Hepatitis C

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Hepatitis C

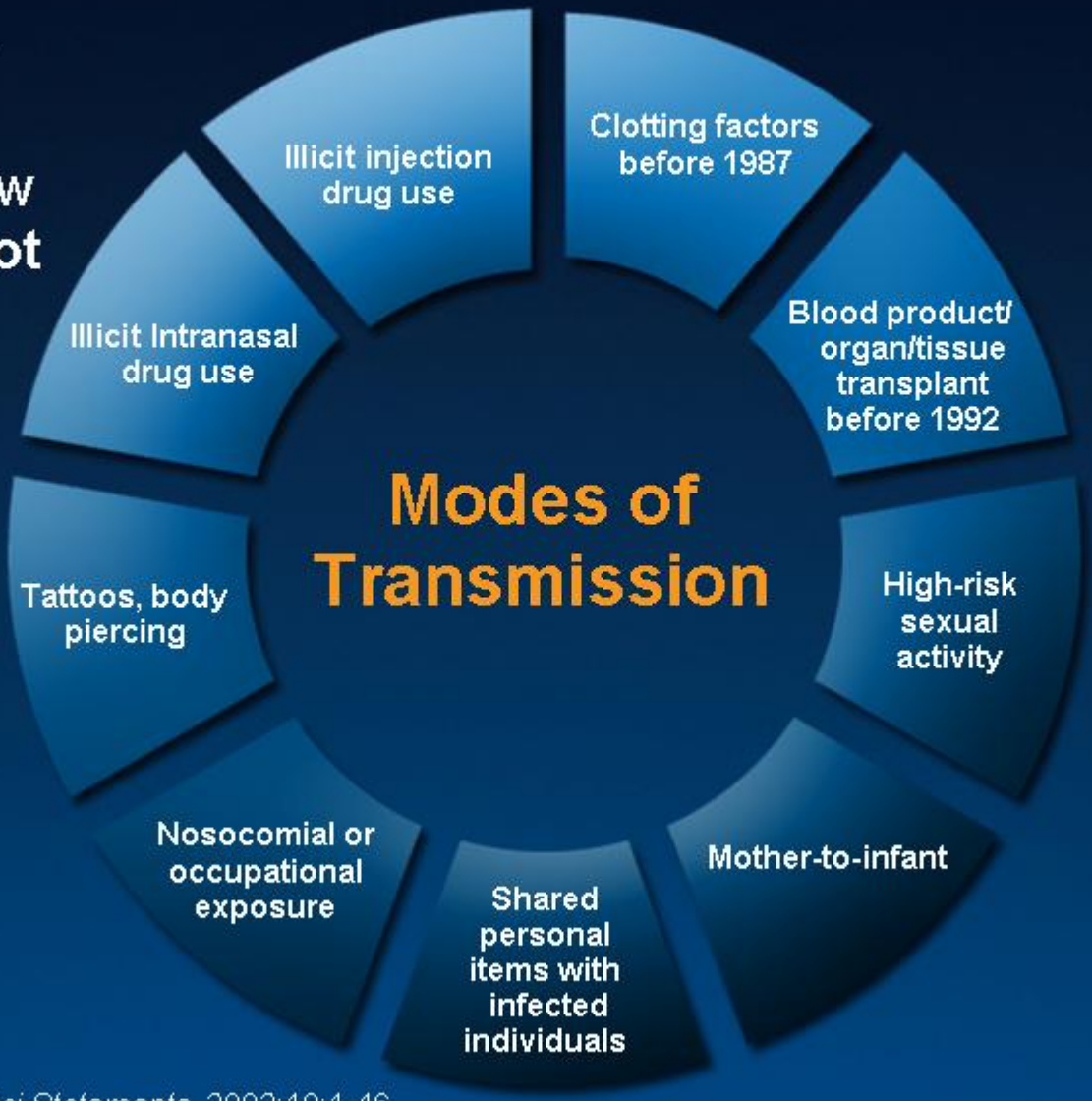
- 50 nm enveloped, positive-sense, single-stranded RNA hepacivirus.
- Seven genotypes and > 100 subtypes.
- 170 million infected worldwide;
- 4 million in USA (1.8%);
- 18,000 new infections/year.
  - 56% recent IVDU
  - 34% had =/> 2 sexual partners in last 6 months
  - 16% had recent sex with HCV (+) partner

Prevalence,

Transmission
&
Disease Burden

Transmission of HCV

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



NIH. *NIH Consens State Sci Statements*. 2002;19:1-46.

Hepatitis C Disease Burden: US

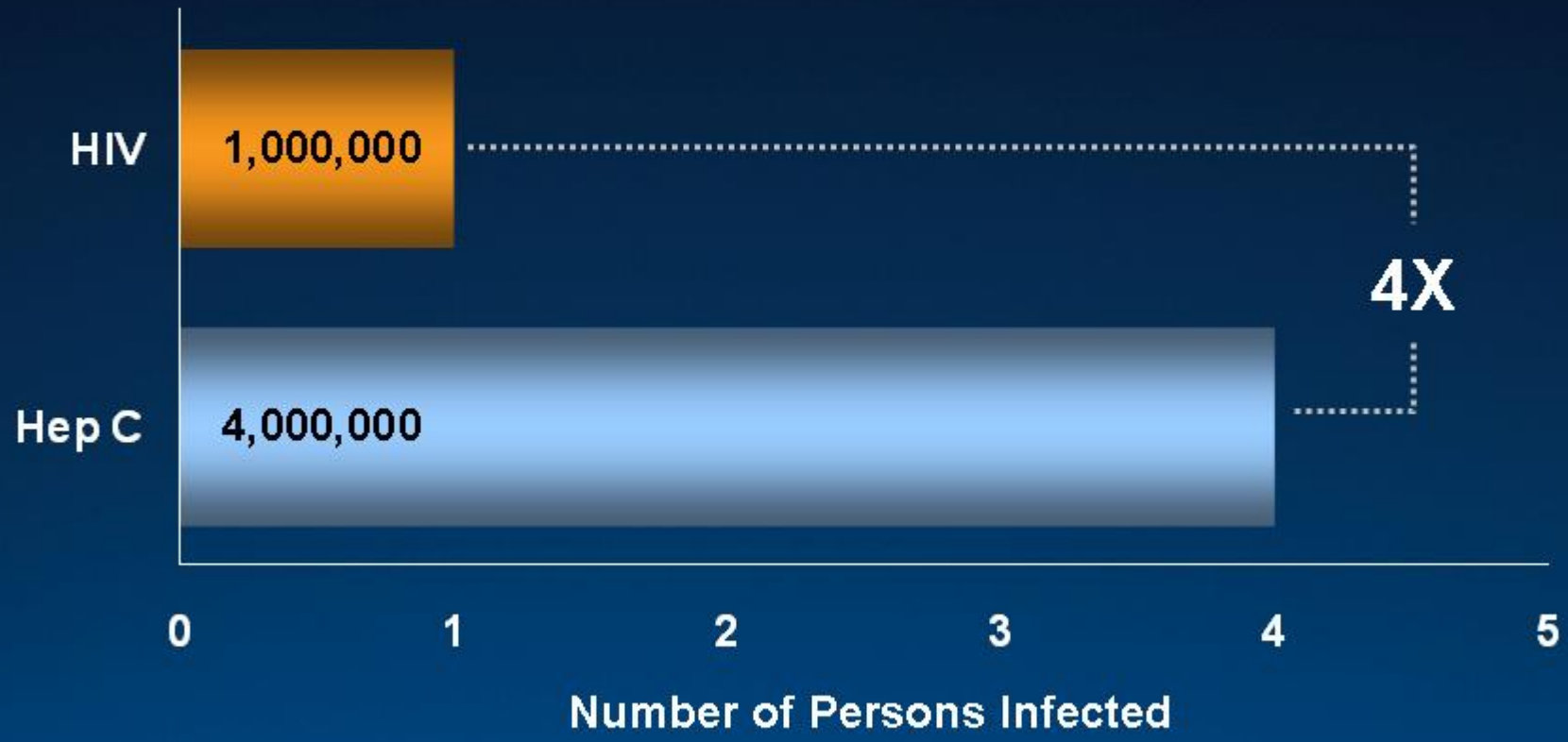
- Hepatitis C is the most common chronic blood-borne viral infection in the US[1]
  - ~ 1/2 of cirrhotic patients[2]
  - ~ 1/3 of HCC patients[3]
  - #1 reason for liver transplants[4]
  - #1 cause of death in HIV patients[5,6]

It is estimated that 4 million Americans are infected with HCV[7]

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

Prevalence of Hepatitis C

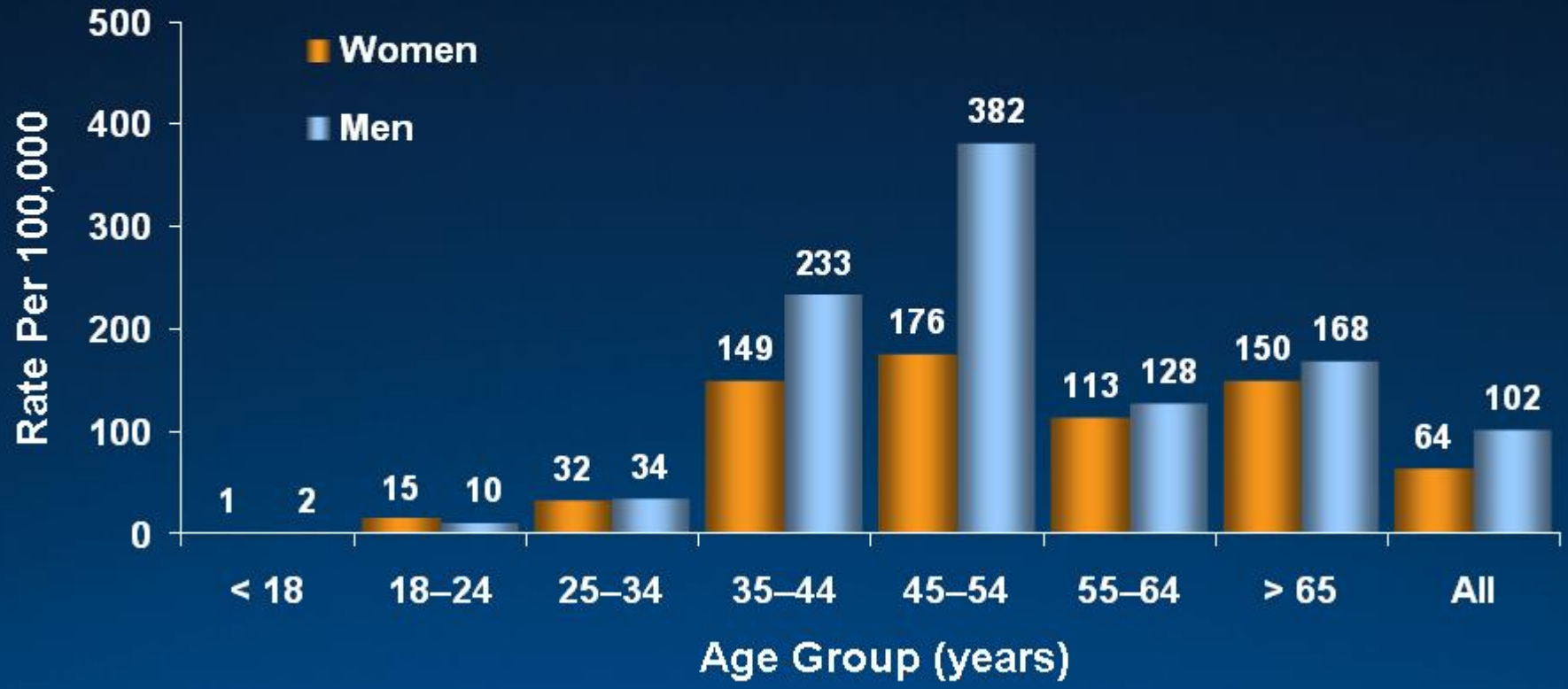
- Hepatitis C is 4 times more prevalent than HIV[1,2]



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

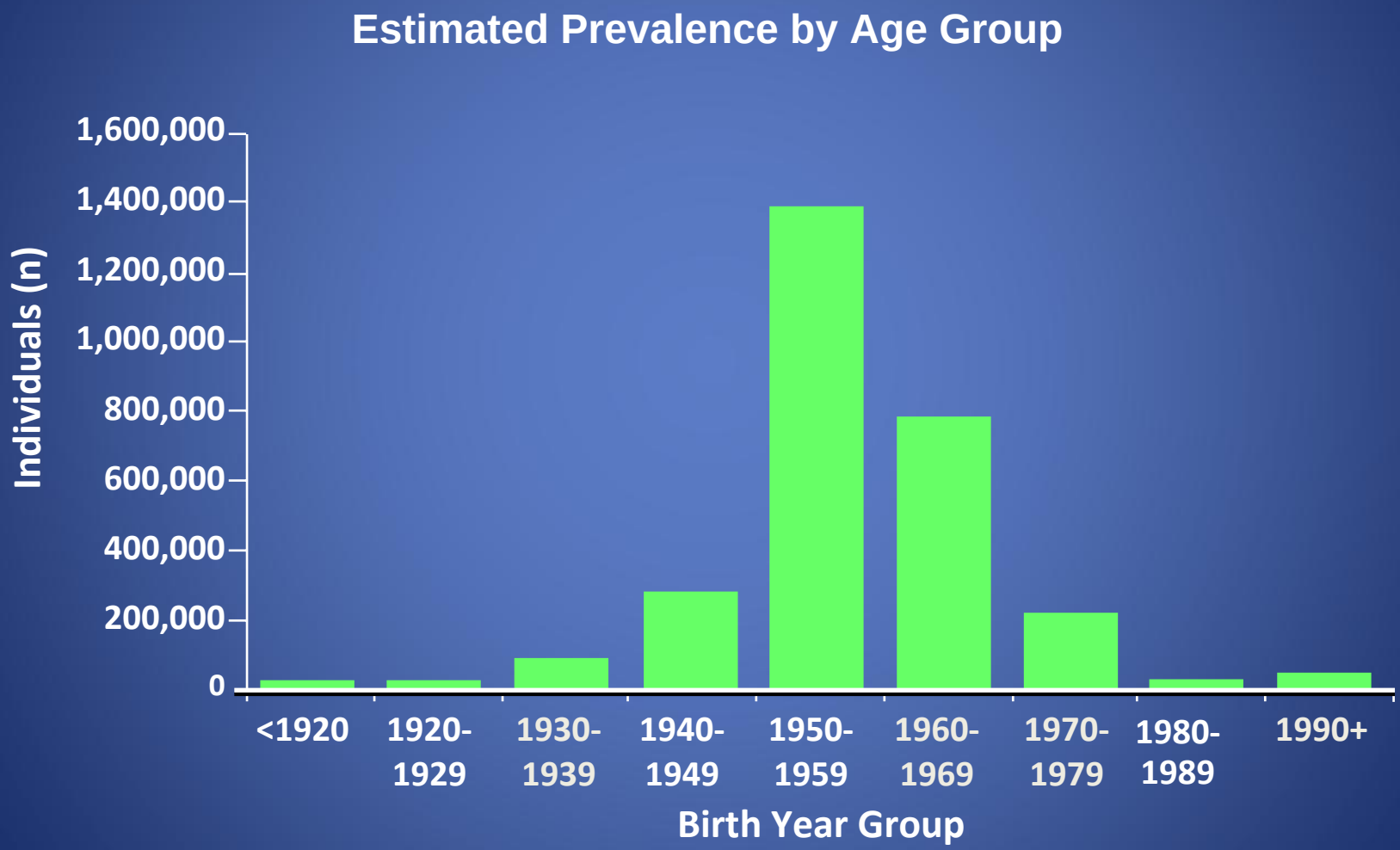
Prevalence of Hepatitis C by Age and Sex

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



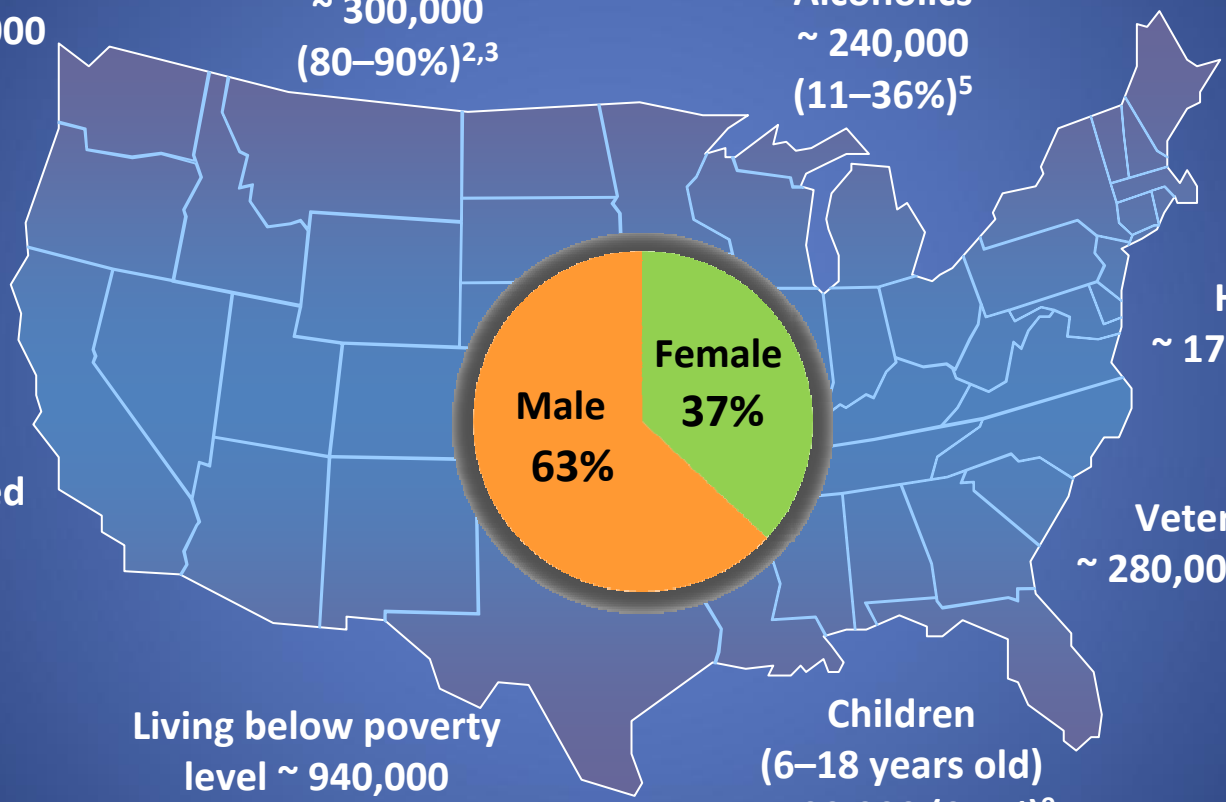
Shatin D, et al. *Am J Manag Care*. 2004;10:250-256.

Two-Thirds of Those With Chronic HCV in the US Were Born Between 1946 and 1964



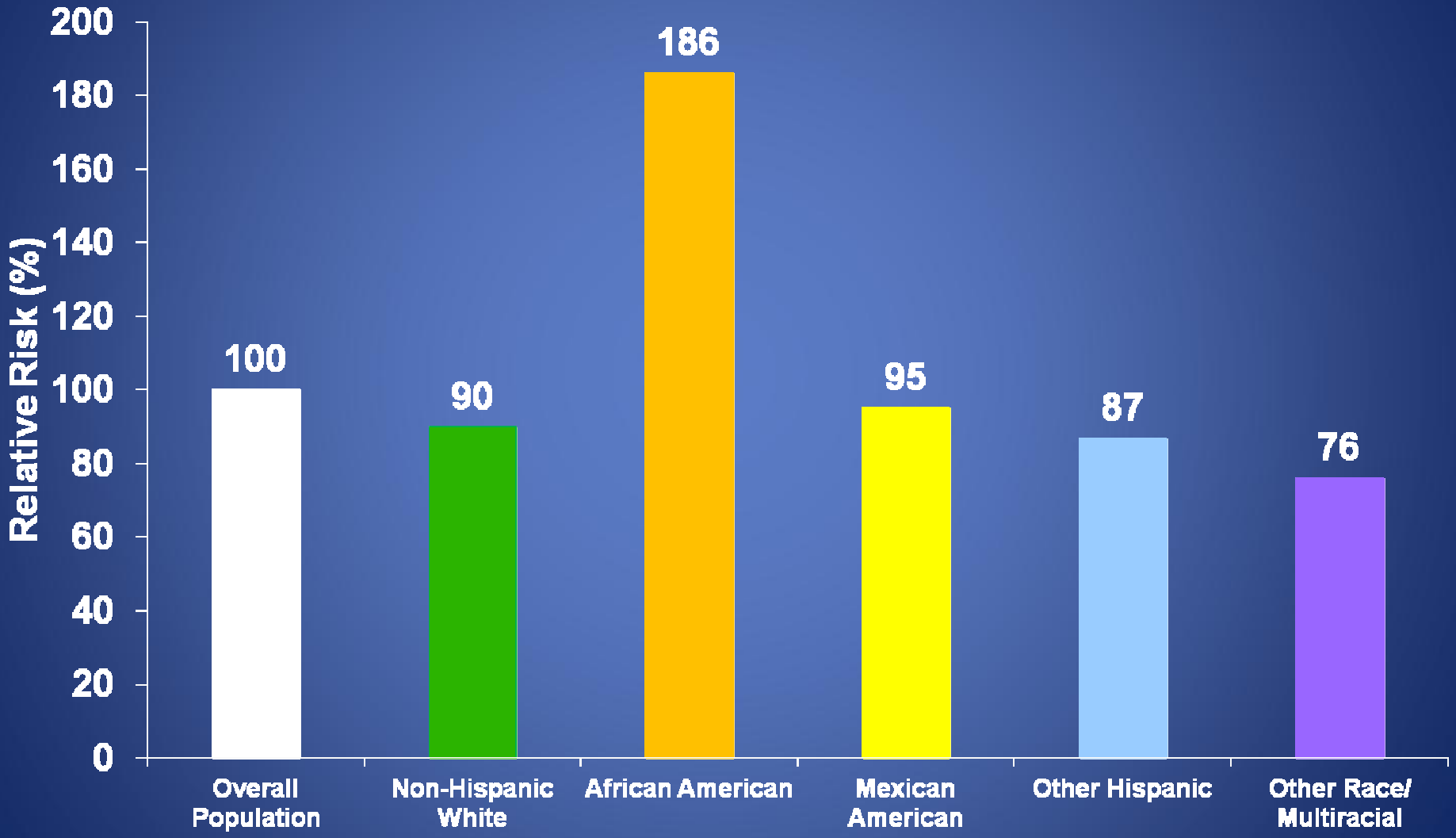
Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

Prevalence of HCV in Select Populations



Adapted from: 1. CDC. *MMWR*. 2003;52(RR-1):1-33; 2. Edlin B. *Hepatol*. 2002;36(5 suppl 1):S210-S219; 3. NHSDA Report 2003; 4. Poles M, et al. *Clin Infect Dis*. 2000;31:154-161; 5. LaBrecque D, et al. *Hepatitis C Choices*. 2002:7-15; 6. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 7. Nyamathi A, et al. *J Gen Intern Med*. 2002;17:134-143; 8. Dominitz J, et al. *Hepatology*. 2005;41:88-96; 9. Jonas M. *Hepatol.* 2002;36(5 suppl 1):S173-S178.

Relative Risk of Being HCV Positive by Race



Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

HCV Prevalence Hemodialysis Patients

	general=	HD=
Egypt	18.1%	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%***
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

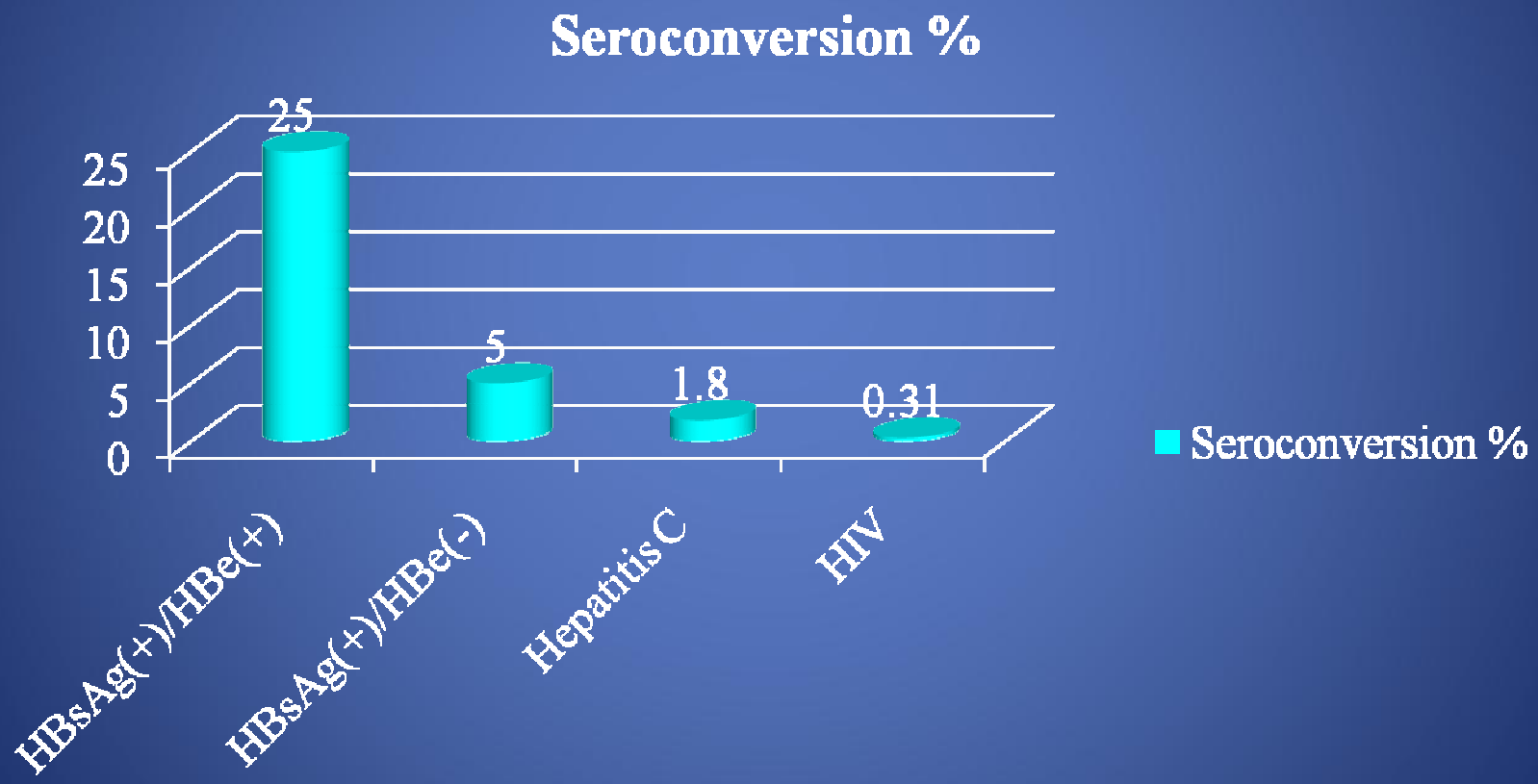
Hepatitis C and Healthcare Workers (HCWs)

HCW exposure to HCV

- Prevalence of HCV in HCWs is similar to that of the general population.
- Testing for HCV in HCWs should be done after percutaneous, mucosal, and nonintact skin exposure to HCV(+) blood and potentially infectious body fluids.
- HCV can survive in environmental surfaces for > 16 hours, but < than 4 days.
- Baseline testing: anti-HCV, HCV-RNA quant, ALT
- F/U testing: ALT, HCV-RNA, anti-HCV @ wk 4, 12 & 24.
- If infection occurs and persists for >/= 12 weeks, treat as acute HCV.

Risk of Seroconversion after percutaneous exposure to infected source (without prophylaxis)

Epidemiol Rev 1994;16:437-450 & MMWR 1998;47(RR-19):1-39



Worldwide Cases of HCW-to-Patient HIV, HBV, or HCV Transmission 1991-2005

Am J Infect Control 2006;34:313-319

	# HCW	# Infected Patients	# Patients tested in look-back	% Infected Patients
HIV	3	3	3527	0.09%
HBV	12	91	3079	2.96%
HCV	11	38	9678	0.36%

Risk of Infection by Mode of Exposure to HCWs

	HBV	HCV	HIV
Percutaneous	6-30%	1.8%	0.2-0.5%
Mucosal	Transmission documented	Transmission documented	0.09%
Nonintact Skin	Transmission NOT documented	Transmission NOT documented	< 0.1%
Human Bite	Transmission documented	Transmission documented	Transmission documented

Infective Material Causing HCWs Infection

	HBV	HCV	HIV
Documented	Blood Blood products	Blood Immunoglobulins	Blood Blood products Body fluids
Possible	Semen Vaginal fluid Bloody fluids Saliva	Blood products Bloody fluids Semen Vaginal Fluids	Semen Vaginal fluid Cerebrospinal fluid Breast milk Serosal fluids Amniotic fluid Exudates Saliva in dental exam
Unlikely	Urine Feces	Saliva Urine Feces	Saliva Urine Feces

Vertical Transmission of HCV

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

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

Vertical Transmission of HCV
Cesarean Section vs Vaginal Delivery

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

Vertical Transmission of HCV

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

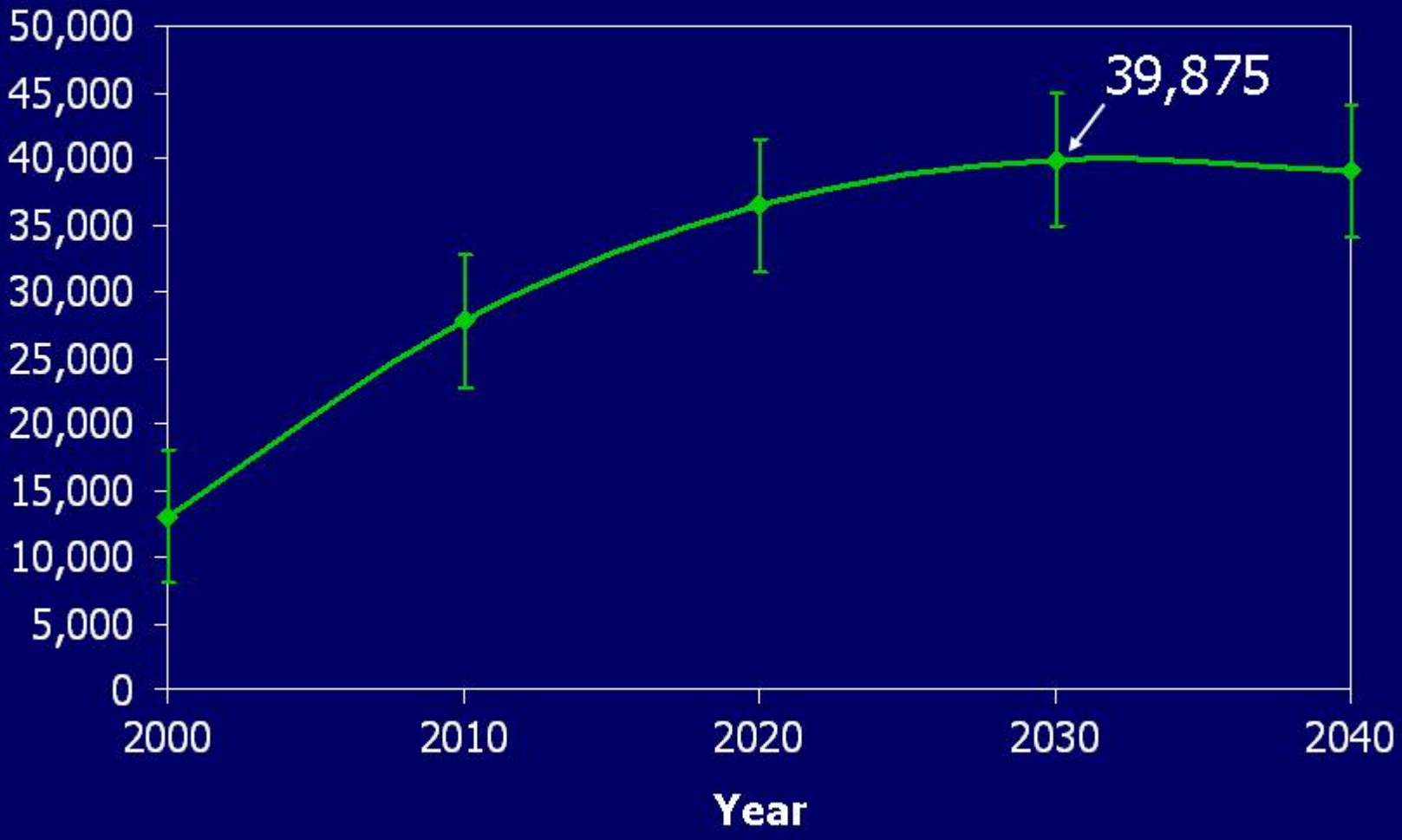
- **In HCV(+)/HIV(-) mothers:**
  - Route of delivery does not influence vertical transmission.
  - There is no need to discourage breast feeding.
- **In HCV(+)/HIV(+) mothers:**
  - Mode of delivery should be based in HIV status.
  - Breast feeding should be discouraged.

Measures to Avoid Transmission of HCV
What an Infected Person Should Do

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

Table adapted from “Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease.” Centers for Disease Control and Prevention. MMWR Recomm Rep 1998;47(RR-19):1-39

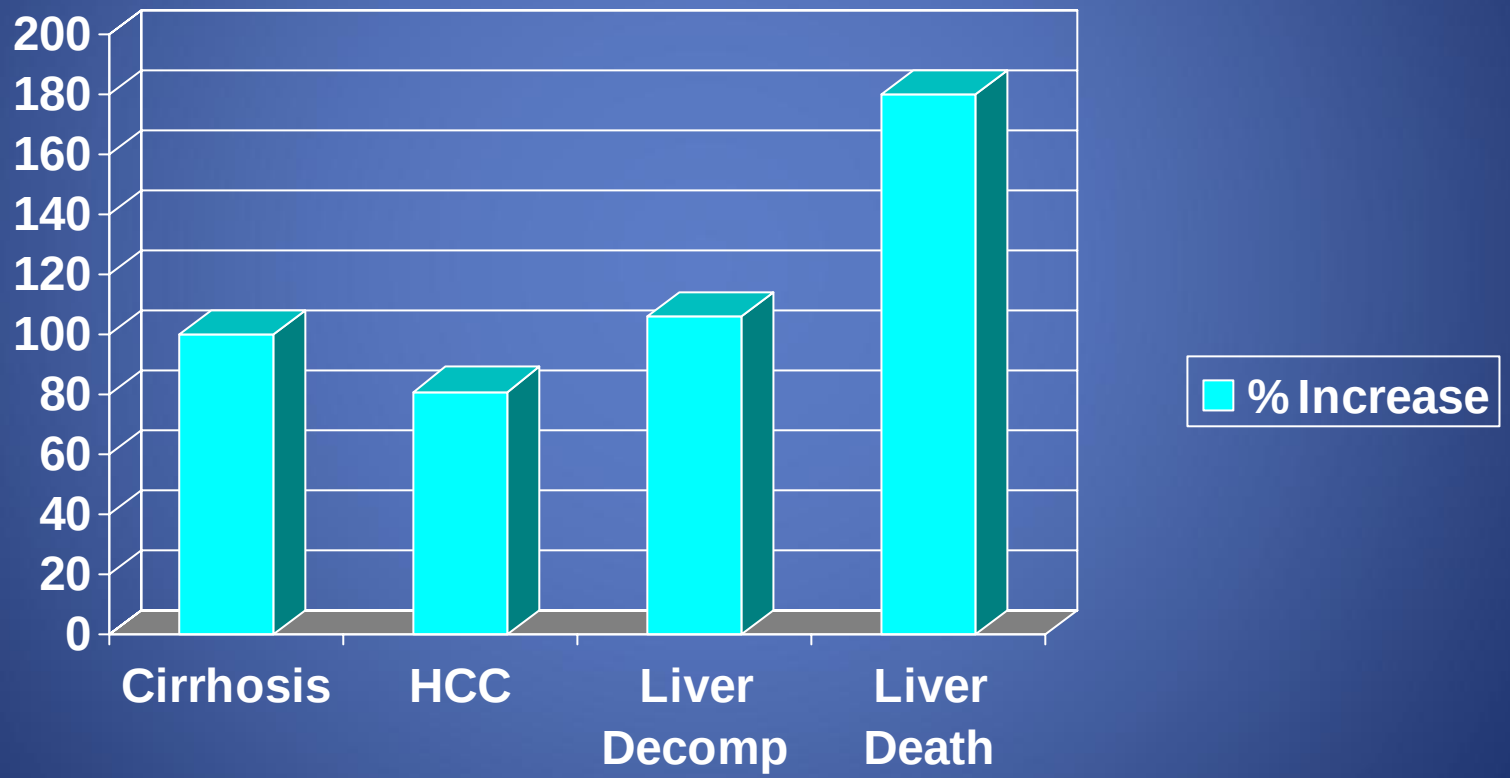
Projected HCV Mortality



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

Future Disease Burden: Estimated Increases from 2000-2020

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

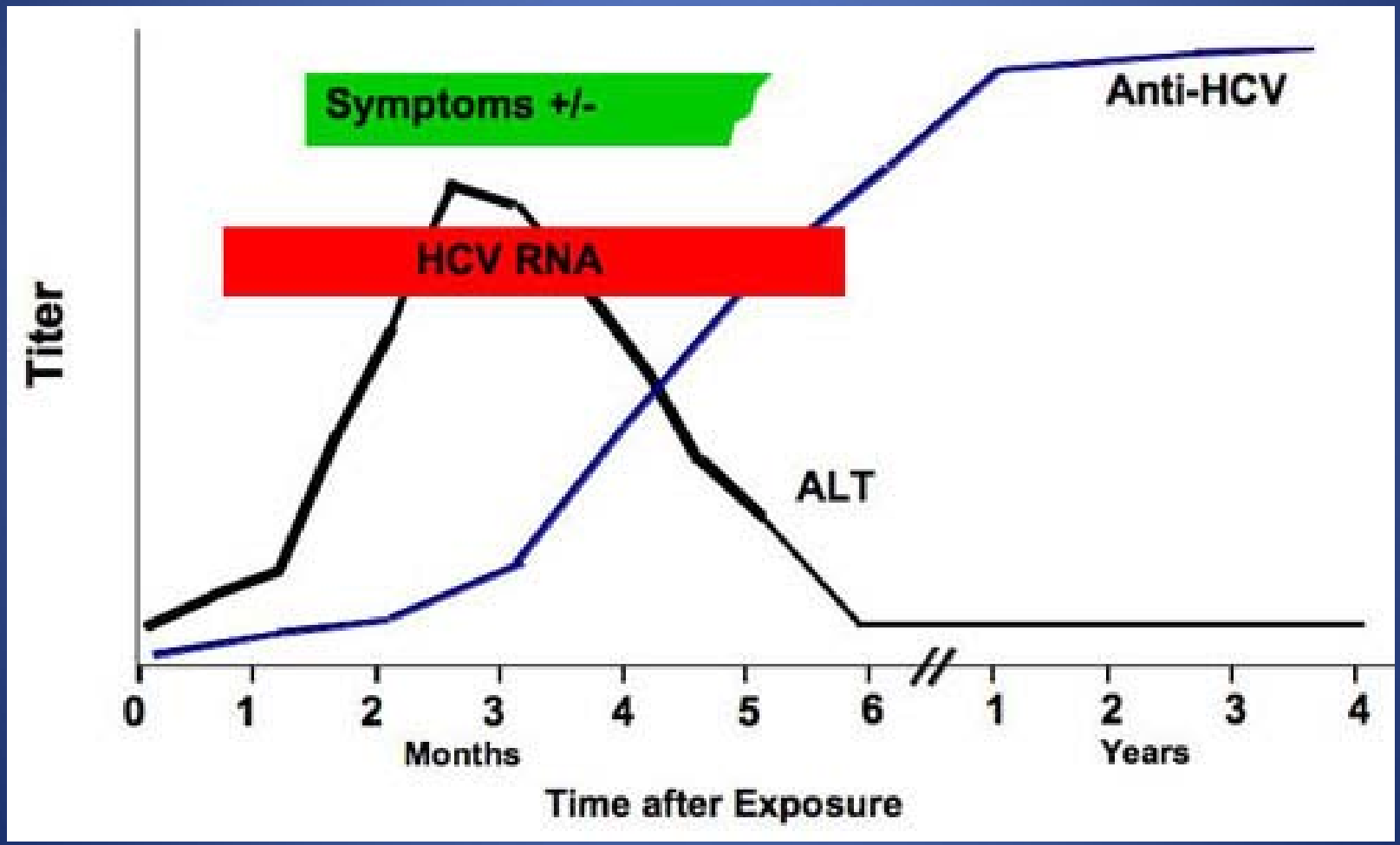


Acute HCV

Acute HCV

- **Incubation**: 2-26 weeks (usually 7-8)
- **Symptoms:** in < 30%, mild & last < 1month;
  - Usually: anorexia, arthralgia, myalgia, fatigue;
  - Rarely: jaundice, fever, or skin rash.
  - Extremely rare: FHF.
- **DX**: HCV-RNA (+) days to weeks after acquisition ; anti-HCV (+) in 6 weeks.
- **Spontaneous HCV clearance**: (within 12 weeks in adults)
  - Children < 2 y.o. & young women = 45%;
  - Others = 23%
  - HIV co-infection = 20%

Acute Hepatitis C



Acute HCV Treatment

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

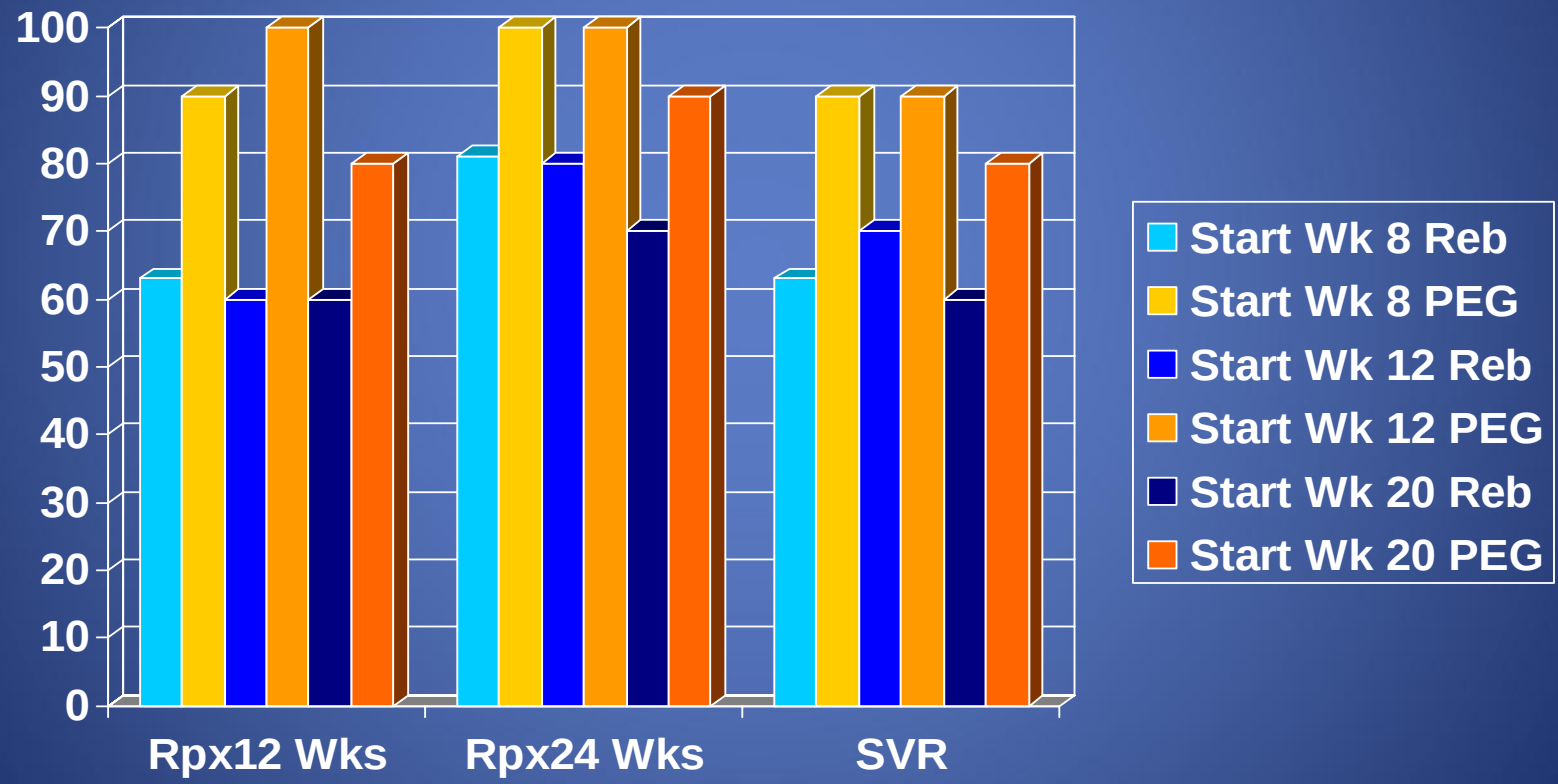
Treatment of Acute HCV @ 8,12, & 20 wks, Pegasys vs Rebetron x 12 wks

Kamal et al Abst # 37 AASLD, 2004

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

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

Kamal et al Abst # 37 AASLD, 2004

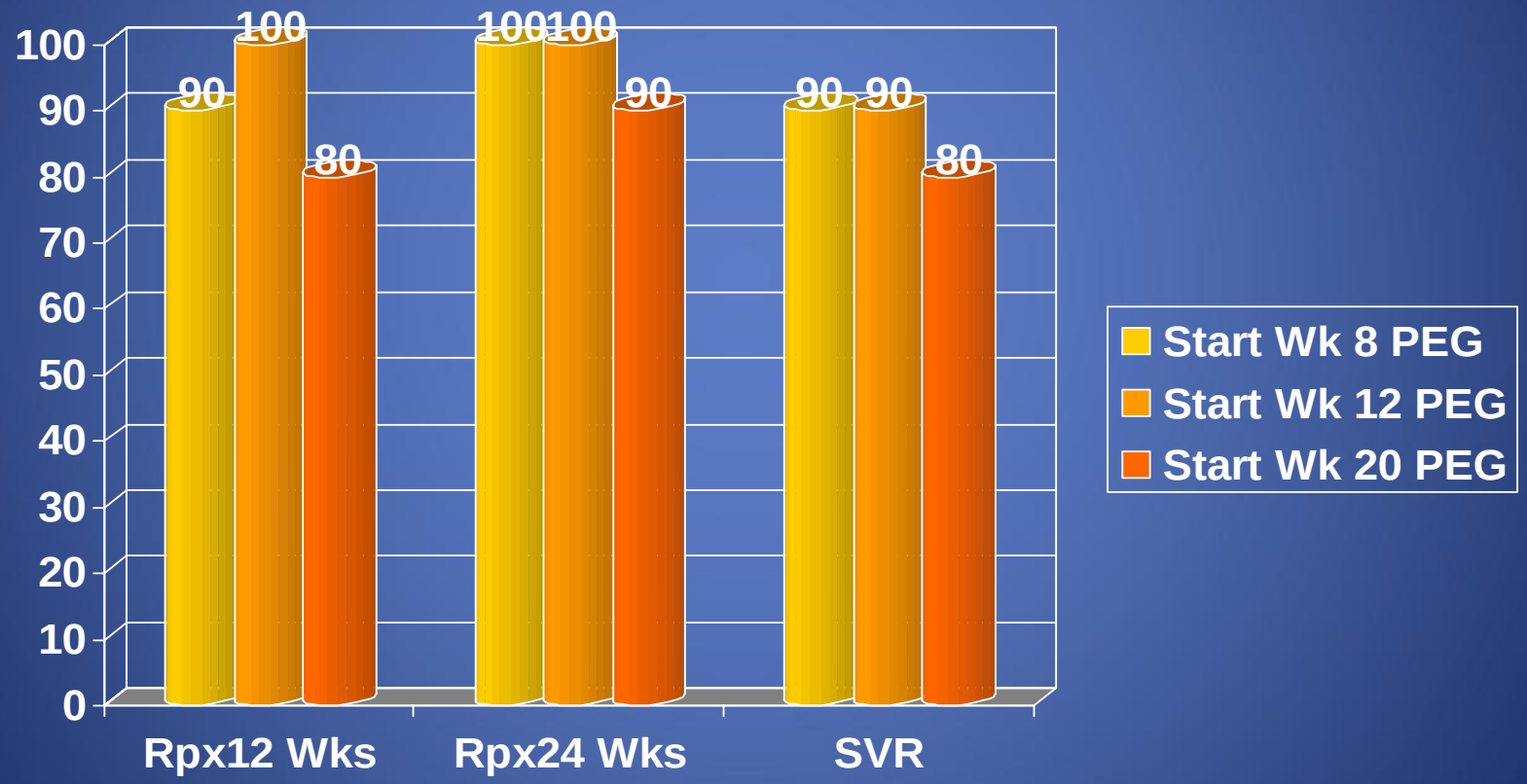


BLUE = Rebetron

ORANGE = Pegasys

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

Kamal et al Abst # 37 AASLD, 2004



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

Kamal et al Abst # 37 AASLD, 2004

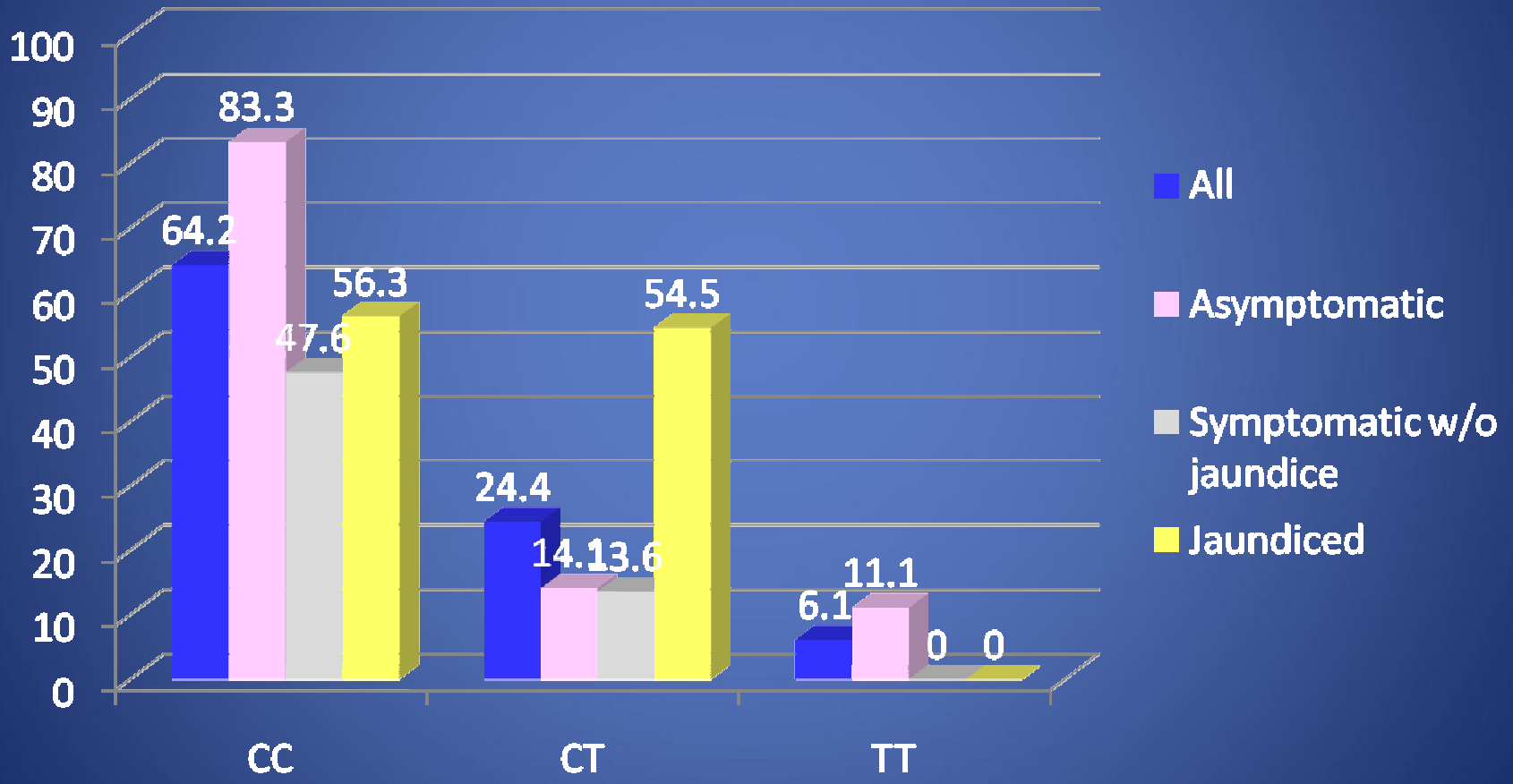
- Starting therapy at week 12 gave best results with SVR of 90%.
- Pegasys 180 mcg/week monotherapy x 12 weeks, was superior to Rebetron treatment x 12 weeks, in all groups.

Practical Approach to Treat Acute HCV

- Wait for 12 weeks from time of acquisition to see if spontaneous clearance occurs.
- Spontaneous clearance is more likely if patient is:
  - IL28B (rs12979860) CC regardless of symptoms or jaundice (65%), or
  - IL28B CT and jaundiced (55%).
- In absence of spontaneous clearance, treat with Peg-IFN + RBV (may improve outcome) for:
  - 3 months if HCV-RNA (-) at 4 weeks;
  - otherwise treat longer.

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

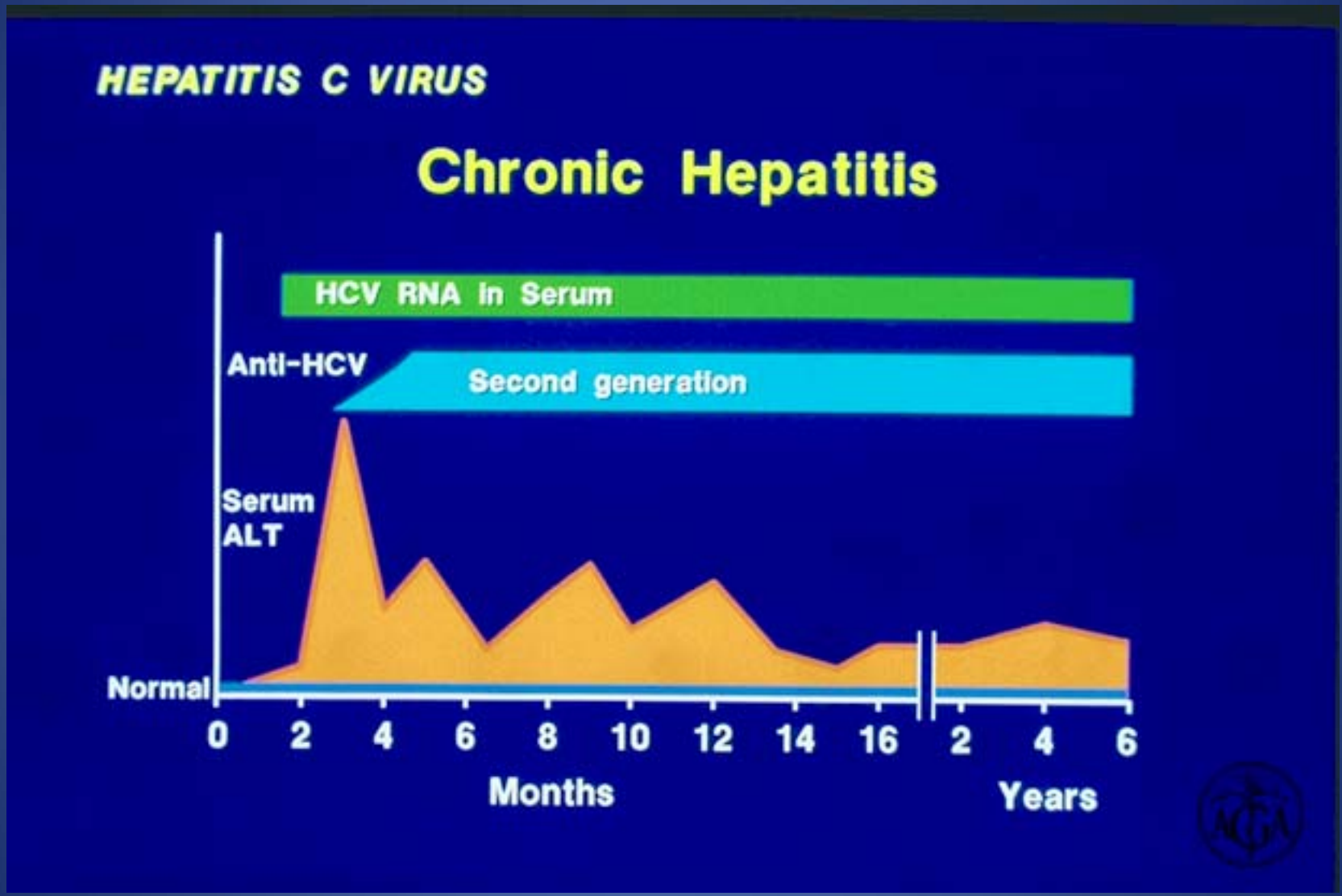
Gastroenterology 2020;139:1586-1592



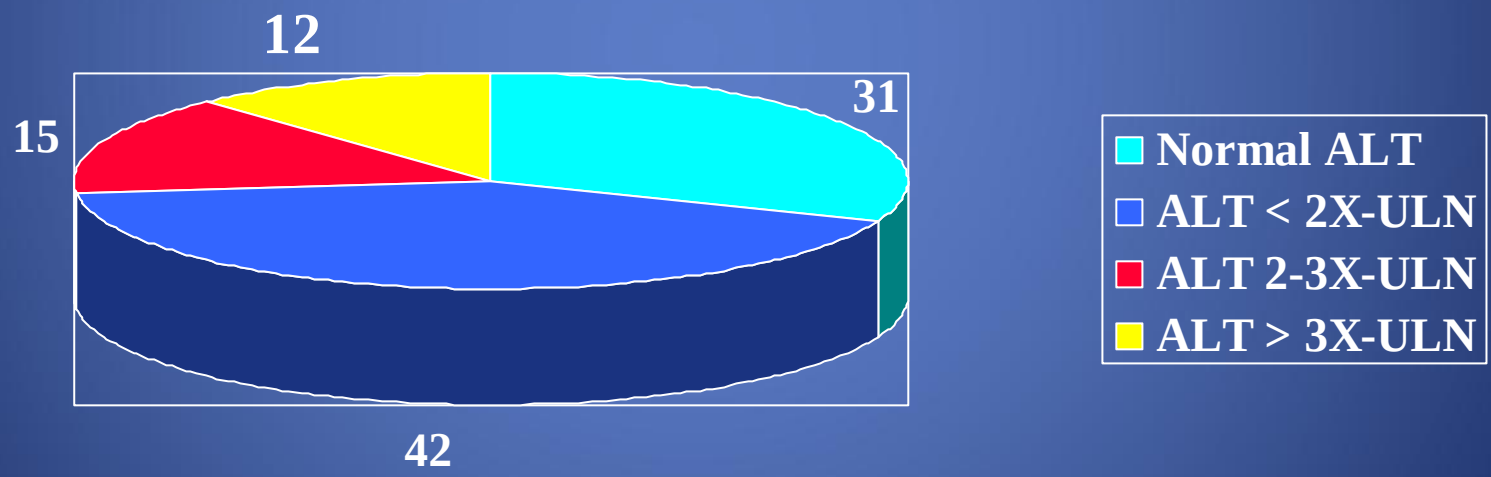
Chronic HCV

Chronic HCV

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

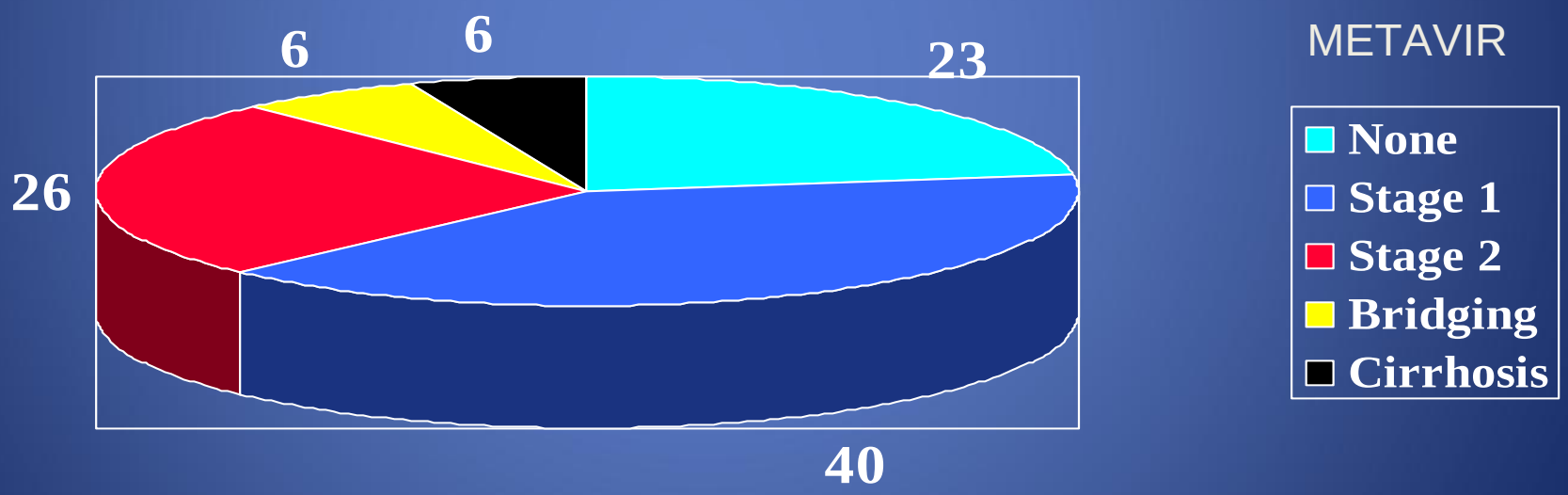

HEPATITIS C VIRUS
Chronic Hepatitis
HCV RNA in Serum
Anti-HCV
Second generation
Serum ALT
Normal
0 2 4 6 8 10 12 14 16 2 4 6
Months
Years

Pattern of ALT Elevation in Chronic HCV



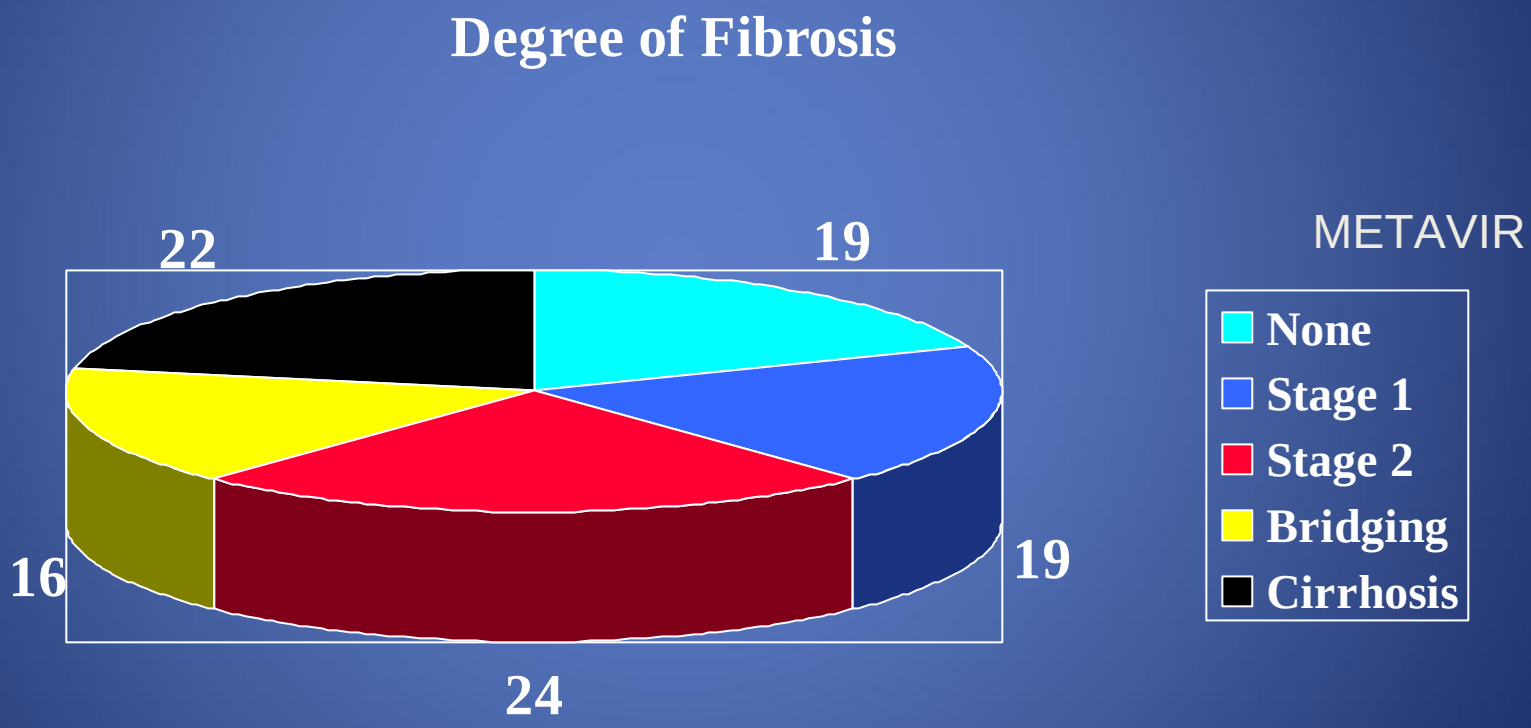
Degree of Fibrosis in Chronic HCV With Normal ALT

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



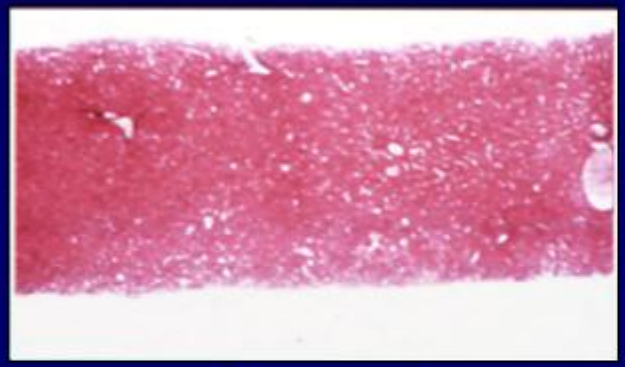
38% qualify for therapy (METAVIR >/= 2)

Degree of Fibrosis in Chronic HCV With Elevated ALT

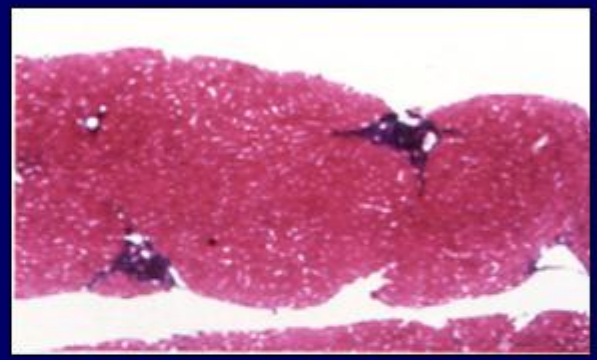


68% qualify for therapy (METAVIR >/= 2)

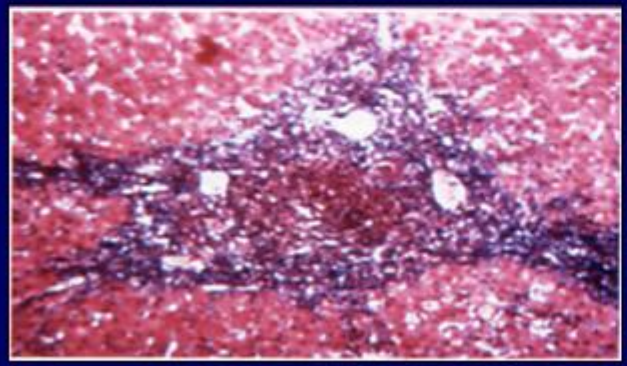
Histologic Progression of HCV on Biopsy



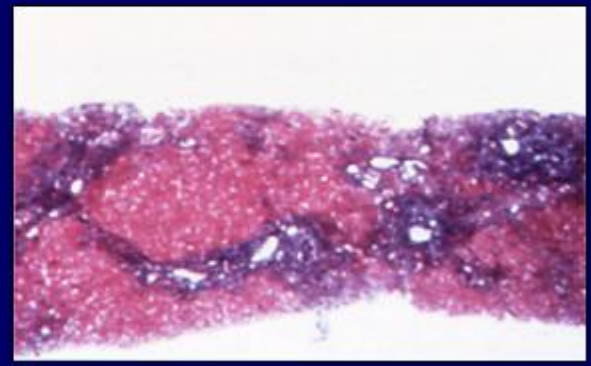
Normal



Mild Chronic Hepatitis



Moderate Chronic Hepatitis



Cirrhosis

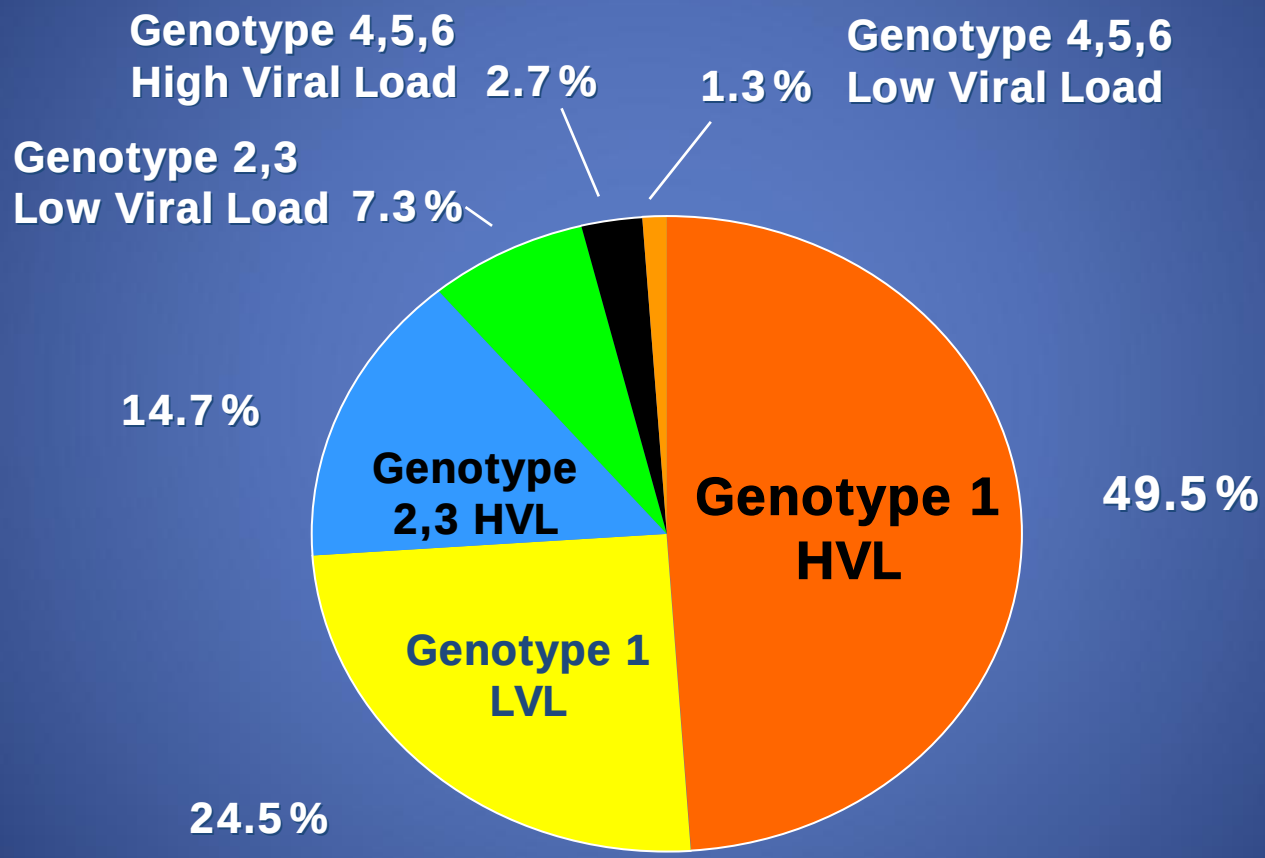
Slide Courtesy of Bennett, MD.

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

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

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

Genotype and Viral Load in US Patients



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

Hepatitis C

Diagnostic Tests

Diagnostic Tests for HCV

EIA (enzyme immunoessay)	Recommended screening test for HCV – Tests for antibodies against infection – 98.8–100% sensitivity
Qualitative HCV RNA	Recommended to confirm HCV diagnosis – May be more sensitive than quantitative test
Quantitative HCV RNA	Obtain viral load and confirm HCV diagnosis – May be less sensitive than qualitative test
Genotype	Used to determine HCV genotype after confirmation of diagnosis
Liver biopsy	May be used by specialist to determine extent of liver fibrosis and guide treatment decisions

Kuritzky L, et al. *Family Practice Recertification*. 2006;28(2):41-57.

Markers of Viral Hepatitis C:
Anti-HCV

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

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

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

Markers of HCV infection:
HCV-RNA Quantitation

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

Markers of Viral Hepatitis C: ***HCV-RNA Quantitation***

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

Quantitative HCV-RNA ASSAYS

	Conversion Factor IU/mL	Dynamic Range IU/mL	FDA Approved
Amplicor HCV Monitor	0.9 copies/mL	600-500,000	Yes
COBAS Amplicor HCV Monitor V2	2.7 copies/mL	600-500,000	Yes
Versant HCV RNA 3 Assay (bDNA)	5.2 copies/mL	615-7'700,000	Yes
LCX HCV RNA-Quantitative Assay	3.8 copies/mL	25-2'630,000	No
SuperQuant	3.4 copies/mL	30-1'470,000 **LLD 8 IU/mL**	No
COBAS Taqman HCV Test		43-69'000,000 **LLD 10 IU/mL**	Yes
Abbott RealTime		12-100'000,000	No

HCV in ESRD

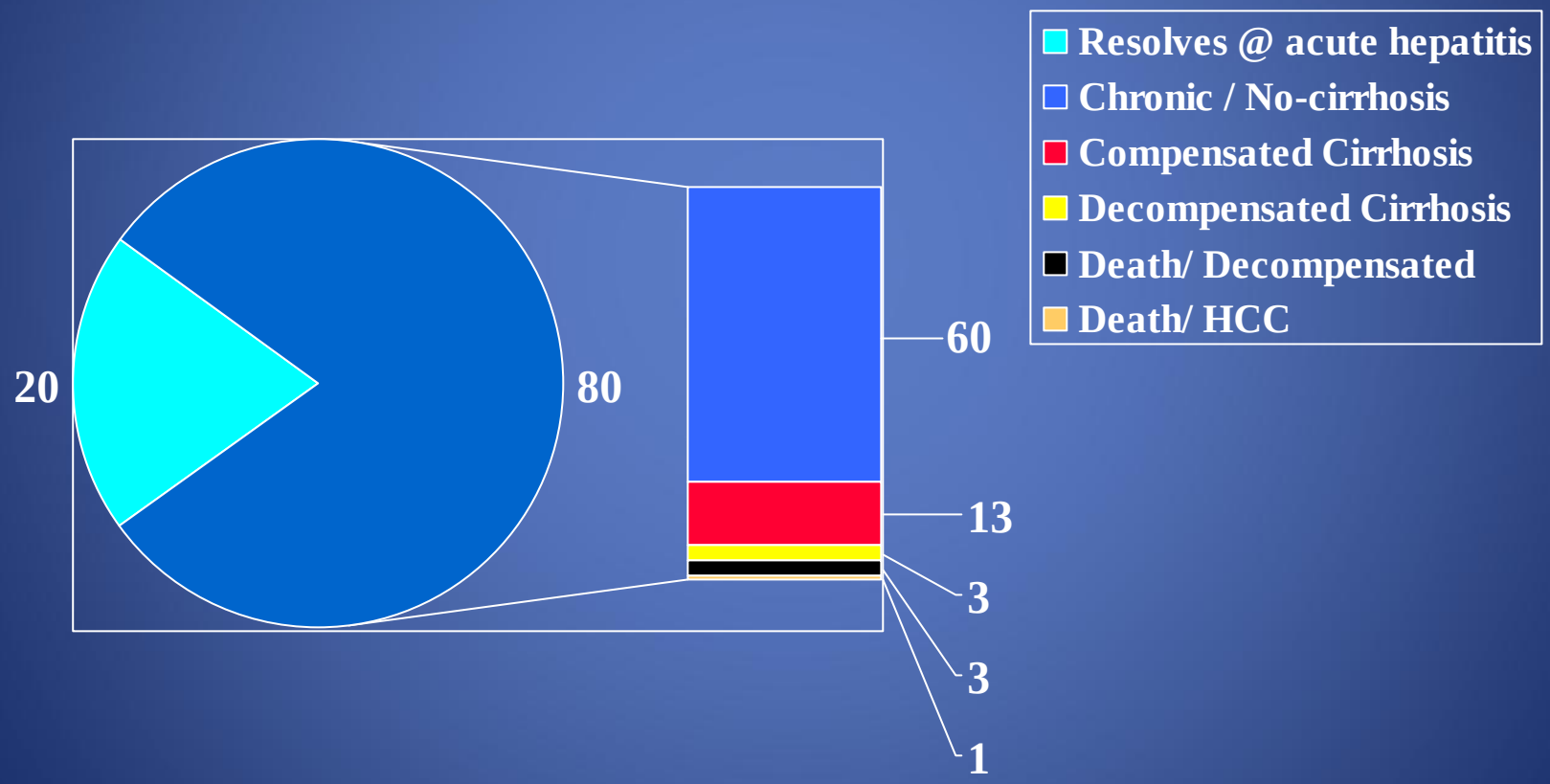
Problems with Diagnosis

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

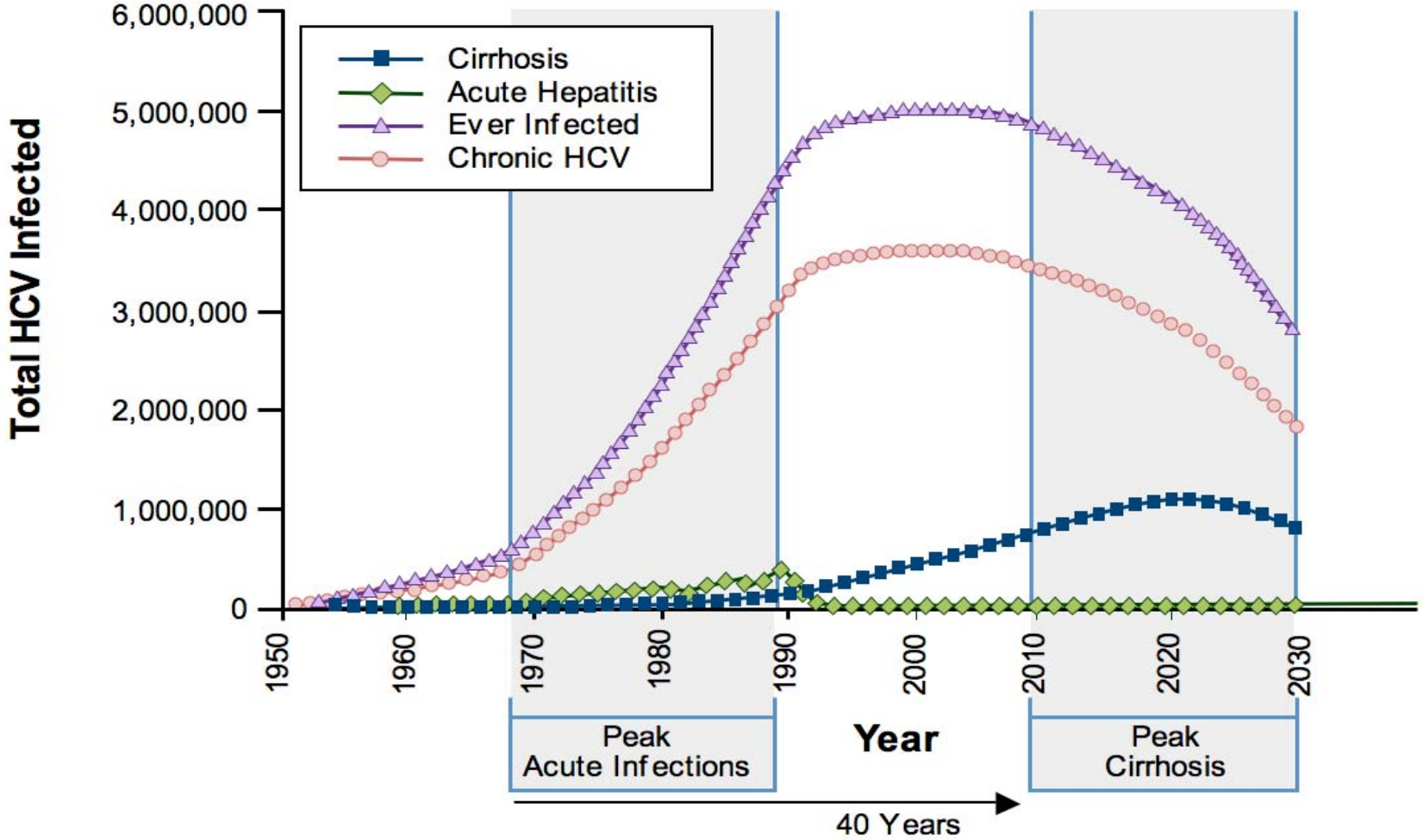
Immunocompetent Host

Natural History

Outcome of HCV
25-30 year Follow-up



Aging of HCV-Infected Persons in the US: Disease Progression



Davis G, et al. *Gastroenterology*. 2010;138:513-521.

Factors Associated With Disease Progression

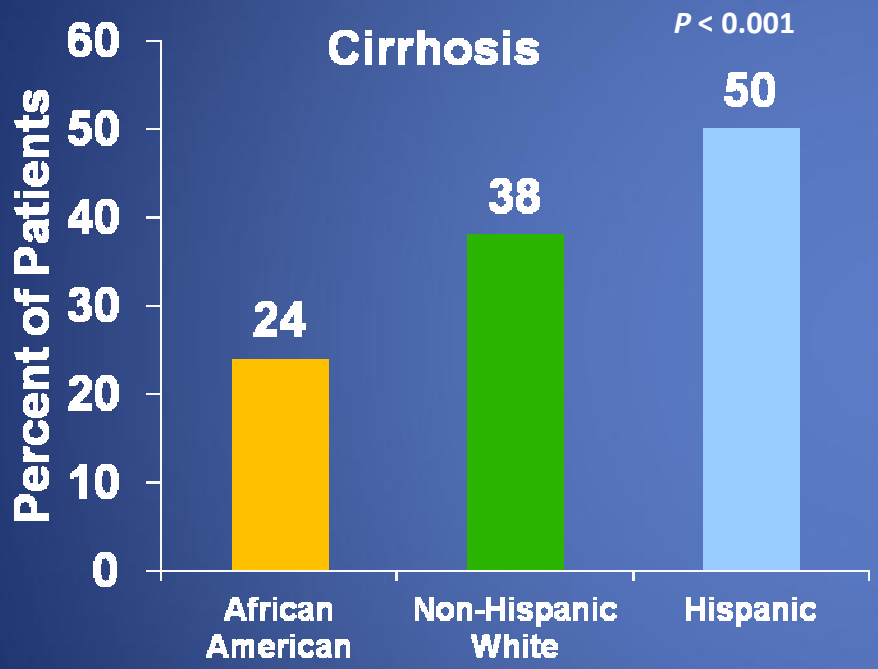
Associated with disease progression[1]	Not Associated with disease progression[1]
Alcohol consumption 30 g/day for males 20 g/day for females ~2 drinks/day	Alanine aminotransferase level
	Viral load
	Transmission mode
Disease acquisition at >40 years	Genotype
Male gender	
Coinfection: HIV or HBV[2]	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

Metabolic factors (steatosis, obesity, diabetes)

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

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

Ethnicity and Cirrhosis on Liver Biopsy



Clinical Factors Associated with Cirrhosis–Multivariate Analysis

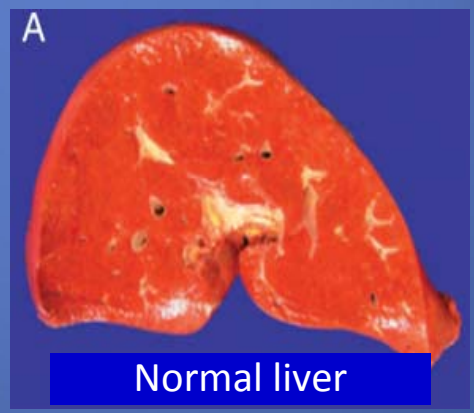
Factor	OR	95% CI	*P*-value
Hispanic*	2.4	1.27-4.42	0.007
Non-Hispanic White*	1.6	0.95-2.79	0.076
BMI	1.1	1.03-1.10	0.001
Duration of infection	1	1.00-1.06	0.062
Diabetes mellitus	1.8	1.00-3.13	0.05
Past alcohol	2	1.22-3.24	0.006

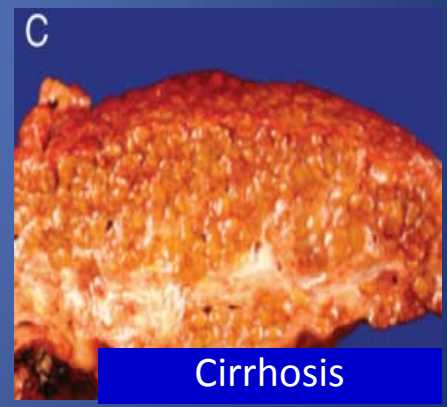
*Compared with African Americans as the reference group

Kallwitz ER, et al. *Clin Gastro Hepatol.* 2010; 8:72-78.

Factors Associated with Fibrosis in HCV

- Age at infection
- Duration of infection
- Metabolic factors (steatosis, obesity, diabetes)
- Compromised immune system
- Genetic factors
- HIV co-infection
- HBV co-infection
- Heavy alcohol use





Poynard T, et al. *Lancet.*1997;349:825-832.
Monto A, et al. *Hepatology.* 2002;36:729-736.
Marcolongo M, et al. *Hepatology*. 2009;50:1038-1044.
Cecil Medicine 23rd edition. Saunders Elsevier, Philadelphia, PA 2008.

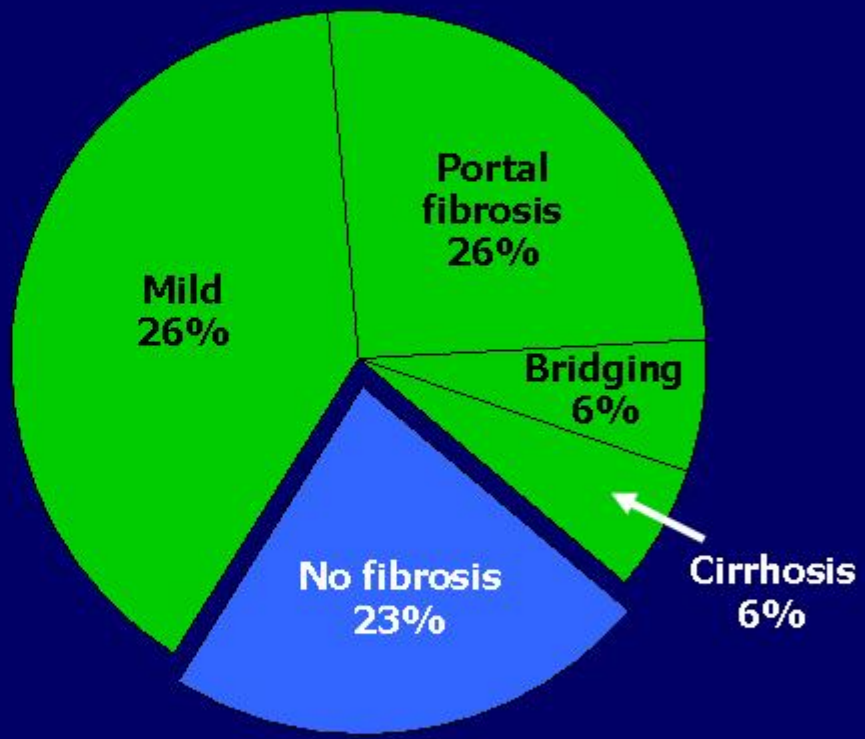
Histological Scoring of Fibrosis

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

Treat METAVIR =/> 2, or Ishak/Batts-Ludwig/Scheuer/Knodell =/> 3

HCV Disease Progression in Patients With Normal ALT

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

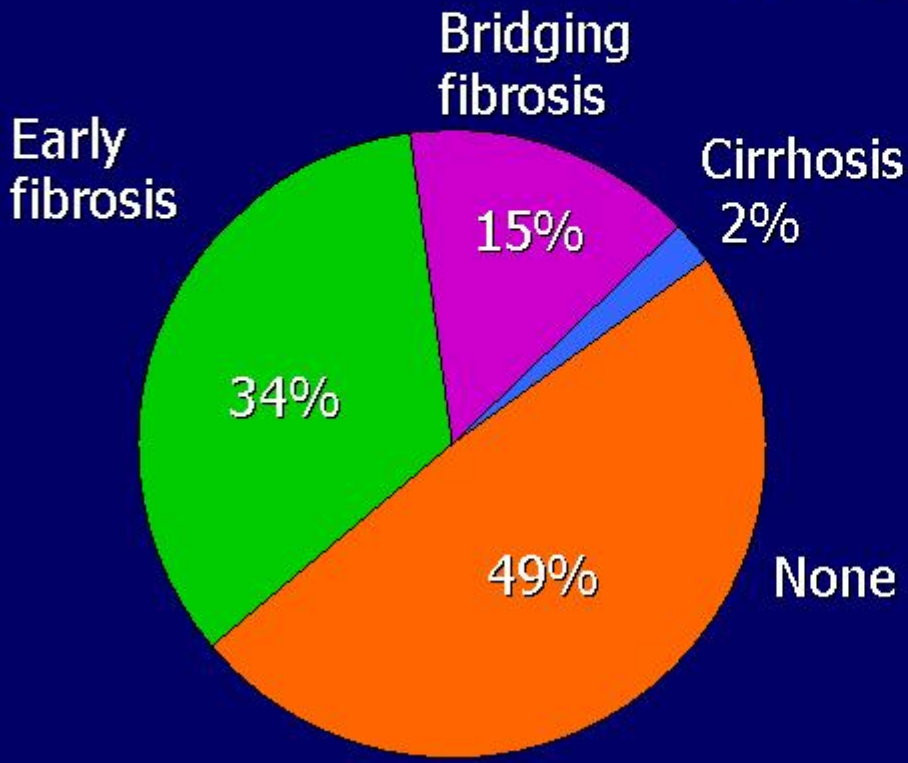


38% qualify for therapy (METAVIR >/= 2)

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

Liver Fibrosis After 17 Years of Infection in Nonalcoholic Young Women

N=363

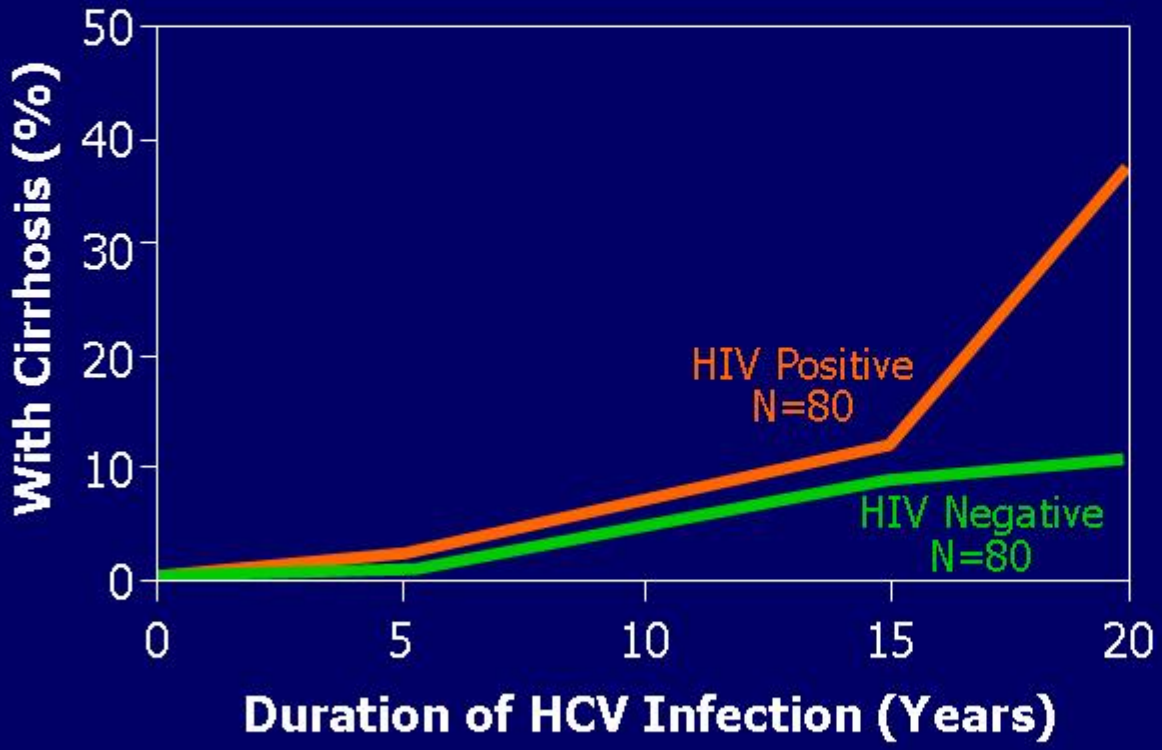


- Young women at infection
- Nonalcoholic
- Not immunosuppressed
- Not coinfected
  - HIV or HBV

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

Profile of Patients at Higher Risk for Disease Progression

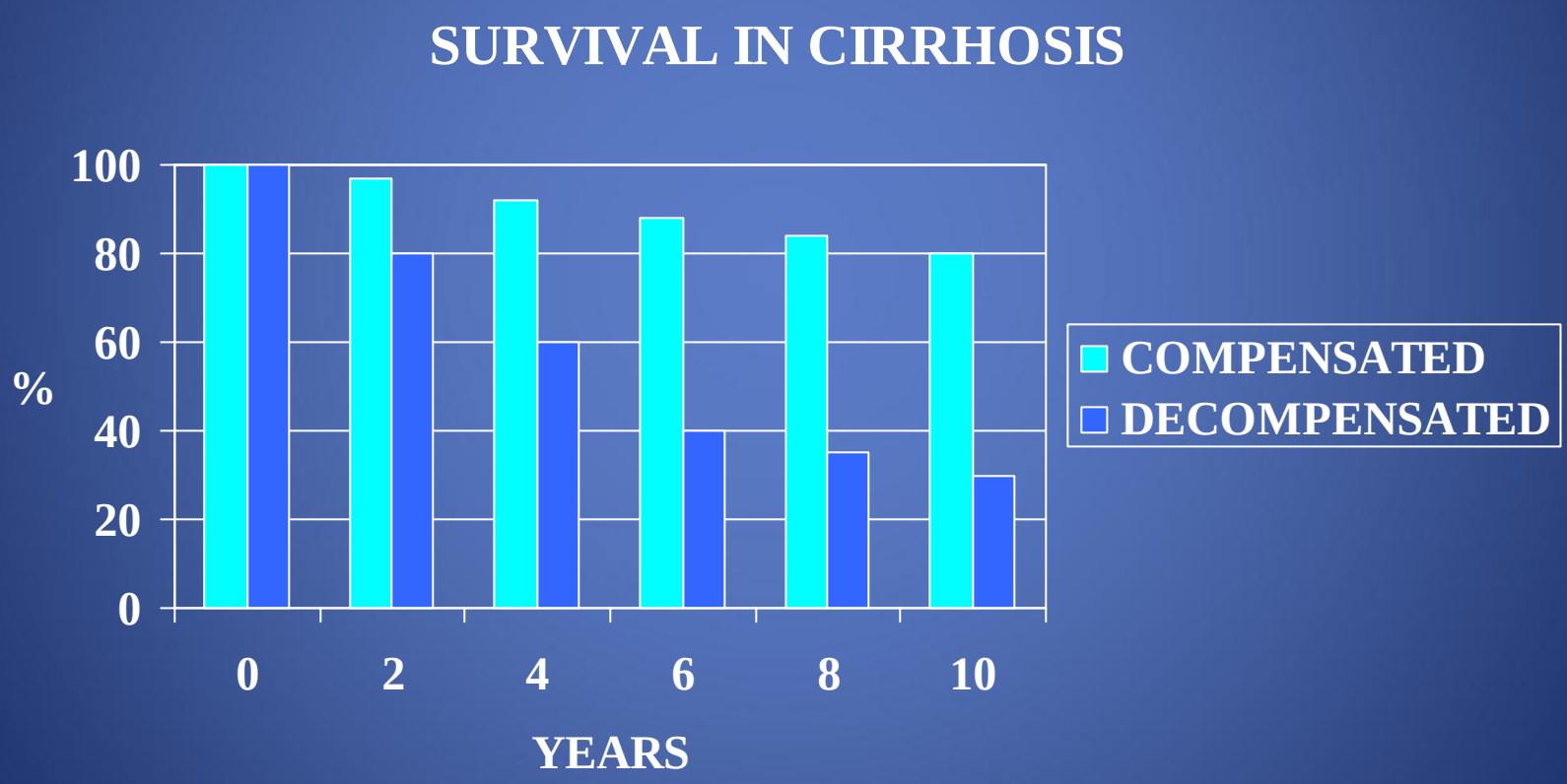
N=160



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

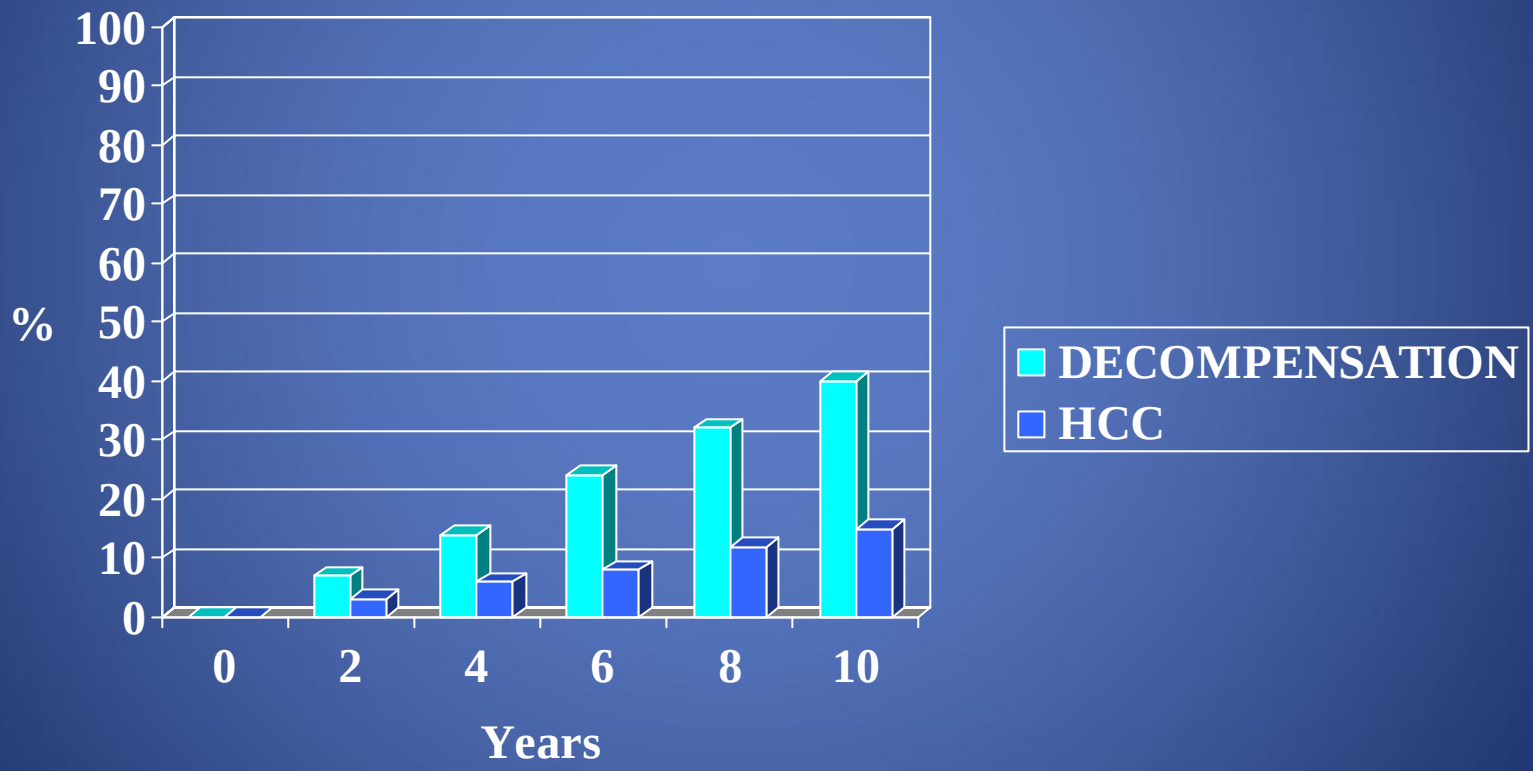
Adapted from Di Martino et al. *Hepatology.* 2001;34(6):1193-1199.

HCV Cirrhosis Survival

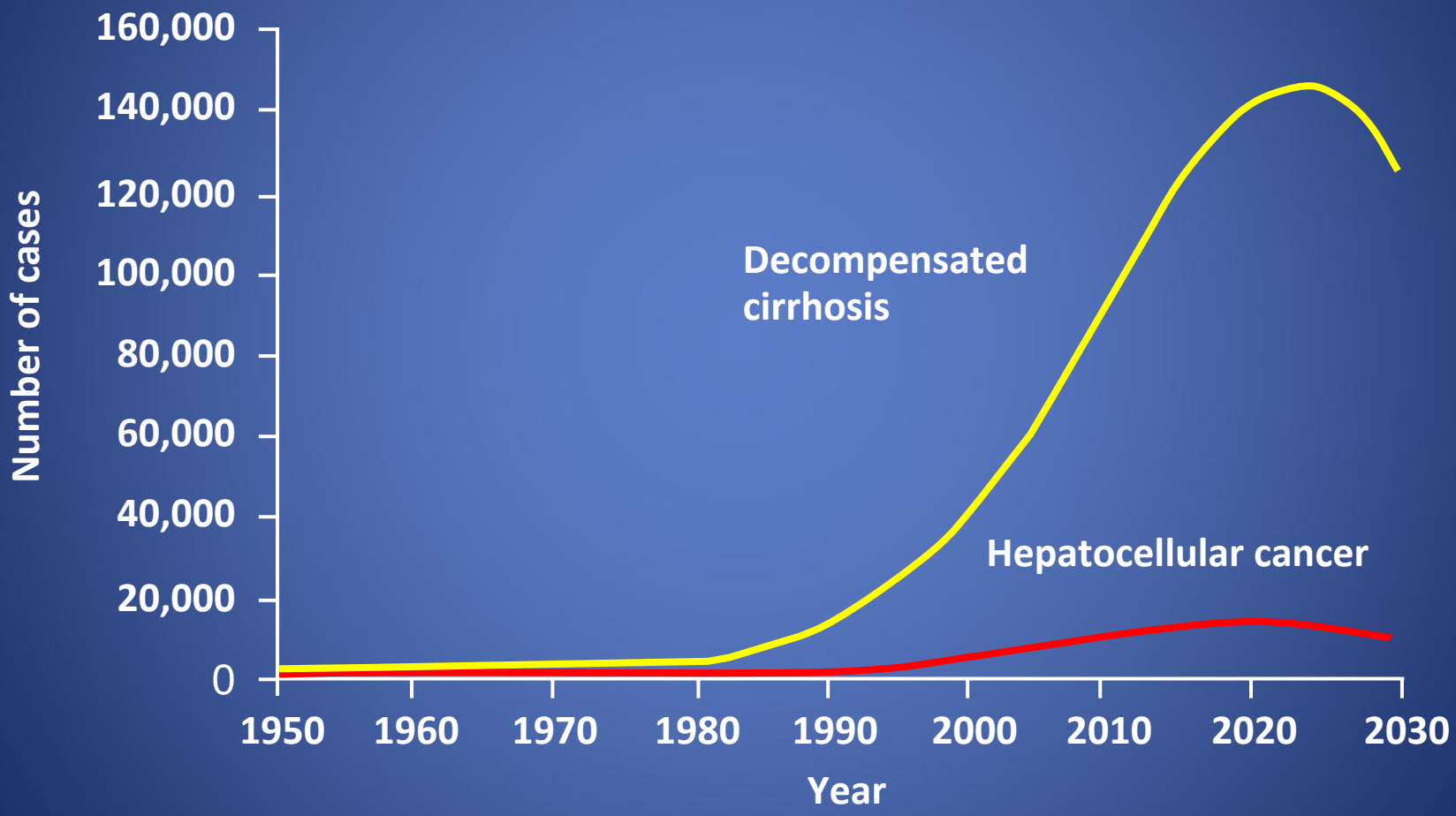


HCV Cirrhosis

Decompensation & Hepatocellular CA



Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV



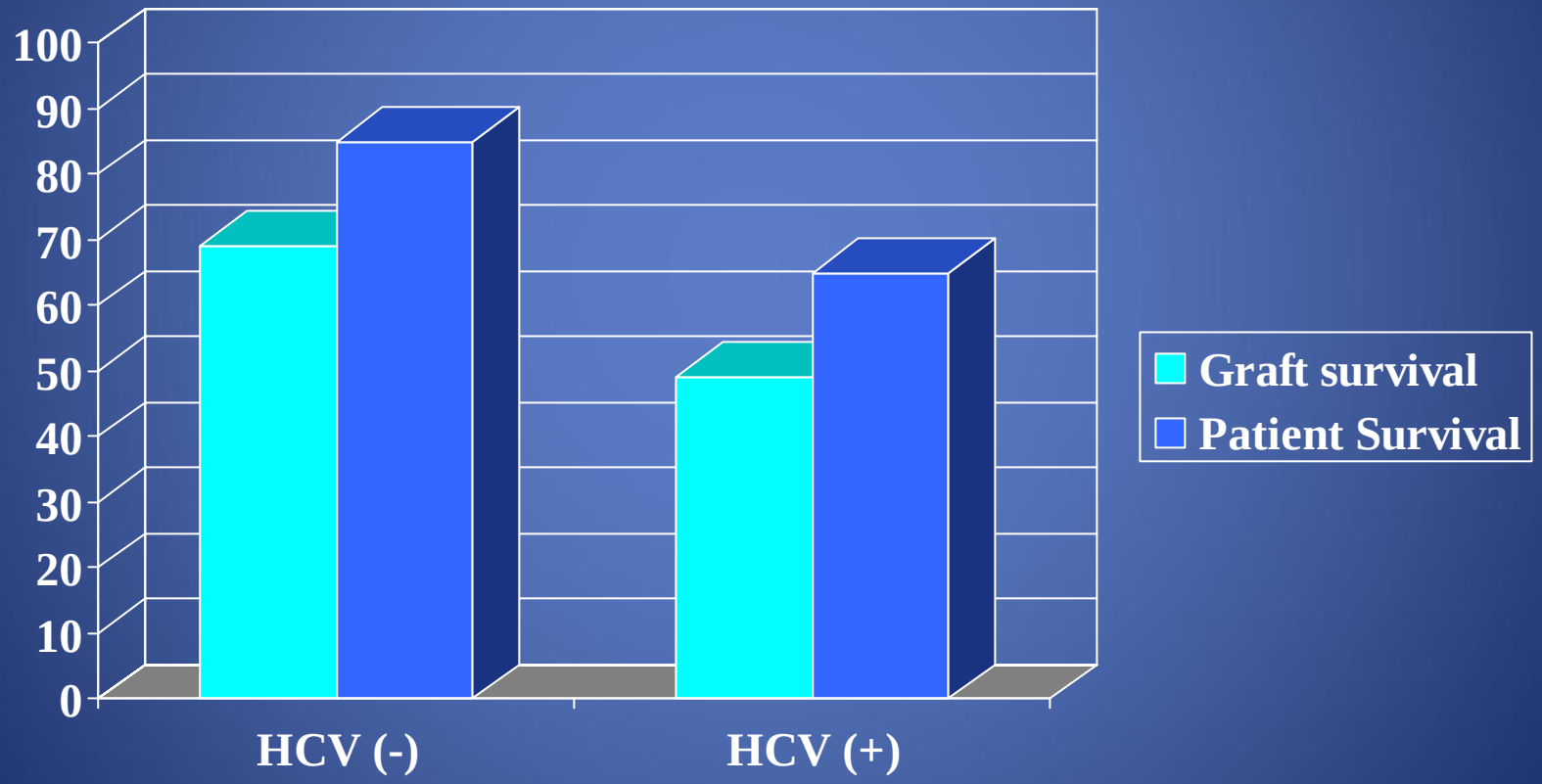
Davis GL, et al. *Gastroenterology*. 2010;138(2):513-521

Chronic HCV in ESRD
Natural History

Chronic HCV in ESRD
Natural History

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

HCV in Renal Tx
Natural History (10 years)



HCV in Renal Transplant

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

Immunocompromised Host

HCV Recurrence Post Liver Transplant

Natural History

Post-OLTx HCV Recurrence

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

Post-OLTx HCV Recurrence

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

Post-OLTx HCV Recurrence

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

Risk Factors Associated to Severity of Recurrence

- **Recipient related**
  - **Female gender:** **lower survival**
  - **Age:** **lower survival**
  - **Non-white race:** **lower survival, more severe**
  - **Severity of illness:** **lower survival**
  - *Hepatitis B co-infection:* *controversial*
- **Donor Related**
  - **Age > 65:** **lower survival, more severe**
  - *HLA-mismatch* *controversial*
  - *Living donor:* *controversial*
  - *Donor-liver fat:* *controversial*
  - *Genetic factors:* *controversial*

Risk Factors Associated to Severity of Recurrence

- **Virological**
  - **Pre-LTx viral load (>1M copies): more severe**
  - **Early post-LTx load: more severe**
  - **CMV infection (+ g-1a): more severe**
  - **HIV co-infection: more severe**
  - *Genotype 1b: controversial*
  - *Quasispecies: controversial*
- **Other**
  - **Time to recurrence: more severe**
  - **Steroid bolus, OKT3: more severe**
  - **Short time to recurrence: more severe**
  - *Cold ischemia time: controversial*

Post-OLTx HCV Recurrence
Factors That Affect Outcome

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

Acute Post-OLTx HCV Recurrence

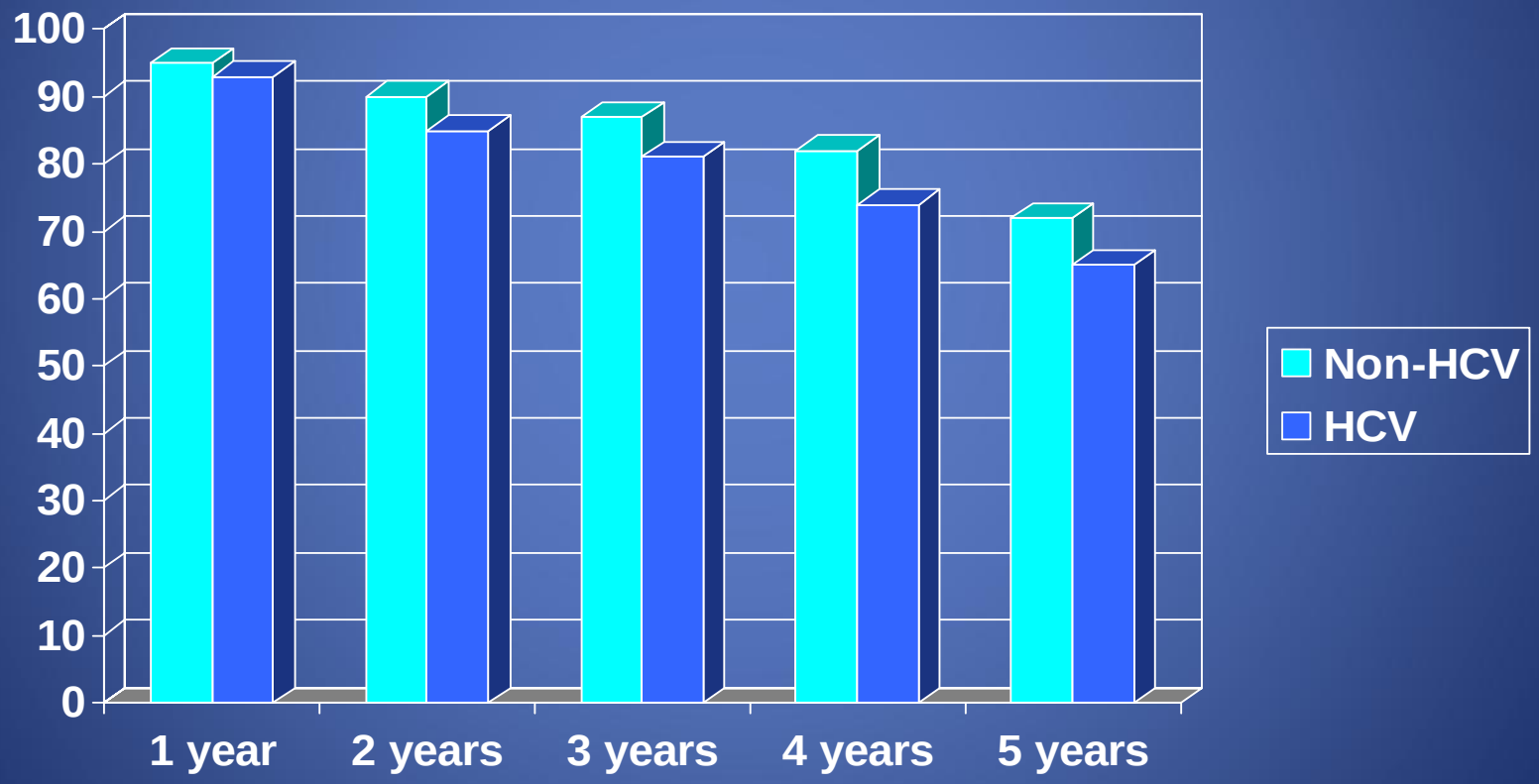
- Mild to moderate ALT/AST elevation
- **Total bilirubin < 6 mg/dL**
- Liver Bx in HCV recurrence: mononuclear lobular infiltrate, variable hepatocyte necrosis, and fatty infiltration;(Il-2, IFN-gamma, and TNF dominate).
- Liver Bx in Acute Cellular Rejection: endothelitis, severe bile duct damage, and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

Chronic HCV Recurrence

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

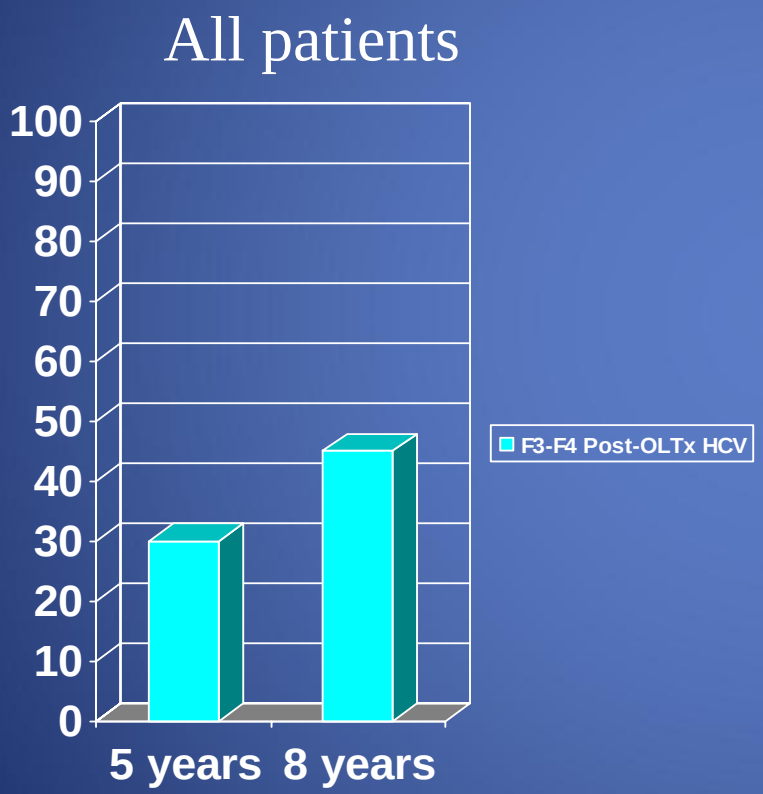
Survival After Liver Transplantation

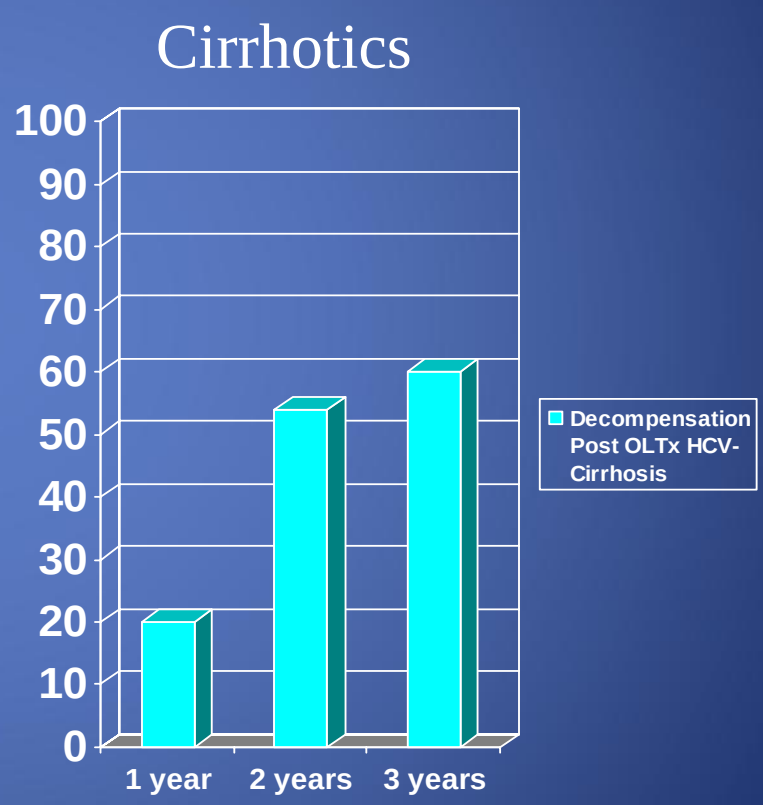
UNOS (1992-98) Gastroenterol 2002;122:889-896



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

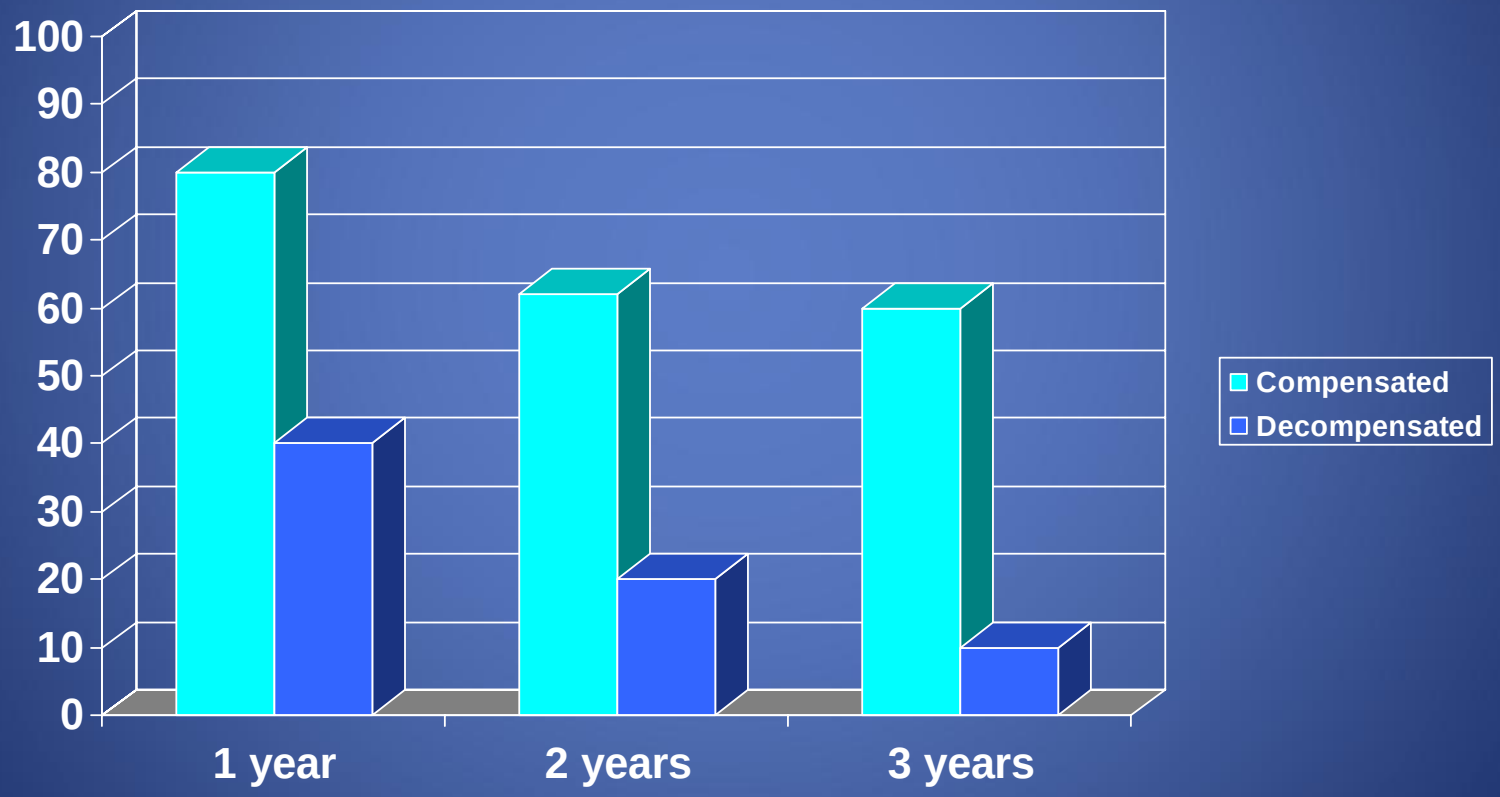
Berenguer et al J. Hepatol 2000;32:673-684 & Hepatology 2000;32:852-858





Survival in Post-OLTx HCV-Cirrhosis

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



Fibrosing Cholestatic Hepatitis C

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

Predictors of Poor Outcome in HCV Re-Transplantation

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

HCV + HIV Co-Infection

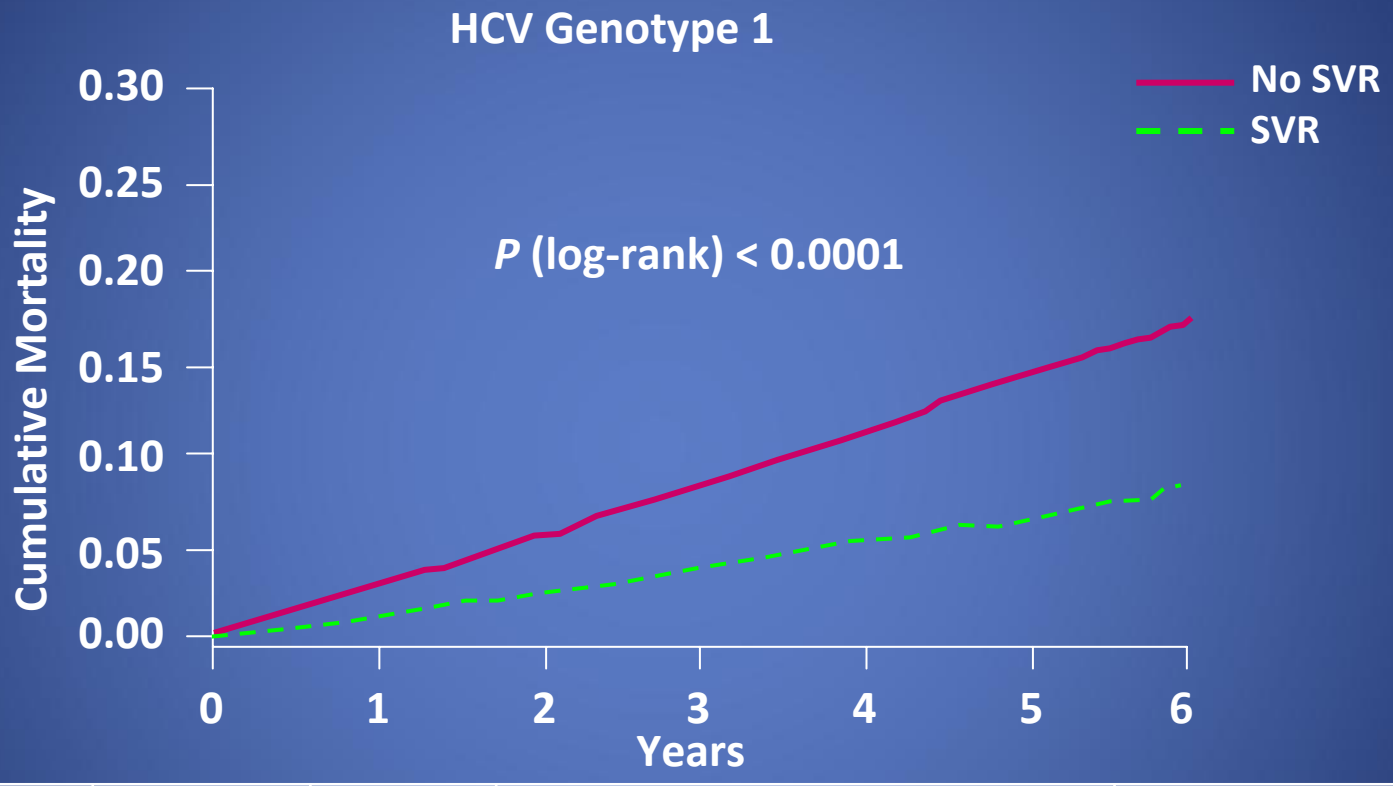
- 43% of HIV deaths are liver related.
- Relative risk of cirrhosis:
  - In antiretrovirals = 1.72
  - Without antiretrovirals = 2.49
- Relative risk of decompensation = 6
- Causes of increased fibrosis:
  - HIV related inflammatory response activates stellate cells.
  - The HIV envelope gp 120 protein signaling activates stellate cells
  - Depleted intestinal lymphocytes increase bacterial translocation.
  - Antiretroviral toxicity.
  - Metabolic syndrome due to ART and/or HIV
  - Excessive alcohol comsuption.

Chronic Hepatitis C

Treatment

SVR and Reduced Risk of All-Cause Mortality

US VA Study: Treatment with Pegylated Interferon/Ribavirin



Genotype	N	SVR	Hazard Ratio for Death with SVR	*P*-value
1	12,166	35%	0.70	< 0.0001
2	2904	72%	0.64	0.006
3	1794	62%	0.51	0.0002

Backus L, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

2009 AASLD Treatment Guidelines

Criteria for Treatment

- Age ≥ 18 years
- HCV RNA positive in serum and
- Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher)
- Compensated liver disease
- Acceptable hematological and biochemical indices
- Willing to be treated and adhere to treatment requirements
- No contraindications

Contraindications

- Major uncontrolled depressive illness
- Solid organ transplant (renal, heart, lung)
- Autoimmune hepatitis
- Untreated thyroid disease
- Pregnant or unwilling to comply with appropriate contraception
- Severe concurrent medical disease
- Age less than 2 years
- Known hypersensitivity to drugs used to treat HCV

Patients for Whom Therapy Should be Individualized

- Failed prior treatment
- Current users of illicit drugs or alcohol, but willing to participate in a substance abuse program
- Liver biopsy evidence of either no or mild fibrosis
- Acute hepatitis C
- Coinfection with HIV
- Under 18 years of age
- Chronic renal disease
- Decompensated cirrhosis
- Liver transplant recipients

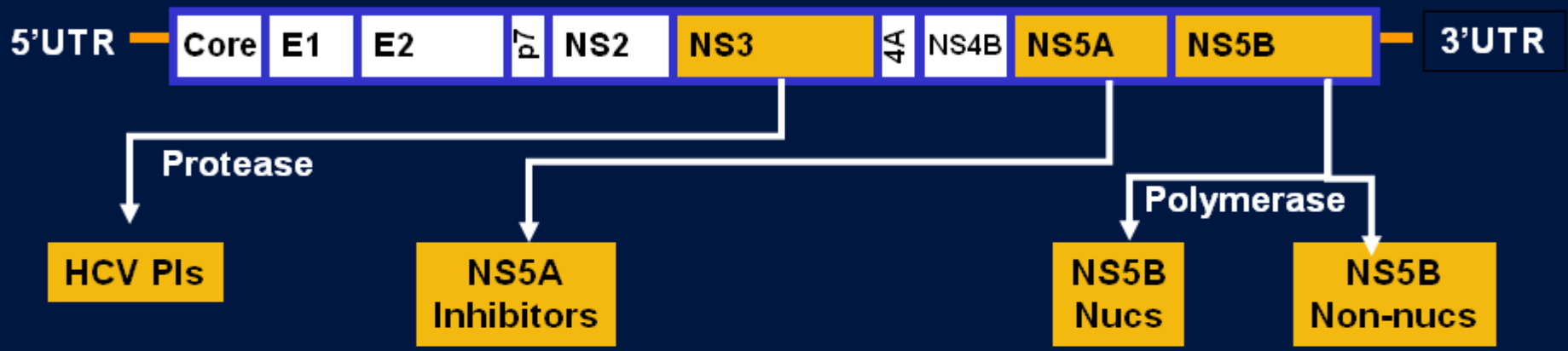
Ghany M, et al. *Hepatology*. 2009;49(4):1335-1374.

Histological Scoring of Fibrosis

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

Treat METAVIR =/> 2, or Ishak/Batts-Ludwig/Scheuer/Knodell =/> 3

Multiple Direct Acting Antivirals



Viral enzyme
Active site

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir
ABT-450
MK-5172
Sovaprevir
ACH-2684

Non-enzyme
Replication complex

Daclatasvir
Ledipasvir
ABT-267
GS-5816
ACH-3102
PPI-668
GSK2336805
Samatasvir
MK-8742

Viral enzyme
Active site

Sofosbuvir
VX-135
IDX20963
ACH-3422

Viral enzyme
Allosteric site

ABT-333
Deleobuvir
BMS-791325
PPI-383
GS-9669
TMC647055

Direct-Acting Antiviral Profiles

	Direct-Acting Antiviral					
	NS3[1]	NS3[2]	NS5A[1]	NS5A[2]	Non Nuc NS5B	Nuc NS5B
Resistance profile	🔴	🟡	🟡	🟡🟢	🔴	🟢
Pan-genotypic efficacy	🔴	🟡🟢	🟡	🟡🟢	🟡	🟢
Efficacy	🟡	🟢	🟢	🟢	🟡	🟢
Adverse events	🔴	🟢	🟡	🟢	🟡	🟡
Drug-drug interactions	🔴	🟡	🟡	🟡	🟡	🟢

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

[1] 1st generation.
[2] 2nd generation.

	Simeprivir (OLYSIO)	Sofosbuvir (SOVALDI)
Drug Group	NS3/4A Protease inhibitor	NS5B polymerase inhibitor Nucleotide analog
Genotypes affected	1a Q80K(-); 1b; (2, 4, 5, 6)	1,2,3,4 (5 & 6)
Dose	150 mg/d with food	400 mg a day
Associated drugs; dose reduction	Peg-IFN; standard RBV (as in RBV prescribing info)	Peg-IFN; standard RBV 1200/1000 by weight; 600 dose reduction
Regimens approved by FDA (see effectiveness in tables; some non-approved regimens may be superior)	G1 Naïve or Relapser: S+P+R x 12 w + PR x 12 w G1 NR, Part R & Null: S+P+R x 12w + PR x 36 w	**G1 & 4: S+P+R 12 w**, G1: S+R x 24 w (IFN Ineligible) **G1 & 4 pre-OLTx: S+R x 48 w** **G2: S+R x 12 w** **G3: S+R x 24 w *(Cirrhosis: S+P+R x 12 is superior but no FDA approved).*** ***HIV: S+P+R x 12 w (all G) is best regimen but no FDA approved.*** HIV G1 & 3: S+R x 24 HIV G2: S+R x 12 w
Renal impairment	No dose change. Not studied in GFR < 30	No if GFR < 30
Stop Rules and Precautions	STOP: if >/= 25 @ 4, 12, or 24 w Precaution: East Asian ancestry.	None
Liver Impairment	No in C-P B or C or decompensation.	MELD</= 14; Compensated C-P A, B, or C. No in decompensation.
Pregnancy	2 anti-conceptives during & until 6 months after.	2 anti-conceptives during &until 6 months after
Ages	19-73	19-75

	Simeprivir	Sofosbuvir
DAA increases drug levels **but can be used with caution and monitoring**	**Antiarrhytmics:** Digoxin, Amiodarone, Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine **Ca Channel blockers:** Amlodipine, Diltiazem , Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil **Statins:** Rosuvastatin max 10 mg, Atorvastatin max 40 mg, Simvastatin lowest possible dose, Pitavastatin lowest possible dose, Pravastatin lowest possible dose, Lovastatin lowest possible dose **Phosphodiesterase 5 inh:** Sildenafil , Tadalafil , Vardenafil all need dose adjustment when treating pulmonary hypertension **Sedatives:** Oral Midazolam and Triazolam	
DAA increases drug levels and **SHOULD NOT BE USED**	Erythromycin, Cisapride	
Drug **increases DAA** level and **SHOULD NOT BE USED**	**Milk Thistle** **Antibiotics:** Erythromycin, Clarithromycin, Telithromycin, **Antifungals (systemic):** Itraconazole, Ketoconazole, Posaconazole, Fluconazole , Voriconazole, **Anti-retrovirals:** Cobicistat-containing product (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate), Darunavir, Ritonavir	
Drug **decreases DAA** level and **SHOULD NOT BE USED**	**St John's wort** **Anticonvulsants:** Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin **Antibiotics:** Rifampin, Rifabutin, Rifapentine **Corticosteroids:** Dexamethasone. **Antiretrovirals:** Efavirenz	**St John's wort** **Anticonvulsants:** Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin **Antibiotics:** Rifampin, Rifabutin, Rifapentine **Antiretrovirals:** tipranavir//ritonavir
Drug has **variable effect in DAA** and **SHOULD NOT BE USED**	**Antiretrovirals:** Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir, Delavirdine, Etravirine, Nevirapine	
DAA has modest effect that requires monitoring	Cyclosporine, Tacrolimus, Sirolimus, Warfarin	

Treatment of HCV
AASLD/IDSA Guidelines

Who should be Tested for HCV?

- **HCV testing is recommended at least once for persons born between 1945 and 1965. Rating:** Class I, Level B
- **Other persons should be screened for risk factors for HCV infection, and one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection. Rating:** Class I, Level B
  - ***Risk behaviors***
    - **Injection-drug use (current or ever, including those who injected once)**
    - **Intranasal illicit drug use**
  - ***Risk exposures***
    - **Long-term hemodialysis (ever)**
    - **Getting a tattoo in an unregulated setting**
    - **Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood**
    - **Children born to HCV-infected women**
    - **Prior recipients of transfusions or organ transplants, including persons who:**
      - **were notified that they received blood from a donor who later tested positive for HCV infection**
      - **received a transfusion of blood or blood components, or underwent an organ transplant before July 1992**
      - **received clotting factor concentrates produced before 1987**
      - **were ever incarcerated**
  - ***Other medical conditions***
    - **HIV infection**
    - **Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels**

Recommendations for patients with HCV

- Avoid sharing toothbrushes and dental or shaving equipment, and cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Stop using illicit drugs and enter substance abuse treatment. If continue to inject drugs should avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment; use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.
- Do not donate blood and discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Interferon Ineligible
Definition

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression
- Clinical features consistent with depression
- A baseline neutrophil count below 1500/µL
- A baseline platelet count below 90,000/µL
- A baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

Grading of the Evidence

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A	Data derived from multiple randomized clinical trials or meta-analyses
Level B	Data derived from a single randomized trial, or nonrandomized studies
Level C	Consensus opinion of experts, case studies, or standard of care

Treatment Naïve or Relapsers after Peg-IFN/RBV

Genotype	Recommended	Alternative	NOT Recommended
1	-IFN eligible -SOF 400 + PEG/RBV 1-1.2g x 12 weeks -IFN ineligible: -SOF 400 + SMV* 150 ± RBV 1-1.2g x 12 weeks	-IFN eligible: -SMV* 150 x 12 weeks + PEG/RBV 1-1.2g x 24 weeks* -IFN ineligible: -SOF 400 + RBV 1-1.2g x 24 weeks	-TVR + PEG/RBV x 24 or 48 weeks (RGT) -BOC + PEG/RBV x 28 or 48 weeks (RGT) -PEG/RBV x 48 weeks -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG or SMV
2	-SOF 400 + RBV 1-1.2g x 12 weeks	-None	-PEG/RBV x 24 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR, BOC, or SMV
3	-SOF 400 + RBV 1-1.2g x 24 weeks	-SOF 400 + PEG/RBV 1-1.2g x 12 weeks (compensated F3/F4 cirrhosis)	-PEG/RBV x 24-48 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR, BOC, or SMV
4	-IFN eligible: -SOF 400 + PEG/RBV 1-1.2g x 12 weeks -IFN ineligible: -SOF 400 + RBV 1-1.2g x 24 weeks	-SMV* 150 x 12 weeks + PEG/RBV 1-1.2g x 24-48 weeks	--PEG/RBV x 48 weeks -Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR or BOC
5 or 6	-SOF 400 + PEG/RBV 1-1.2g x 12 weeks	-PEG/RBV 1-1.2g x 48 weeks	Monotherapy with PEG, RBV, or a DAA -Any regimen with TVR or BOC

* No in Q80K polymorphism (add RBV if with SOF)

Previous Peg-IFN/RBV Failures (Non-responders or Null-Responders)

Genotype	Recommended	Alternative	NOT Recommended
1	-SOF 400 + SMV* 150 ± RBV 1-1.2g x 12 weeks	-SOF x 12 weeks + PEG/RBV 1-1.2g x 12 weeks -SMV* x 12 weeks + PEG/RBV 1-1.2g x 24 weeks**	-PEG/RBV ± telaprevir or boceprevir -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG or SMV
2	-SOF 400 + RBV 1-1.2g x 12 weeks	-SOF 400 + PEG/RBV 1-1.2g x 12 weeks	-PEG/RBV ± telaprevir or boceprevir -Monotherapy with PEG, RBV, or a direct-acting antiviral agent -Do not treat decompensated cirrhosis with PEG
3	-SOF 400 + RBV 1-1.2g x 24 weeks	-SOF 400 + PEG/RBV 1-1.2g x 12 weeks	-PEG/RBV ± any current protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG
4	-SOF 400 x 12 weeks + PEG/RBV 1-1.2g x 12 weeks -SOF 400 + RBV 1-1.2g x 24 weeks	-SMV* 150 x 12 weeks + PEG/RBV 1-1.2g x 24-48 weeks	-PEG/RBV ± any current HCV protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG
5 or 6	-SOF 400 x 12 weeks + PEG/RBV 1-1.2g x 12 weeks	-SOF 400 + RBV 1-1.2g x 24 weeks	-PEG/RBV ± any current HCV protease inhibitor -Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG

* No in Q80K polymorphism (add RBV if with SOF)

Previous Failure with Peg-IFN/RBV + Telaprevir or Boceprevir

Genotype	Recommended	Alternative	NOT Recommended
1a	-SOF 400 x 12 weeks + PEG/RBV 1-1.2g x 24 weeks	-SOF 400 + RBV 1-1.2g x 24 weeks	-PEG/RBV ± telaprevir or boceprevir or SMV
1b	-SOF 400 x 12 weeks + PEG/RBV 1-1.2g x 12-24 weeks	-SOF 400 + RBV 1-1.2g x 24 weeks	-Monotherapy with PEG, RBV, or a DAA -Do not treat decompensated cirrhosis with PEG or SMV

A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure is not provided due to potential risk of preexistent resistance to protease inhibitor (PI) treatment.

NOTE: In “desperate, rescue use” of SIM, add RBV to minimize possible PI resistance effect).

Wait for Ledipasvir that is NS5A inhibitor and will not be affected by PI resistance.

Treatment in Cirrhosis

- **Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma**: should receive the same treatment as recommended for patients without cirrhosis. **Rating: Class I, Level A**
- ***Patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C):*** *should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).* **Rating: Class I, Level C**
- ***Patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C)*** *who may or may not be candidates for liver transplantation,* ***including those with hepatocellular carcinoma****. This regimen should be used only by highly experienced HCV providers*
  - **Daily sofosbuvir (400 mg) plus weight-based RBV** (with consideration of the patient's creatinine clearance and hemoglobin level) **for up to 48 weeks. Rating: Class IIb, Level B**
- *The following regimens are* ***NOT recommended for patients with decompensated cirrhosis*** *(moderate or severe hepatic impairment; CTP class B or C):*
  - Any IFN-based therapy. **Rating: Class III, Level A**
  - Monotherapy with PEG, RBV, or a DAA. Rating: **Class III, Level A**
  - Telaprevir-, boceprevir-, or simeprevir-based regimens. **Rating: Class III, Level A**

Child-Pugh Classification

"Decompensated Cirrhosis" = Child-Pugh B or C

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (µmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/international normalized ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

Treatment Post-Liver Transplant

Genotype	Recommended	Alternative	NOT Recommended
1 (including compensated cirrhosis)	**Daily sofosbuvir (400 mg) plus simeprevir (150 mg), with or without RBV** (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg), **for 12 weeks to 24 weeks**. Rating: Class IIb, Level C	**Daily sofosbuvir (400 mg) and RBV** (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCL value and hemoglobin level, **with or without PEG** (in the absence of contraindication to its use), **for 24 weeks**. Rating: Class IIb, Level C	-Monotherapy with PEG, RBV, or a DAA Rating: Class III, Level A -Telaprevir- or boceprevir- based regimens should not be used for patients with compensated allograft hepatitis C infection. Rating: Class III, Level A
2 or 3 (including compensated cirrhosis)	**Daily sofosbuvir (400 mg) and RBV** (initial dose 600 mg/day, increased monthly by 200 mg/day as tolerated to weight-based dose of 1000 mg [<75 kg] to 1200 mg [≥75 kg] 1200 mg) with consideration of the patient's CrCL value and hemoglobin level **for 24 weeks** . Rating: Class IIb, Level C		
Any with decompensated cirrhosis	Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; CTP class B or C). Rating: Class I, Level C		

Treatment of HIV/HCV Co-infection

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
1 Treatment Naïve or PEG/RBV Relapsers	-IFN eligible: -SOF 400 + PEG/RBV 1-1.2g x 12 weeks -IFN ineligible: -SOF 400 + RBV 1-1.2g x 24 weeks -SOF 400 + SMV* 150 ± RBV 1-1.2g x 12 weeks	-IFN eligible: -SMV* 150 x 12 weeks + PEG/RBV 1-1.2g x 24 weeks* -IFN ineligible: -None	-TVR + PEG/RBV x 24 or 48 weeks (RGT) -BOC + PEG/RBV x 28 or 48 weeks (RGT) -PEG/RBV x 48 weeks -SMV x 12 weeks + PEG/RBV x 48 wks	**For SOF use:** ALL except didanosine, zidovudine **For SMV use:** LIMITED to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir
1 PEG/RBV Nonresponders	**Regardless of treatment history:** -SOF 400 + SMV* 150 ± RBV 1-1.2g x 12 weeks (regardless of IFN eligibility)	-IFN eligible: -SOF 400 + PEG/RBV 1-1.2g x 12 Weeks -IFN ineligible: -SOF 400 + RBV 1-1.2g x 24 Weeks		Same as above
4	**Regardless of treatment history:** -IFN eligible: -SOF 400 + PEG/RBV 1-1.2g x 12 weeks -IFN ineligible: -SOF + RBV x 24 weeks	None	-PEG/RBV x 48 weeks -Any regimen with TVR or BOC	ALL except didanosine, zidovudine
5 or 6	**Regardless of treatment history:** -SOF 400 + PEG/RBV 1-1.2g x 12 weeks	None	-PEG/RBV x 48 weeks -Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine

* No in Q80K polymorphism (add RBV if with SOF)

Treatment of HIV/HCV Co-infection

Genotype	Recommended	Alternative	NOT Recommended	Allowable Antiretroviral Therapy
2 Treatment Naïve or Peg/RBV Relapsers	-SOF 400 + RBV 1-1.2g x 12 weeks regardless of treatment history	-None	-PEG/RBV x 24-48 weeks -Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
2 Treatment Nonresponders		-IFN eligible: -SOF 400 + PEG/RBV 1-1.2g X 12 Weeks -IFN ineligible: -None		
3 Treatment Naïve or Peg/RBV Relapsers	-SOF 400 + RBV 1-1.2 x 24 weeks regardless of treatment history	-None	-PEG/RBV x 24 - 48 weeks -Any regimen with TVR, BOC, or SMV	ALL except didanosine, zidovudine
3 Treatment Nonresponders		-IFN eligible: -SOF 400 + PEG/RBV 1-1.2g X 12 Weeks -IFN ineligible: -None		

Dose Adjustment for Renal Impairment

Renal Impairment	eGFR/CrCl level (mL/min/ 1.73 m^2)	Interferon	Ribavirin	Sofosfovir	Simeprevir
Mild	50-80	180 µg PEG (2a); PEG (2b) 1.5 µg/kg	Standard	Standard	Standard
Moderate	30-50	180 µg PEG (2a); PEG alfa-2b1 µg/kg or 25% reduction	Alternating doses 200 and 400 mg every other day	Standard	Standard
Severe	<30	135 µg PEG (2a); PEG (2b)1 µg/kg or 50% reduction	200 mg/d	Data not available	Standard
ESRD/HD		PEG (2a) 135 µg/wk or PEG (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk	200 mg/d	Data not available	Data not available

Dose Adjustment for Renal Impairment

- When using sofosbuvir to treat or retreat HCV infection in patients with appropriate genotypes, no dosage adjustment is required for patients with mild to moderate renal impairment (CrCl ≥30 mL/min). Sofosbuvir is not recommended in patients with severe renal impairment/ESRD (CrCl <30 mL/min) or those who require hemodialysis, because no dosing data are currently available for this patient population. **Rating: Class IIa, level B**
- When using simeprevir in treatment/retreatment of HCV-infected patients, no dosage adjustment is required for patients with mild to moderate to severe renal impairment. Simeprevir has not been studied in patients with ESRD, including those requiring hemodialysis. **Rating: Class IIa, level B**
- In patients with renal impairment/ESRD/HD, dosing of PEG and RBV should follow updated FDA recommendations or package insert recommendations based on calculated GFR. Caution should be used in administering RBV to these patients, and close monitoring of hemoglobin is required. **Rating: Class IIa, level B**

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)	>/= 100 mL/min	80 mL/min	60 mL/min	40 mL/min	20 mL/min	< 20 mL/min
RBV (mg/day)	1200	1000	800	600	400	200

SVR by Treatment Regimen

Genotype 1 Naive

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
1 all	naive	all	Sof+R	24	52-68
1a	**naive**	**F0-2**	**Sof+P+R**	**12**	**91-100**
		F3/F4	"		**89/78**
1b		**F0-2**	"		**92**
		F3-4	"		**80**
1a	Naïve Q80K(-)	All	Sim12+P+R	24(92%)-48	84
	Q80K(+)	All	"		58
1b	Naive	All	"		85
1 all		F0-2	"		84
		F3/4	"		73/60
1 all	**Naive**	**All**	**Sof+Ledipasvir**	**8**	**100**

Genotype 1 Relapser, Null, & Experienced

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
1a	**Relapser**	**All**	**Sim12+P+R**	**24-48**	**70**
1b		**All**			**86**
1 all		F0-2			82
1 all		F3			73
1 all		F4			74
1 all	**Null**	**F0-2**	**Sof+Sim+/-R**	**12**	**93/96** (90% in 1a Q80K(+))
1 all		**F3-4**			**93/96** (90% in 1a Q80K(+))
1 all	Experienced	All	Sof+Ledipasvir	12	95

Genotype 2

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
2 all	**Naive**	**F0-2**	**Sof+R**	**12**	**97**
2 all		**F3-4**	**“**		**100**
2 all	Experienced	F0-2	Sof+R	12	91
2 all		F3-4	“		88
2 all	**Experienced**	**F0-2**	**Sof+P+R**	**12**	**100**
2 all		**F3-4**	**“**		**93**

Genotype 3

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
3 all	**Naive**	**F0-2**	**Sof+R**	**24**	**94**
		F3-4	**“**		**92**
3 all	**Experienced**	**F0-2**	**Sof+R**	**24**	**87**
		F3-4	“		60
3 all	Experienced	F0-2	Sof+P+R	12	83
3 all	**Experienced**	**F3-4**	**Sof+P+R**	**12**	**83**

Genotype 4

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
4 all	**Naive**	**All**	**Sof+R**	**12**	**79**
				24	**100**
4 all	Experienced	All	Sof+R	12	59
4 all	**Experienced**	**All**	**Sof+R**	**24**	**93**

HCV + HIV Naive

Genotype	Status	Fibrosis	Regimen	Weeks	% SVR
1 all	Naive	All	Sof+R	24	76
2 all	"	"	"	12	88
3 all	"	"	"	12	67
1a	**Naive**	**All**	**Sof+P+R**	**12**	**87-89**
1b	**"**	**"**	**"**	**12**	**100**
2	**"**	**"**	**"**	**12**	**100**
3	**"**	**"**	**"**	**12**	**100**
4	**"**	**"**	**"**	**12**	**100**

HIV/HCV Coinfection

- Broad inclusion criteria
  - Cirrhosis permitted with no platelet cutoff
  - Hemoglobin: ≥12 mg/dL (males); ≥11 mg/dL (females)
- Wide range of ART regimens allowed
  - Undetectable HIV RNA for >8 weeks on stable ART regimen
- Baseline CD4 count
  - ART treated: CD4 T-cell count >200 cells/mm^3 and HIV RNA < 50 c/mL
  - ART untreated: CD4 T-cell count >500 cells/mm^3
- Tenofovir DF/emtricitabine plus
  - Efavirenz
  - Atazanavir/ritonavir
  - Darunavir/ritonavir
  - Raltegravir
  - Rilpivirine

Predictors of Virologic Response
Pegylated interferon + Ribavirin

Host IL28B genotype (rs12979860)		
T/T	**C/T**	**C/C**
Other important pretreatment factors		
Genotype 1	**Viral Genotype**	Genotypes 2 and 3
> 600,000	**Viral Load (IU/mL)**	< 600,000
African American (AA)	**Race**	Non-AA
F3 and F4	**Fibrosis (METAVIR grade)**	F0 and F1
Male	**Gender**	Female
> 40	**Age (years)**	< 40
Low	**LDL**	High
Obese	**Weight**	Slender
Less likely to respond	⟷	More likely to respond

Orange Color = Factors still worsening response with "Triple Therapy"

Clark, PJ et al. *Am J Gastroenterol*. 2011;106:38-45.

Conditions That May Require Treatment Before Starting Antiviral Therapy

- Diabetes with poor glycemic control
- Metabolic syndrome
  - Obesity
  - Glucose intolerance
  - Hypertension
  - Hyper- and dyslipidemia
- Depression and other mental illnesses
- Drug or alcohol dependence
- HIV disease
- Vitamin D Deficiency

Early Parameters of Response

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**	**< 2 log drop**

No Responder

No Responder

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

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

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

Viral Monitoring on Treatment: Terms

Terms	Definition
Rapid virological response (RVR)	HCV RNA undetectable after 4 weeks of treatment
Extended rapid virological response (eRVR)	HCV RNA undetectable at treatment week 4 and extending to week 12
Early virological response (EVR)	Partial EVR: ≥ 2 log reduction in HCV RNA at 12 weeks compared to baseline, or Complete EVR: HCV negative RNA at treatment week 12
End of treatment response (ETR)	HCV RNA negative by a sensitive test at the end of the planned 24 or 48 weeks of treatment
Sustained virological response (SVR)	HCV RNA negative 24 weeks after cessation of treatment
Response-guided therapy (RGT)	Using assessments of viral kinetics during treatment to make individualized therapeutic adjustments and optimize outcomes

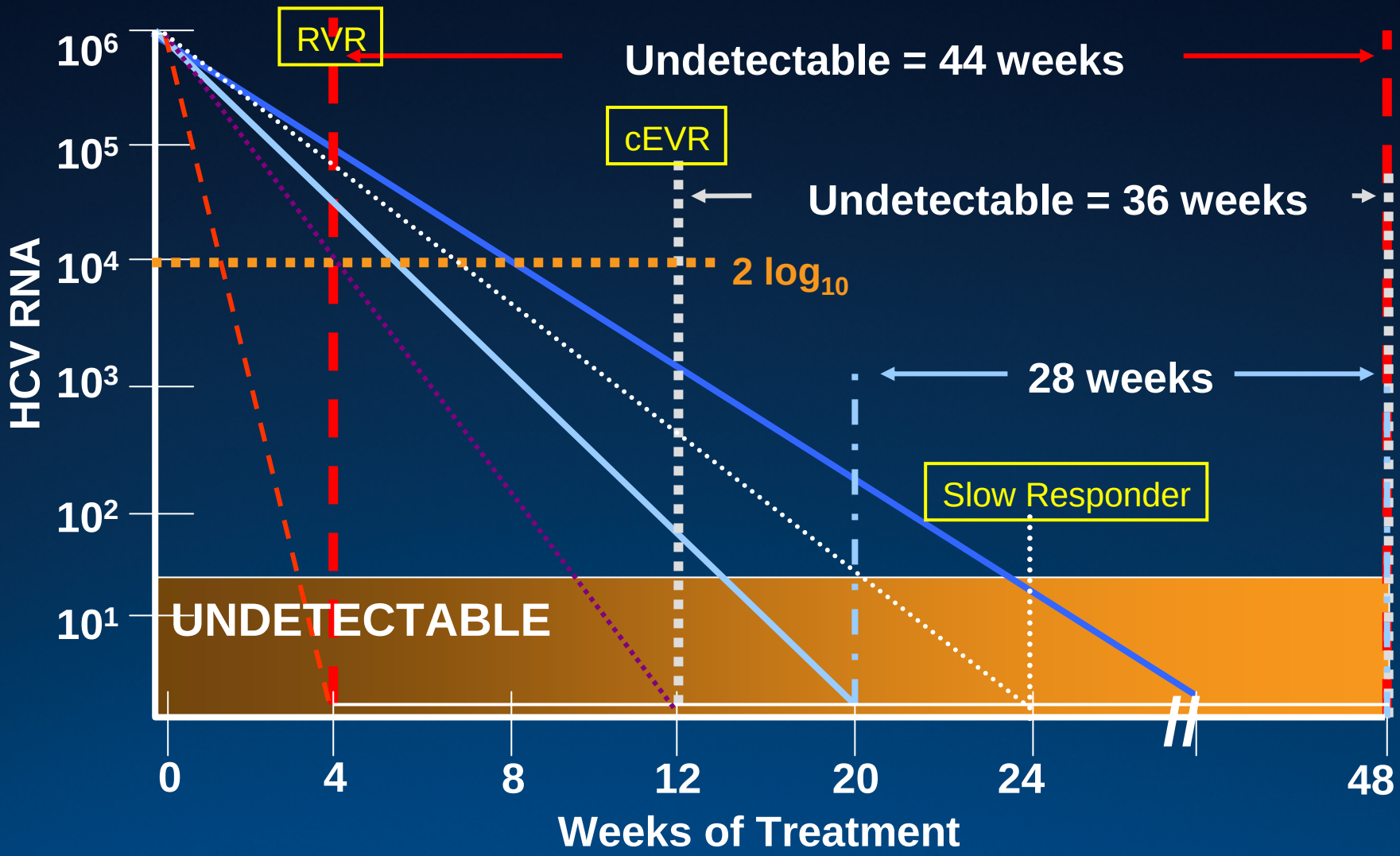
Ghany M, et al. *Hepatology*. 2009;49(4):1335-1374.

Viral Monitoring on Treatment: Terms

Terms	Definition
Breakthrough	Reappearance of previously undetectable HCV RNA in plasma while still on therapy
Relapse	Reappearance of HCV RNA in plasma after therapy is discontinued
Nonresponder	Failure to clear HCV RNA after 24 weeks of therapy
Null response	Failure to reduce HCV RNA by ≥ 2 log after 12 weeks of treatment
Early null response	Failure to reduce HCV RNA by ≥ 1 log after 4 weeks of treatment
Partial response	≥ 2 log reduction in HCV RNA, but still HCV RNA positive at week 24

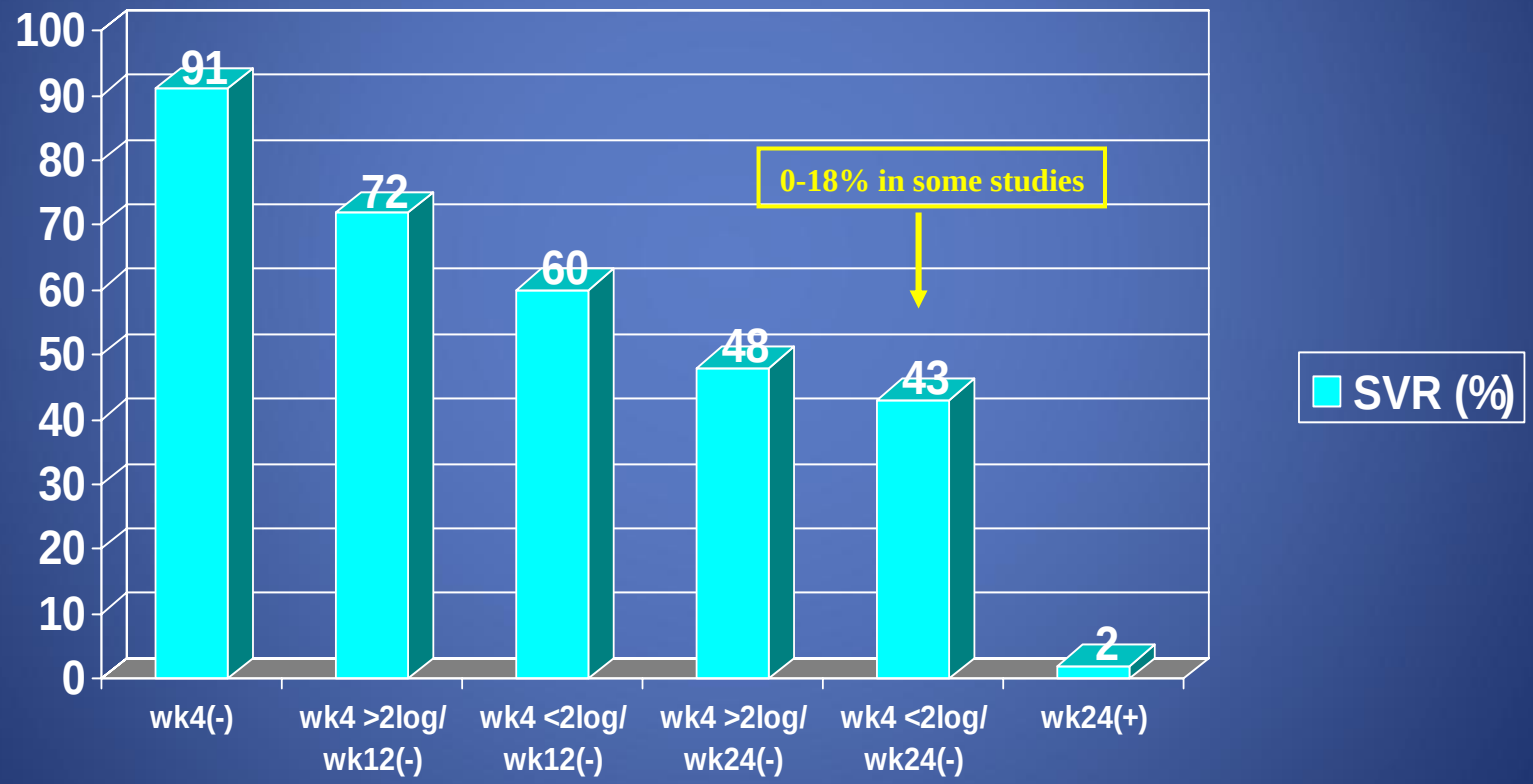
Ghany M, et al. *Hepatology*. 2009;49(4):1335-1374.
Reau N, et al. *Am J Gatroenterol*. 2010;106(3):452-458.

Rate of Viral Decline Determines Period of HCV RNA Negativity



Darling JM, et al. *Clin Liver Dis*. 2006;10:835-850.
Adapted from http://www.hepatitis.va.gov/vahep?page=prtop04-wp-03. Accessed January 4, 2008.

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



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

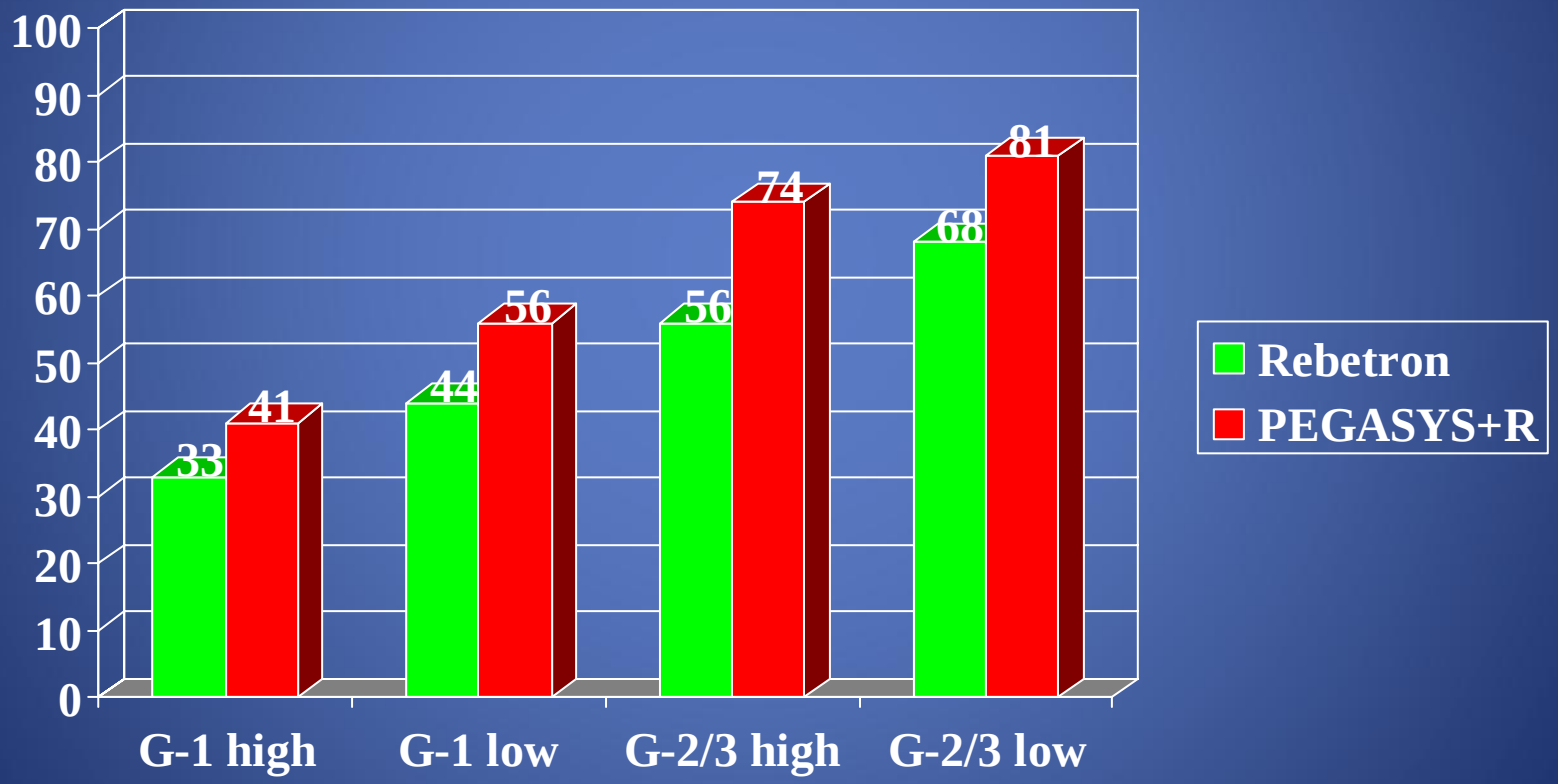
Standard Therapy for Chronic HCV

- **Genotype 1:** Triple therapy with:
  - Peg-IFN (a2a: 180 mcg/wk, or a2b: 1.5 mcg/kg/wk) +
  - RBV with dose depending on weight (13.3 mg/kg up to 1400 mg/d) +
  - either Boceprevir or Telaprevir
  - with therapy length based as “Response Guided Therapy”
- **Genotype 2 or 3:**
  - Peg-IFN (a2a: 180 mcg/wk, or a2b: 1.5 mcg/kg/wk) +
  - RBV 800 mg/d
  - for 24 weeks.
- **Genotype 4, 5, or 6:**
  - Peg-IFN (a2a: 180 mcg/wk, or a2b: 1.5 mcg/kg/wk) +
  - RBV with dose depending on weight (13.3 mg/kg up to 1400 mg/d)
  - for 48 weeks.

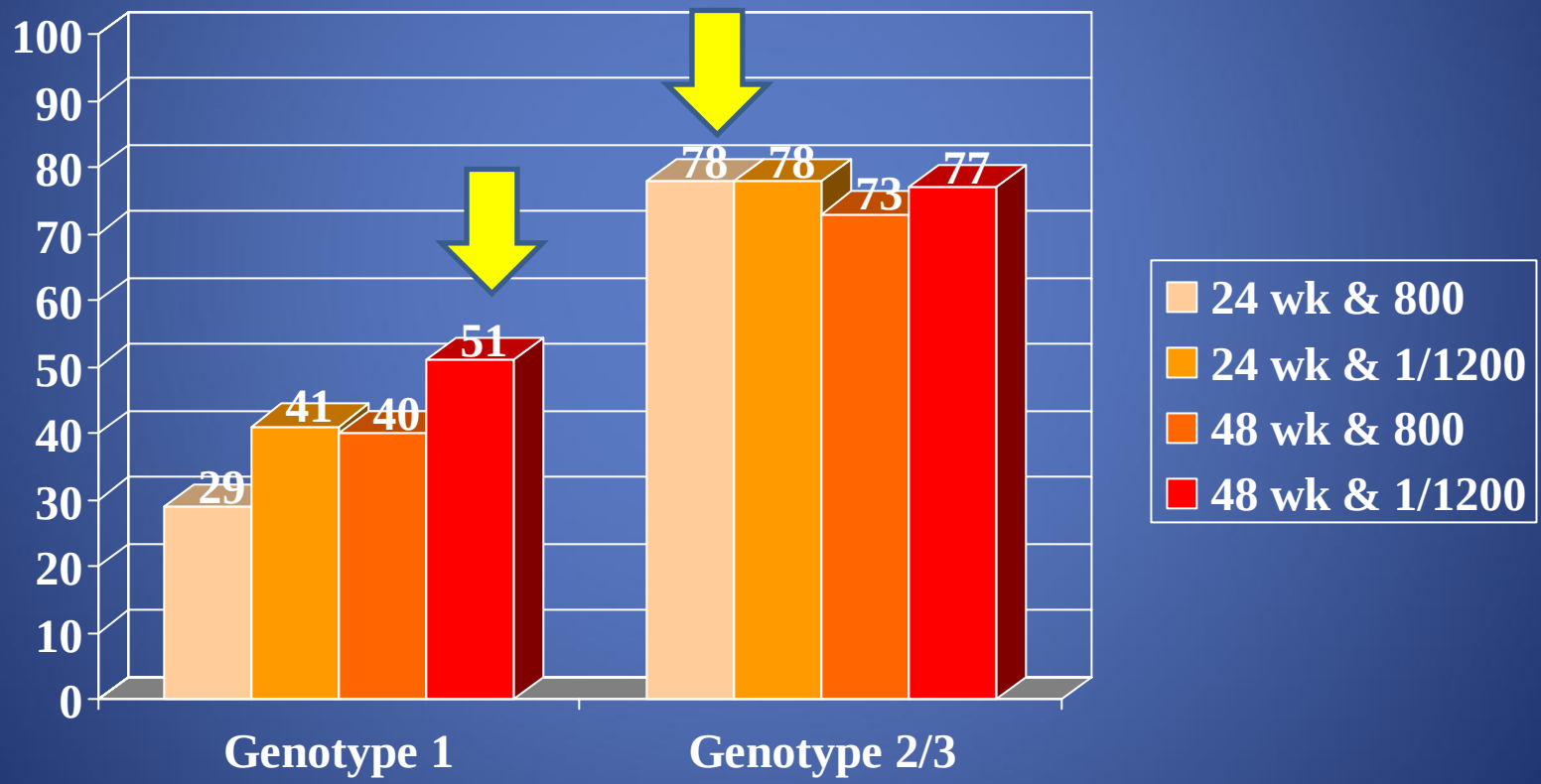
Evolving Concepts In Treatment of Chronic HCV

- **Genotype 2 & 3**
  - Correction of Vitamin D deficiency and "pre-loading" with RBV, for 2-4 weeks before starting Peg-IFN, may improve SVR.
  - 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.
  - Patients who tolerate therapy poorly and had baseline HCV-RNA < 200000 IU/mL, can have therapy shorten to 16 weeks.
- **Genotype 4, 5, & 6**
  - Correction of Vitamin D deficiency and "pre-loading" with RBV, for 2-4 weeks before starting Peg-IFN, may improve SVR.
  - Higher dose of RBV (15.2 mg/Kg, up to 1600 mg/d) 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.

PEGASYS + Ribavirin 1-1200
Genotype & Viral Load on ***SVR***

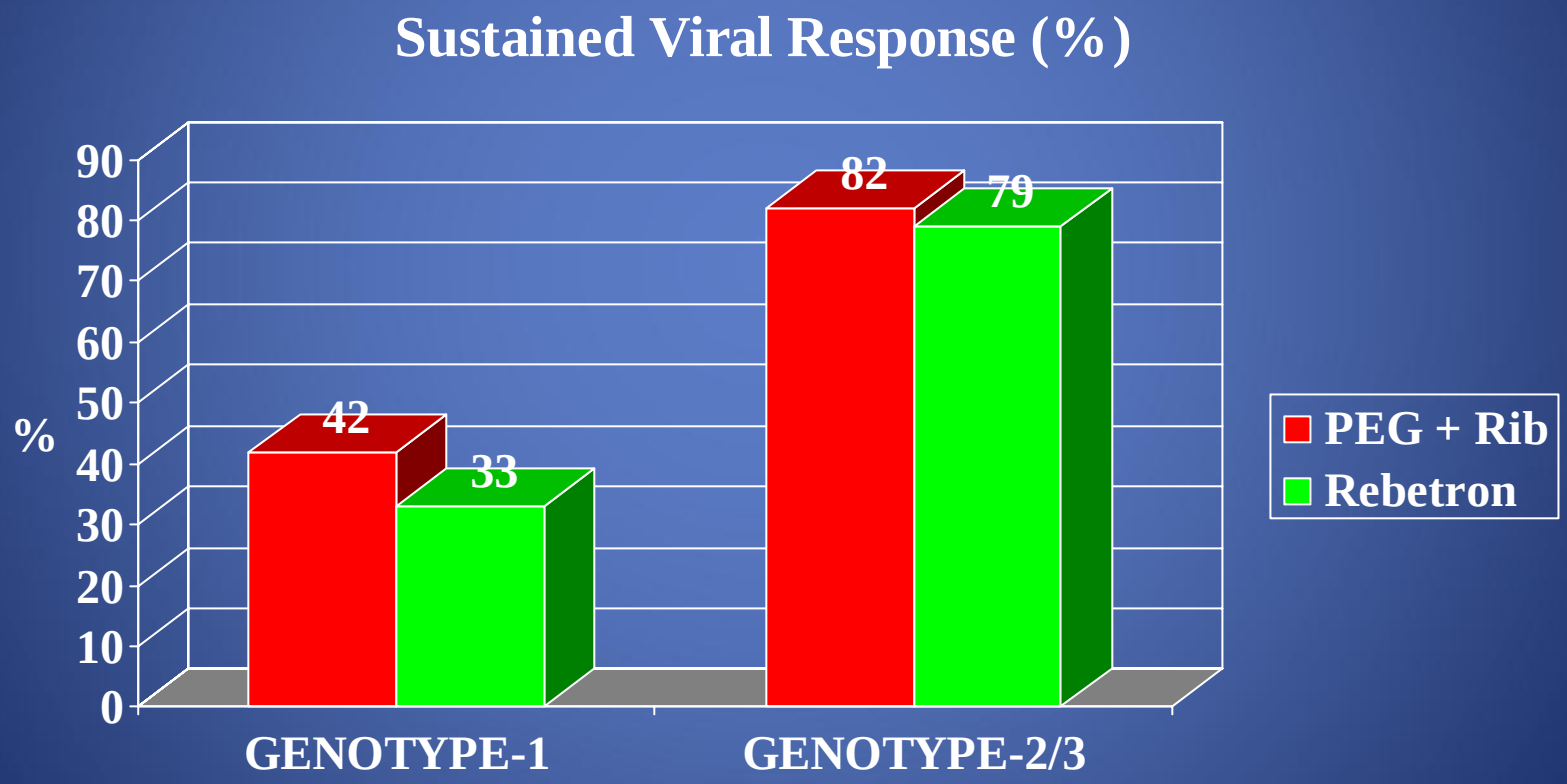


PEGASYS + Ribavirin
Sustained Virologic Response

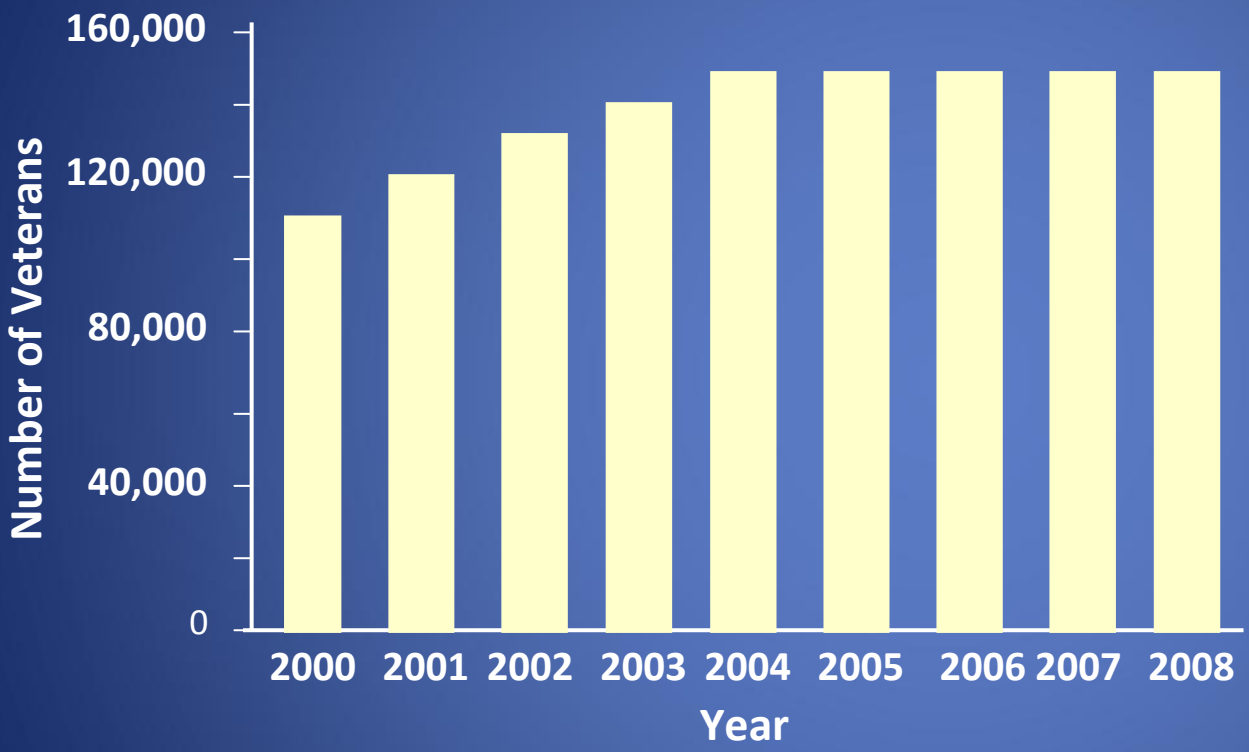


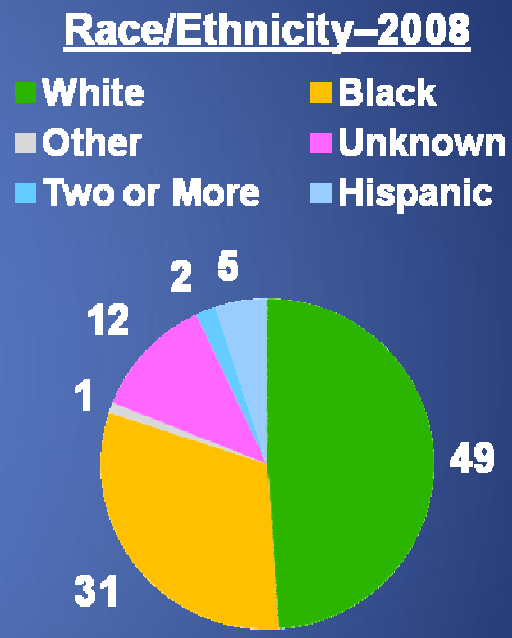
PEG-INTRON + Ribavirin 800

SVR Genotype-1 vs G-2/3 *Naive*



Veterans with Chronic HCV in VHA Care





Among the 20,477 veterans who initiated their 1st course of PegIFN + ribavirin between 2002 and 2006, SVR was:

- 26% for genotype 1
- 62% for genotype 2
- 52% for genotype 3

US Dept of Veterans Affairs. http://www.hepatitis.va.gov/provider/policy/HCV-state-of-care-2010.asp. Accessed June 2011.

Parameters for Dose-Reductions

Dose Reduction or Discontinuation

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

RBV dose
High & Constant
Corrected by Creatinine Clearance

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

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

Practical Considerations Associated with the Use of Triple Therapy for Patients with HCV Genotype-1

Drug Administration

	Boceprevir	Telaprevir
Dose	800 mg q 8+/-1 h (6-14-22 h)	750 mg q 8+/-1 h (6-14-22 h)
Tablet Strength	200 mg tablets	375 mg tablets
Length	24-44 wks	12 wks
Administration	PO with food	PO with fatty (> 20gm fat) food
Missed dose	If < 6 h post-time: take and keep schedule. If > 6 h post-time: skip and keep schedule.	If < 4 h post-time: take and keep schedule. If > 4 h post-time: skip and keep schedule
Co-therapy	Can only be given with both Peg-IFN and RBV. Discontinue if any of them is discontinued.	Can only be given with both Peg-IFN and RBV. Discontinue if any of them is discontinued.
Futility: D/C if	HCV-RNA >/= 100 IU/mL @ wk 12 HCV-RNA >/= 9.3 IU/mL @ wk 24	HCV-RNA > 1000 IU/mL @ wk 4 or 12 HCV-RNA > 10 IU/mL @ wk 24

CONTRAINDICATIONS

Class	Boceprevir	Telaprevir	Effect
Alfa1 adrenoreceptor antagonist	Alfuzosin	Alfuzosin	Hypotension, arrhythmia
Anticonvulsant	Carbamazepine, phenobarb, phenytoin		Viral escape
Anti-TB	Rifampin	Rifampin	Viral escape
Ergot derivate	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Vasospasm, ischemia
GI Motility	Cisapride	Cisapride	Arrhythmia
Herbal	St John's Wort	St John's Wort	Viral escape
HMG-CoA Reduct inh	Lovastatin, simvastatin	Lovastatin, simvastatin, atorvastatin	Myopathy, rhabdomyolysis
Contraceptive	Drosperinone		Hyperkalemia
PDE5 enz inhibitor	Sildenafil, tadalafil.	Sildenafil, tadalafil.	Hypotension, syncope, priapism
Neuroleptic	Pimozide	Pimozide	Arrhythmia
Sedative	Midazolam, triazolam (oral)	Midazolam, triazolam (oral)	Oversedation, Resp depression

Drug-Drug Interactions

- Both boceprevir and telaprevir are inhibitors of **CYP3A**
- Many common medications are metabolized by this enzyme, and boceprevir and telaprevir may affect their plasma concentrations
- Consult the package inserts for all drugs used for triple therapy for specific drug interactions

FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed June 2011.
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed June 2011.

Treatment Guidelines for Treatment Naïve Chronic HCV Genotype-1

- 1. Optimal therapy for genotype 1, chronic HCV infection is:
  - boceprevir or telaprevir in combination with peginterferon alfa and ribavirin (Class 1, Level A).
- 2. No single nor dual therapy:
  - Boceprevir and telaprevir should not be used without peginterferon alfa and ribavirin (Class 1, Level A).
- **For Treatment-Naive Patients:**
- 3. Boceprevir Regimen:
  - Four weeks of "lead-in" with Peg-IFN and weight-based Ribavirin (13.3 mg/kg; 800-1400 mg/d) dual therapy followed by
  - Boceprevir 800 mg administered with food three times per day (every 7- 9 hours) together with peginterferon alfa and weight-based ribavirin (13.3 mg/kg; 800 to 1400 mg) for 24-44 weeks (total 28-48 weeks) (Class 1, Level A).

Treatment Guidelines for Treatment Naïve Chronic HCV Genotype-1

- 4. Boceprevir in patients without cirrhosis (guided therapy):
  - Patients whose HCV RNA level at weeks 8 and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (4 weeks lead-in with peginterferon and ribavirin followed by 24 weeks of triple therapy) (Class 2a, Level B).
- 5. Boceprevir futility rule:

  Treatment with all three drugs (boceprevir, peginterferon alfa, and ribavirin) should be stopped if:
  - HCV RNA level is >100 IU/mL at treatment week 12 or
  - HCV-RNA is “Detectable” (> 9.3 IU/mL) at treatment week 24 (Class 2a, Level B).

Treatment Guidelines for Treatment Naïve Chronic HCV Genotype-1

- 6. Telaprevir Regimen:
  - telaprevir 750 mg administered with food (not low-fat) three times per day (every 7-9 hours) together with peginterferon alfa and ribavirin (1000-1200 mg/d) for 12 weeks
  - followed by a additional 12-36 weeks of peginterferon alfa and ribavirin (Class 1, Level A).
- 7. Telaprevir in patients without cirrhosis (guided therapy):
  - if HCV RNA level at weeks 4 and 12 is undetectable, they should be considered for a shortened duration of therapy of 24 weeks (Class 2a, Level A).

Treatment Guidelines for Treatment Naïve Chronic HCV Genotype-1

- 8. Telaprevir futility rule:
  Treatment with all three drugs (telaprevir, peginterferon alfa, and ribavirin) should be stopped if:
  - the HCV RNA level is >1,000 IU/mL at treatment weeks 4 or 12 and/or detectable at treatment week 24 (Class 2a, Level B).
- 9. Boceprevir or Telaprevir in patients with cirrhosis:
  - Patients should receive therapy for a duration of 48 weeks (Class 2b, Level B).

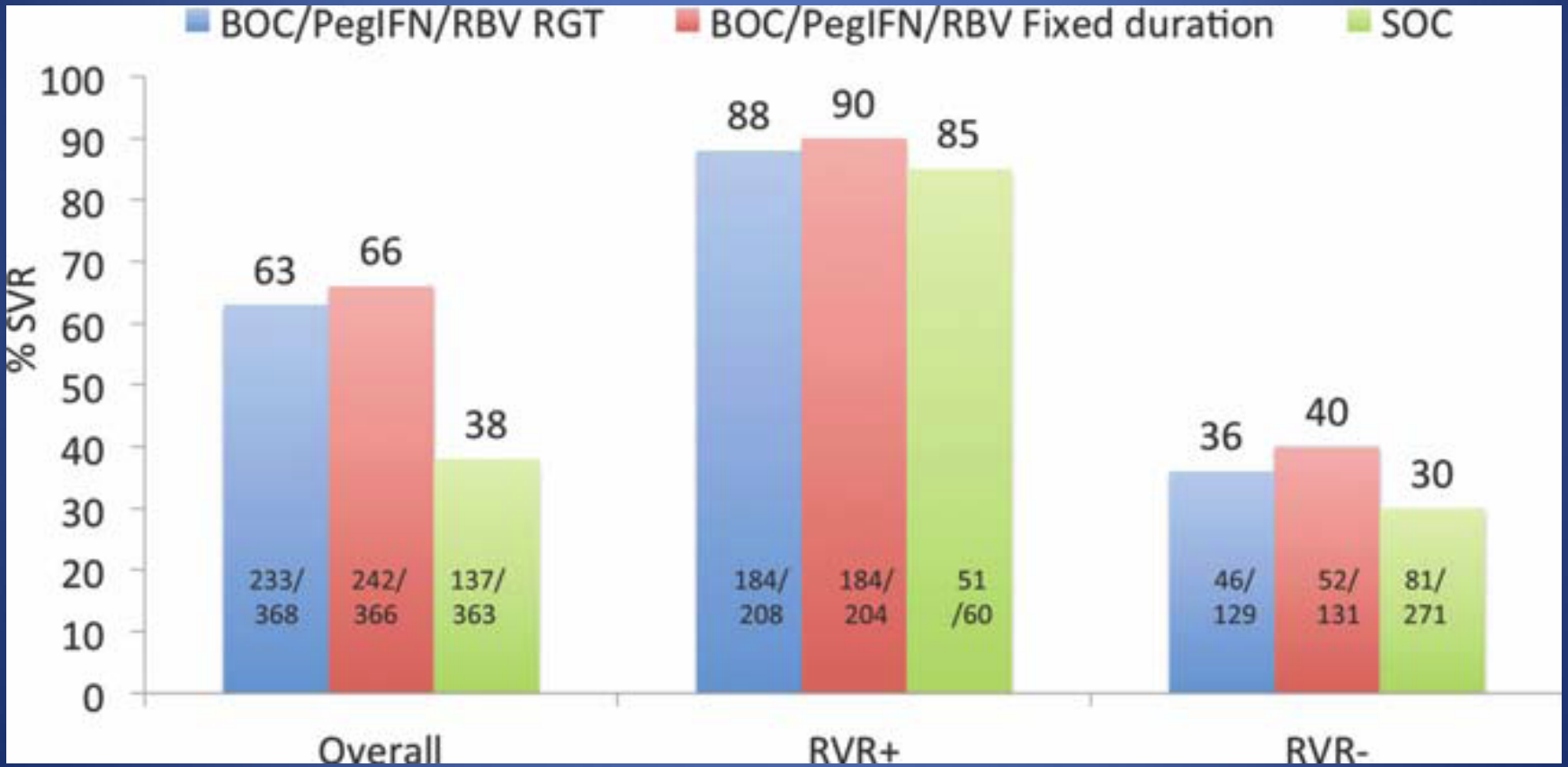
Treatment Naïve Genotype1 Patients: Boceprevir

	Assessment (HCV RNA)		Recommendation
	Treatment Week 8	Treatment Week 24	
*Boceprevir + PegIFN alfa/ ribavirin	Undetectable	Undetectable	Complete 3-medicine regimen at TW28
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer PegIFN/ribavirin and finish through TW48
Futility rules: If HCV-RNA ≥ 100 IU/mL at TW12, discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, discontinue three-medicine regimen.			
Patients with cirrhosis: *Boceprevir + PegIFN alfa/ribavirin for 44 weeks			

***Following 4 wk lead in with PegIFN/ribavirin**

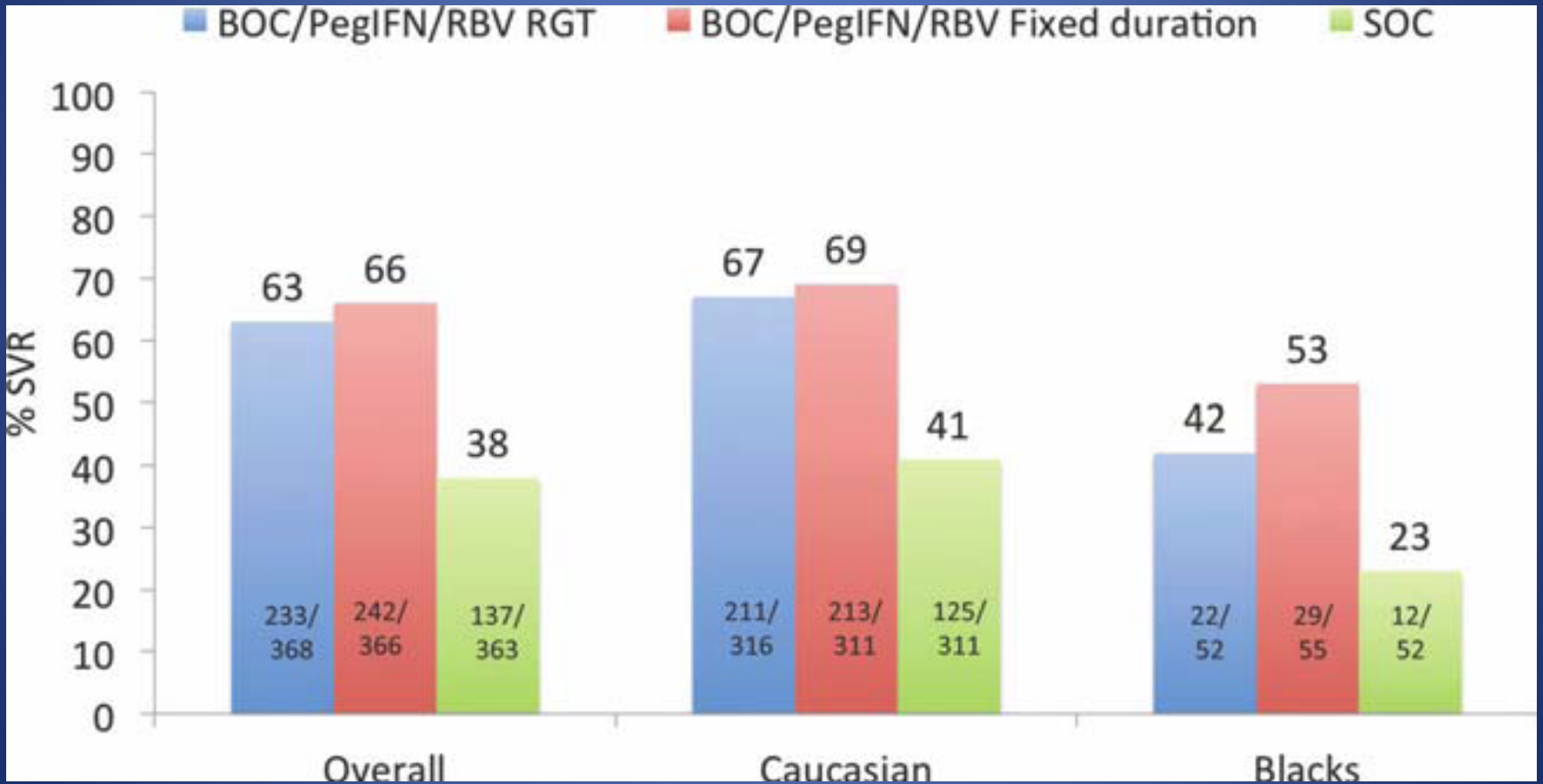
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed June 2011.

BOCEPREVIR/PEG/RBV: SVR rates, overall and based on a rapid virological response (RVR) in treatment-naive patients with genotype 1



(RVR = undetectable HCV-RNA at week 8 [week 4 of triple therapy])

BOCEPREVIR/PEG/RBV: SVR rates, overall and according to race, in treatment-naive patients with genotype 1

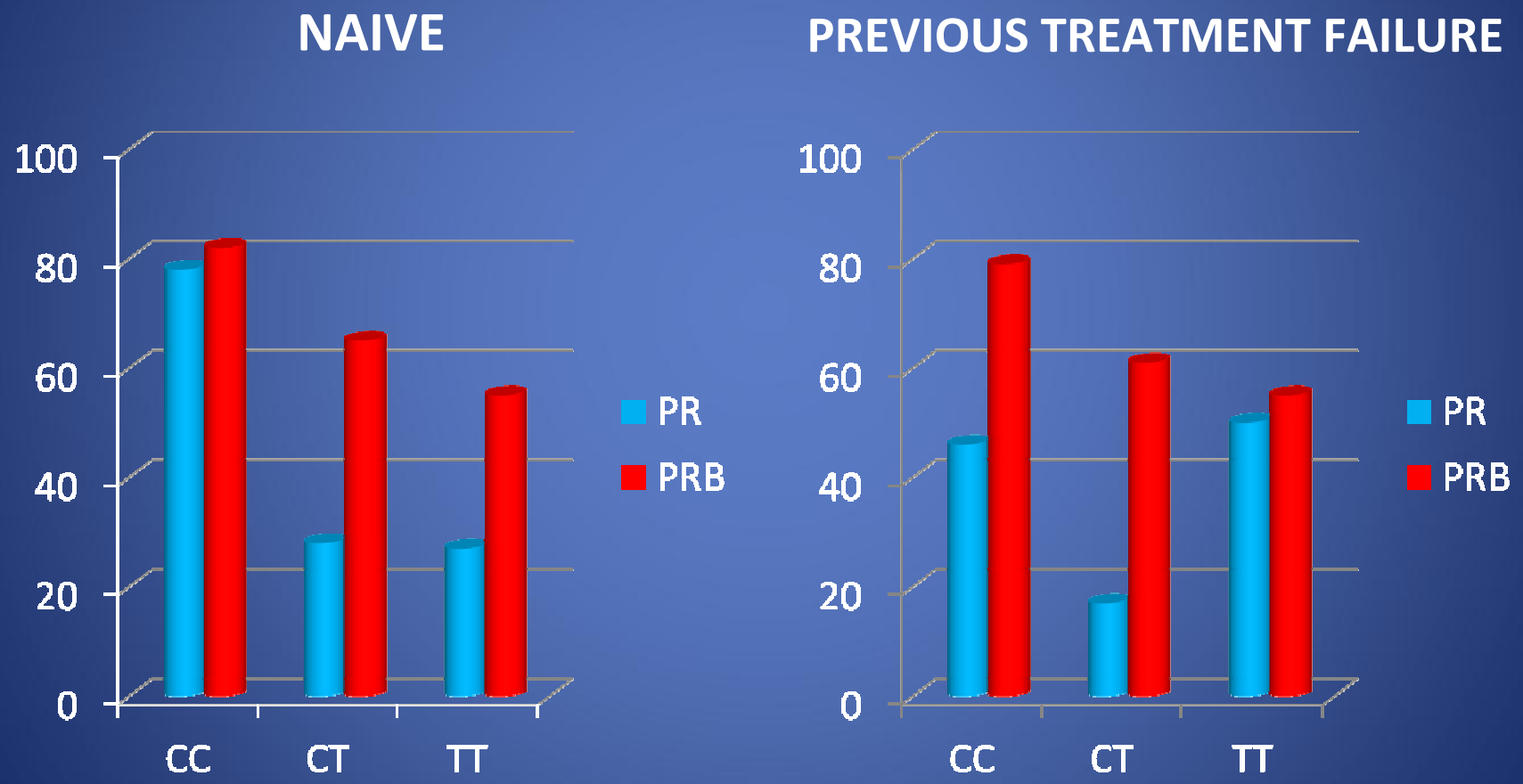


Boceprevir FDA Algorithms Genotype-1 Naive
Response-Guided Therapy (RGT) by HCV-RNA drop

	TW-0	TW-4	TW-8	TW-12	TW-24	TW-28	TW-36	TW-48	SVR
	Start P/R	Add B PRB	PRB	PRB *	PRB **	PRB	PRB	(PRB)	
NAÏVE All				< 100	< 9.3				**63-66**
NAÏVE (56%)		drop > 0.5 log	< 9.3	< 9.3	< 9.3	**EOT**			**88**
NAIVE		drop > 0.5 log	> 9.3	< 100	< 9.3		D/C B	PR **EOT**	**75**
Cirrhosis NAIVE				< 100	< 9.3			**EOT**	**42**
Af Am NAÏVE				< 100	< 9.3	RGT	RGT	RGT**/EOT**	**42/53**
Any		drop < 0.5 log		< 100	< 9.3			**EOT**	**30**

* If HCV-RNA >/= 100 IU/mL at week 12: Discontinue therapy
** If HCV-RNA >/= 9.3 IU/mL at week 24: Discontinue therapy

BOCEPREVIR/PEG/RBV: Effect of IL-28B rs12979860 Genotype in SVR in Chronic HCV G-1

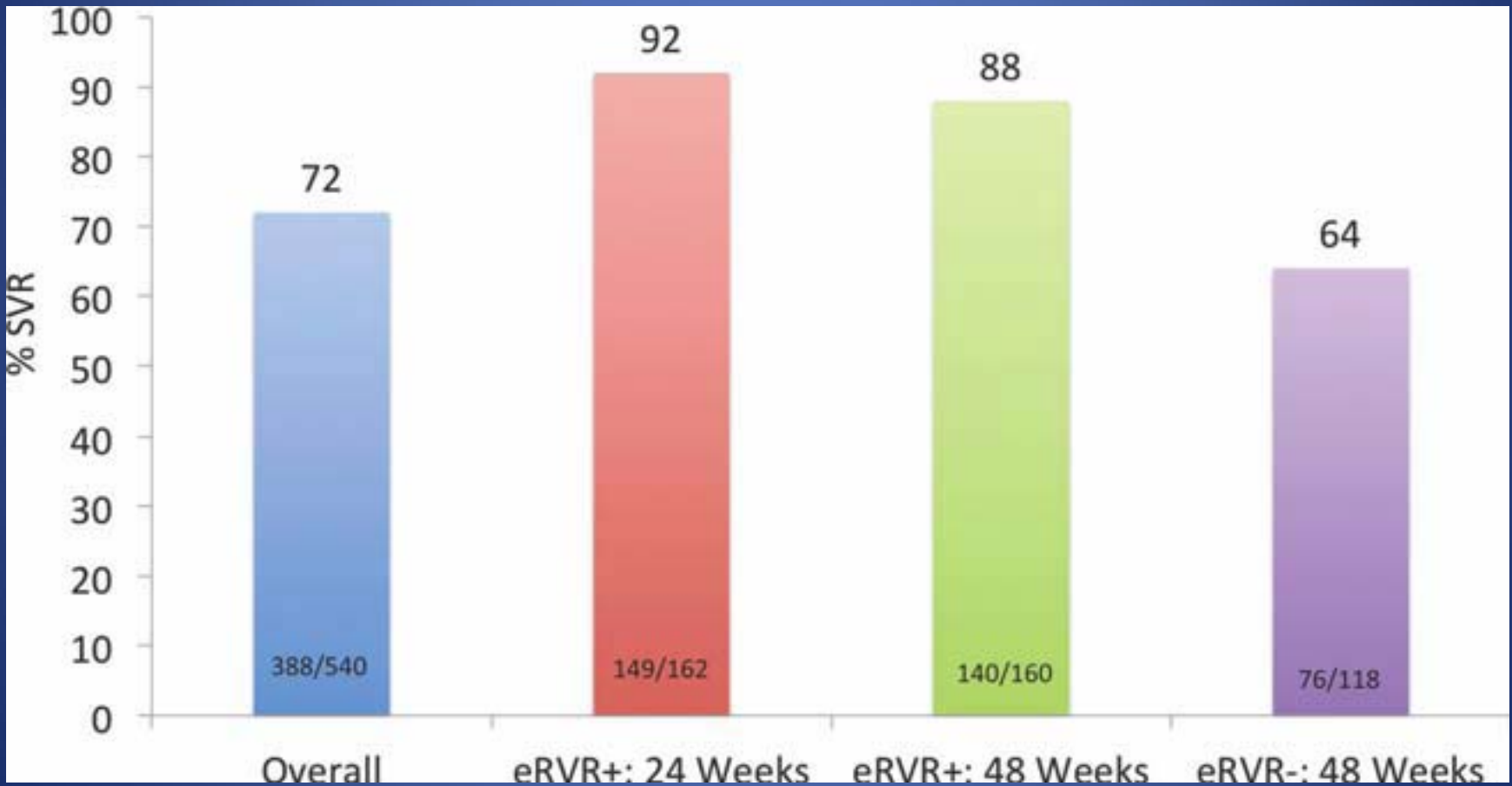


Treatment Naïve and Prior Relapse Genotype1 Patients: Telaprevir

HCV-RNA	**Triple Therapy** Telaprevir, Peginterferon alfa/ ribavirin	**Dual Therapy** Peginterferon alfa/ ribavirin	**Total Treatment Duration**
Undetectable at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1000 IU/mL or less) at Weeks 4 and 12	First 12 weeks	Additional 36 weeks	48 weeks
Futility Rules HCV RNA Week 4 or 12 > 1000 IU/mL: Discontinue telaprevir + Peginterferon alfa/ribavirin HCV RNA Week 24 detectable: Discontinue Peginterferon alfa/ribavirin			
Treatment naïve patients with cirrhosis with undetectable HCV-RNA at weeks 4 and 12 of triple therapy may benefit from an additional 36 weeks of Peginterferon alfa/ribavirin (48 weeks total)			

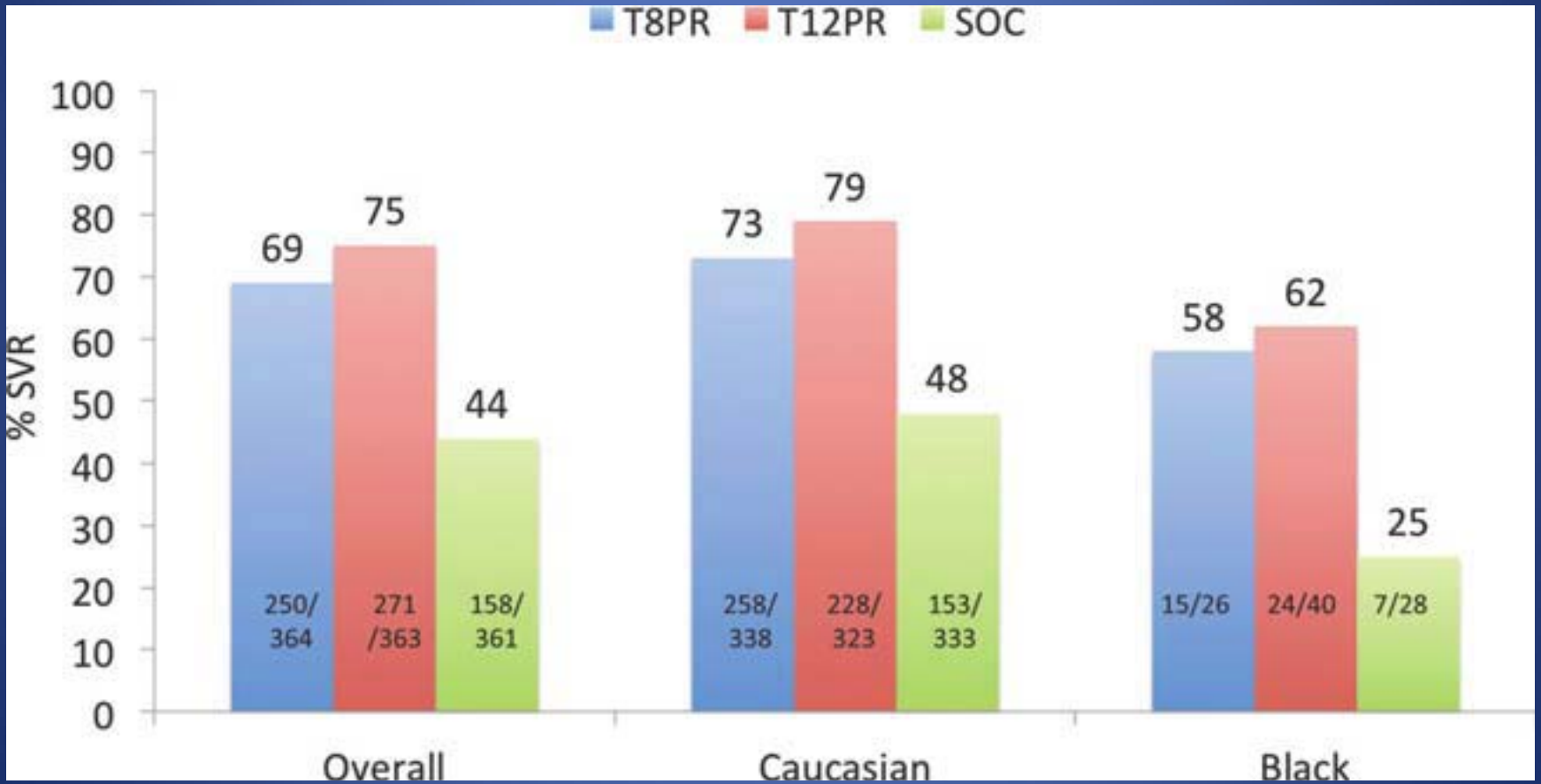
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed June 2011.

TELAPREVIR/PEG/RBV: SVR rates in treatment naıve patients with genotype 1 chronic HCV infection: results overall and among those who did or did not achieve an eRVR*



*eRVR = extended rapid virological response; undetectable HCV RNA at weeks 4 and 12

TELAPREVIR/PEG/RBV: Sustained virological response (SVR) rates, overall and according to race, in treatment naive patients with genotype 1



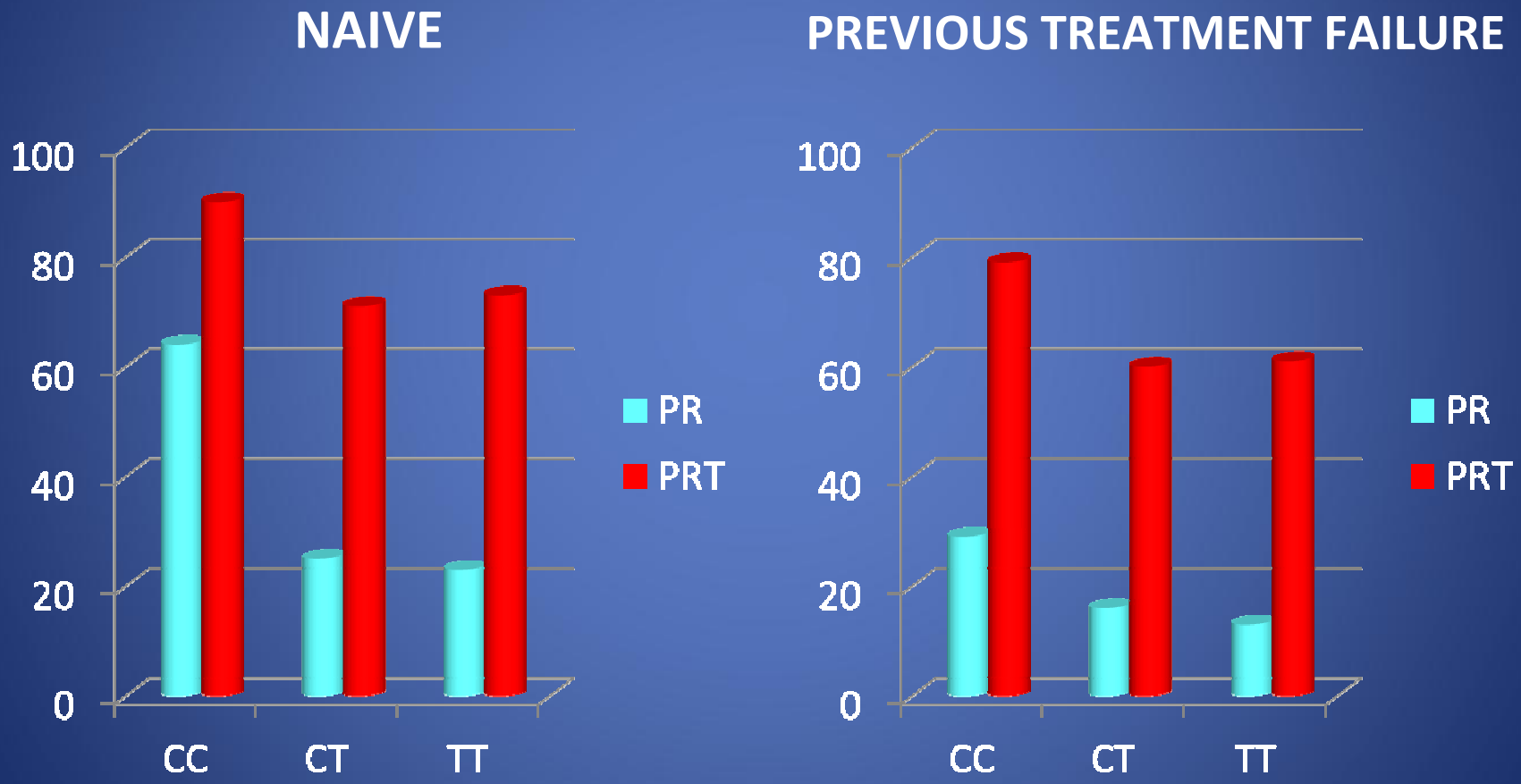
Telaprevir FDA Algorithms Genotype-1 Naive

Response-Guided Therapy by HCV-RNA drop

	TW-0	TW-4	TE-12	TW-24	TW-48	SVR
	PRT	PRT *	D/C T *	PR **	(PR)	
NAÏVE (All)		< 1000	< 1000	< 10		**79**
NAÏVE (58%)		< 10	< 10	**EOT**		**92**
NAÏVE (42%)		10-1000	10-1000	< 10	**EOT**	**60**
NAÏVE Af Am (31%)		< 10	< 10	**EOT**		**89**
NAÏVE Af Am (69%)		10-1000	10-1000	< 10	**EOT**	**44**
NAÏVE Cirrhosis (43%)		< 10	< 10	**EOT**		**78**
NAÏVE Cirrhosis (57%)		10-1000	10-1000	< 10	**EOT**	**33**

* If HCV-RNA > 1000 IU/mL @ wk 4 or 12: Discontinue therapy
** If HCV-RNA > 10 IU/mL @ wk 24: Discontinue therapy

TELAPREVIR/PEG/RBV:
Effect of IL-28B rs12979860 Genotype in SVR in Chronic HCV G-1



Treatment Guidelines for Treatment-Experienced Chronic HCV Genotype-1

- 10. Retreatment of patients "experienced" with standard interferon alfa or peginterferon alfa and ribavirin:
  Re-treatment with boceprevir or telaprevir regimens can be recommended for:
  - Patients who had virological relapse, or
  - Patients who were partial responders (Class 1, Level A).
- 11. Re-treatment of prior "null responders" to a course of standard interferon alfa or peginterferon alfa and ribavirin (< 2 log drop @ week 12) :
  - Telaprevir, together with peginterferon alfa and ribavirin (1000-1200 mg/d), may be considered (Class 2b, Level B.)

Treatment Guidelines for Treatment-Experienced Chronic HCV Genotype-1

- 12. Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir- based regimen:
  - can be considered for relapsers (Class 2a, Level B for boceprevir; Class 2b, Level C for telaprevir),
  - may be considered for partial responders (Class 2b, Level B for boceprevir; Class 3, Level C for telaprevir), but
  - cannot be recommended for null responders (Class 3, Level C).
- 13. Futility Rule for Boceprevir in re-treated patients:
  - Patients with HCV RNA > 100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).
- 14. Futility Rule for Telaprevir re-treated patients:
  - Patients with HCV RNA > 1,000 IU at weeks 4 or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance (Class 1, Level B).

Telaprevir FDA Algorithms Genotype-1 Experienced

Response-Guided Therapy by HCV-RNA drop

	TW-0	TW-4	TE-12	TW-24	TW-48	SVR
	PRT	PRT *	D/C T *	PR **	PR	
Relapsers (All)		< 1000	< 1000	< 10	**EOT**	**86**
Relapser (76%)		< 10	< 10	< 10	**EOT**	**95**
Relapser (24%)		10-1000	10-1000	< 10	**EOT**	**15**
pEVR (All)		< 1000	< 1000	< 10	**EOT**	**59**
< 2 log w12 (All)		< 1000	< 1000	< 10	**EOT**	**32**
Relapser Cirrhosis		< 10	< 10	< 10	**EOT**	**87**
pEVR Cirrhosis		< 1000	< 1000	< 10	**EOT**	**20**
< 2 log w12 Cirrhosis		< 1000	< 1000	< 10	**EOT**	**10**

* If HCV-RNA > 1000 IU/mL @ wk 4 or 12: Discontinue therapy
** If HCV-RNA > 10 IU/mL @ wk 24: Discontinue therapy

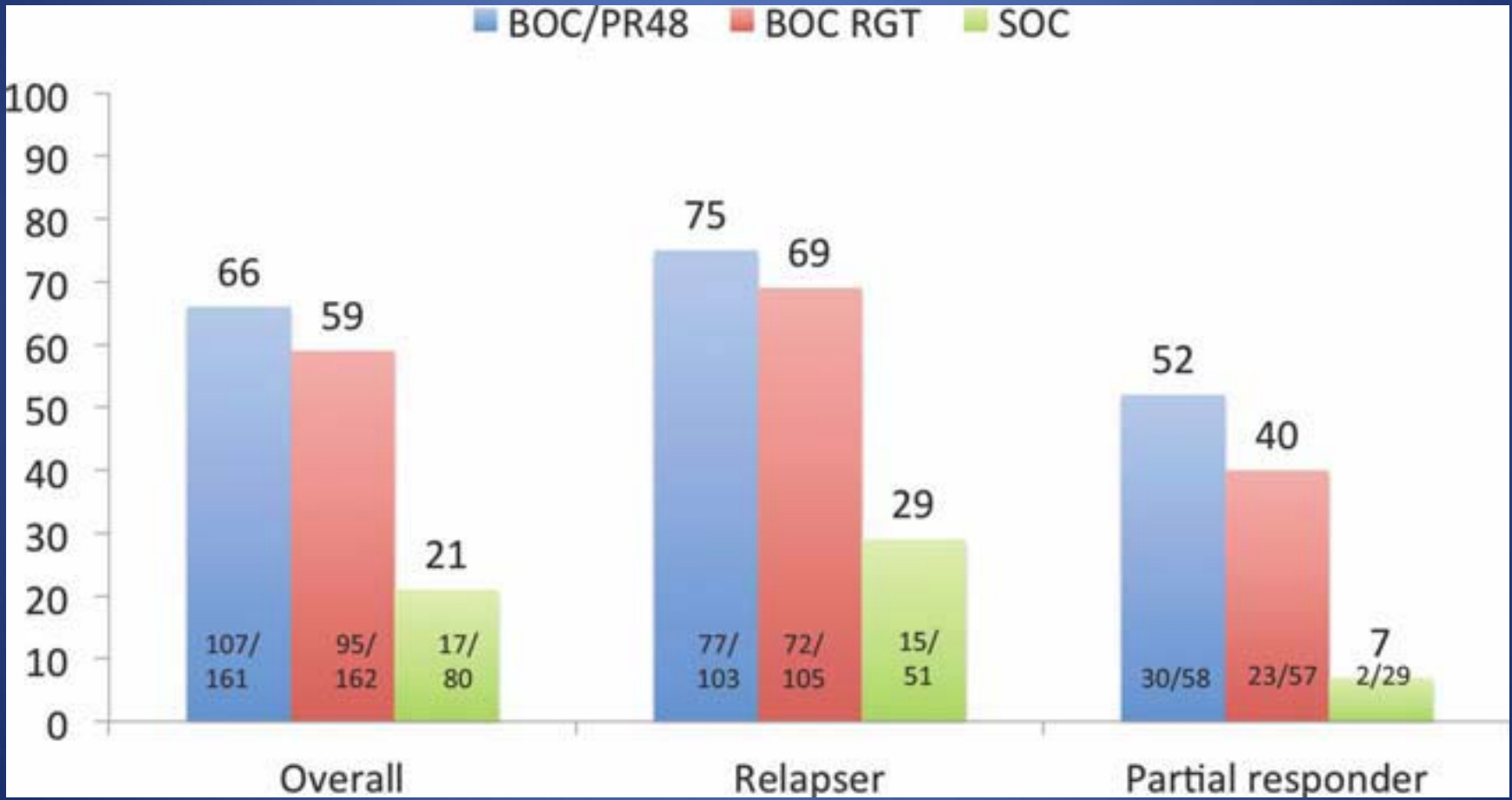
Previous Partial Responders or Relapsers Boceprevir

	Assessment (HCV RNA)		Recommendation
	Treatment Week 8	Treatment Week 24	
*Boceprevir + PegIFN/ ribavirin	Undetectable	Undetectable	Complete 3-medicine regimen at TW36
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer PegIFN/ribavirin and finish through TW48
Stopping rules: If HCV-RNA ≥ 100 IU/mL at TW12, discontinue three-medicine regimen. If the patient has confirmed, detectable HCV-RNA at TW24, discontinue three-medicine regimen.			
Patients with cirrhosis: *Boceprevir + PegIFN + ribavirin for 44 weeks			

***Following 4 wk lead in with PegIFN + ribavirin**

FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed June 2011.

BOCEPREVIR/PEG/RBV: SVR rates, overall and among Relapsers and Partial Responders*, in treatment experienced patients with genotype 1 HCV



*Partial Responders are persons whose HCV RNA level dropped by at least 2 log IU/mL at treatment week 12 but in whom HCV RNA was still detected at treatment week 24.

Boceprevir FDA Algorithms Genotype-1 Experienced

Response-Guided Therapy by HCV-RNA drop

	TW-0	TW-4	TW-8	TW-12	TW-24	TW-28	TW-36	TW-48	SVR
	Start P/R	Add B PRB	PRB	PRB *	PRB **	PRB	PRB	(PRB)	
Past pEVR or Relapser (48%)		drop > 0.5 log	< 9.3	< 9.3	< 9.3		**EOT**		**88**
Past pEVR or Relapser		drop > 0.5 log	> 9.3	< 100	< 9.3		D/C B	PR **EOT**	**79**
Cirrhosis pEVR				< 100	< 9.3			**EOT**	**35**
Any		drop < 0.5 log		< 100	< 9.3			**EOT**	**30**
Past P/R wk12 drop < 2 log				< 100	< 9.3			**EOT**	**?**

* If HCV-RNA >/= 100 IU/mL at week 12: Discontinue therapy
** If HCV-RNA >/= 9.3 IU/mL at week 24: Discontinue therapy

Prior Partial and Null Responder Patients
Telaprevir

	Triple Therapy Telaprevir, Peginterferon alfa/ ribavirin	**Dual Therapy** Peginterferon alfa/ ribavirin	**Total Treatment Duration**
All patients	First 12 weeks	Additional 36 weeks	48 weeks

Futility Rules

HCV RNA Week 4 or 12 > 1000 IU/mL: Discontinue telaprevir and Peginterferon alfa/ribavirin

HCV RNA Week 24 detectable: Discontinue Peginterferon alfa/ribavirin

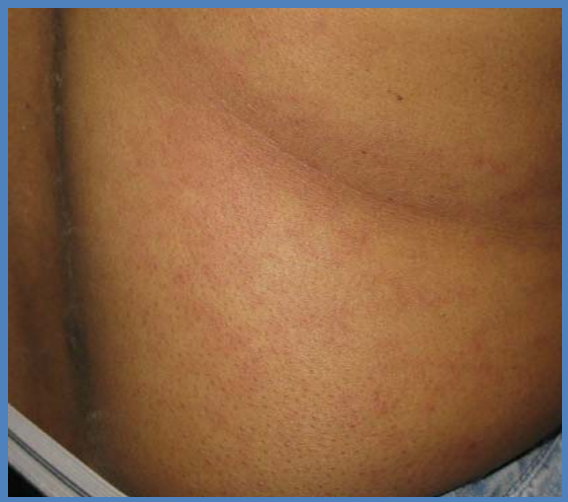
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed June 2011.

Adverse Events (%)

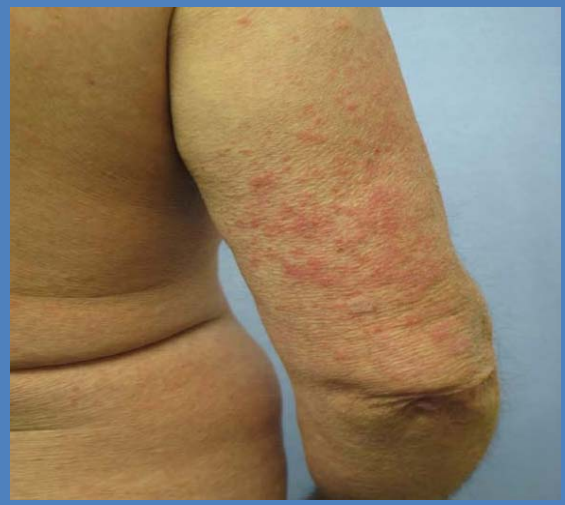
Event	Boc + Peg/Riba	Tel + Peg/Riba	Peg/Riba
Rash	17	**56**	19-34
Fatigue	58	56	50
Anemia	**50**	36	17-30
Pruritus		47	28
Nausea	**46**	39	28-38
Chills	34		30
Diarrhea	25	26	17
Neutropenia	**25**	15	14
Dizzines	19		13
Vomiting	20	13	8
Hemorrhoids		**12**	3
Anorectal discomfort		**11**	3
Dysgeusia	**35**	10	3
Pruritus ani		**6**	1

Rash in Patients from Phase 3 Studies Treated with Telaprevir + PegIFN/RBV

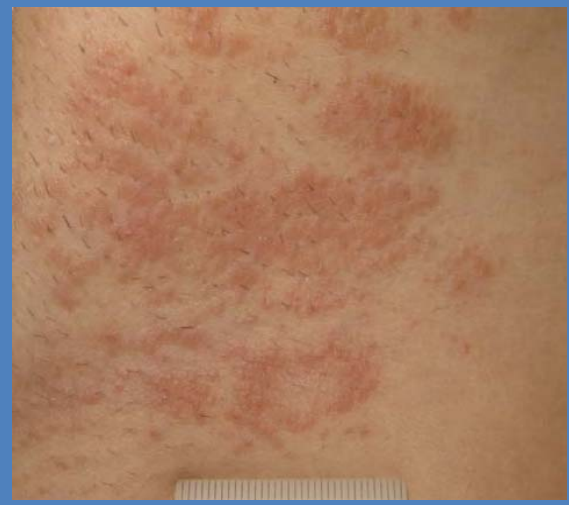
Mild (localized)



Moderate (< 50% BSA)



Severe (> 50% BSA)



- 93% of all rash events were mild -to-moderate severity
- Less than 1% of subjects experienced suspected serious cutaneous adverse reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms-DRESS)
- Rash events resulted in discontinuation of telaprevir alone in 6% of patients and discontinuation of telaprevir and Peginterferon alfa + ribavirin combination in 1% of patients
- Rash may take weeks to resolve

BSA: body surface area

FDA Antiviral Drugs Advisory Committee. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm. Accessed June 2011.

Treatment Guidelines for Minimization of Viral Resistance

- 15. Management of Anemia:
  - Patients who develop anemia on protease inhibitor- based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose (usually to 600 mg/d, or by 50%) (Class 2a, Level A).
- 16. Management of Viral Breakthrough:
  - Patients should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (>1 log increase in serum HCV RNA above nadir) is observed (Class 1, Level A).

Treatment Guidelines for Minimization of Viral Resistance

- 17. Management of patients who fail with a Protease Inhibitor:
  - Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with the other protease inhibitor (Class 2a, Level C).
- 18. Utility of IL28B genotype testing:
  - IL28B genotype is a robust pretreatment predictor of SVR to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with genotype 1 chronic hepatitis C virus infection.
  - Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment duration needed (Class 2a, Level B).

Treatment of HIV/HCV Co-Infection

Telaprevir in G-1 HIV/HCV Coinfection

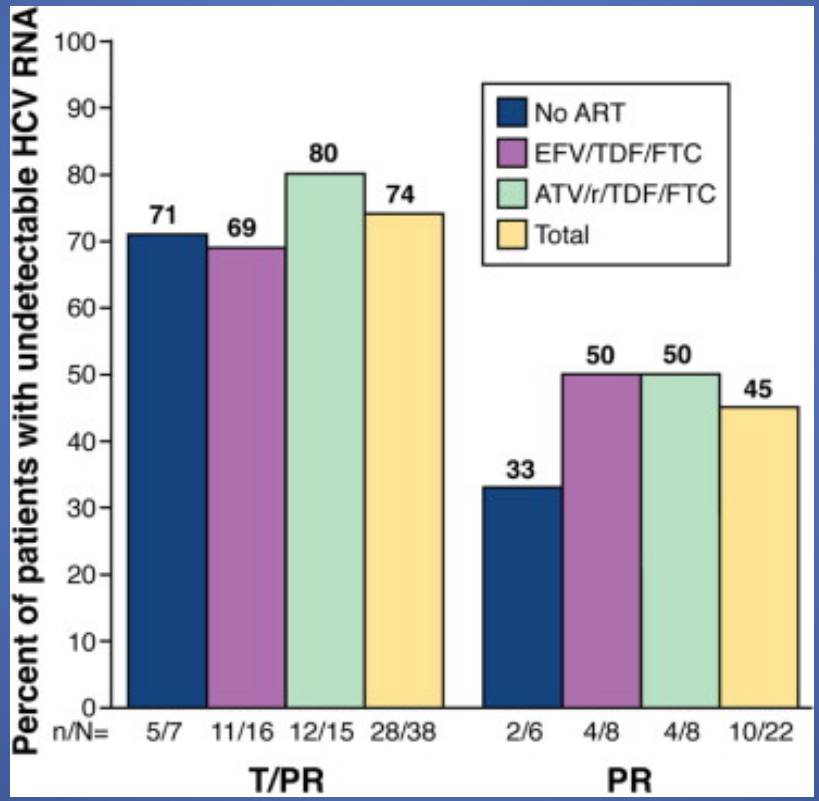
- Telaprevir x 12 weeks:
  - 750 q 8h may be used with Tenofovir (Viread), Emtricitabine (Emtriva), Truvada, Atazanavir (Reyataz) boosted with Ritonavir (Norvir), and Raltegravir (Isentress);
  - If used with Efavirenz (Sustiva) dose should be 1125 q8h.
- Peg-IFN is alfa 2a 180 mcg/week.
- RBV dose is >/= 800 mg/d (ideally 13.3 mg/kg)
- Length of therapy is 48 weeks
- Futility:
  - HCV-RNA > 1000 IU/mL at week 4, 8 or 12
  - Drop < 2 log at week 12
  - Detectable at week 24

Telaprevir Drug-Drug Interaction with HAART

HEP-CCO

HIV Antiretroviral	Recommendation
Studies completed	
Atazanavir/ritonavir	Clinical and laboratory monitoring for hyperbilirubinemia is recommended
Darunavir/ritonavir Fosamprenavir/ritonavir Lopinavir/ritonavir	Coadministration not recommended
Efavirenz	Telaprevir dose increase necessary (1125 mg every 8 hrs)
Raltegravir	No dose adjustment required
Etravirine Rilpivirine	No dose adjustment required
Tenofovir	Increased clinical and laboratory monitoring is warranted
Studies not completed	
Abacavir; zidovudine	An effect of telaprevir on UDP-glucuronyltransferases cannot be ruled out and may affect plasma concentrations of abacavir or zidovudine (not studied)

Telaprevir in G-1 Coinfected Patients



Boceprevir in G-1 HIV/HCV Coinfection

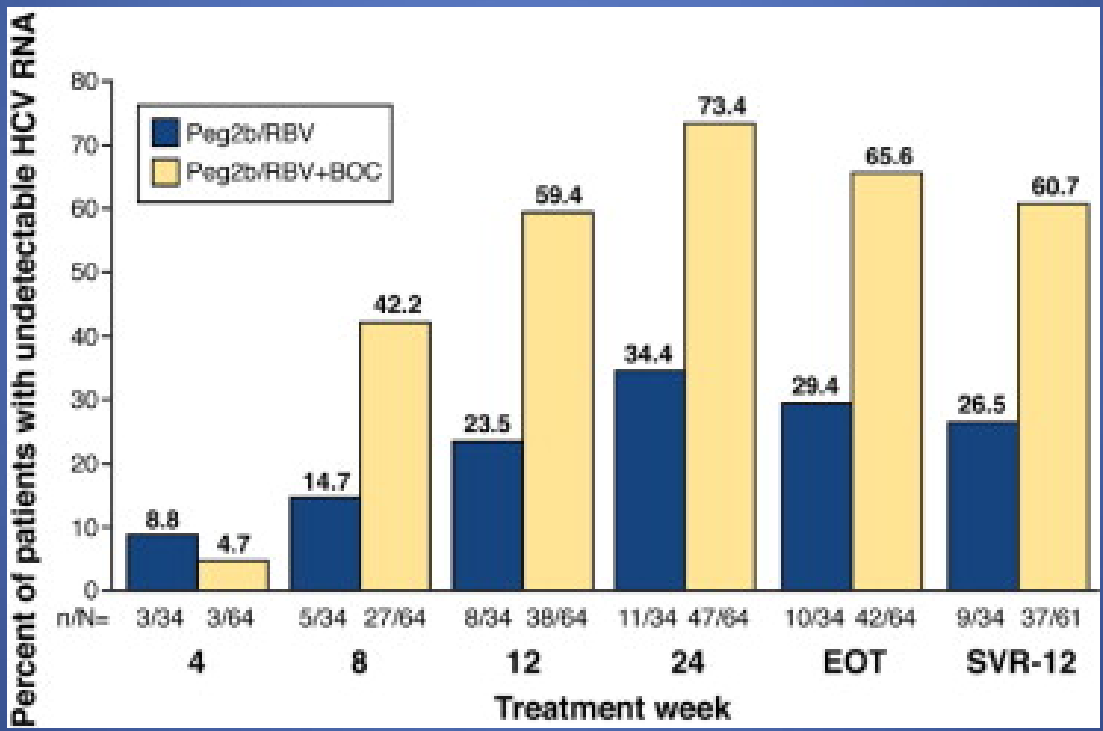
- Boceprevir for 44 weeks (wk 4 to 48)
  - 800 mg q 8h may be used with Abacavir (Ziagen), Lamivudine (Epivir), Epzicom, Tenofovir (Viread), Emtricitabine (Emtriva), Truvada, Raltegravir (Isentress).
  - Do not use with Ritonavir (Norvir) boost.
- Peg-Ifn alfa 2b 1.5 mcg/kg/week.
- RBV weight based (13.3 mg/kg) 600-1400 mg/d.
- Length of therapy: 48 weeks
- Futility:
  - Drop < 2 log at week 12
  - Detectable at week 24

Boceprevir Drug-Drug interaction with HAART

CCO-HCV

HIV Antiretroviral	Recommendation
Studies completed	
Atazanavir/ritonavir	In general not recommended; European Medicines Agency says can be considered on a case-by-case basis if patient has no previous HIV drug resistance and is suppressed
Darunavir/ritonavir Fosamprenavir/ritonavir Lopinavir/ritonavir	Not recommended
Efavirenz	Not recommended
Etravirine	No dose adjustment required
Raltegravir	No dose adjustment required

Boceprevir in G-1 Coinfected Patients



DHHS Recommendations (3/2012) for Therapy of HIV/HCV G-1

CCO-HEP

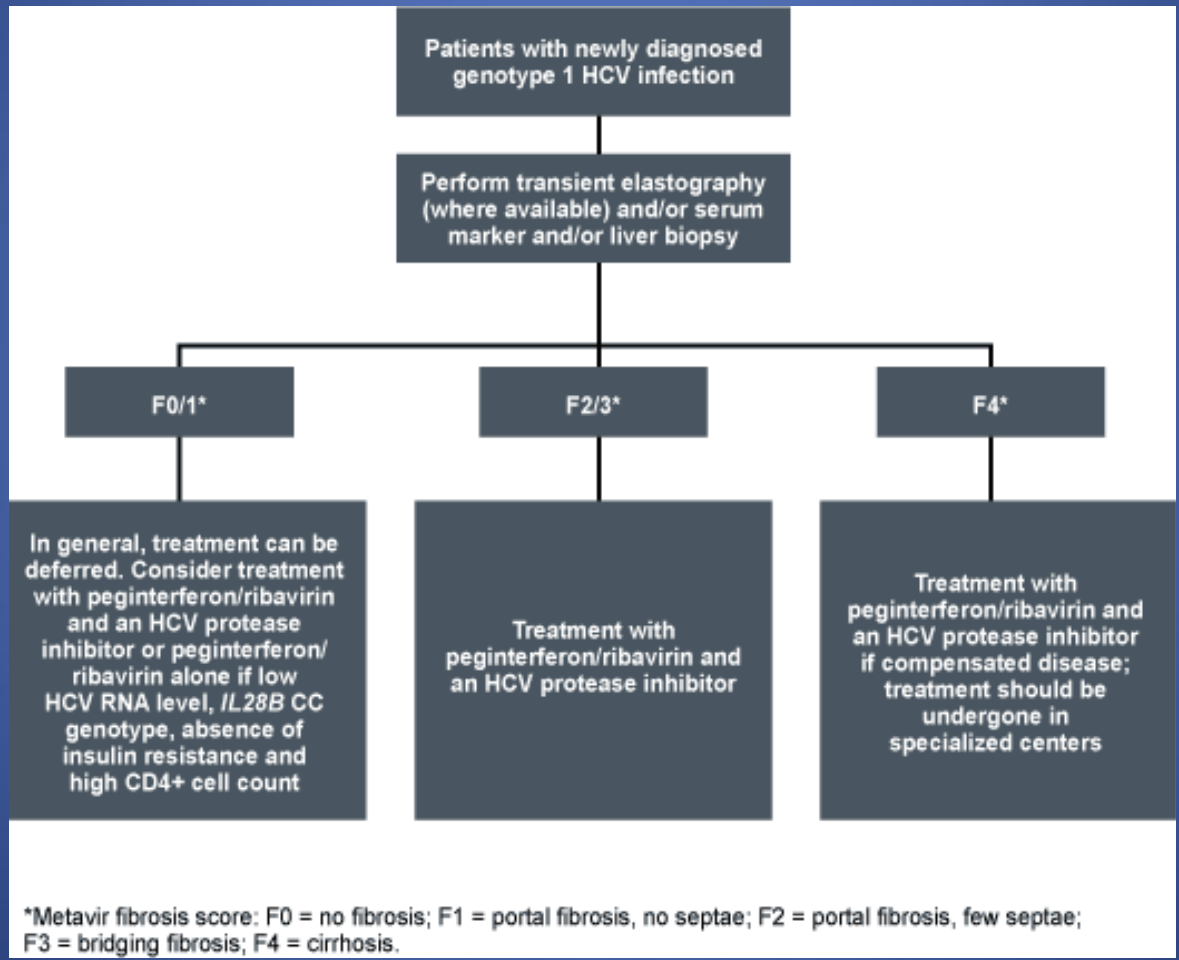
http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.

Patient Group	Recommendation*
Patients not receiving antiretroviral therapy	Use either boceprevir or telaprevir
Patients receiving raltegravir + 2 NRTIs	Use either boceprevir or telaprevir
Patients receiving atazanavir/ritonavir + 2 NRTIs	Use telaprevir at the standard dose; do not use boceprevir
Patients receiving efavirenz + 2 NRTIs	Use telaprevir at increased dose of 1125 mg every 7-9 hrs

*These recommendations may be modified as new drug interaction and clinical trial information become available.

Algorithm to treat HCV/HIV G-1

CCO-HEP



Management of HIV/HCV G-1 by Fibrosis and Previous Treatment Outcome

HCV-CCO

	Treatment Naive	Previous Relapser	Previous Nonresponder
F0/1	Individual decision	Individual decision/ triple therapy	Defer
F2/3	Triple therapy	Triple therapy	Defer*
F4	Triple therapy	Triple therapy	Triple therapy

*Monitor fibrosis stage annually, preferably with 2 established methods. Treat with triple therapy, if rapid progression.

Protease Inhibitors and Resistance

- Replication of HCV is dependent on an error-prone RNA-dependent RNA polymerase
  - Gives rise to resistant variants that pre-exist before therapy and can be selected by antiviral agents
- Pre-existing resistance associated variants present at baseline are not predictive of outcome (SVR)
- While SVR was achieved in many patients treated with triple therapy, resistant variants were detected in 15% of patients treated with boceprevir and 12-22% of patients treated with telaprevir
- Resistant variants decline over time
- Patients who fail 1 protease inhibitor should not be treated with another

FDA. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm. Accessed June 2011.

Monitoring During Treatment

- Monthly visit with HCV provider to assess adherence and side effects; frequency can be adjusted as clinically needed
- Assess response to treatment: HCV RNA
  - Response guided therapy milestones
  - Boceprevir: wk 4 (lead-in), wk 8 and 24
  - Telaprevir: wk 4 and 12
  - EOT/ SVR
  - Assay with LLQ of < 25 IU/ml and LLD <10 IU/ml
  - Laboratory monitoring

LLQ: lower limit of quantitation; LLD: lower limit of detectability

Treatment Monitoring Guidelines

	Weeks					Frequency thereafter				
Labs	0	2	4	8	12	Every 4 wks	PRN	Week 24	End of Tx	6 mo Post-tx
CBC	✓	✓	✓	✓	✓	✓	✓	✓		
LFTs	✓	✓	✓	✓	✓	✓		✓		
Psychiatric analysis	✓	✓	✓	✓	✓	✓				
Renal/Uric acid	✓				✓		✓			
Glucose	✓				✓		✓			
TSH	✓				✓		✓			
Pregnancy	✓		✓	✓	✓	✓				
HCV RNA	✓		✓	✓	✓			✓	✓	✓

Pretreatment Counseling and Patient Education

- Dosing schedules
- Importance of medication adherence
- Protease inhibitors should not be used as monotherapy
- Protease inhibitors are not to be dose-reduced or interrupted
- Managing missed doses
- Contraception/Pregnancy
  - Important for both partners
  - Requires 2 forms of contraception during and extending ≥ 6 months after treatment
- Signs and symptoms of possible side effects
  - Such as rash, anemia, neutropenia, dysgeusia
  - Supportive care for side effects

Special Groups

Indolent B-Cell Non-Hodgkin Lymphoma

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

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

Ann-Arbor Classification of NHL

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

A: no systemic symptoms;
B: unexplained fever, night sweats, or weight loss > 10% during 6 months before diagnosis

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

- Type II mixed: 95% of patients have HCV infection.
- Some cases of type-III mixed cryoglobulinemia are also HCV-related.
- Palpable purpura, skin necrosis in exposed areas, hepatosplenomegaly, hypocomplementemia C3, C4, C1q (C4 < C 3), & IgM kappa Rheumatoid Factor.
- Renal disease: hematuria, proteinuria (nephritic range), hypertension (80%), moderate renal insufficiency (50%).
- HCV-containing immune complexes cause the renal disease.

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

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

HCV-related Mixed (IgG/IgM) Cryoglobulinemia

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

HCV-Related Renal Disease

HCV-Related Renal Disease
Peg-IFN + RBV Treatment

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

Treatment of Chronic HCV in ESRD on Dialysis

HCV in ESRD & post-KTx Treatment

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

Peg-IFN-a2a in ESRD
Pharmacokinetics

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

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

Author	Treatment	Result
Kokoglu (J Gastroenterol Hepatol 2006;21:575-580)	Rp(12): Peg 135 x 48w C(13): no therapy	Rp: EOT(-) 84%, 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	EOT(-): 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%

Treatment According to Stages of Chronic Kidney Diseases

Stage	Description	GFR (ml min1 1.73 m2)	Recommended Treatment
1.	Kidney damage with normal or increased GFR	90	A
2.	Kidney damage with mild decrease GFR	60-90	A
3.	Moderate decrease GFR	30-59	B
4.	Severe decrease GFR	15-29	B
5.	Kidney failure	15	B
5D.	Dialysis (hemo-or peritoneal)		C

A: Routine combination therapy according to viral genotype.

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

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

Treatment

Pre-Transplantation

&

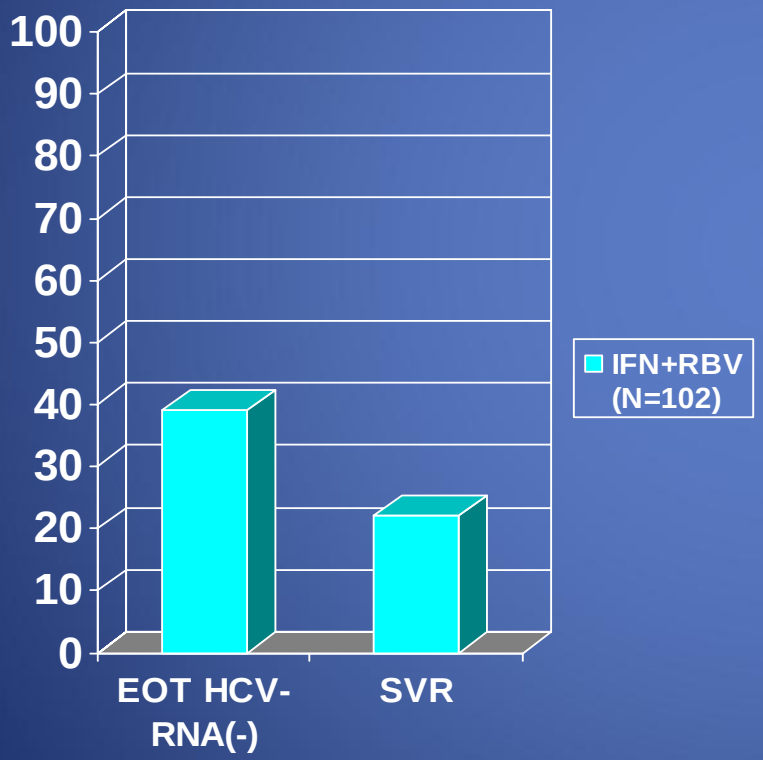
Post-Transplantation

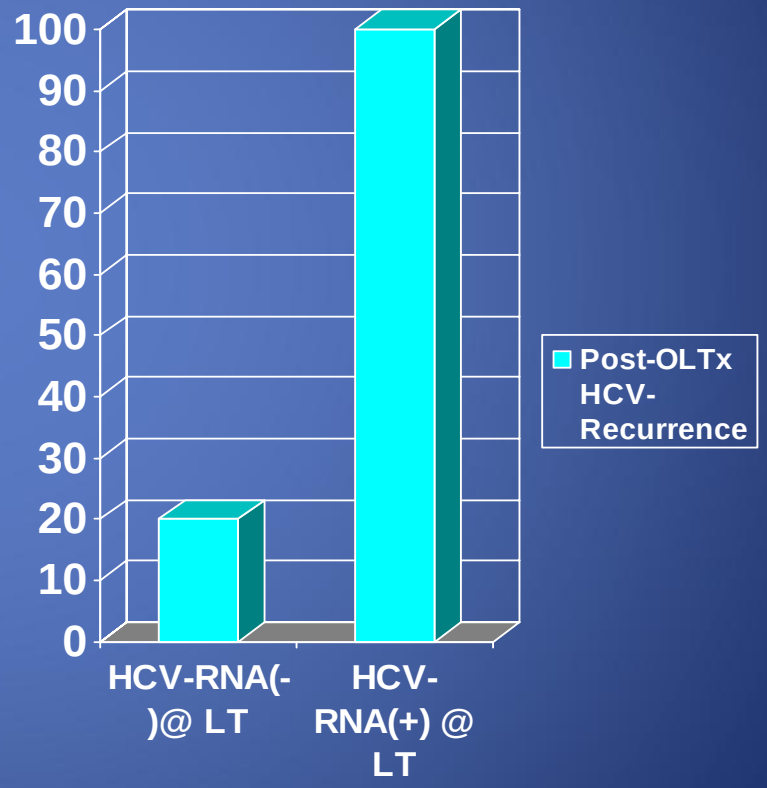
Pre-LTx Treatment Candidates

- **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. They benefit from antibiotic prophylaxis during therapy (Norfloxacine).
- **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

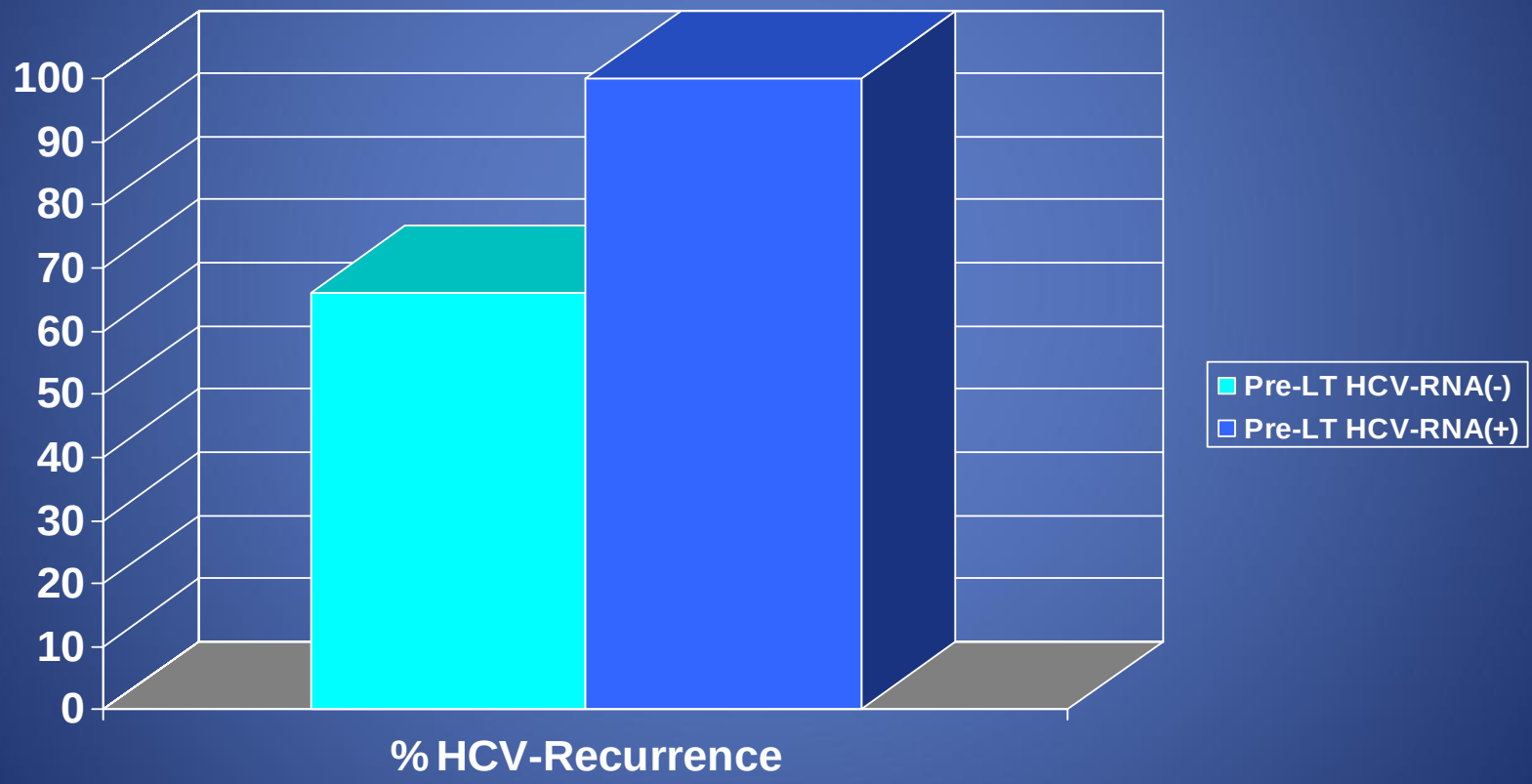
Everson et al. Rev. Gastrointest Disord 2004;4 Suppl 1:S31-38





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

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



Treatment of Recurrent HCV
Preemptive

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

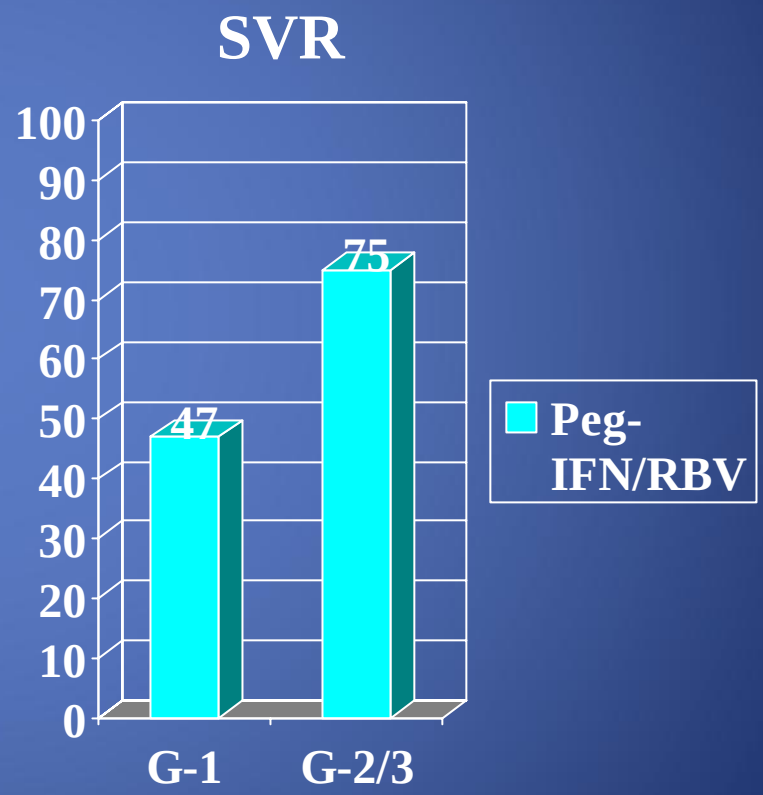
Treatment of Recurrent HCV After METAVIR Stage 2 (occasional bridging)

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

Peg-IFN + RBV for HCV Recurrence in OLTx Recipients

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

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



Questions ?

Risk Factors Associated to Severity of Recurrence

- **Recipient related**
  - **Female gender:** **lower survival**
  - **Age:** **lower survival**
  - **Non-white race:** **lower survival, more severe**
  - **Severity of illness:** **lower survival**
  - *Hepatitis B co-infection:* *controversial*
- **Donor Related**
  - **Age > 65:** **lower survival, more severe**
  - *HLA-mismatch* *controversial*
  - *Living donor:* *controversial*
  - *Donor-liver fat:* *controversial*
  - *Genetic factors:* *controversial*

Risk Factors Associated to Severity of Recurrence

- **Virological**
  - **Pre-LTx viral load (>1M copies): more severe**
  - **Early post-LTx load: more severe**
  - **CMV infection (+ g-1a): more severe**
  - **HIV co-infection: more severe**
  - *Genotype 1b: controversial*
  - *Quasispecies: controversial*
- **Other**
  - **Time to recurrence: more severe**
  - **Steroid bolus, OKT3: more severe**
  - **Short time to recurrence: more severe**
  - *Cold ischemia time: controversial*

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**	**< 2 log drop**

No Responder

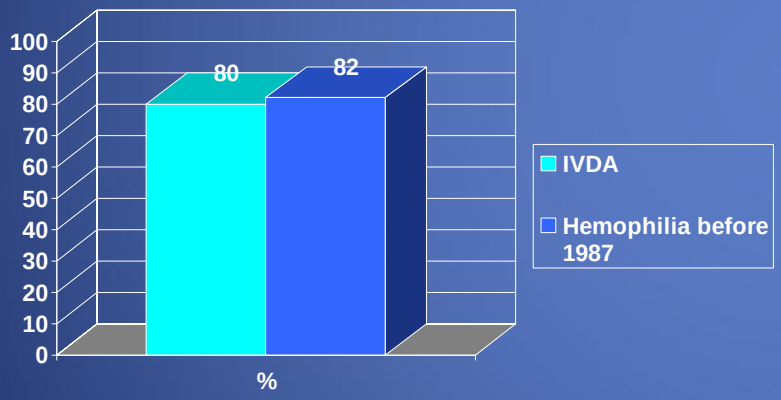
No Responder

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

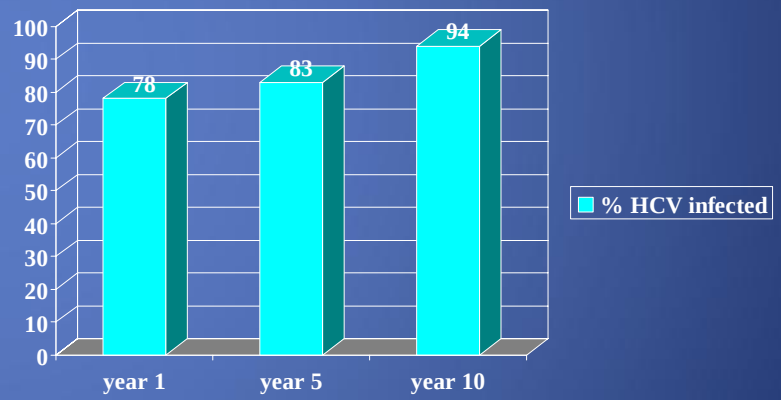
Relapse: from (-) to (+) after treatment

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

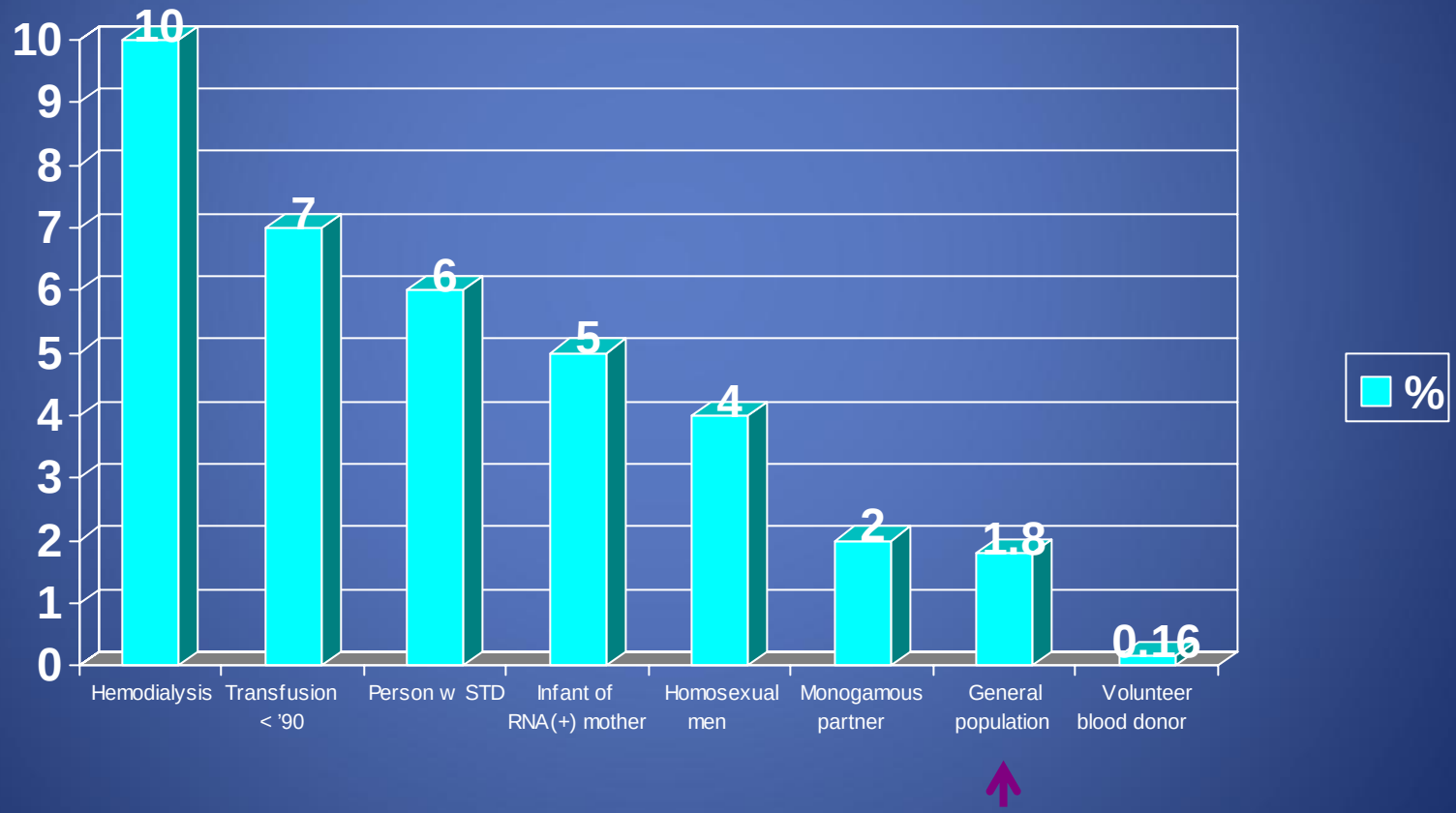
Extremely High HCV Prevalence



Risk of HCV in IVDA



HCV Prevalence in Other Groups



Characteristics of Persons for Whom Therapy Is Widely Accepted

- **Age 18 years or older, and**
- **HCV RNA positive in serum, and**
- **Liver biopsy showing chronic hepatitis with significant fibrosis (bridging fibrosis or higher), and**
- **Compensated liver disease (total serum bilirubin 1.5 g/dL; INR 1.5; serum albumin 3.4, platelet count 75,000 mm and no evidence of hepatic decompensation (hepatic encephalopathy or ascites), and**
- **Acceptable hematological and biochemical indices (Hemoglobin 13 g/dL for men and 12 g/dL for women; neutrophil count 1500 /mm3 and serum creatinine 1.5 mg/dL, and**
- **Willing to be treated and to adhere to treatment requirements, and**
- **No contraindications**

Characteristics of Persons for Whom Therapy Is Currently Contraindicated

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

Characteristics of Persons for Whom Therapy Should Be Individualized

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

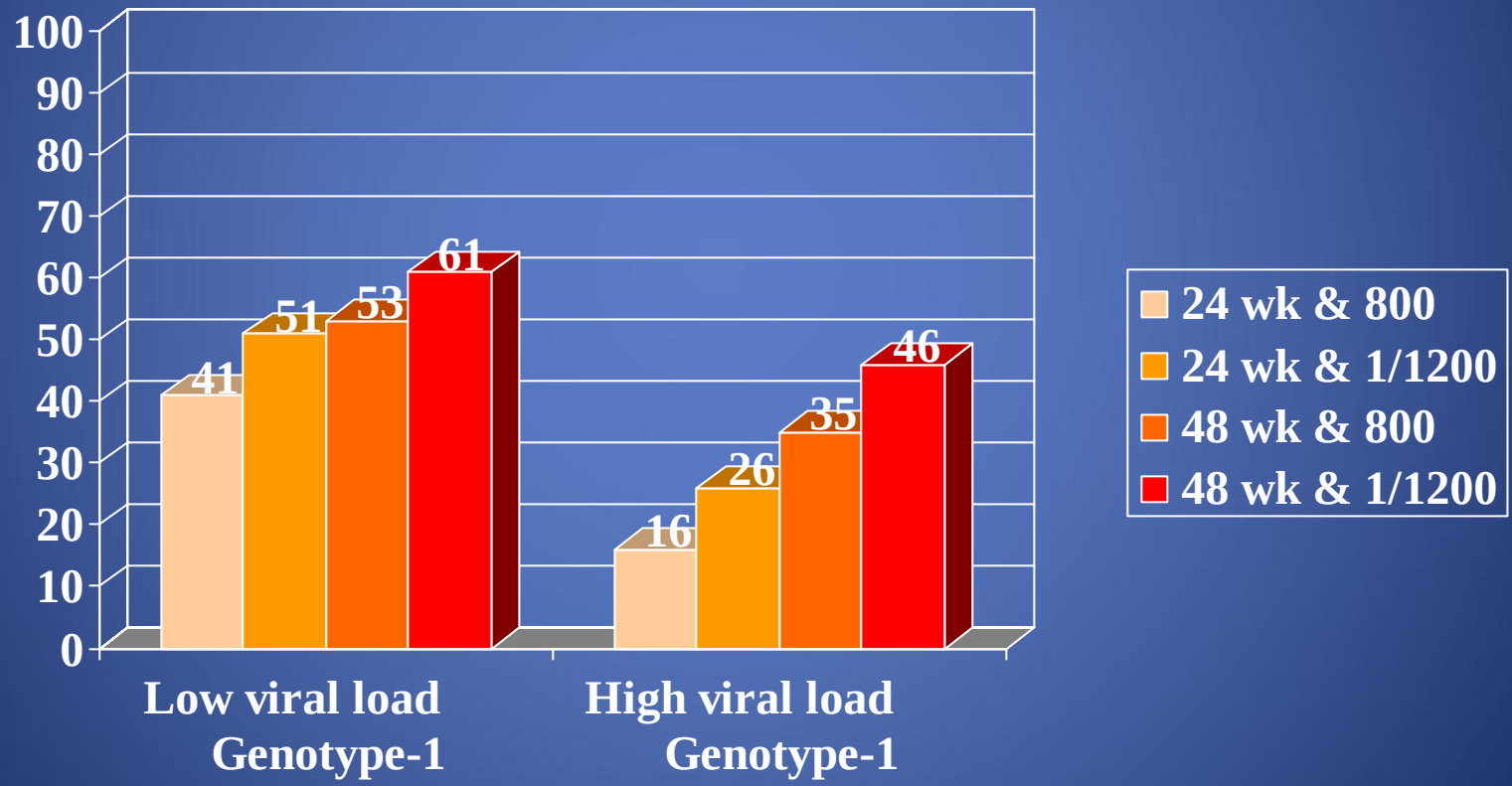
Prediction of SVR (Naïve)

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**

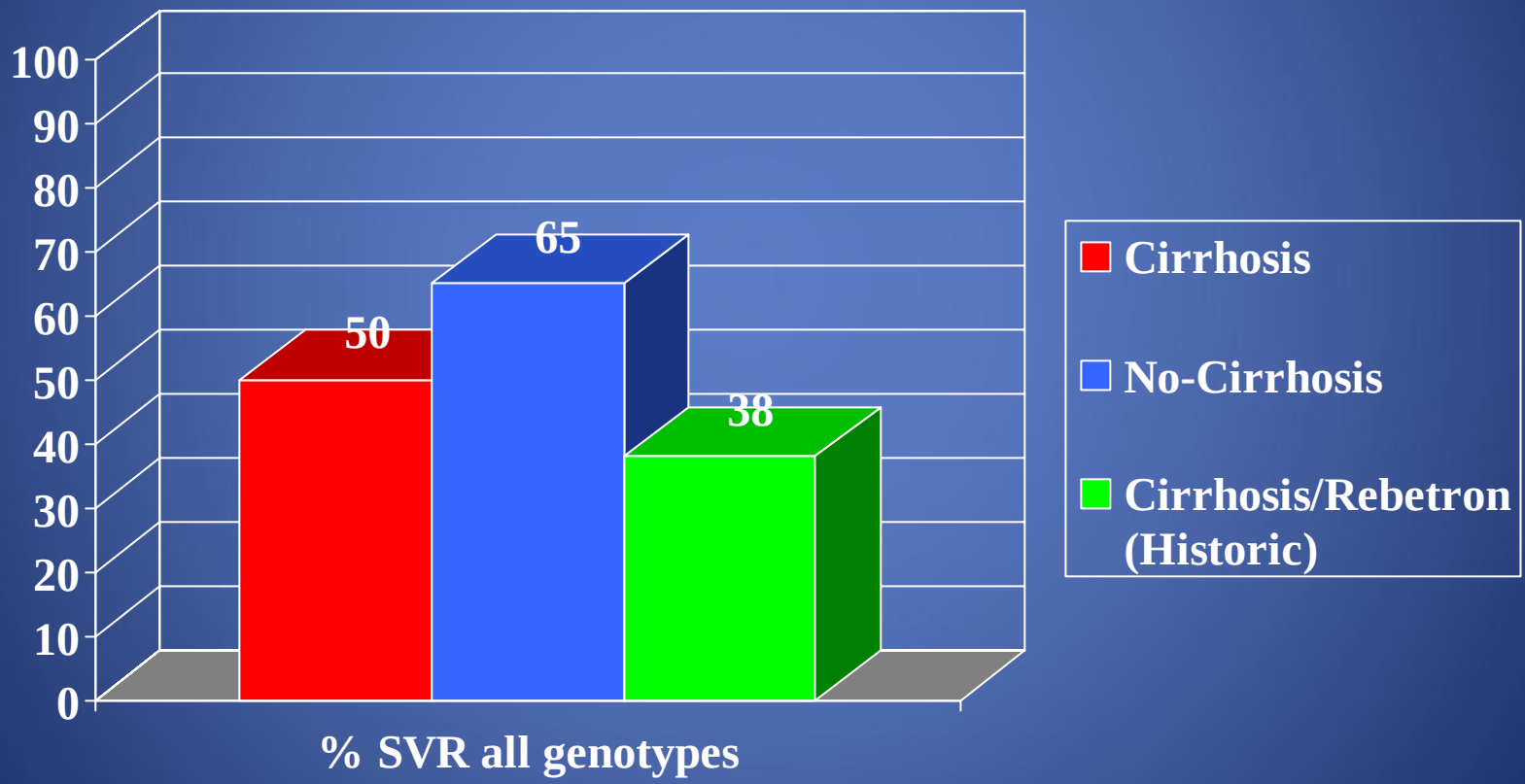
Peg-Interferon/RBV vs Interferon/RBV

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



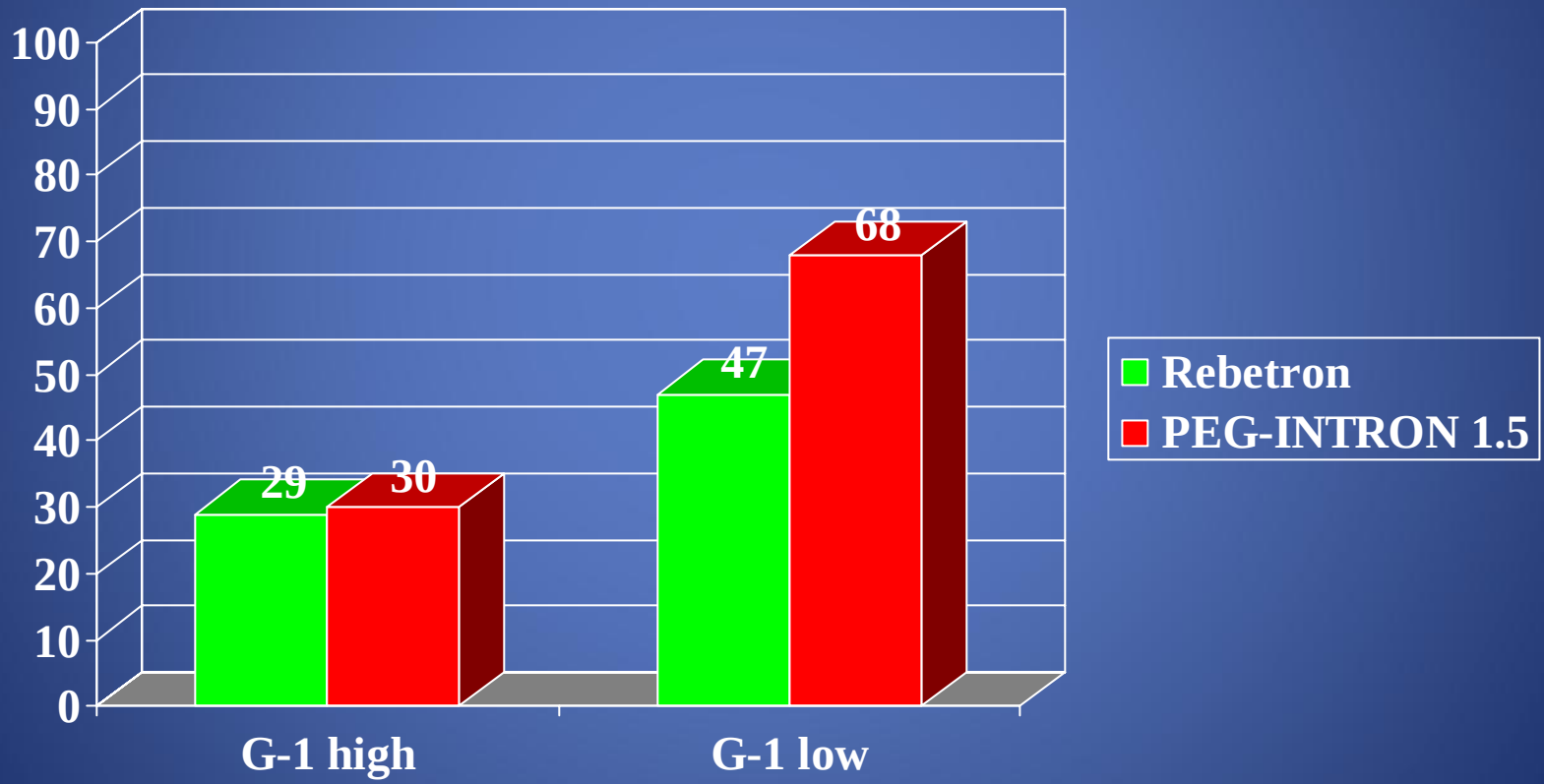
HCV Cirrhosis vs No-Cirrhosis

Pegasys + Ribavirin 1/1200 x 48 wks



PEG-INTRON + Ribavirin 800

Effect of **Viral load** in **Genotype-1**



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

Jensen D et al. AASLD 2005, Abstr

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

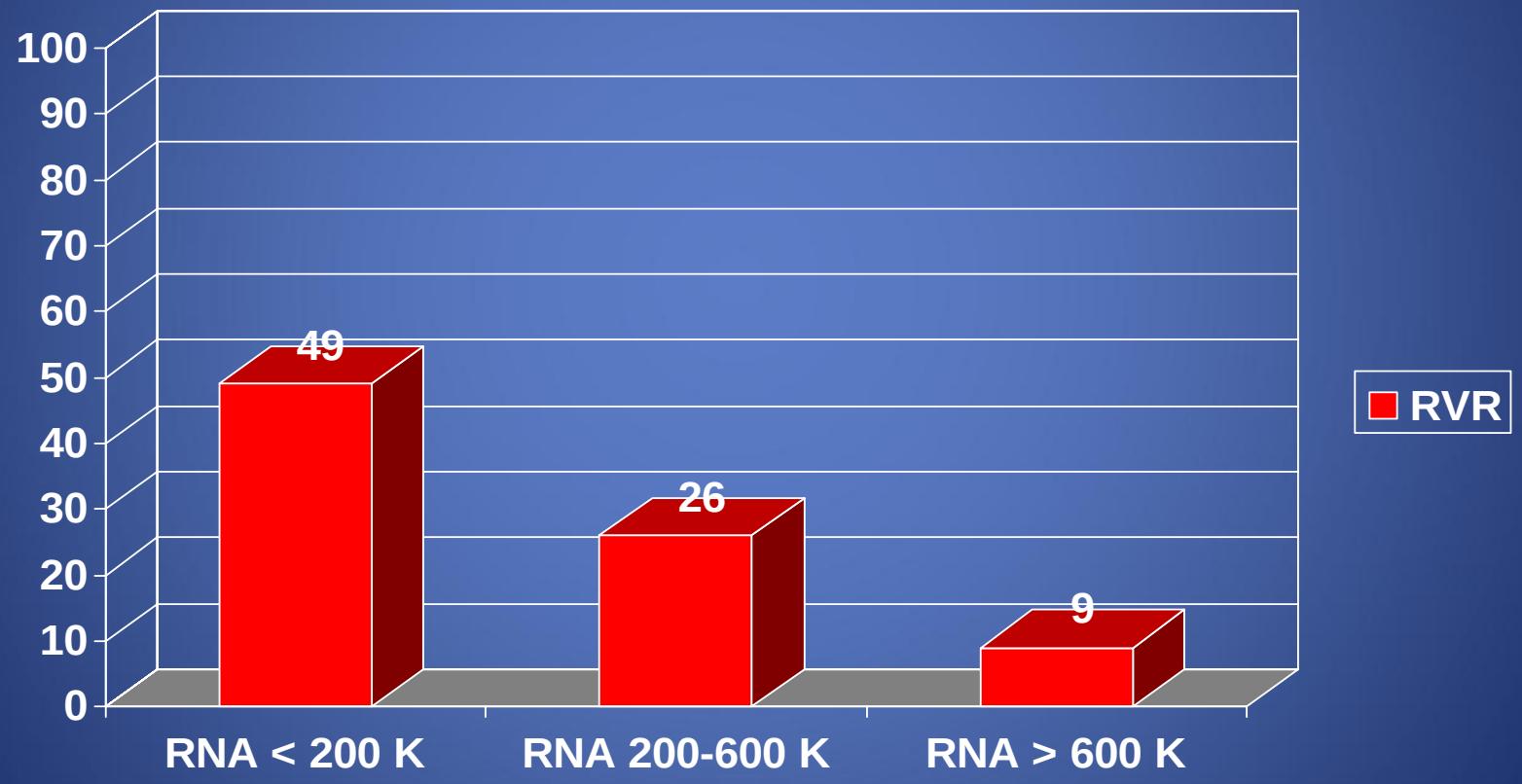
Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4) predicts SVR in genotype-1, with Pegasys + RBV x 24 wks

RESULTS

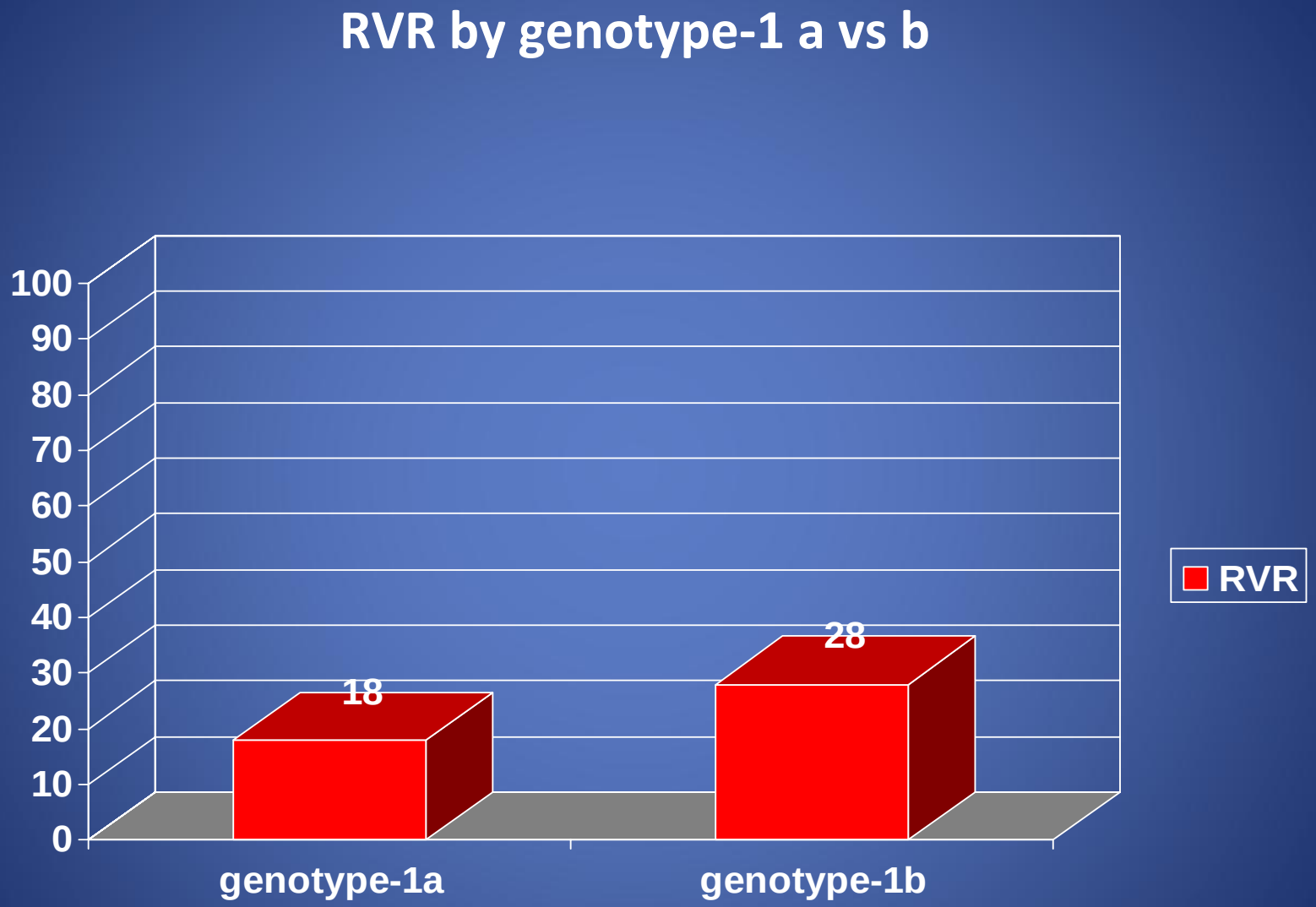
- 51 patients (24%) had RVR (HCV-RNA< 50 IU/mL @ wk 4):
  - 18% of g-1a &
  - 28% of g-1b.
- RVR was:
  - 18.2% with 800 RBV &
  - 28.2% with 1-1200 RBV;
- 20% of F3/F4 patients had RVR.

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

RVR by Baseline Viral Load



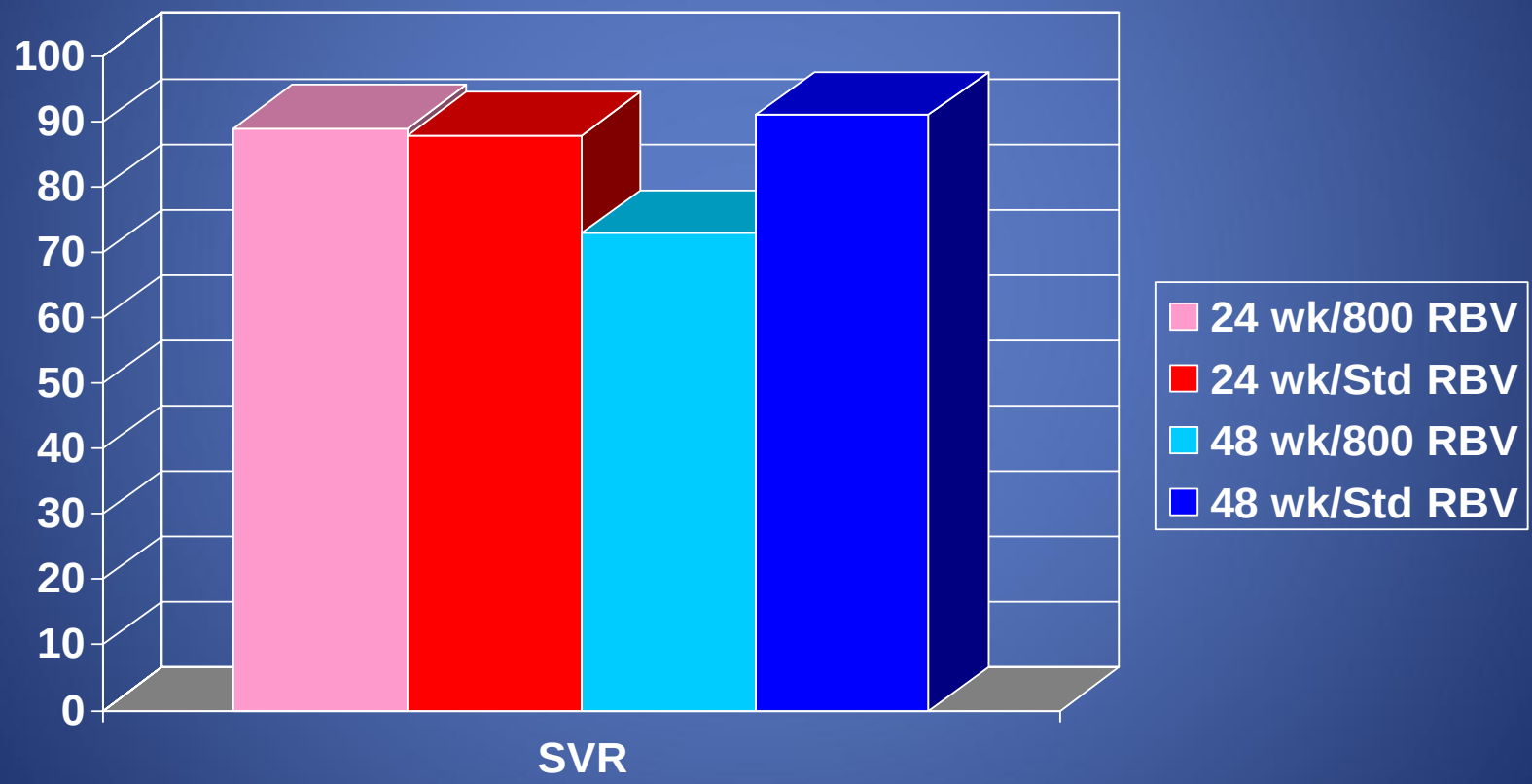
Rapid Virological Response (HCV-RNA < 50 IU/mL @ wk 4) predicts SVR in genotype-1, with Pegasys + RBV x 24 wks



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

Jensen D et al. AASLD 2005, Abstr

SVR of RVR-patients, by type of therapy



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

CONCLUSION

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

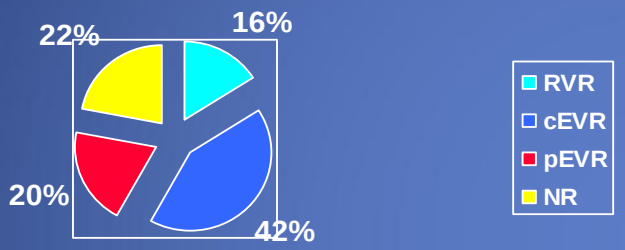
Rapidity of Response and SVR

Rapidity of Response by Genotype

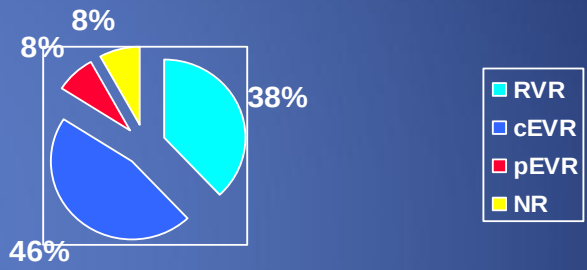
Fried MW, EASL 2008; Abstr #7

Genotype-1
N: 569

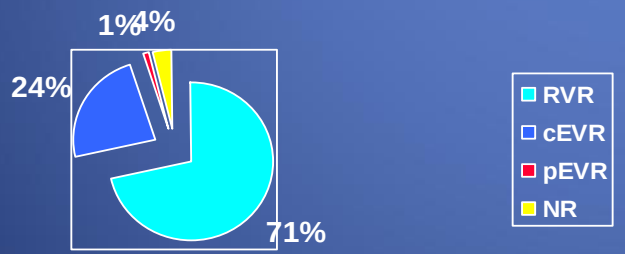
PEG 180
RBV 1000-1200
48 wks

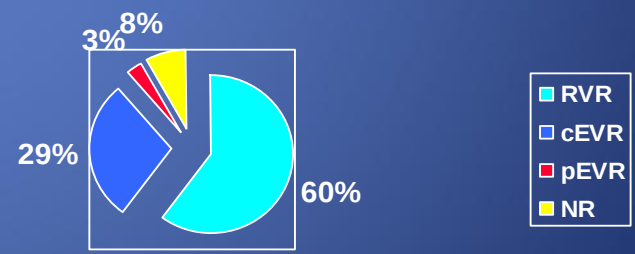


Genotype-4
N: 24



PEG 180
RBV 800
24 wks



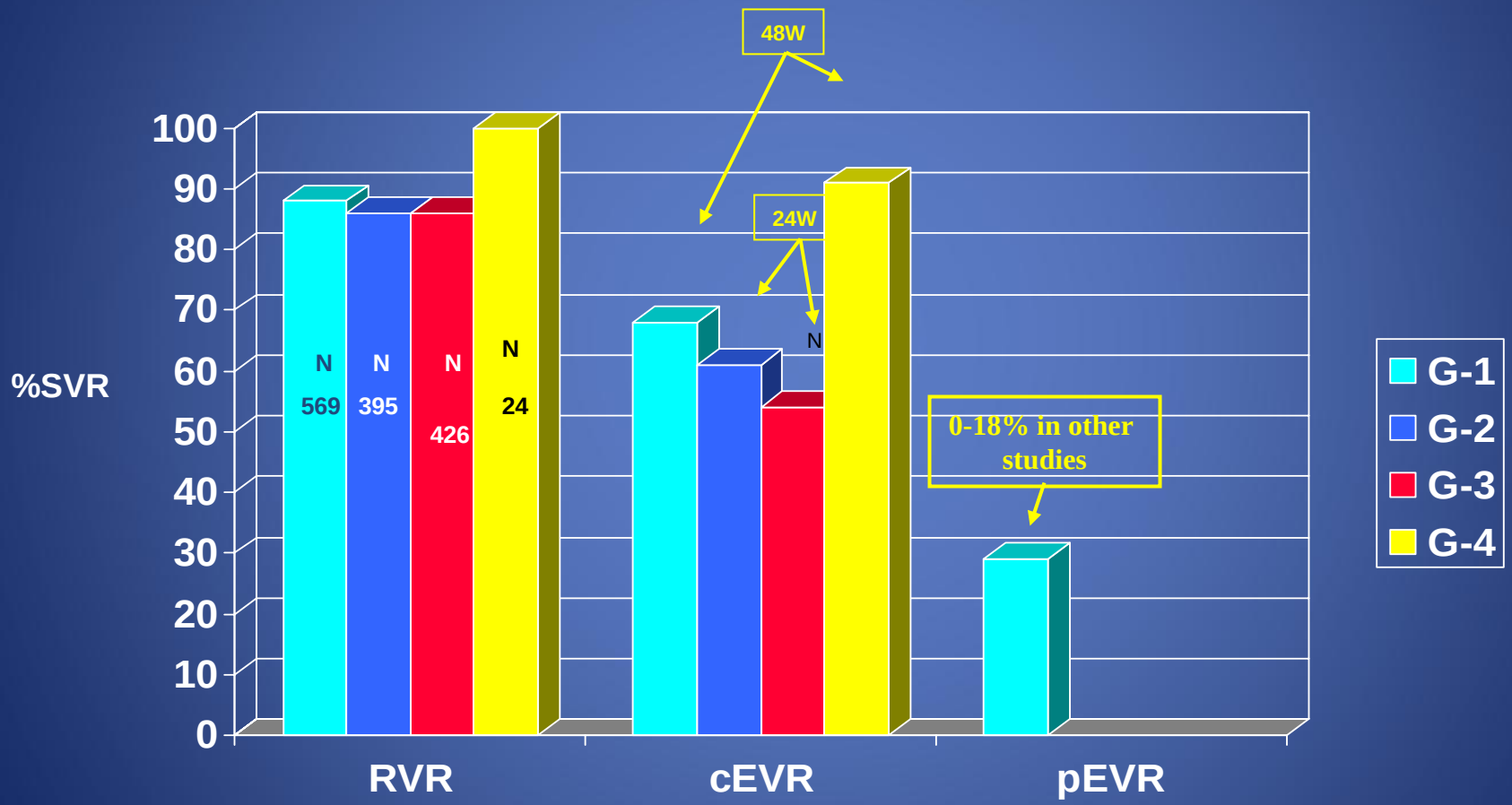


Genotype-2
N: 395

Genotype-3
N: 426

SVR by Response Type & Genotype

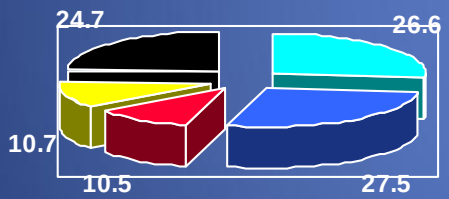
Fried MW, EASL 2008; Abstr #7



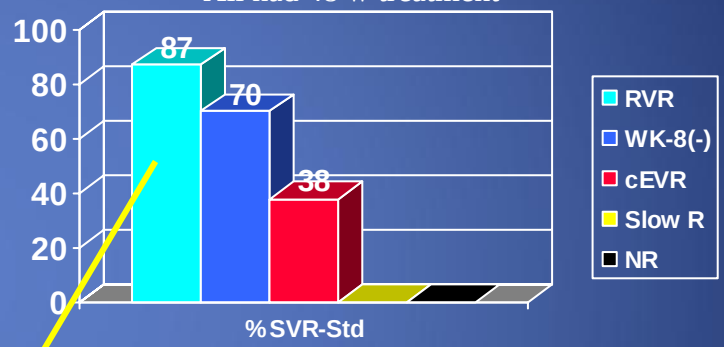
Individualized Treatment Duration in HCV G-1

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

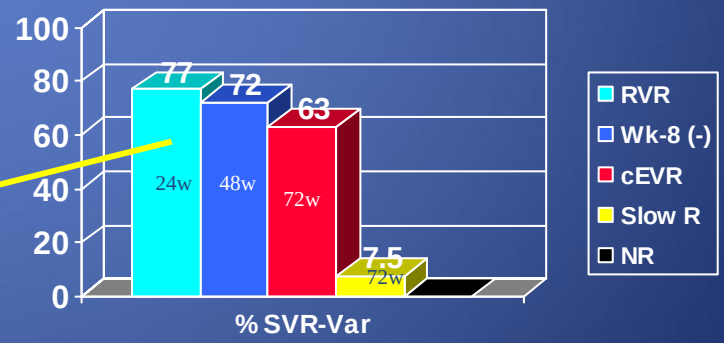
646 HCV G-1 patients
Peg-IFNa or b + RBV 1-1200



All had 48 w treatment



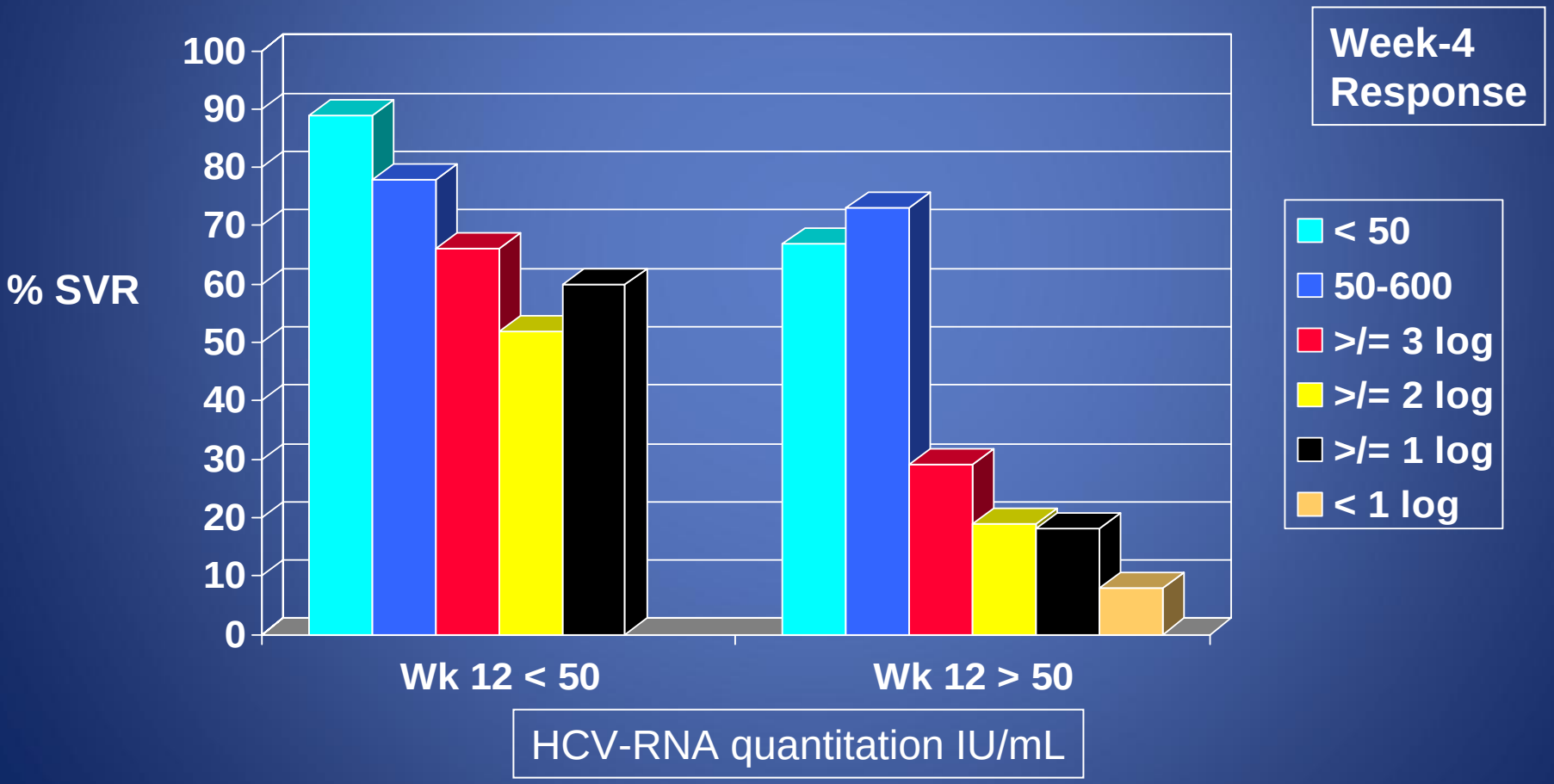
85% SVR if Baseline
HCV-RNA < 400K IU



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

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

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



Conclusion from Data

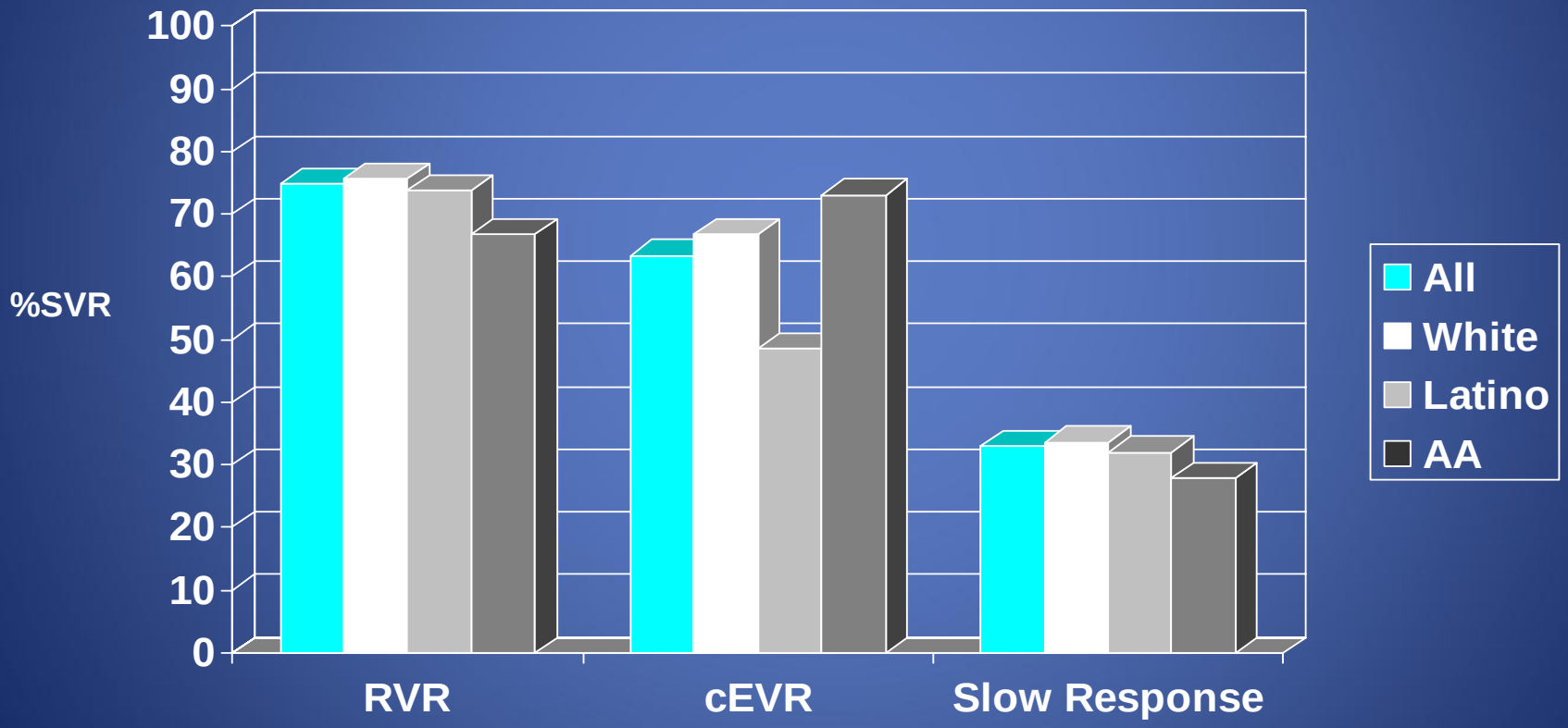
- Patients who at week 12 of PEG/RBV have HCV-RNA > 600 IU/mL should be considered for Treatment Modification.
- Proposed Treatment Modification Options:
  - Change to daily Interferon alfacon-1 @ 15 mcg/d + RBV for 48 more weeks (total 60 wk) if tolerating therapy well (preferred option)
  - Continue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

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

Different Ethnicities,
Baseline Viral Load and
Degree of Fibrosis

Type of Response, Ethnicity and SVR in G-1

Shiffman ML. ESLD 2008; Poster 835

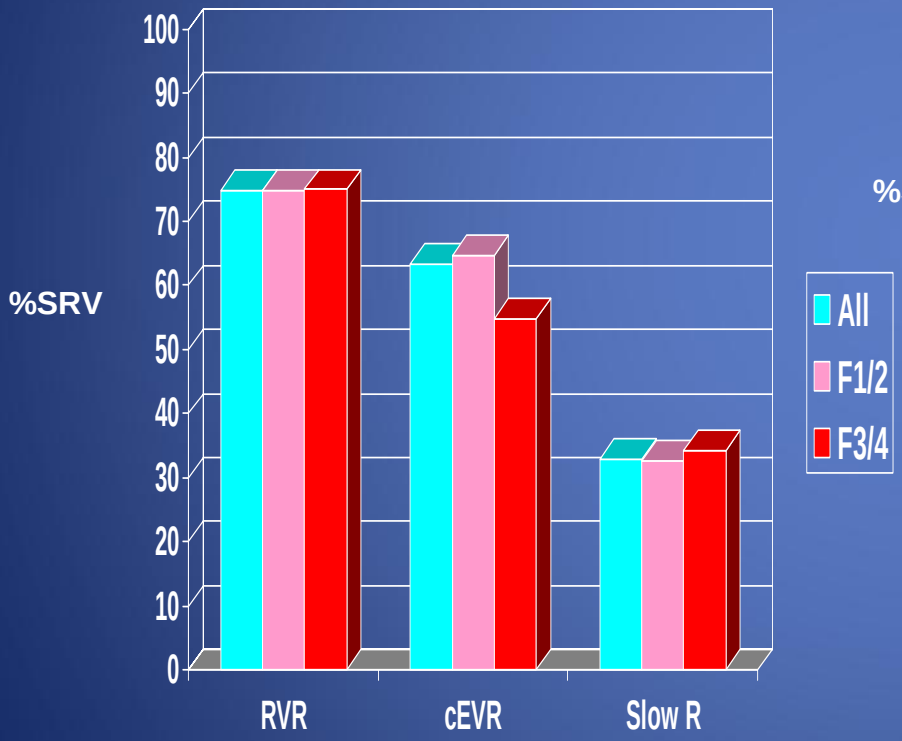


1243 pts G-1 infection (Fried, Hadziyannis, Virahep-C, LATINO studies)

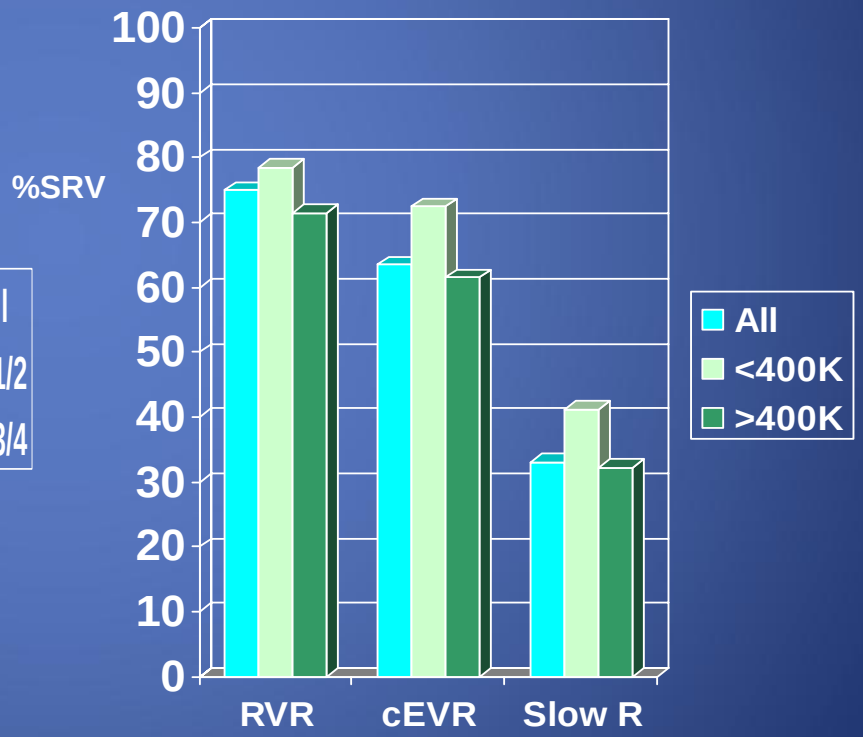
Effect of Fibrosis & Viral Load in G-1 SVR

Shiffman ML. ESLD 2008; Poster 835

SVR by Response-Type & Fibrosis



SVR by Response-Type & Viral-Load

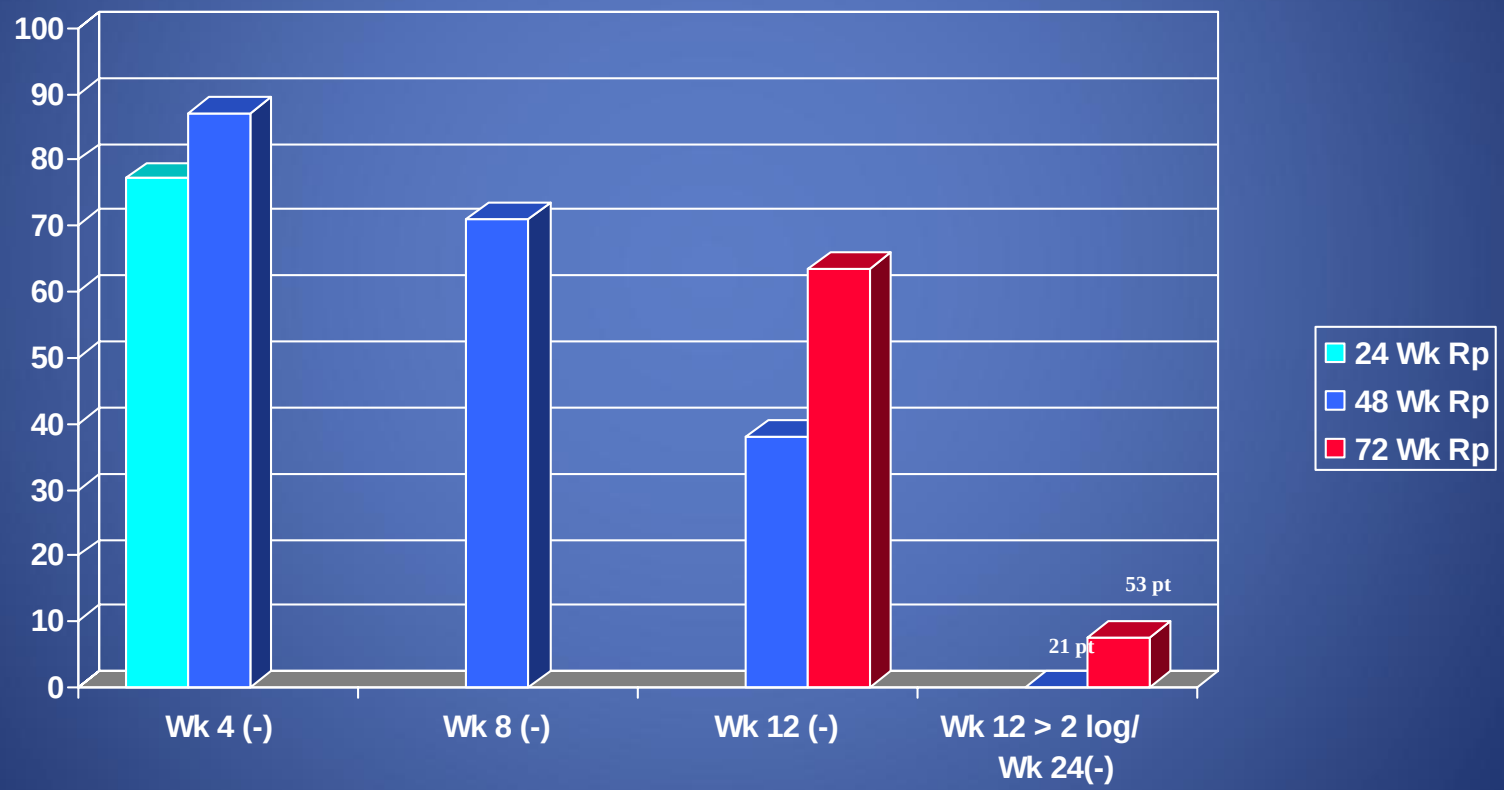


1243 pts G-1 infection (Fried, Hadziyannis, Virahep-C, LATINO studies)

Effect of Treatment Prolongation

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

Mangia et al Hepatology 2008; 47:43-50

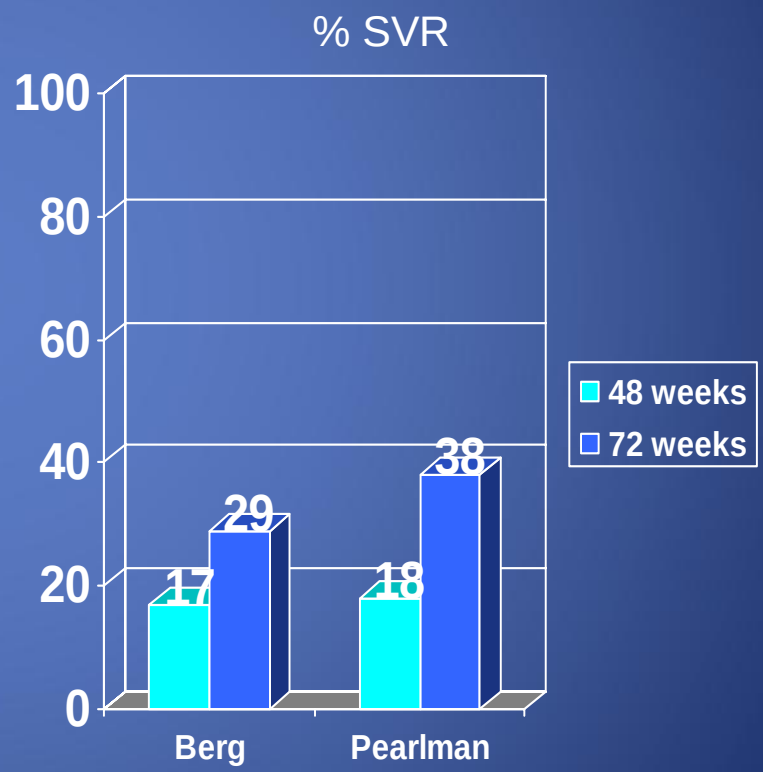


Prospective Randomized Study (Mean BMI 27)

Prolonged Therapy in HCV g-1
Slow Responders [> 2 log drop but (+) at week 12]

- Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, etal. Extended treatment duration for hepatitis C virus type 1: comparing48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 2006;130:1086-1097. (retrospective analysis; 100 (48 w) vs 106 (72 w) pts; RBV dose 800 mg/d)

- Pearlman BL, Ehleben C, Saifee S. Treatment extension to 72 weeks ofpeginterferon and ribavirin in hepatitis c genotype 1-infected slow responders. HEPATOLOGY 2007;46:1688-1694. (prospective, randomized, Peg 1.5/kg, RBV 800-1400, 49 (48 w) vs 52 (72 w) pts; no growth factors)



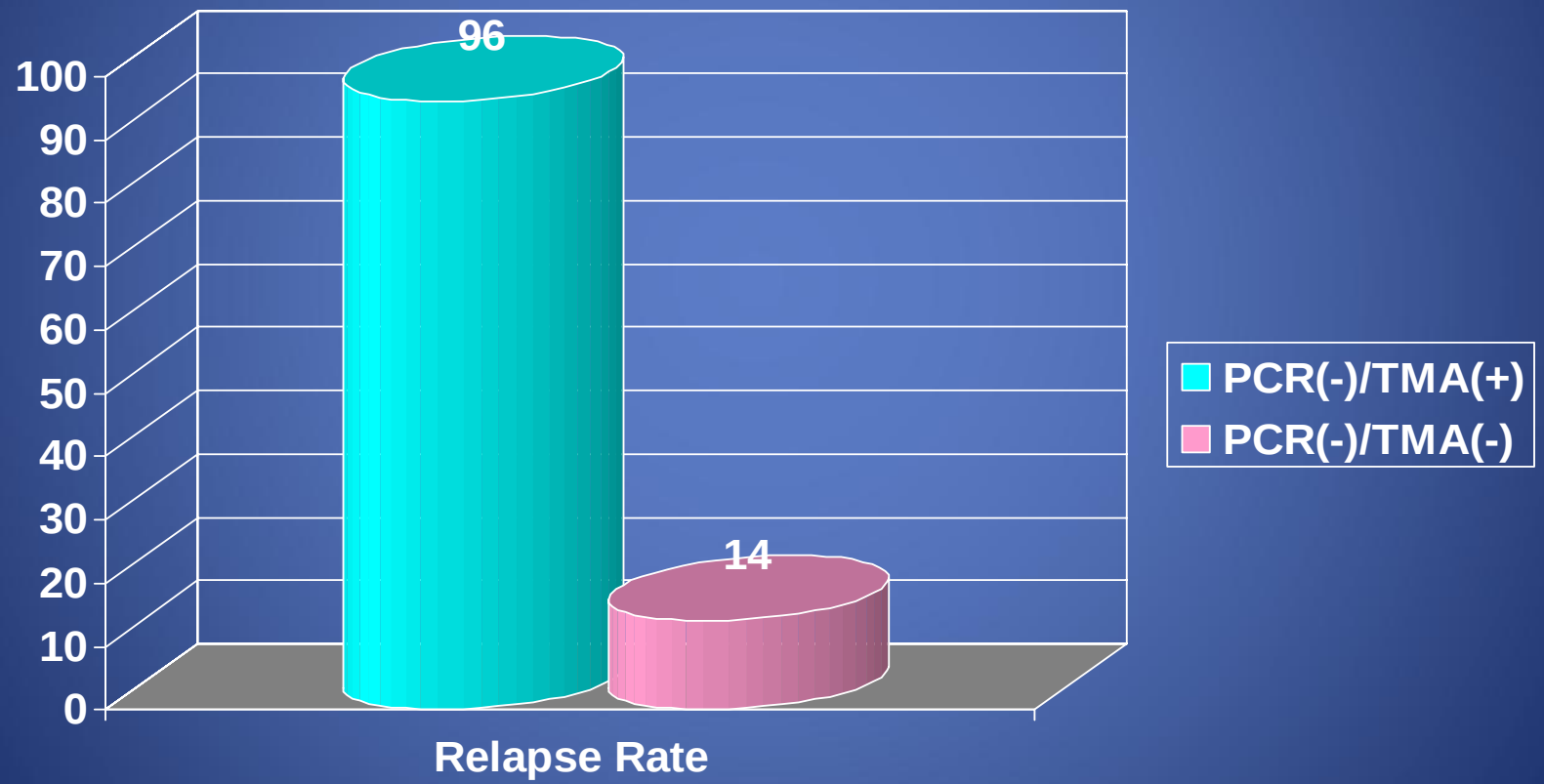
“Minimal Residual Viremia” @ EOT predicts post-treatment HCV relapse

Gerotto et al Abstr. AASLD # 40, 2004

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

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

Gerotto et al Abstr. AASLD # 40, 2004

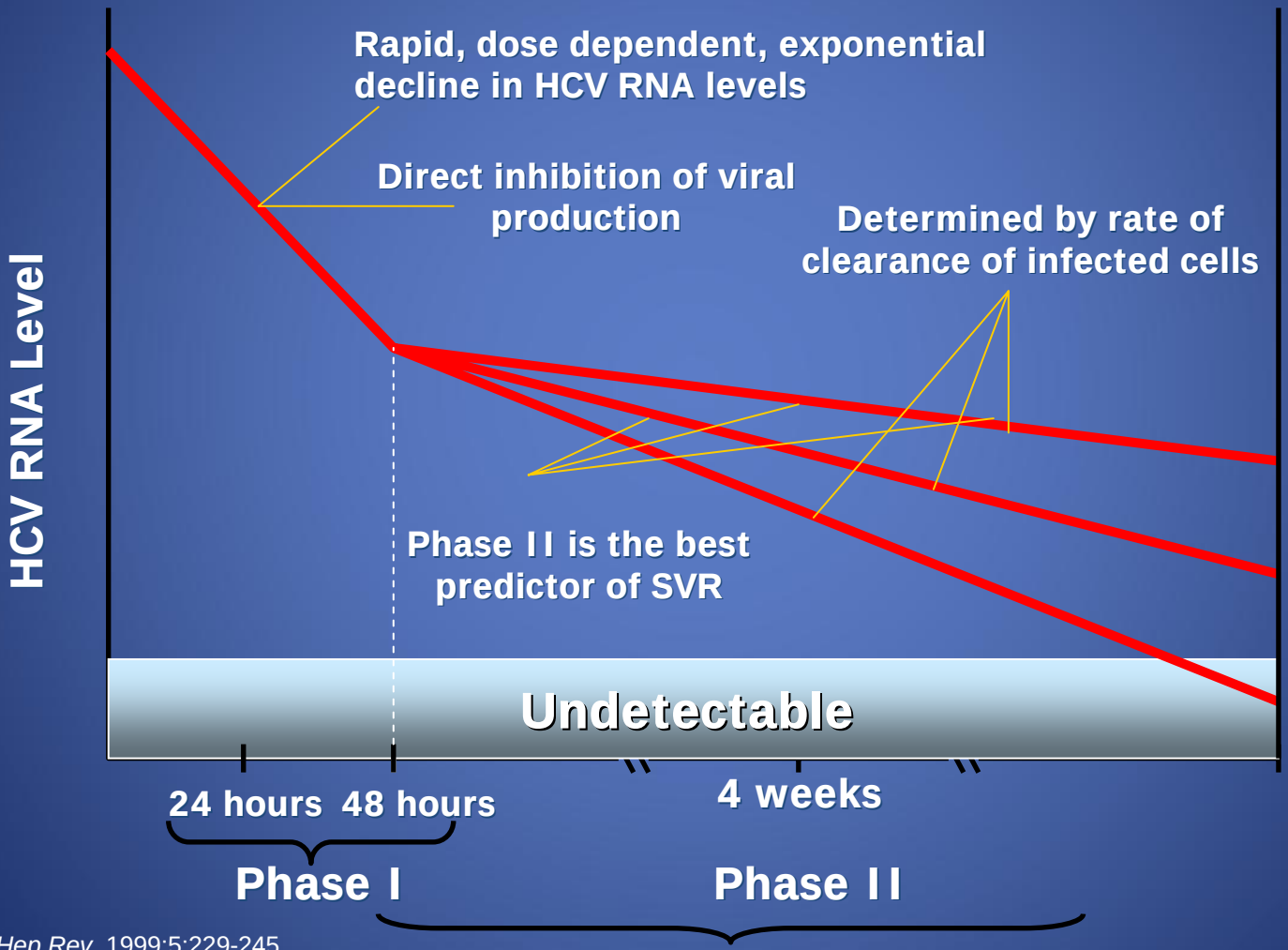


Conclusion

Abstr # 40

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

Biphasic Model of Viral Load Reduction on IFN



Ferenci P. *Viral Hep Rev*. 1999;5:229-245.
Layden-Almer and Layden, Seminars in Liver Disease, Vol.23, Suppl.1, 2003, pp.29-33.

Effect of Ribavirin in HCV
Phase-I Kinetics

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

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

Effect of Ribavirin in HCV Phase II & III Kinetics

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

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

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

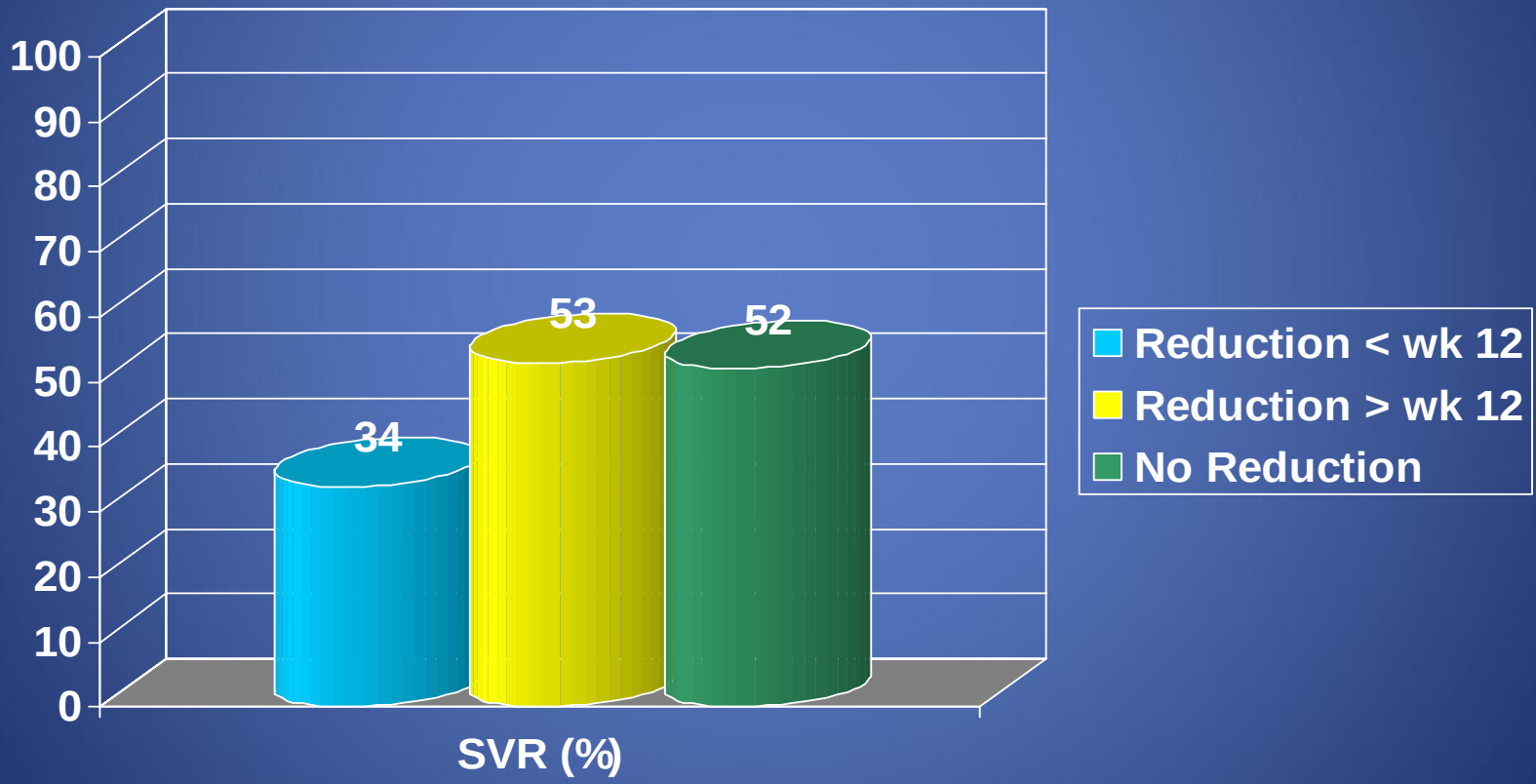
Lee et al. Abstr # 394, AASLD 2004

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

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

SVR by Time of RBV-Reduction

Lee et al. Abstr # 394, AASLD 2004



CONCLUSION

Abstr # 394

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

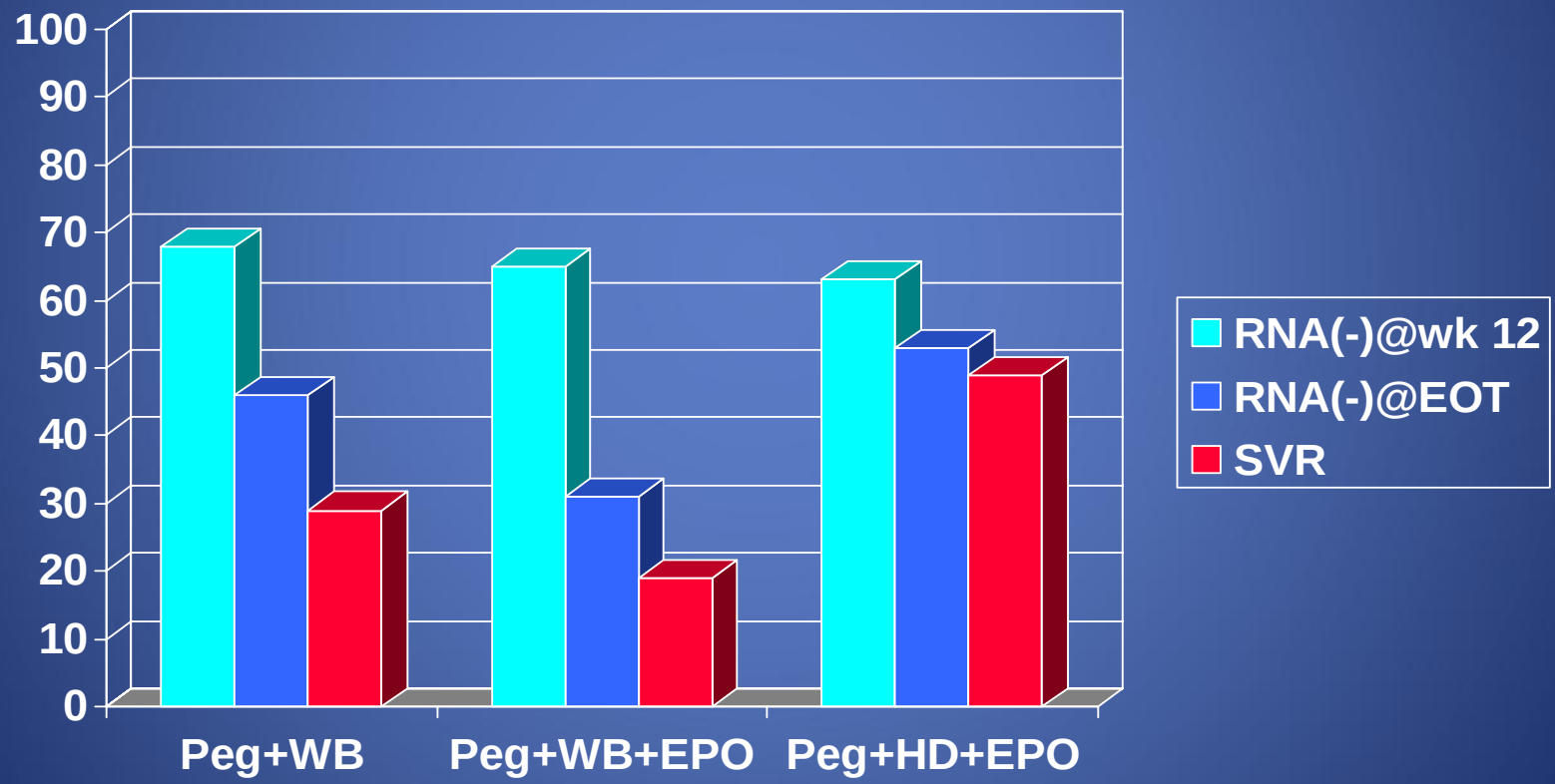
Peg-Intron + {[WB-RBV] vs [WB-RBV/EPO] vs [HD-RBV/EPO]} in HCV g-1 naïve

Shiffman M et al AASLD 2005, abstr 55

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

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

Shiffman M et al AASLD 2005, abstr 55



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

Shiffman M et al AASLD 2005, abstr 55

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

CONCLUSION

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

Importance of Maintaining Peg-Interferon Dose

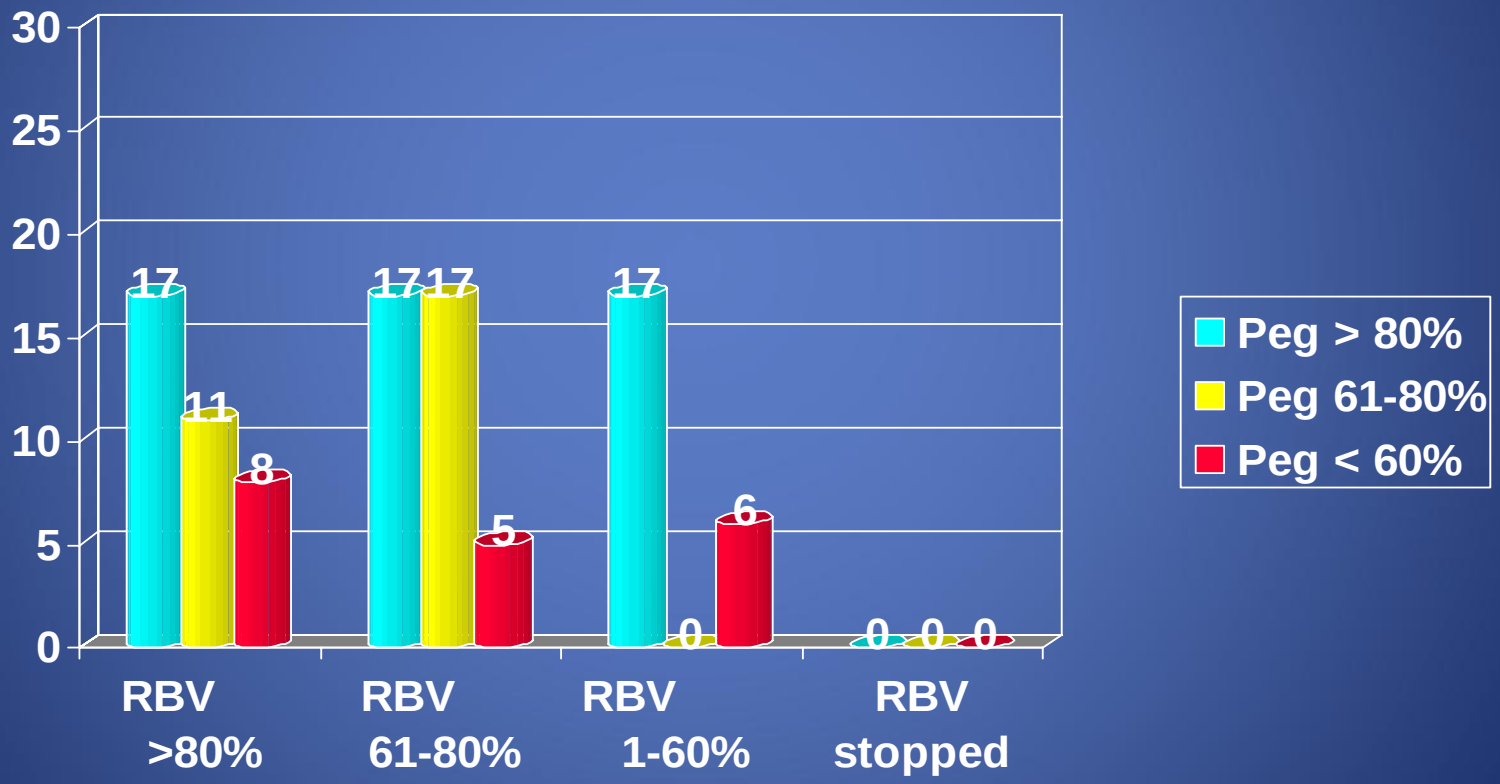
Effect of Pegasys & RBV dose in G-1 Ifn/Rebetron-NR with advanced fibrosis

Shiffman et al. AASLD Abstr # 349, 2004

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

SVR by Dose Maintained at week 20

Shiffman et al. AASLD Abstr # 349, 2004



CONCLUSION

Abstr # 349

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

Boceprevir and Telaprevir Contraindications

Drug Class	Contraindicated Drugs	Boceprevir	Telaprevir
Alpha 1-Adrenoreceptor antagonist	Alfuzosin	✓	✓
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	✓	
Antimycobacterial	Rifampin	✓	✓
Ergot Derivatives	Dihydroergotamine, ergonovine, ergotamine, methylergonovine	✓	✓
GI Motility Agent	Cisapride	✓	✓
Herbal Products	St. John's Wort (hypericum perforatum)	✓	✓

FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed June 2011.
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed June 2011.

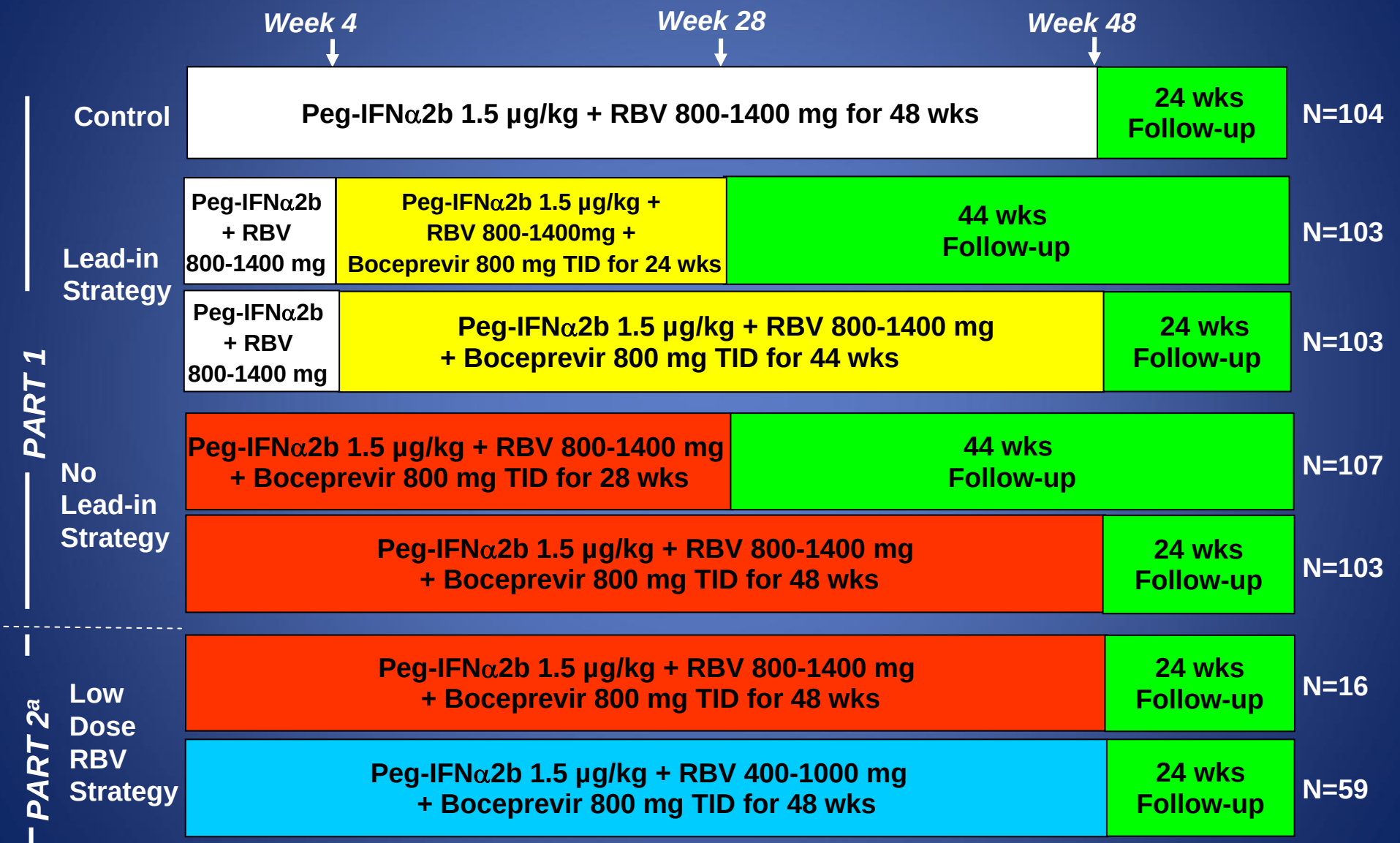
Boceprevir and Telaprevir Contraindications (cont)

Drug Class	Contraindicated Drugs	Boceprevir	Telaprevir
HMG CoA Reductase Inhibitors	Lovastatin, simvastatin	✓	✓ (also atorvastatin)
Oral Contraceptives	Drosperinone	✓	
PDE5 Enzyme Inhibitor	Sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension	✓	✓
Neuroleptic	Pimozide	✓	✓
Sedative/Hypnotics	Triazolam; orally administered midazolam	✓	✓

FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf. Accessed June 2011.
FDA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf. Accessed June 2011.

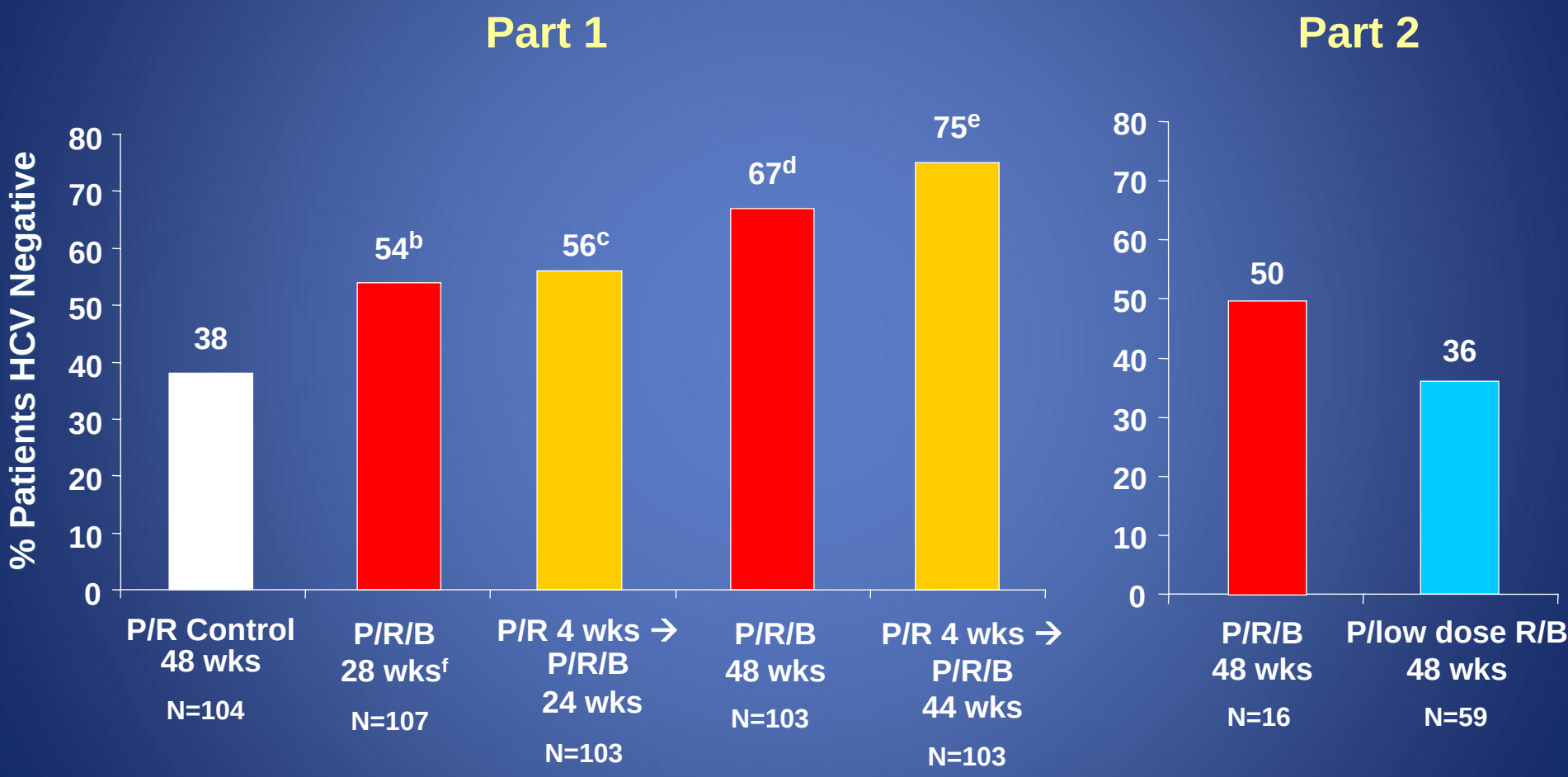
Boceprevir and Telaprevir in Chronic HCV Genotype-1

SPRINT-1 Study Design



[a]Part two consisted of 75 patients in 10 US sites, 1:4 randomization.

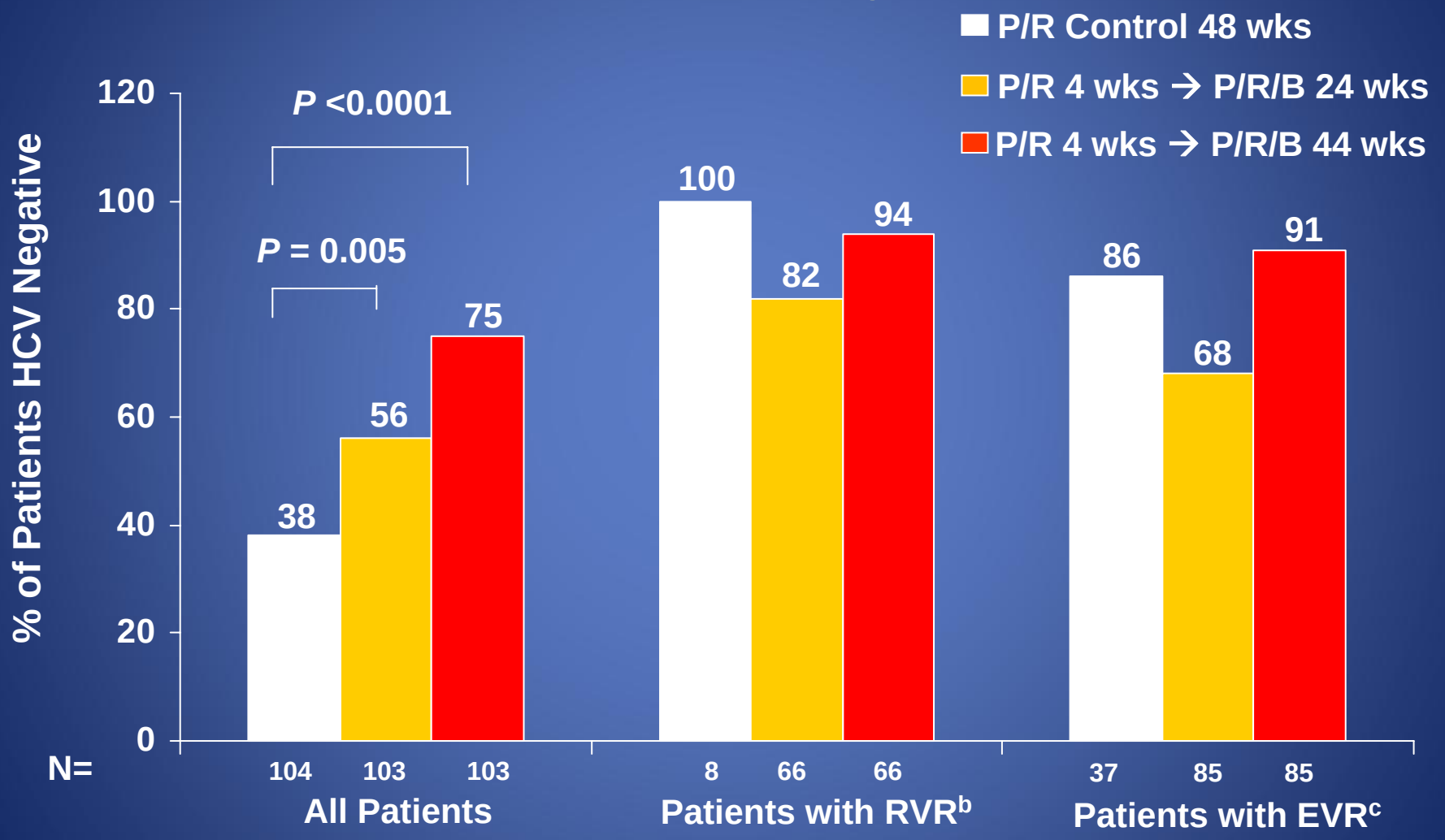
Sustained Virologic Response[a]



[a]Roche COBAS TaqMan LLD <15 IU/mL; [b]*P* = 0.013; [c]*P* = 0.005; [d]*P* <0.0001; [e]*P* <0.0001 compared to P/R Control;
[f]1 late relapser after follow-up week 24, not included n SVR.

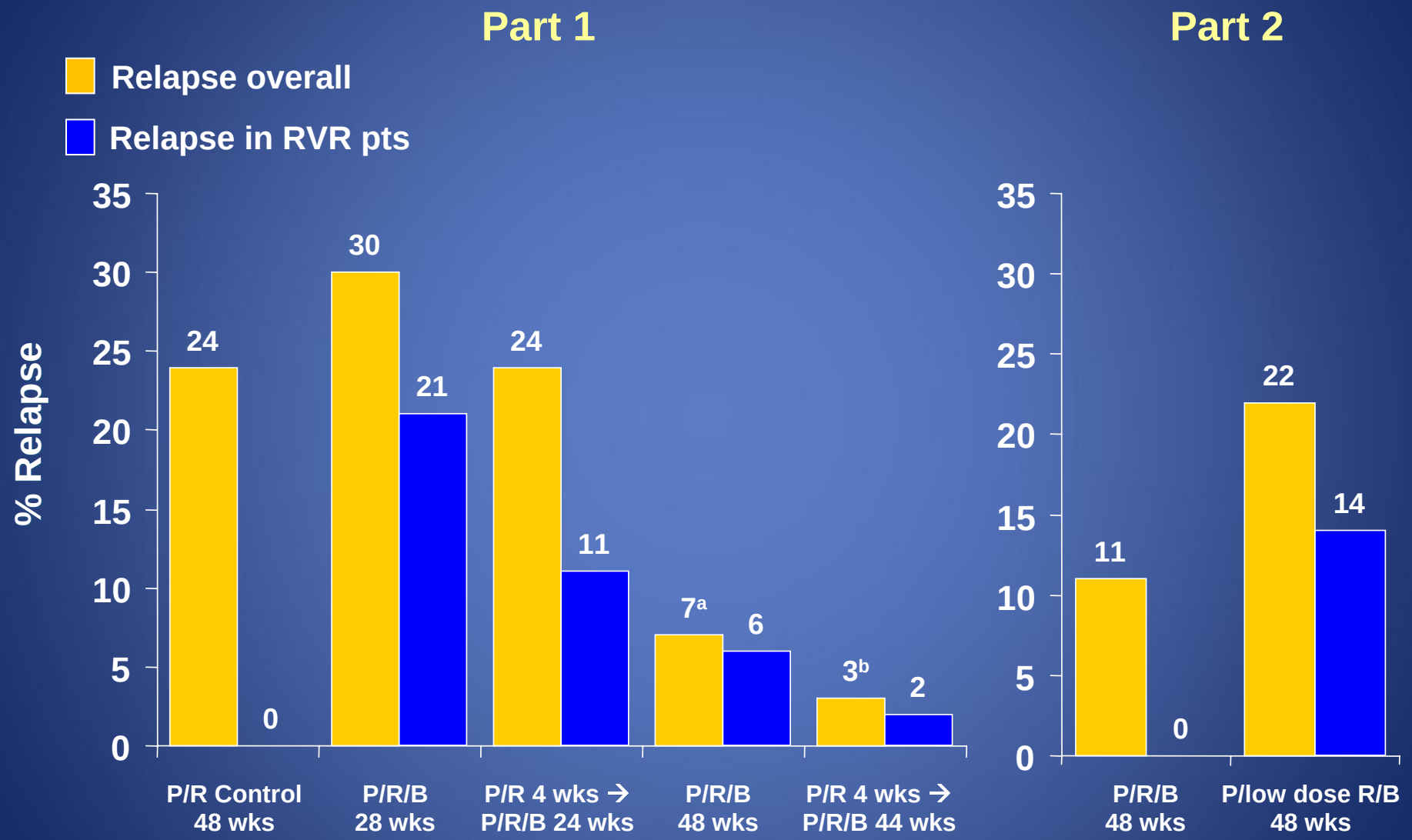
Predictability of SVR: RVR and EVR

SVR[a] by time to first PCR-negative HCV RNA



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

Overall Relapse and Relationship to RVR



[a]*P* = 0.0079; [b]*P* = 0.0002 compared to P/R Control.

Summary

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

Non-Responders to PEG/RBV

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

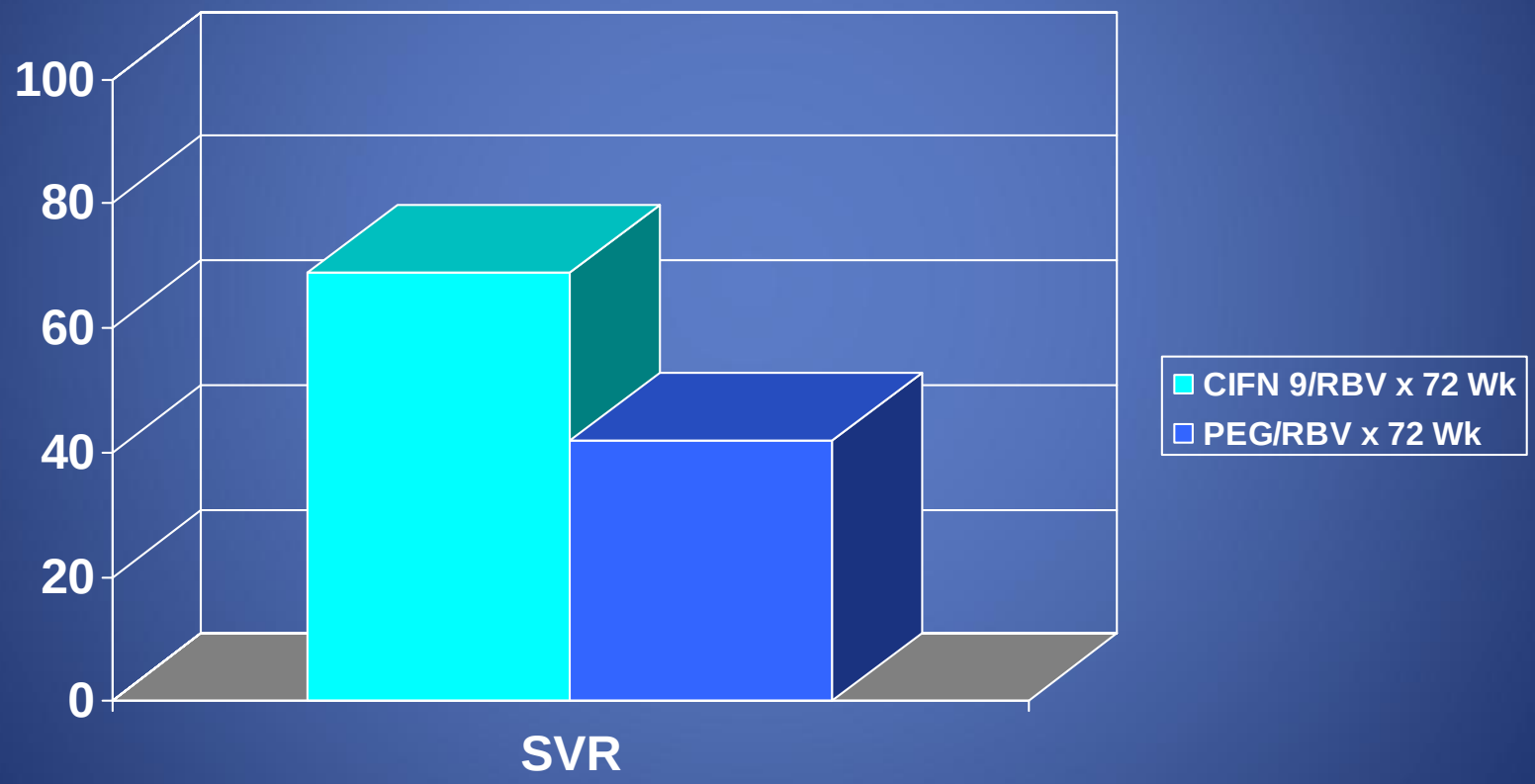
Bacon et al. Hepatology 2009; 49:1938-1846

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

Relapsers to PEG/RBV

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

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



N = 120 patients in the prospective study.