

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



# HCV Treatment Failure

*Gamal Esmat*

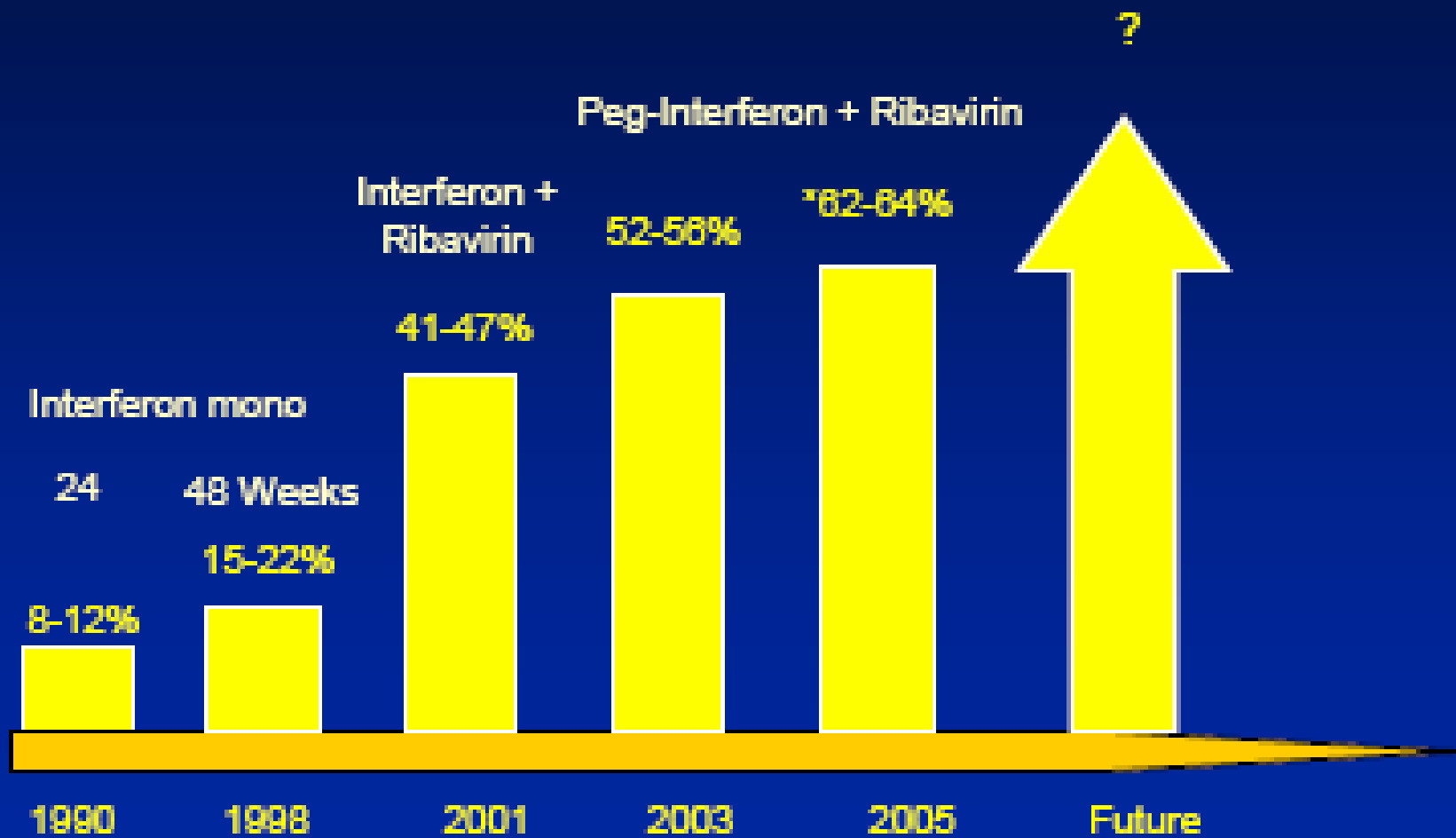
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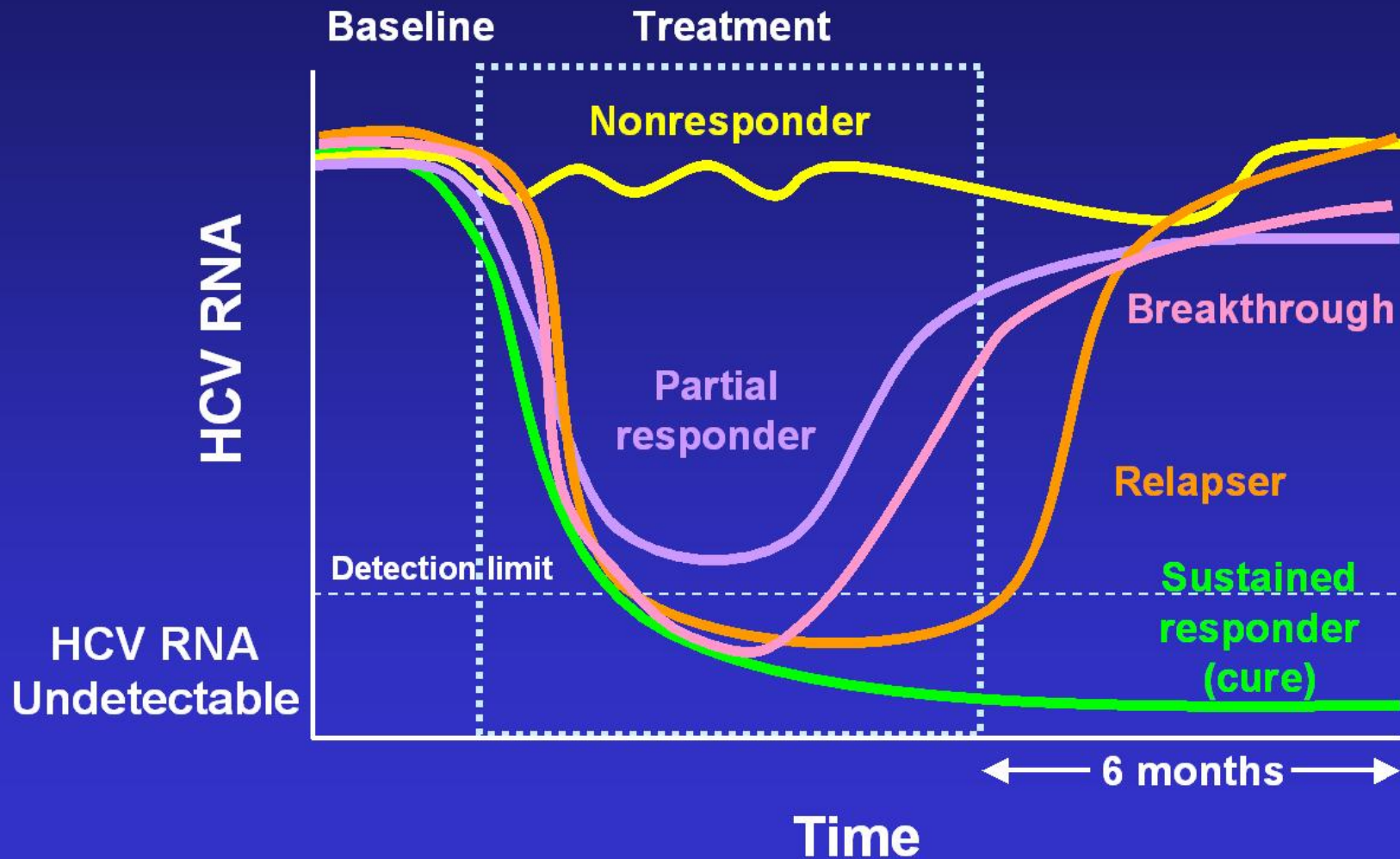
[www.gamalesmat.com](http://www.gamalesmat.com)

# Treatment evolution in chronic hepatitis C: „sustained virologic response rates“



\*80% treatment duration and dosage

# Patterns of Virological Response



# Determinants OF RESPONCE

Viral Factors:(Genotype,, Viral load,  
Quaispecies)

Drug Factors : (Type of INF , Dose, Duration)

Patient Factors:

Age, Sex, Ethnicity

Infections (HIV,HBV, Schistosomiasis)

Metabolic ( D.M, Weight, BMI)

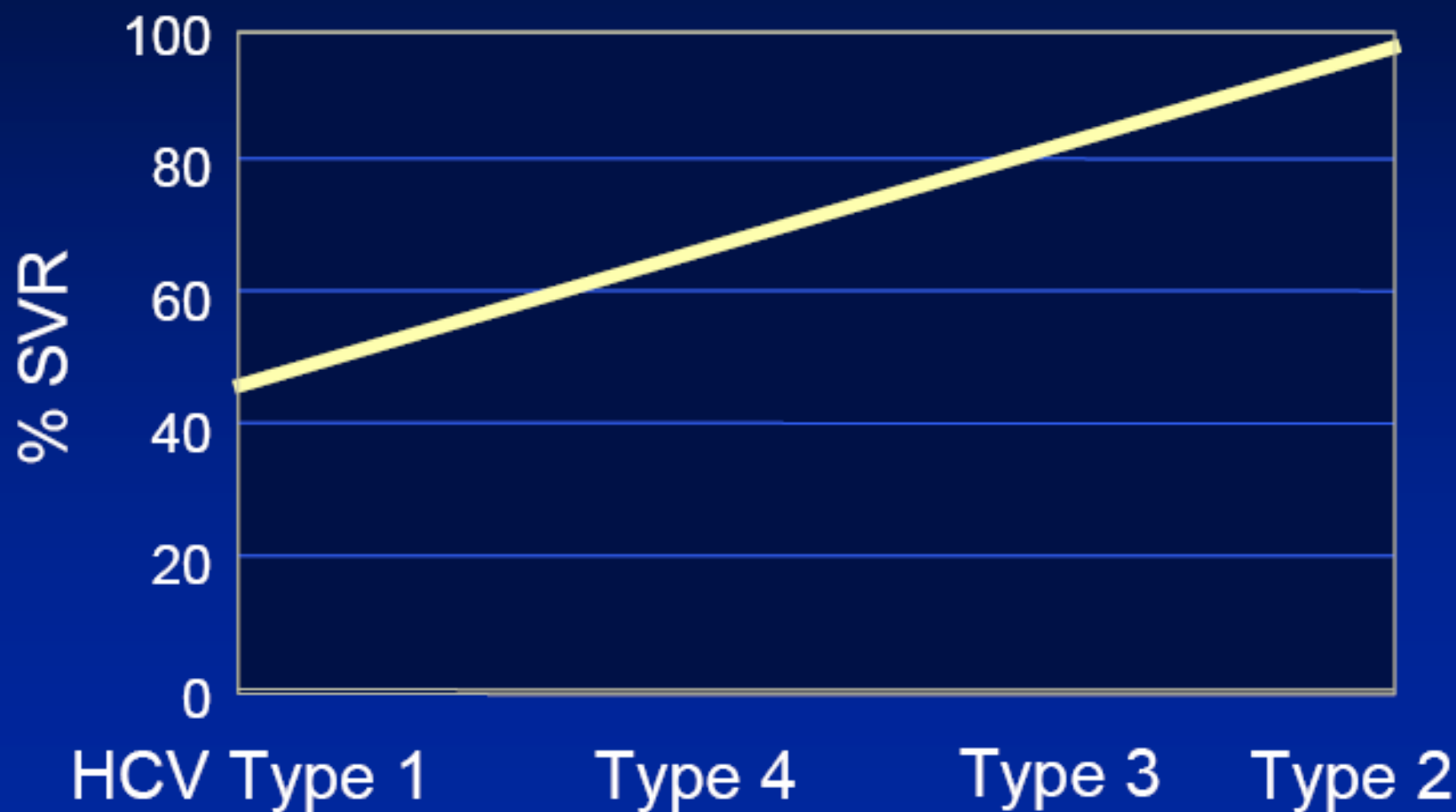
Liver histopathology (Cirrhosis ,Steatosis,Iron)

# Predictors of Treatment Failure

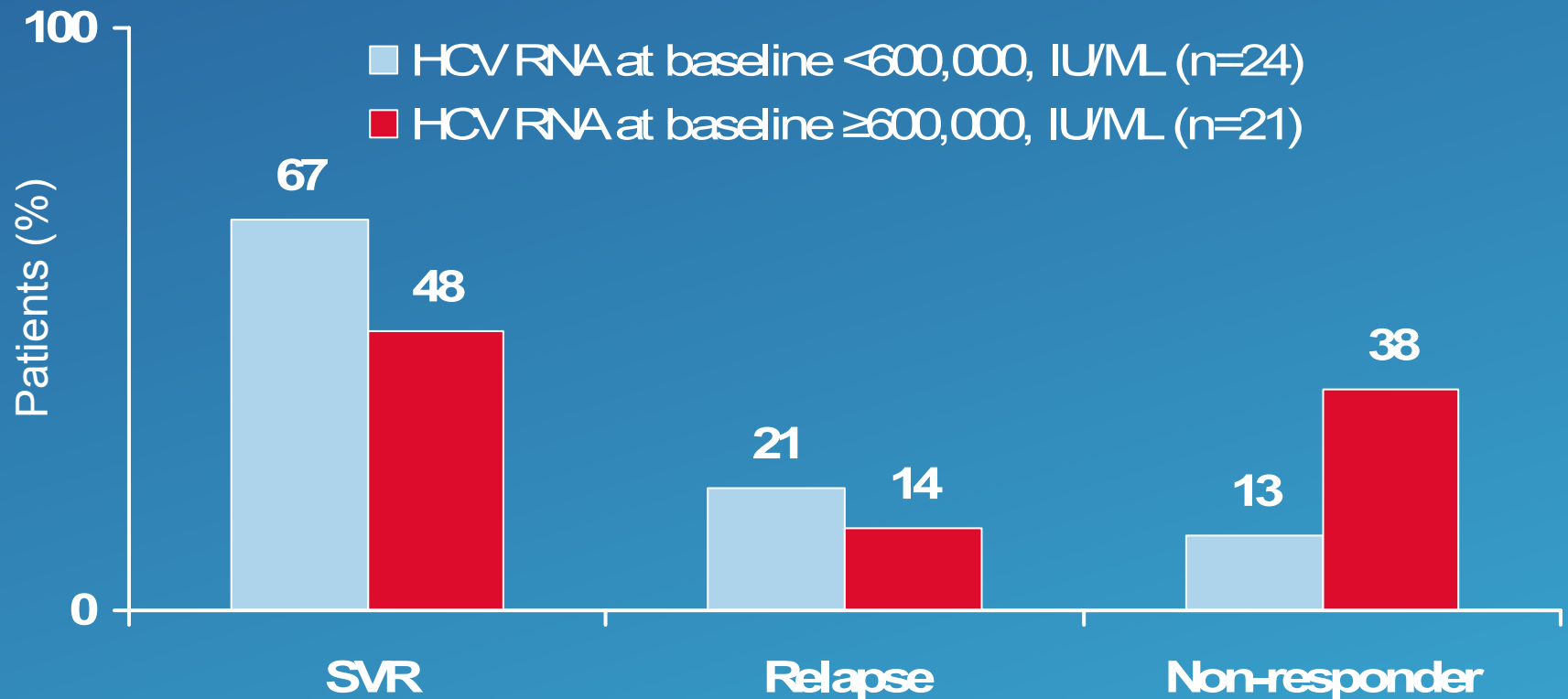
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- Genotype
  - High pre-treatment HCV RNA
  - Advanced fibrosis
  - BMI >30
  - Age >60
-

# Sustained virologic response rates (SVR) in relation to HCV genotype

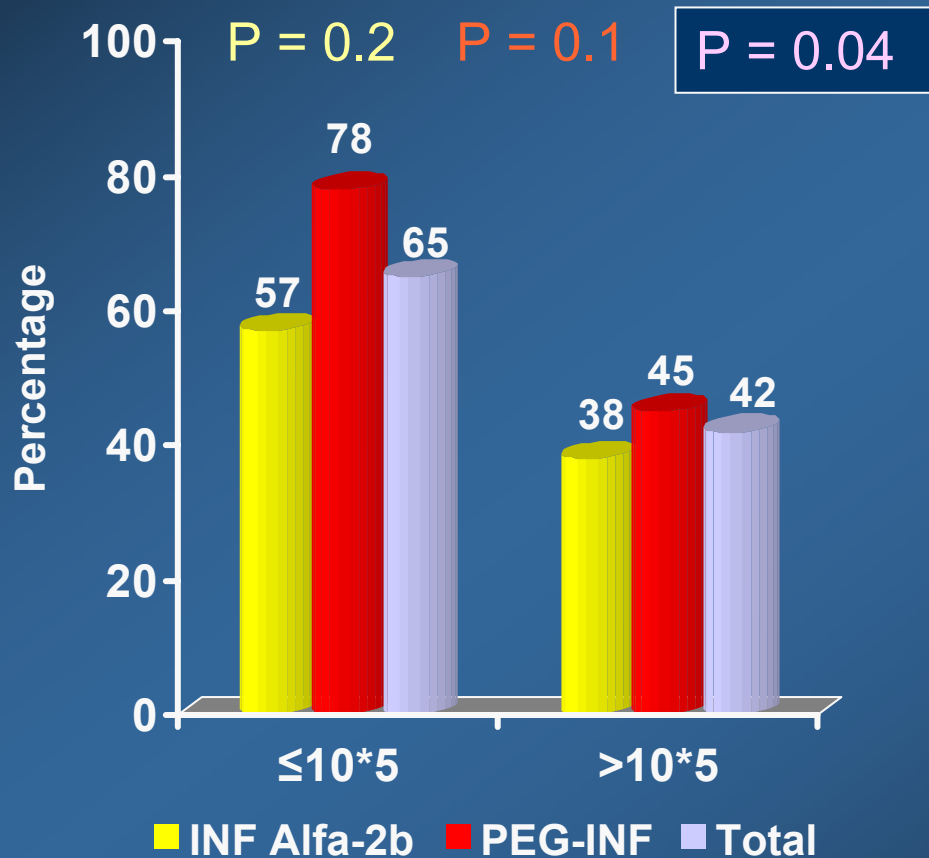


# Effect of baseline viral load in HCV-4 patients

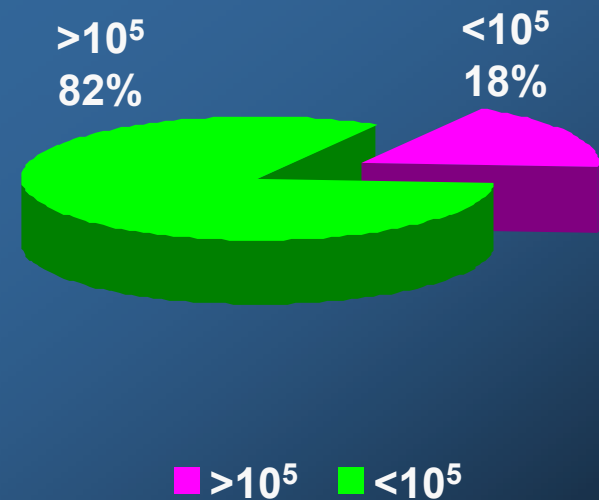


# Predictors of SVR

## Viral Load

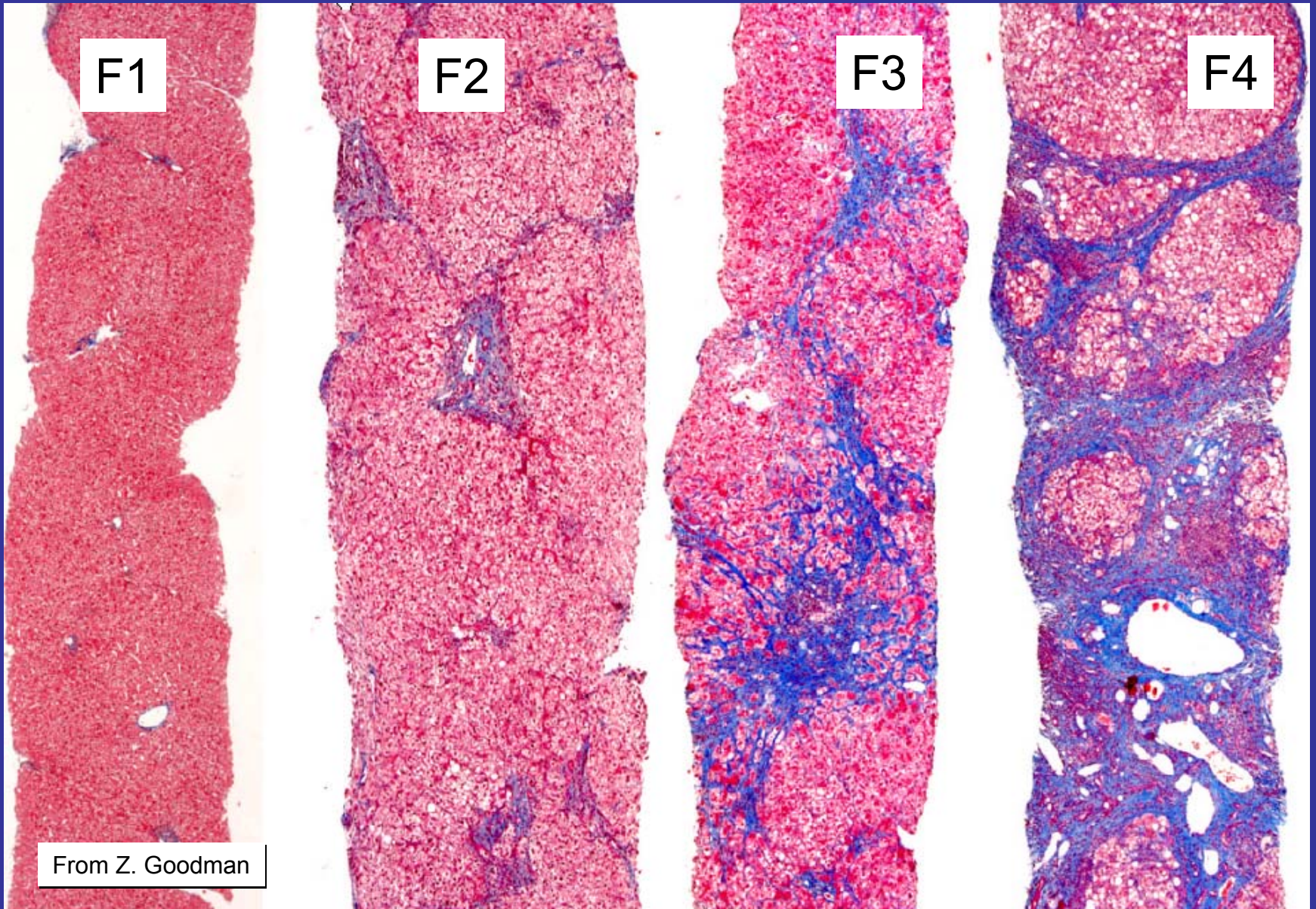


Esmat et al, UEGW, 2003, Madrid



By COBAS Amplicor HCV RNA 2.0 Assay Measured by IU / ML

# Liver biopsy : METAVIR scoring system



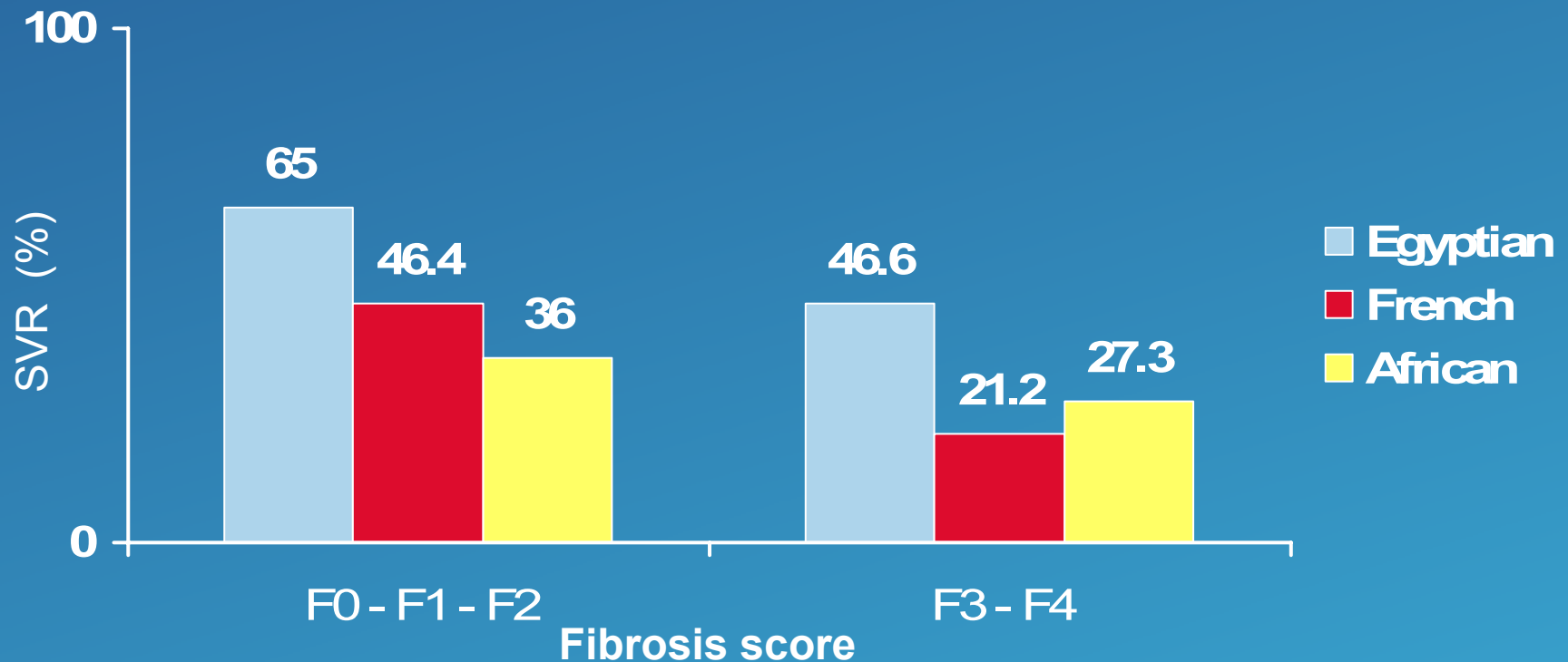
From Z. Goodman

## Cirrhosis

**The presence of portal fibrosis or cirrhosis is independently associated with decreased SVR rates (Wright, 2002).**

**The use of interferon in patients with cirrhosis has been limited by concerns regarding adverse effects, particularly myelosuppression that can lead to clinically significant thrombocytopenia or neutropenia (Heathcote, 2000).**

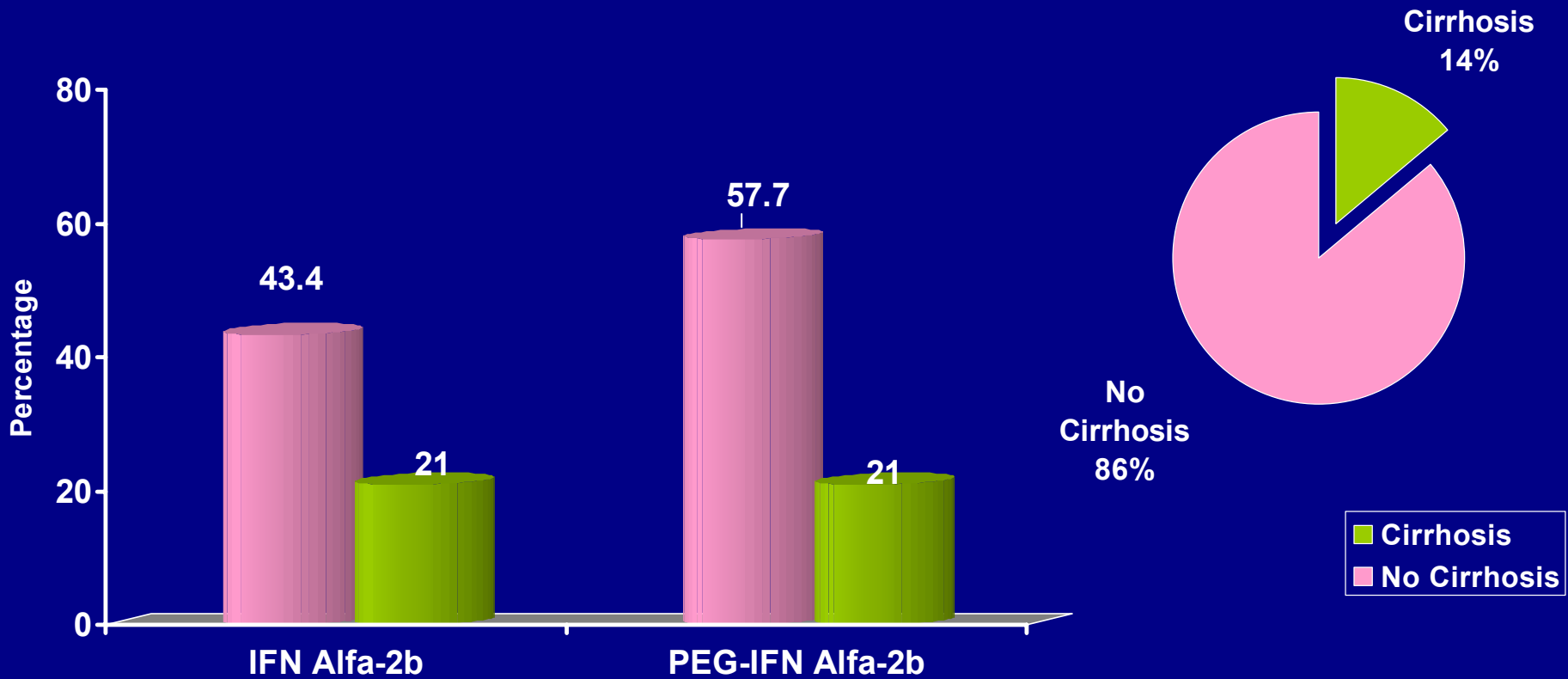
# SVR rates and impact of fibrosis in patients with HCV-4



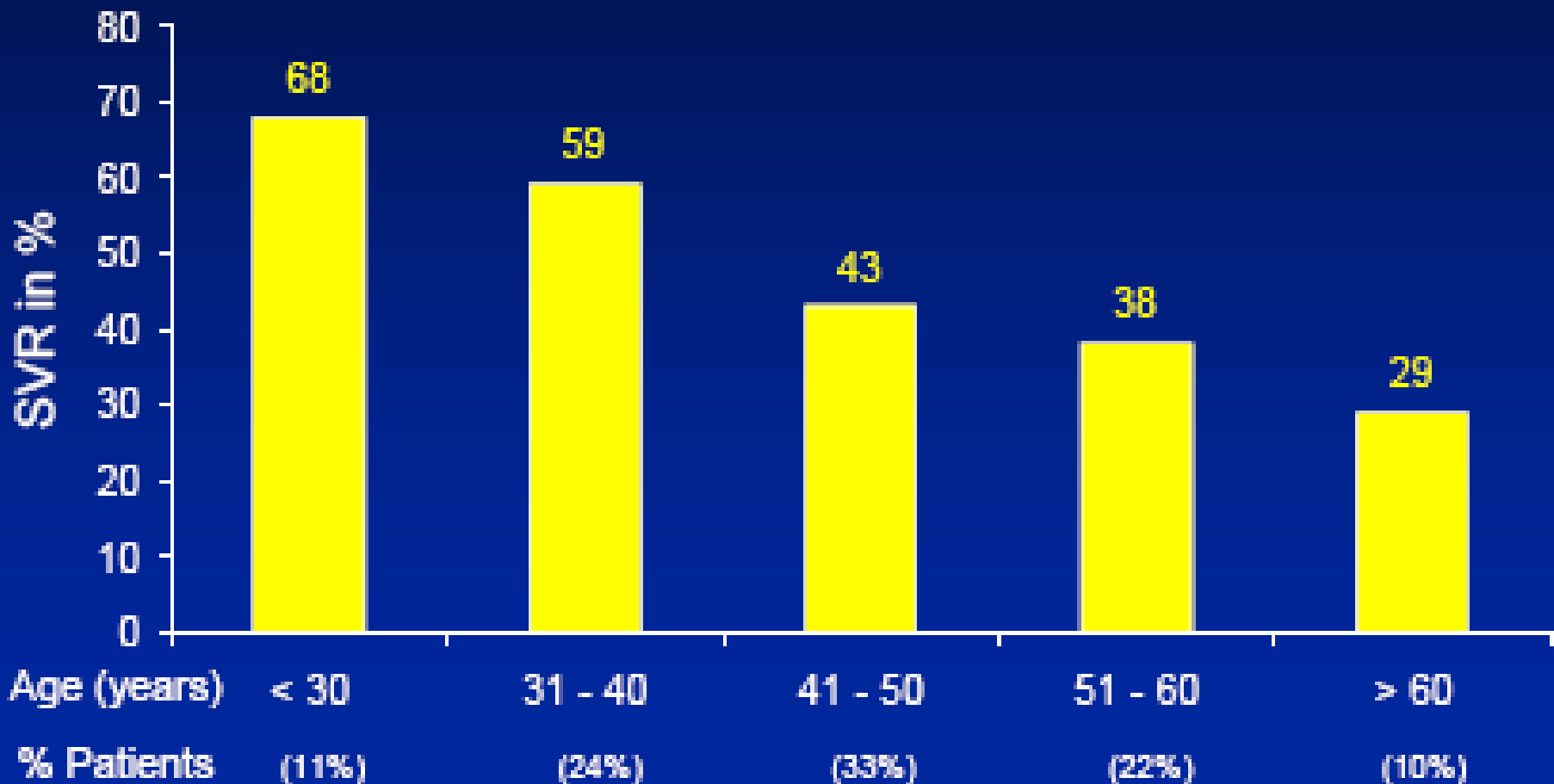
p=0.01

pegIFN $\alpha$ -2b (1.5  $\mu$ g / kg / week) plus RBV (1,000 – 1,200 mg / day) for 48 weeks

# Impact of cirrhosis on SVR in Chronic Hepatitis

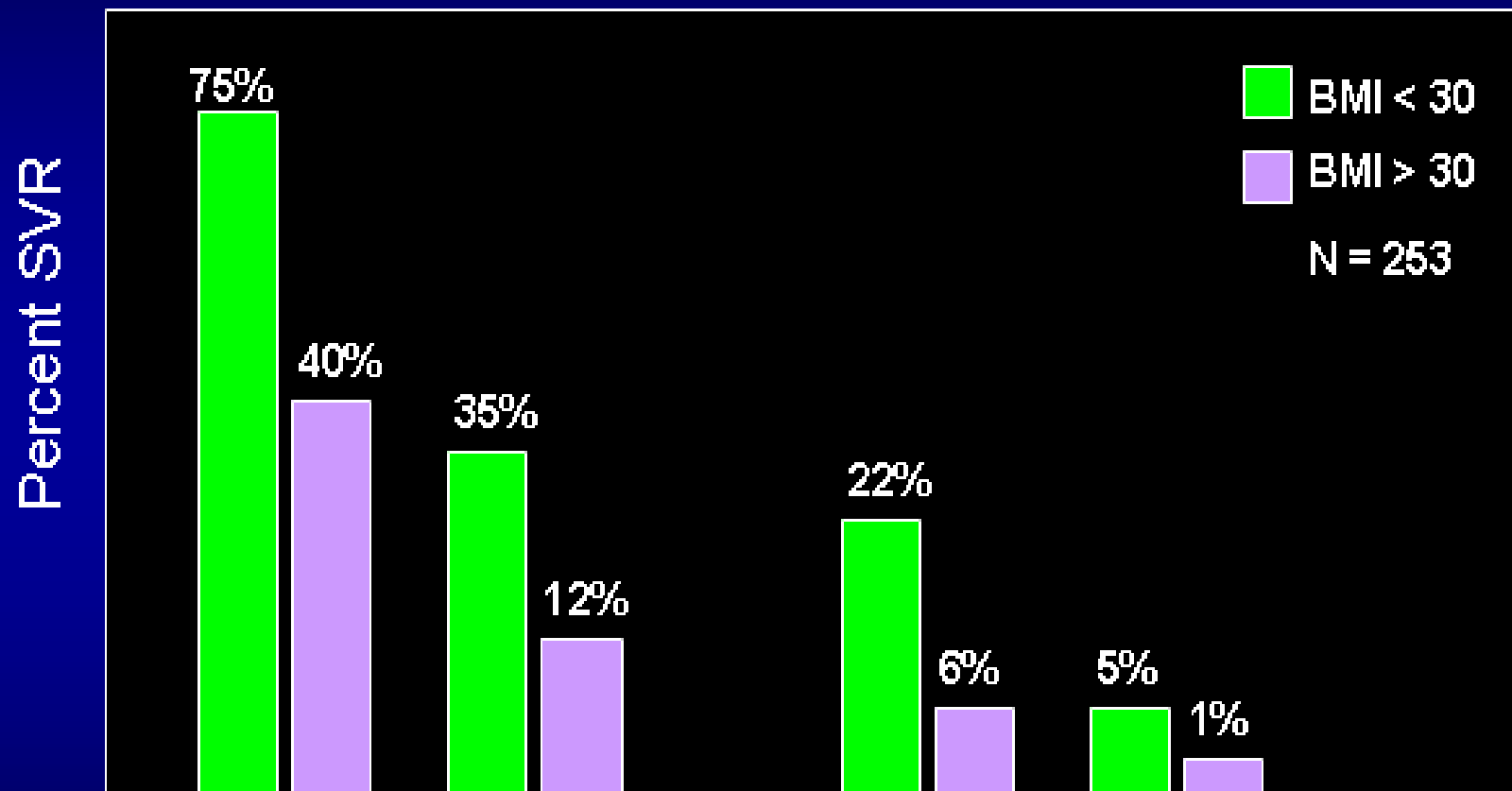


# Sustained virologic response (SVR) rate in HCV type 1: impact of patient's age (N=697)





# Does steatosis effect response to treatment?



Cirrhosis  
BMI > 30

N  
N

N  
Y

Y  
N

Y  
Y

Y  
N

Y  
Y

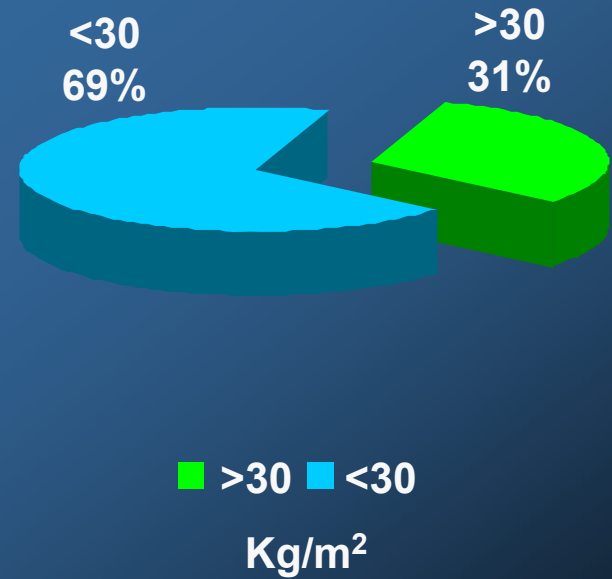
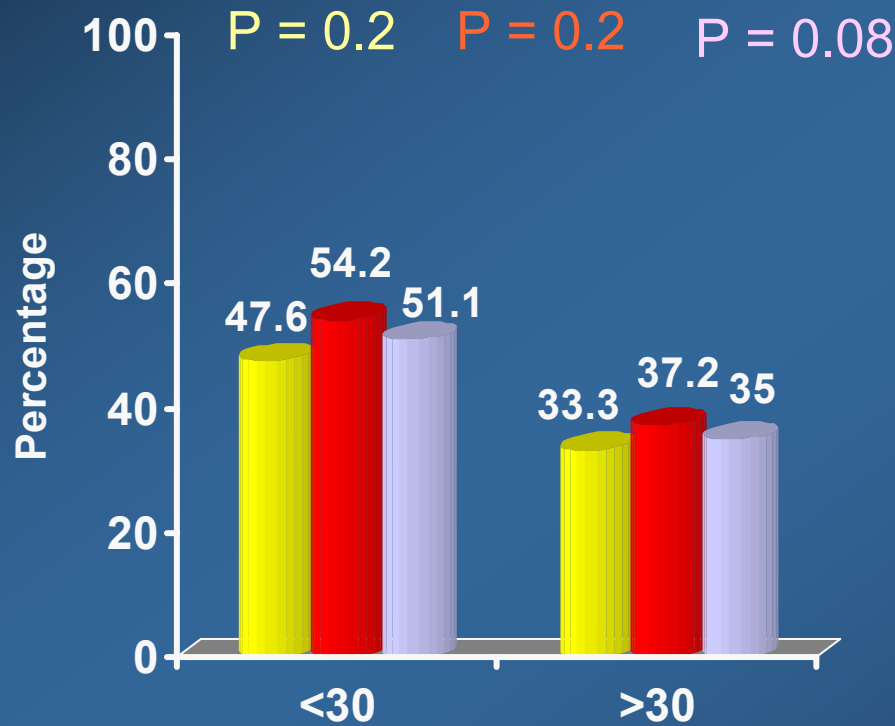
Y  
N

Y  
Y

# Predictors of SVR

## Body Mass Index

■ IFN Alfa-2b ■ PEG-IFN Alfa-2b ■ Overall



# Predictors of treatment failure

In univariate analysis:

Weight > 80 kg

METAVIR score  $\geq$  F3

Steatosis

AFP levels > median value

In multivariate analysis:

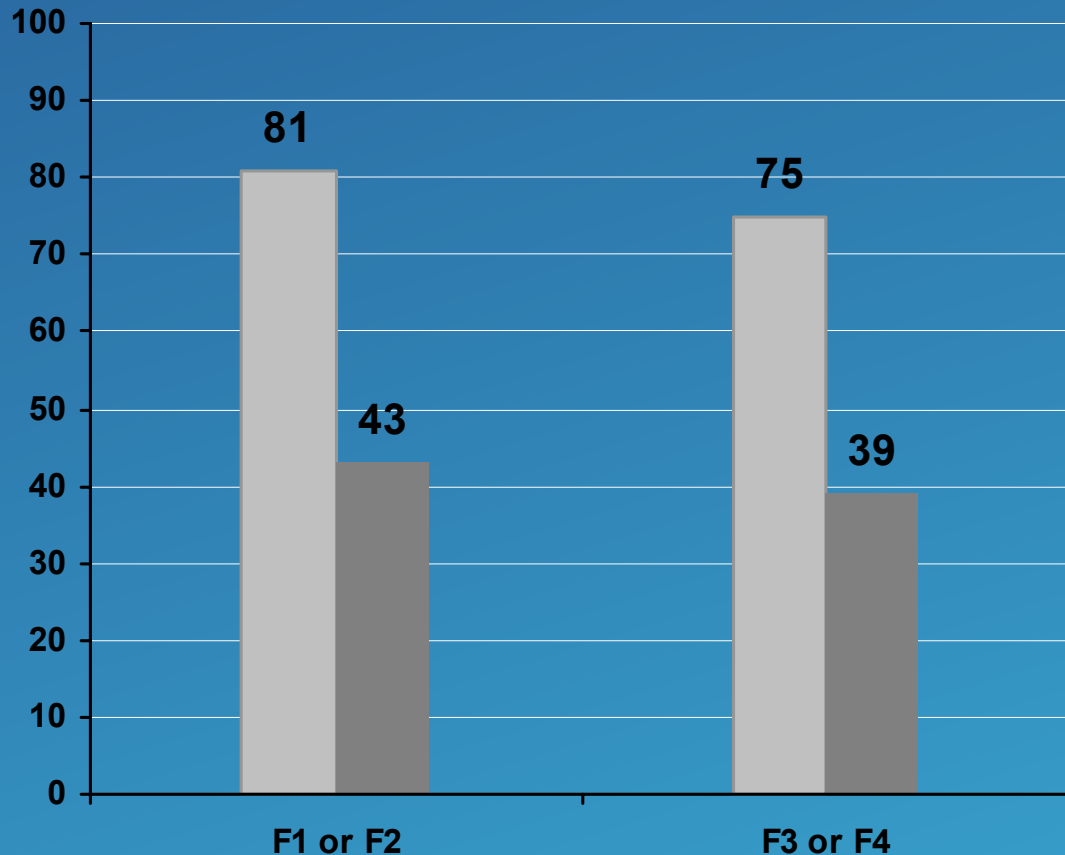
AFP levels only

# AFP analysis

- Median (range) serum AFP level was 4.5 (1.2 – 49.8) ng/mL
- Overall SVR rate was 61.0% (61/100):
  - 80.4% in those with AFP  $\leq$  4.5 ng/ml
  - 40.8% in those with AFP  $>$  4.5 ng/ml
- None of the 7 patients with AFP pretreatment  $>$  15 ng/mL achieved SVR

Antiviral Therapy, 2007, 12:797

# SVR (%) according to the Metavir fibrosis score and median AFP values



Light grey:  
AFP ≤ 4.5 ng/ml

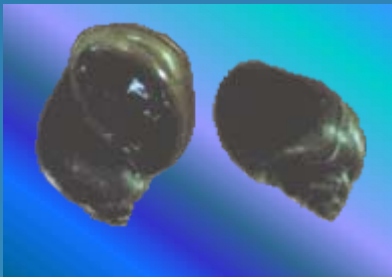
Dark grey:  
AFP > 4.5 ng/ml

Among genotype 4 chronic hepatitis C patients, •  
severe fibrosis,  
severe steatosis,  
treatment with standard interferon and  
a high serum AFP level  
were all **negatively** associated with SVR.

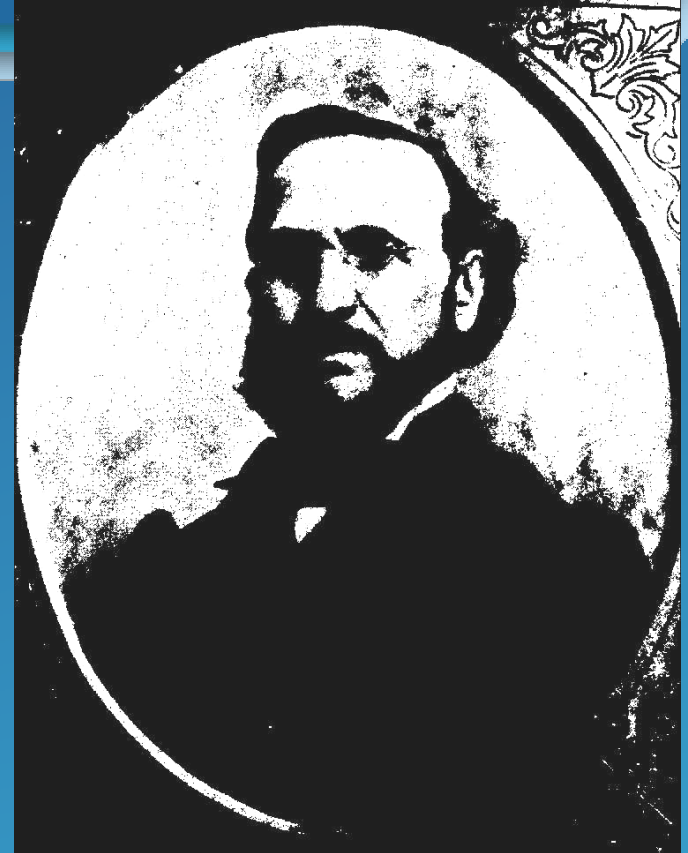
Pretreatment serum AFP level should be  
considered in the routine assessment  
of factors predictive of a treatment response.

# Schistosomiasis

- ◆ Trematode parasitic infection
- ◆ Intermediate host: water snails



- ◆ Debilitating disease, severity depends on “worm load”

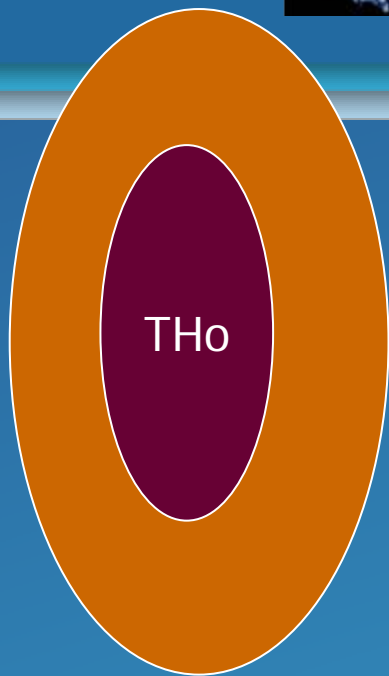
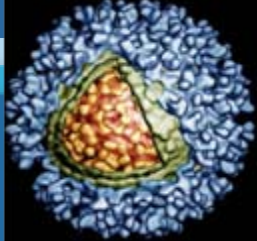


Theodor Bilharz (1825-1862) first described the trematode working at Kasr El Ainy hospital in Cairo in 1851

# Is schistosomal infection has an influence on anti-viral therapy?

EL-Shazly et al., (1994); reported **low rate of response** in combined infection than in HCV alone.

The presence of associated schistosomiasis has determined the response of Egyptians with chronic hepatitis C to therapy with interferon (Abdel Basset et al., 1994).

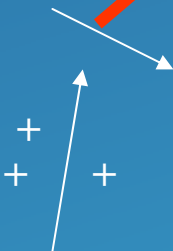


IL-2  
IFN- $\gamma$



**Viral  
clearance**

IL-2  
IFN- $\gamma$   
IL-4  
IL-5  
IL-10



IL-4  
IL-5  
IL-10



**Immunopathogenesis  
of  
Combined infection**

# Immunopathogenesis of Combined Infection

Schistosomiasis appears to **induce Th2 cytokine** profile, with  $\uparrow$  IL-4, IL-10. It **downregulate** the stimulatory effect of HCV on **Th1 cytokines** and this may lead to chronicity of HCV infection in **coinfected patients (El-Kady et al., 2004& 2005).**

# Predictors of Treatment Failure

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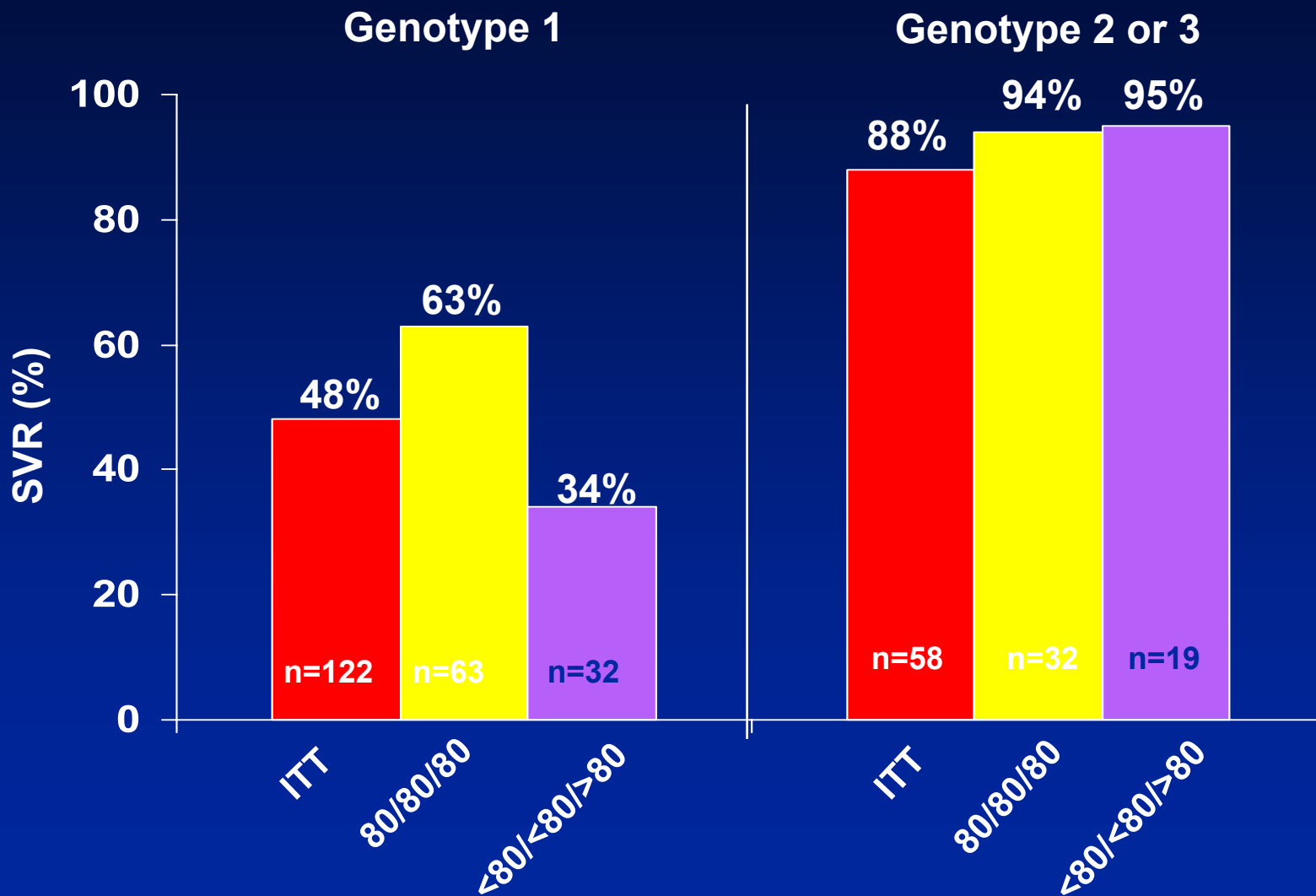
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**Poor Adherence to therapy?**

**A Modifiable Risk Factor!**

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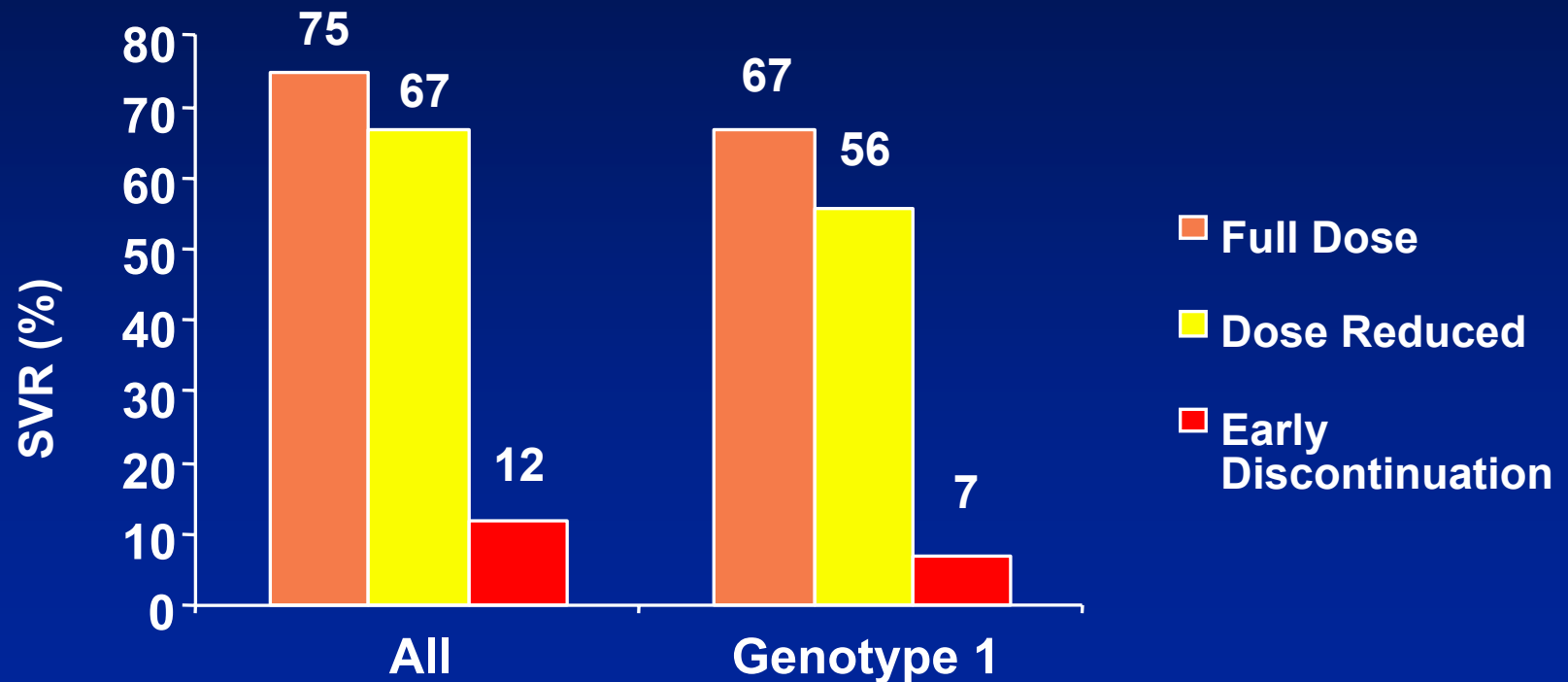
# Impact of Adherence on HCV Response Rates: PEG-IFN + RBV and 80/80/80



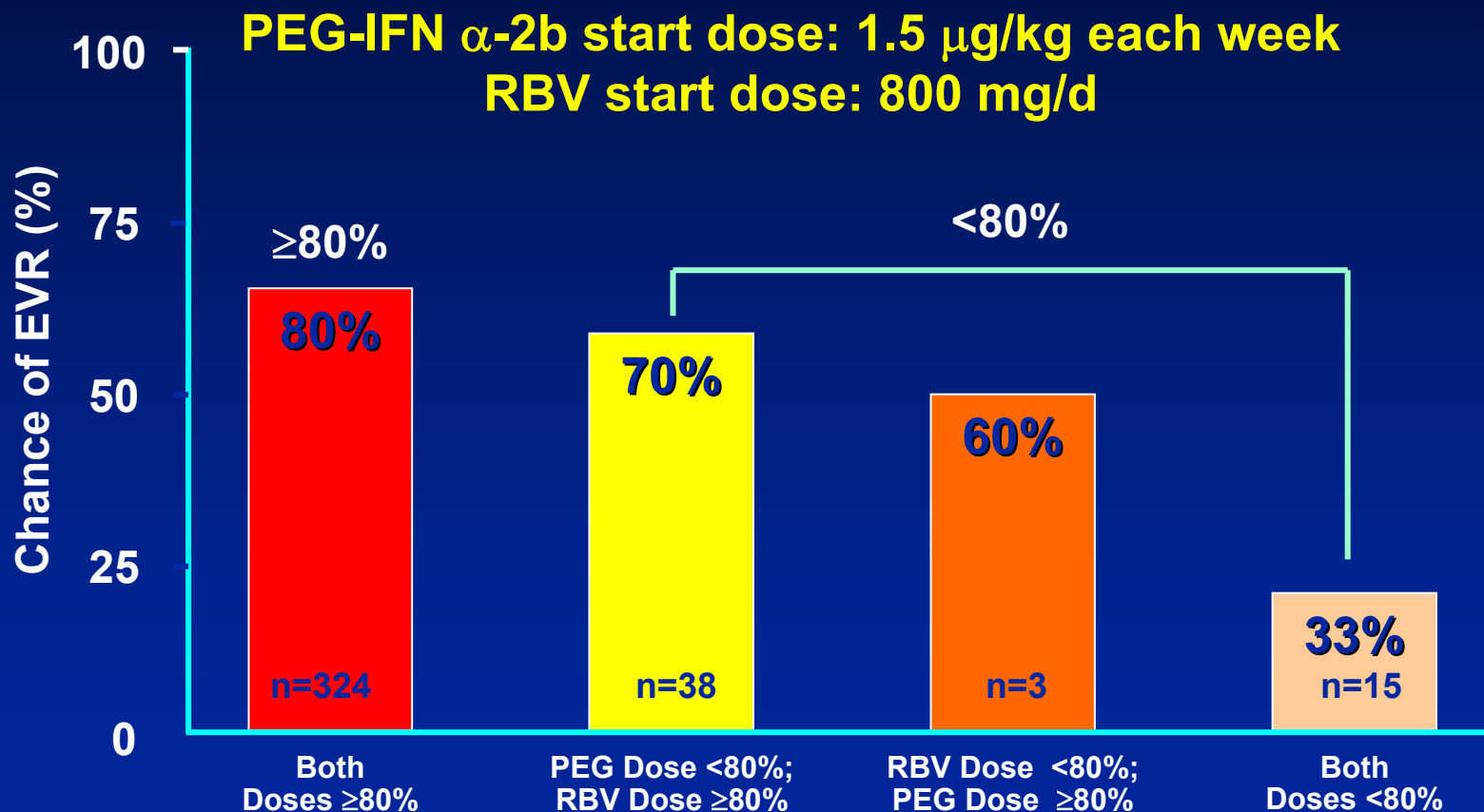
PEG-IFN  $\alpha$ -2b 1.5  $\mu$ g/kg/wk + RBV 800 mg/day x 48 wks  
McHutchison JG et al. *Gastroenterology* 2002;123:1061-1069.

# Drug Discontinuation Significantly Compromises SVR Rates

PEG-IFN  $\alpha$ -2a 180  $\mu$ g qwk + RBV 1000-1200 mg



# Adherence During First 12 Wks of PEG-IFN $\alpha$ -2b + RBV Therapy Affects Early Virologic Response



# Adherence: Take-home Messages

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- **Adherence critical for SVR**
    - Discontinuations have major impact on SVR
  - **Adherence in first 12 weeks of treatment affects EVR**
  - **Reasons for lack of adherence:**
    - Lack of patient education
    - Lack of support system
    - Side Effects...By far the most common
-

# No Two Patients Are Alike



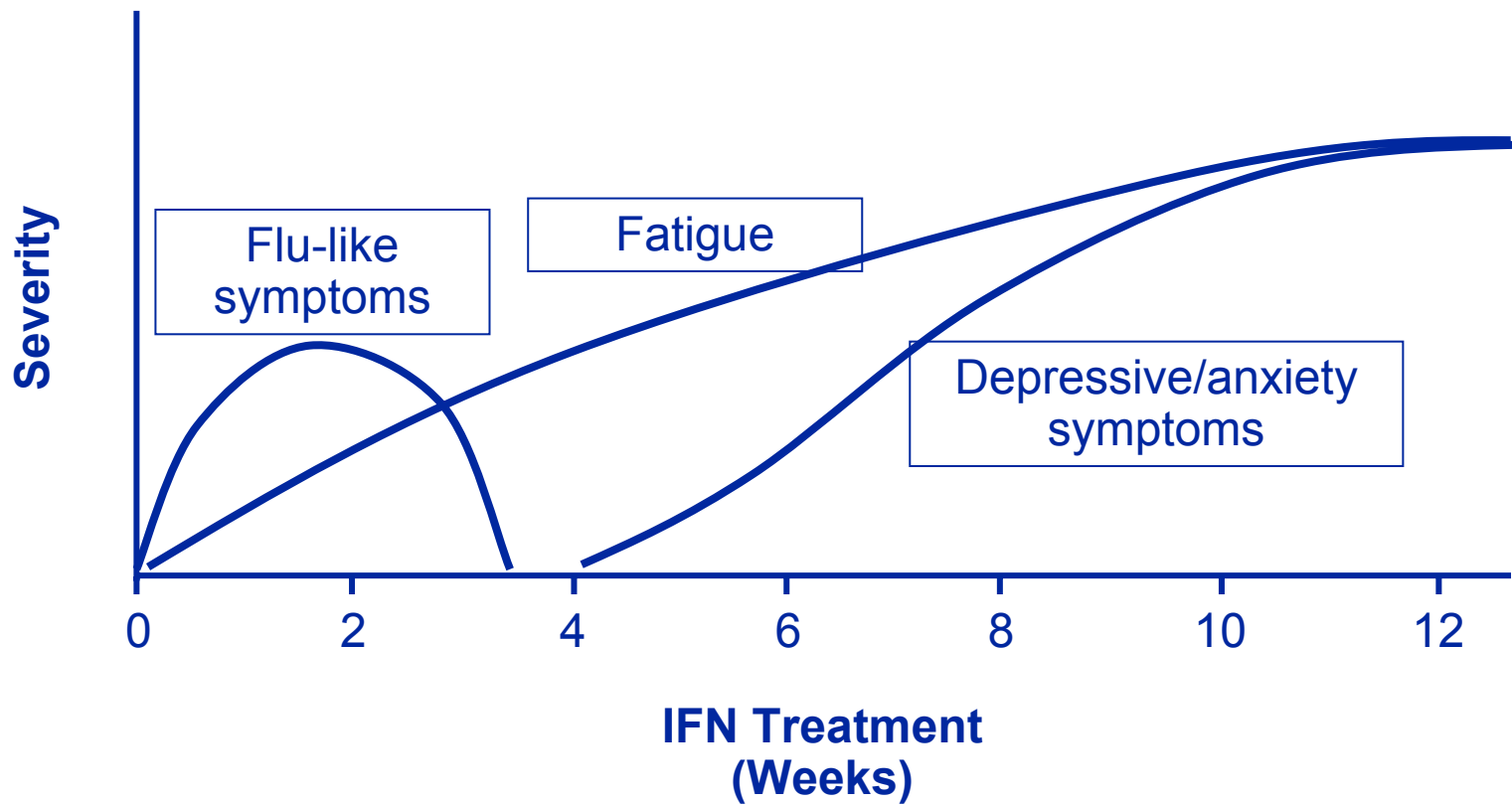
# PEG Interferon/Ribavirin

## Side Effect Profile

● Headache	62%	● Cough	23%
● Fatigue	66%	● Dyspnea	26%
● Myalgia	56%	● Pharyngitis	12%
● Anorexia	32%	● Alopecia	36%
● Nausea		● Pruritus	29%
	43%	● Rash	24%
*			
● Diarrhea	22%	● Fever	46%*
● Anxiety	47%	● Inj Site Rxn	75%*
● Depression	31%		
● Insomnia	40%		

\* > 10% difference from interferon/ribavirin

# Time Course of Interferon Side Effects



# Side Effect Management

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## General Strategies

- **GOAL: Encourage patient adherence to treatment regimen**
  - Patient education about expectations
  - Patient self-management techniques
  - **Regular follow-up visits in a supportive environment**
    - Permits early detection of emerging AE
    - Permits early intervention when needed
    - **Ideal utilization of trained physicians**
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# Side Effect Management

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- **Most adverse events are mild to moderate regardless of therapy**
  - **Dose discontinuation appears to increase with longer therapy (48 vs 24 weeks)**
  - **Patients can achieve expected response rates only if they can adhere to treatment**
  - **Side effect management strategies can improve outcome and QOL**
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# Predictors of Treatment Failure

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- Advanced fibrosis
- BMI >30
- Age >60
- AFP
- Schistosomiasis

**Poor Adherence to therapy?**

**A Modifiable Risk Factor!**

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Thank you  
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