
بسم الله الرحمن الرحيم
"قالوا سبحانك لا علم لنا إلا ما
علمتنا إنك أنت العليم الحكيم"
سورة البقرة: الآية ٣٢

HCV RELAPSERS AND NONRESPONDERS:

How to deal with them ?

BY

Prof. Mohamed Sharaf-Eldin

Prof. of Hepatology and Gastroenterology

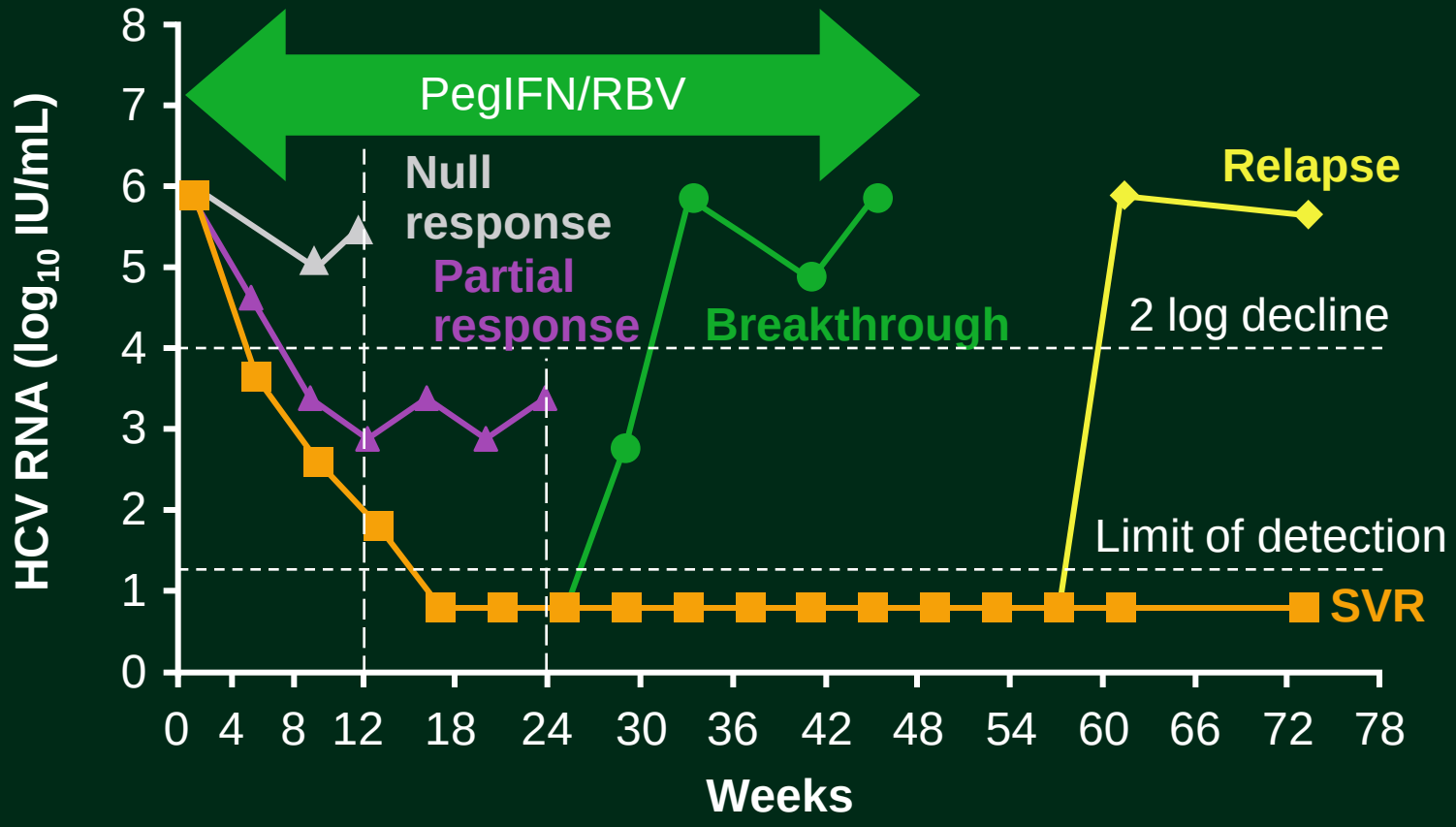
Tanta University

Achieving SVR

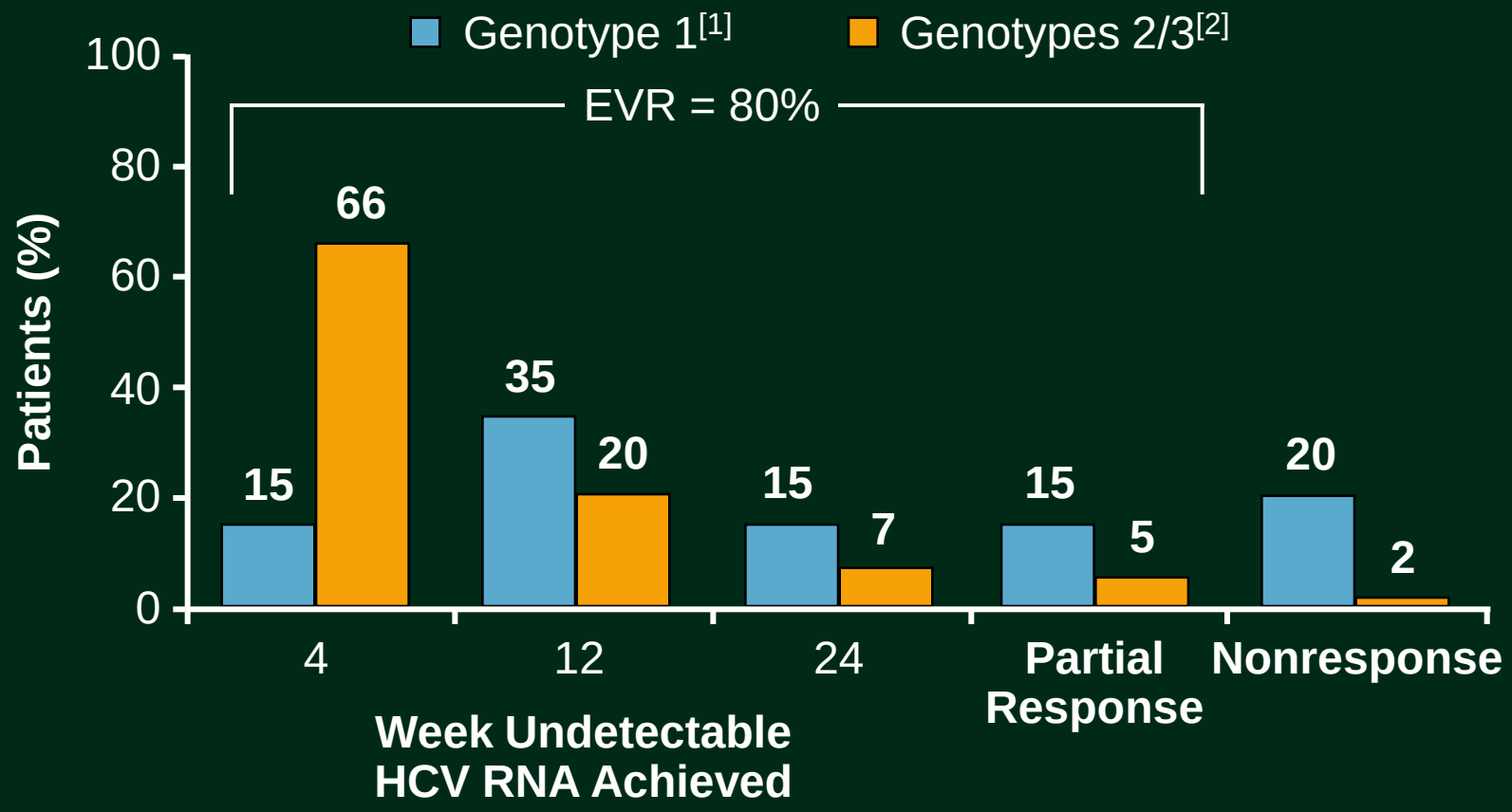
- The ability to achieve a SVR is the result of 3 independent steps
  - The patient must achieve a virologic response
  - The patient must maintain the response
  - The patient must not relapse
- To overcome nonresponse and relapse, the reasons for failure must be defined

Defining an Initial Virologic Response

Chronic Hepatitis C: Defining an Initial Virologic Response



Frequency of Responses



1. Ferenci P, et al. J Hepatol. 2005;43:425-433.
2. Shiffman ML, et al. N Engl J Med. 2007;357:124-134.

Medical Need in Chronic Hepatitis C Retreatment Is Growing

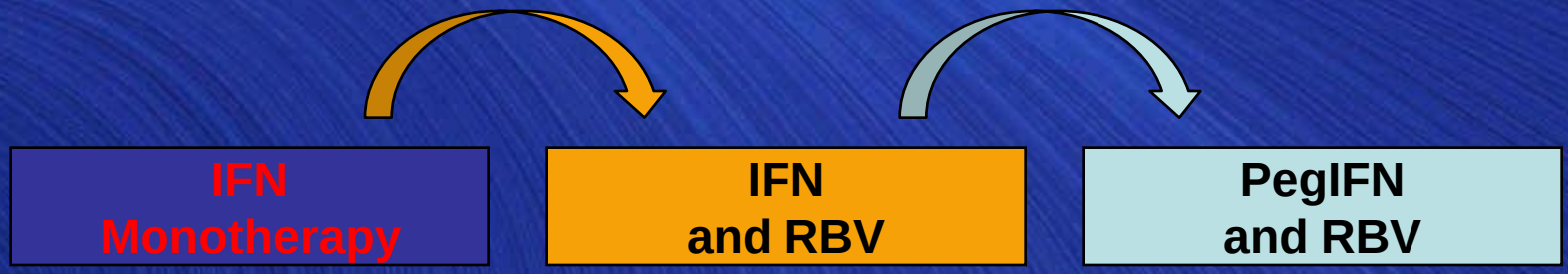
- Despite significant advances in HCV therapy, approximately half of genotypes 1 and 4 patients do not achieve SVR on initial treatment.
- First generation HCV oral direct antivirals are several years from approval

1. Manns M, et al. Lancet, 2001;358:958-965. 2. Fried M, et al. NEJM, 2002;347:975-982.
3. Poynard T, et al. AASLD, 2006; Abstract 1123.

Initial Approach to the Patient With Treatment Failure

- Review of records to assess status of previous response to therapy
  - **End-of-treatment HCV RNA level critically important**
  - **Duration of previous treatment**
  - **Degree of HCV RNA reduction as a result of previous therapy**
- Determination of previous degree of compliance
  - **Which interferon alfa regimen was taken and at which dose?**
  - **How many ribavirin tablets/day at starting dose?**
  - **How many missed doses?**
  - **How many dose reductions?**
  - **May have to ask patients repeatedly to get accurate answers**

Populations of Nonresponders

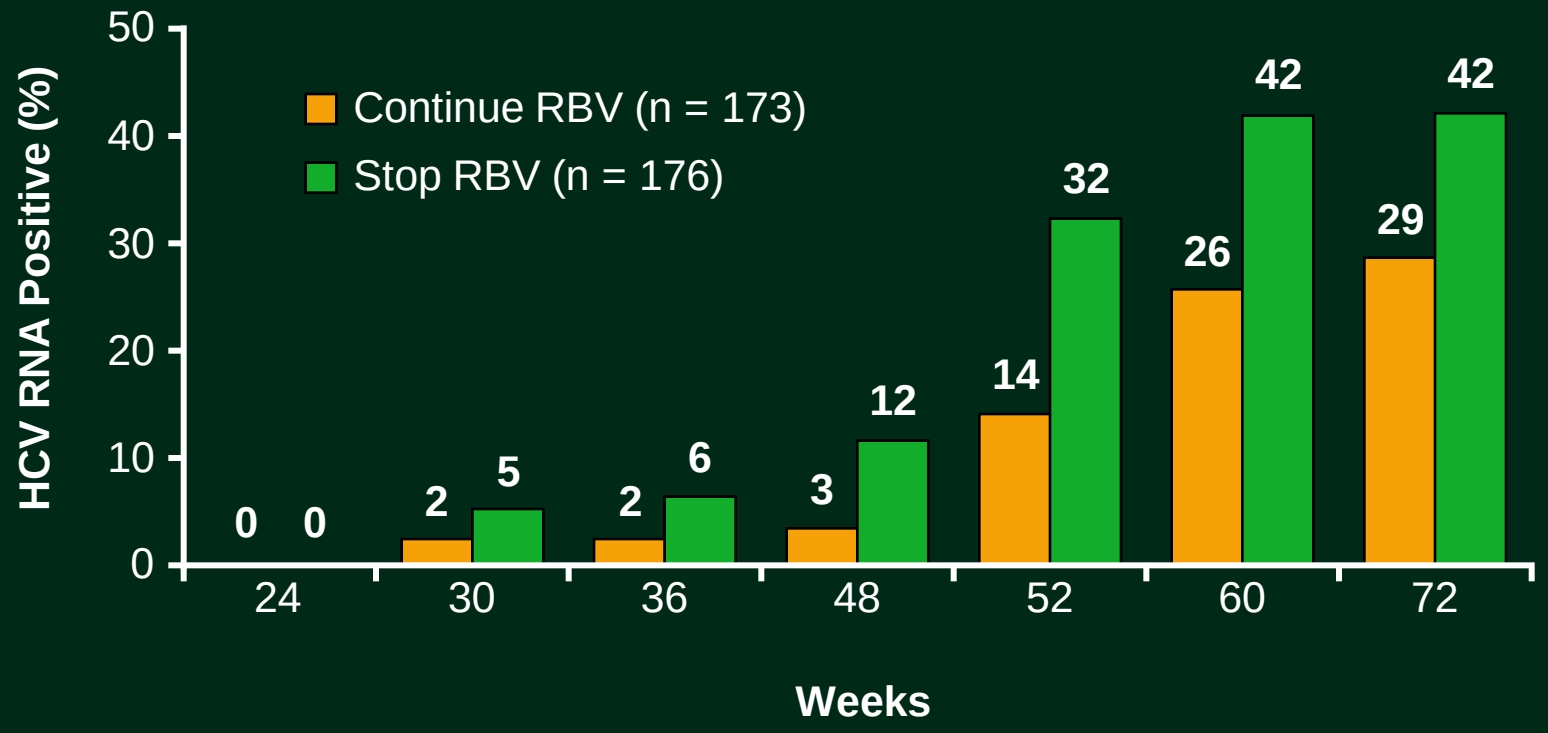


Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time

Treatment of Chronic Hepatitis C: Impact of Stopping RBV

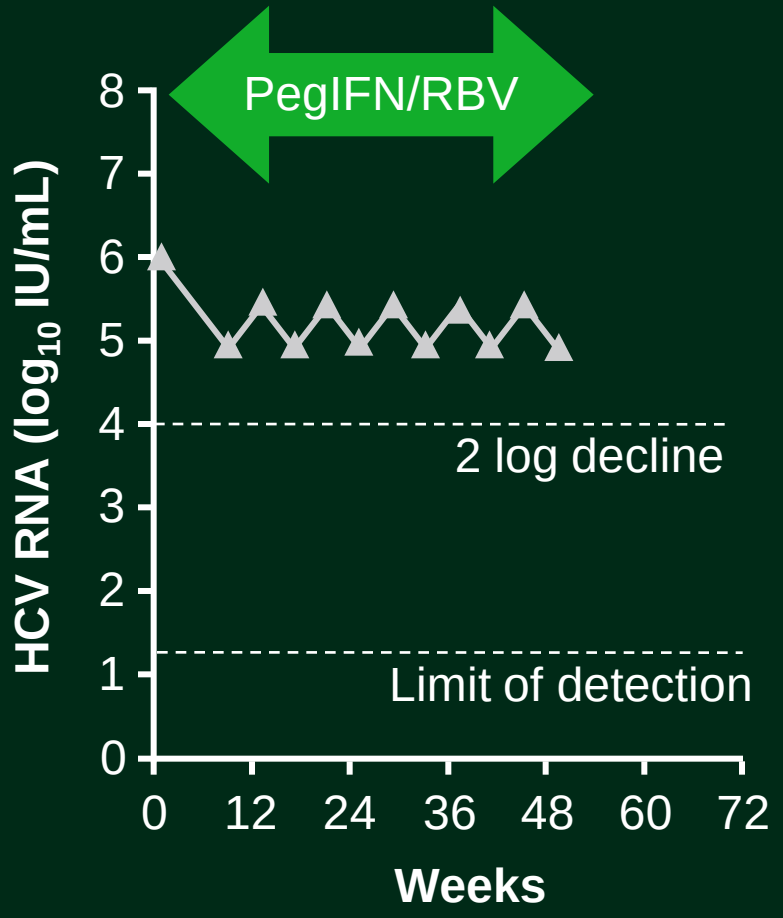
- Those who stopped RBV at Wk 24 had higher breakthrough and relapse rates



Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time

The Null Response



- No significant decline in HCV RNA despite full-dose pegIFN
- Occurs in 20% of patients
- Patients likely resistant to the effects of IFN
- Pattern more common in blacks
- May not be overcome by higher doses of pegIFN?

Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time

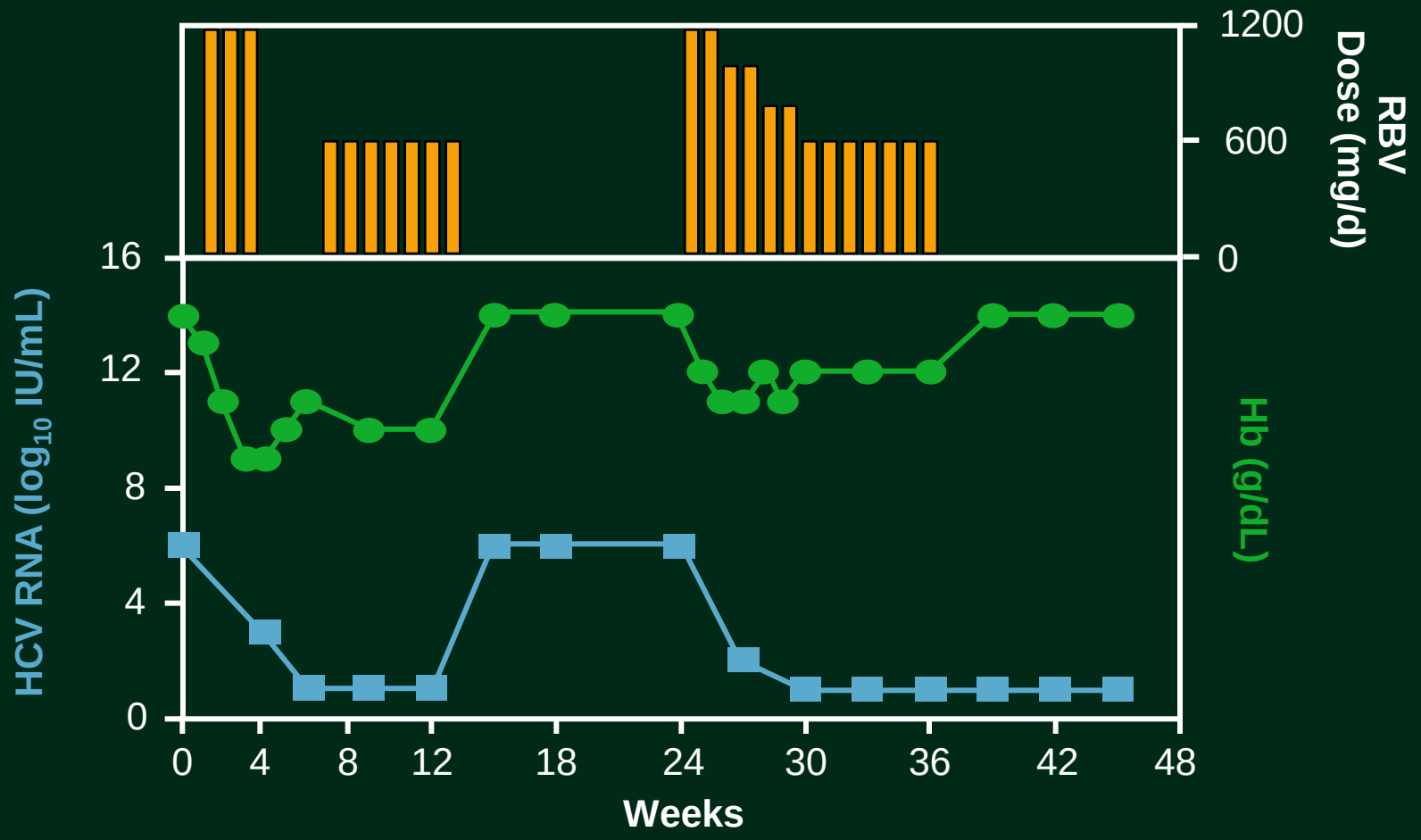
- **HCV RNA should be measured at monthly intervals until the patient either has undetectable HCV RNA or a nonresponse pattern has been defined and treatment is discontinued.**

Once undetectable, it is recommended that HCV RNA be monitored every 3 months until 24 weeks after treatment is discontinued

Why Patients Fail HCV Therapy

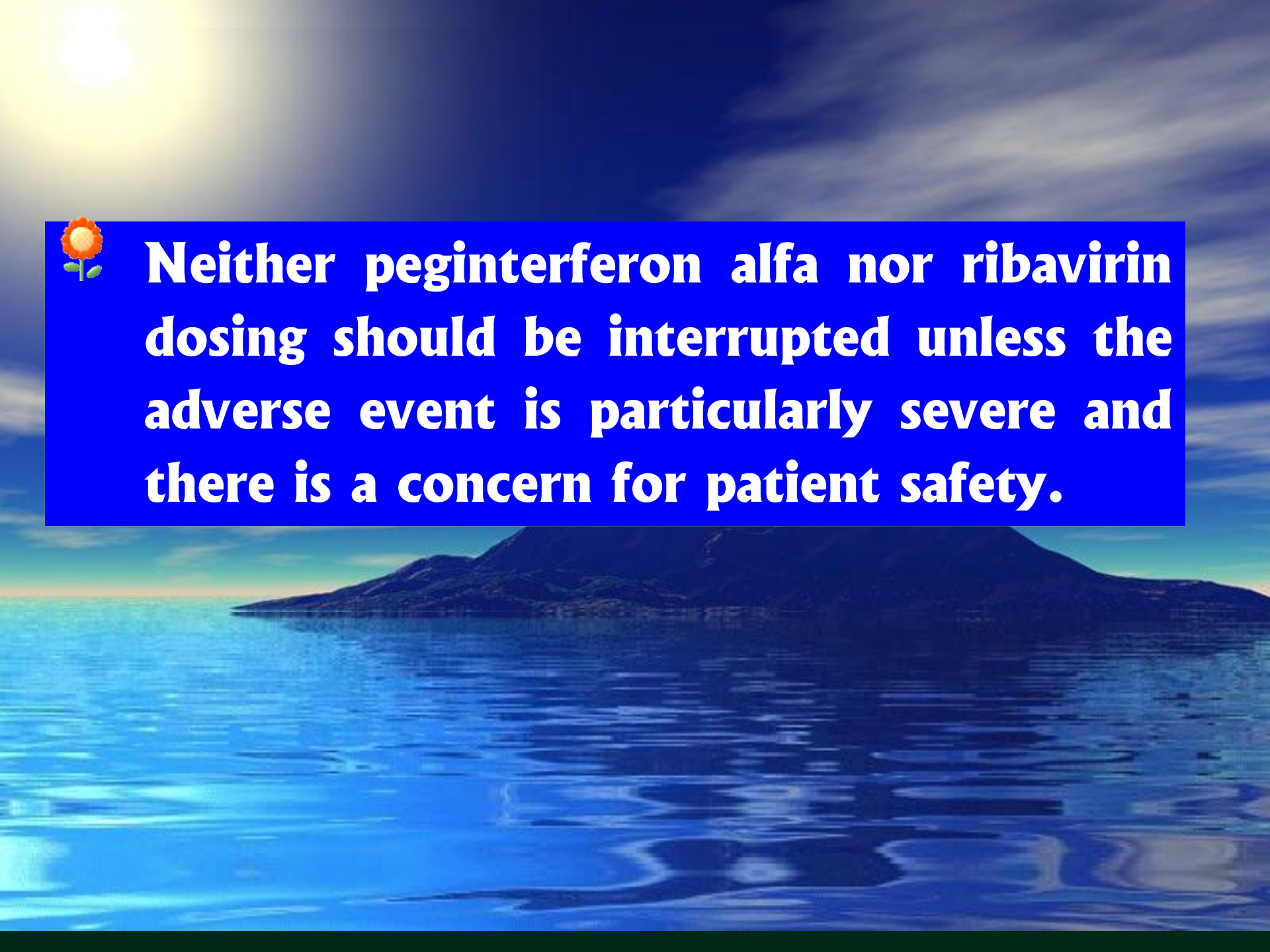
- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Reduced dose of pegIFN and/or RBV
  - Treatment not continued for a sufficient period of time

Adjusting Dose—Do Not Stop

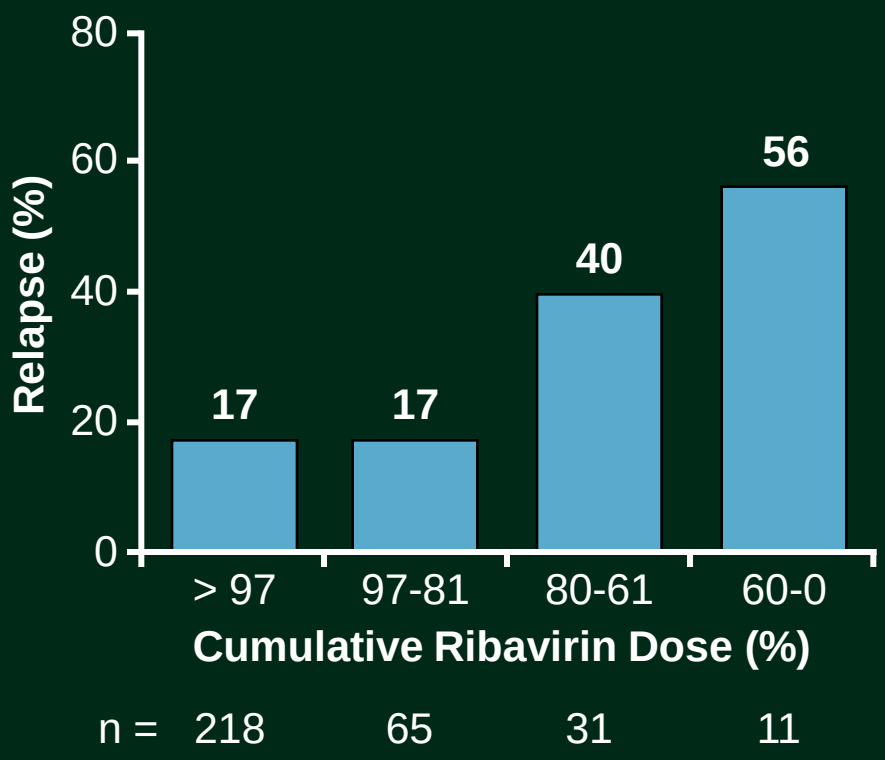


- It is difficult for many patients to tolerate even the standard duration of peginterferon alfa and ribavirin therapy.

- Many studies have suggested that at least 20% patients have adverse events that are severe enough to require either a reduction in the dose of peginterferon alfa and/or ribavirin , a temporary treatment interruption, or a permanent discontinuation of treatment.


Neither peginterferon alfa nor ribavirin dosing should be interrupted unless the adverse event is particularly severe and there is a concern for patient safety.

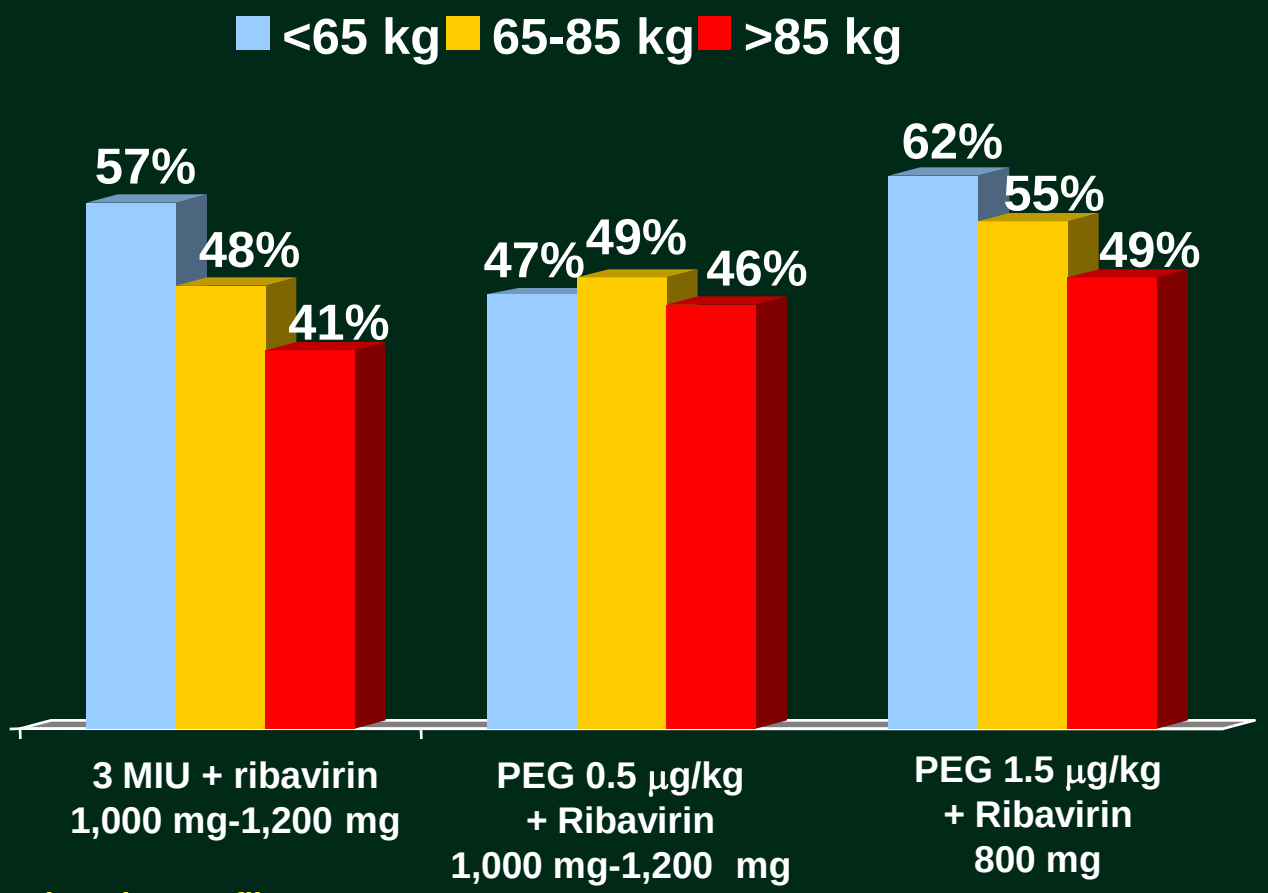
Impact of RBV Dose after 12 Weeks



- Patients received > 97% of RBV during Weeks 1-12
- Completed all 48 weeks of treatment
- Any reduction in RBV dose occurred after Week 12

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

Peginterferon ∝2b + Ribavirin
Sustained Virologic Response by Weight



Schering Corporation, data on file
Manns et al., Lancet 2001

Why Patients Fail HCV Therapy

- Noncompliance with physician recommendations
- Inherently resistant to IFN
- Response not recognized
- Adverse events
  - Therapy stopped
  - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time

Adherence to therapy

Patients achieving the 80/80/80 adherence goal:

- Taking 80% of the interferon dose
- And 80% of the ribavirin dose
- For 80% of the expected duration of therapy.

Why Retreat?

Two Schools of Thought: Retreat Now vs. Wait for Newer Agents Before Retreating

RETREAT NOW	WAIT TO RETREAT
Eradicate virus	Concerns about efficacy
Stop or reverse fibrosis	Side effects of therapy
Decrease risk of HCC	New antivirals coming soon

Who Can Benefit from Retreatment?

When Considering Retreatment, Results from Small-Scale Studies Using PEG-IFN alfa-2b Aid Patient Selection

Factor	Study Parameters	Impact on Retreatment SVR
Initial Treatment Response (Relapser vs. Nonresponder)	N=152 (Relapsers=46; N/R=95). 48 wks of treatment	Relapsers more likely to achieve retreatment SVR[1]
Genotype	N=182 (G1=87%). 48 wks of treatment	Genotype 2 and 3 are more likely to achieve retreatment SVR[2]
Retreatment Baseline Viral Load	N=141 (52%=HVL). 48 wks of treatment	Baseline low viral load more likely to achieve retreatment SVR[3]

How Should We Approach Retreatment?

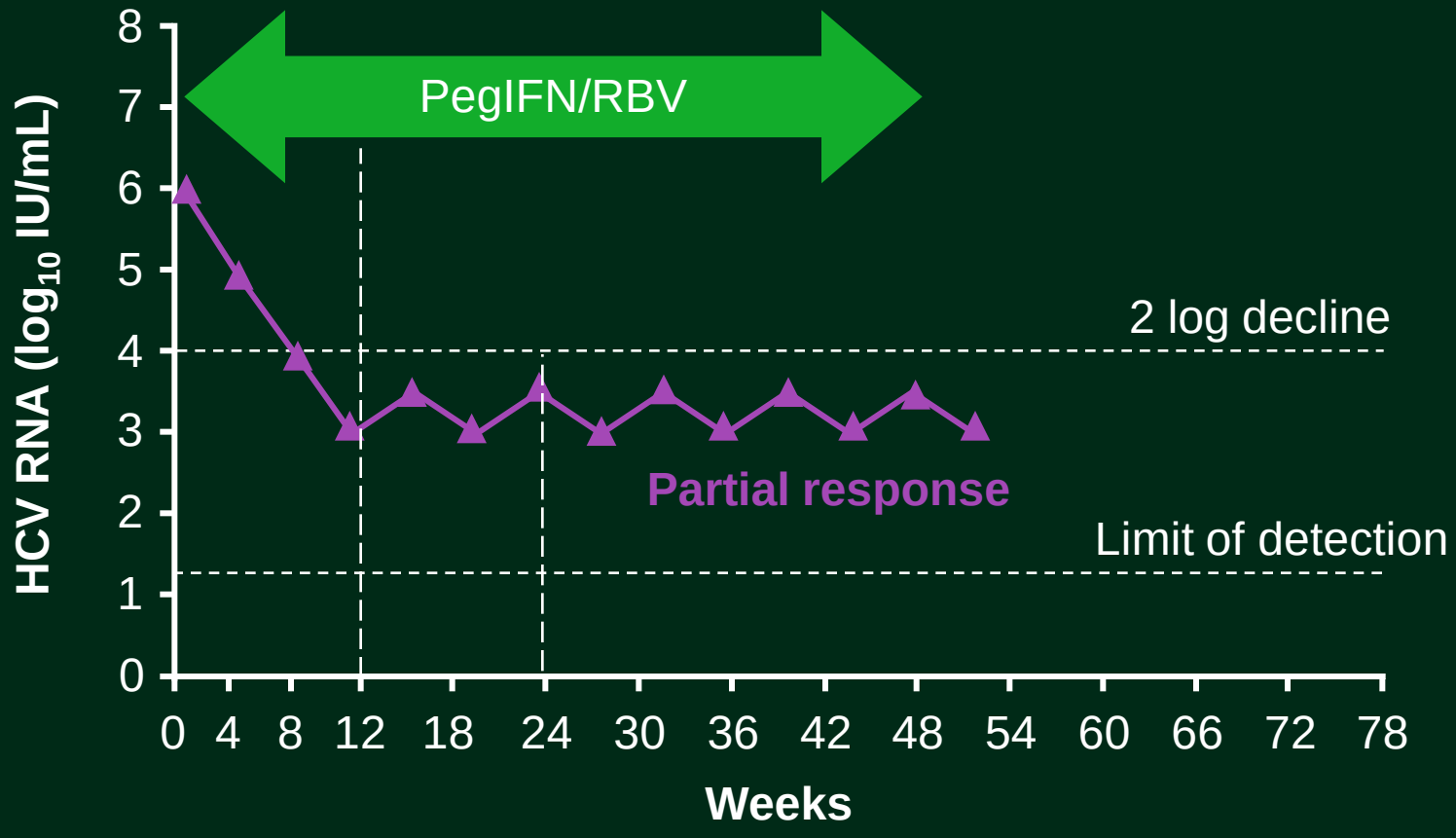
Management Strategies

- Increase induction dose of pegIFN + weight-based RBV
- Initiate treatment with albumin IFN + weight-based RBV
- Low-dose pegIFN to manage sequelae
- Watch and wait

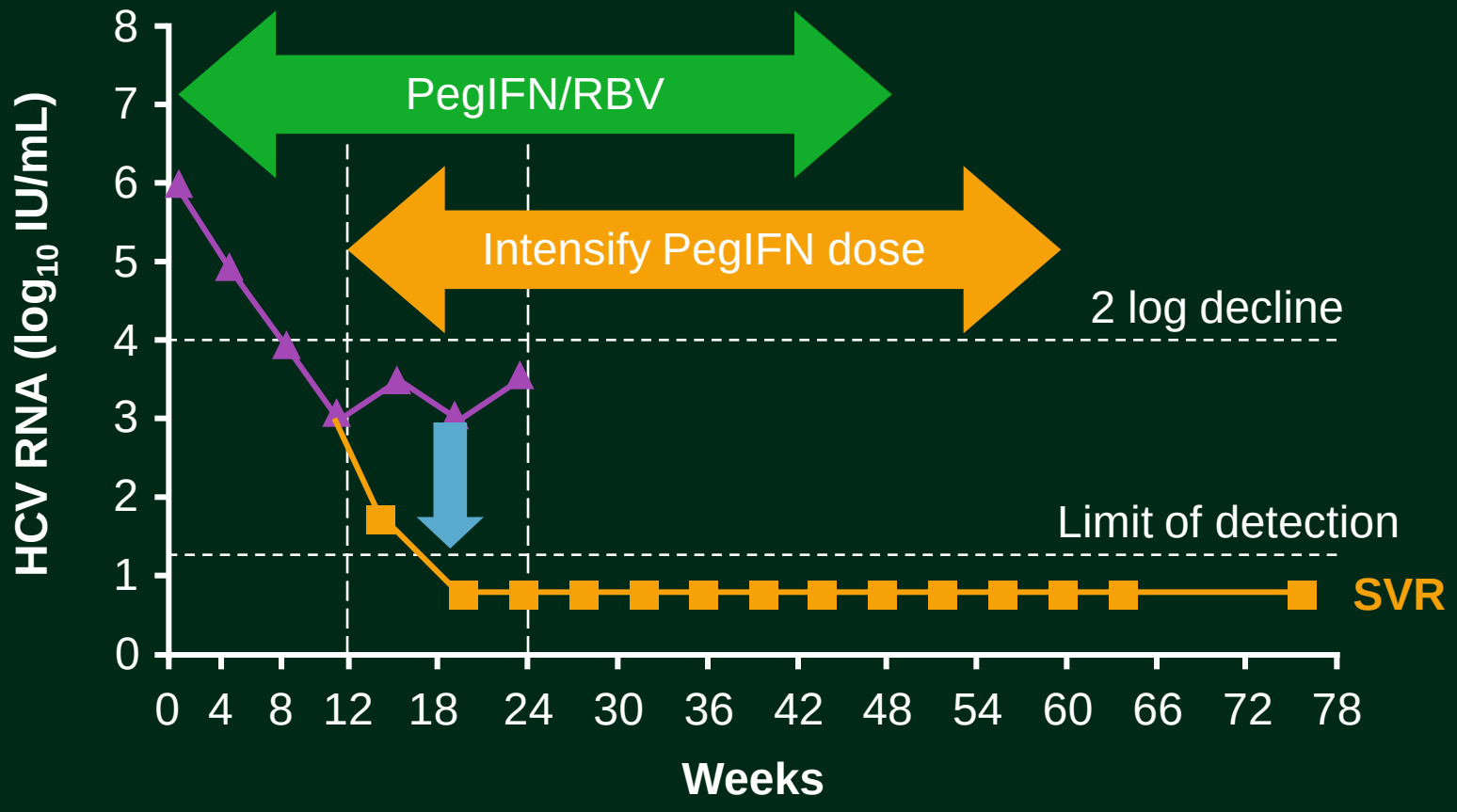
Options in PegIFN + RBV Nonresponders

- Retreat in the event of poor adherence to previous therapy
- Longer course of treatment for relapsers
  - Extrapolation of 48- vs 72-wk results in slow responders
- Other IFNs (consensus IFN, albumin IFN)
- Maintenance therapy
- Clinical trials of new agents
- “Watching and waiting”: an option not to be ignored

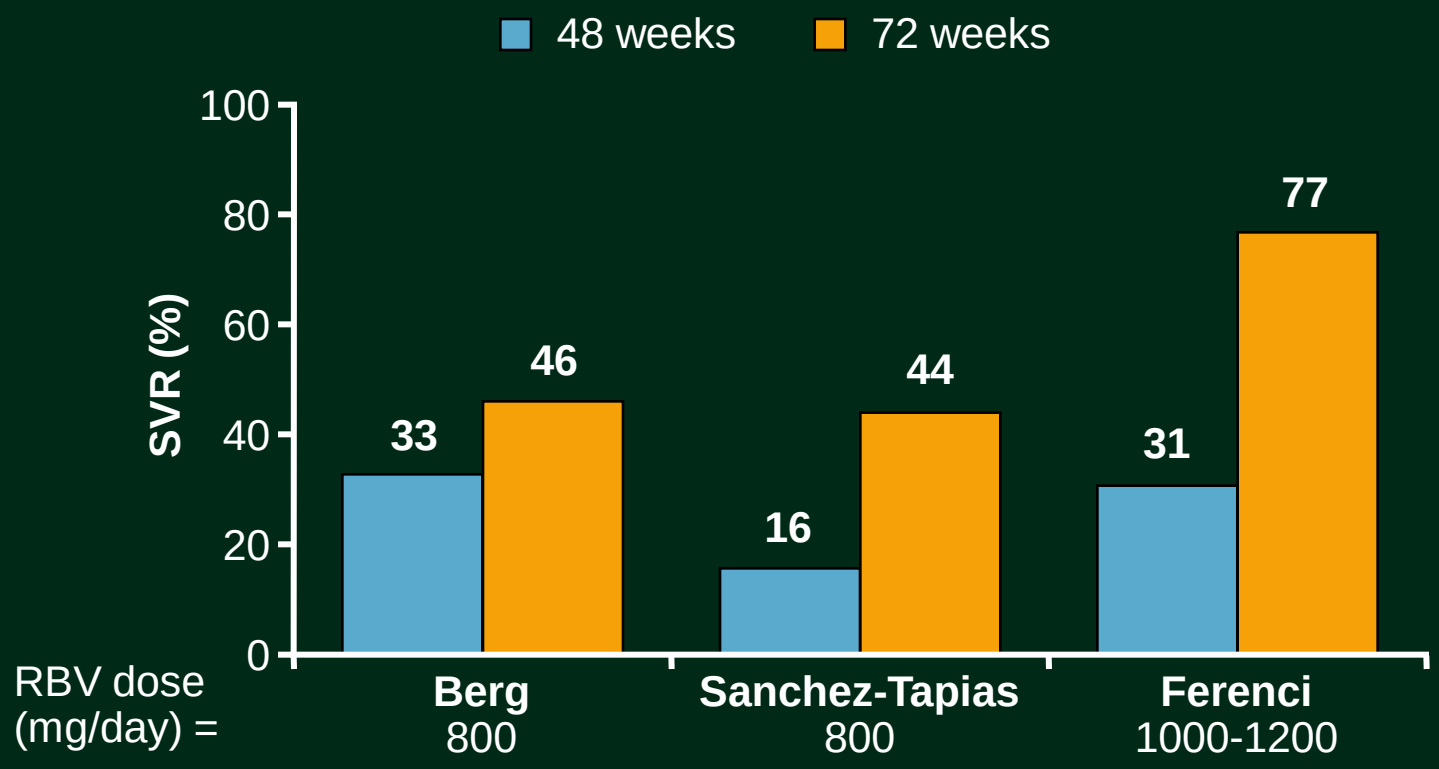
Partial Responder: Impact of Intensifying Therapy



Partial Responder: Impact of Intensifying Therapy (cont'd)



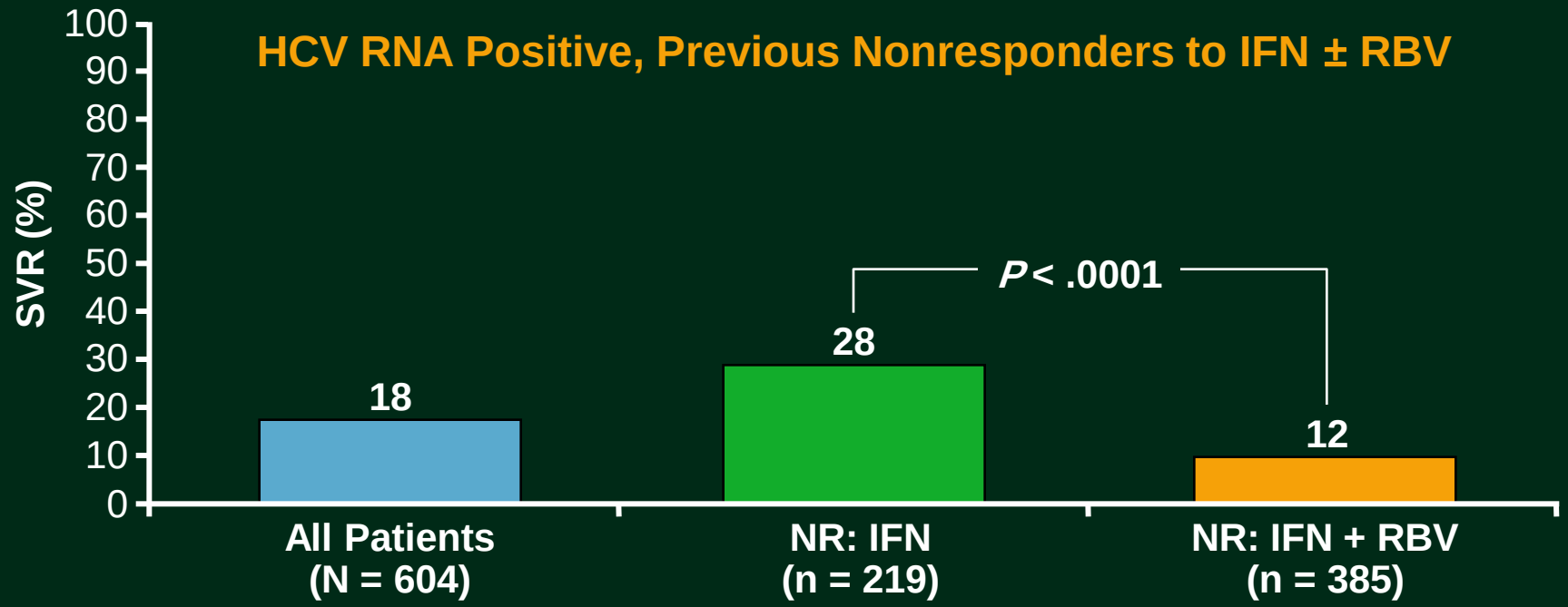
Slow-to-Respond Patients: Extending Therapy



Berg T, et al. Gastroenterology. 2006;130:1086-1097. Sanchez-Tapias JM, et al. Gastroenterology. 2006;131:451-460. Ferenci P, et al. AASLD 2006. Abstract 390.

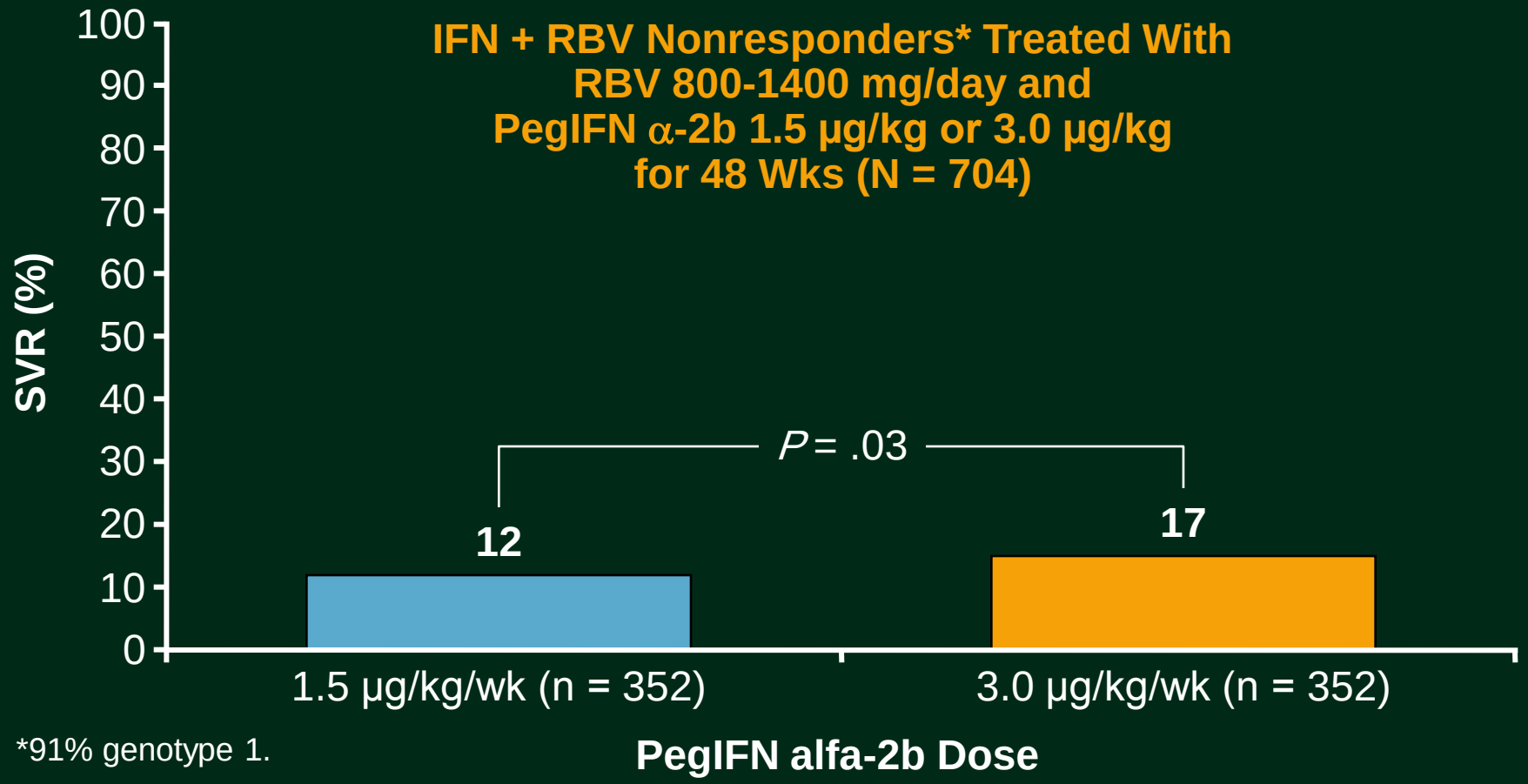
HALT-C: Retreatment of Standard IFN Nonresponders With PegIFN + RBV

- PegIFN alfa-2a 180 µg/wk + RBV 1000-1200 mg/day
- Patients with bridging fibrosis or cirrhosis included
- If viral clearance achieved at 20 wks → continue treatment through 48 wks



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

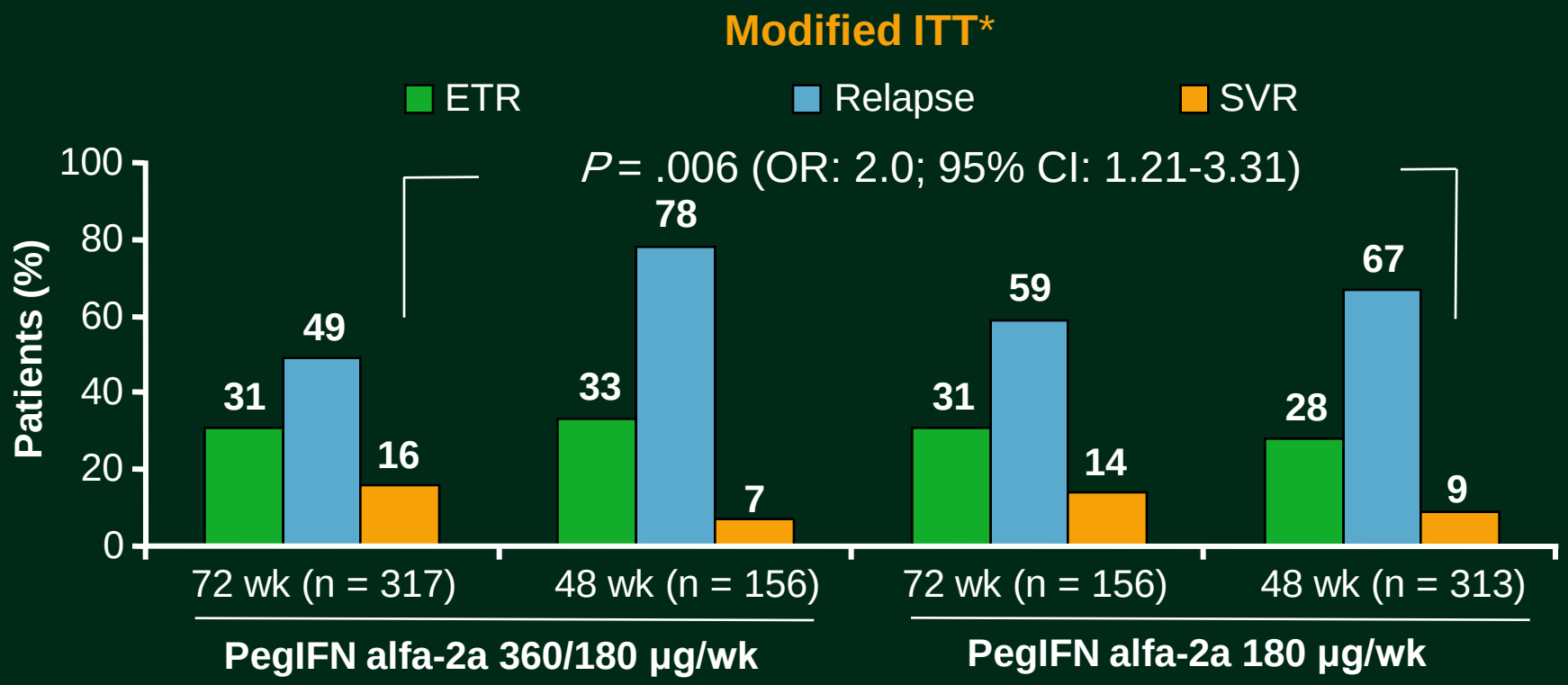
RENEW: Higher-Dose PegIFN alfa-2b Increases SVR Rate



*91% genotype 1.

Gross J, et al. 2005 AASLD. Abstract 80.

REPEAT: No Benefit Associated With High-Dose Induction



- Extended treatment did not increase ETR but did decrease relapse

*Patients randomized who received at least one dose of study medication

Jensen D, et al. AASLD 2007. Abstract LB4.

Testing a Stringent Week 12 Stopping Rule with PEG-IFN alfa-2b: EPIC^3 Retreatment Study Design

Patients enrolled on or before April 1, 2004
n = 1354

Efficacy population
n = 1336

12 Weeks*

HCV RNA undetectable**
n = 499

HCV RNA Positive with ≥2 log drop in HCV RNA
n = 293

HCV RNA Positive with <2 log drop in HCV RNA
n = 457

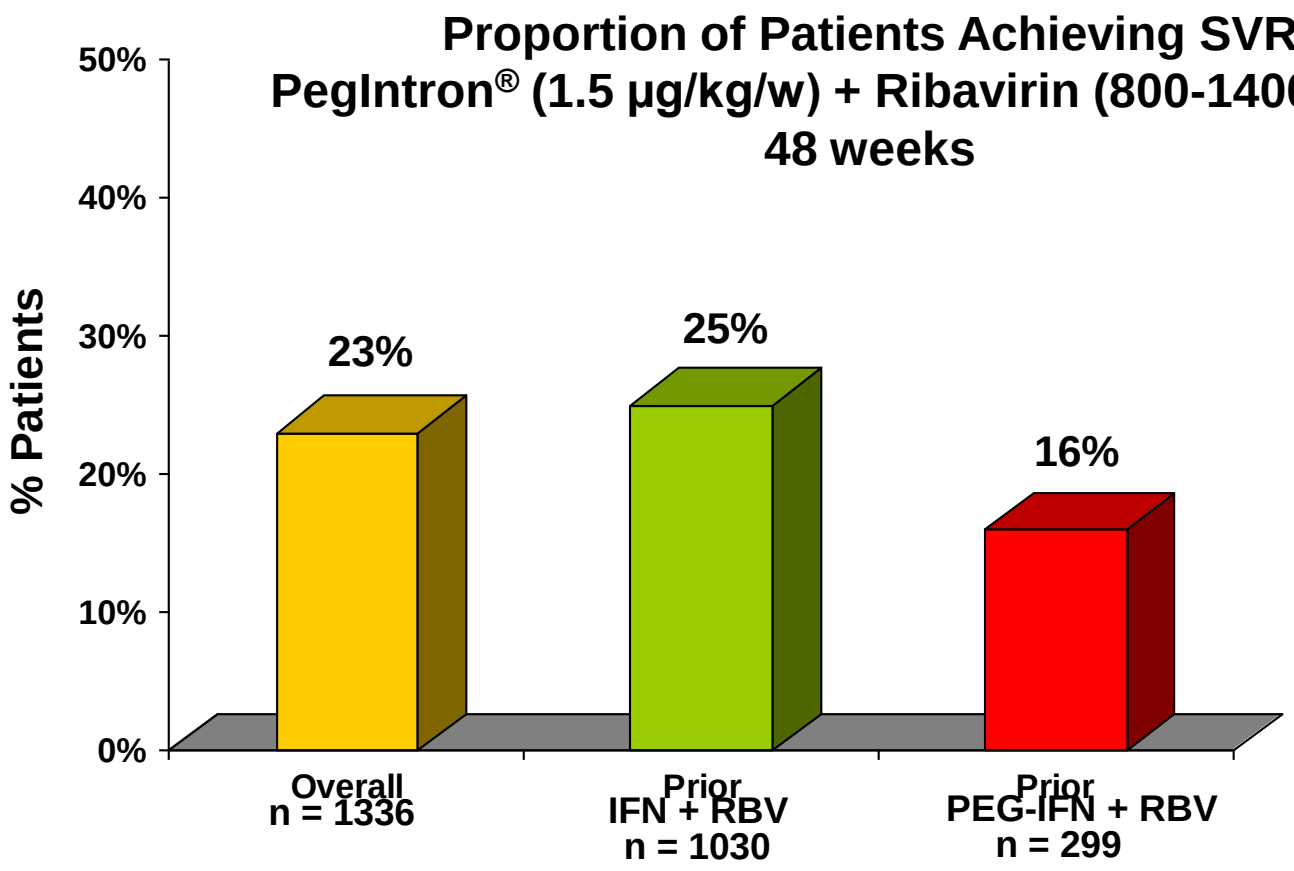
n = 143†

Completed 48 weeks of therapy and 24-week follow-up
n = 650

Entered maintenance protocols or discontinued
n = 599

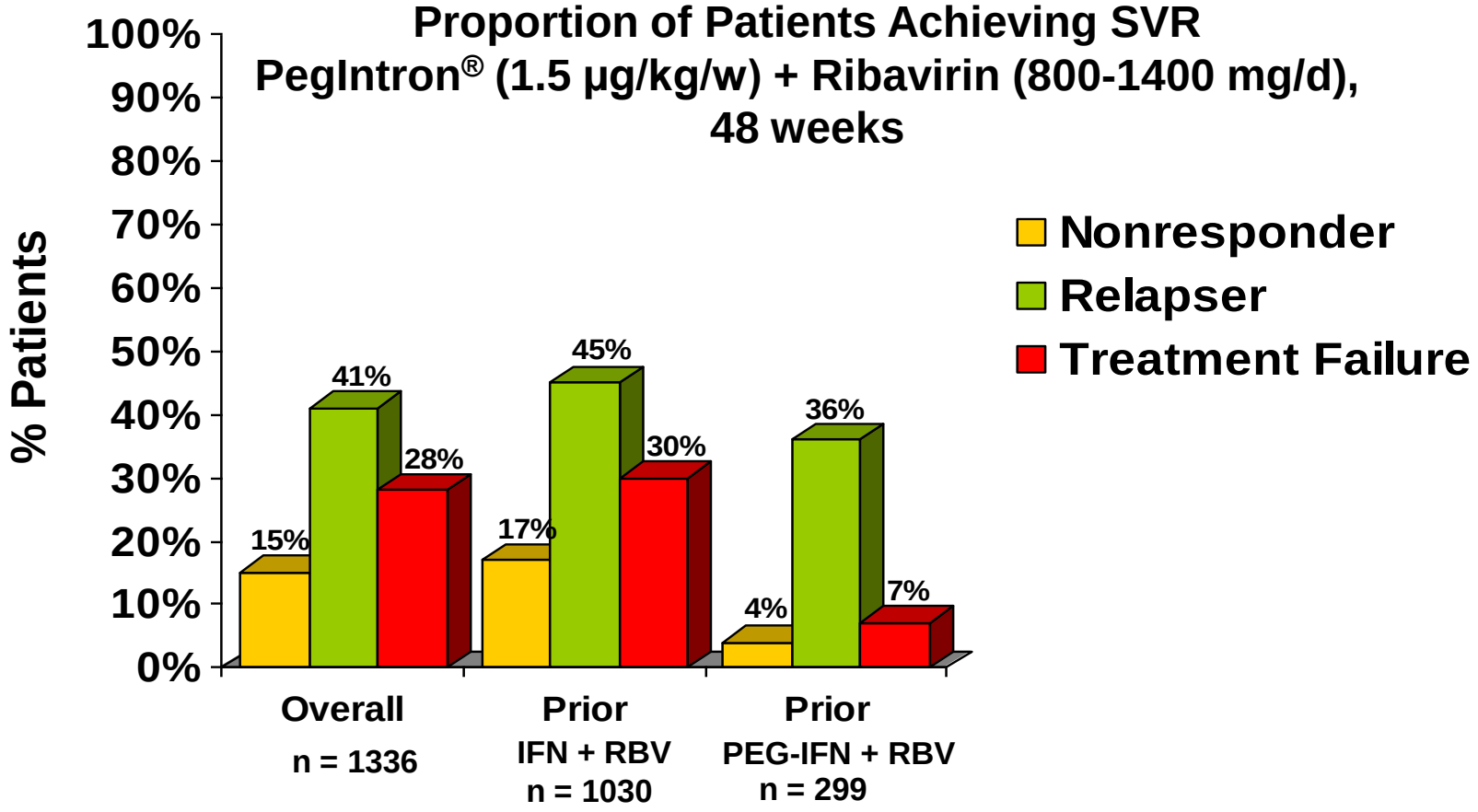
*87 patients did not have 12-week data; 1 missing baseline HCV RNA
**LLD <125 IU/mL
†Continued in the protocol at the discretion of the investigator
Poynard T, et al. HepDART 2007, Poster 110.

Efficacy Results Overall by Prior Treatment



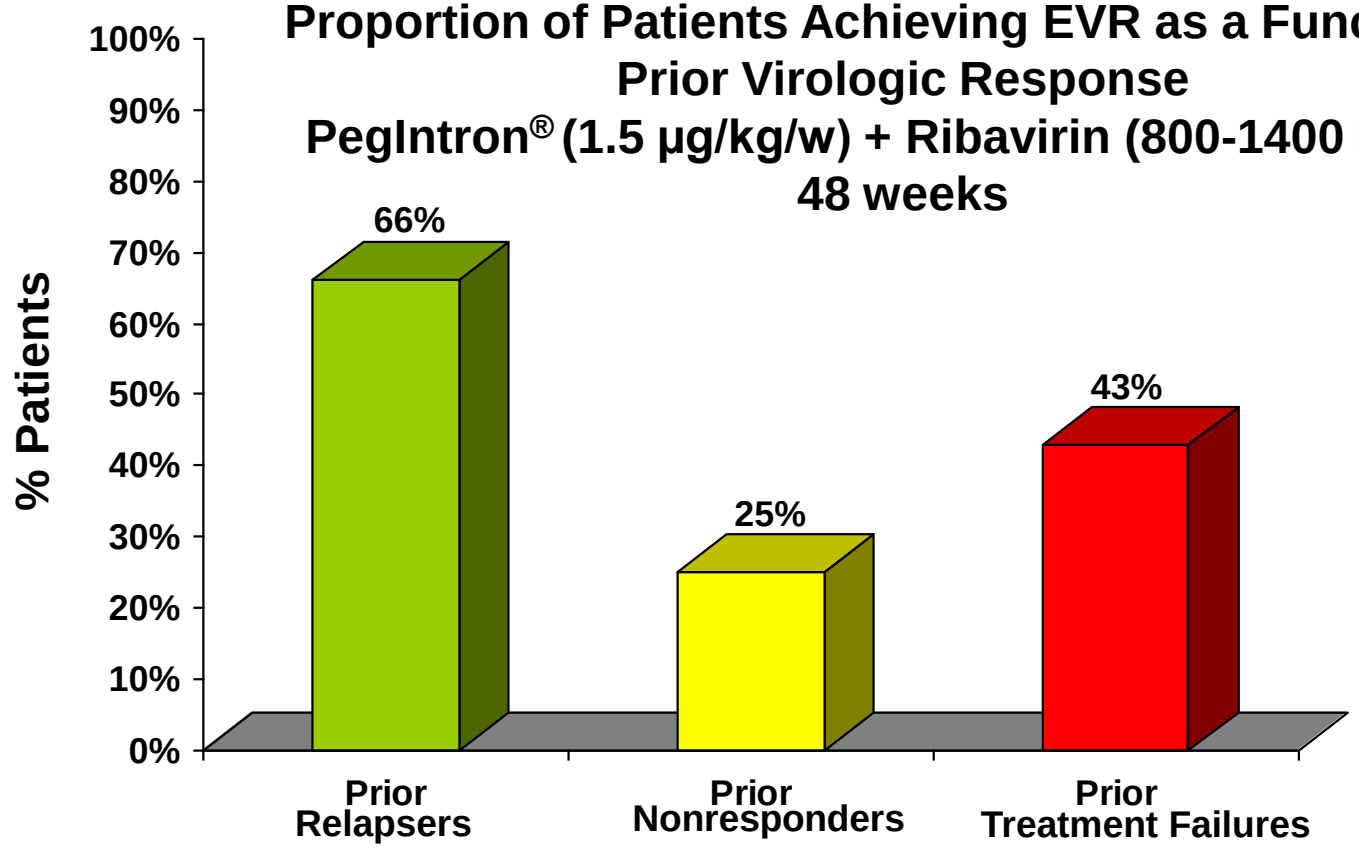
Poynard T, et al. HepDART 2007, Poster 110.
PegIntron SmPC

Whether Prior Therapy Was with Pegylated or Non-Pegylated IFN, Prior Relapsers More Likely to Achieve Retreatment SVR



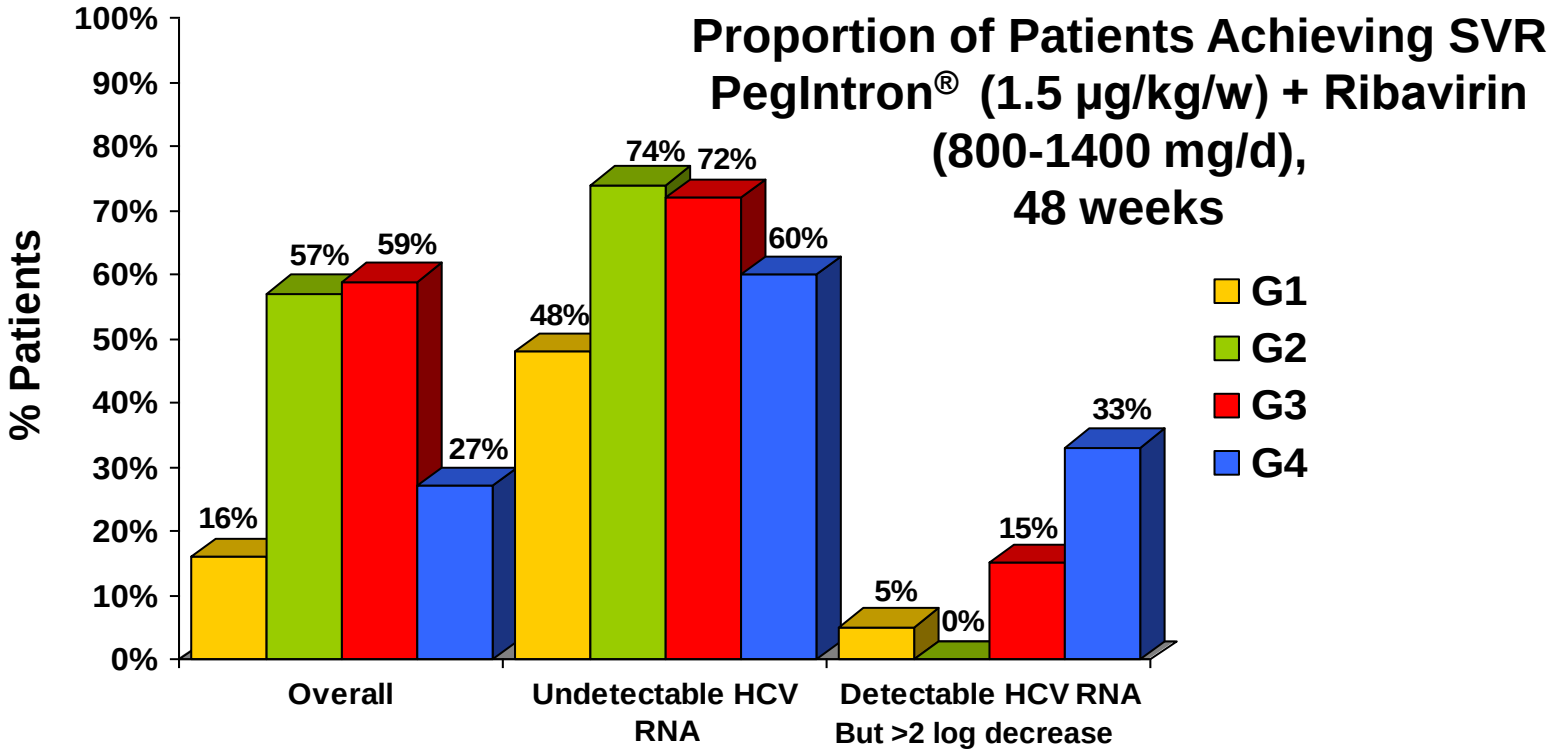
Schering-Plough. Data on File

Overall, Relapsers Were More Likely to Achieve Viral Negativity at Treatment Week 12



Schering-Plough Data on File.

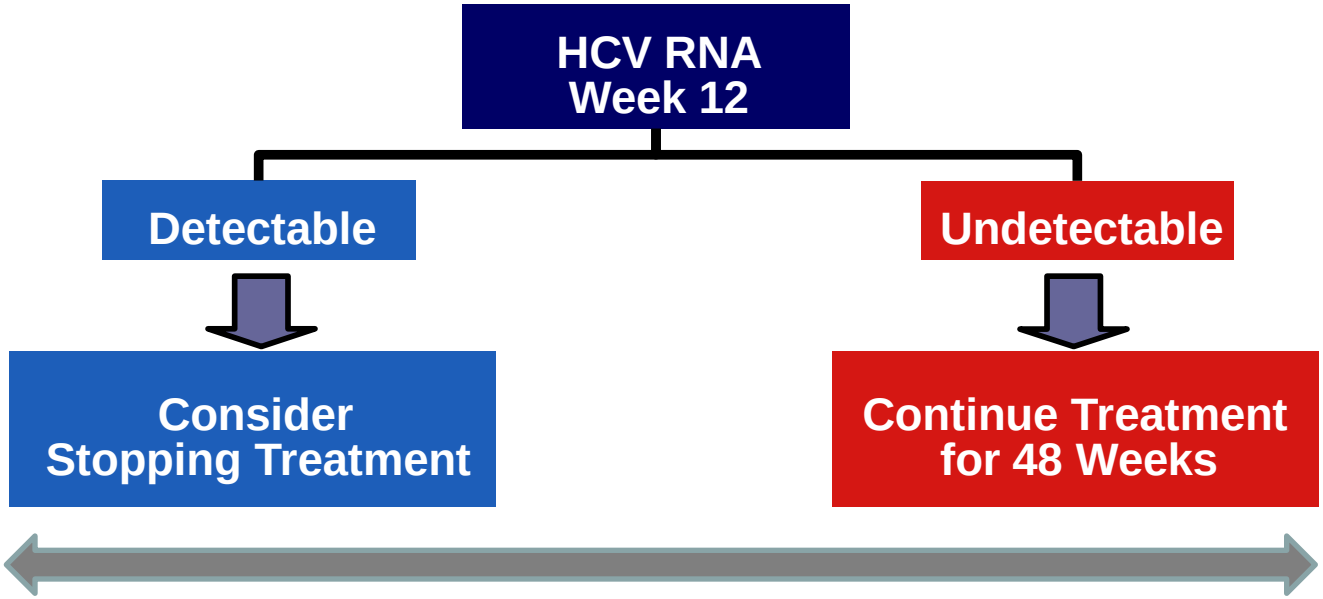
The Week 12 Response Is Highly Predictive of SVR Regardless of Genotype



Week 12

Poynard T, et al. HepDART 2007, Poster 110.

The New Week 12 Retreatment Milestone Derived from EPIC[3] Response Analyses



- ✓ EPIC[3] data establish a Week 12 decision point for continuing retreatment with PEG-IFN + RBV
- ✓ Patients with undetectable HCV RNA at Week 12 have a >50% chance of attaining an SVR
- ✓ For those with detectable HCV RNA at Week 12, the odds of attaining an SVR are low

Summary

- Depending on the reasons for initial failure, many patients are likely to achieve SVR with a second course of treatment

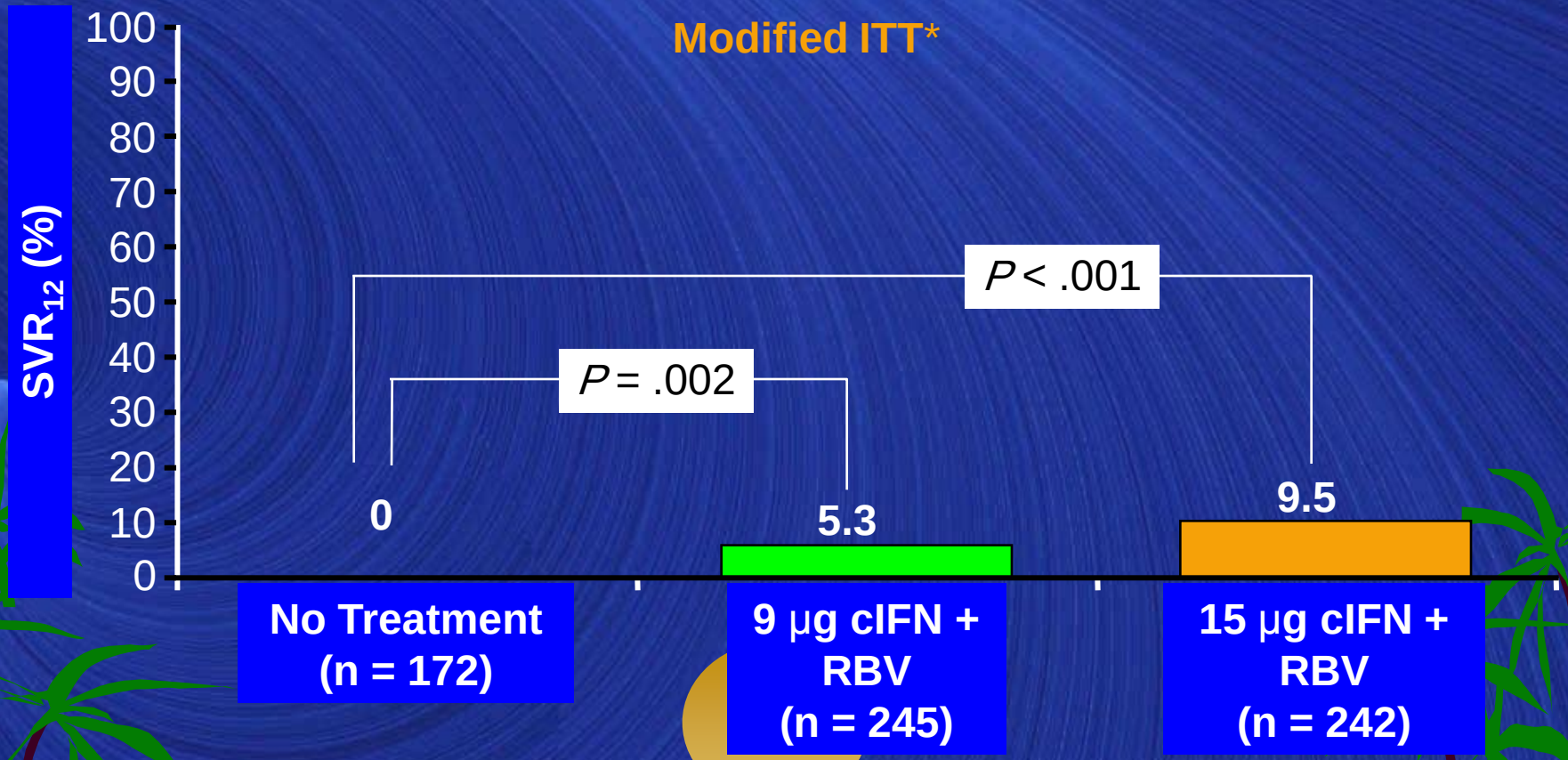
- In the EPIC[3] study, SVR was attained by 23% of patients overall

- Among those who were negative at week 12
  - 57% achieved SVR: 59% of prior non-pegylated failures and 47% of prior pegylated failures

- Applying a stringent week 12 stopping rule can be a powerful motivator to encourage patients toward another course of treatment.

Novel Agents in Development

DIRECT: cIFN 9 µg vs 15 µg + RBV in PegIFN/RBV Nonresponders



*Patients with at least 12 wks of viral negativity after end of treatment; RBV dosed at 1000-1200 mg/day.

Bacon B, et al. AASLD 2007. Abstract 108.

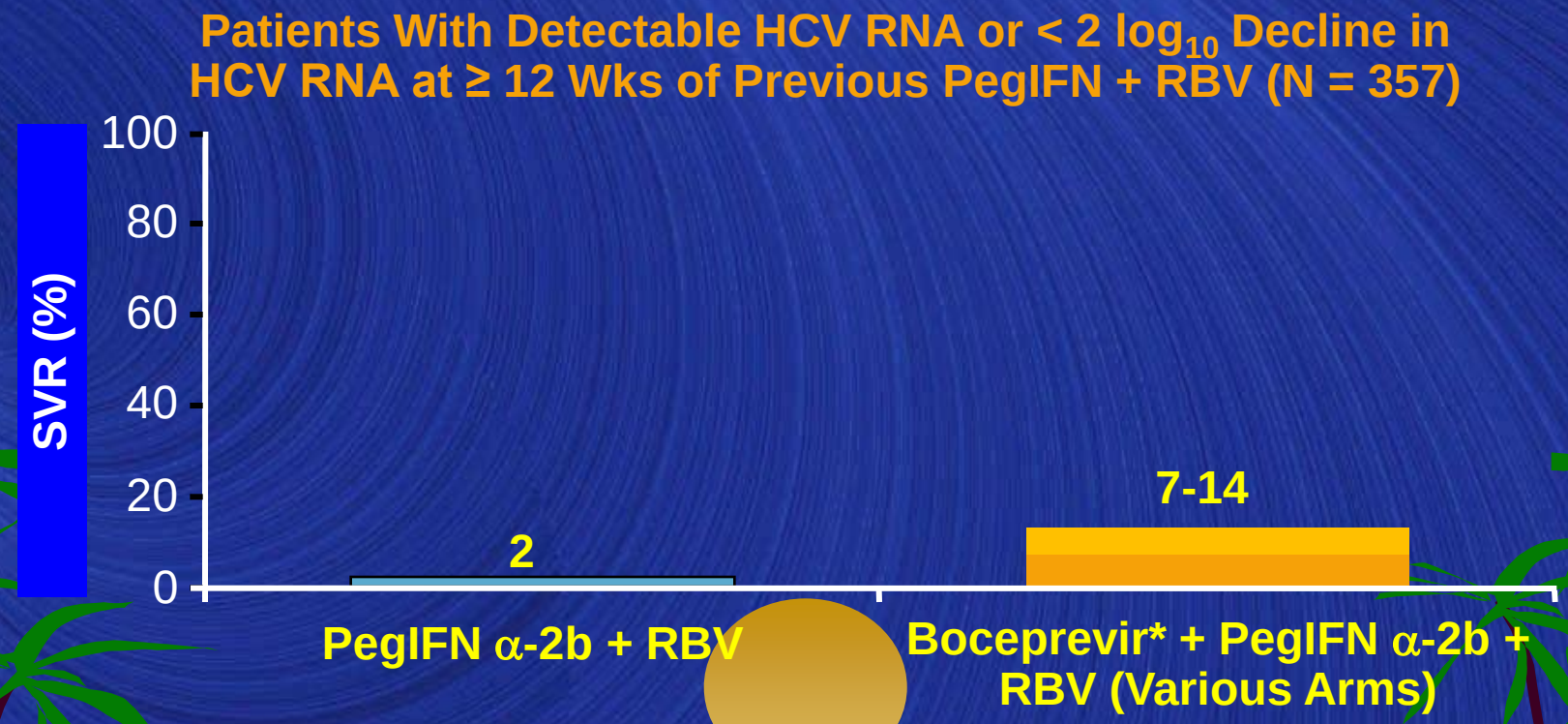
DIRECT: Summary

- Patients with lower fibrosis stages experienced improved responses with cIFN
- Noncirrhotic patients with greater HCV RNA reductions during previous pegIFN/RBV therapy had the best response
- 15 µg cIFN group consistently experienced a better response than the 9 µg cIFN group
- cIFN/RBV had an acceptable tolerability profile at doses up to 15 µg

Bacon B, et al. AASLD 2007. Abstract 168.

Boceprevir + PegIFN/RBV: Phase II Nonresponder Study, GT 1

- **Response dependent on interferon responsiveness**



*100, 200, 400, and 800 mg TID boceprevir.

Schiff E, et al. EASL 2008. Abstract 104.

Conclusion: Management of PegIFN + RBV Nonresponders

- Consider longer duration of retreatment in relapsers
- Potential benefit of pegIFN alfa-2a/b crossover concept still to be proven
- Optimize weight-based RBV dose in retreated patients
- Higher doses of pegIFN alfa may be superior to standard dose in selected patients

Conclusion: Management of PegIFN + RBV Nonresponders

- Potential role for cIFN in selected patients (eg, partial responders, noncirrhotics, relapsers)
- Longer treatment durations in nonresponders should be considered, depending on viral kinetics, tolerability, degree of fibrosis
- Maintenance therapy of uncertain efficacy
- Watch and wait approach is reasonable in many patients

- Thank you