

# Nonresponder/Relapser With HCV Infection: Optimizing Current Therapeutic Modalities

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# Educational Objectives

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- ◆ Evaluate patient eligibility for retreatment
- ◆ Optimize patient retreatment with currently available therapeutic modalities
- ◆ Address correctable and noncorrectable factors that contribute to treatment failure in patients with hepatitis C virus (HCV)

# Question 1

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What percentage of patients with HCV genotype 1 treated with pegylated interferon (peg-IFN) + ribavirin (RBV) are able to achieve HCV-RNA negativity by week 12?

- A. 5%
- B. 20%
- C. 40%
- D. 60%

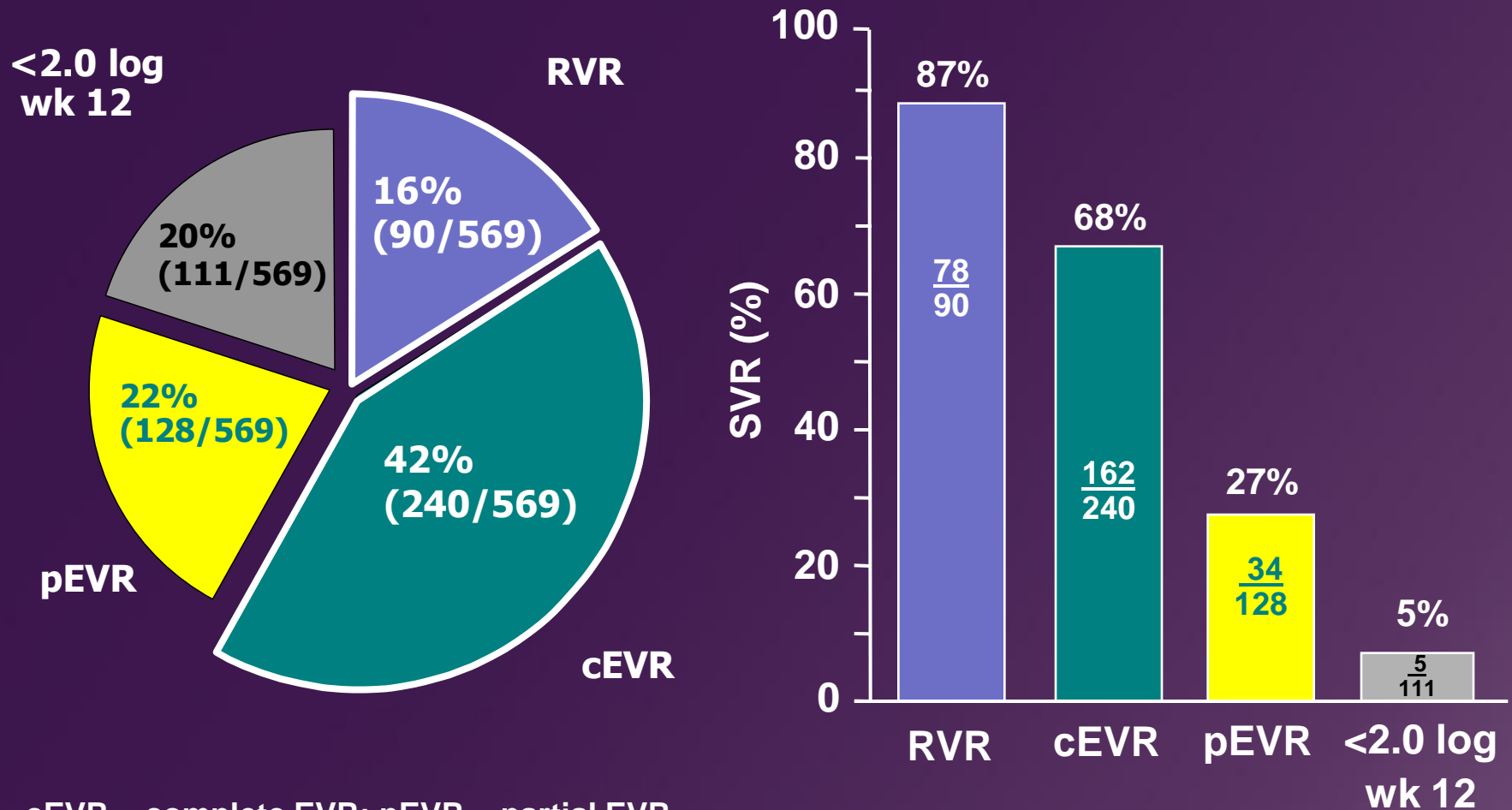
# Response to Treatment: Definitions

Response		Definition
RVR		HCV-RNA negative (<50 IU/mL) at week 4
EVR	Complete EVR	HCV-RNA positive at week 4 but negative at week 12
	Partial EVR	HCV-RNA positive at weeks 4 and 12 but $\geq 2 \log_{10}$ drop from baseline at week 12
Non-EVR		$< 2 \log_{10}$ drop from baseline at week 12

RVR = rapid virologic response; EVR = early virologic response.

# Virologic Response and Predictors of SVR in Patients With Genotype 1 Treated With Peg-IFN $\alpha$ -2a + RBV

Retrospective review of phase 3 trials of peg-IFN  $\alpha$ -2a 180  $\mu$ g/wk and ribavirin 1000/1200 mg/d for 48 weeks



cEVR = complete EVR; pEVR = partial EVR.  
Marcellin P et al. EASL 2007. Abstract 613.

# Patient RN: History and Physical

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- ◆ 30-year-old Caucasian female with a history of HCV who is referred for treatment evaluation
- ◆ No admission of alcohol consumption
- ◆ Past medical history: past marijuana use, obesity, diabetes
- ◆ Physical examination is normal except for obesity
  - BMI is 33 kg/m<sup>2</sup>; weight is 91 kg

# Patient RN: Laboratory Panel

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- ◆ CBC: WBC 5400/mm<sup>3</sup>, Hct 41%, platelets 250,000/mm<sup>3</sup>
- ◆ LFTs: albumin 4.0 g/dL, bilirubin 1 mg/dL, ALT 90 IU/L, AST 55 IU/L
- ◆ TSH: normal range
- ◆ HCG: negative
- ◆ HbA1c: 8.2% (diabetes not well controlled)
- ◆ SCr: 0.8 mg/dL
- ◆ HCV-RNA: 1,275,000 IU/mL; genotype 1
- ◆ Hepatitis A and B, HIV serology: negative

## Question 2

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Would you do a liver biopsy in this patient?

A. Yes

B. No

# Patient RN: Further History

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- ◆ Previously treated with pegylated interferon  $\alpha$ -2b and 800 mg/d of ribavirin
- ◆ Ribavirin dose was reduced to 400 mg/d starting at week 4 due to severe fatigue and anemia
- ◆ While not virus negative at week 12, the doctor told her she was close. On repeat testing at week 24, she was negative
- ◆ Her ribavirin dose was eventually increased to 600 mg daily some time after week 12
- ◆ Patient is in strict compliance with medications.
- ◆ She relapsed after completing 48 weeks of therapy

## Question 3

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Which factor is most predictive of not achieving an SVR?

- A. Ribavirin dose reduction
- B. Time to virus negativity
- C. Not extending therapy
- D. Not using erythropoetin

# Factors to Consider in Retreatment

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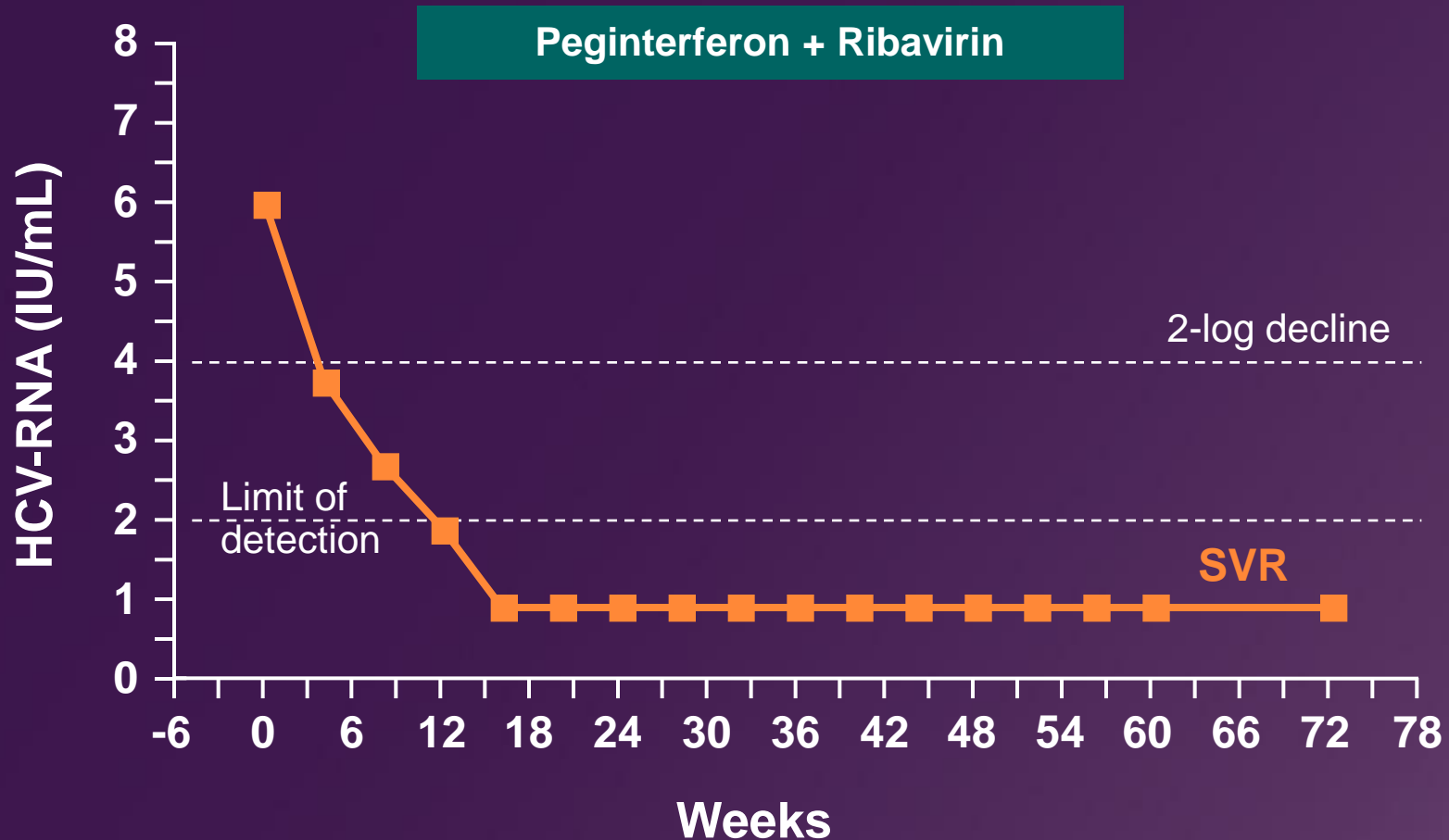
- ◆ Type of response to prior treatment
  - Null response
  - Partial response
  - Breakthrough
  - Relapse
- ◆ Inadequate dosing
  - IFN + RBV vs peg-IFN + RBV, dose reductions, etc
- ◆ Insufficient duration of prior treatment
- ◆ Nonadherence
- ◆ Interfering habits (marijuana, alcohol, etc)

# Factors to Consider in Retreatment (cont)

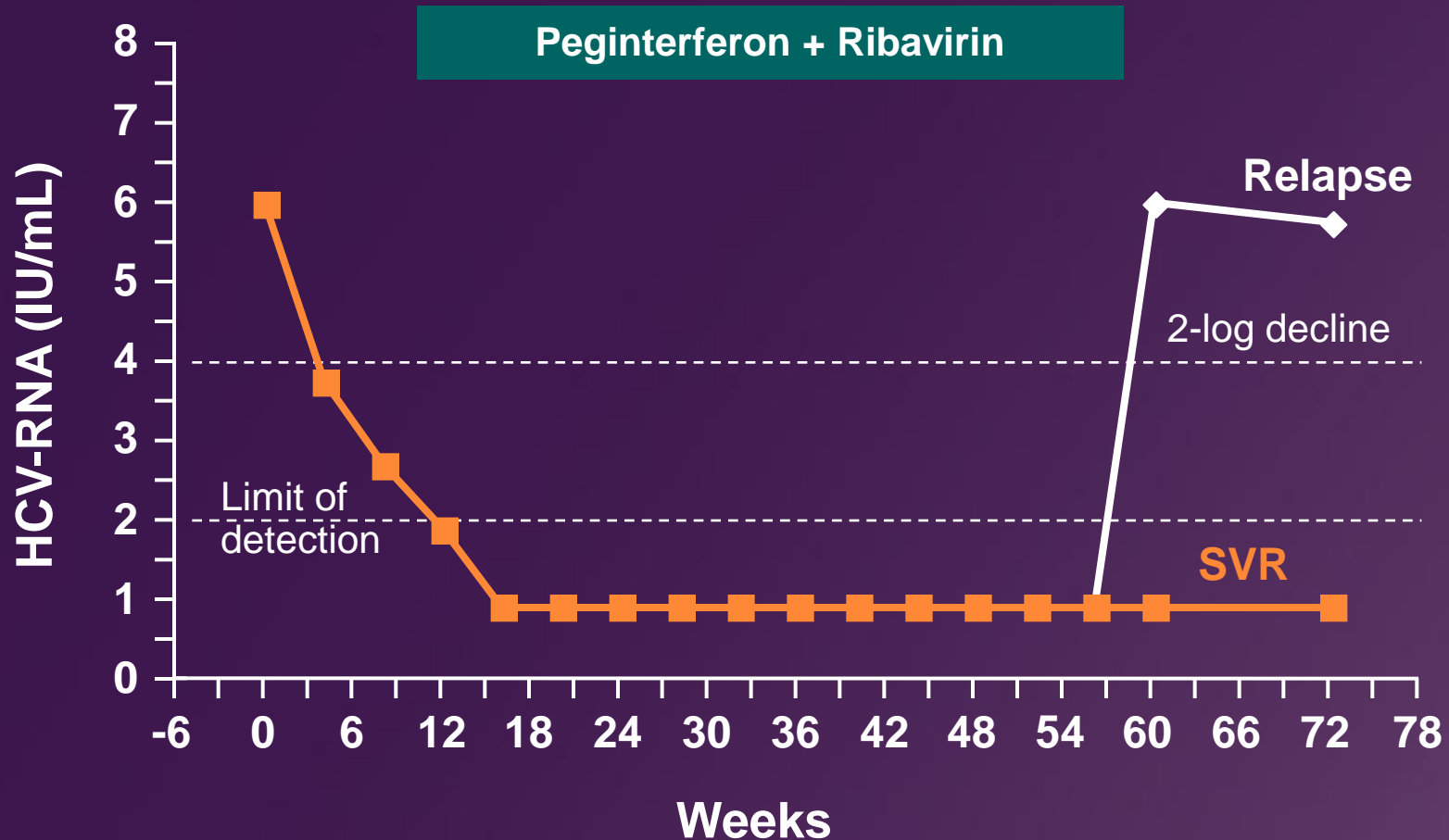
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- ◆ Viral factors
  - Genotype
  - Viral load
- ◆ Host factors
  - Age
  - Advanced fibrosis
  - Ethnicity
  - Obesity
  - Insulin resistance or steatosis
- ◆ Achieving SVR may
  - Improve histology
  - Decrease progression to hepatocellular carcinoma (HCC)

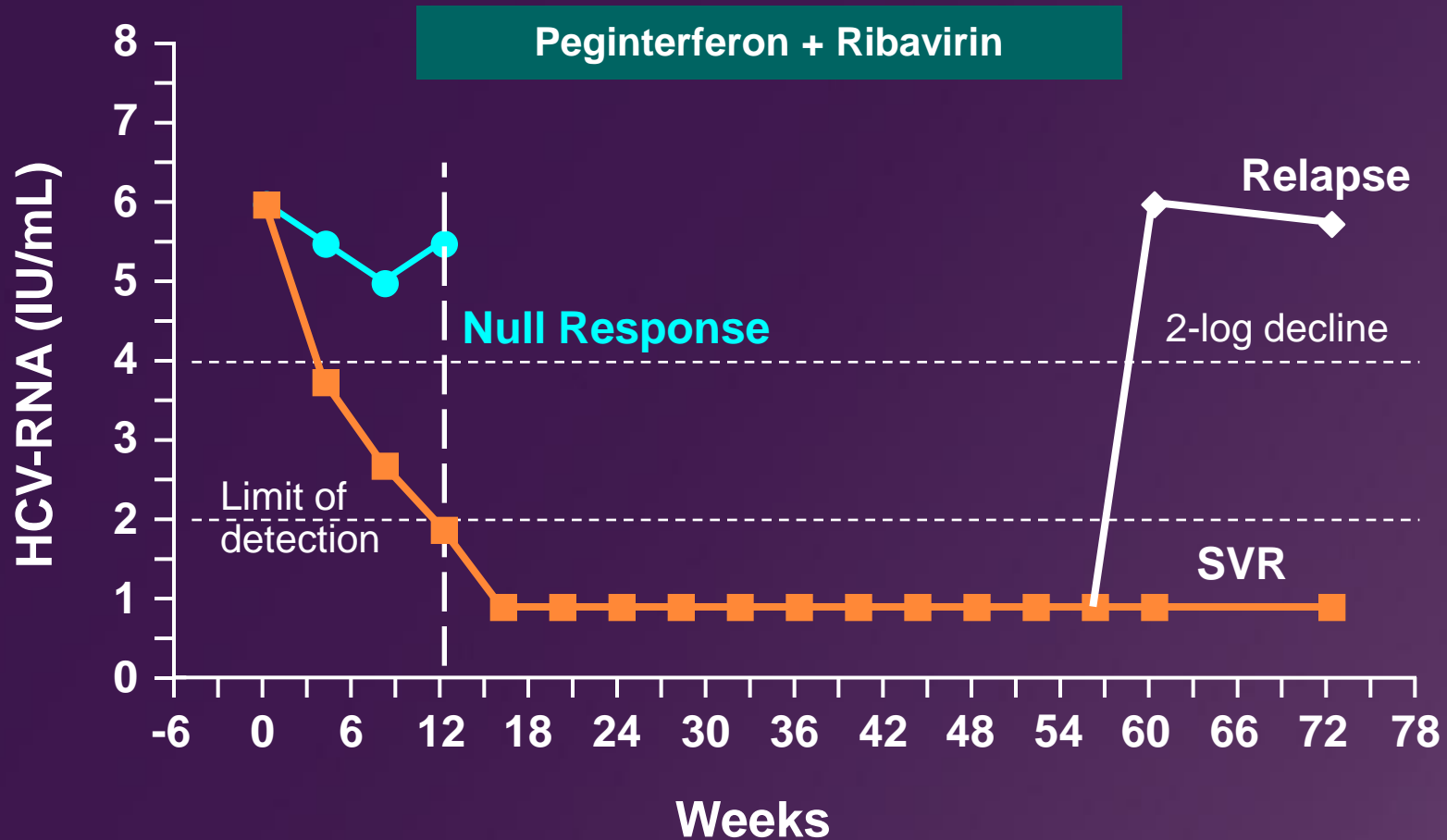
# Treatment of Chronic HCV: Sustained Virologic Response



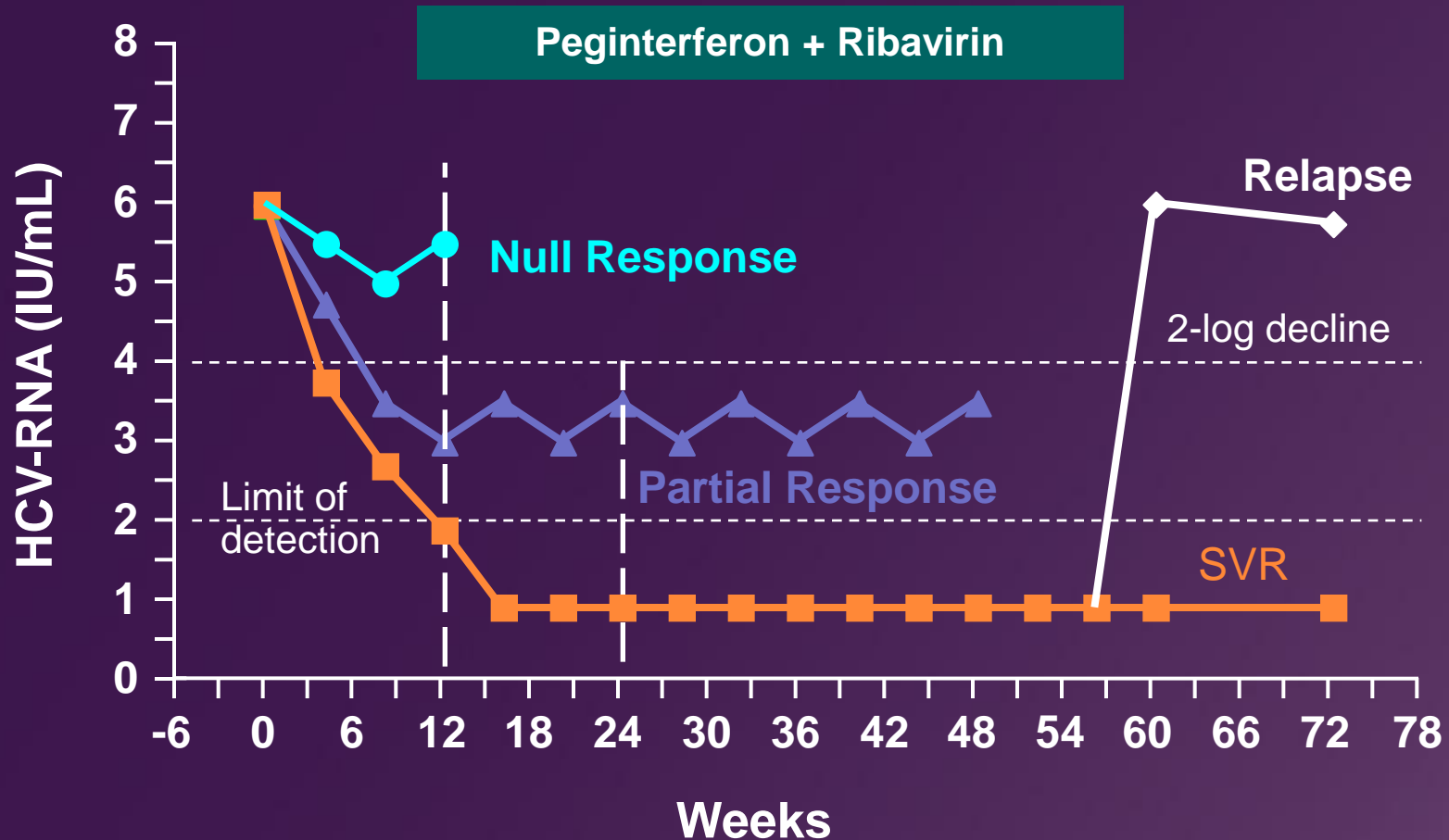
# Treatment of Chronic HCV: Relapse



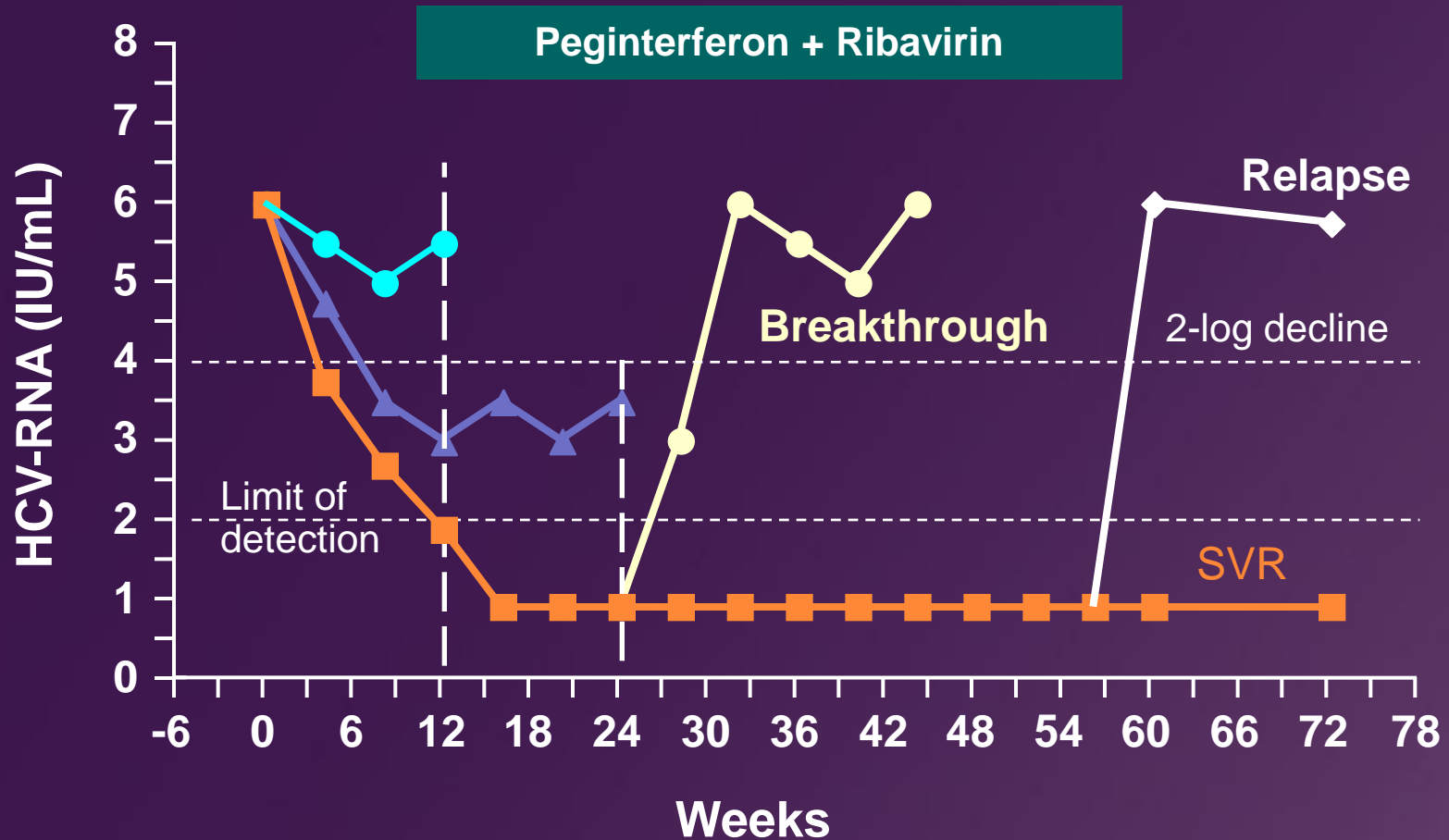
# Treatment of Chronic HCV: Null Response



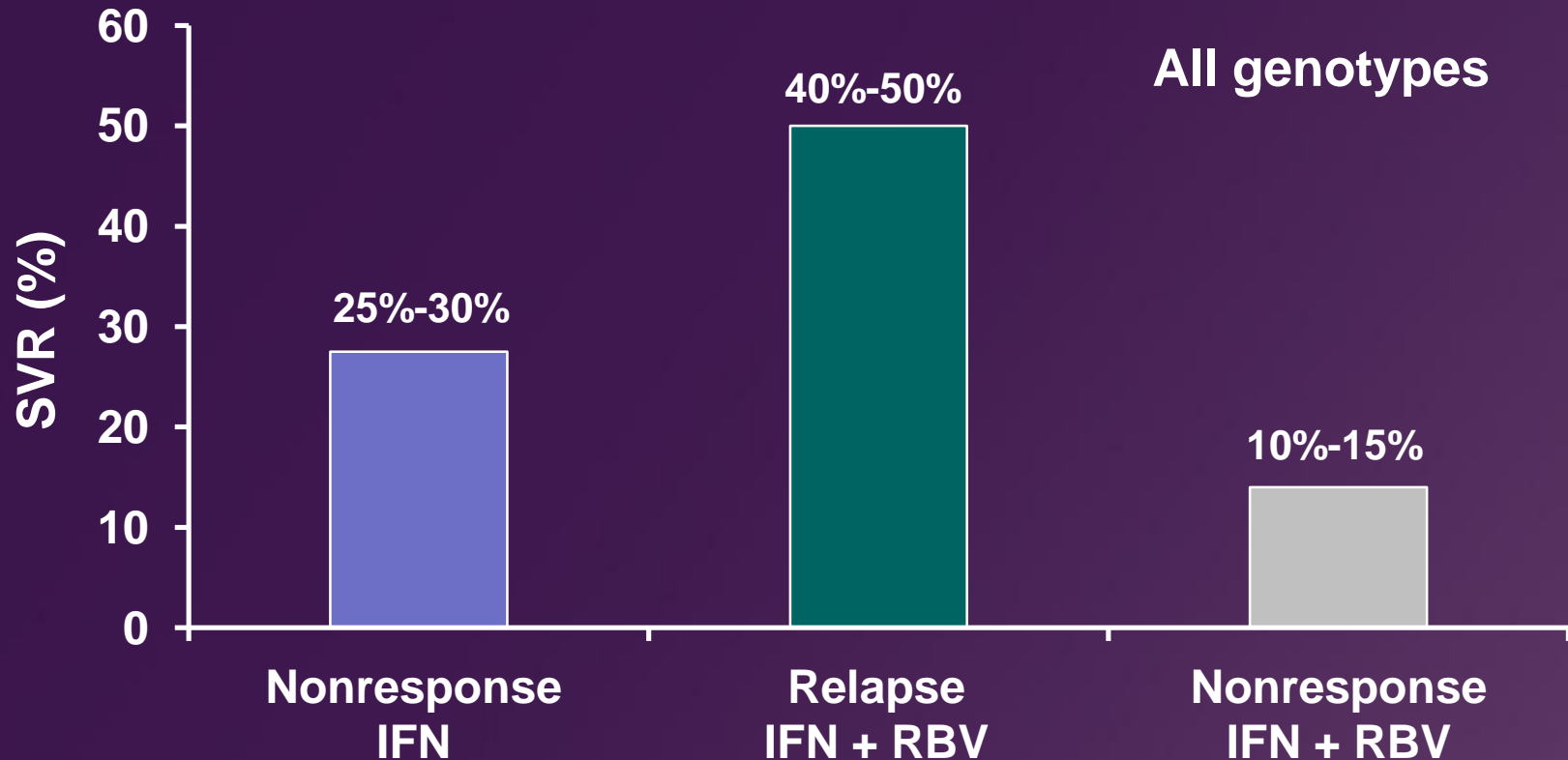
# Treatment of Chronic HCV: Partial Virologic Response



# Treatment of Chronic HCV: Breakthrough



# Response Rates With Peg-IFN + RBV in Relapsers/Nonresponders to Prior IFN ± RBV



Jacobson IM et al. *Am J Gastroenterol*. 2005;100:2453-2462.

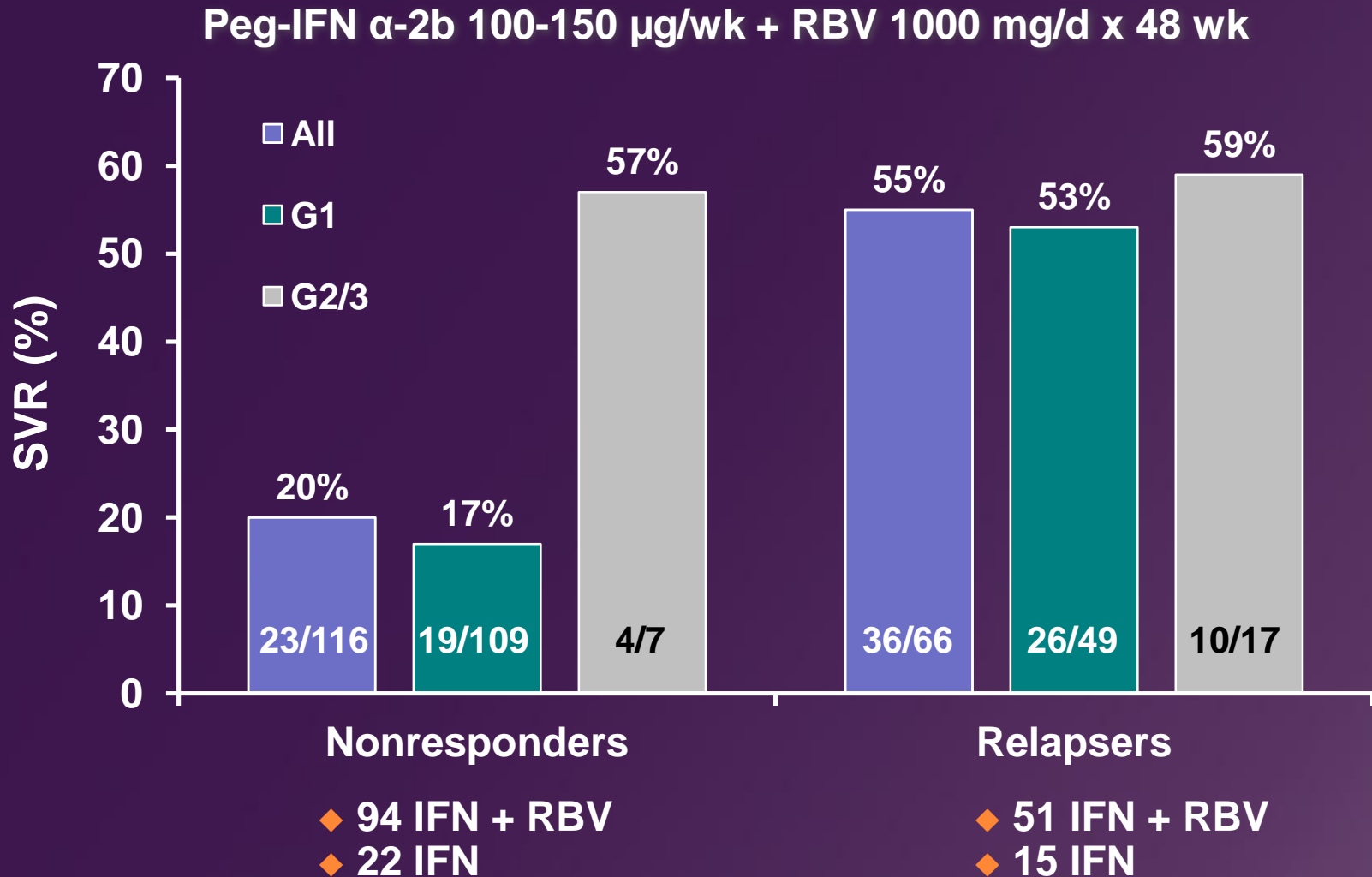
Dantzler TE et al. *Curr Gastroenterol Rep*. 2003;5:78-85.

Shiffman ML et al. *Gastroenterology*. 2004;126:1015-1023.

Gross J et al. *Hepatology*. 2005;42(suppl 1):219A-220A.

Krawitt EL et al. *J Hepatol*. 2005;43:243-249.

# Response Rates With Peg-IFN + RBV in Relapsers/Nonresponders to Prior IFN ± RBV by Genotype



# Retreatment of Patients Who Failed Prior IFN or IFN + RBV Treatment

		SVR (%)		
		Jacobson et al <sup>1</sup> (n = 321)	HALT-C <sup>2</sup> (n = 1 <sup>st</sup> 604)	EPIC <sup>3</sup> (n = 1 <sup>st</sup> 575)
Overall response in prior treatment failures:		16%	18%	21%
Race:	White	18%	20%	
	African American	4%	6%	--
Genotype:	2 or 3	31%	60%	54%
	1	14%	14%	16%
Serum HCV-RNA level:	Low	21%	27%	
	High	13%	15%	--
Cirrhosis:	No		23%	27%
	Yes	--	11%	14%
Multiple poor prognostic factors:		--	6%	--

1. Jacobson IM et al. *Am J Gastroenterol*. 2005;100:2453-2462; Retreatment: peg-IFN  $\alpha$ -2b

1.5  $\mu$ g/kg/wk + RBV 800 mg/d or peg-IFN  $\alpha$ -2b 1.0  $\mu$ g/kg/wk + RBV 1000-1200 mg/d.

2. Shiffman ML et al. *Gastroenterology*. 2004;126:1015-1023; Retreatment: peg-IFN  $\alpha$ -2a 180  $\mu$ g/wk + RBV 1000-1200 mg/d.

3. Poynard T et al. EASL 2005. Abstract 96. Retreatment: peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800–1400 mg/d.

## Question 4

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What is the SVR rate in patients who are nonresponders to peg-IFN + RBV and retreated with peg-IFN + RBV?

- A. 5%-15%
- B. 20%
- C. 40%-50%
- D. 70%

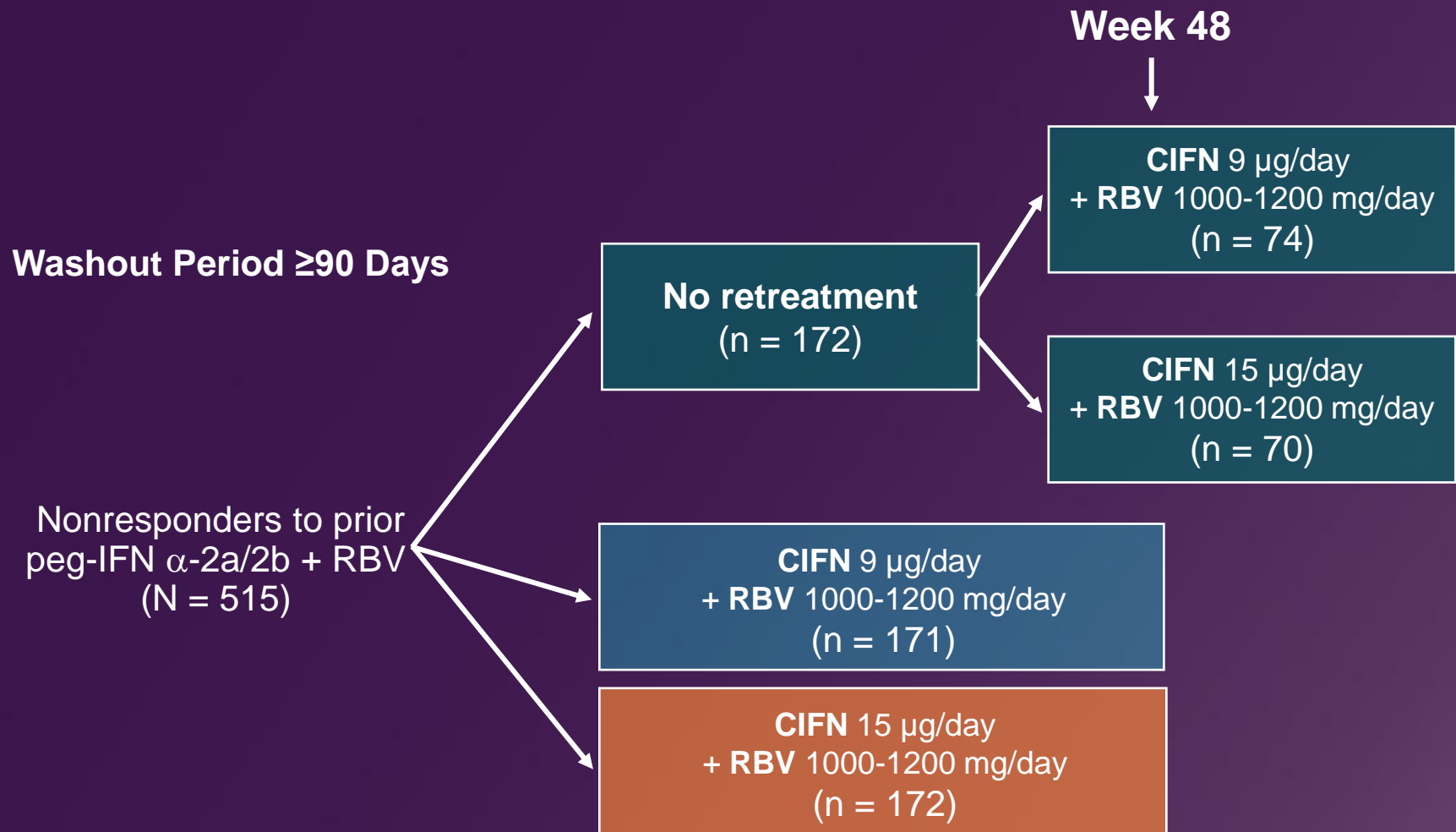
# Retreatment of Nonresponders/Relapsers to Prior Peg-IFN Treatment

Population	Retreatment (Duration: 48 wks)	Study	SVR
Nonresponders to prior IFN or peg-IFN + RBV	Peg-IFN + RBV	EPIC <sup>1</sup>	15%
Nonresponders to prior peg-IFN + RBV	Peg-IFN + RBV	Rustgi <sup>2</sup>	3%
		REPEAT <sup>3*</sup>	7%-16%
	CIFN	Leevy <sup>4</sup>	37%
		Kaiser <sup>5†</sup>	18%-41%
		DIRECT <sup>6</sup>	5%-10%
Relapsers to prior IFN or peg-IFN + RBV	Peg-IFN + RBV	EPIC <sup>1</sup>	39%
Relapsers to prior peg-IFN + RBV	CIFN vs Peg-IFN + RBV	Kaiser <sup>7‡</sup>	69% vs 44%

Treatment duration: \*12-weeks; †48-72-weeks; ‡72-weeks.

1. Poynard T et al. EASL 2005. Abstract 96;
2. Rustgi VK et al. *Aliment Pharmacol Ther.* 2008;27:433-440;
3. Jensen DM et al. AASLD 2007. Abstract LB4;
4. Leevy C et al. *Gastroenterology.* 2005;128:A-715;
5. Kaiser S et al. DDW 2006. Abstract S1061;
6. Bacon B et al. AASLD 2007. Abstract 168;
7. Kaiser S et al. DDW 2006. Abstract S1060.

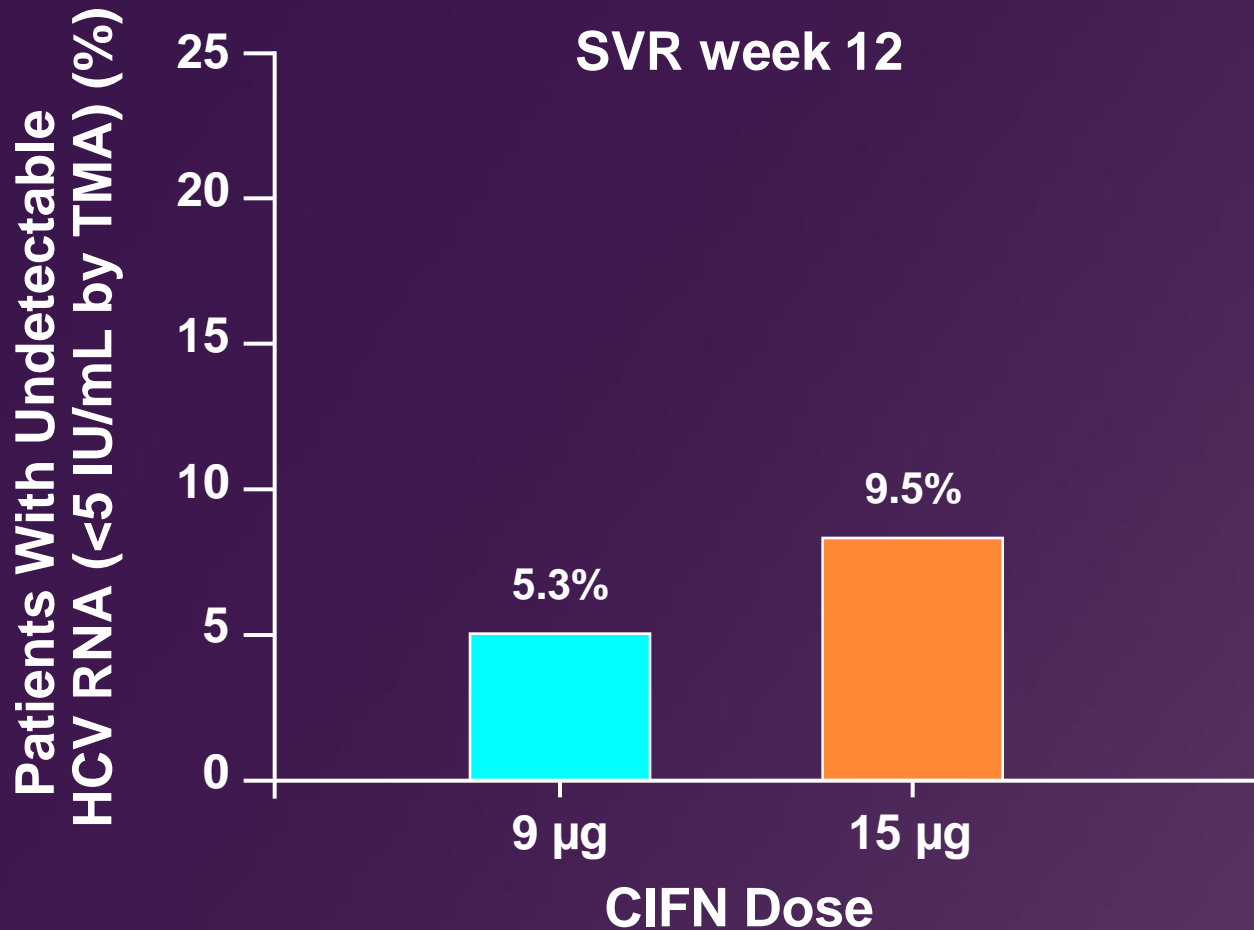
# DIRECT: Retreatment With CIFN + RBV in Nonresponders to Prior Peg-IFN + RBV



DIRECT = Daily-Dose Consensus Interferon and Ribavirin: Efficacy of Combined Therapy;  
CIFN = consensus interferon.

Bacon B et al. AASLD 2007. Abstract 168.

# DIRECT: Response by CIFN Dose



TMA = transcription-mediated amplification.

Bacon B et al. AASLD 2007. Abstract 168.

# DIRECT: Response in Patients With and Without Cirrhosis

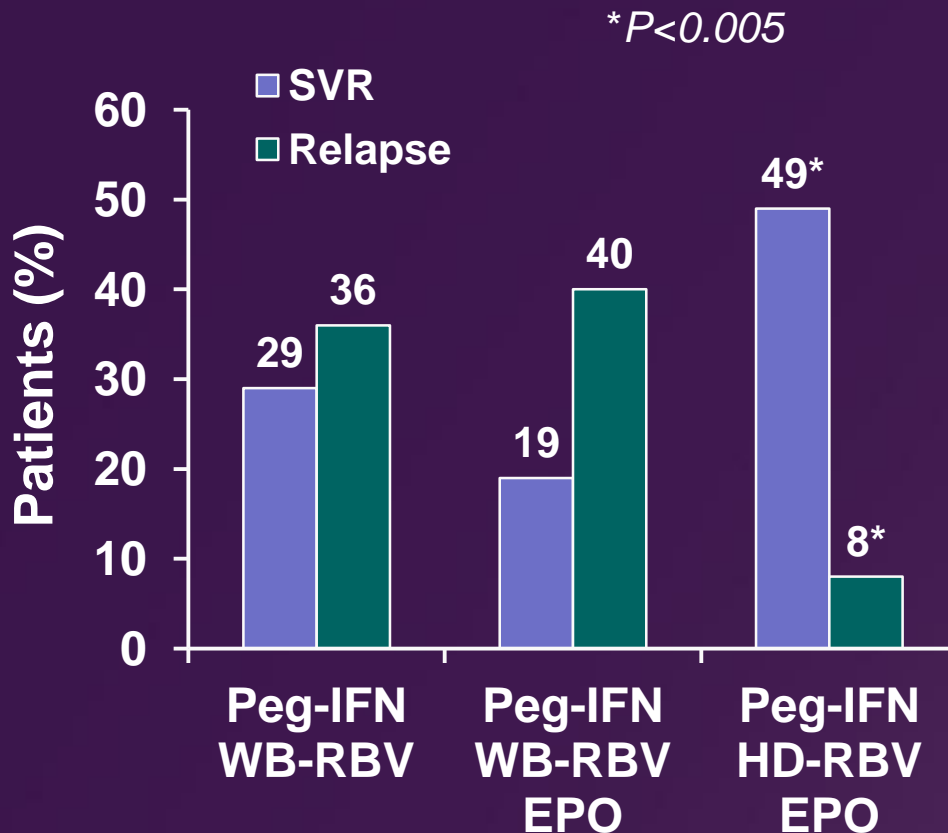
WK 12 <sup>†</sup>	Patients Without Cirrhosis (SVR*)		Patients With Cirrhosis (SVR*)	
	mITT (n = 158)	PP (n = 62)	mITT (n = 65)	PP (n = 29)
<1 log	6%	13%	0%	0%
1-2 log	19%	31%	10%	10%
>2 log	26%	38%	8%	25%

\*SVR at week 12 in patients treated with CIFN 15 µg/day + RBV.

<sup>†</sup>Previous response to peg-IFN + RBV.

mITT = modified intent to treat; PP = per protocol.

# Ribavirin Dosing to Achieve Optimal SVR



◆ 146 patients randomized to receive Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk plus:

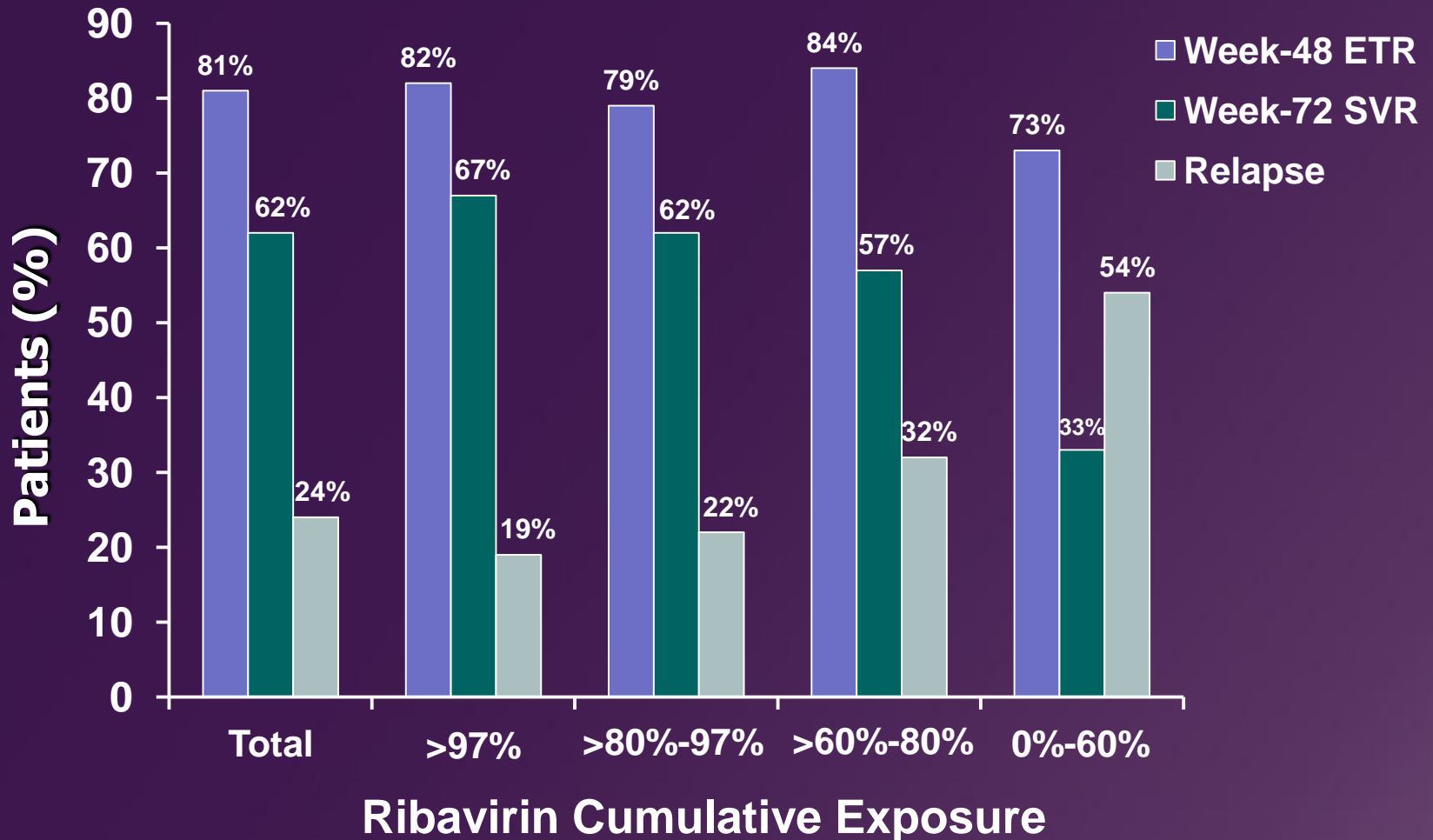
1. Weight-based (WB) RBV (13.3 mg/kg/d) vs
2. WB RBV (13.3 mg/kg/d plus EPO) vs
3. Higher-dose (HD) RBV (15.2 mg/kg/d plus EPO)



Higher doses of RBV enhance SVR rates compared to standard dosing

Starting dose of RBV may be more important at reducing risk of relapse and small dose reductions may not affect relapse rate

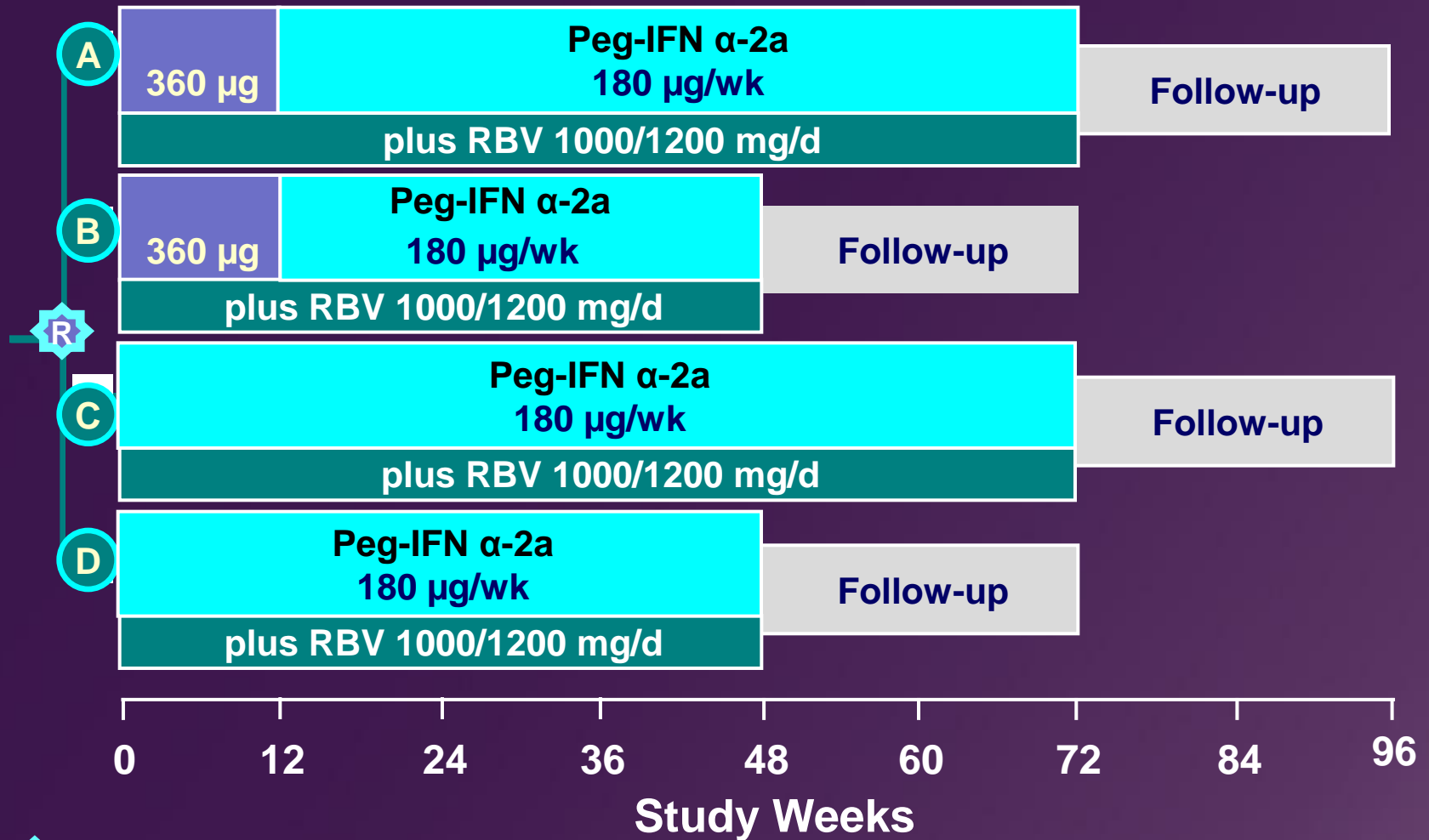
# Influence of Cumulative RBV: Virologic Responses



ETR = end of treatment response.

Reddy KR et al. *Clin Gastroenterol Hepatol*. 2007;5:124-129.

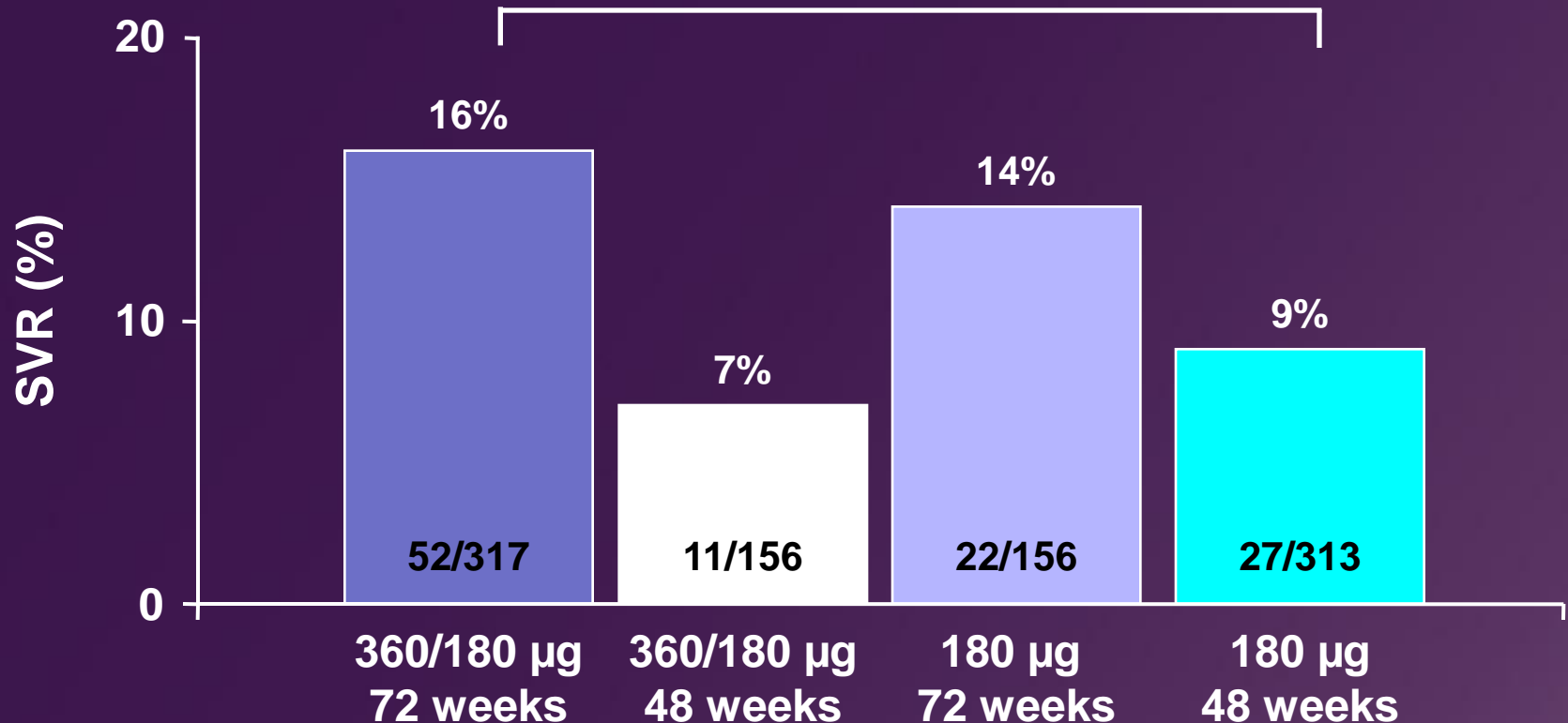
# Retreatment of Nonresponders to Peg-IFN $\alpha$ -2b + RBV Utilizing High-Dose Peg-IFN $\alpha$ -2a + RBV: REPEAT



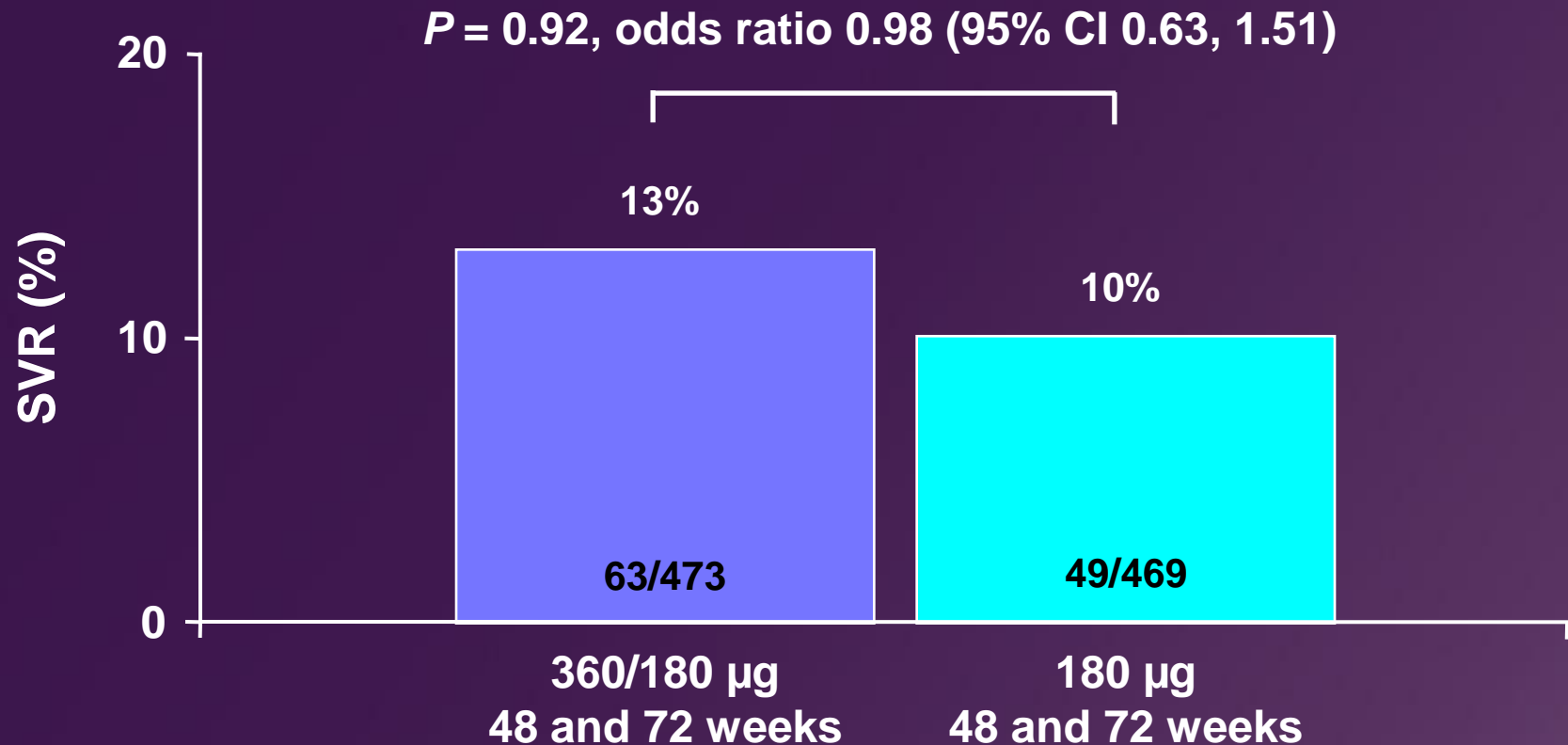
**R** Randomization (2:1:1:2, n = 942)

# Primary Comparison: 72-Week Induction vs 48-Week Non-Induction

$P = 0.006$ , odds ratio 2.0 (95% CI 1.21, 3.31)

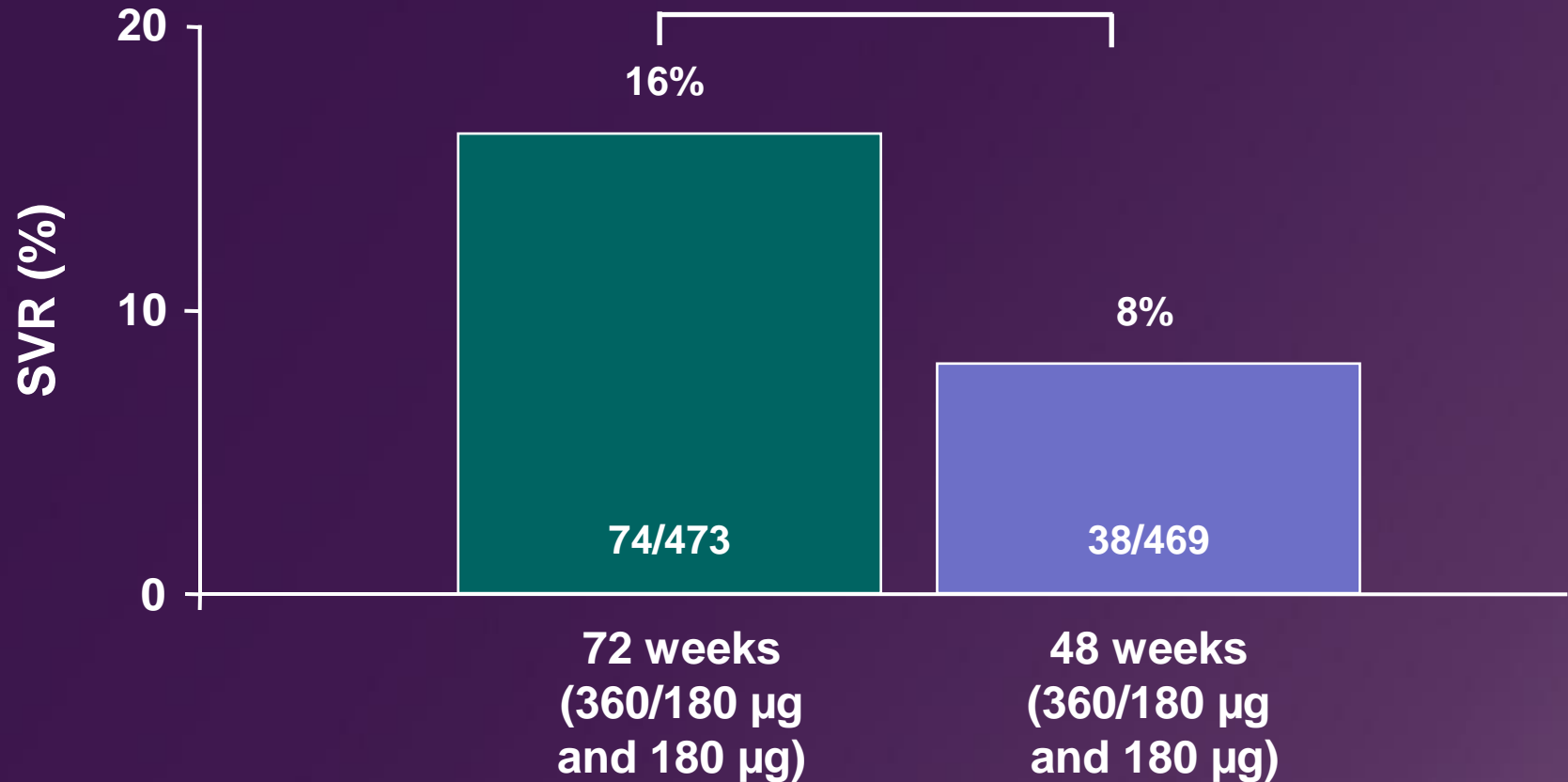


# Pooled Results: Induction vs Non-Induction

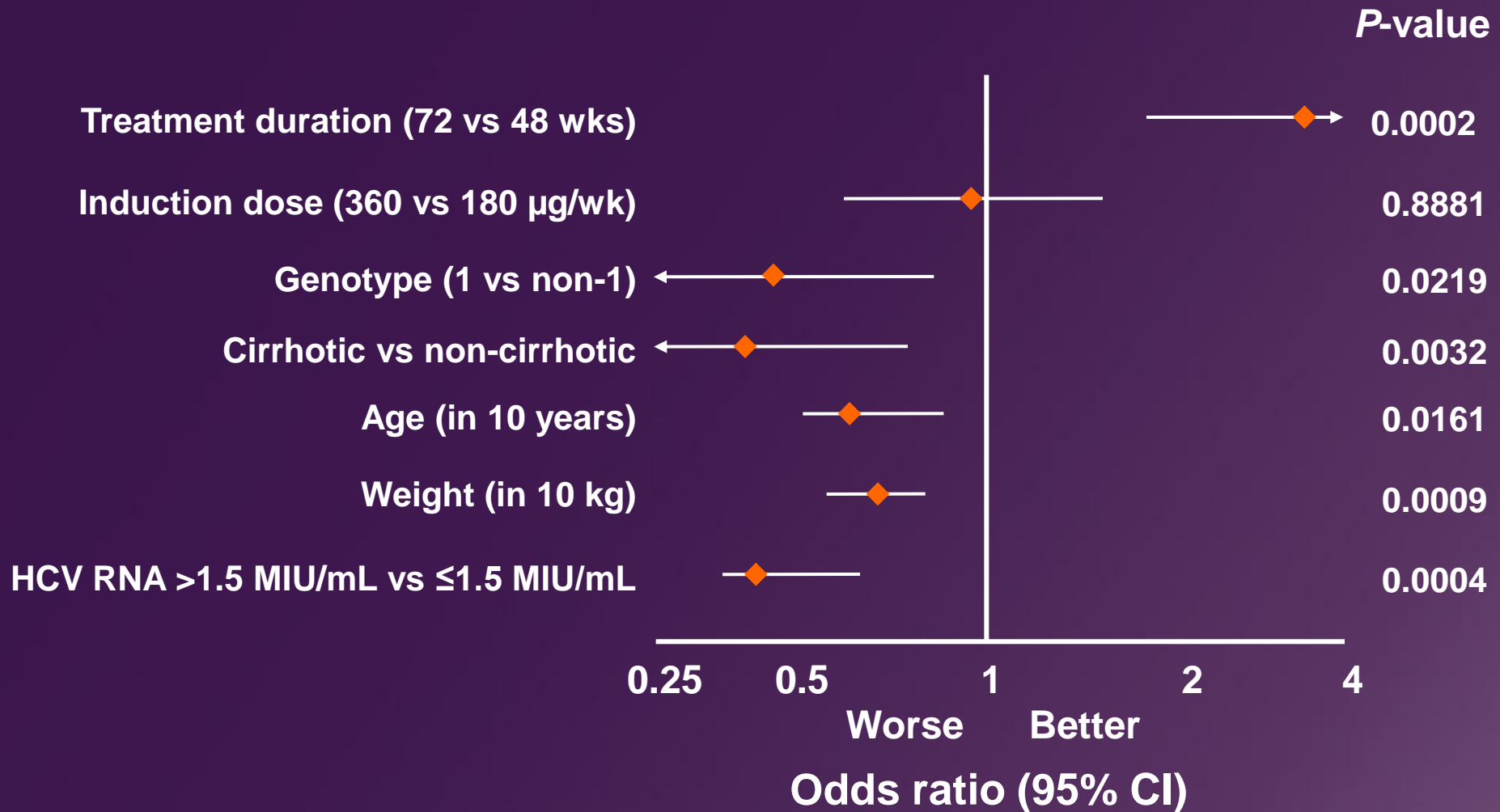


# Pooled Results: 72 Weeks vs 48 Weeks

$P = 0.0006$ , odds ratio 2.22 (95% CI 1.40–3.52)



# REPEAT: Predictors of Response



# Strategies Based on Response to Prior Treatment

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- ◆ Nonresponders to peg-IFN + RBV (<1 log drop by week 12)
  - Careful review of treatment history looking for
    - Inadequate dosing
    - Nonadherence
    - Interfering habits such as alcohol or IVDA
  - Would not retreat unless convinced of one of the above findings
  - Maintenance therapy is not effective
  - Enroll nonresponders in clinical trials when possible
  - Reassure patients that the field is rapidly evolving

# HALT-C Trial: 3.5-Year Results

- ◆ Patients with HCV and advanced liver disease who failed to achieve an SVR with full-dose peg-IFN  $\alpha$ -2a were randomized to low-dose maintenance therapy or observation for 3.5 years
  - Clinical outcomes: progression of fibrosis, complications of cirrhosis, HCC, transplantation, death
- ◆ Primary analysis (N = 1050) showed maintenance therapy did not reduce clinical outcomes<sup>1</sup>
- ◆ Secondary analysis (N = 764) found clinical outcomes reduced in patients who achieved  $>4$  log HCV-RNA decline during full-dose treatment whether or not on maintenance therapy<sup>2</sup>
  - 23% (178/764) had  $>4$  log HCV-RNA decline during lead-in period

1. Di Bisceglie AM et al. AASLD 2007. Abstract LB1.

2. Shiffman ML et al. EASL 2008. Abstract 144.

# Strategies Based on Response to Prior Treatment

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- ◆ All patients other than nonresponders to peg-IFN + RBV
  - Increase treatment duration
  - Treat with CIFN + RBV
  - Treat heavier patients with higher doses of peg-IFN + RBV
  - Encourage weight loss and exercise prior to initiating therapy

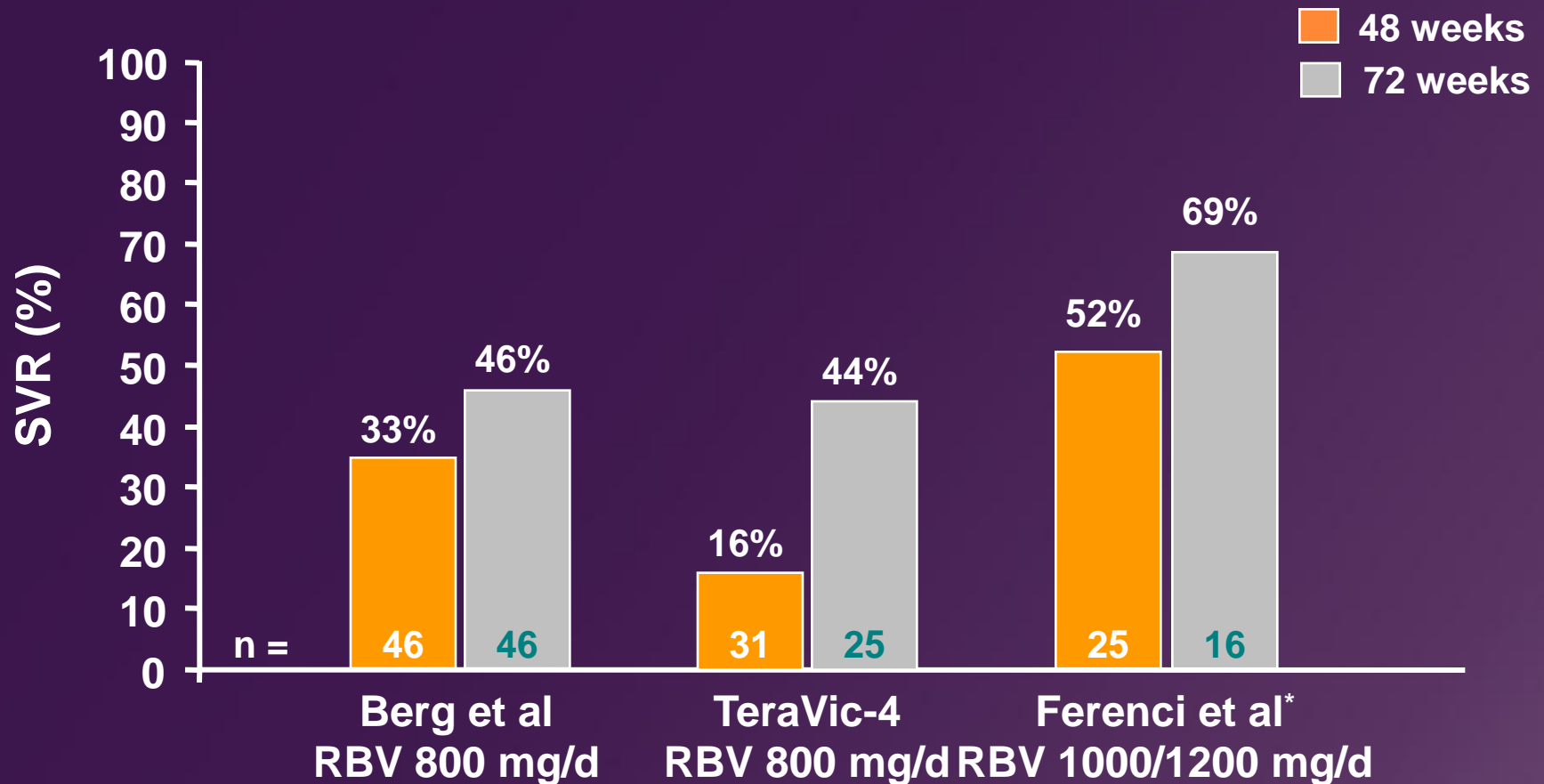
## Question 5

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Which patients would be candidates for extending therapy to 72 weeks?

- A. Patients who are virus negative at week 4
- B. Patients who are virus negative at week 12 (complete EVR)
- C. All patients with cirrhosis
- D. Patients who have had at least a 2-log drop by week 12 (partial EVR)

# SVR Rates in Patients With Partial EVR: Consistent Improvement With 72 Weeks of Therapy



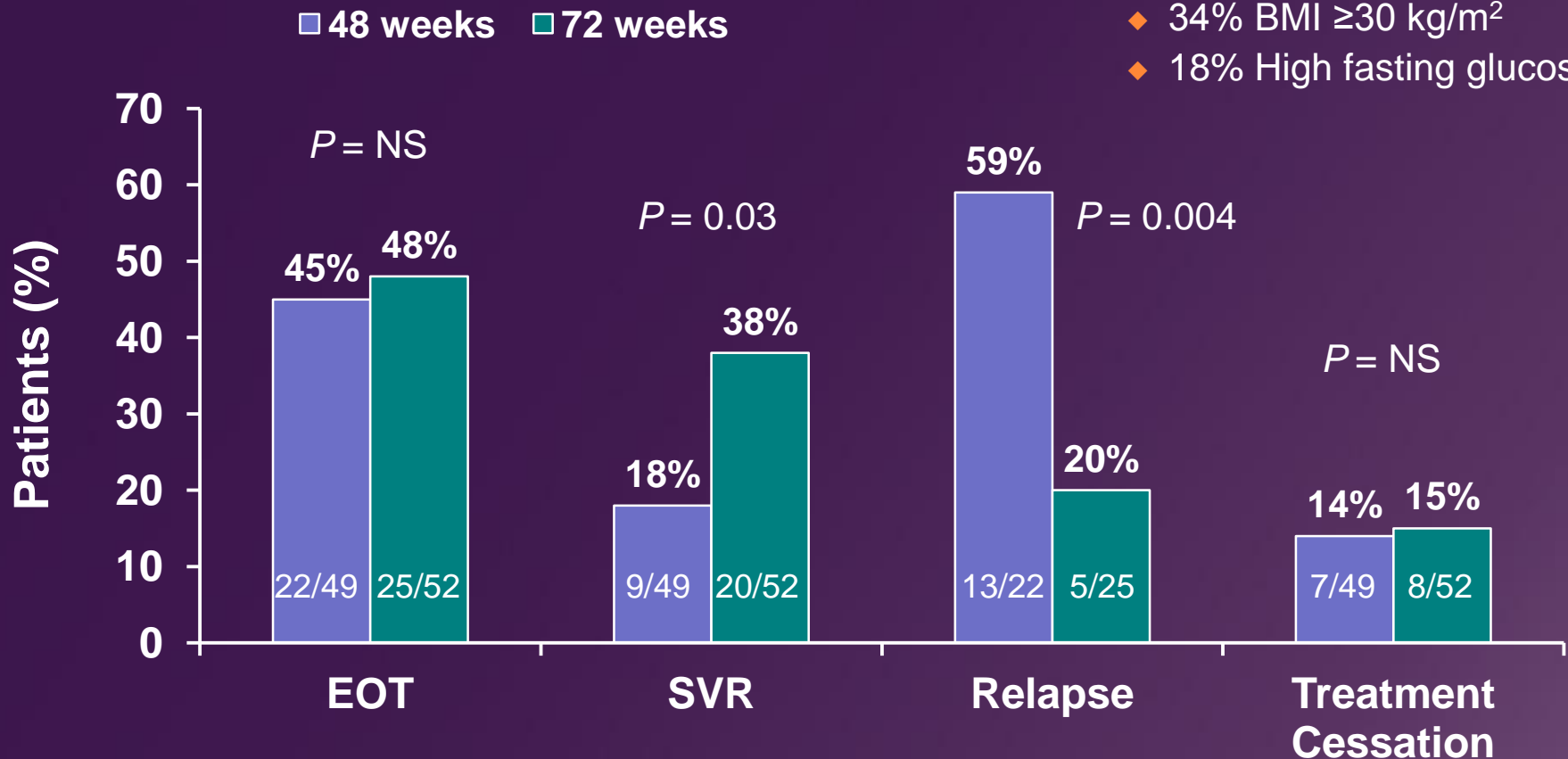
Slow (partial) EVR = no RVR and  $>2\text{-log}_{10}$  drop but HCV RNA  $>50$  IU/mL at week 12.

\*Includes small number ( $<10\%$ ) of patients with genotype 4.

# Improved SVR Rates With 72 Weeks of Treatment in Patients With Genotype 1 and Partial EVR

- ◆ Peg-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800-1400 mg/d
- ◆ HCV RNA (+) at week 12 (n = 101 slow responders)

- ◆ 48% African American
- ◆ 78% High viral load
- ◆ 26% F3/4 fibrosis
- ◆ 34% BMI  $\geq$ 30 kg/m<sup>2</sup>
- ◆ 18% High fasting glucose



# Strategies to Maximize Treatment Efficacy

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- ◆ Increase treatment duration
- ◆ Treat with CIFN + RBV
- ◆ Treat heavier patients with higher doses of peg-IFN + RBV
- ◆ Encourage weight loss and exercise prior to initiating therapy

# DIRECT: Response in Patients With and Without Cirrhosis

WK 12 <sup>†</sup>	Patients Without Cirrhosis (SVR*)		Patients With Cirrhosis (SVR*)	
	mITT (n = 158)	PP (n = 62)	mITT (n = 65)	PP (n = 29)
<1 log	6%	13%	0%	0%
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\*SVR at week 12 in patients treated with CIFN 15 µg/day + RBV.

<sup>†</sup>Previous response to peg-IFN + RBV.

mITT = modified intent to treat; PP = per protocol.

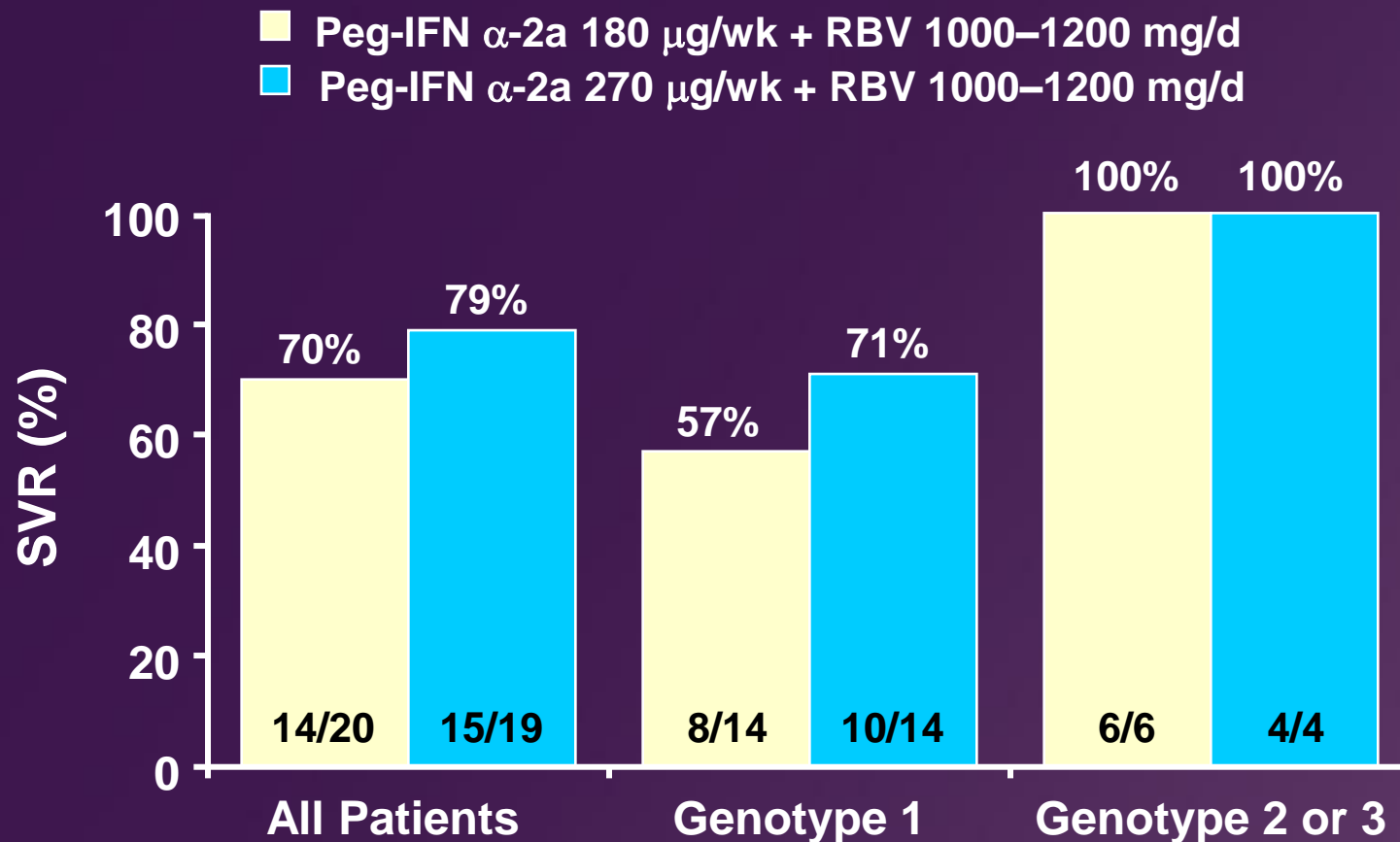
# Strategies to Maximize Treatment Efficacy

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- ◆ Increase treatment duration
- ◆ Treat with CIFN + RBV
- ◆ Treat heavier patients with higher doses of peg-IFN + RBV
- ◆ Encourage weight loss and exercise prior to initiating therapy

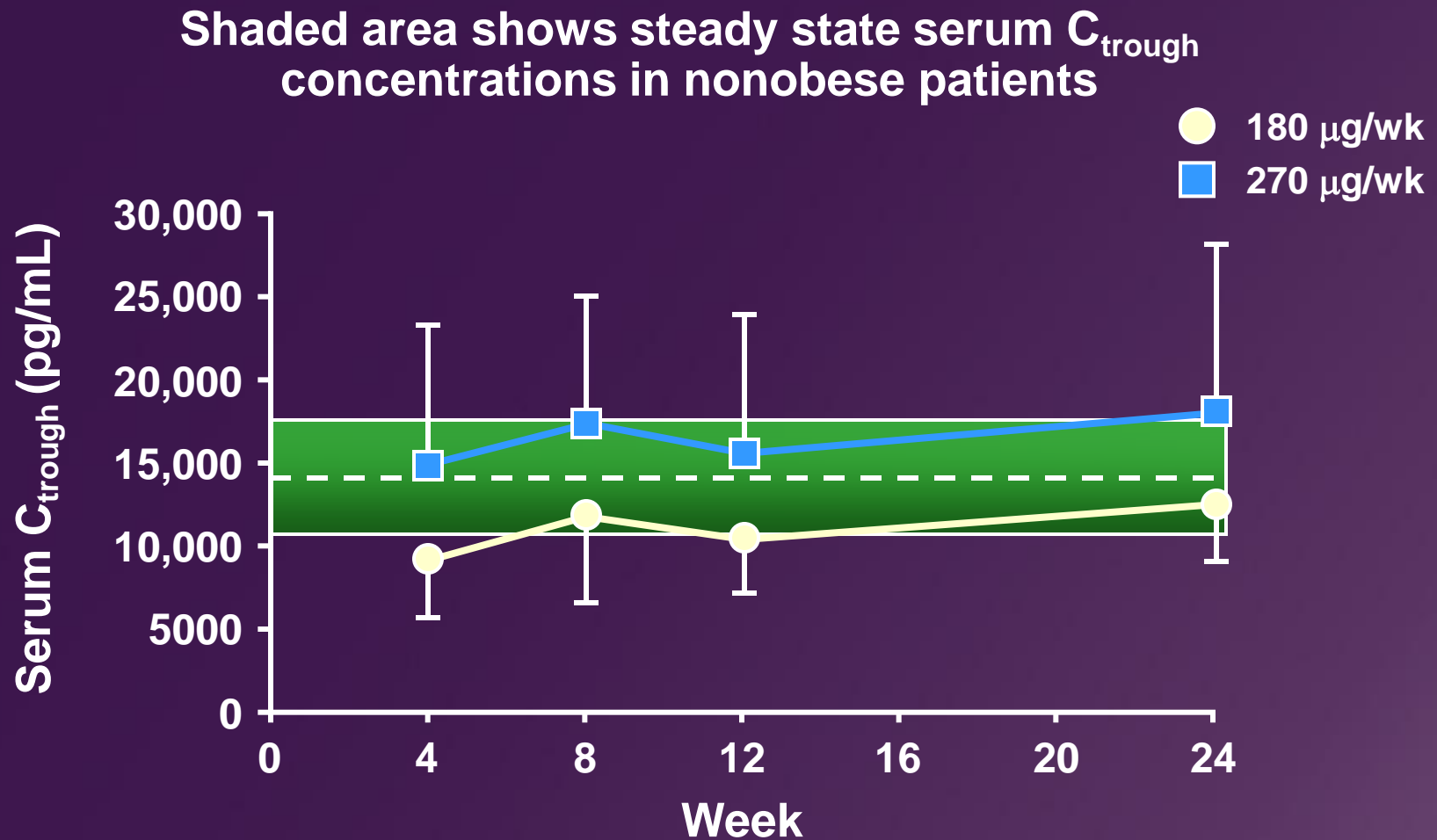
# Standard vs Higher Doses of Peg-IFN $\alpha$ -2a + RBV in Obese Patients With Chronic HCV

39 noncirrhotic obese\* patients with chronic HCV treated for 48 wk



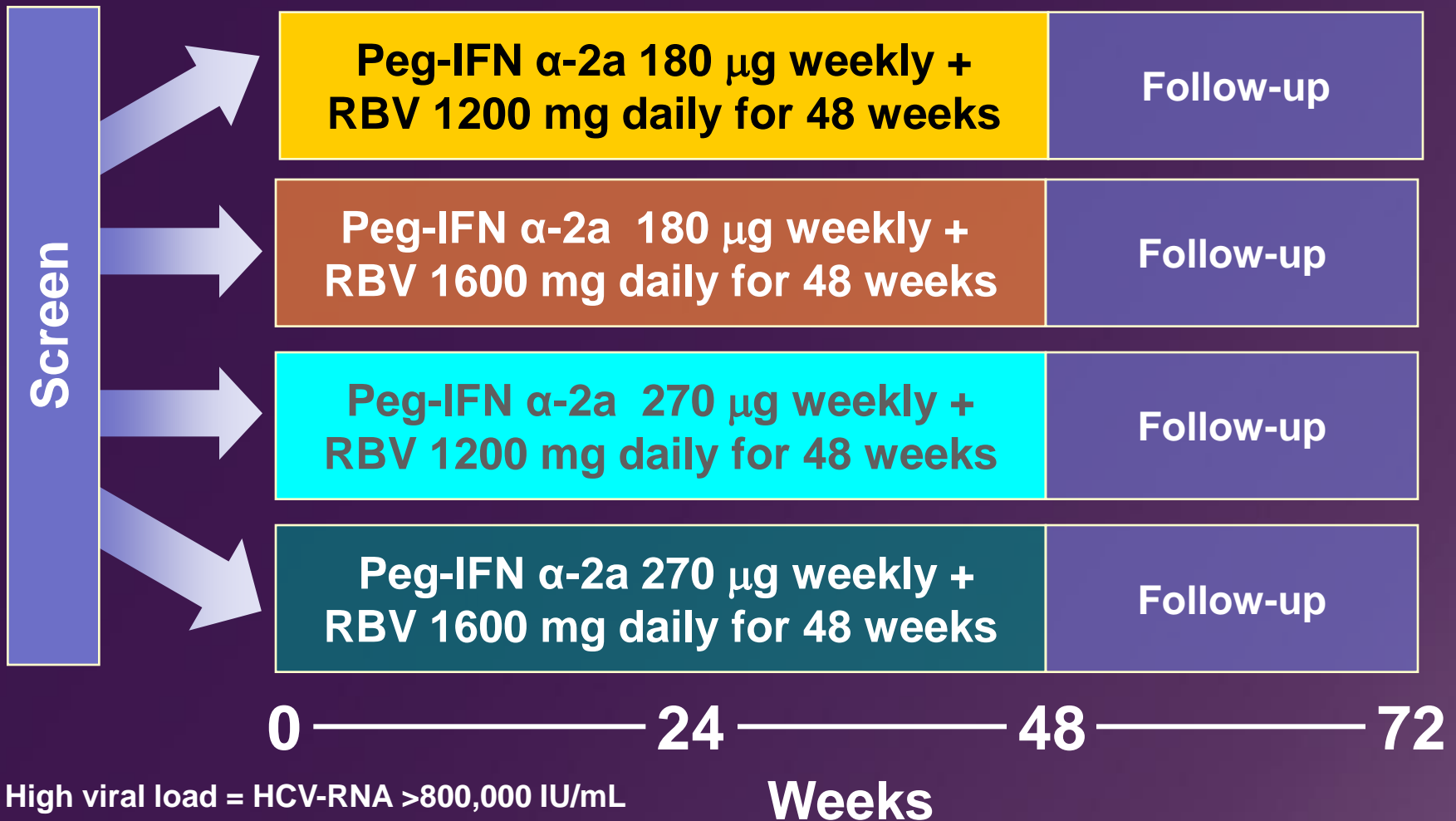
\*BMI >30 kg/m<sup>2</sup>.

# Trough Concentrations of Standard and Higher Doses of Peg-IFN $\alpha$ -2a in Obese Patients With Chronic HCV Over 24 Weeks

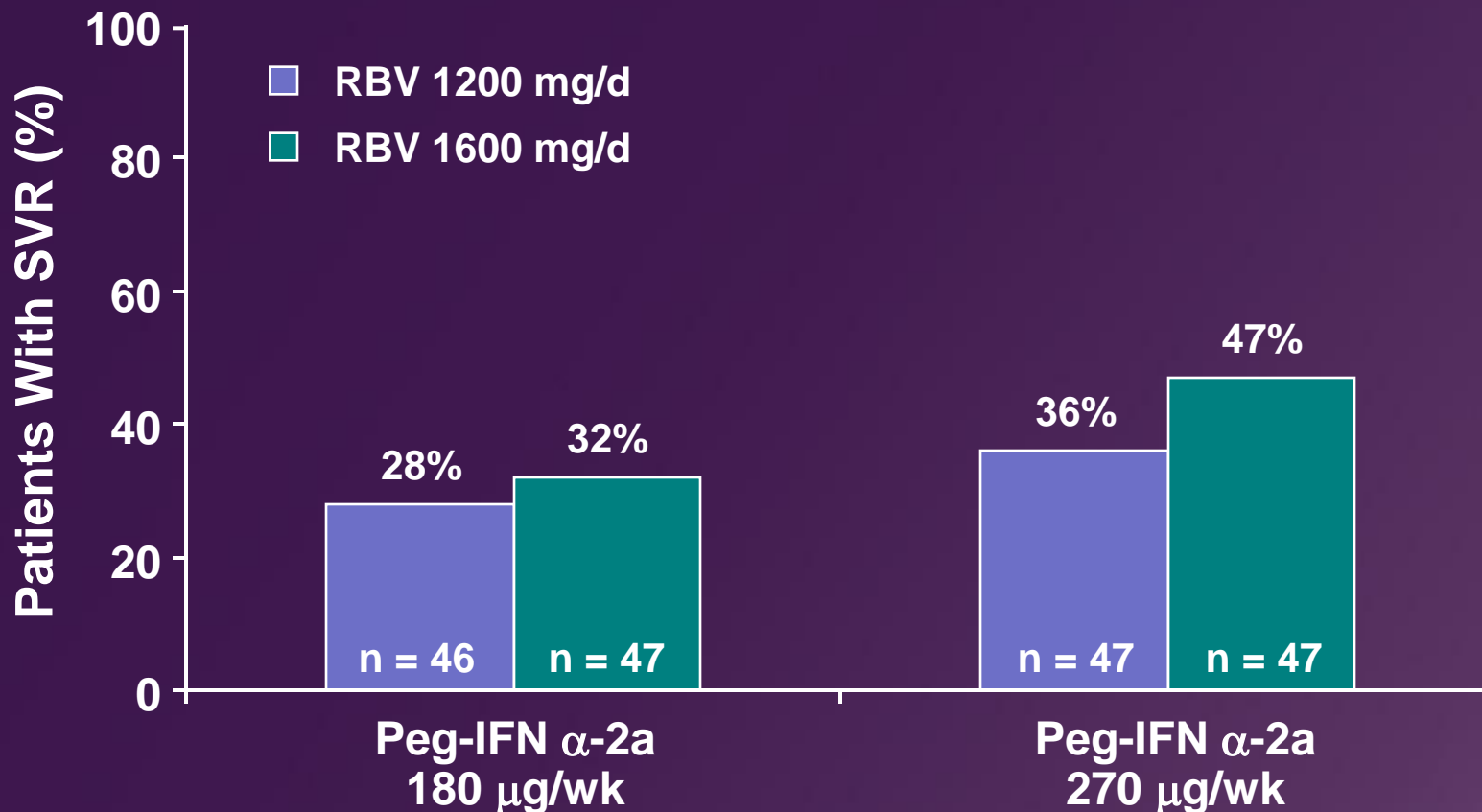


# Intensive Regimen in Patients With Genotype 1 >85 kg + High Viral Load: Study Design

N = 188



# Improved SVR With Higher Fixed Doses of Peg-IFN $\alpha$ -2a + RBV in “Difficult-to-Treat” Cases



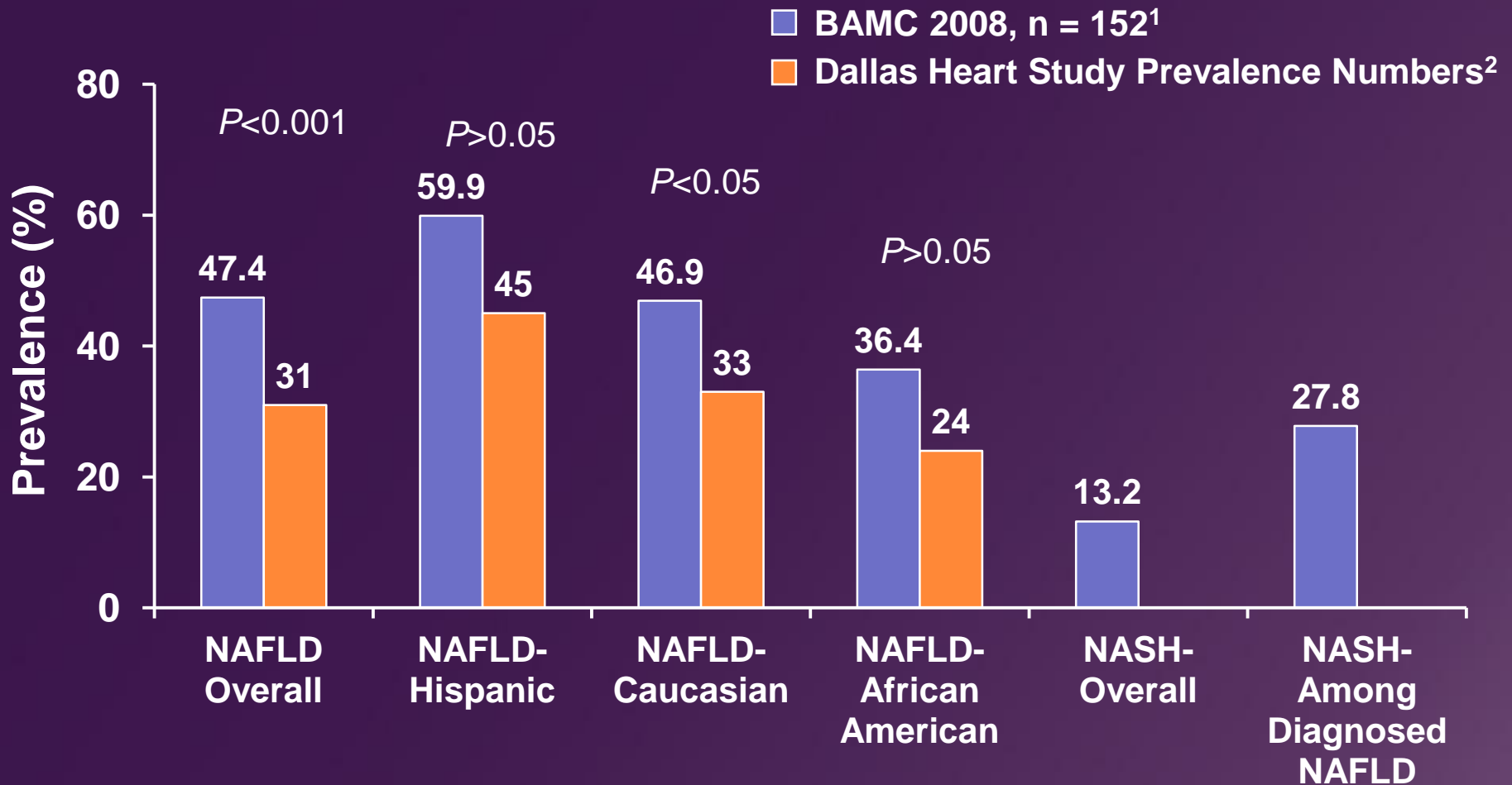
Difficult-to-treat = patients with HCV genotype 1, HCV RNA >800,000 IU/mL, and body weight >85 kg.

# Strategies to Maximize Treatment Efficacy

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- ◆ Increase treatment duration
- ◆ Treat with CIFN + RBV
- ◆ Treat heavier patients with higher doses of peg-IFN + RBV
- ◆ Encourage weight loss and exercise prior to initiating therapy
  - ~30% of patients with HCV in the US are obese and have associated insulin resistance

# NAFLD-NASH Prevalence



1. Williams CD et al. AASLD 2008. Abstract 1133.

2. Browning JD et al. *Hepatology*. 2004;40:1387-1395.

# Prevalence of Insulin Resistance in HCV

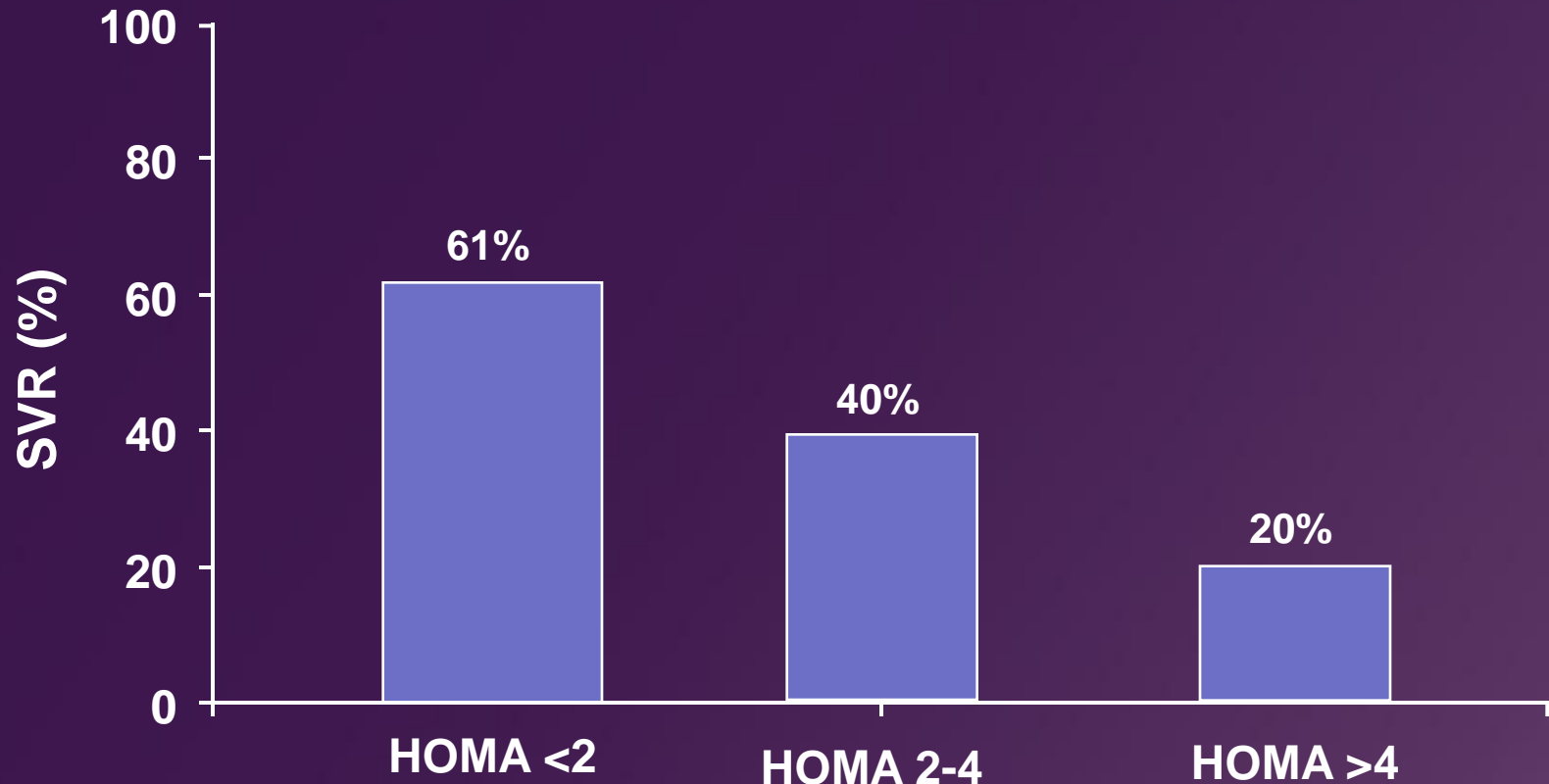
1. Prospective, single-center, observational cohort study of 500 patients with chronic hepatitis C (CHC)<sup>1</sup>
  - 32.4% (n = 150) overall prevalence of insulin resistance (IR), excluding diabetic patients
  - 40.1% prevalence of IR in patients with genotype 1 and genotype 4
2. Retrospective single-center study of 64 patients with CHC genotype 1<sup>2</sup>
  - 69% prevalence of IR
3. Prospective single-center study of 201 patients with CHC genotype 1<sup>3</sup>
  - 52.7% prevalence of IR (38.3% excluding diabetic patients)

1. Moucari R et al. *Gastroenterology*. 2008;134:416-423.

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

3. Petta S et al. *Am J Gastroenterol*. 2008;103:1136-1144.

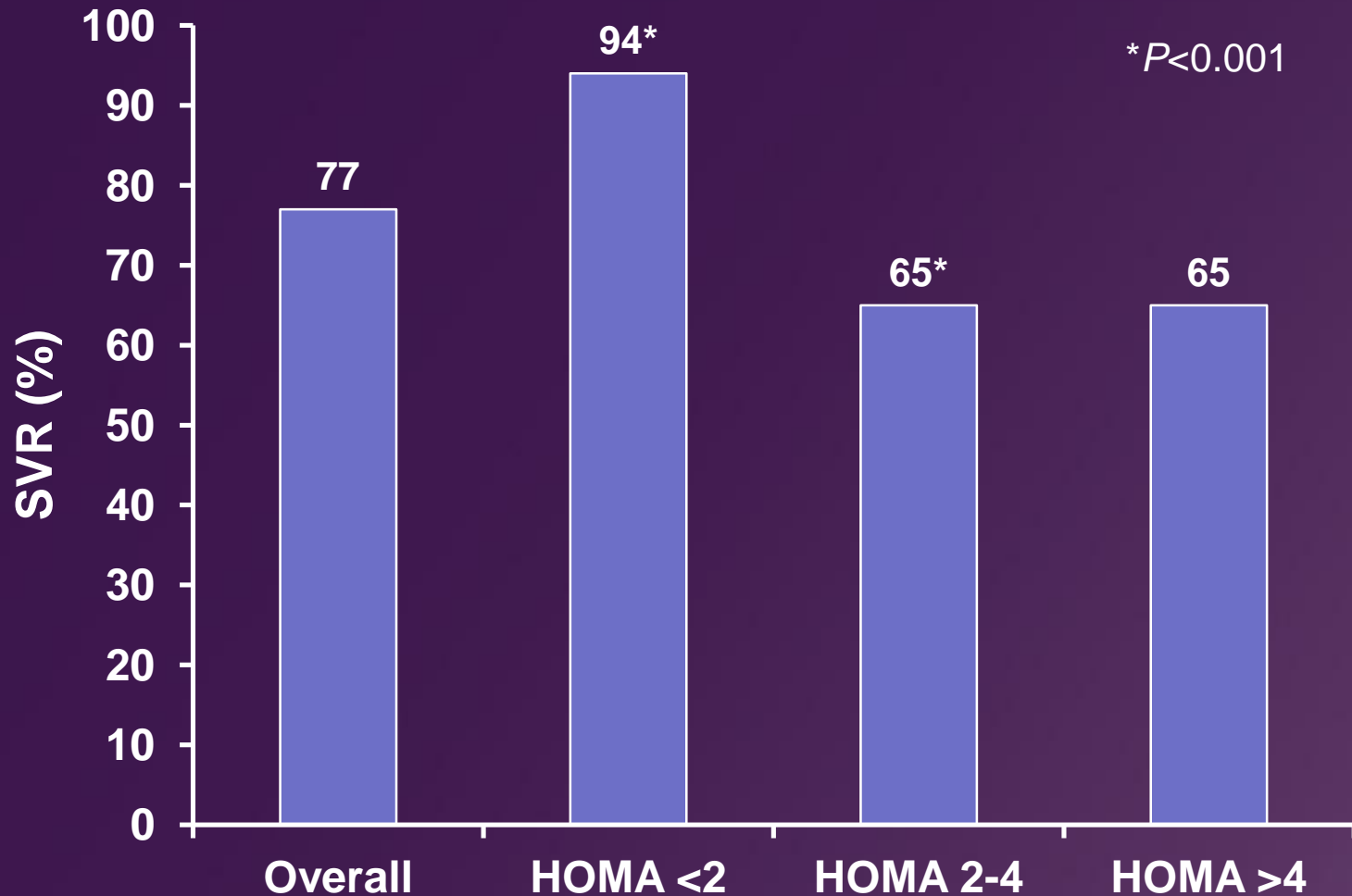
# SVR Decreased in Patients With HCV Genotype 1 and Insulin Resistance



HOMA = homeostasis model of assessment.

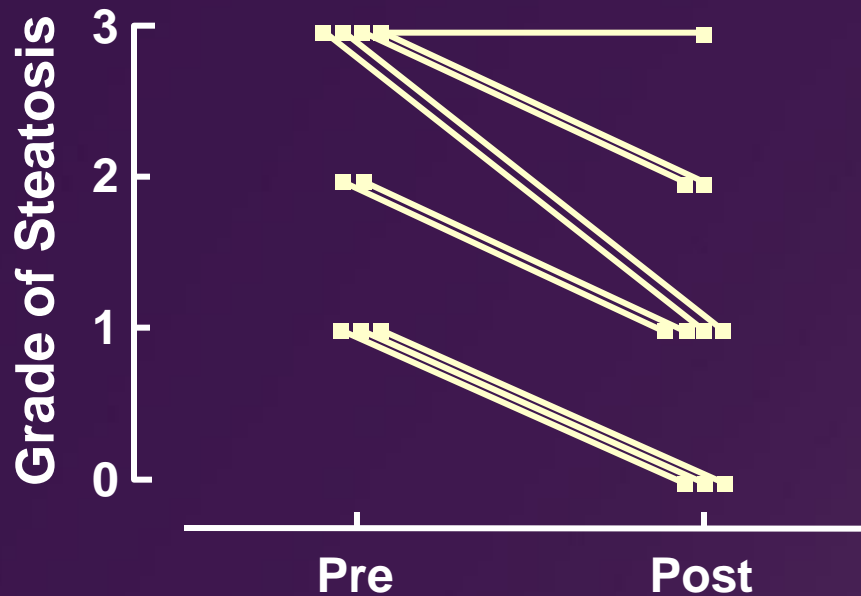
Reprinted from *Gastroenterology*. 128, Romero-Gómez M et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. Copyright 2005, with permission from Elsevier.

# SVR Decreased in Patients With HCV Genotype 2 or 3 and Insulin Resistance

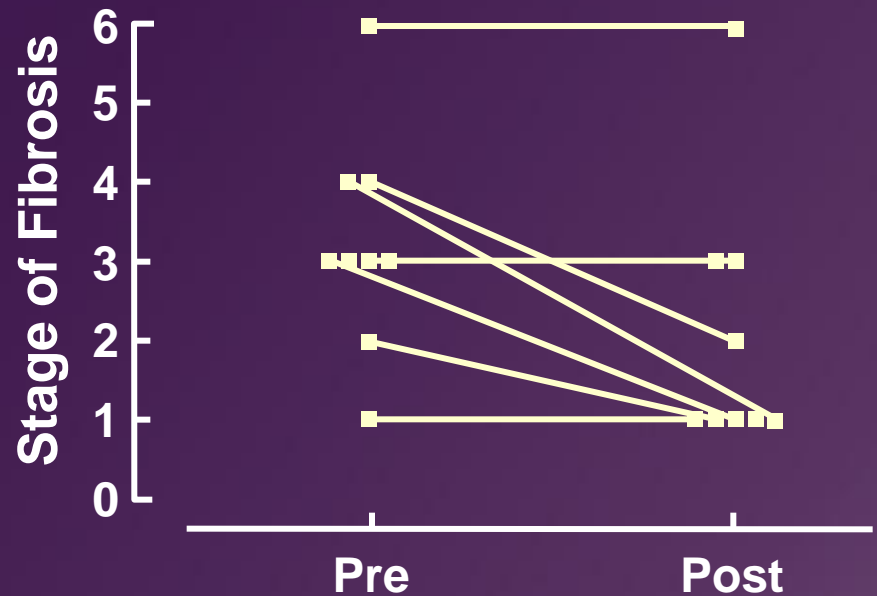


# Effects of Weight Reduction on Hepatic Histology in Chronic HCV

Insulin resistance fell from HOMA score 4.2 to 2.5 ( $P = 0.03$ )



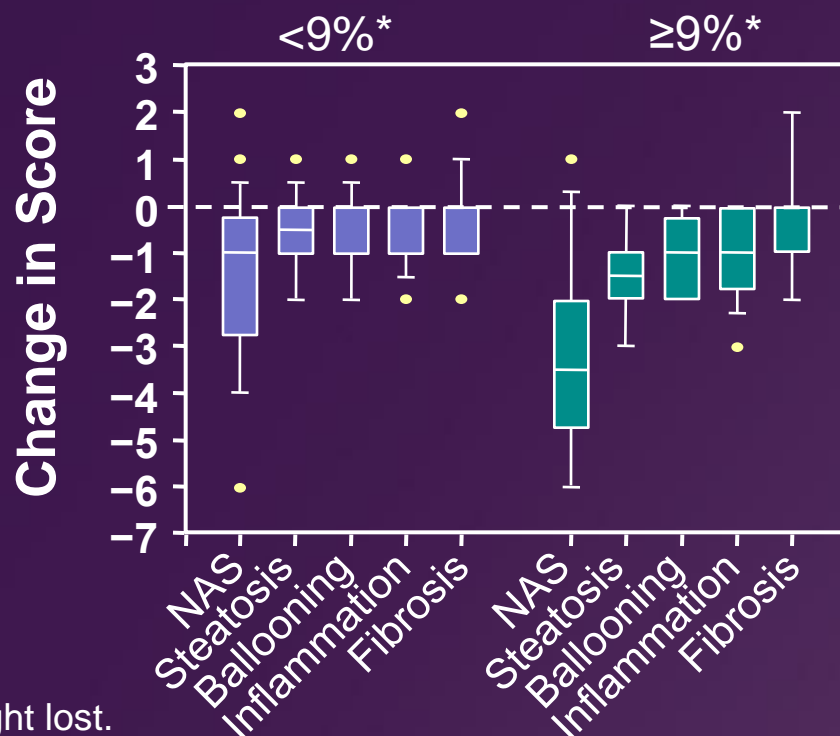
$P < 0.005$



$P = 0.04$

# Orlistat Study: Results

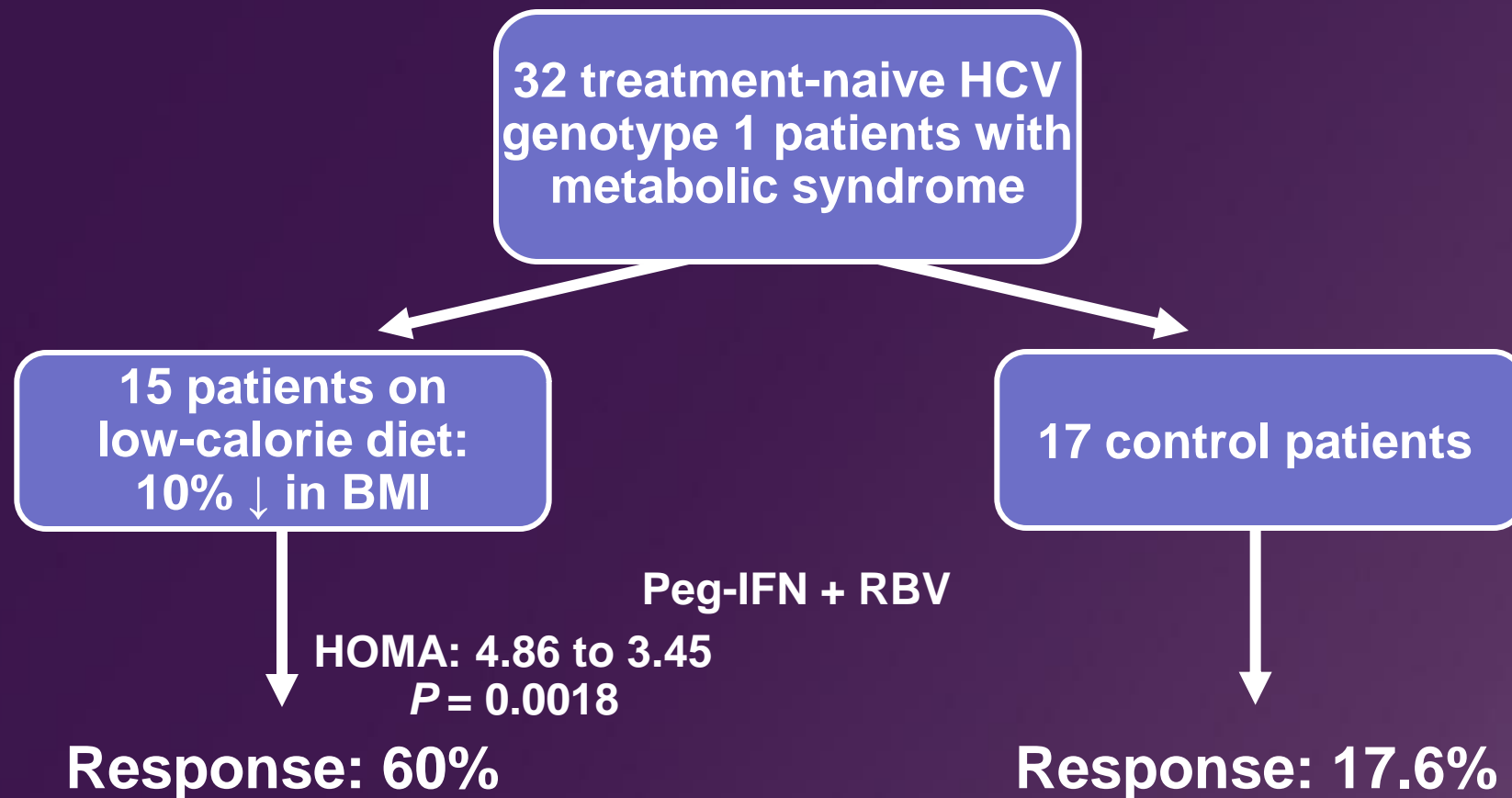
- ◆ Orlistat plus diet group lost a mean of 8.3% body weight
- ◆ Diet alone group lost a mean of 6% body weight
- ◆ No difference between groups in reference to histologic outcomes



\*Percent body weight lost.

- ◆ **Patients losing  $\geq 9\%$  body weight, in either group, improved IR, steatosis, inflammation, ballooning and NAFLD activity score (NAS)**

# Effect of Weight Loss on Antiviral Response



# Patient RN

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- ◆ Decision made to retreat with peg-IFN  $\alpha$ -2a 180  $\mu$ g/wk + RBV 1400 mg/d given the low dose of RBV received on initial treatment
  - Week 12 viral load: 8000 IU/mL
  - Patient tolerating therapy well but had to add epoetin alfa 40,000 units/wk
  - Week 24 viral load is undetectable (<50 IU/mL)
  - Extended treatment to 72 weeks
  - Achieved SVR!

# Additional Slides

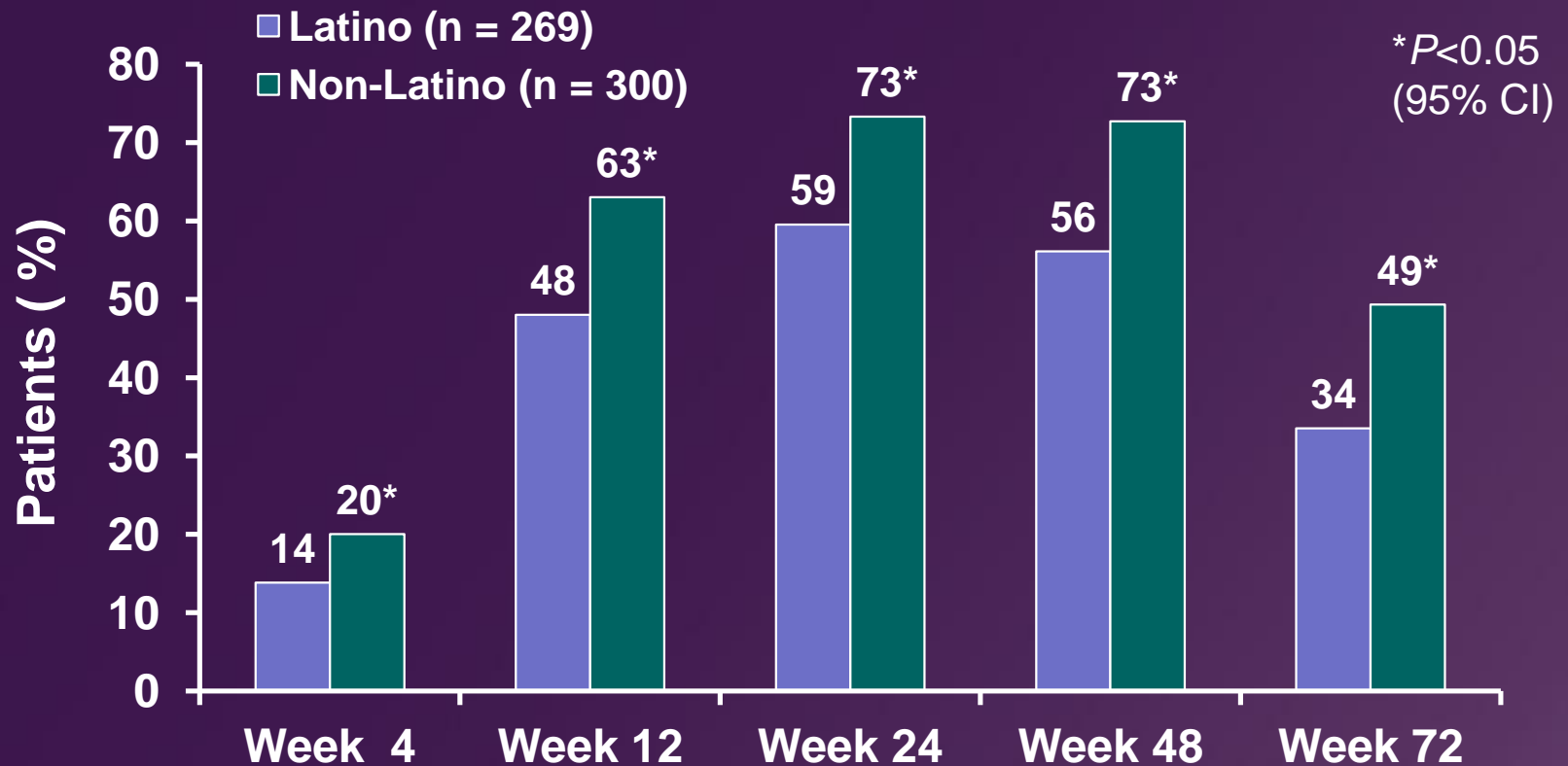
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# The LATINO Study

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- ◆ Prospective, open-label, nonrandomized study
- ◆ Objective: to compare the virologic response of peg-IFN  $\alpha$ -2a + RBV in treatment-naïve Latino and non-Latino white patients with HCV genotype 1
- ◆ Results:
  - SVR rate was higher in non-Latino white patients than in Latino patients (49% vs 34%;  $P < 0.0001$ )
  - Tolerability was similar in both populations
  - Discontinuation from the study due to AEs was less common for Latino than for Caucasian patients but more Latinos than Caucasians withdrew for non-safety reasons—primarily, insufficient response

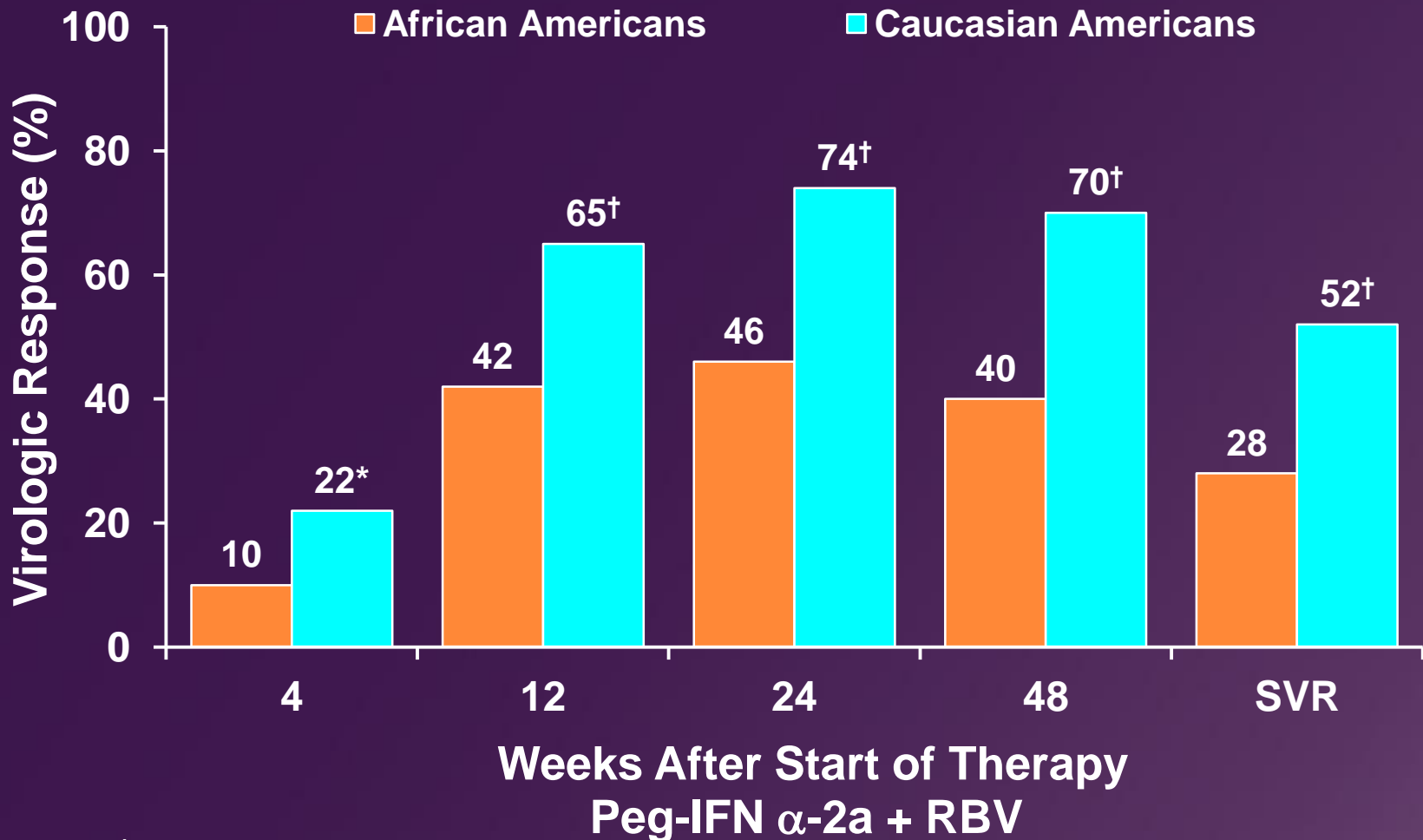
# The LATINO Study: Virologic Response Rates



SVR was higher in the non-Latino group than in the Latino group  
(49% vs 34%;  $P<0.0001$ )

Rodriguez-Torres M et al. *N Engl J Med* Jan 15;360(3):257-67. Copyright © 2009 Massachusetts Medical Society. All rights reserved.

# VIRAHEP-C: Virologic Response and Race



\* $P < 0.01$ ; † $P < 0.0001$ .