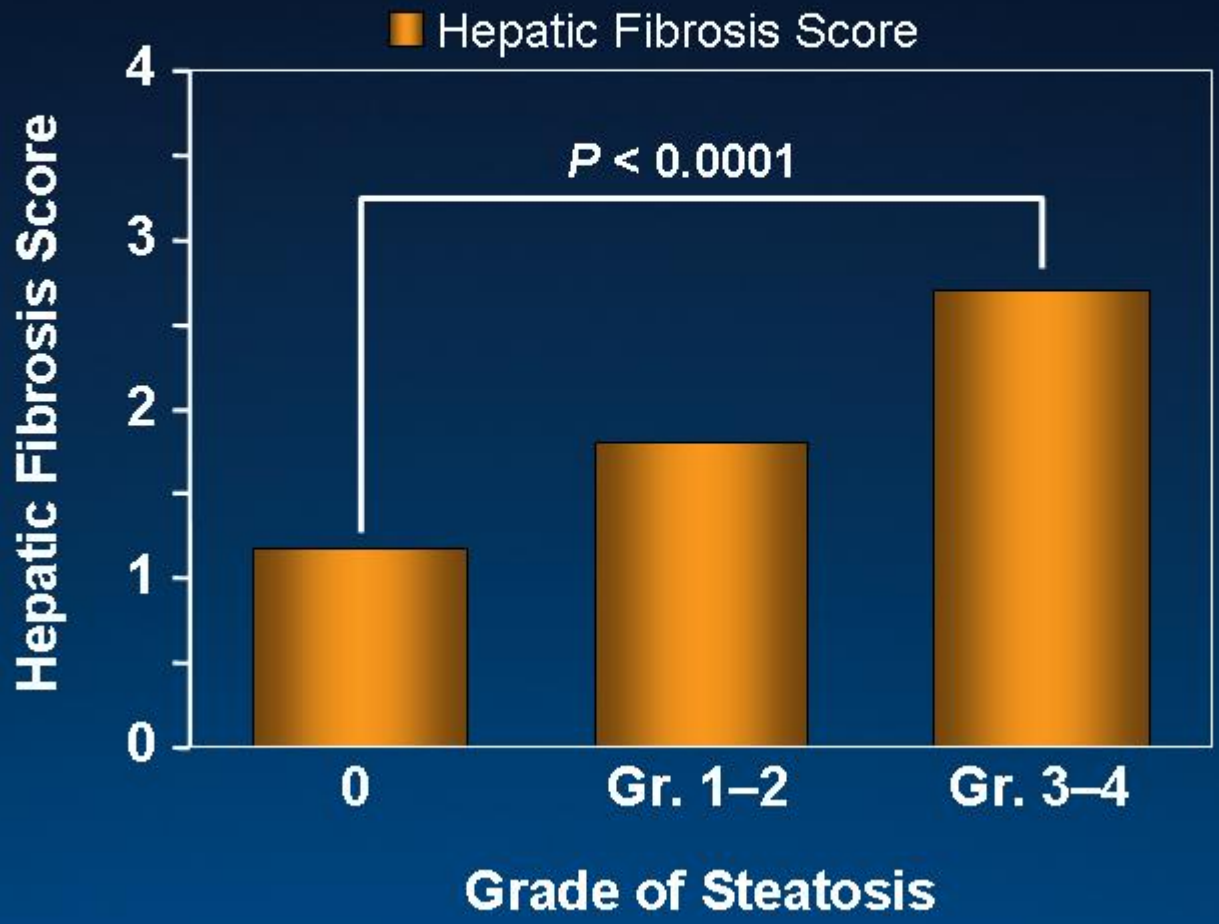
Host
- Obesity
- Diabetes Mellitus
- Insulin Resistance
- Alcohol Intake
- Medications

HCV + Steatosis

(50% of all HCV+ patients)

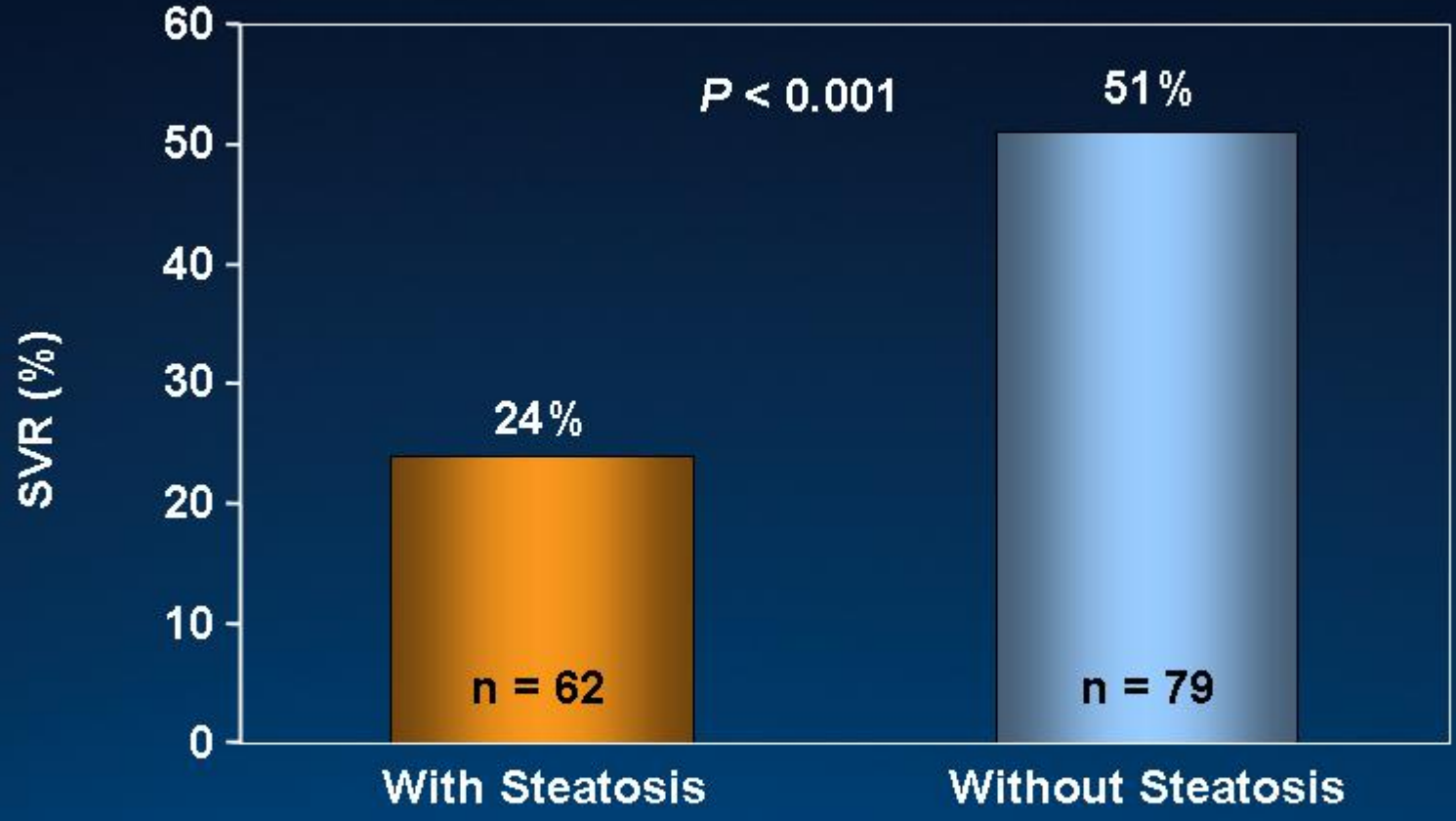
Patel K, et al. *Clin Liver Dis*. 2005 Aug 9(3):399-410.

Association of Hepatic Steatosis and Fibrosis



Adinolfi LE, et al. *Hepatology*. 2001;33(1):1358-1364.

Impact of Steatosis on SVR

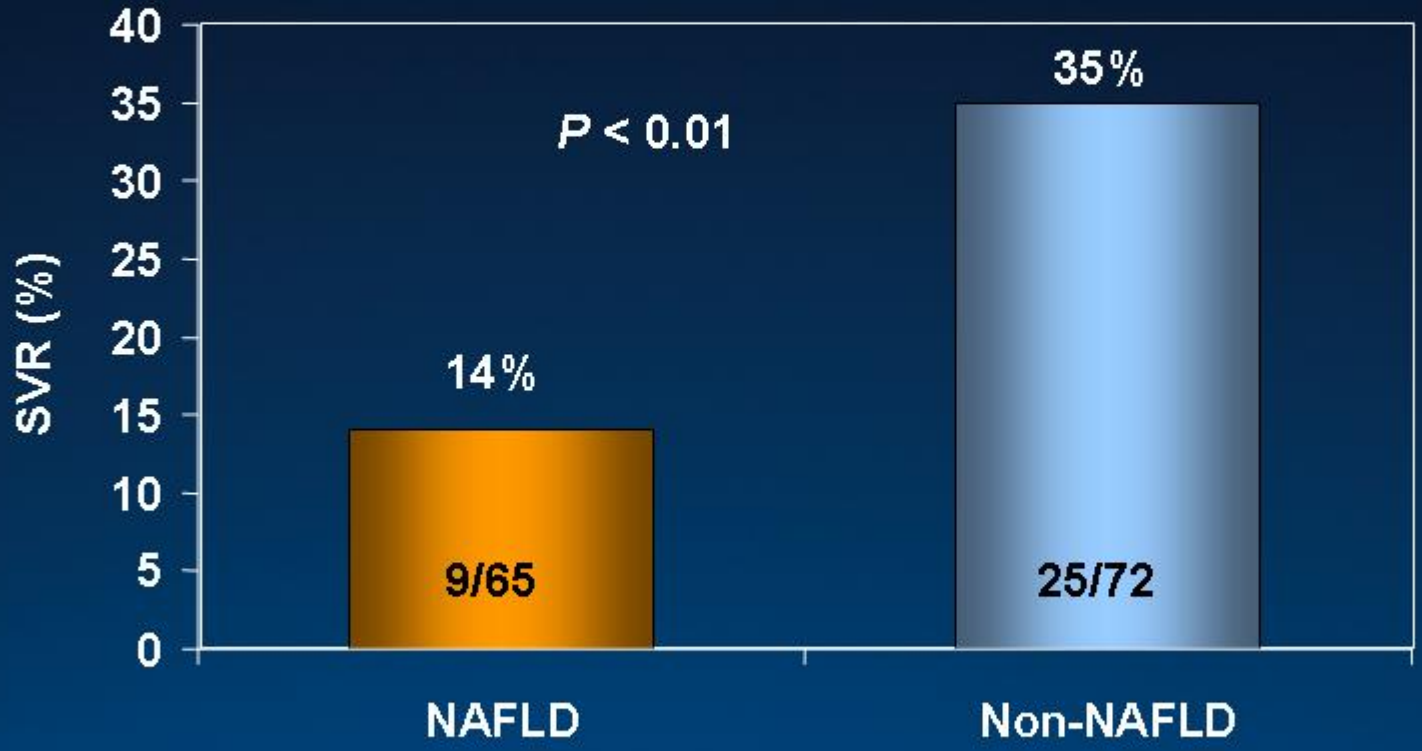


Genotypes 1, 4, 5, and 6, High Viral Load

HVL > 3.5 million copies/mL

Poynard T, et al. *Hepatology*. 2003;38:75-85.

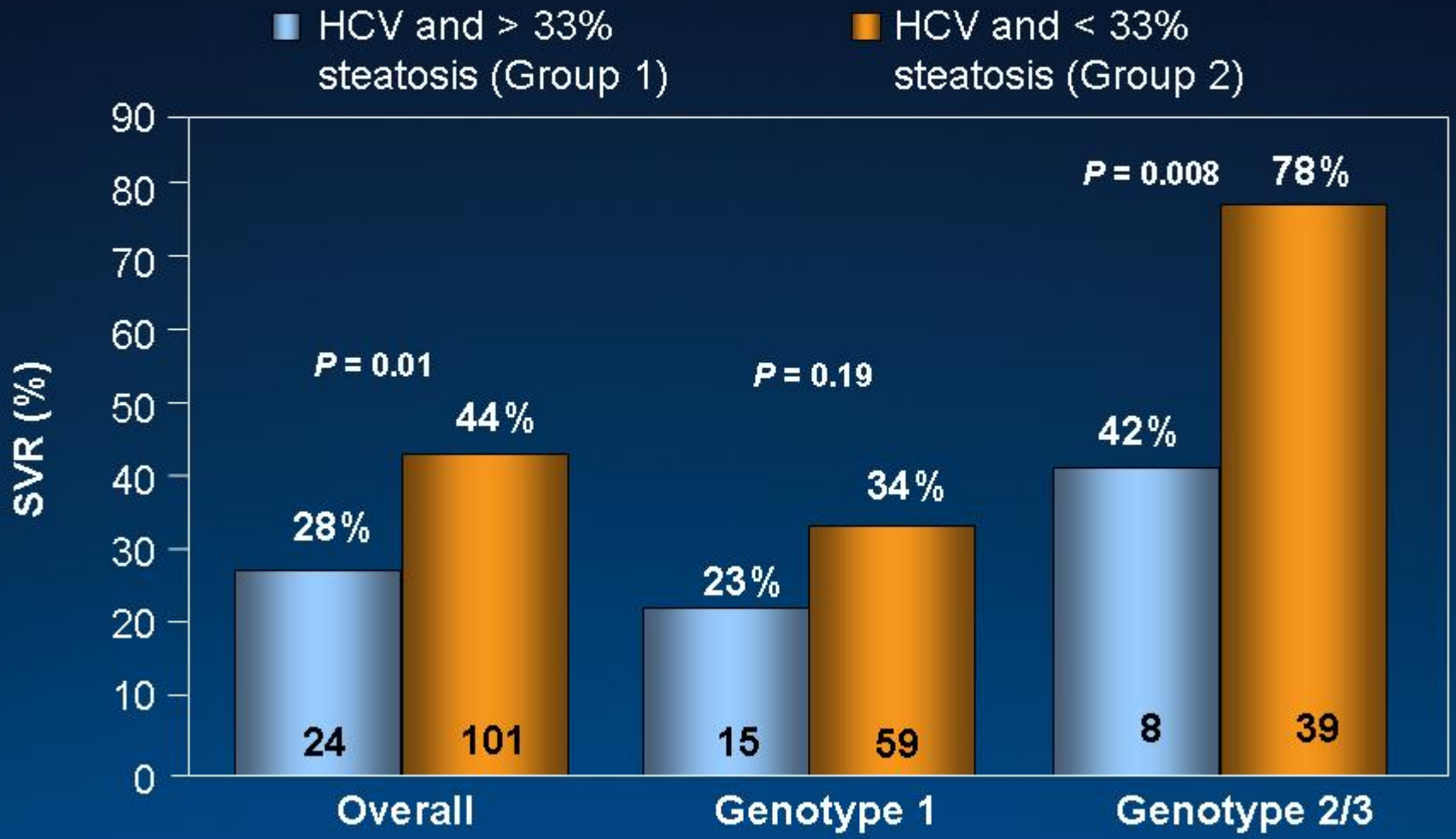
Impact of Coexisting NAFLD on Virologic Response to Anti-HCV Therapy



Sanyal A, et al. *Am J Gastroenterol.* 2003;98(9):2064-2071.

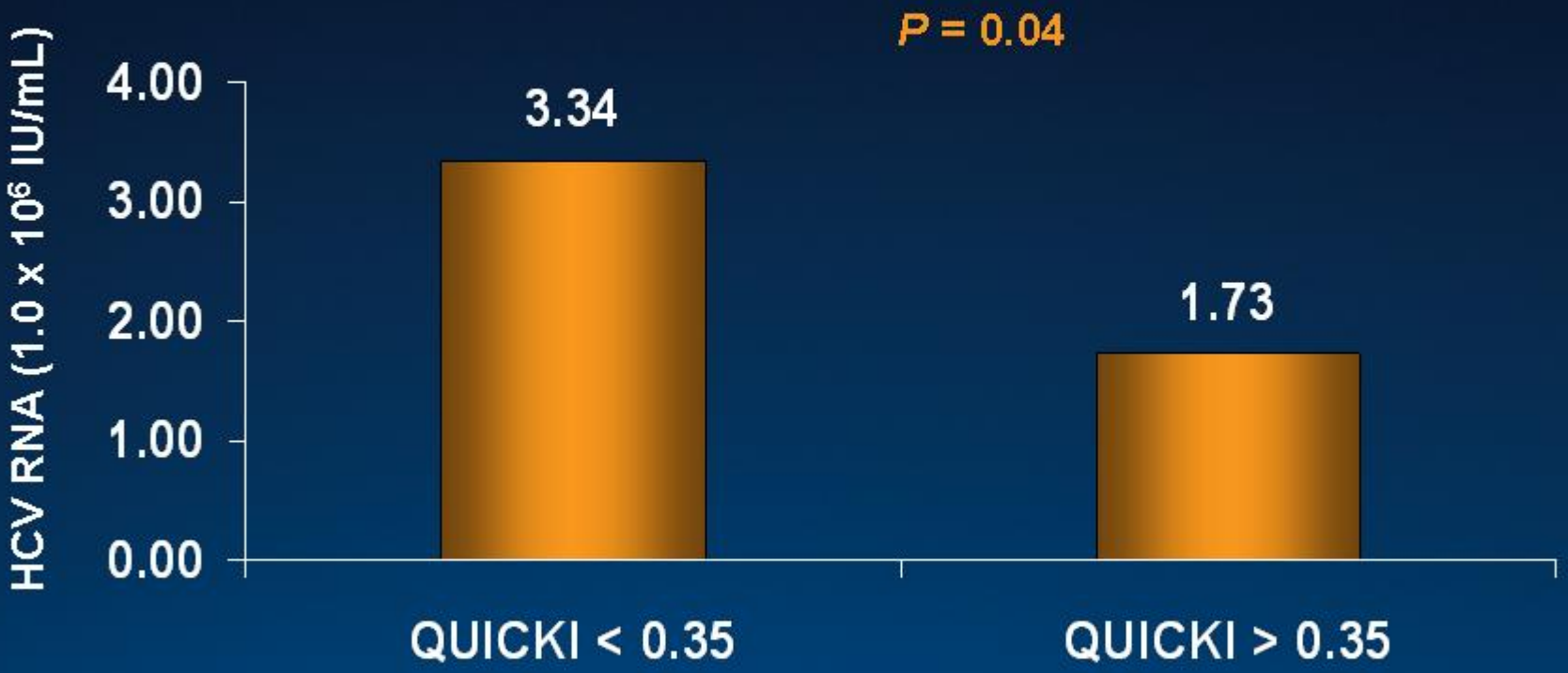
EFFECT OF INSULIN RESISTANCE

Decreased Response to Antiviral Therapy in HCV Patients With Coexistent Steatosis



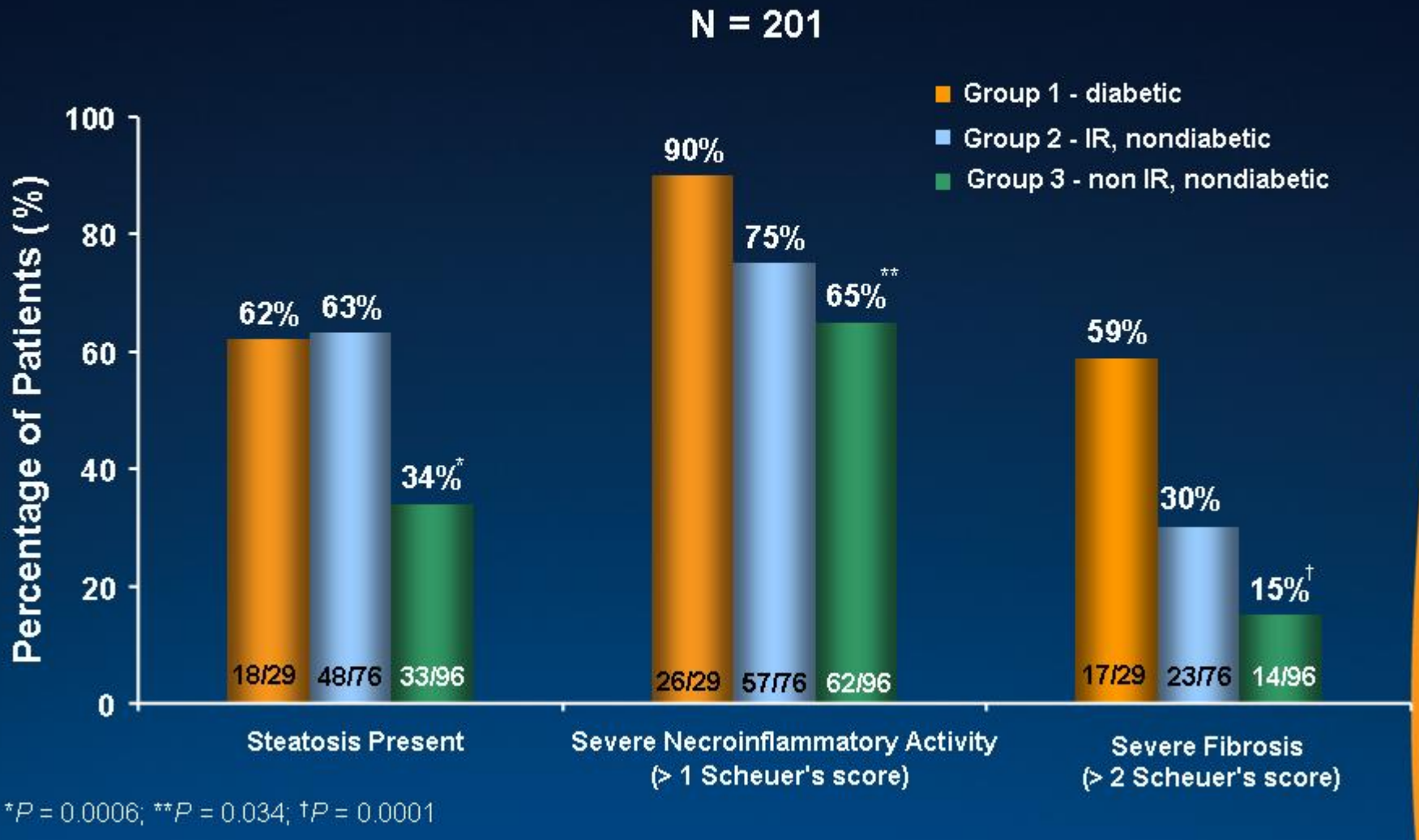
Harrison SA. *Gastroenterol Hepatol.* 2005;3:604-609.

Impact of Insulin Resistance on HCV Viral Load



Harrison SA. *Hepatology*. 2006;43(5):1168.

Insulin Resistance and Severity of Fibrosis: *Study Results*

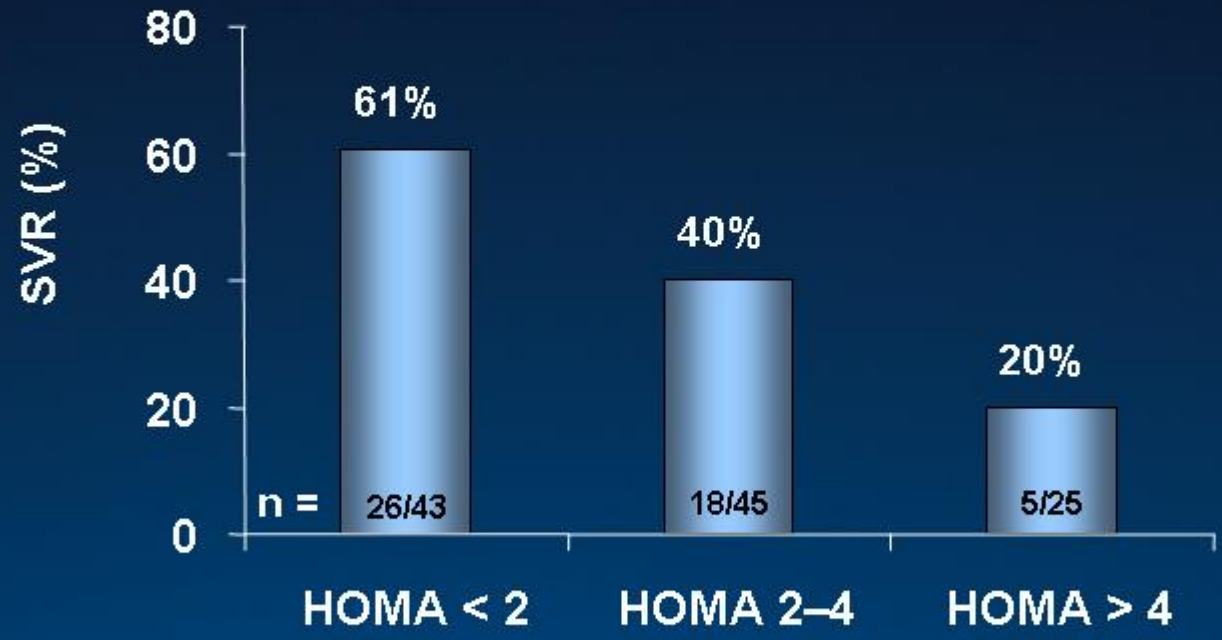


*P = 0.0006; **P = 0.034; †P = 0.0001

Petta S, et al. Presented at AASLD 2007. Nov 2-6, 2007; Boston, MA. Abstract #1455.

Impact of Insulin Resistance on Virologic Response in Genotype 1

159 consecutive patients treated with either Pegasys/Ribavirin or PEG-Intron/Ribavirin



(HOMA < 2, 2–4, and > 4: odds ratio, 2.43; 95% CI, 1.41–4.20; *P* = 0.004)

HOMA = homeostasis model assessment

$$\text{HOMA-IR} = \frac{\text{fasting insulin (mIU/L)} \times \text{fasting glucose (mmol/L)}}{22.5}$$

Romero-Gomez M, et al. *Gastroenterology*. 2005;128:636-641.

Once the Patient has RVR, cEVR, or pEVR:

Does Ethnicity, Fibrosis, or pre-Treatment Viral Load effect SVR ?

Time to HCV RNA Undetectability as Predictor for SVR in Genotype 1

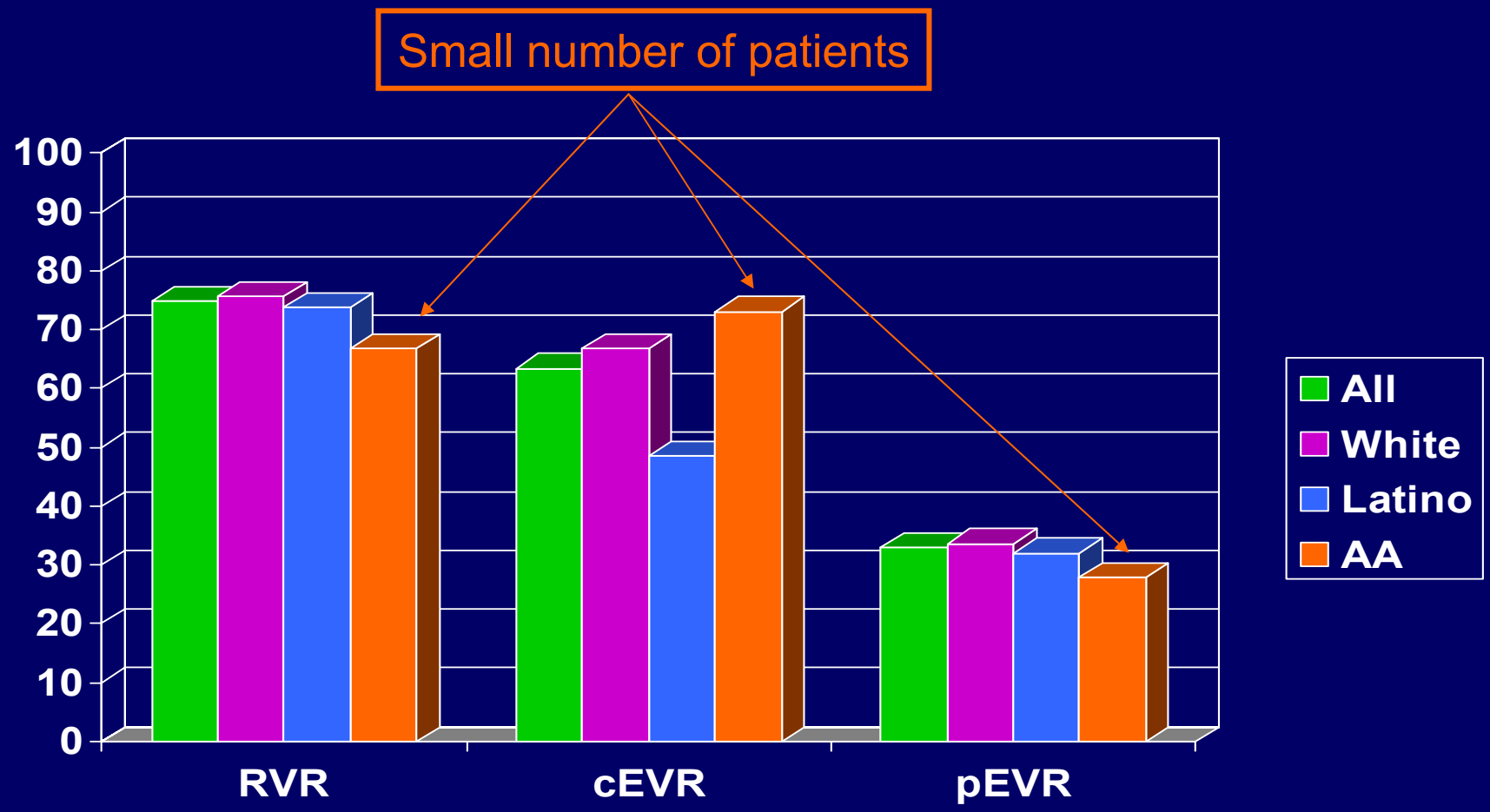
- Methods: Data from 1,243 genotype 1 patients in the following four clinical trials: Fried, Hadziyannis, Virahep-C, and LATINO, treated with Pegasys 180 mcg plus RBV 1,000/1,200 mg
- Retrospective analysis includes African American and Latino patients

	SVR (%) HCV RNA Undetectability		
	Week 4 (n = 195)	Week 12 (n = 505)	Week 24 (n = 194)
All (N = 1,243)	146 (74.9%)	320 (63.4%)	64 (33%)
Race/Ethnicity			
White	106 (75.7%)	239 (66.8%)	40 (33.6%)
Latino	28 (73.7%)	51 (48.6%)	17 (32.1%)
African American	4 (66.7%)	19 (73.1%)	5 (27.8%)
Cirrhosis Classification			
Non-Cirrhotic	131 (74.9%)	286 (64.6%)	52 (32.7%)
Cirrhotic	15 (75%)	34 (54.8%)	12 (34.3%)
Baseline HCV RNA, IU/mL			
≤ 400,000	76 (78.4%)	63 (72.4%)	7 (41.2%)
> 400,000	70 (71.4%)	257 (61.5%)	57 (32.2%)

Shiffman ML, et al. Presented at EASL 2008. April 23-27, 2008; Milan, Italy. Poster #835.

Type of Response, Ethnicity and SVR in G-1

Shiffman ML. ESLD 2008; Poster 835

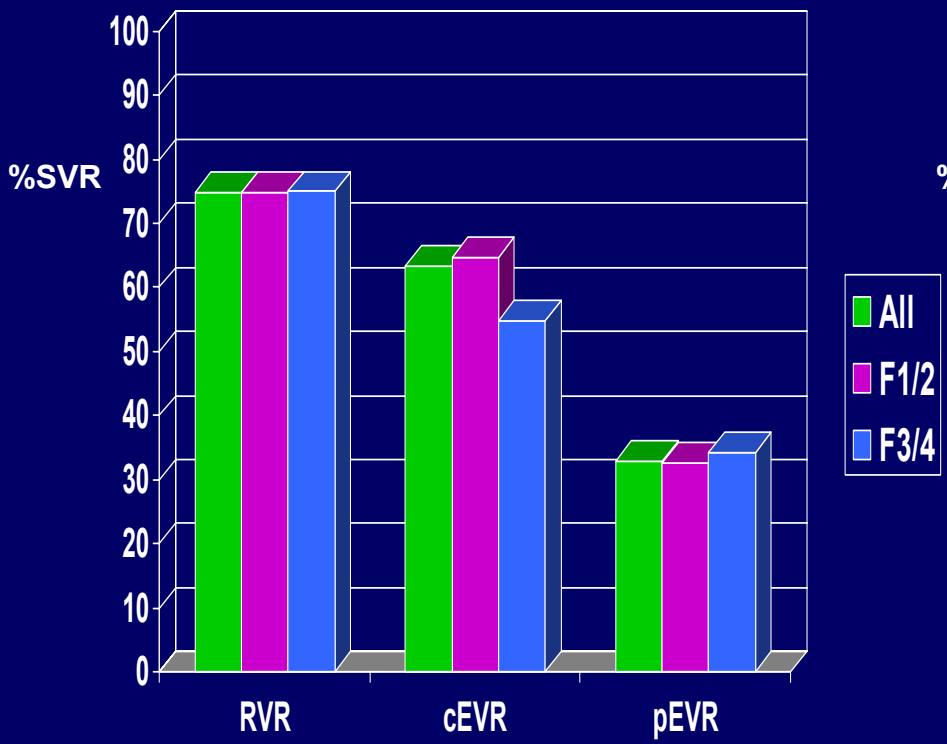


1243 pts G-1 infection (Fried, Hadziyannis, Virahep-C, LATINO studies)

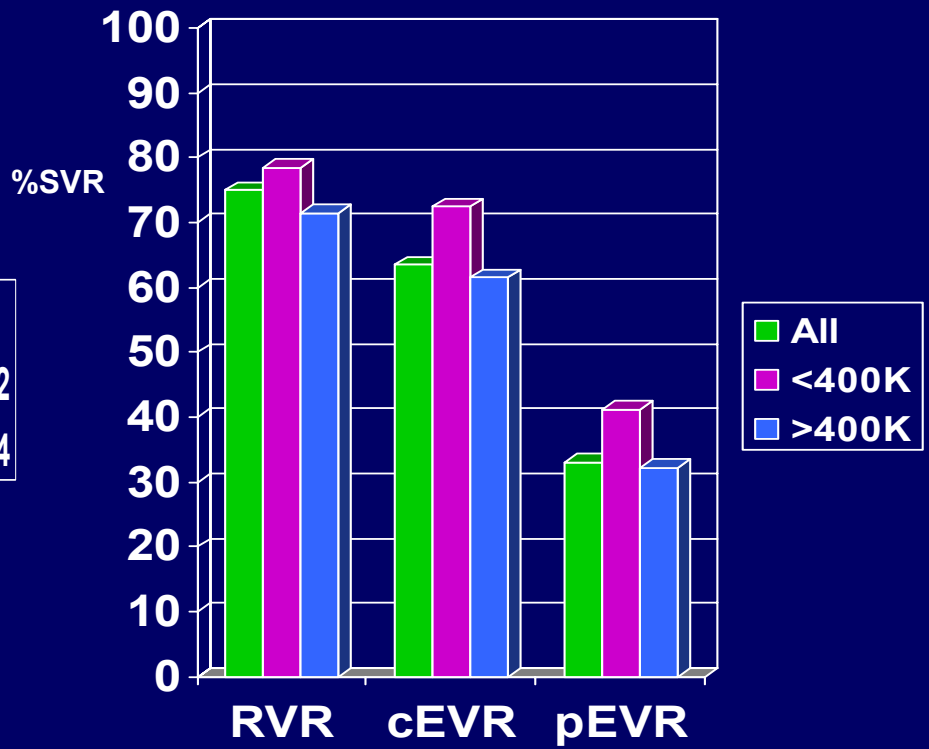
Effect of Fibrosis & Viral Load in G-1 SVR

Shiffman ML. ESLD 2008; Poster 835

SVR by Response-Type & Fibrosis



SVR by Response-Type & Viral Load



Conclusion

Most of the effects of:

- Viral Genotype,
- Ethnicity,
- Severity of Fibrosis, and
- Baseline Viral Load

are explained by how they affect the time to reach a negative HCV-RNA (% of RVR, cEVR, & pEVR).

Effect of Treatment Prolongation

Peginterferon-alfa2a plus ribavirin 800 mg for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment.

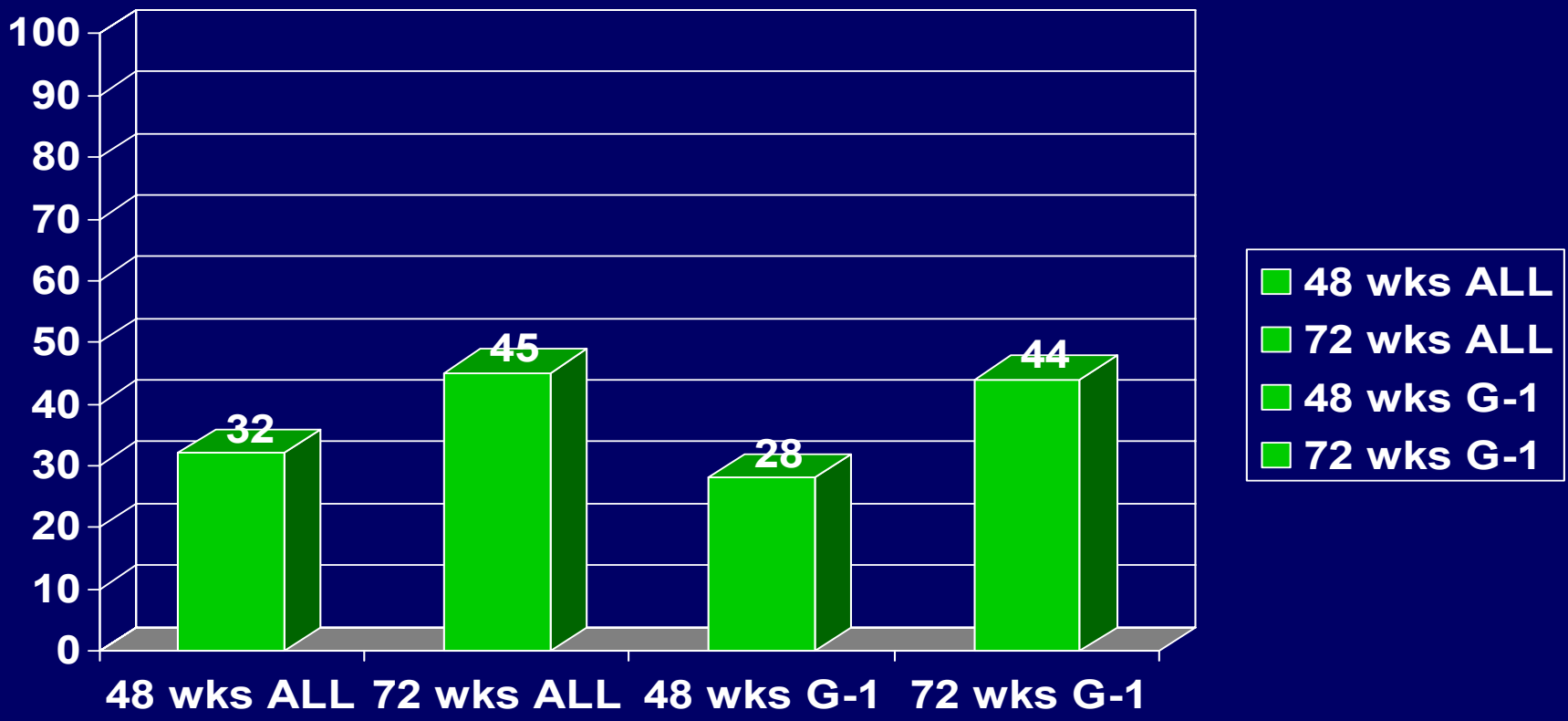
Sanchez-Tapias et al. Gastroenterology. 2006 Aug;131(2):451-60

- **Population**: 510 treatment naïve patients
- **Treatment**: 180 mcg Pegasys + RBV 800 mg
- Groups randomized **at week 4**:
  - A) HCV-RNA > 50 IU/mL treated 48 wks (165),
  - B) HCV-RNA > 50 IU/mL treated 72 wks (161),
  - C) HCV-RNA < 50 IU/mL treated 24 wks (148),
  - D) HCV-RNA < 50 IU/mL treated 48 wks (36)

RVR

Peginterferon-alfa2a plus ribavirin 800 mg for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment.

Sanchez-Tapias et al. Gastroenterology. 2006 Aug;131(2):451-60



Treatment of Chronic HCV in Chronic Kidney Disease, and ESRD on Dialysis

Chronic Kidney Disease
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

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

HCV in ESRD & post-KTx Treatment Considerations

- 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.

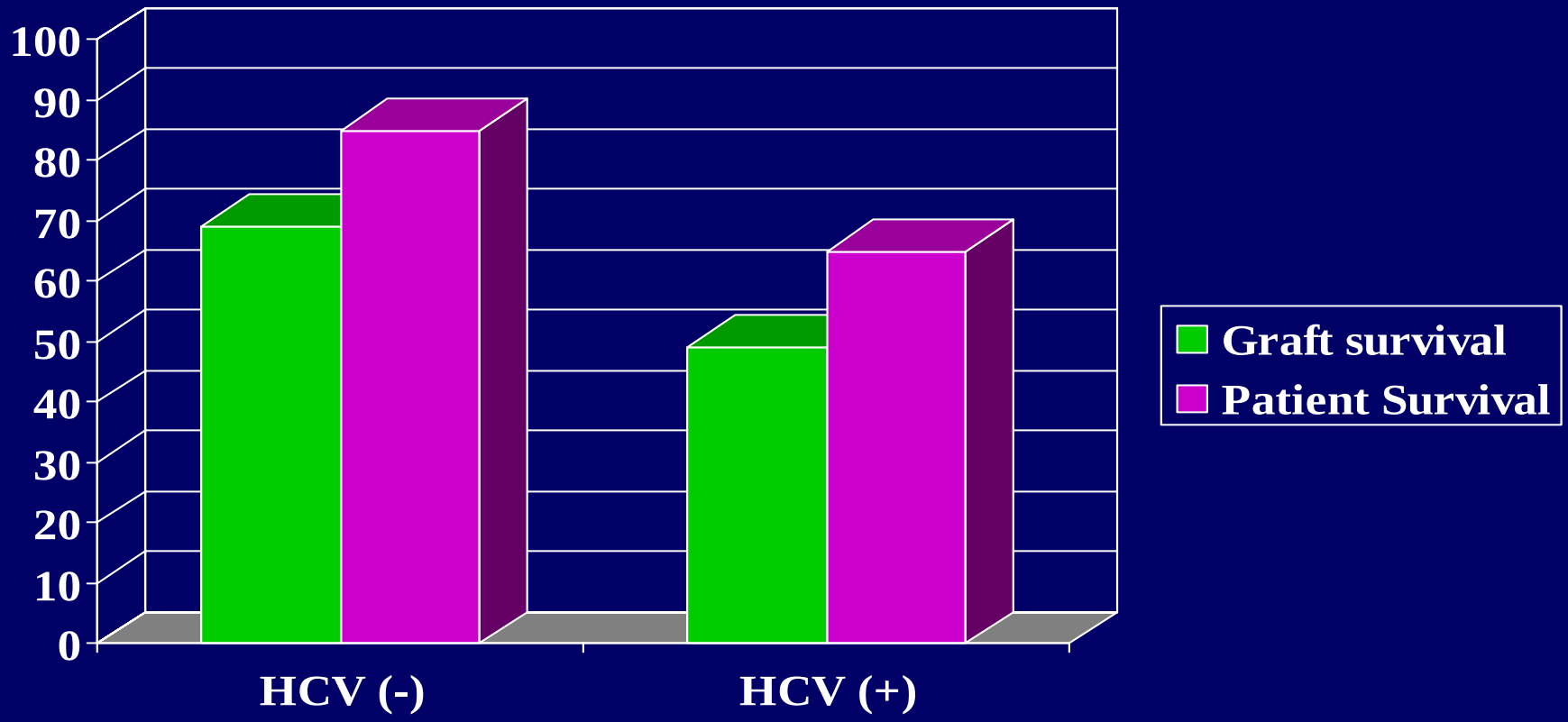
Chronic HCV in ESRD
Natural History

- 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 Transplant

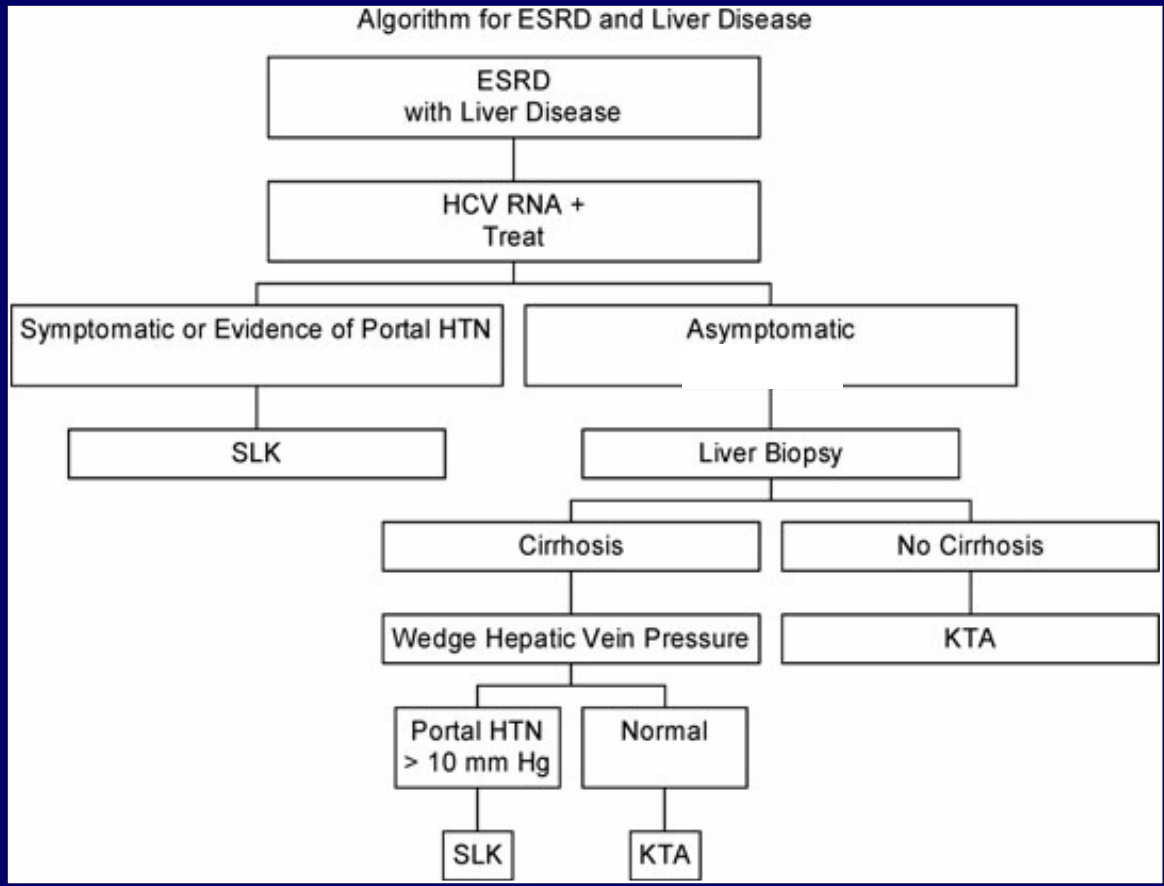
- Survival: same 5-year but lower @ 10-years
- Survival better than if continue on HD
- Liver damage accelerated by Azathioprine and anti-lymphocyte globulin
- Higher risk of membranous and membranoproliferative glomerulonephritis.
- Decreased renal graft function

HCV in Renal Tx
Natural History (10 years)



Algorithm for ESRD & Liver Disease

Am J. Transplant 2008;8:2243-2251



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%, SVR 75% C: EOT(-) 8%, SVR 8%
Sporea (World J Gastroenterol 2006;12(26):4191-4194)	Rp(10): Peg 180 x 48w	SVR: ITT 30%, PP 50%
Chan (Nephrology 2007;12:11-17)	Rp(6): Peg 135 x 48 w	EOT(-) 83%, SVR 33%
Teta (Nephrol Dial Transplant 2005;20:991-993)	Rp(3): Peg 90-180 x 24-48 w	SVR 66%
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	SVR 41%

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: SVR 97% (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	OET(-): 79%, SVR 63%
Carriero (AASLD Abstr. Oct 2006)	Rp(15): Peg 135-180/RBV 200 qd x 4-76 w + EPO	SVR 31%
Bruchfeld (J Viral Hepatitis 2006;13:316-321)	Rp(2): Peg 135/RBV 1400-2000 mg per w + EPO	SVR 100%

Indications for Simultaneous Liver-Kidney Transplant (SLK)

Am J. Transplant 2008;8:2243-2251

- Automatic approval
  - CKD stage IV or V + cirrhosis + symptomatic portal HTN or HVWPG >/= 10 mm Hg
  - Liver failure + CKD with eGFR </= 30 mL/min for > 90 days
  - Liver failure + AKI or HRS with creat > 2 mg/dL + dialysis >/= 8 weeks
  - Liver failure + CKD + Kidney Bx with > 30% glomerulosclerosis or > 30% interstitial fibrosis.
- MELD exception by Regional Review Board
  - All other cases; comorbidities like DM, HTN, other pre-existing kidney disease, age > 65 will increase potential benefit for SLK.

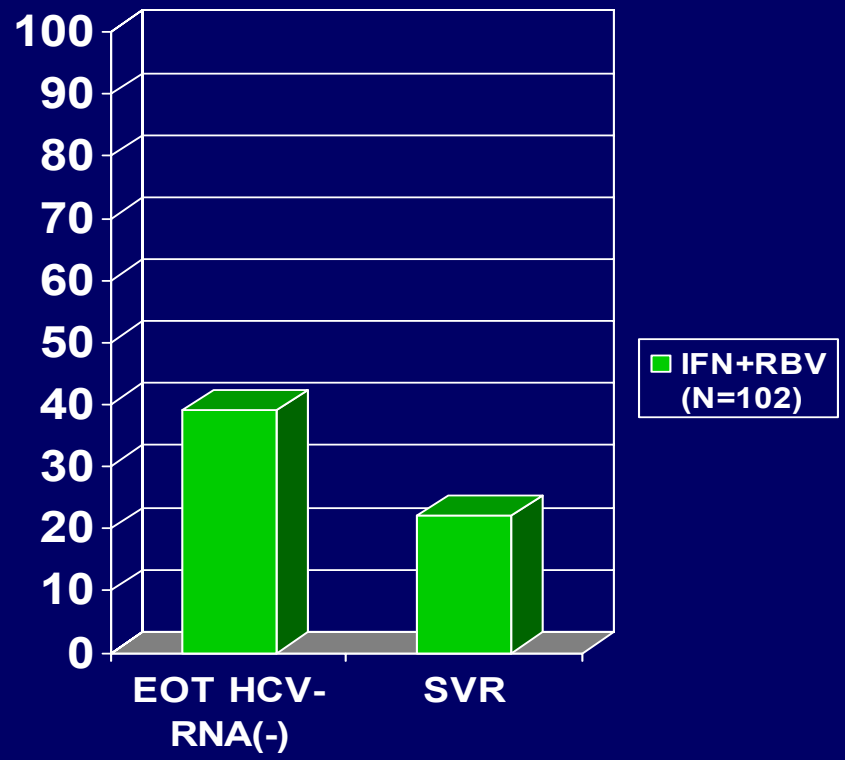
Treatment
Pre-Liver Transplantation

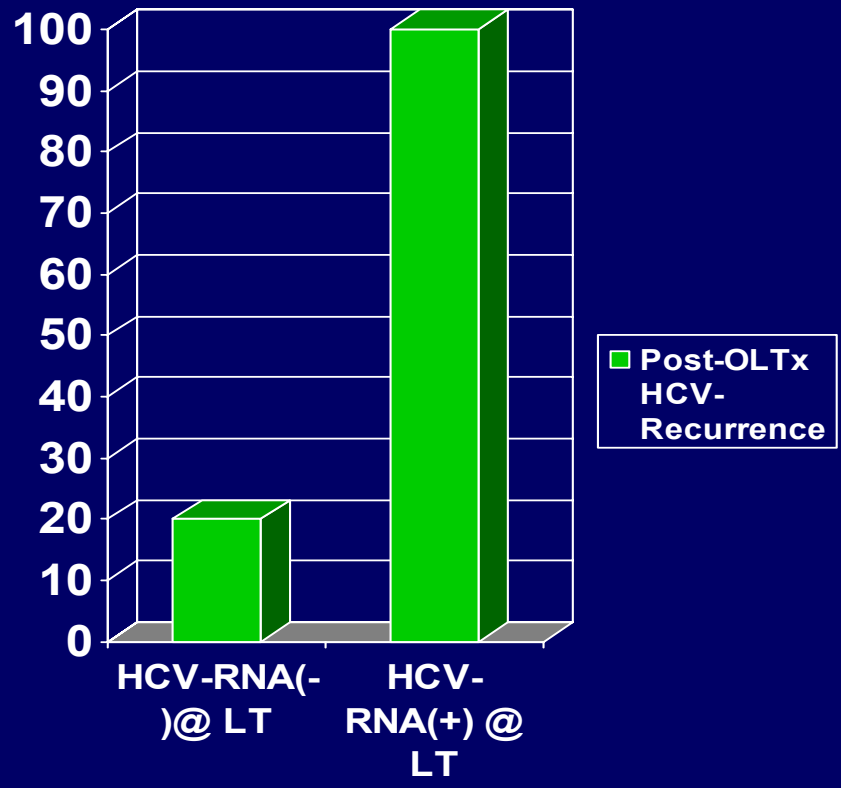
Pre-LTx Treatment Candidates

- **Best Candidates:**
  - **Child-Turcotte score = / < 7**
  - **MELD = / < 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.
- **Patients with Child-Turcotte = / > 11, or MELD = / > 25 are not treatment candidates.**

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

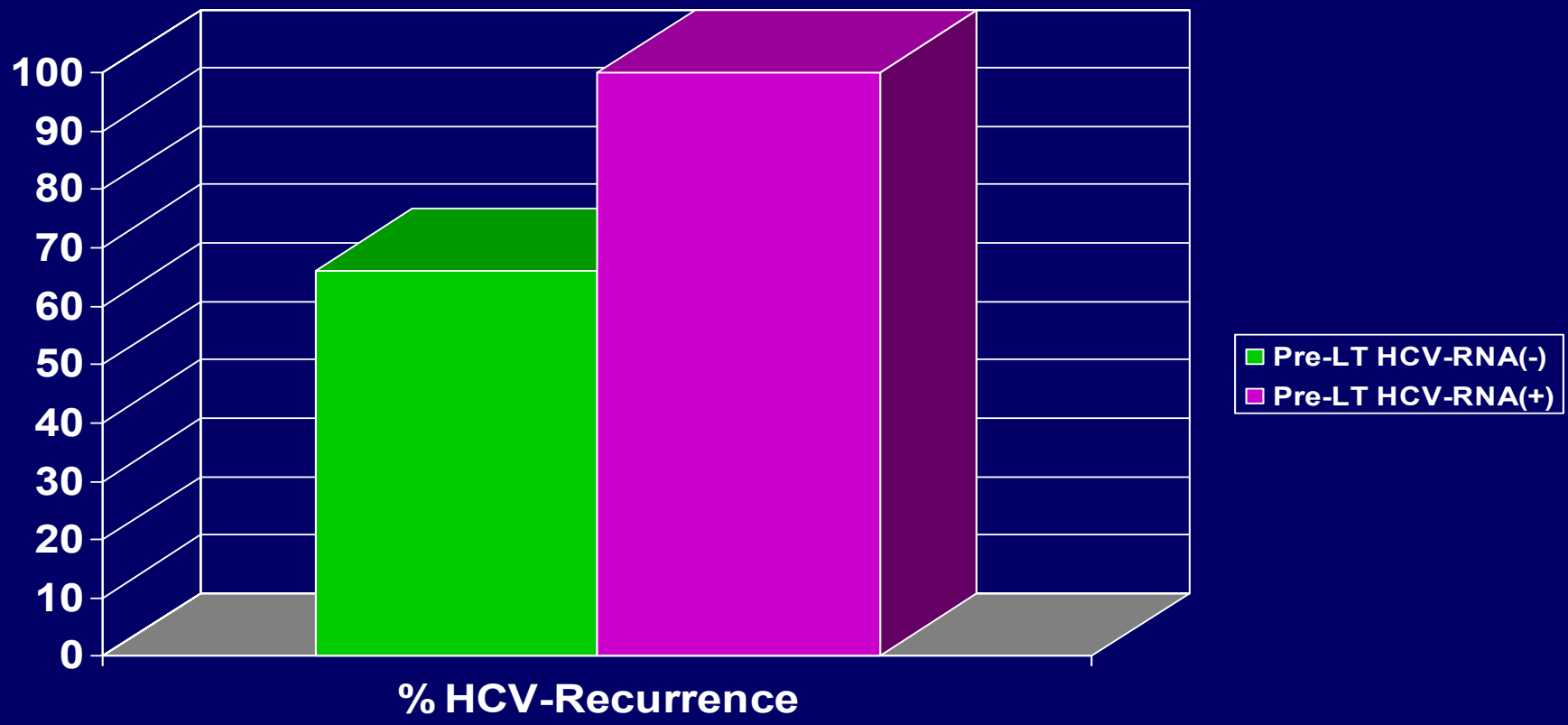
Everson et al. Rev. Gastrointest Disord 2004;4 Suppl 1:S31-38





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

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



Treatment
Post-Transplantation

Treatment of Recurrent HCV Preemptive

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

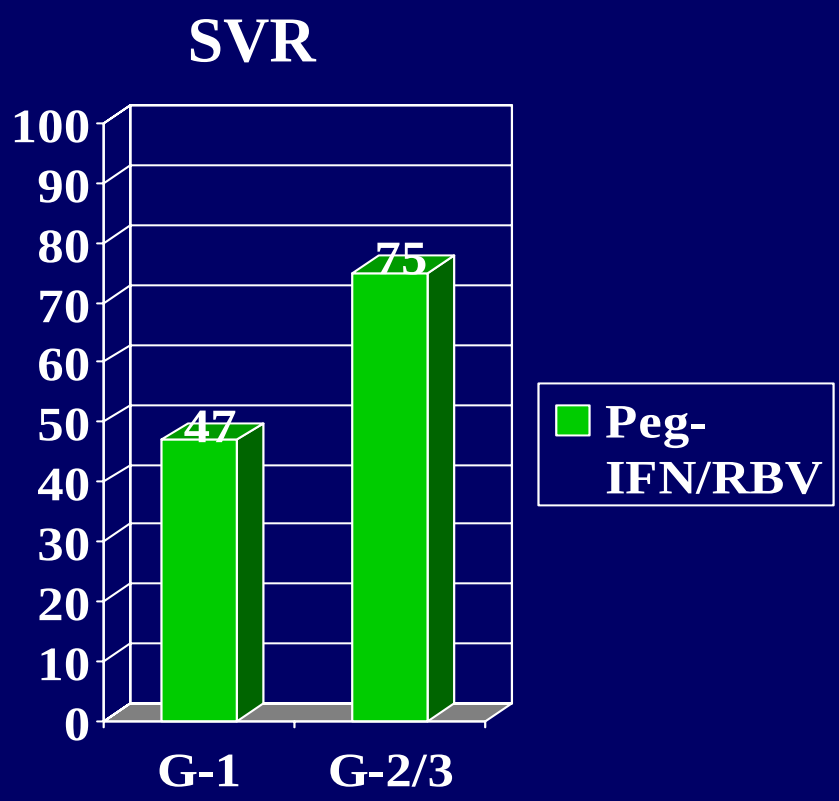
Treatment of Recurrent HCV After METAVIR Stage 2 (occasional bridging)

- 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.

Peg-IFN + RBV for HCV Recurrence in OLTx Recipients

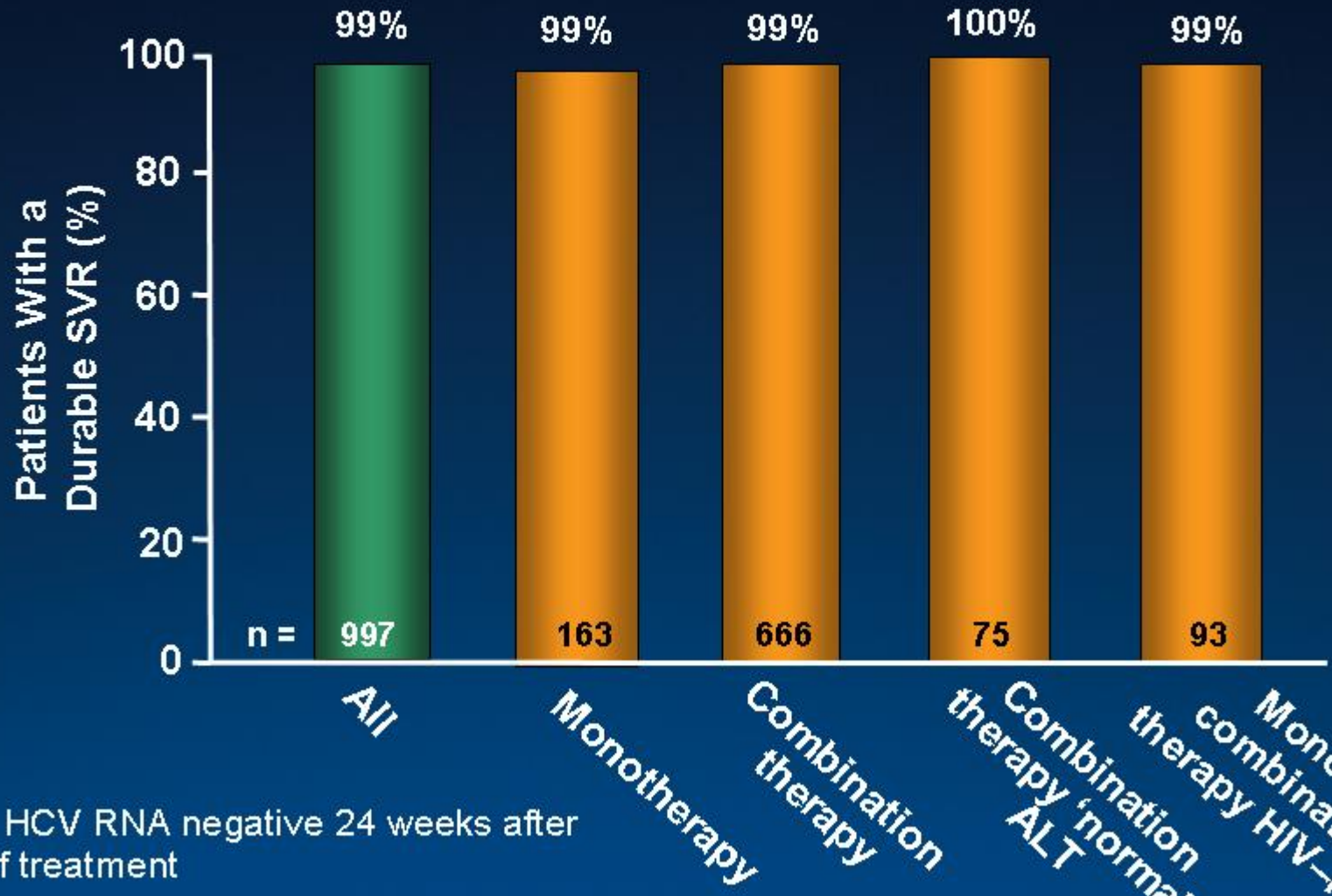
Berenguer M et al. Liver Transpl 12:1067-1076, 2006

- 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



Is SVR “Cure” ?

Patients With a Durable SVR at Mean 4.1 (0.4 to 7) Years Follow-up



SVR: HCV RNA negative 24 weeks after end of treatment

Swain M, et al. Presented at EASL 2007. April 11-15, 2007; Barcelona, Spain. Abstract #1.

Evolving New Concepts
Peg-Interferon + RBV Therapy

- Genotype 1 (and 4, 5, & 6)
  - Higher dose of RBV (15.3 mg/Kg) improves SVR by decreasing relapses.
  - If HCV-RNA has fallen > 2 log but is still (+) by week 12, SVR can be improved by prolonging therapy, from standard 48 weeks to 72 weeks.
- Genotype 2 & 3
  - RBV dose of 11.2 mg/Kg or higher improves SVR.
  - If HCV-RNA is still (+) at week 4, SVR will improve by prolonging therapy, from standard 24 weeks to 48 weeks.

Question Being Investigated

- Can we improve SVR by adding to [Peg-Ifn/RBV] either a protease inhibitor, RNA-polymerase inhibitor, NS5A inhibitor, or cyclophilin inhibitor, and making most patients HCV-RNA negative by week 4 or earlier ?
- Can we improve SVR by decreasing insulin resistance and/or hepatic steatosis ?

Emerging Therapy in HCV

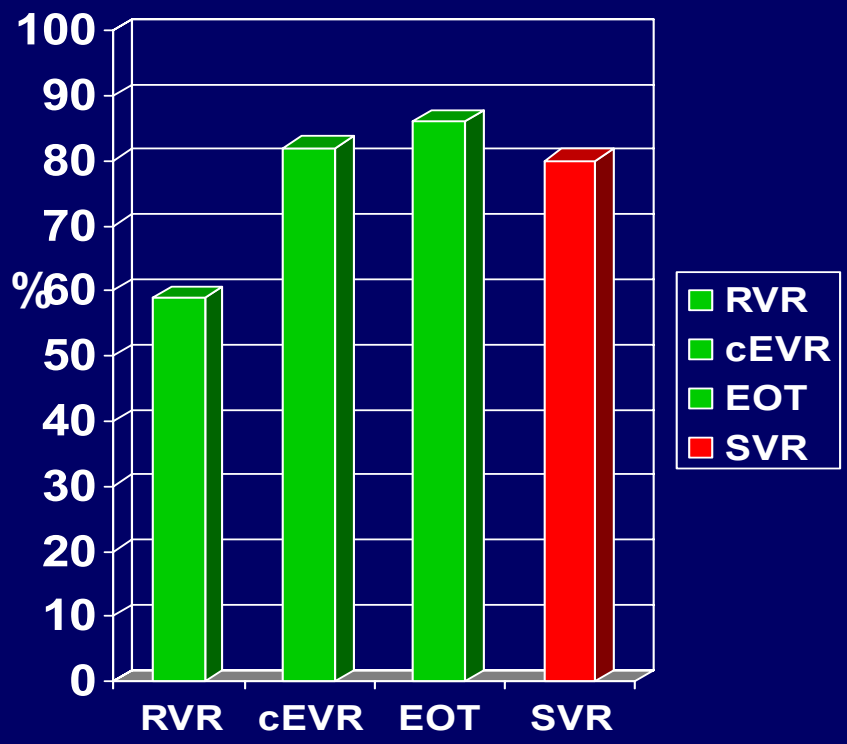
- NS5B RNA-dependent RNA-polymerase inhibitor: Non-nucleoside
  - BILB-1941
  - A-837093
  - GS-9190
- NS5B RNA-dependent RNA-polymerase inhibitor: Nucleoside analogue
  - R1626 (phase-2)
  - MK-608
  - R1656
  - R7128
- NS3/4 serine protease inhibitors
  - Telaprevir (phase-2)
  - Boceprevir (phase-2)
  - GS9132/ACH-806
  - ITMN-191
- NS5A inhibitors
  - A-831
  - A-689
- Cyclophilin inhibitors
  - DEBIO-25
  - NIM-811

4-week lead-in Nitazoxanide + (Peg-Ifn alfa-2a + Nitazoxanide) x 36 w in Chronic HCV **(AASLD 2008, Abstr 1848)**

- NTZ is a small molecule Thiazolide which inhibits HCV in Replicon system.
- NTZ enhances intracellular activity of IFN by inducing PKR and eIF2-alpha
- NTZ monotherapy for 24-weeks gives SVR of 17.4% in g-4 HCV.
- 12 w lead-in of NTZ + either (NTZ+Peg-Ifn+RBV) or (NTZ+Peg-Ifn) x 36 w were superior to 48 w Peg-Ifn+RBV in g-4 HCV (SVR = 79%, vs 61%, vs 50%)

- **STUDY:** open label, prospective.
- **Population:** 44 IFN-Naïve patients (Egypt)- (g-1 = 3, g-2 =1, g-4 = 40 patients)
- **Intervention:** NTZ 500 mg BID with food x 4 weeks, followed by Peg-Ifn 180 mcg/week + NTZ 500 BID x 36 weeks
- **Monitoring:** monthly CBC, CMP & HCV-RNA (LLD 12 IU/mL)
- **Analysis:** SVR by ITT

4-week lead-in Nitazoxanide + (Peg-Ifn alfa-2a + Nitazoxanide) x 36 w in Genotype-4 HCV **(Abstr 1848)**



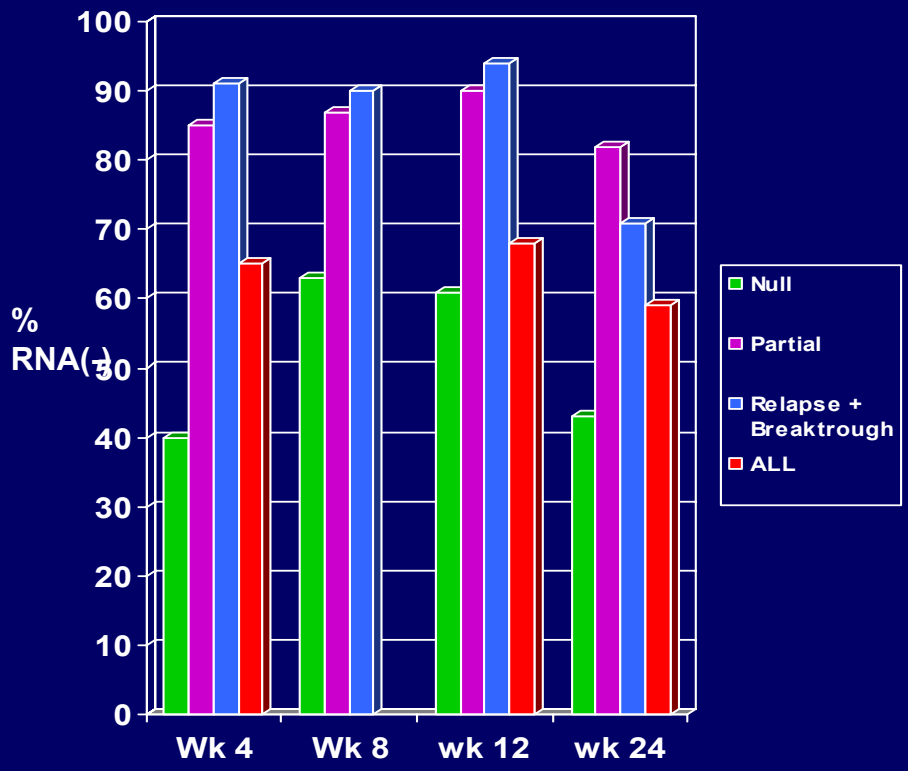
- **AE:** Those of Peg-Ifn. No ALT elevations, drug reductions nor discontinuations.
- Two of 3 patients with g-1 had RVR; all 3 had SVR.
- Patient with g-2 had cEVR & SVR.
- **CONCLUSIONS:**
  - **4-week lead-in NTZ followed by 36 wks of Peg-IFN, is adequate and very promising (80% SVR)**
  - **Studies are ongoing in naïve and relapsed patients, with NTZ + [Peg-Ifn & Peg-Ifn + RBV]**

Telaprevir (TVR) + Peg-Ifn/RBV in HCV G-1 Non-Responders & Relapsers: 24 week Interim Analysis (AASLD 2008, Abstr 1852)

- **Population:** Patients with g-1 HCV, who were "Peg-Ifn/RBV control" in previous Telaprevir studies, and have received at least 4 w of TVR + Peg-IFN + RBV therapy (104 of 107 pts)
- **Subgroups:**
  - Null-response (49),
  - Partial Response (33),
  - Breakthrough (1),
  - Relapse (24)
- **Trial:** Open Label Treatment
- **Analysis:** ITT

- **INTERVENTION:**
  - TVR 750 mg q 8h x 12wks together with:
  - (Peg-Ifn 180 mcg/w + RBV 1000-1200 mg/d) x 24 or 48 wks
- **STOP RULE:**
  - Wk4 = HCV-RNA > 100 IU/mL,
  - Wk 8 = > 25 IU/mL,
  - Anytime breakthrough = increase > 1 log, or titer > 100 after being (-)

Telaprevir (TVR) + Peg-Ifn/RBV in HCV G-1 Non-Responders & Relapsers: 24 week Interim Analysis (Abstr 1852)



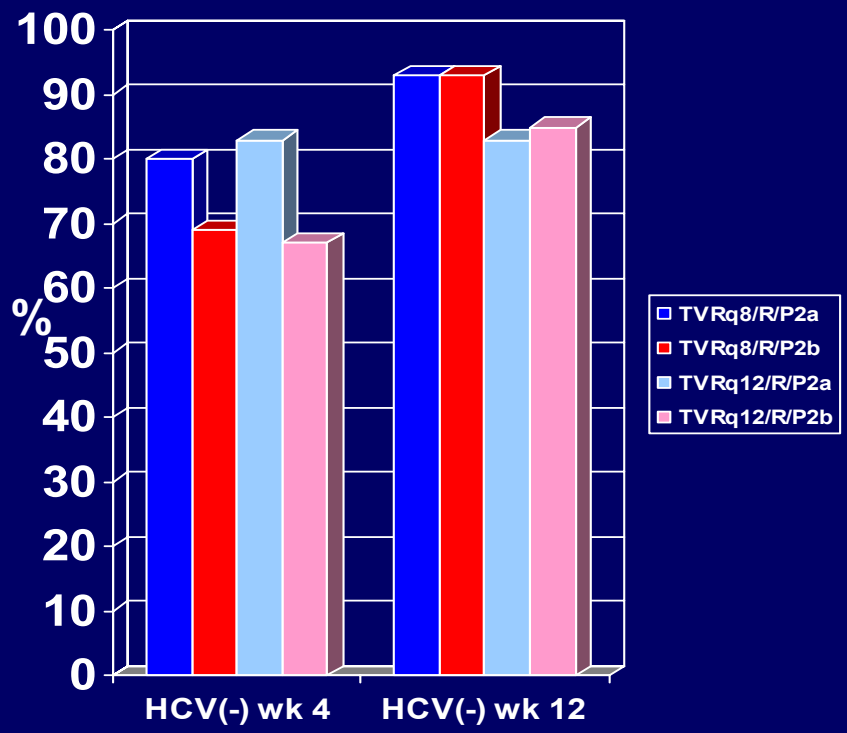
- **AEs:** Rash (4 d/c), Anemia, pleuritis, Itching, fatigue, depression
- **Breakthrough:**
  - Relapsed = 0/24,
  - Breakthrough = 1/1,
  - Partial = 2/33 (6%),
  - Null = 10/49 (20%)
- **CONCLUSION:** Results are promising during initial 24 weeks of therapy of Non-responders and Relapsers.

Telaprevir (TVR) q 8 or q 12, with Peg-Ifn Alfa 2a or 2b plus RBV, in Naïve G-1 HCV: 12 wk Interim Results (AASLD 2008, Abstr 1854)

- **Study:** Open label, multicenter, randomized, Phase 2
- **Patients:** 161 adult, treatment naïve, genotype-1, non-cirrhotic.
- **Intervention:**
  - TVR 750 mg (q 12, or q 8 h) x 12 wks +
  - RBV 1-1.2 g +
  - (Peg-Ifn a2a, or Peg-Ifn a2b)
- **Treatment duration:**
  - 24 wks if HCV-RNA (-) from wk 4 to 20;
  - 48 weeks all others
- **Analysis:** ITT

- **Demographics:**
  - 50% male,
  - mean age 44.3,
  - 91% caucasian,
  - median BMI 24 (18-46),
  - HCV-RNA 6.41 log
- **AEs:**
  - itching 56%, nausea 56%,
  - flu-like 51%, anemia 49%,
  - headache 41%, rash 41%,
  - anorexia 39%, fatigue 39%,
  - asthenia 36%, diarrhea 33%
  - vomiting 31%, fever 28%.

Telaprevir q 8 or q 12, with Peg-Ifn Alfa 2a or 2b plus RBV, in Naïve G-1 HCV: 12 wk Interim Results (Abstr 1854)

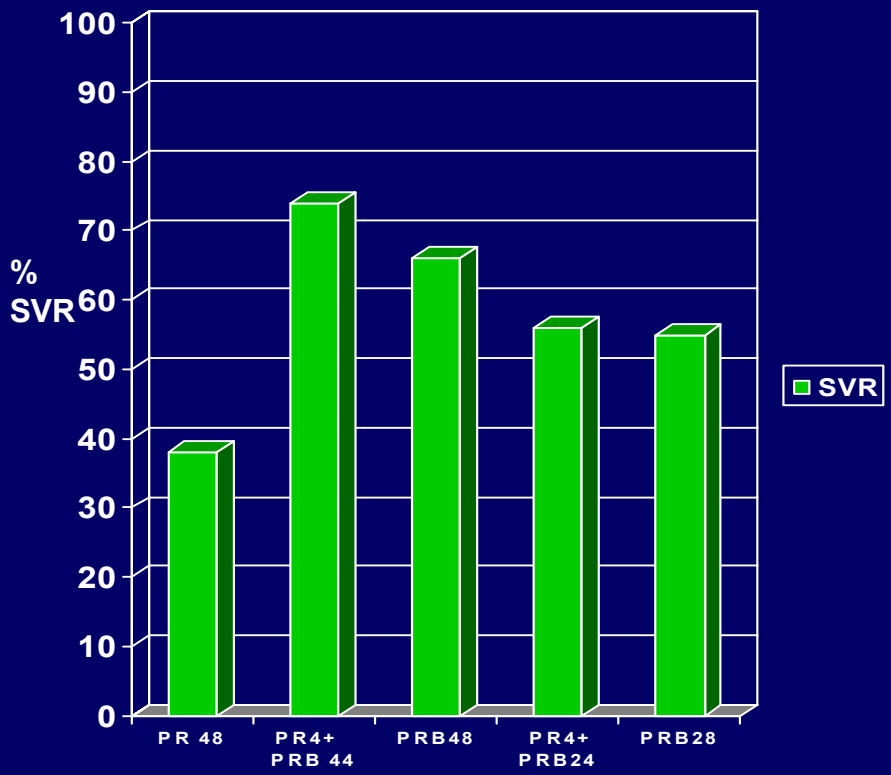


- **CONCLUSION:**
  - All 4 regimens were similar in efficacy.
  - High proportion achieved HCV(-) at weeks 4 & 12.
  - Viral breakthrough was low (5.6%)
  - Further studies with TVR q 12 are warranted.
  - Results from the first 12 weeks of therapy of Naïve patients are promising.

Boceprevir + Peg-IFNa2b/RBV in Treatment Naïve g-1 chronic HCV **(AASLD 2008, Abstr LB16)**

- Boc is an oral HCV-NS3 protease inhibitor.
- Phase 2 study of Boc (with or without Peg/RBV lead in) + Peg/RBV for 24 vs 48 weeks, in naïve g-1 HCV.
- **Population:**
  - 595 patients,
  - 77% US,
  - 16% black,
  - 7% cirrhotic,
  - 89% > 600,000 IU/mL
- **Doses:**
  - Boc 800 mg p.o. TID
  - Peg-IFNa2b 1.5 mcg/kg/week
  - RBV 13.3 mg/kg (800-1400 mg/d)
- **Treatment arms:**
  - Peg/RBV x 4 weeks + Peg/RBV/Boc x 24 weeks (103)
  - Peg/RBV x 4 weeks + Peg/RBV/Boc x 44 weeks (103)
  - Peg/RBV/Boc x 28 weeks (107)
  - Peg/RBV/Boc x 48 weeks (103)
  - Peg/RBV x 48 weeks (104)
- **Outcomes:**
  - HCV-RNA (-) (LLD = 15 IU/mL)
  - SVR

Boceprevir + Peg-IFNa2b/RBV in Treatment Naïve g-1 chronic HCV **(Abstr LB16)**



- **Resistance:** Lower viral breakthrough with P/R lead in (11 & 7% vs 4 & 5%).
- **AEs:** higher anemia, neutropenia, dysgeusia, myalgia & pruritus.
- **CONCLUSION:**
- **Boc was safe up to 48 weeks.**
- **Lead-in with Peg/RBV x 4 weeks decreases viral breakthrough.**
- **Boc x 28 w improves SVR, and Boc x 48 weeks doubles SVR over Peg/RBV x 48 w.**

Conclusions

- Hepatitis C is a common disorder with serious and costly effects to the individual and society.
- A directed history can identify patients at risk.
- Identification of infected patients, followed by appropriate staging, counseling and treatment, can decrease liver damage to the individual and cost to society.

Questions ?

Annual Liver Symposium
Saturday 12/7/07 – 8am

UNIVERSITY of LOUISVILLE
dare to be great

8:00-8:10 Welcome Craig McClain, M.D.

8:10-8:45 Hepatitis C Update

Guy Neff, M.D.

8:45-9:20 NASH/ASH Matthew Cave, M.D., Craig McClain, M.D.

9:20-9:55 HCC

Joseph Buell, M.D., F.A.C.S., Ashutosh Barve, M.D., Ph.D.

9:55-10:10 BREAK

10:10-10:35 Skin and Eye Problems in Liver Disease

Ann Neff, M.D.

10:35-11:10 Hepatitis B and Other Liver Disease

Luis Marsano, M.D.

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, membrano-proliferative glomerulonephritis, xerostomy, low-grade B-cell lymphoma, corneal ulcers and idiopathic pulmonary fibrosis, lichen planus.

Prevalence of HCV

GROUP	%
Hemophilia <'87	82
IVDA	80
Hemodialysis	10
Transfusion < '92	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

Prevalence of HCV Infection: US

- 3.9 million antibody positive (1.8% of US population)[1]
  - CDC estimates may be as high as 7 million carriers[1]
- 2.7 million are chronically infected with HCV[2]
- Highest prevalence in 30- to 54-year-olds[3]

[1]CDC. *MMWR*. 1998;47(RR-19):1-39.

[2]CDC. Hepatitis C Fact Sheet. Available at: www.cdc.gov. Accessed March 29, 2005.

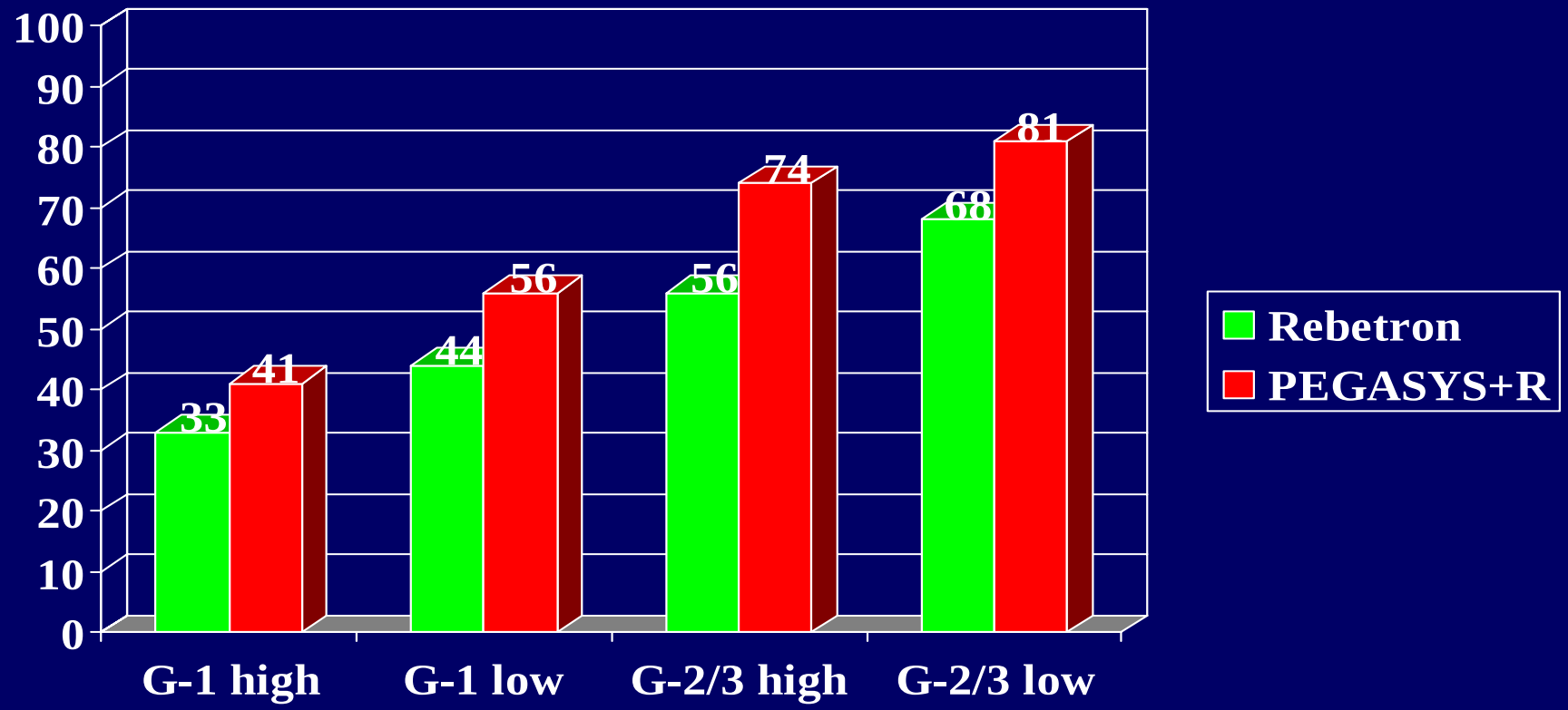
[3]Armstrong et al. AASLD; Oct 29-Nov 2, 2004; Boston, MA. Abstract 31.

Prediction of SVR (Naïve)
PEG-Interferons + Ribavirin

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

PEGASYS + Ribavirin 1-1200 x 48 weeks

Genotype & Viral Load **on** *SVR*

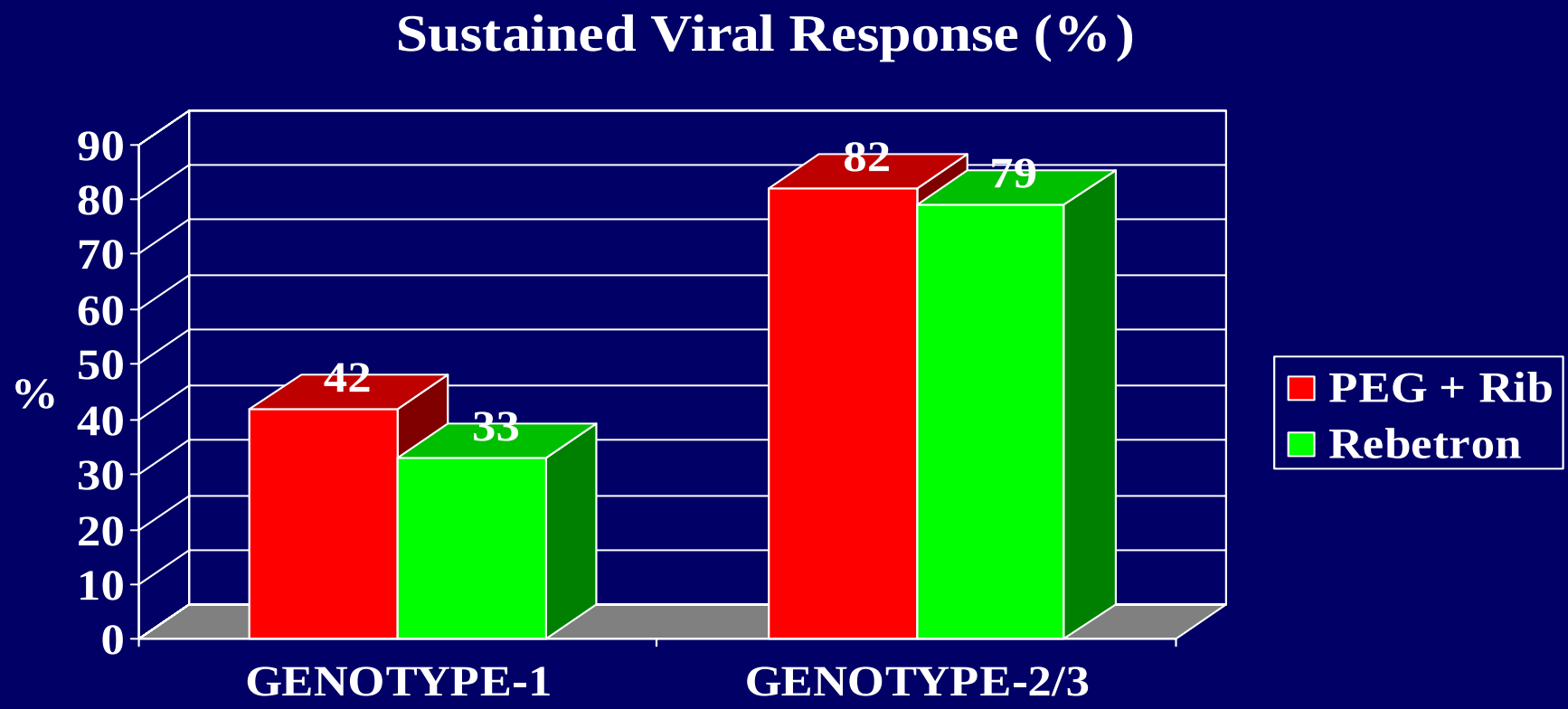


Considerations for Initiating Copegus Therapy Related to Teratogenicity

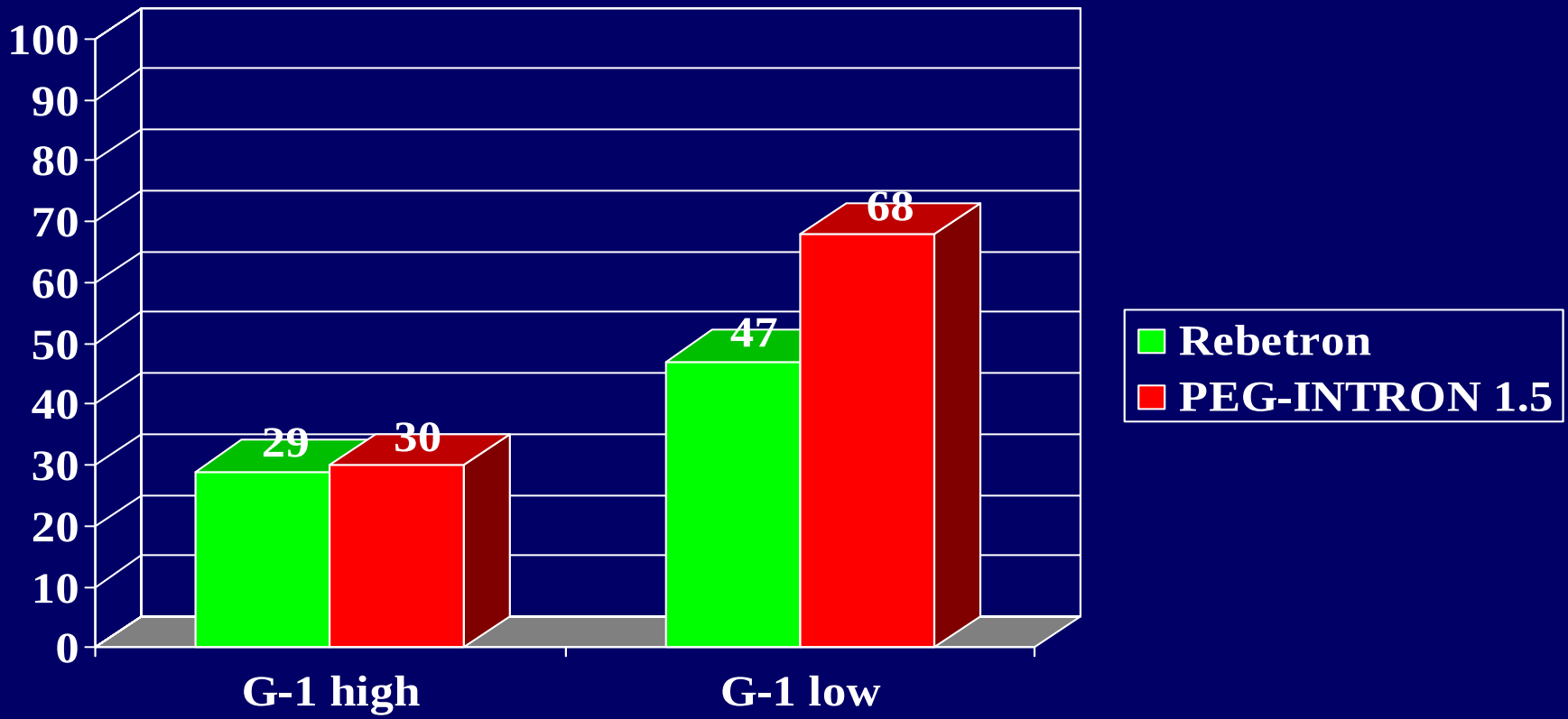
- Copegus therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy
- Women of childbearing potential and men must use two forms of effective contraception during treatment and during the 6 months after treatment has concluded
- Routine monthly pregnancy tests must be performed during this time
- If pregnancy should occur during treatment or during 6 months post-therapy the patient must be advised of the significant teratogenic risk of Copegus therapy to the fetus
- Healthcare providers and patients are strongly encouraged to immediately report any pregnancy in a patient or partner of a patient during treatment or during 6 months after treatment cessation to the Ribavirin Pregnancy Registry at (800) 593-2214

COPEGUS® (Ribavirin, USP) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.
PEGASYS® (Peginterferon alfa-2a) [package insert]. Nutley, NJ: Hoffmann-La Roche Inc.

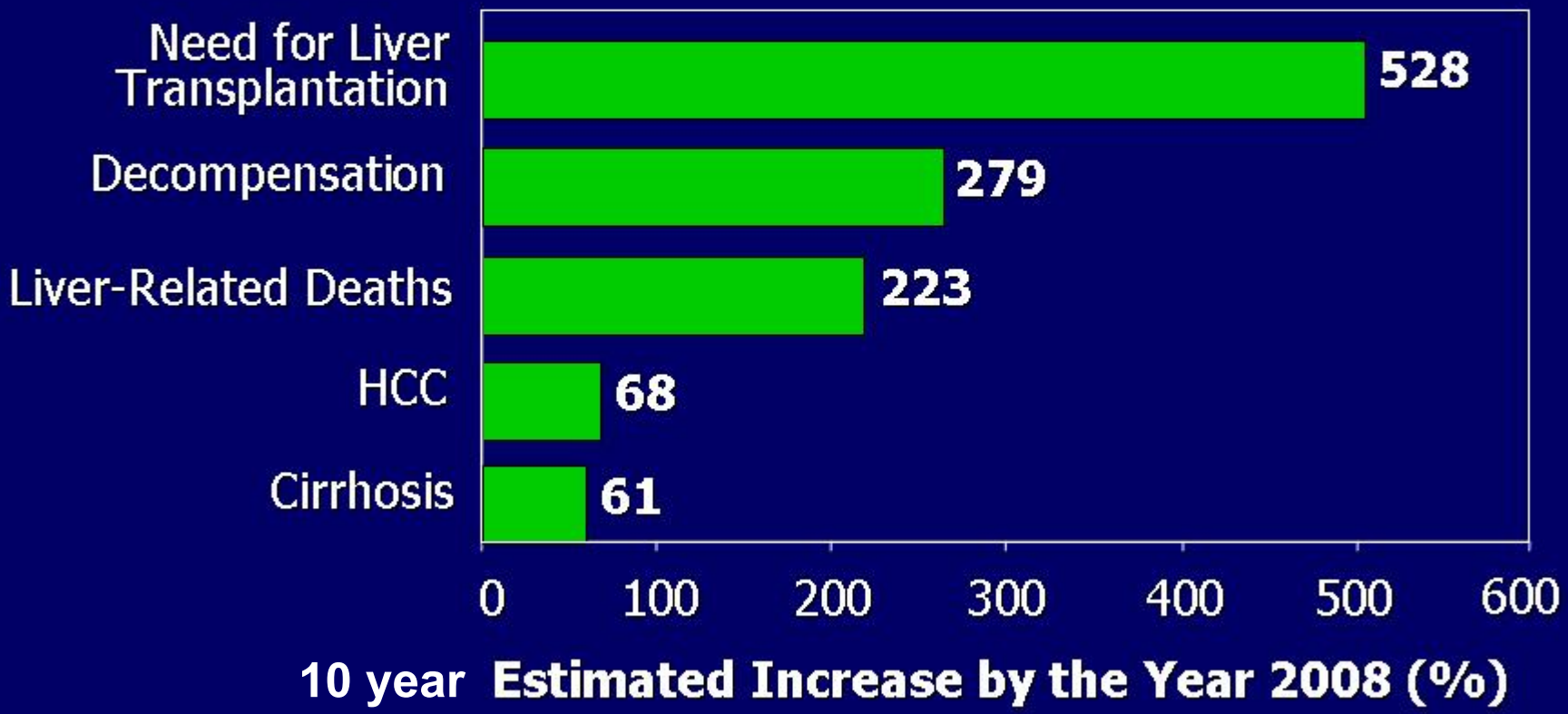
PEG-INTRON + Ribavirin 800
SVR Genotype-1 vs G-2/3 *Naive*



PEG-INTRON + Ribavirin 800
Effect of Viral load **in** Genotype-1



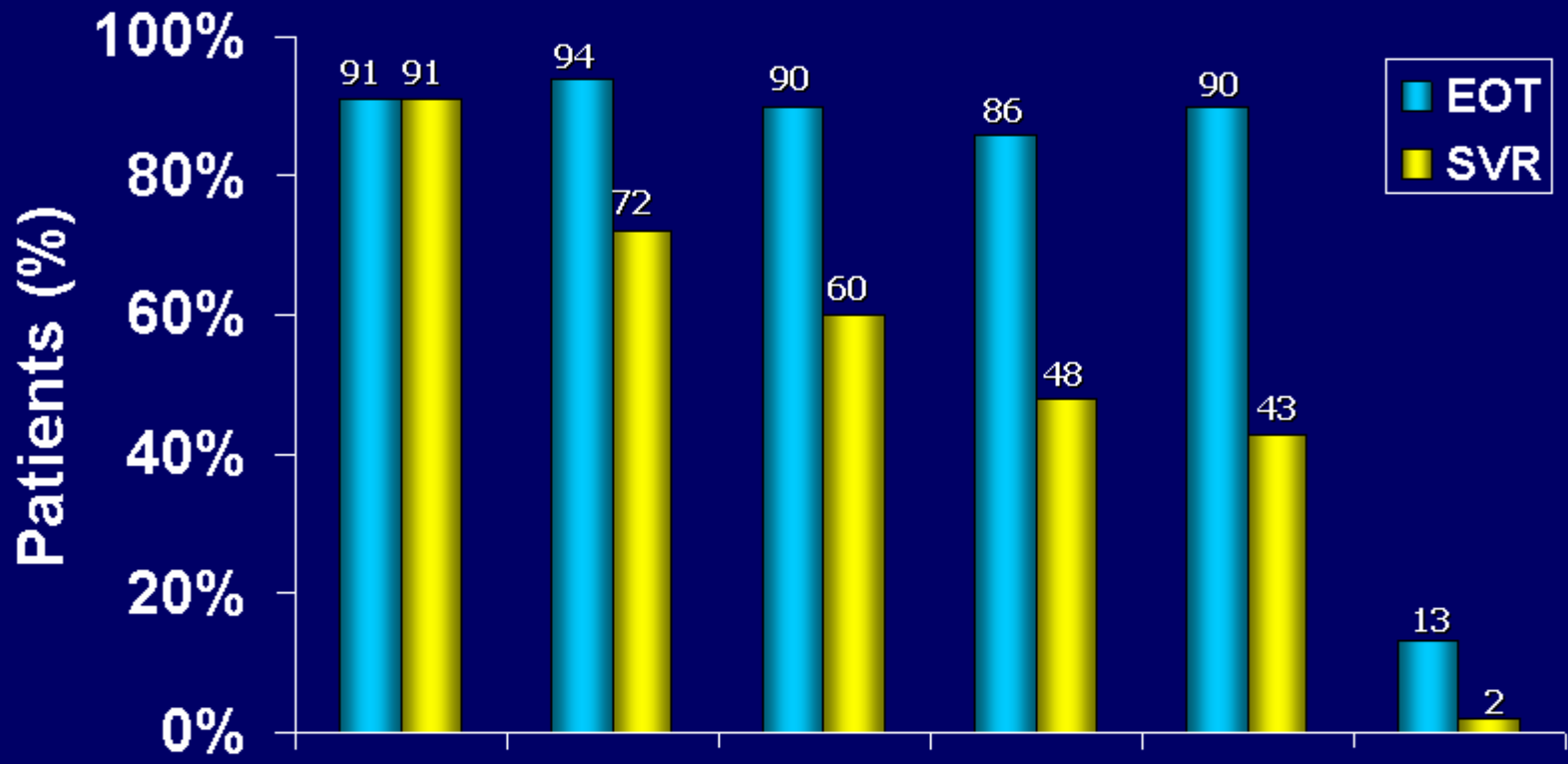
Future Disease Burden Related to HCV: 2008



HCC = hepatocellular carcinoma.

Davis et al. *Hepatology*. 1998;28(4 pt 2):390A.

Predicting SVR in Patients Treated with Pegasys and Copegus



HCV RNA Status							
	Wk 4	Neg	>2 Log	<2 Log	>2 Log	<2 Log	Any
	Wk 12	Neg	Neg	Neg	>2 Log	>2 Log	Any
	Wk 24	Neg	Neg	Neg	Neg	Neg	Pos

Ferenci P, et al. *J Hepatol.* 2005;43:425-433.

Vertical Transmission of HCV Cesarean Section vs Vaginal Delivery

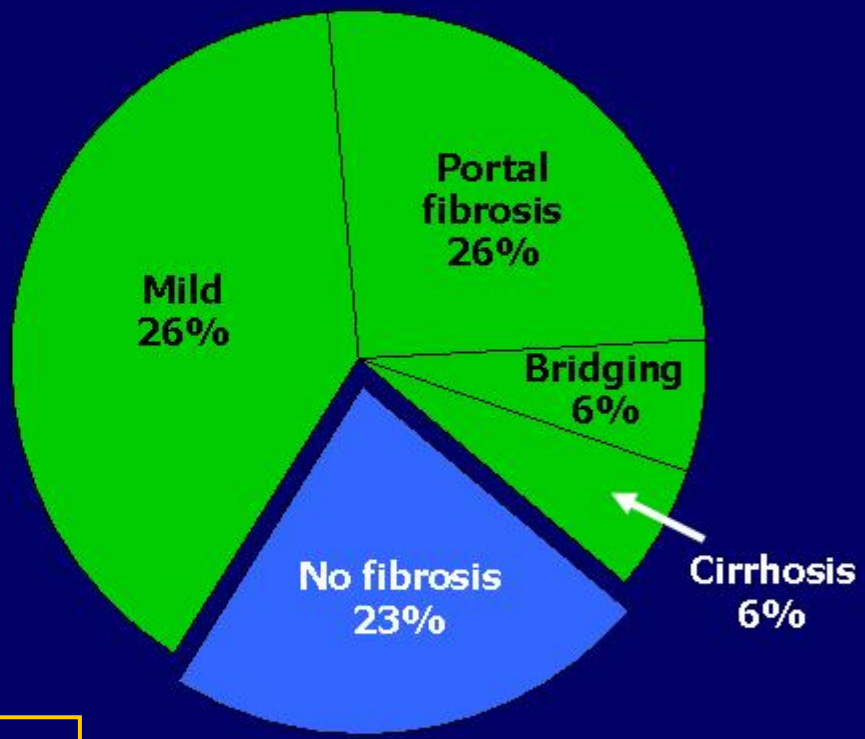
- The “Cochrane Pregnancy and Childbirth Group’s Trial Register”, and the “Cochrane Central Register of Controlled Trials” were analyzed until April 2006.
- No randomized controlled trials were found (Cochrane Database Syst Rev 2006; Oct 18).
- Systematic review of observational studies (subject to biases)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

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

HCV Disease Progression in Patients With Normal ALT

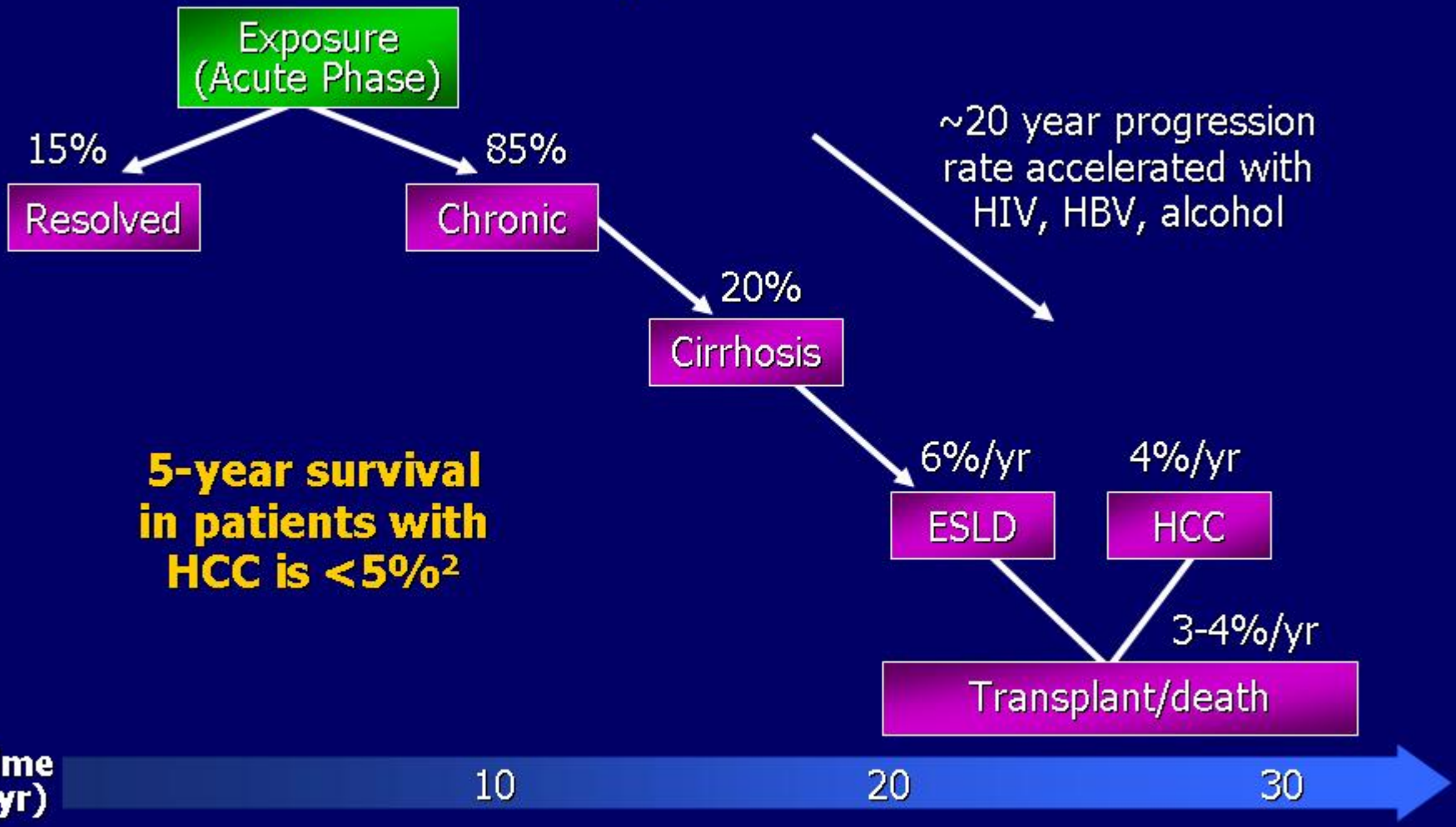
Despite 'persistently normal' ALT levels, >75% have some degree of liver damage on biopsy, with 32% having portal and bridging fibrosis



38% qualify for therapy (METAVIR >/= 2)

Shiffman et al. *J Infect Dis.* 2000;182:1595-1601.

Natural History of HCV Infection



5-year survival in patients with HCC is <5%[2]

HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

Di Bisceglie et al. *Hepatology*. 2000;31(4):1014-1018.

Treatment of Acute HCV @ 8,12, & 20 wks, Peg-IFN alpha-2a vs (IFN + RBV) x 12 wks

Kamal et al Abst # 37 AASLD, 2004

- 68 pts with Acute hepatitis C;
  7 had spontaneous clearance.
- Treatment started at:
  - A) Week 8 (21),
  - B) Week 12 (20),
  - C) Week 20 (20)
- IFN+RBV vs Peg-IFN alpha 2a x 12 wks; if HCV-RNA (+) at wk 12, treated 12 more wks.

Treatment of Acute HCV @ 8,12, & 20 wks, Peg-IFN alpha 2a vs IFN+RBV x 12 wks

Kamal et al Abst # 37 AASLD, 2004

- Starting therapy at week 12 gave best results.
- Peg-IFN alpha 2a 180 mcg/week monotherapy x 12 weeks, was superior to IFN+RBV treatment x 12 weeks, in all groups.

Hepatitis C Update

Luis S. Marsano, MD

Professor of Medicine

Director, Clinical & Transplant Hepatology

University of Louisville &

Louisville VAMC

Barriers to Screening

2 Out of 3 Patients With HCV Are Undiagnosed Because of Screening Barriers[1]

- General population not aware of risk factors[2]
- Routine HCV risk factor assessment not current primary care physician (PCP) practice[2]
- Patient concerned about admitting risk factors[4]
  - No risk factor identified in 69% of cases
- Persons infected with HCV are often asymptomatic[3]
- Elevated ALT is current marker for ordering liver panel[4]

[1]ALF. Hepatitis C Factsheet. Available at: www.liverfoundation.org. Accessed March 14, 2005.
[2]Shehab et al. *J Viral Hepat.* 2001;8(5):377-383.
[3]CDC. *MMWR.* 1998;47(RR-19):1-39.
[4]Rawls et al. *J Clin Gastroenterol.* 2005;39(2):144-151.

Should we test for Hepatitis C only if ALT is elevated ?

Correlation of ALT and Detection of HCV

- Elevated ALT levels lead to workup and diagnosis of hepatitis C
- Many hepatitis C positive patients have persistently normal ALT levels[1]
  - Caution should be used with over-reliance on abnormal ALT as the screening trigger
  - ALT often fluctuates
- Up to 46% of patients with CHC have ALT levels within the currently defined 'normal' range[2]

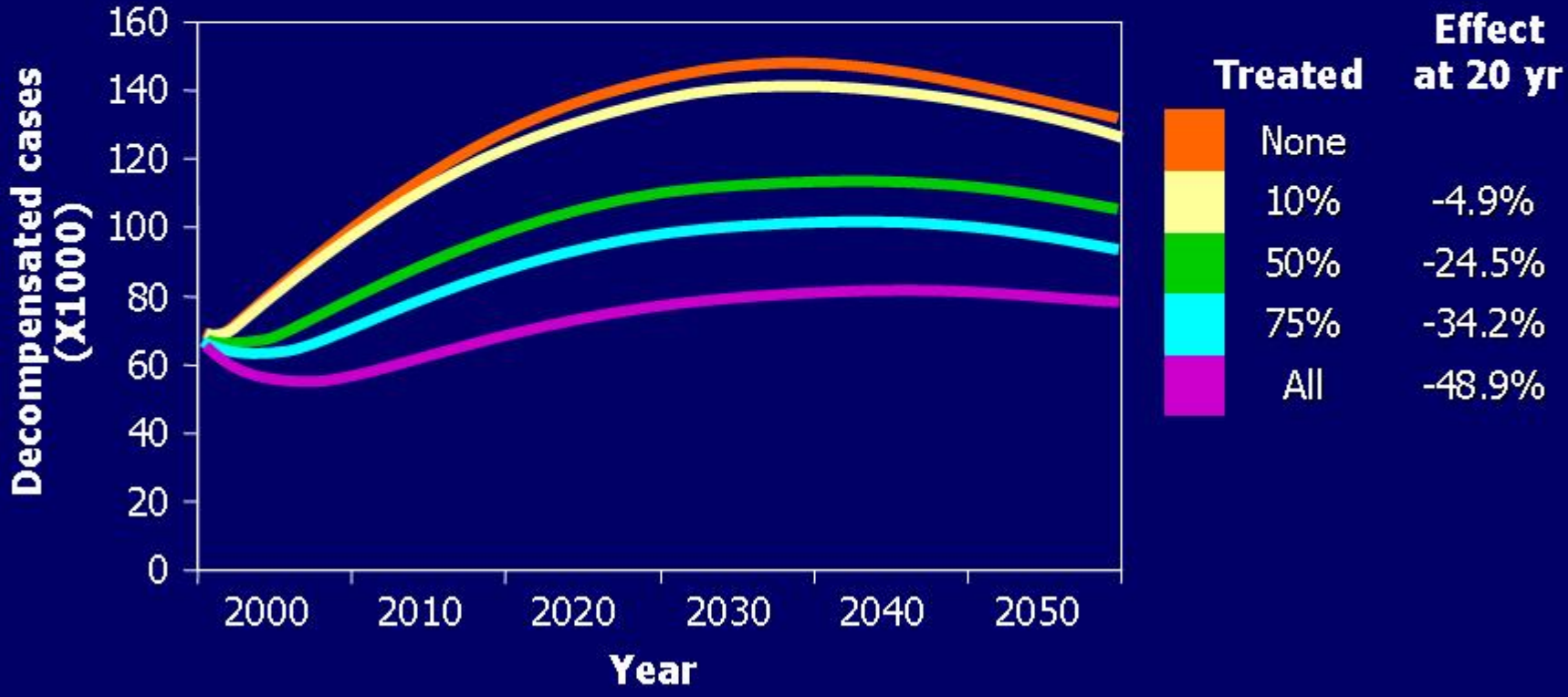
[1]NIH. *NIH Consens State Sci Statements*. 2002;19(3):1-46.
[2]Alberti et al. *Ann Intern Med*. 2002. 2002;19(3):1-46.

Summary: Barriers to Screening

- Lack of disease awareness in general US population
- Routine risk-factor screening not common practice for primary care physician
- Persons with HCV are often asymptomatic
- A biochemical marker, such as ALT, should not be the only indicator for further evaluation and/or treatment of HCV

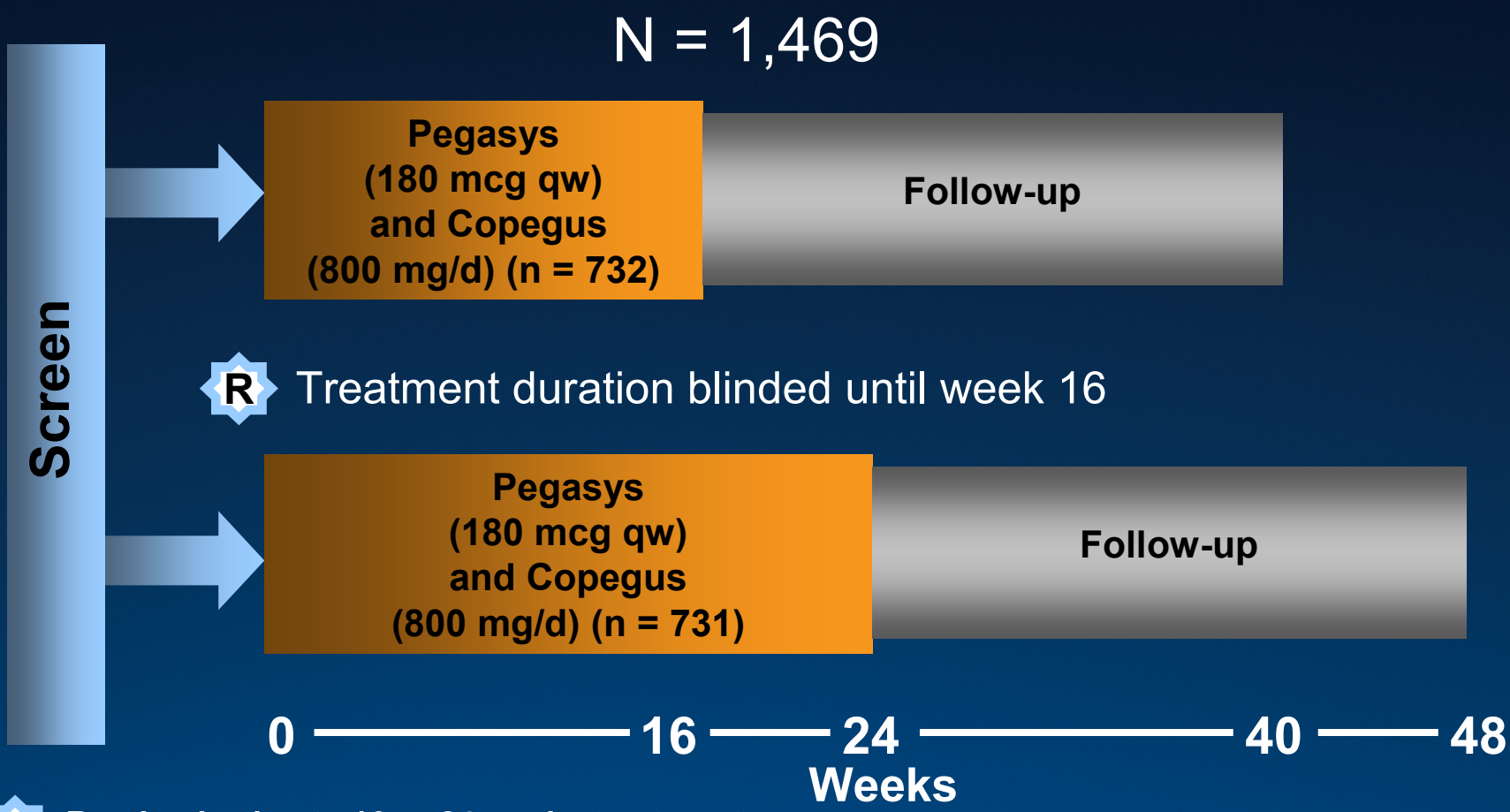
Projecting Future Complications of CHC in the US

Identification and treatment of patients with CHC reduces the number of cases of decompensated cirrhosis



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

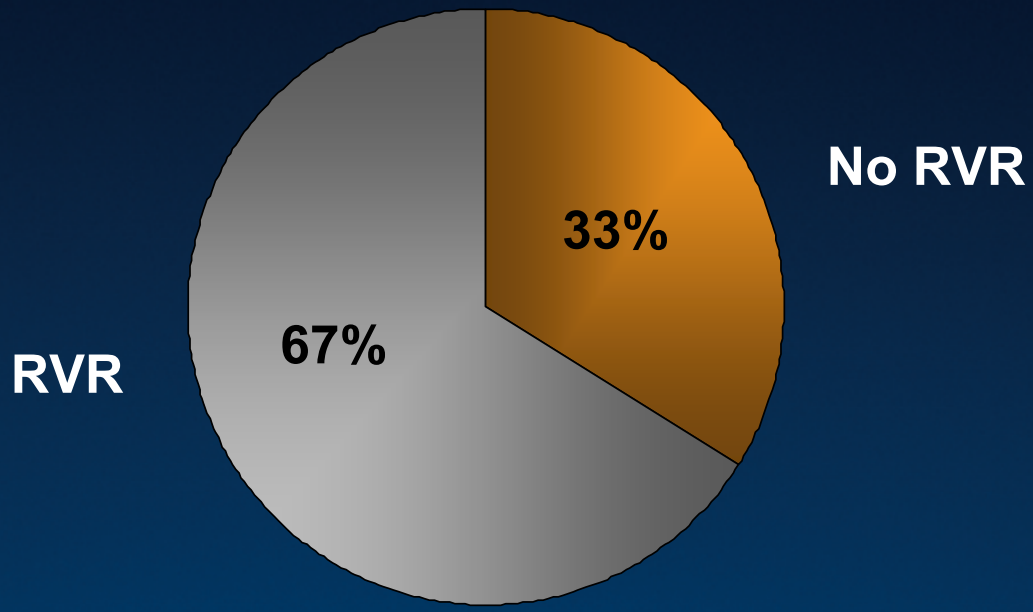
ACCELERATE Trial:
Study Design



R **Randomization to 16 or 24 weeks treatment**
Patients with genotype 2 or 3

Shiffman ML, et al. *NEJM*. 2007;357:124-134.

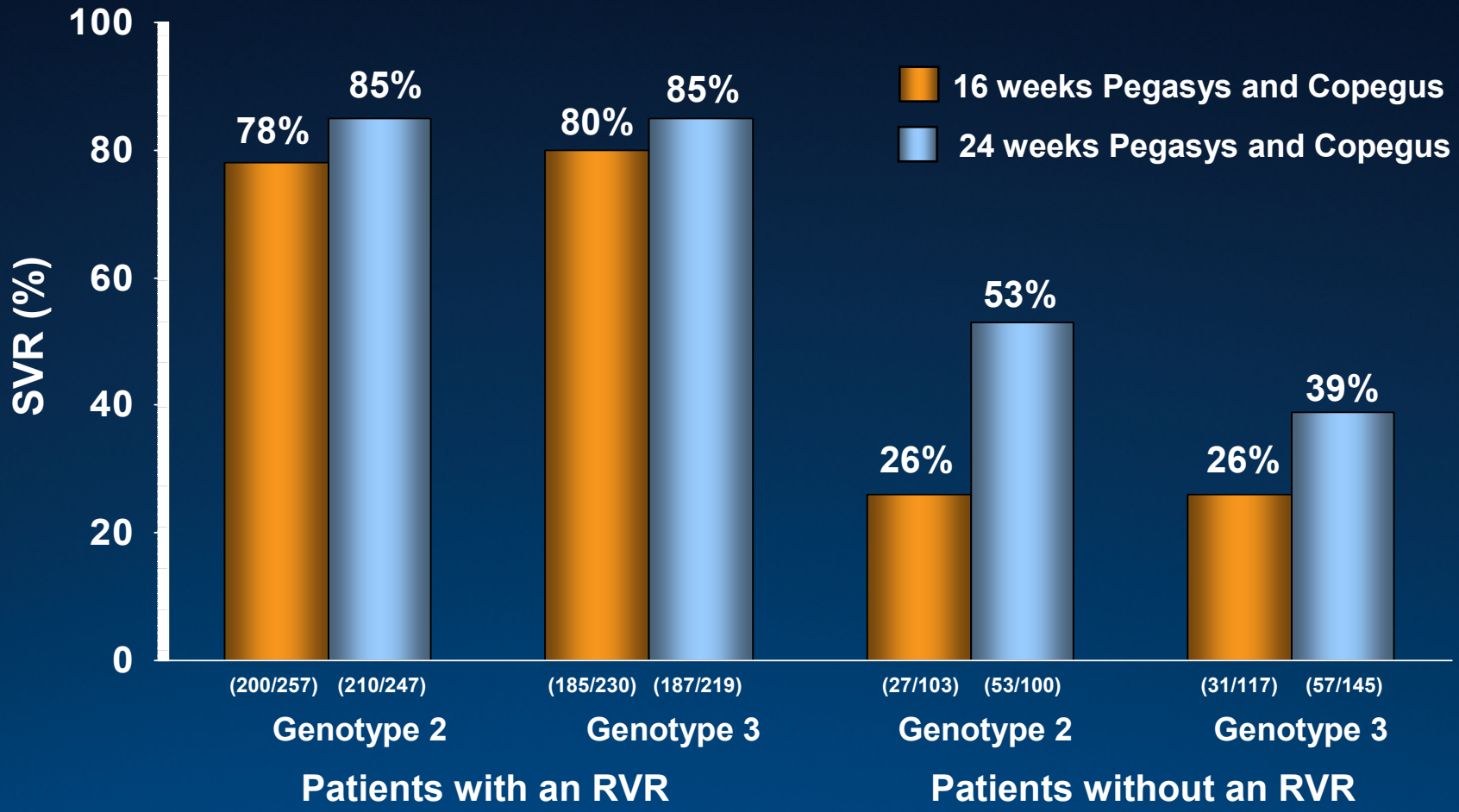
ACCELERATE Trial: *Proportion of G2/3 Patients Who Achieved an RVR*



- A total of 1,469 patients were included in ACCELERATE, with 1,455 patients having HCV RNA measurements at week 4 in the standard population analysis
- Among these 1,455 patients, 955 (67%) achieved an RVR

Shiffman ML, et al. *NEJM*. 2007;357:124-134.

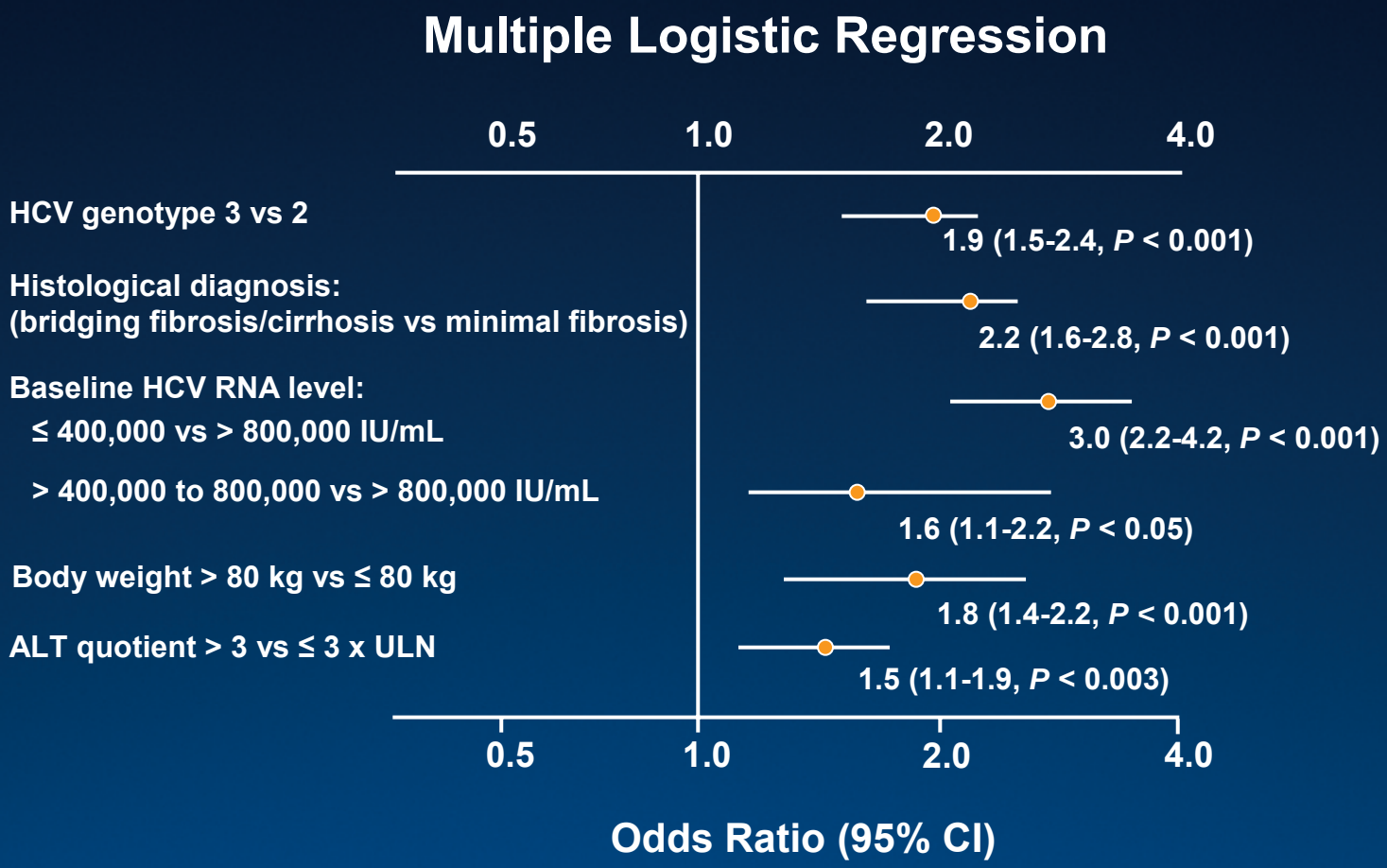
ACCELERATE Trial:
Virologic Response by RVR and Genotype



Standard population

Shiffman ML, et al. *NEJM*. 2007;357:124-134.

ACCELERATE Trial: *Predictive Factors of SVR*



Shiffman ML, et al. *NEJM*. 2007;357:124-134.

New Definitions of Early Virologic Response to Antiviral Therapy for Hepatitis C[1-2]

EVR Early Virologic Response	HCV RNA negative or > 2 $\log_{10}$ drop at week 12
– Complete EVR (cEVR)	No RVR but HCV RNA negative (< 50 IU/mL) at week 12
– Partial EVR (pEVR)	No RVR and detectable but ≥ 2 $\log_{10}$ drop in HCV RNA at week 12
• **Slow responder**	≥ 2 $\log_{10}$ drop in HCV RNA at week 12 and HCV RNA negative at week 24
• **Partial responder**	≥ 2 $\log_{10}$ drop in HCV RNA at week 12 but HCV RNA positive at week 24

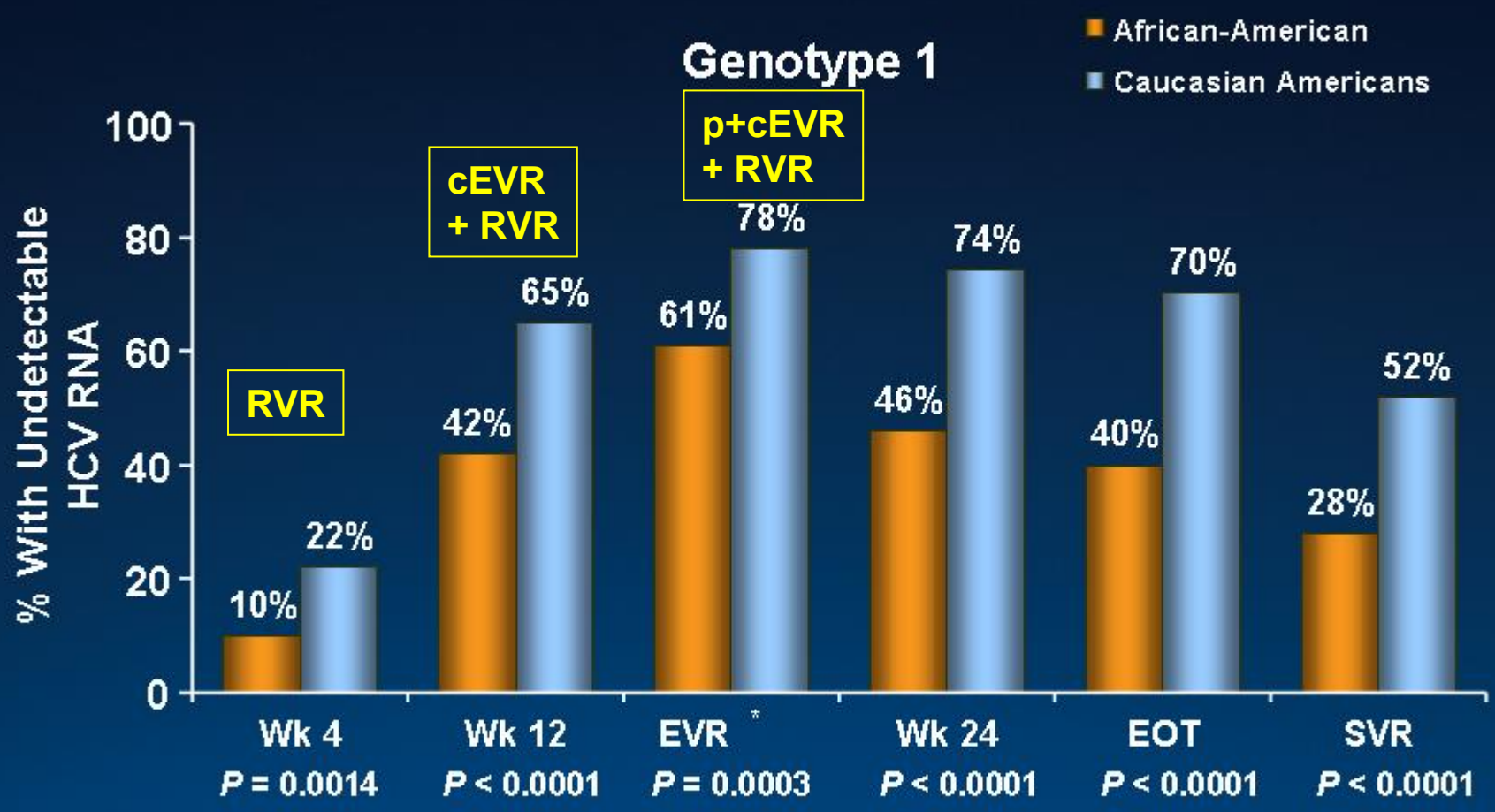
1. Marcellin P, et al. Presented at AASLD 2007. Oct. 2-6, 2007; Boston, MA. Poster #1308.
2. Sánchez-Tapias JM, et al. Presented at EASL 2007. April 11-15, 2007; Barcelona, Spain. Poster #641.

Definitions of Virologic Response to Antiviral Therapy for Hepatitis C[1-4]

Response	Definition
RVR Rapid Virologic Response	HCV RNA negative at 4 weeks as defined by HCV RNA < 50 IU/mL
EVR Early Virologic Response	HCV RNA negative or > 2 $\log_{10}$ drop at week 12
Relapse	HCV RNA negative at end of treatment but HCV RNA positive after treatment cessation
SVR Sustained Virologic Response	HCV RNA negative 24 weeks after end of treatment

1. Ferenci P, et al. Presented at EASL 2006. April 26-30, 2006; Vienna, Austria. Abstract #8.
2. Paulon E, et al. *Eur J Gastroenterol Hepatol.* 2006;18(4):321-325.
3. Pawlotsky JM. *Hepatology*. 2002;36(suppl 1):S65-S73.
4. Adapted from http://www.hepatitis.va.gov/vahep?page=prtop04-wp-03. Accessed January 4, 2008.

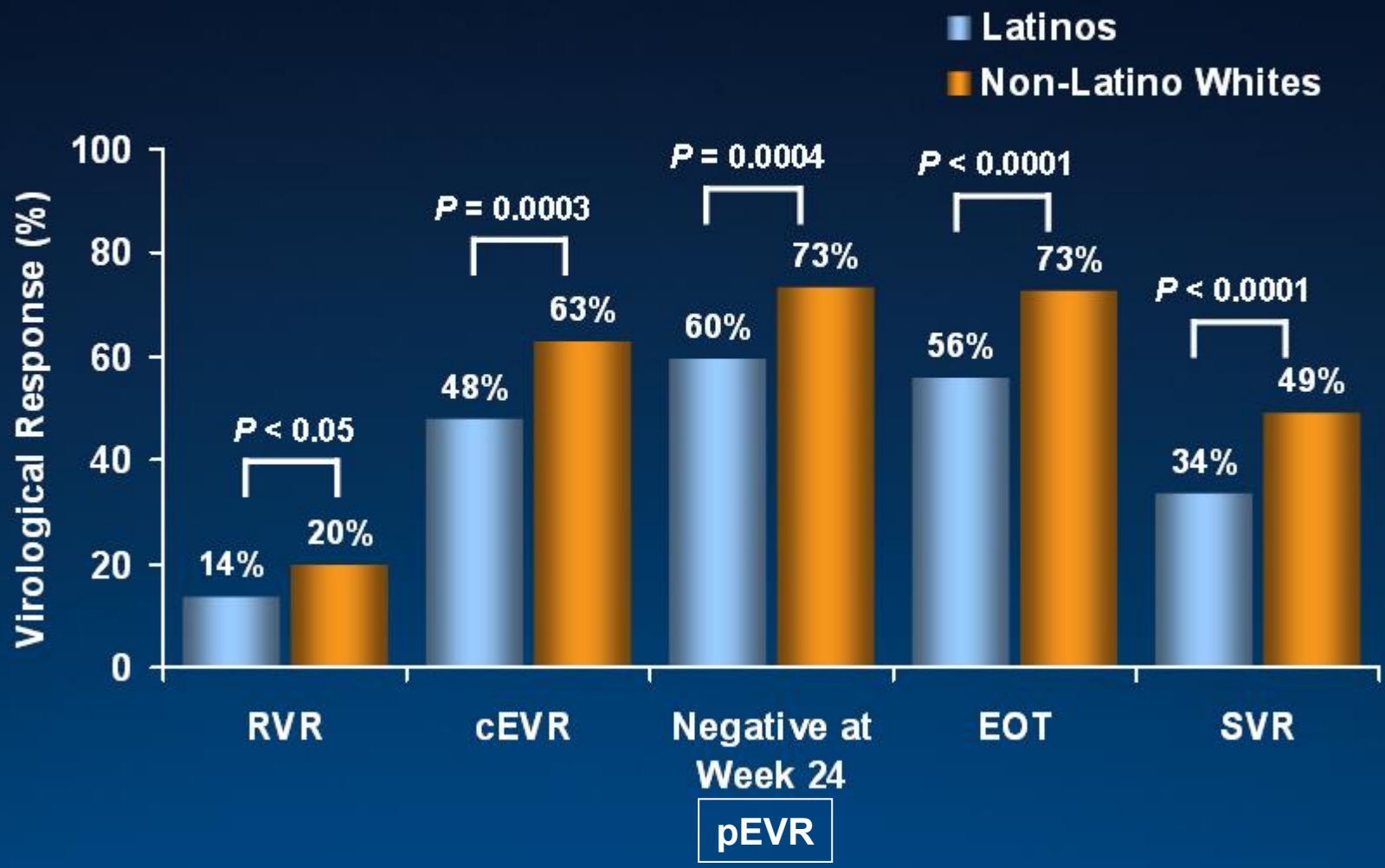
Virahep-C Trial: *Virologic Response*



*Negative or ≥ 2 $\log_{10}$ drop at Week 12

Conjeevaram HS, et al. *Gastroenterology*. 2006;131:470-477.

LATINO Study:
Results in Genotype 1 Patients



Rodriguez-Torres M, et al. Presented at EASL 2008. April 23-27, 2008; Milan, Italy. Poster #2553.