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# Hepatitis C Choices in Care

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## Western Management of Hepatitis C

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Allopathy – A therapeutic system in which a disease is treated by producing a second condition that is incompatible with or antagonistic to the first.

( *G. allo* – other + *G. pathos* – suffering)

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/ə **lopp** ə thi/ - the treatment of diseases by conventional means, i.e. with drugs having effects opposite to the symptoms

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# Western (Allopathic) Medicine

## Basic Concepts

- Determine cause of disease
- Eliminate or correct cause of disease
- Use medicines proven effective and safe
  - Evidence based, controlled trials
  - FDA approved
  - Placebo effect

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# Western (Allopathic) Medicine

## Basic Concepts

- If disease cannot be cured, then
  - Prevent progression
  - Relieve symptoms
  - Improve overall health, sense of well-being

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# Goals of HCV Therapy

- Eliminate virus
- Restore normal liver function
- Prevent further liver damage
- Improve overall health and well-being
- Permanent, life-long response

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# Goals of HCV Therapy

- Primary goal
  - Eradicate HCV infection
- Secondary goals
  - Slow disease progression
  - Improve histology
  - Reduce risk of hepatocellular carcinoma
  - Improve health-related quality of life

# Western Medicine Treatment Choices

- standard therapy is interferon-based
- current standard of care is pegylated interferon + ribavirin
- only method of treatment proven in clinical trials to reduce HCV to undetectable levels
  - overall sustained viral response (SVR) rate is ~50%

**Sustained Viral Response (SVR)  
means HCV is cured!**

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# Benefits of Sustained Viral Response

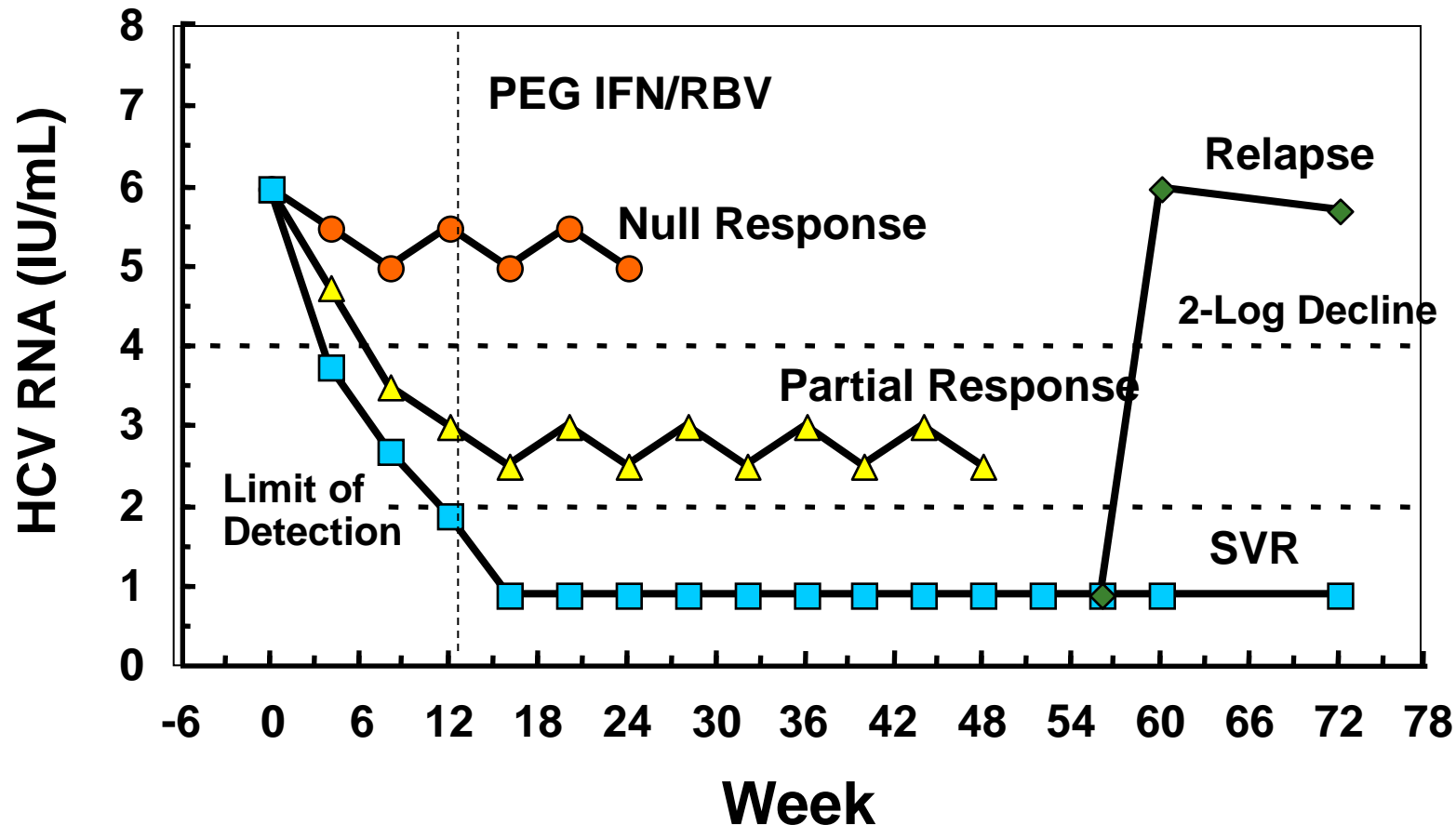
- improved liver function
- improved liver histology
- decreased infectivity
- loss of HCV RNA virus from the liver
- improved quality of life
  - increased productivity, fewer missed days of work, and less likely to work shorter hours

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# Other Benefits of Sustained Viral Response

- markedly decreased risk for hepatocellular carcinoma
- reduce risk for hepatic decompensation
- improved overall survival

# Definitions of Response to Anti-HCV Therapy



# Definitions of Response to Anti-HCV Therapy

- **Relapse**

HCV RNA becomes undetectable during treatment but reappears after treatment is stopped.

- **Non-response**

HCV RNA drops by two logs but never becomes undetectable

- **Null response**

HCV RNA drops less than one log after four weeks and less than two logs after 12 weeks of treatment

- **Viral breakthrough**

HCV RNA reemerges after it becomes undetectable while on treatment

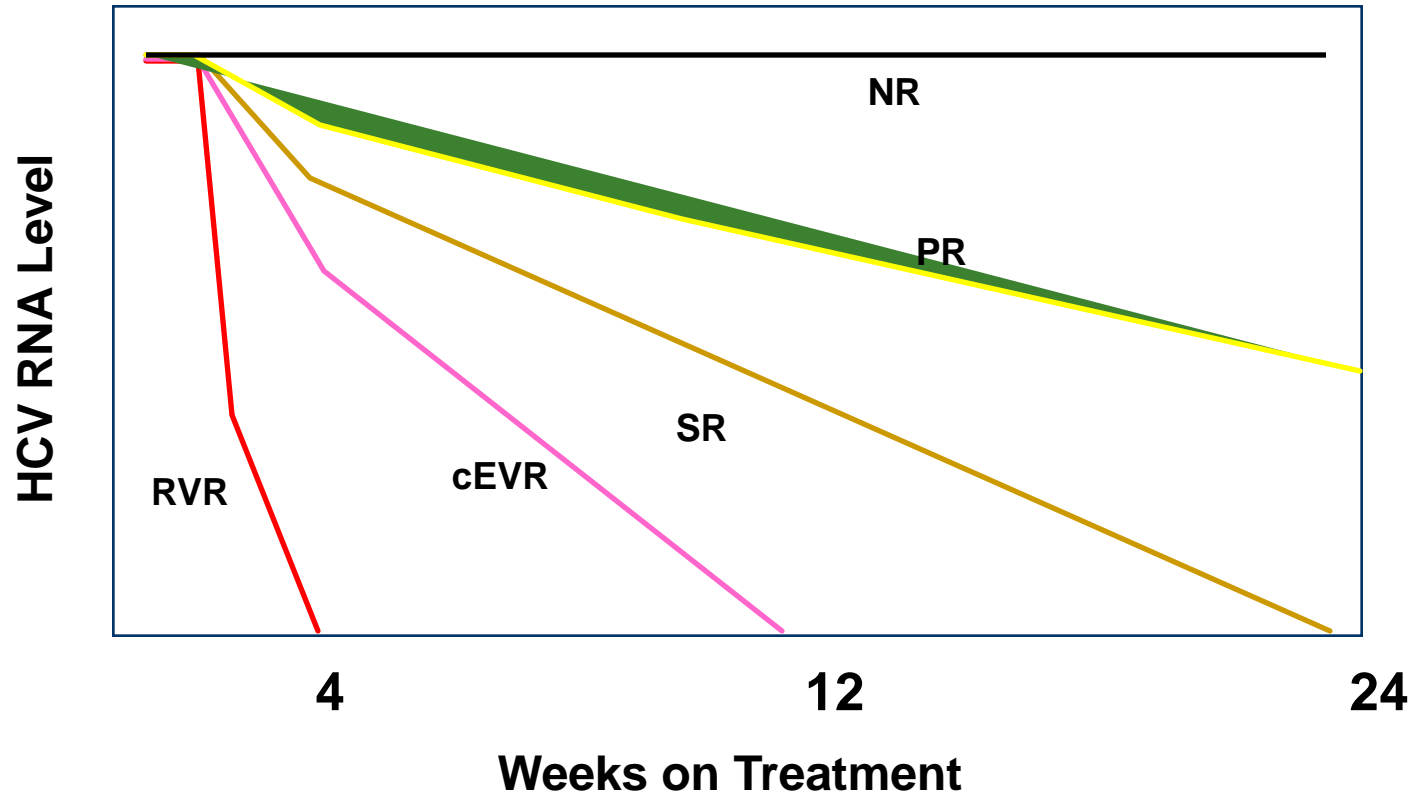
# Definitions of Response to Anti-HCV Therapy

- **Very rapid virological response (vRVR)**  
HCV RNA becomes undetectable after 14 days of treatment
- **Rapid virological response (RVR)**  
HCV RNA becomes undetectable after 4 weeks of treatment
- **Extended rapid virological response (eRVR)**  
HCV RNA becomes undetectable after 4 weeks of treatment and remains undetectable at week 12
- **Partial early virological response (pEVR)**  
HCV RNA drops by at least 2 logs at week 12

# Definitions of Response to Anti-HCV Therapy

- **Complete early virological response (cEVR)**  
HCV RNA remains undetectable after 12 weeks of treatment
- **End-of-treatment response (EOT)**  
HCV RNA remains undetectable at the end of treatment
- **Slow Virologic response (SR)**  
2 log drop at week 12 and HCV RNA negative at week 24
- **Sustained virological response (SVR)**  
No HCV RNA detectable 6 months after completion of treatment  
- **Cure**

# Which patient has the best likelihood of achieving an SVR?



Use of viral kinetics to define on-treatment predictors of response

# Predictors of Response

## Original

- genotype 2/3
- absence of fibrosis
- low viral load
- younger age
- female gender
- lower weight

## Additional

- lack of steatosis
- insulin resistance
- adherence
- early viral response
- ribavirin dosage
- ethnicity
- 4-week viral clearance

# Standard Interferon-Based Therapy

- two pegylated interferons are now FDA-approved
  - peginterferon alfa-2a (Pegasys® - Genetech)
  - peginterferon alfa-2b (PEG-Intron® - Merck)
- Four ribavirins are now FDA-approved
  - Copegus® (Genentech)
  - Rebetol® (Merck)
  - Ribasphere® (generic, Three Rivers Pharma.)
  - generic ribavirin (Novartis)

# Standard Interferon-Based Therapy

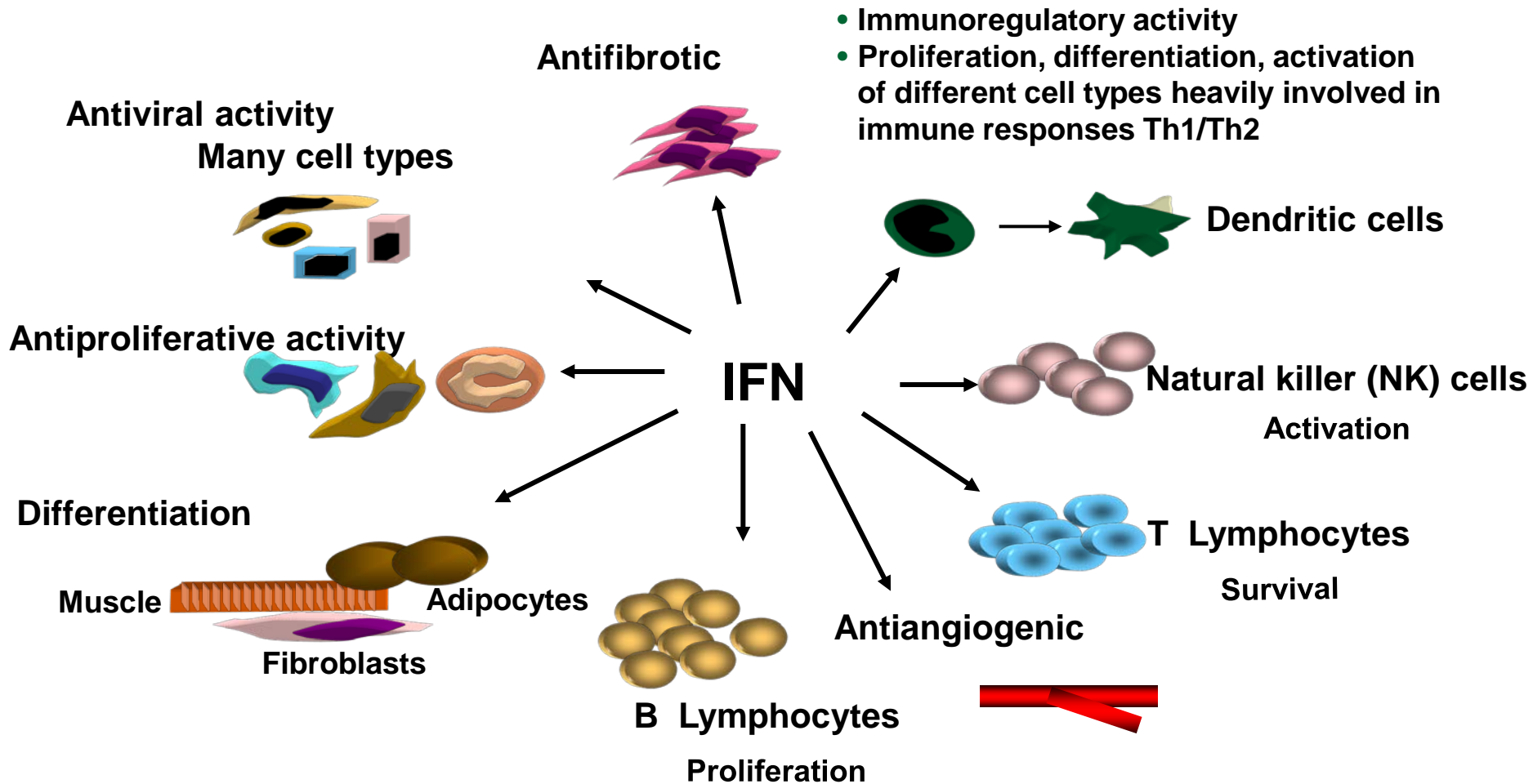
- genotype 1a/b
  - pegylated interferon alfa-2a or 2b (see below) plus ribavirin (1000-1200 mg/d) for 48 weeks
- genotypes 2, 3
  - pegylated interferon alfa-2a or 2b plus ribavirin (800 mg/d) for 24 weeks
- emerging data
  - genotype 1 - treat for up to 72 weeks or only 24 weeks
  - genotype 2, 3 - treat for 14-16 weeks
  - treatment duration is based on early (4 week) virologic response

## Pegylated Interferon Dosing

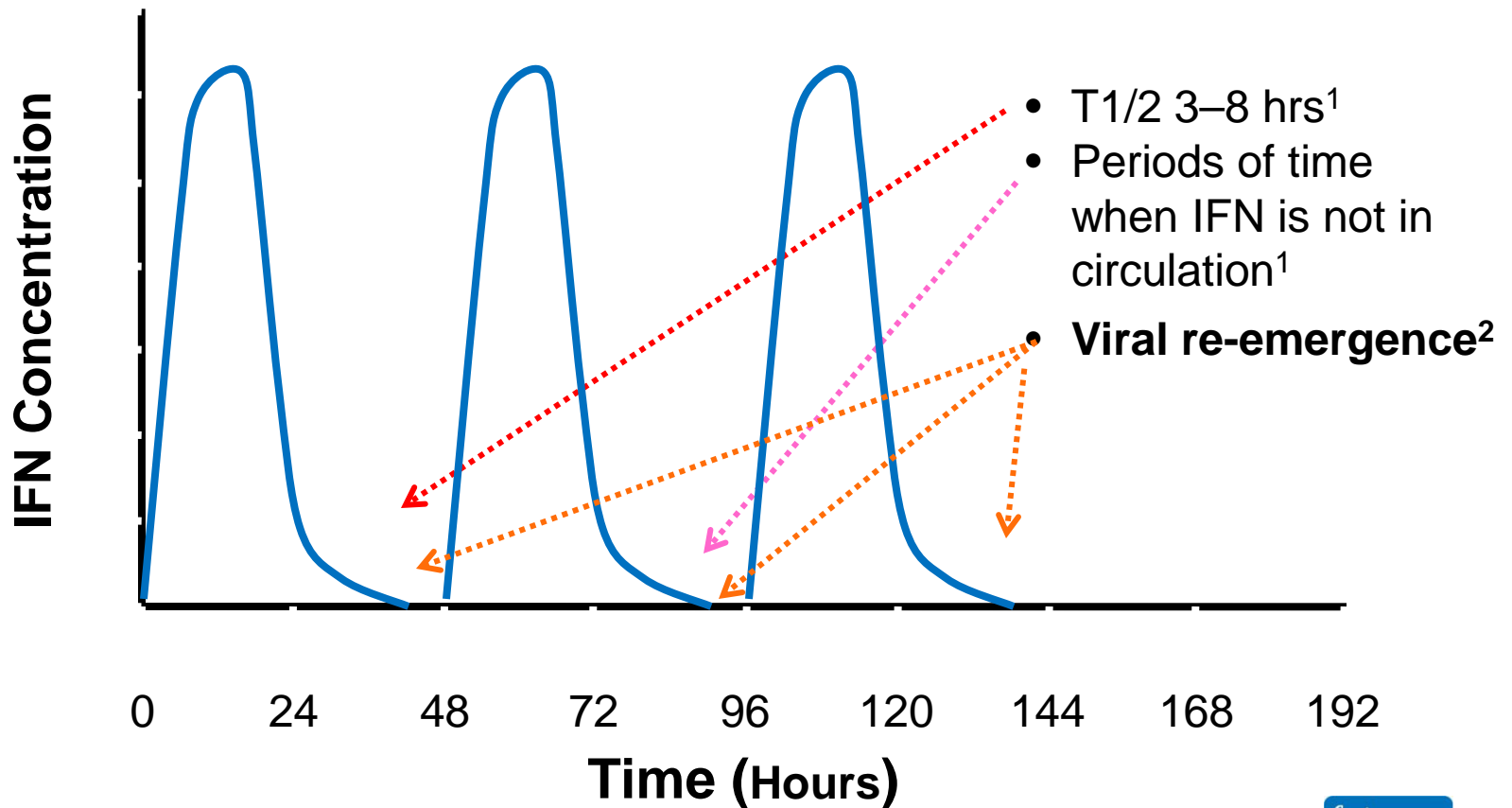
- peginterferon alfa-2b – 1.0-1.5 $\mu$ g/kg once weekly
- peginterferon alfa-2a – 180  $\mu$ g once weekly

# Why Interferons?

## IFNs Exhibit Multiple Activities



# Limitations of Standard Interferon



1. Xu ZX, et al. *Hepatology*. 1998;28(suppl):702A.

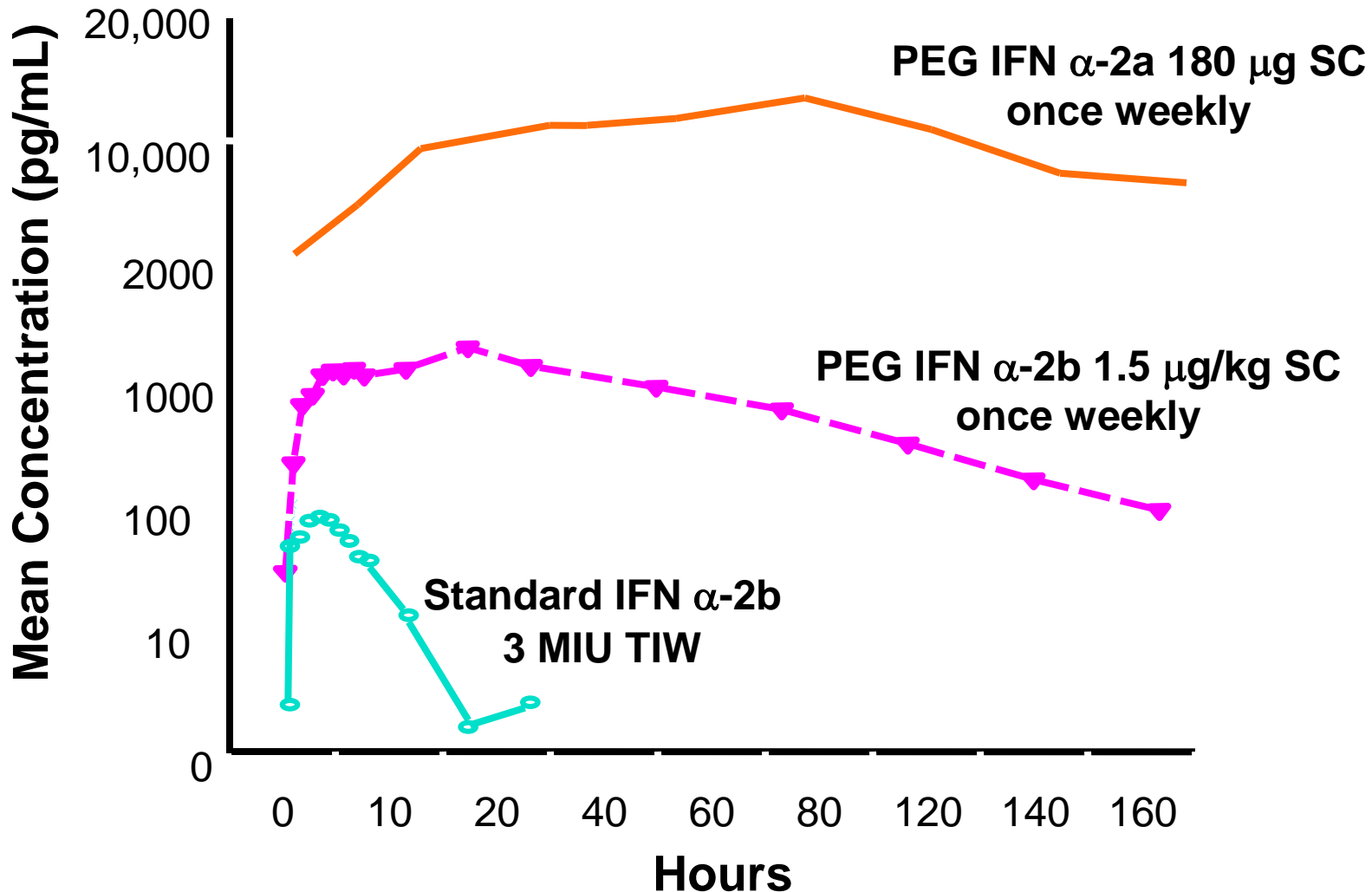
2. Lam NP, et al. *Hepatology*. 1997;26:226.

# Why Pegylated Interferons?

- covalent attachment of variably configured **polyethylene glycol (PEG)** chains to sites on the interferon molecule
  - delays absorption
  - decreases clearance rate
  - allows once per week dosing
  - alters properties and activity of parent compound
  - prolongs immune activation and cytokine-derived antiviral effects

**Result: potentially greater efficacy**

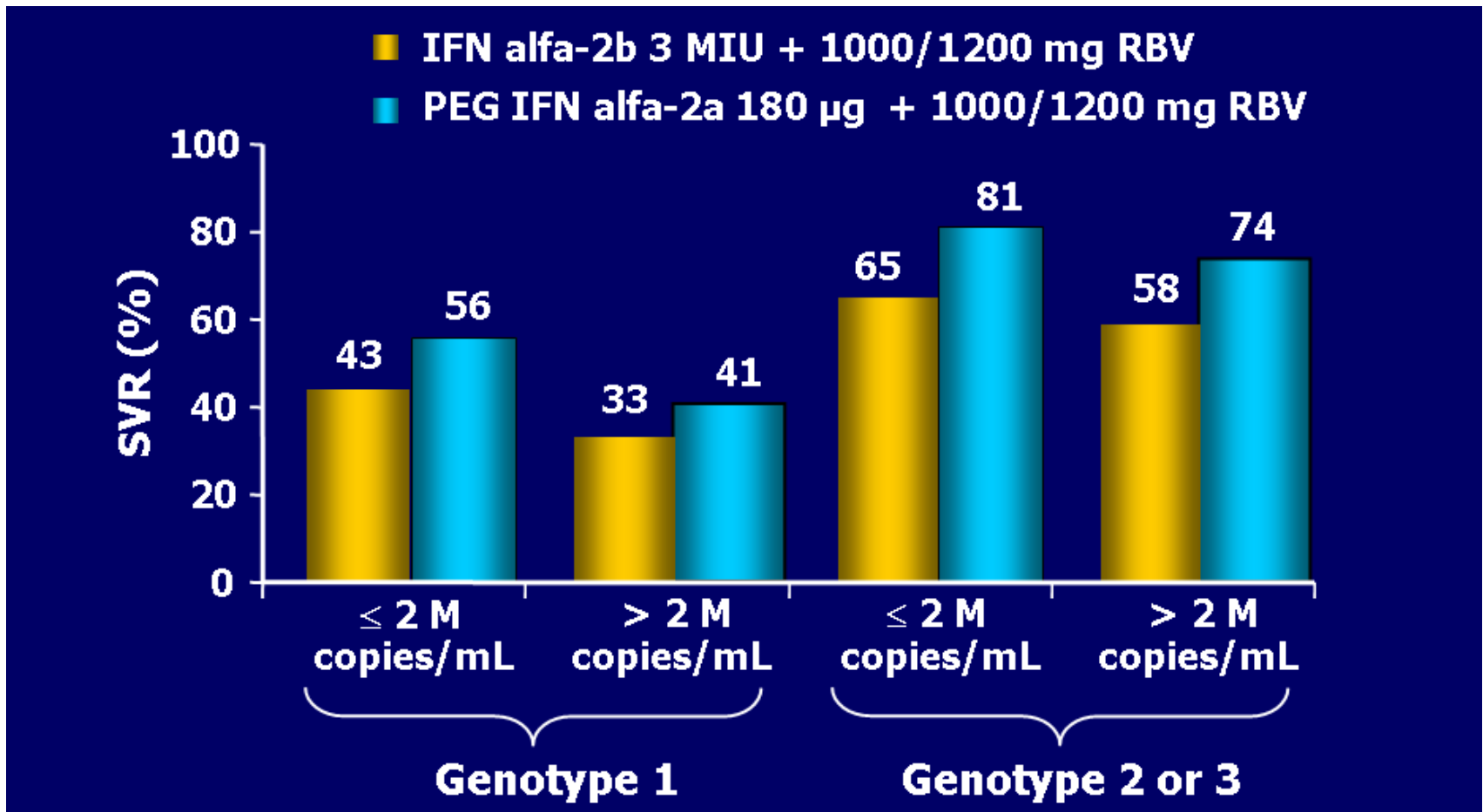
# Concentration-Time Profiles: Week 4



# Antiviral Activity of Ribavirin

- Limited antiviral activity when used as monotherapy
- Unclear which single proposed mechanism is key to the outcomes of HCV antiviral therapy
- Clinical data support ribavirin is key during all stages of HCV therapy:
  - **Initiation of therapy** – Impact of initial dose and early dose reductions/discontinuations
  - **Throughout the treatment** – Continued impact of dose reductions/discontinuations
  - **End of therapy** – Preventing virologic breakthrough and relapse rates

# Pegasys and Copegus: SVR by Genotype and Viral Load



# Treatment of Chronic Hepatitis C: SVR With Peginterferon and Ribavirin

	Peg-IFN $\alpha$ -2a <sup>1,2</sup>	Peg-IFN $\alpha$ -2b <sup>3</sup>
Overall	56% & 63%	54% (61%)*
Genotype 1	46% & 52%	42% (48%)*
Genotype 1, HVL	41% & 46%	30% (37%)*
Genotypes 2 & 3	76% & 84%	82% (88%)*

\*RBV >10.6 mg/kg by post hoc analysis.

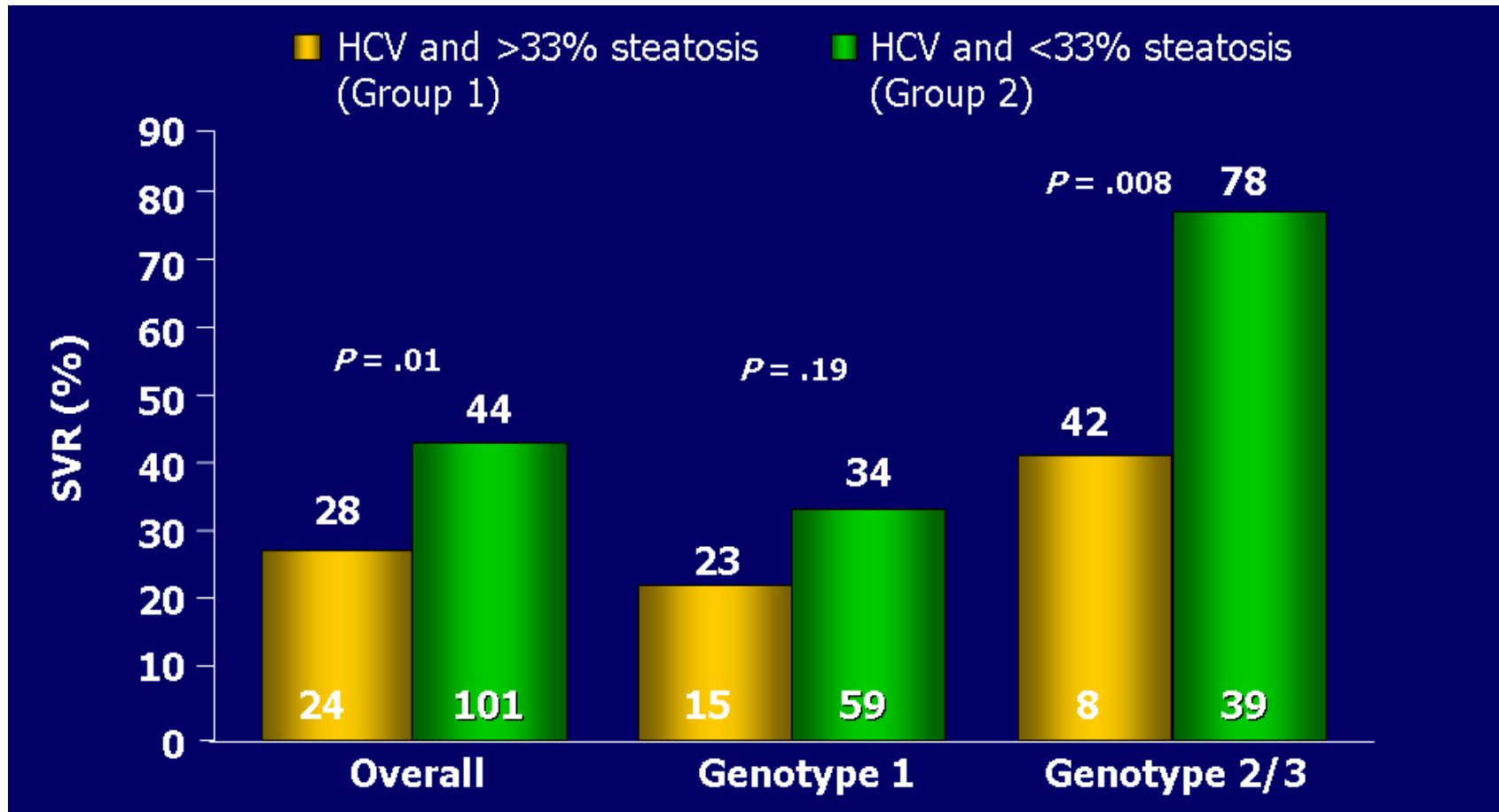
SVR = sustained virologic response; HVL = high viral load.

1. Fried MW et al. *N Engl J Med.* 2002;347:975-982; 2. Hadziyannis SJ et al. *Ann Intern Med.* 2004;140:346-355;

3. Manns MP et al. *Lancet.* 2001;358:958-965.

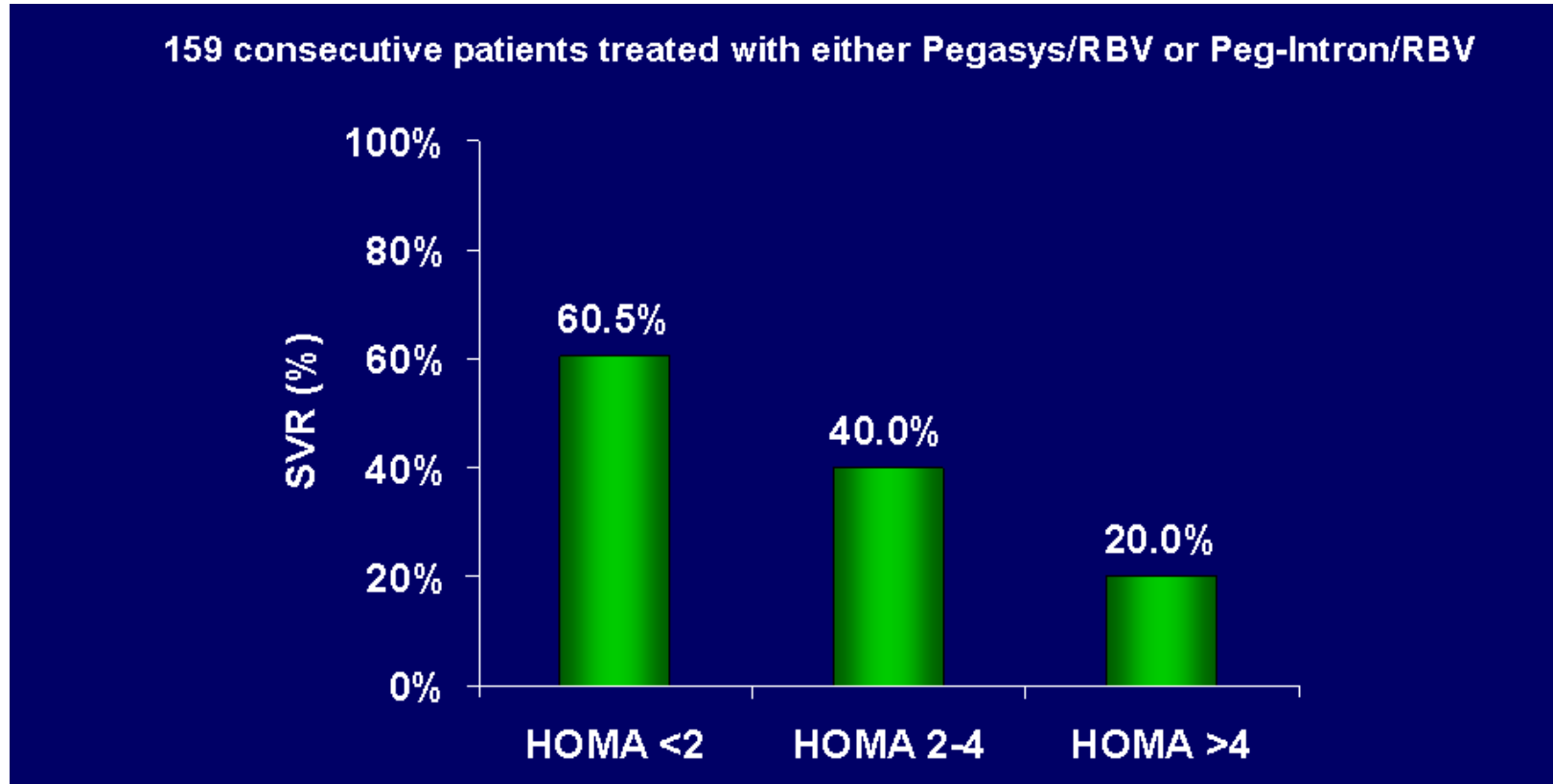


# Patients with Fatty Liver Demonstrate Lower Viral Response



1. Pegasys (Peginterferon alfa-2a) [package insert], Nutley, NJ Hoffman-La Roche Inc.
2. Fried MW et al N Engl J Med 2002;347(13):975-982
3. Peg-Intron® (peginterferon alfa-2b) [package insert] Kenilworth, NJ: Schering Corporation
4. Manns M, et al. Lancet, 2001;358:958-965.

# Impact of Insulin Resistance on Virologic Response in Genotype 1



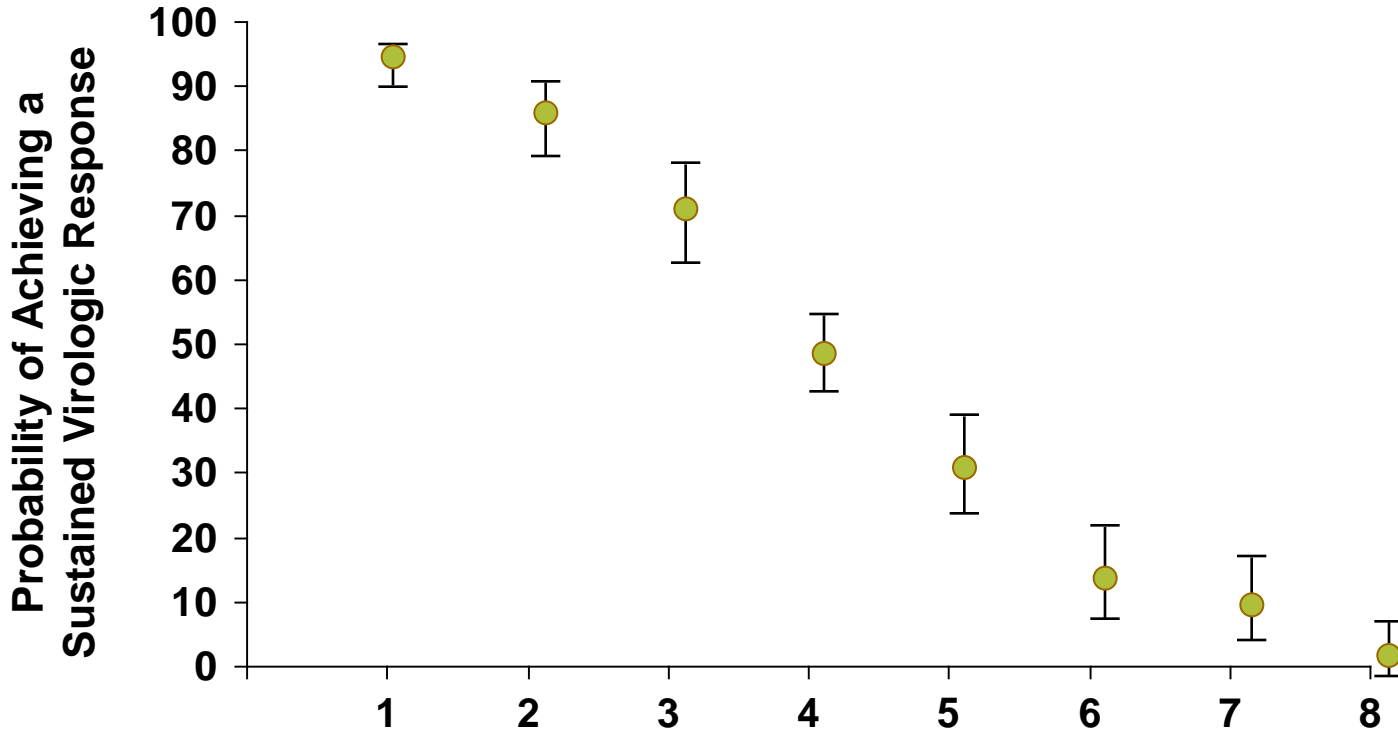
(HOMA <2, 2-4, and >4 odds ratio, 2.43. 95% CI, 1.41-4.20, P = 004)

HOMA = homeostasis model assessment

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

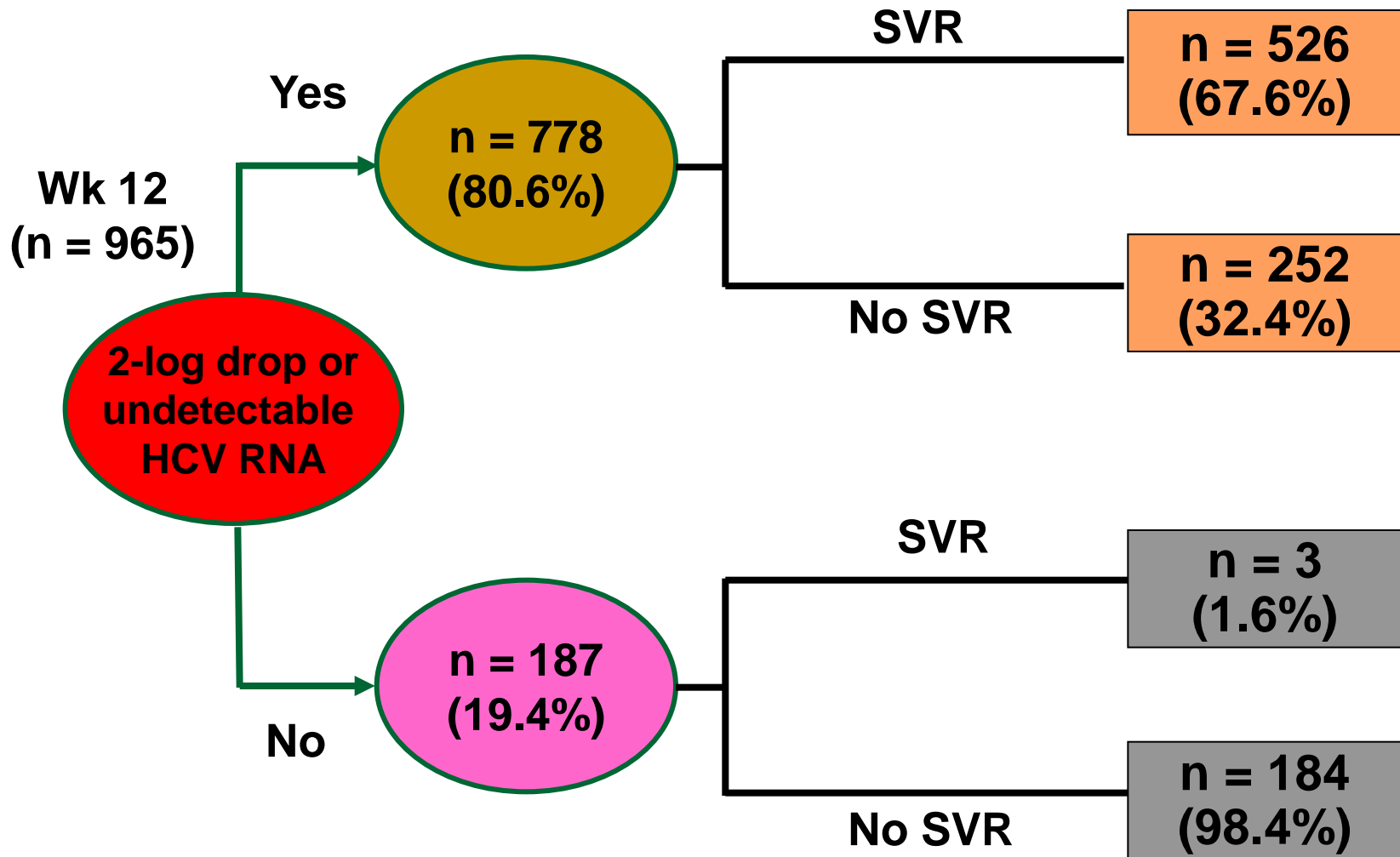


# Probability of Sustained Virologic Response: Interactions of Multiple Factors



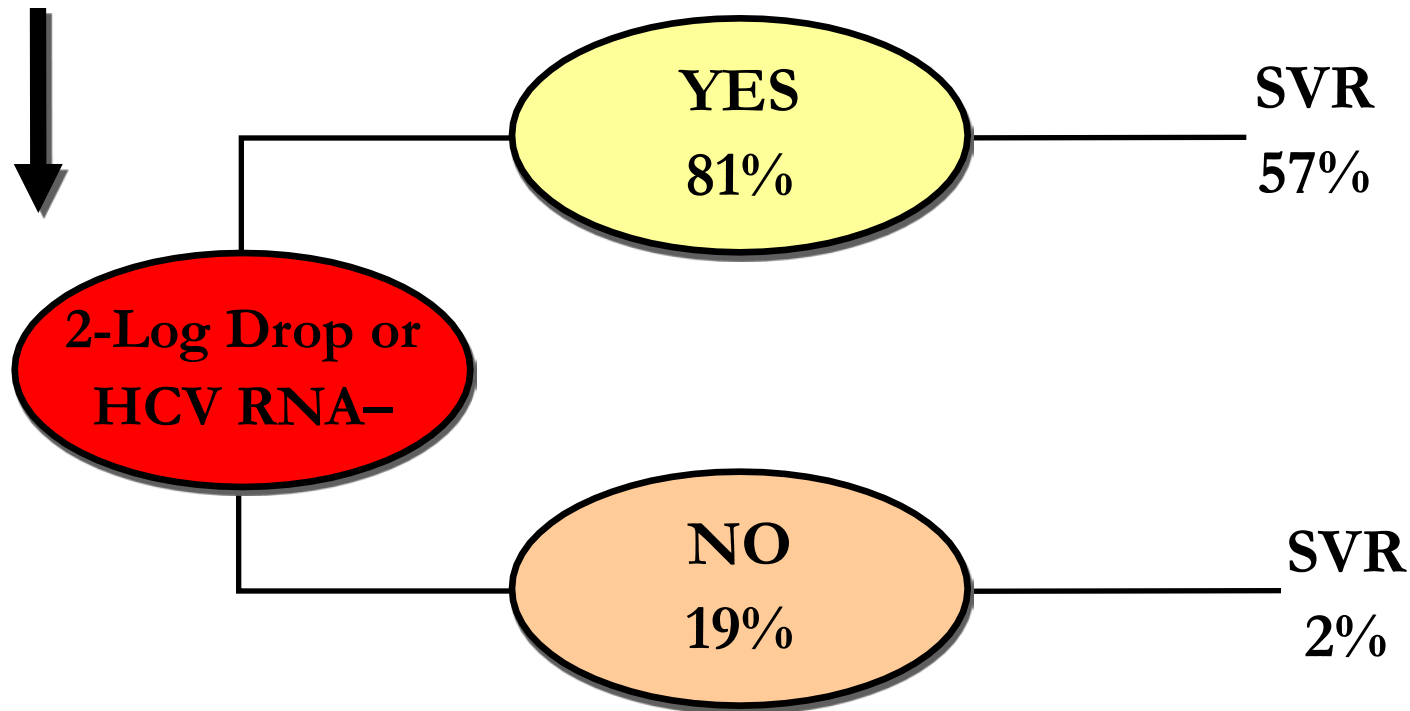
<b>Cirrhosis</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>No</b>	<b>Yes</b>
<b>ALT quotient</b>	<b>7</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>2</b>	<b>1</b>	<b>1</b>
<b>Age (years)</b>	<b>20</b>	<b>20</b>	<b>43</b>	<b>43</b>	<b>43</b>	<b>60</b>	<b>60</b>	<b>60</b>
<b>BMI (kg/m<sup>2</sup>)</b>	<b>20</b>	<b>20</b>	<b>26</b>	<b>26</b>	<b>26</b>	<b>30</b>	<b>30</b>	<b>30</b>
<b>HCV RNA (IU/mL × 10<sup>3</sup>)</b>	<b>40</b>	<b>40</b>	<b>40</b>	<b>1200</b>	<b>9000</b>	<b>9000</b>	<b>9000</b>	<b>9000</b>

# Early Prediction of Nonresponse: Pooled Results of Peg-IFN $\alpha$ -2a/2b + RBV



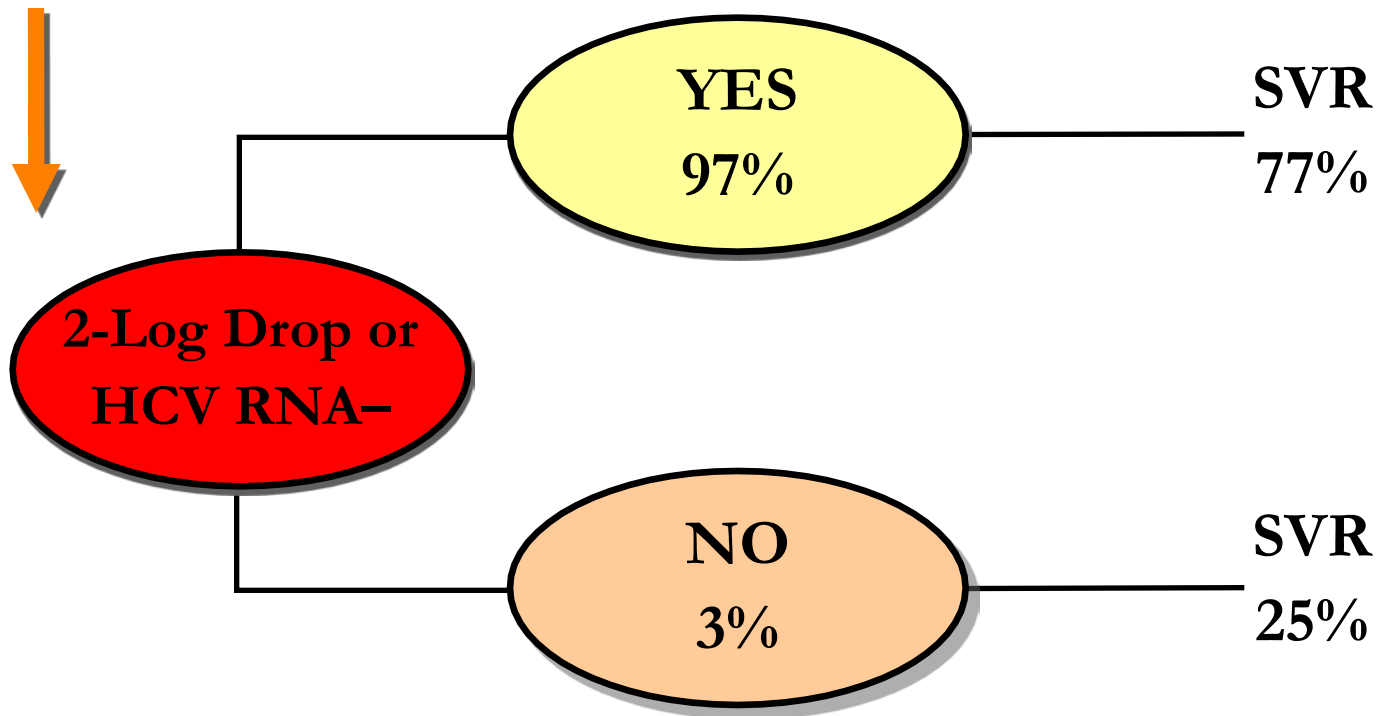
# Early Virologic Response to PegIFN alfa-2a + Riba, Genotype 1

Week 12

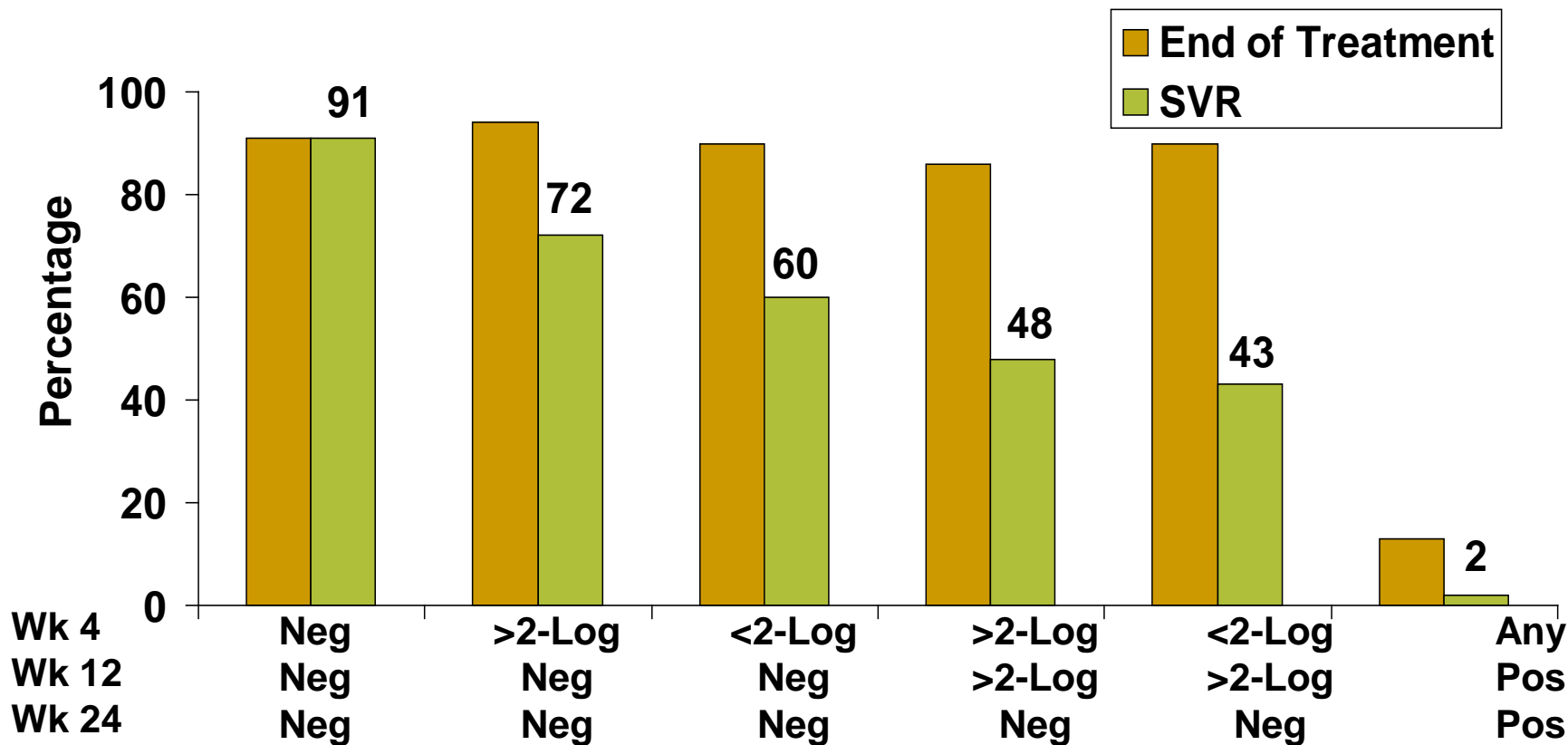


# Early Virologic Response to PegIFN alfa-2a + Riba, Genotypes 2/3

Week 12

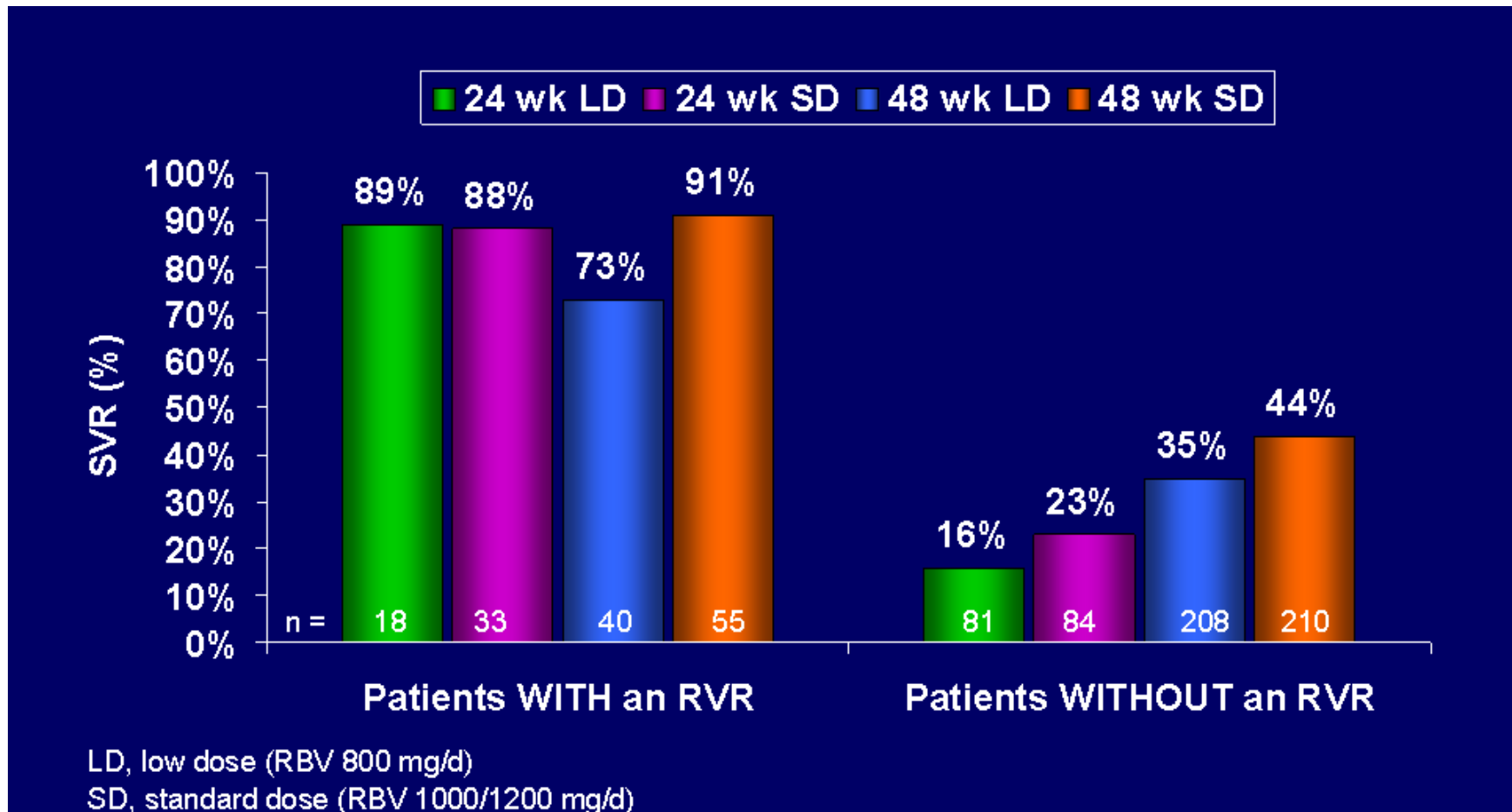


# Viral Kinetics and Outcome: Importance of Rapid Virologic Response

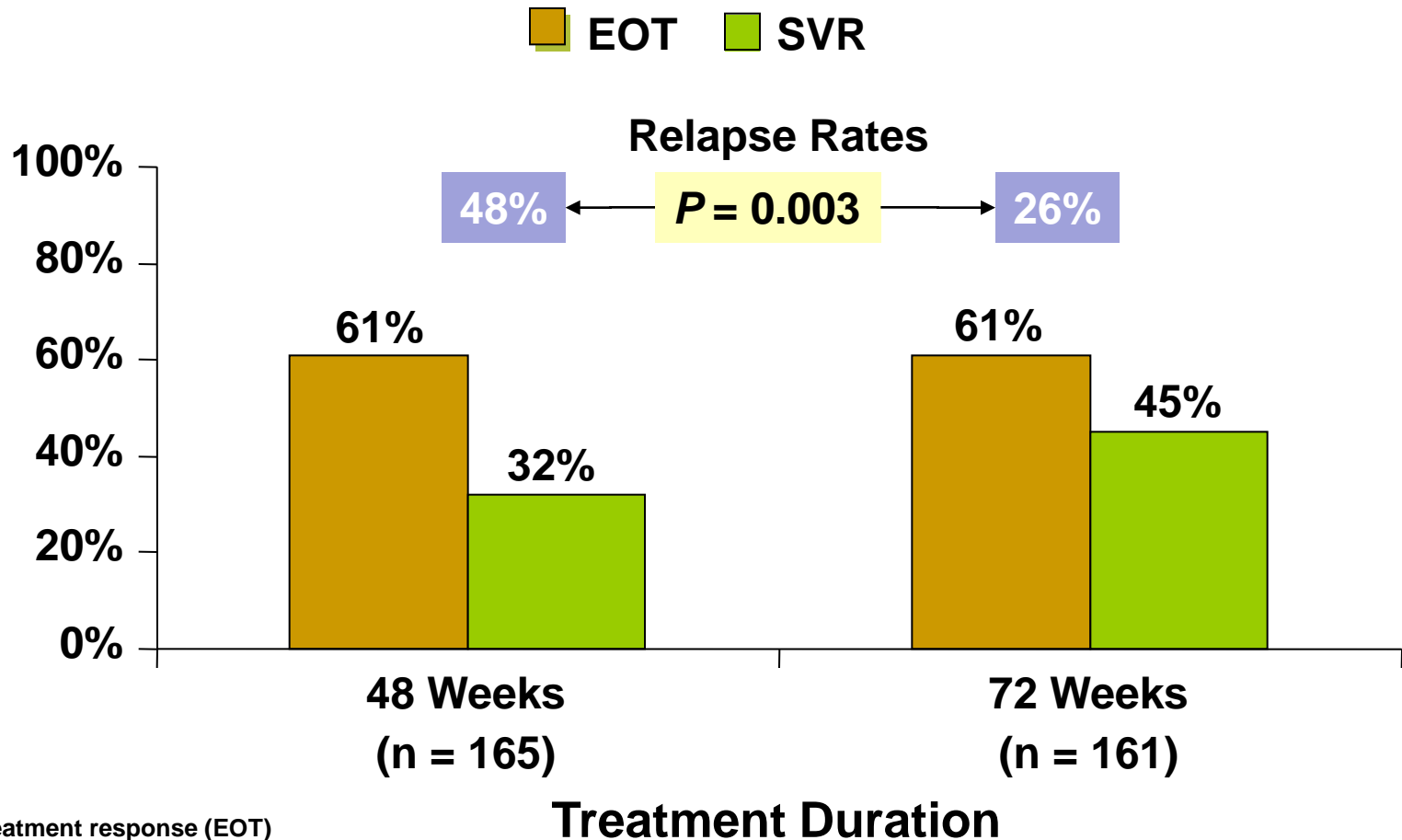


Virologic response (VR) = neg or >2-log decrease;

# Pegasys and Copegus: Genotype 1 Rapid Virologic Responders



# Duration of Therapy by RVR: Relapse Rate in Patients Without RVR at 4 Weeks



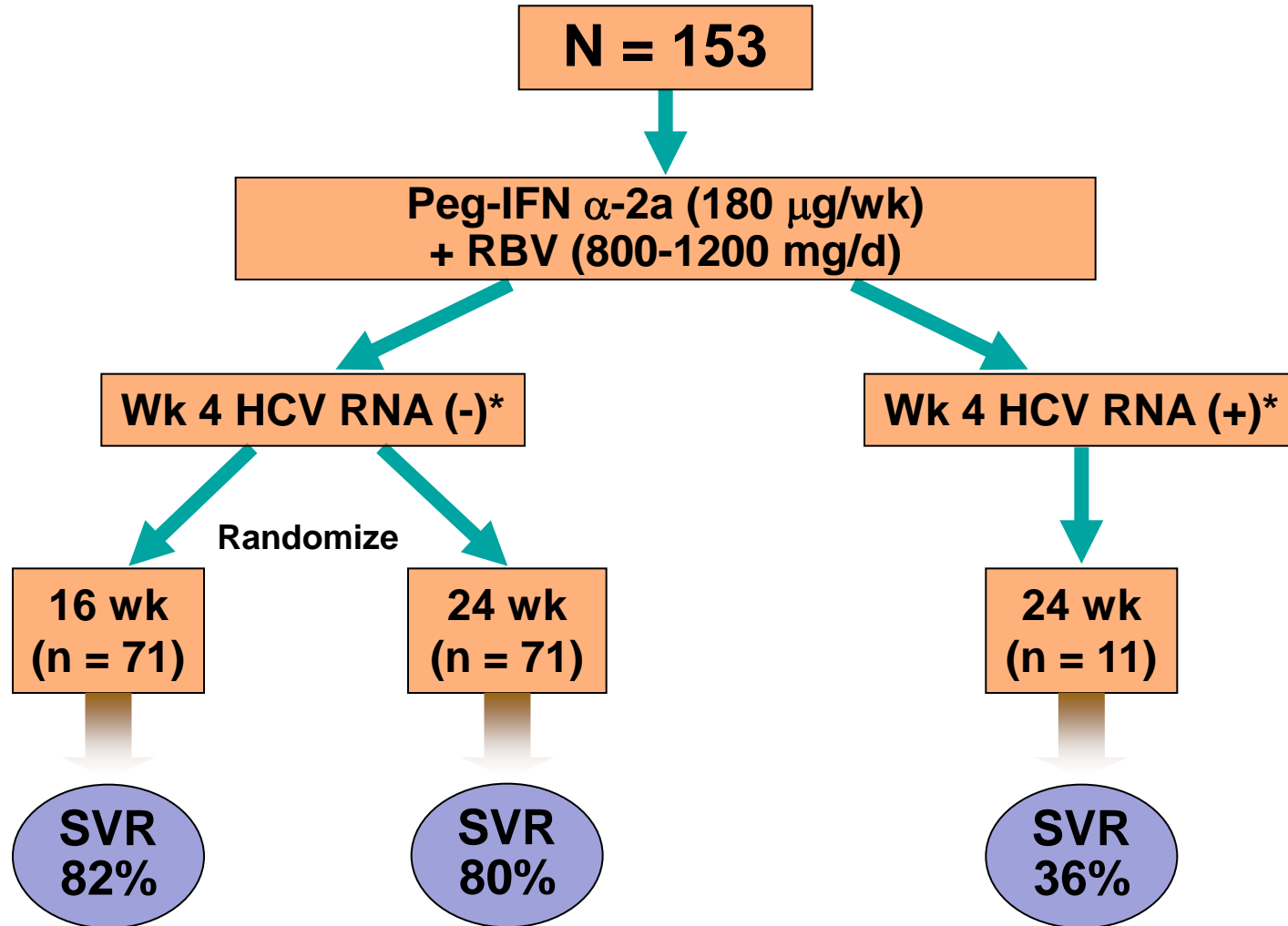
End-of-treatment response (EOT)  
Sustained virological response (SVR)

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# Duration of Treatment for HCV Genotypes 2 and 3

- Early studies confirmed: higher response rates for non-1 genotypes
  - No difference in response rates between 24 weeks and 48 weeks
  - 800 mg ribavirin is sufficient dose
- But, what is the optimal treatment duration?

# Shorter Treatment for Genotypes 2 and 3: 16 vs 24 Weeks



\*HCV was assessed after 4 weeks with a lower limit of detection of 600 IU/mL.

Von Wagner M et al. Gastroenterology. 2005;129:522-527.

# Shorter Treatment for Genotypes 2 and 3: 14 vs 24 Weeks

N = 122

Peg-IFN  $\alpha$ -2b (1.5  $\mu$ g/kg/wk)  
+ RBV (800-1400 mg/d)

PCR (-) at 4 & 8 wk?

YES

95 (78%)

NO

27 (22%)

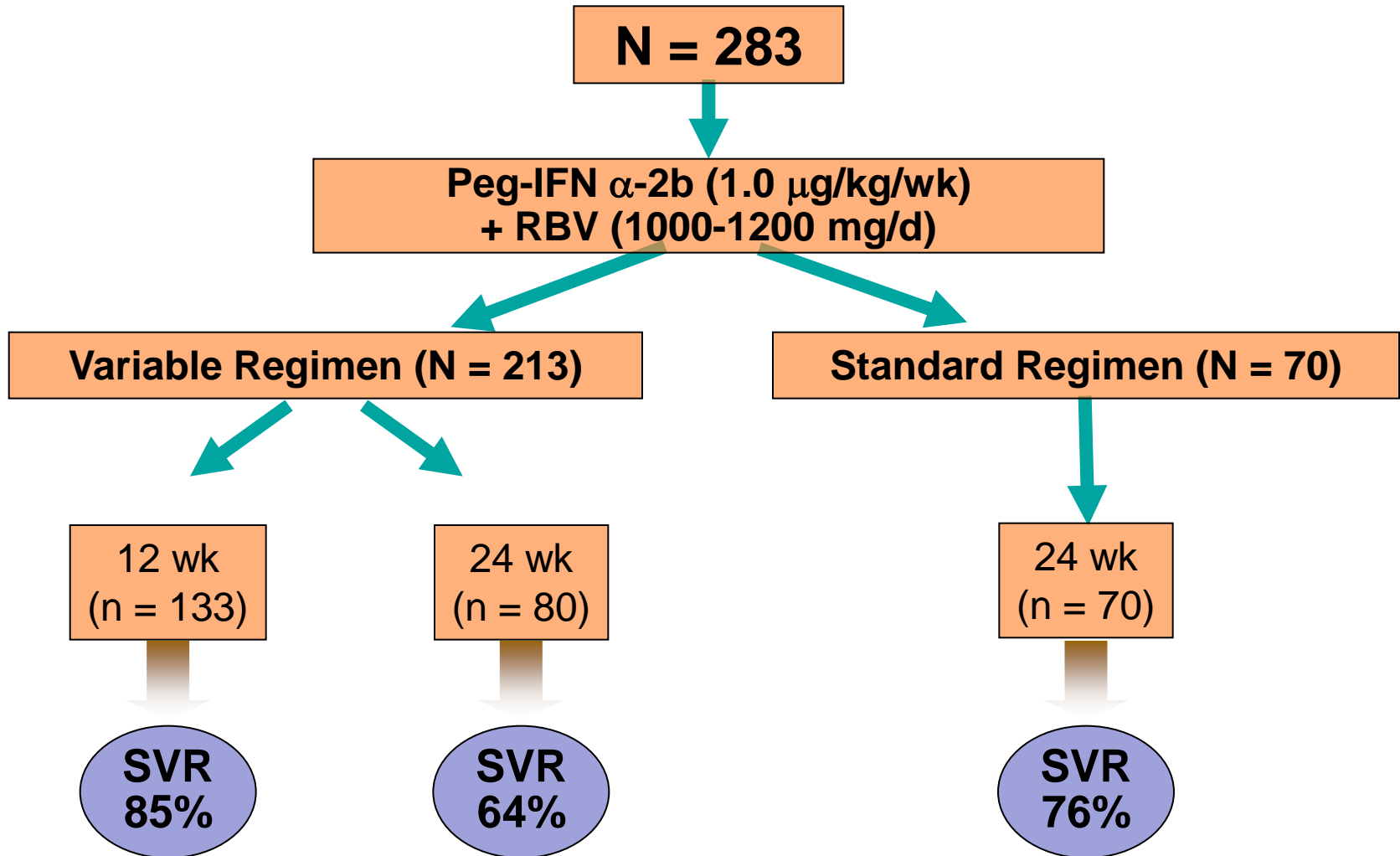
SVR  
90%

Treated x 14 wk

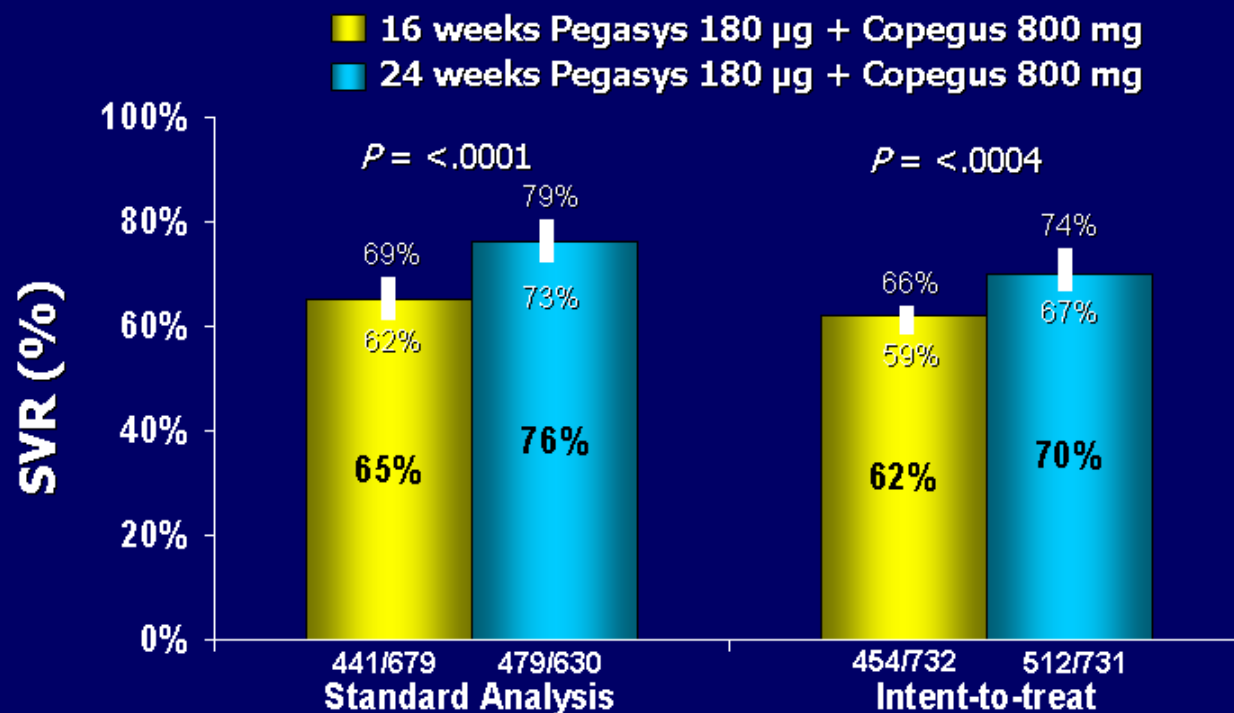
Treated x 24 wk

SVR  
56%

# Shorter Treatment for Genotypes 2 and 3: 12 vs 24 Weeks



# ACCELERATE Trial: Primary Endpoint (SVR)

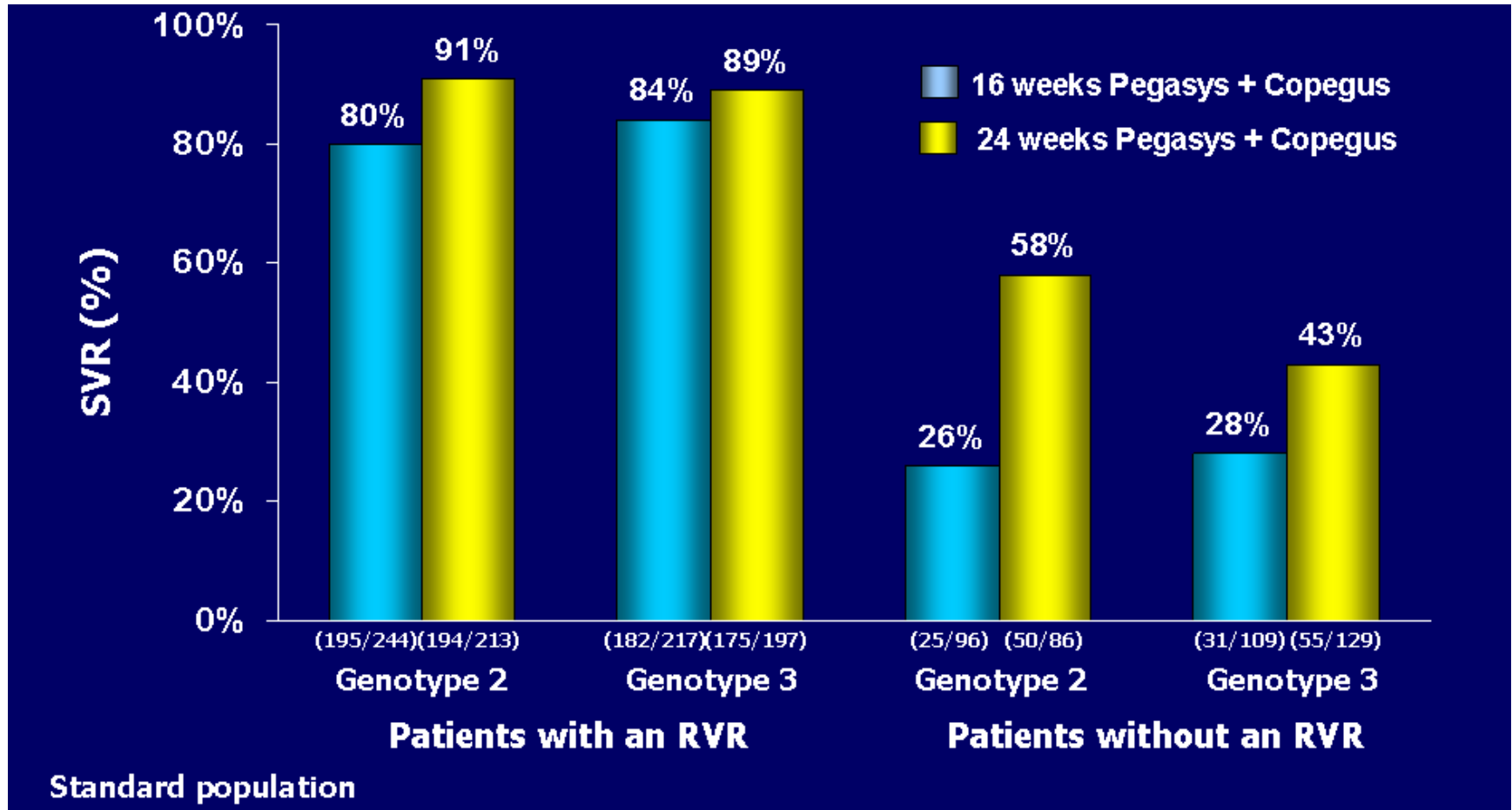


## Patients with genotype 2 or 3

Standard Population Analysis is primary efficacy analysis

SVR = HCV RNA < 50 IU/mL at 24 weeks after treatment

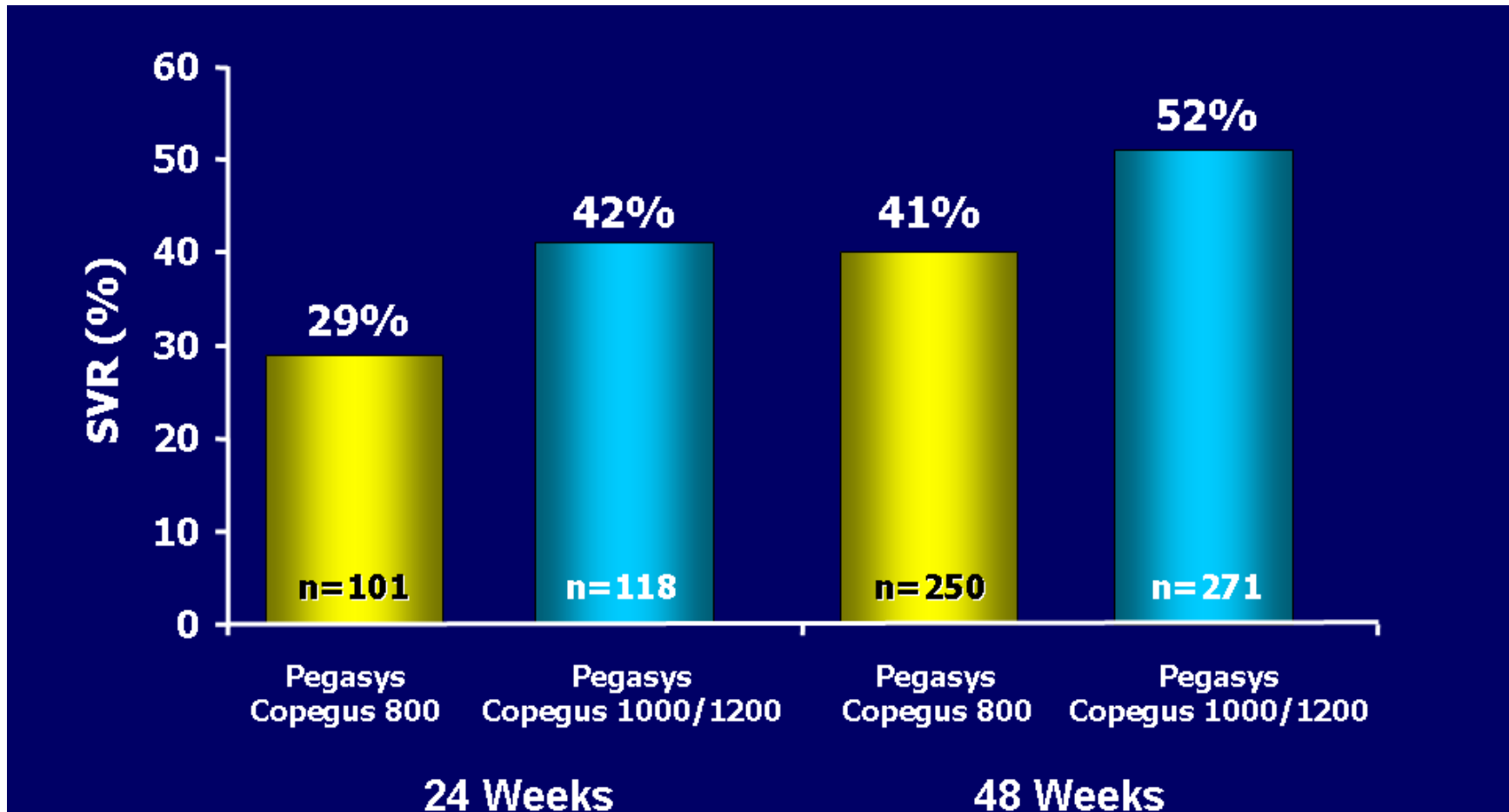
# ACCELERATE Trial: SVR in Patients with and without an RVR by Genotype



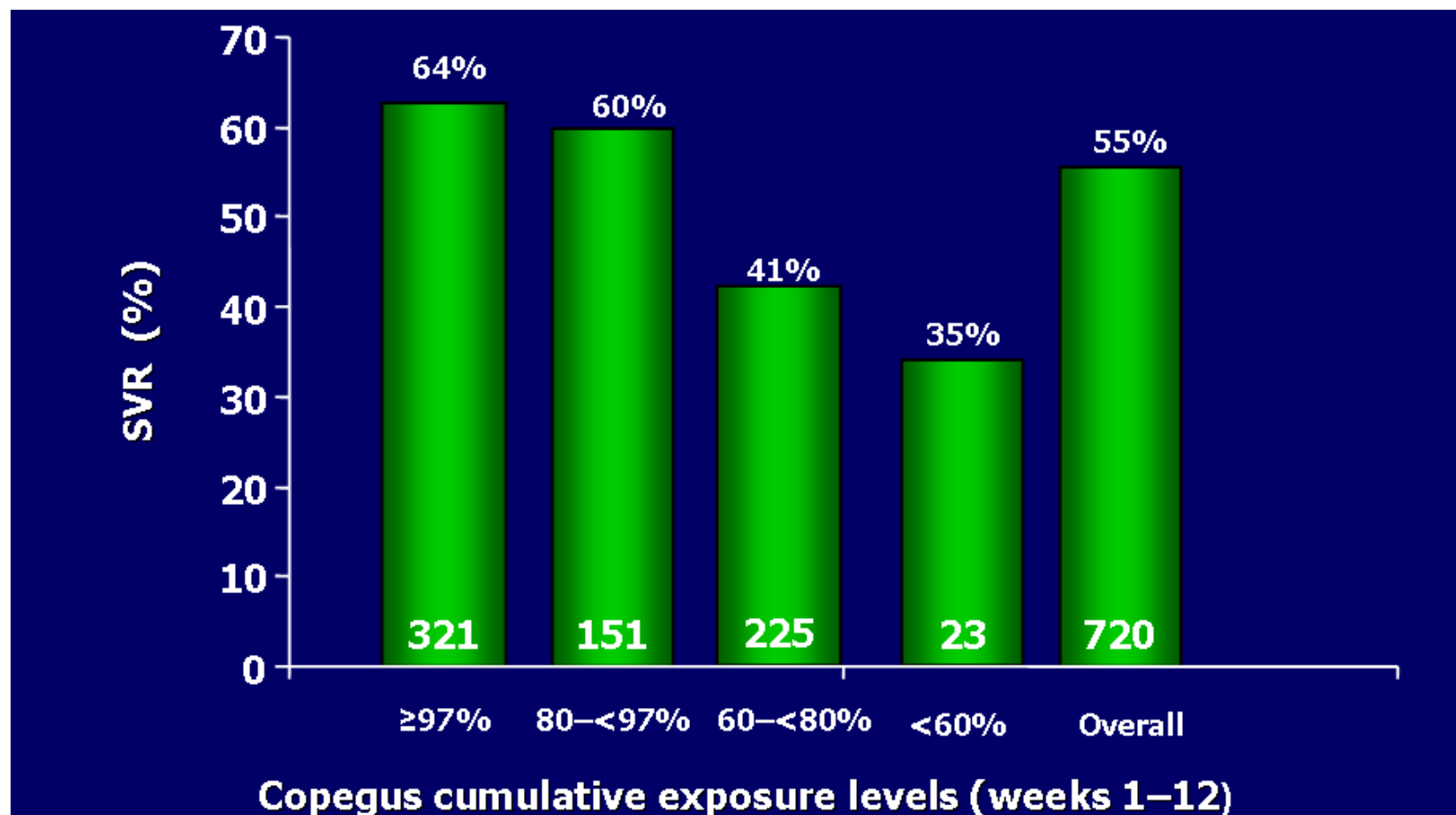
# Therapy of HCV in African-Americans

- SVR lower regardless of treatment regimen
  - pegIFN/riba, genotype 1: 26% vs. 39% in Caucasians
- several potential factors:
  - genetic differences (IL-28)
  - genotype 1
  - higher BMI
  - more dose reductions for neutropenia (37%)
  - virus relatively refractory to interferon by kinetic studies; receptor-independent
  - perhaps related to cell signaling differences

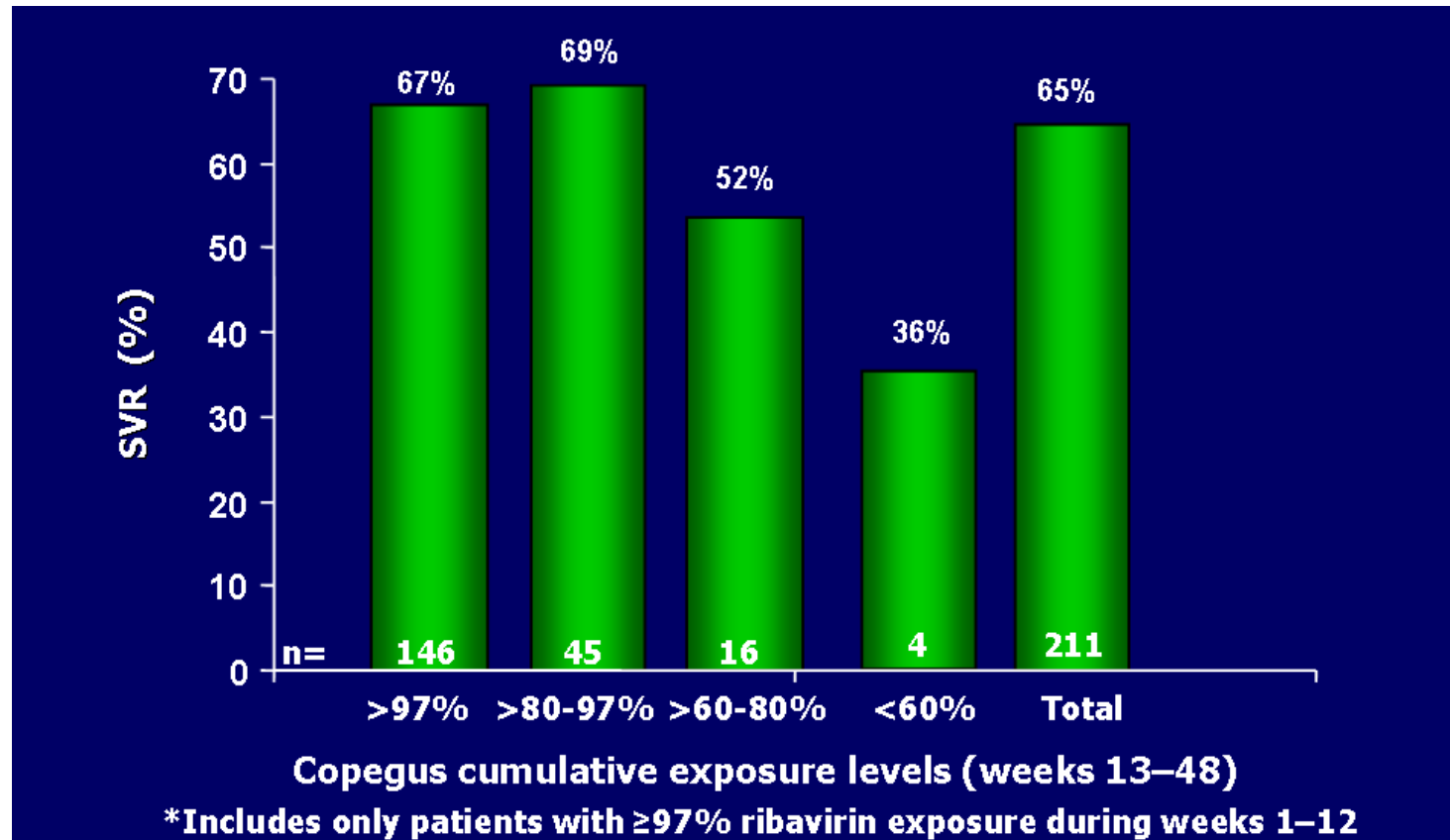
# Importance of Initial Dose of Ribavirin SVR in Patients with Genotype 1



# Ribavirin Exposure Predicts Virologic Response in Genotype 1 Patients



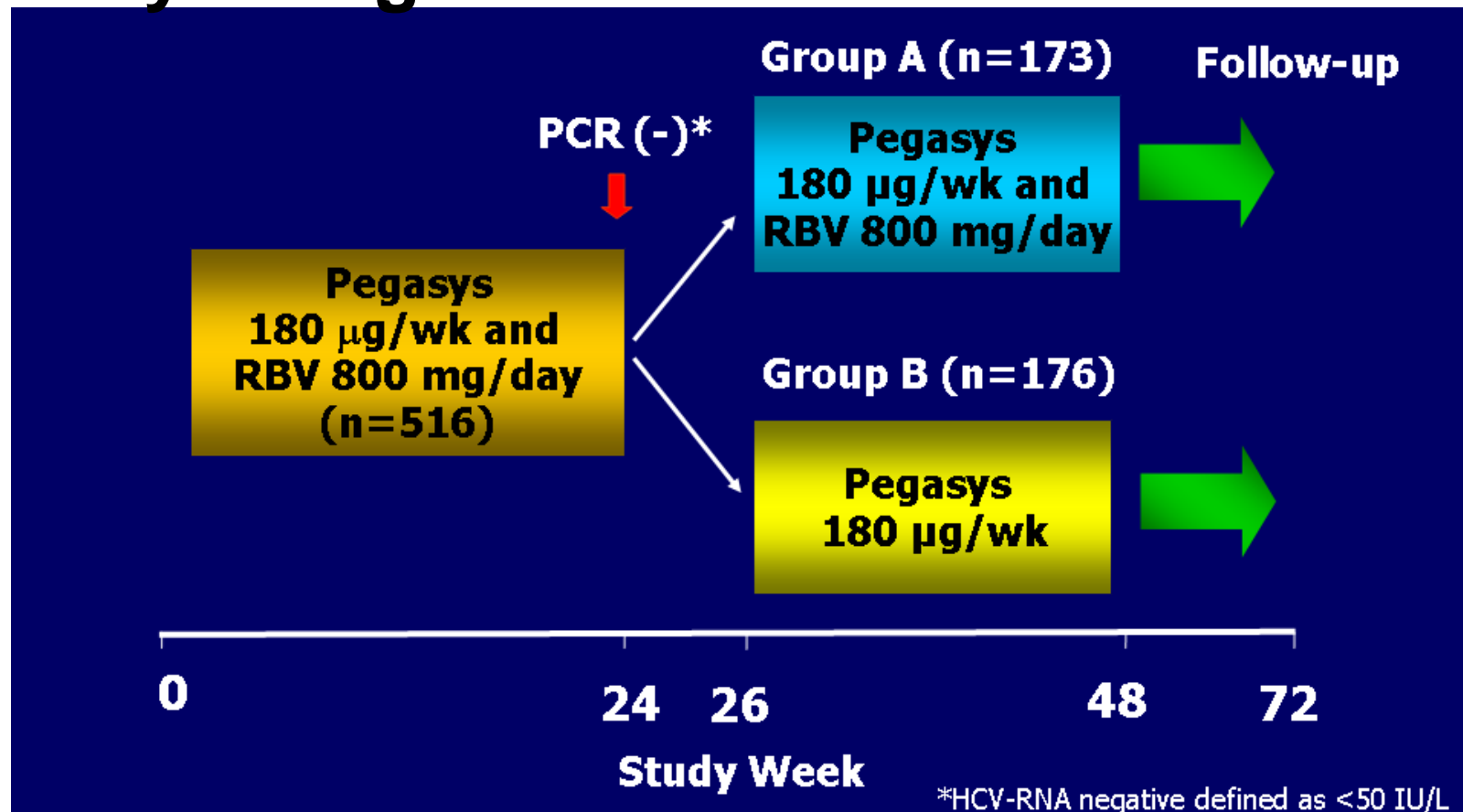
# Influence of Cumulative Copegus Exposure on SVR in Genotype 1



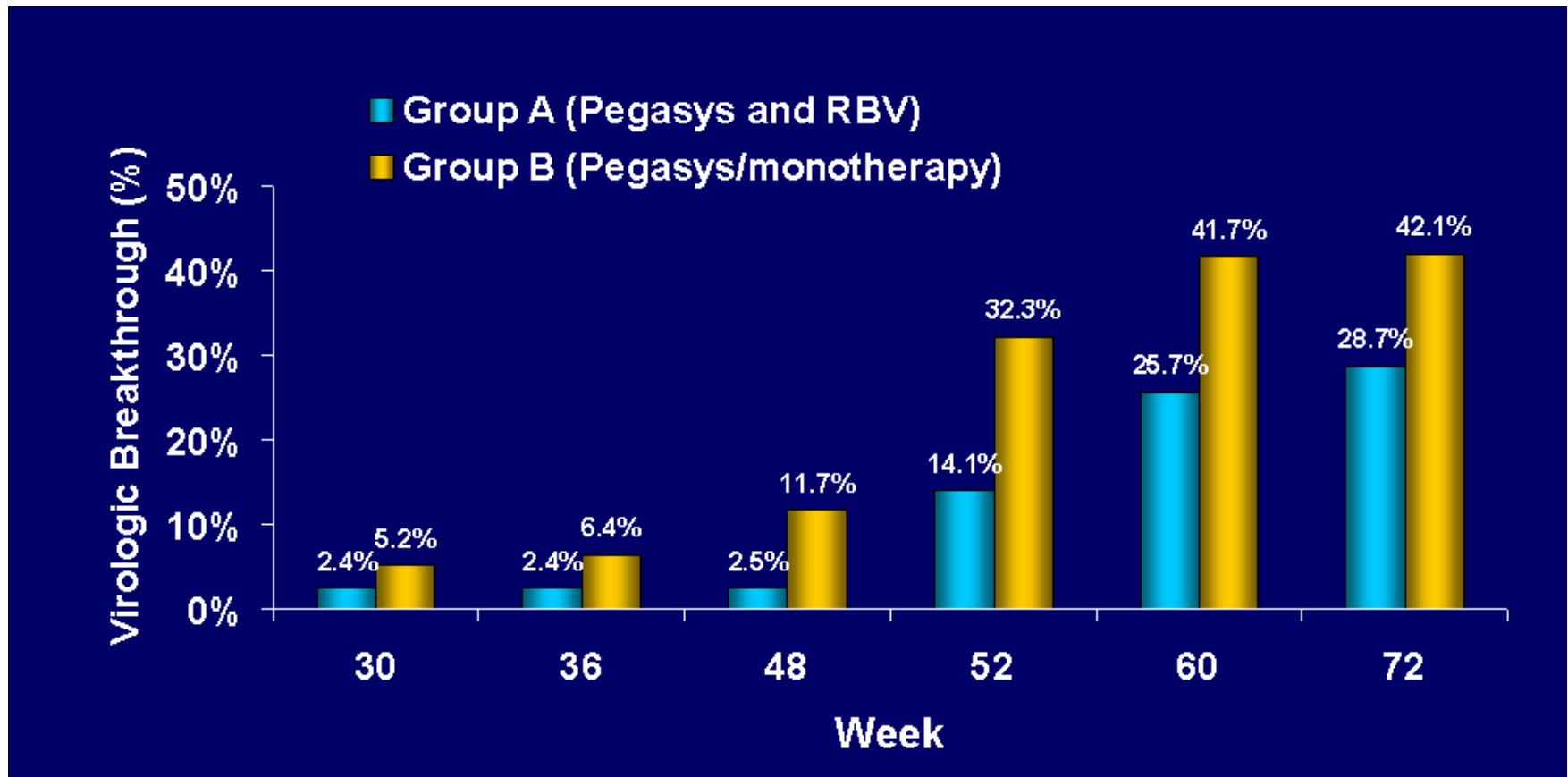
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Ribavirin is a key  
component to viral  
eradication

# Effect of Discontinuing Ribavirin on Patients Responding to Therapy: Study Design



# Effect of Discontinuing Ribavirin on Patients Responding to Therapy: Virologic Breakthroughs



# Adherence to Therapy

- Adherence rates are typically lower in patients with chronic conditions as compared with those with acute conditions
  - Among patients with chronic conditions greatest drops in adherence rates occur after the first 6 months of treatment
- Poor adherence to treatment accounts for substantial worsening of disease, death, and increased health burden
  - Approximately \$100 billion a year
- Patients undergoing HCV treatment may often have several factors predictive of poor adherence

# Major Predictors of Poor Adherence to Medication

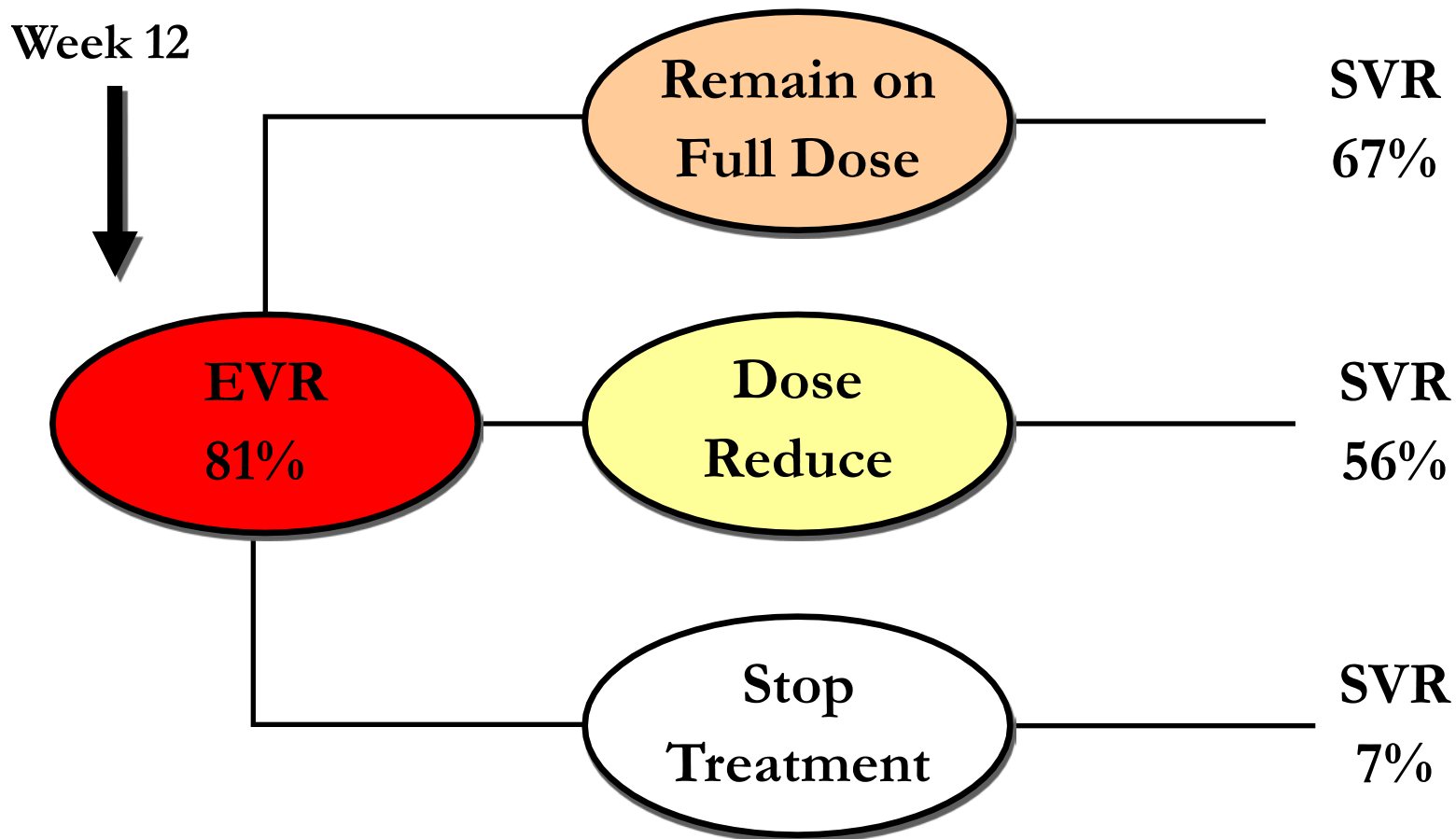
## Patient and Treatment Factors

- Treatment of asymptomatic disease
- Presence of psychological problems, particularly depression
- Patient's lack of belief in benefit of treatment
- Complexity of treatment
- Side effects of medication

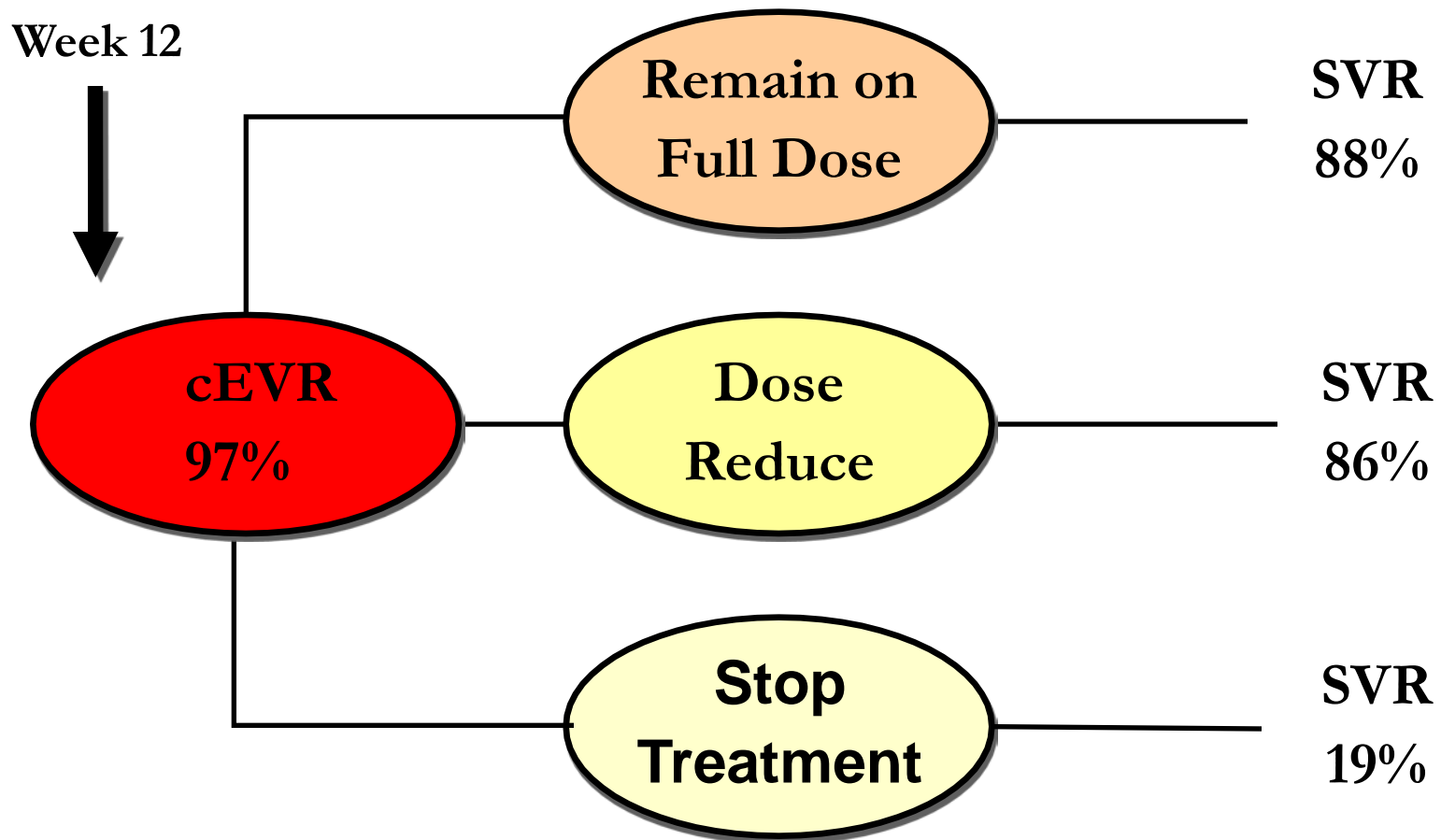
## Other Factors

- Poor provider-patient relationship
- Inadequate follow-up or discharge planning
- Missed appointments
- Cost of medication, copayment, or both

# Adherence to Therapy with PegIFN alfa-2a+Riba, Genotype 1



# Adherence to Therapy with PegIFN alfa-2a+Riba, Genotypes 2/3



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# Improving Treatment Adherence

- **The patient**

- address depression/substance abuse first
- patient education – HCV disease, treatment regimen, consequences of non-adherence
- support systems – family/peers/RNs/NPs/PAs

- **The regimen**

- pill organizers/reminders
- accessible refills

- **The side effects**

- be proactive/educate
- easy access to staff
- antidepressants
- erythropoietin

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# Interferon: Side Effects and Adverse Events

- flu-like symptoms
  - headache
  - fatigue or asthenia
  - myalgia, arthralgia
  - fever, chills
- nausea
- diarrhea
- psychiatric symptoms
  - depression
  - insomnia
- alopecia
- injection-site reaction
- leukocytopenia
- thyroiditis
- autoimmunity
- thrombocytopenia

# Life-Threatening Complications of Interferon Therapy

- survey of 11,241 patients treated with interferon in Italy<sup>1</sup>
  - 5 patients died (0.04%)
  - 2 suicide attempts
  - 4 seizures (other studies as high as 1%)
  - treatment may be riskier than liver biopsy
- 68,276 biopsies 1973-83 in Italy<sup>2</sup>
  - 3 cirrhotic patients and 3 patients with tumors died (deaths < 1/10,000)

1 Fattovich et al J Hepatol 1996;24,38

2 Piccinino et al J of Hep, 1986;2:165

# Life Threatening Complications of Interferon Therapy (cont.)

- incidence of depression during interferon therapy:
  - 24% depressive symptoms and 12% with major depression on 3MU TIW
  - 45% major depression on 20MU/m<sup>2</sup> for 5d/wk
  - 29-31% developed depression with pegylated interferon

<sup>1</sup> Castera et al, Hepatology 2002;35:978

<sup>2</sup> Musselman et al NEJM 2001;344:961

<sup>3</sup> Manns et al, Lancet 2001;358:958



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# Ribavirin: Side Effects and Adverse Events

- usually mild
- include cough, shortness of breath, itching, rash, and reduced appetite
- serious adverse events associated with ribavirin:
  - hemolytic anemia
  - birth defects

# Anemia Associated with HCV Combination Therapy

- anemia occurs to some degree in every patient treated with combination antiviral therapy<sup>1</sup>
  - risk factors for severe anemia – female, older, impaired renal function, iron deficiency
- hemoglobin decreases 2-3 g/dL within the first 4 weeks of pegIFN/ribavirin<sup>2</sup>
- 9%-22% of patients require dose modification due to changes in hemoglobin <sup>1, 3</sup>
- 36% of treatment discontinuations are secondary to anemia<sup>4</sup>

1 Russo MW, et al. *Gastroenterology*. 2003;124:1711.

2 De Franceschi, et al. *Hepatology*. 2000;31:997.

3 Rebetol PI. Kenilworth, NJ: Schering Corp; 2001.

4 Gaeta GB, et al. *Aliment Pharmacol Ther*. 2002;16:1633.



# Consequences of Hematologic Side Effects of Combination Therapy

## ■ anemia

- fatigue, impaired QoL and reduced adherence
- theoretic risk of myocardial ischemia, other cardiovascular abnormalities
- ↓ RBV dose = ↓ SVR

## ■ neutropenia

- ↓ pegIFN dose
- theoretic risk of predisposing to infection

## ■ thrombocytopenia

- ↓ pegIFN dose
- theoretic risk of predisposing to bleeding

# Prevalence of Neuropsychiatric Effects with PegIFN/Riba

## pegIFN $\alpha$ -2a/RBV<sup>1</sup>

- irritability, anxiety, nervousness: 33%
- insomnia: 30%
- depression: 20%
- concentration impairment: 10%
- mood alteration: 5%

## pegIFN $\alpha$ -2b/RBV<sup>2</sup>

- anxiety, emotional lability, irritability: 47%
- insomnia: 40%
- depression: 31%
- concentration impairment: 17%
- agitation: 8%
- nervousness: 6%

1. Pegasys PI. Nutley, NJ: Roche Pharmaceuticals; 2002.

2. Manns MP, et al. Lancet. 2001 Se22;358(9286):958-65p.



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# Depression and HCV

- Depression is present in persons with HCV in greater numbers than in the general population.
- Because of the risks of new-onset depression, worsening of pre-existing depression, or reactivation of clinical depression associated with interferon-based therapy, depression must be carefully evaluated and managed.
- Active suicidal ideation is a contraindication to interferon-based therapy.

# Psychiatric Issues & Interferon-Based HCV Treatment

- pegIFN is associated with psychiatric adverse effects
  - most common reason for treatment discontinuation <sup>1,2</sup>
  - depression is leading cause of treatment nonadherence for all medical conditions<sup>3</sup>
- etiology of IFN-induced depression is likely related to alterations in serotonin pathway<sup>4</sup>
- patients with psychiatric history are more susceptible to IFN-induced depression

1. Manns MP, et al. *Lancet*. 2001 Sep 22;358(9286):958-65p.

2. Pegasys PI. Nutley, NJ: Roche Pharmaceuticals; 2002.

3. DiMatteo MR, Lepper HS, Croghan TW. *Arch Intern Med*. 2000;160(14):2101-7.

4. Zdilar D, et al. *Hepatology*. 2000;31:1207.



# Depression and PegIFN/Riba

- 24-week prospective cohort of PEG IFN a-2b + fixed or weight-based RBV study
- Mean Zung Self-Rating Depression Scale (SDS) score depression rating increased from 41.8 at baseline to maximum 55.6 during 24 weeks of treatment
- 38% developed clinically significant symptoms of moderate-to-severe depression (SDS >60); 11% met criteria for major depression

# Depression and PegIFN/Riba, cont.

- factors correlating with clinically significant depression
  - weight-based RBV dosing (OR 2.43)
  - past history of depression (OR 3.3)
  - baseline SDS predicted clinically significant depression
    - OR 2.0 for each 5-point increase in baseline SDS

# Depression and HCV Treatment: Practical Considerations

- take psychiatric history
- treat/stabilize pre-existing neuropsychiatric conditions before starting pegIFN/ribavirin
- consider evaluating patients for depression every week during first 2 months of anti-HCV therapy, then at least every 2-4 weeks
- consider
  - antidepressants
  - pegIFN dose reduction/discontinuation
  - other management as appropriate
- develop relationship with mental health providers

# Depression Screening Tools

- Beck Depression Inventory
  - restandardized (BDI-II)
  - better for medical patients because it emphasizes cognitive over somatic symptoms
  - completed by patient
- Center for Epidemiologic Studies-Depression Scale (CES-D)
  - older
  - used in research but not renormed
  - derived from items on Zung, Beck, and MMPI
  - less specific

# Depression Screening Tools (cont.)

- Hamilton Depression Scale
  - clinician-administered
- structured clinical interview for DSM-IV
  - follows DSM-IV but is cumbersome
  - used only in research, but clinical version available
- symptom check list 90-R
  - general symptom checklist, revised version
- Zung self-rating depression scale
- Hospital Depression and Anxiety Scale-D
  - good for establishing presence of psychiatric disease

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# When is Therapy Strongly Recommended?

- Significant fibrosis on liver biopsy  
(METAVIR 2-4; stage 3,4)
- Genotypes 2,3 (all stages)
- Severe symptoms
- Clinical cryoglobulinemia
- Patient concerns

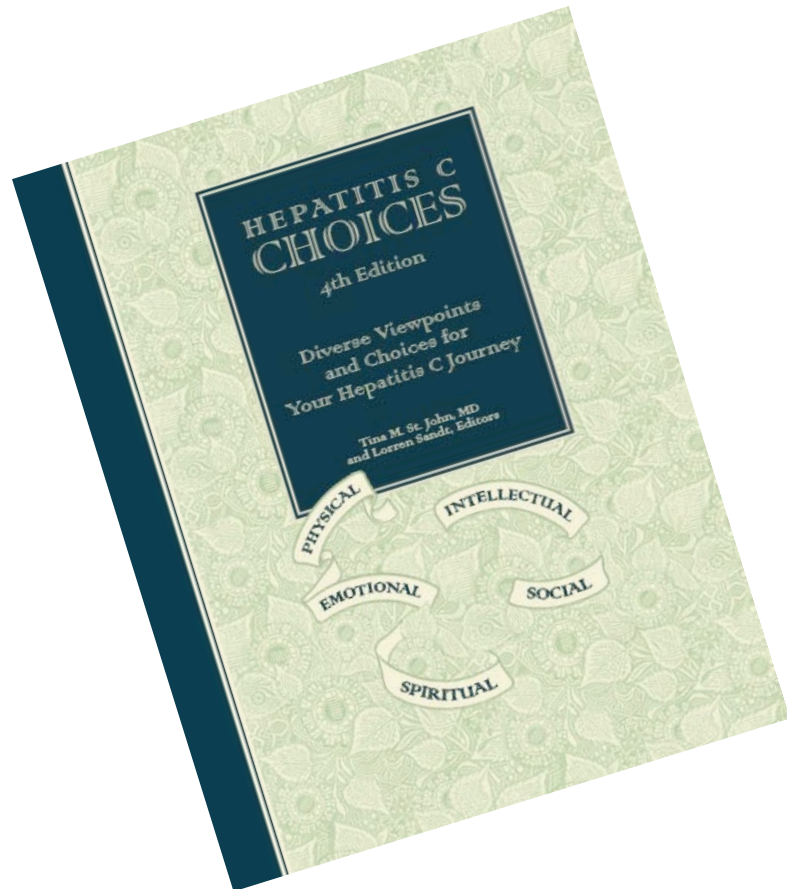
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# When Therapy May Be Deferred

- long duration with minimal disease on biopsy (especially genotype 1)
- older patient with minimal disease
- other major medical problem with minimal liver disease

**BUT, followup with periodic liver biopsy is required**

# For more information



## **Chapter 8: Western (Allopathic) Medicine**

### **Section 1: Allopathic Hepatitis C Treatment Overview**

[http://www.hepcchallenge.org/choices/pdf/Chapter\\_08\\_01\\_OL.pdf](http://www.hepcchallenge.org/choices/pdf/Chapter_08_01_OL.pdf)

### **Section 2: Initial Treatment Options**

[http://www.hepcchallenge.org/choices/pdf/Chapter\\_08\\_02\\_OL.pdf](http://www.hepcchallenge.org/choices/pdf/Chapter_08_02_OL.pdf)

### **Section 4: Future of Allopathic Hepatitis C Treatment**

[http://www.hepcchallenge.org/choices/pdf/Chapter\\_08\\_04\\_OL.pdf](http://www.hepcchallenge.org/choices/pdf/Chapter_08_04_OL.pdf)

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