



**Treatment for HCV 2009:  
What Are The Options?**

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**Disclosures**

- I receive research support from:
  - Roche
  - Schering-Plough
  - Novartis
  - Human Genome Sciences
  - Vertex
  - Debiovision
  - Glaxo
  - Idenix
  - BMS
  - Pharmasset

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**Educational Goals:**

You should:

- Formulate a customized plan for **treatment** of HCV
- Be aware of the state of the HCV treatment options
- Be able enumerate new strategies to improve the outcome of treatment

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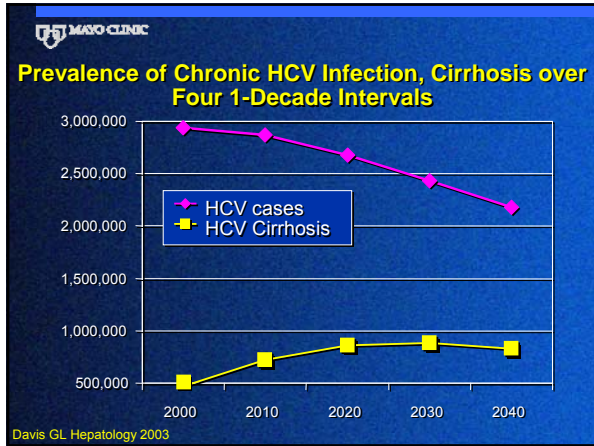
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# Treatment of Hepatitis C 2009: What Are the Options?




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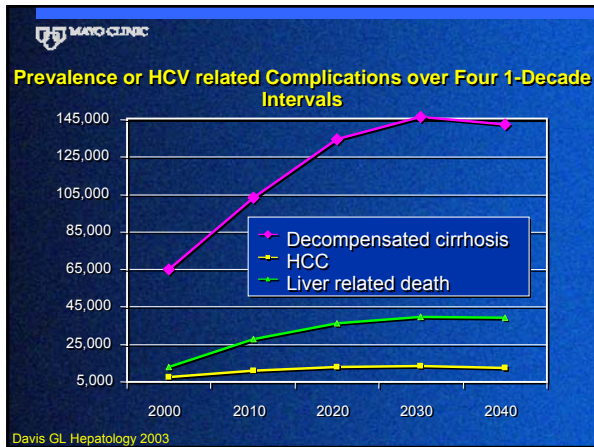
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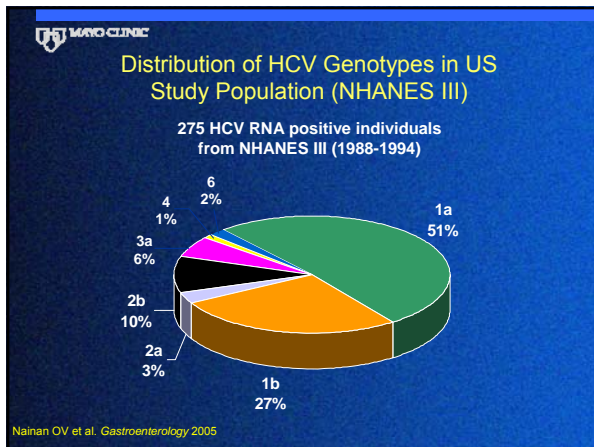
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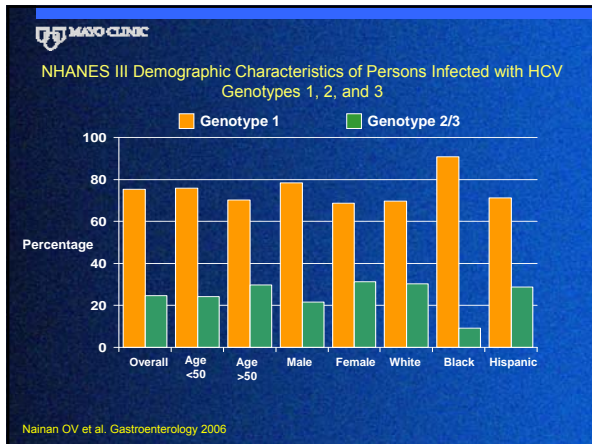
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# Treatment of Hepatitis C 2009: What Are the Options?



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- MAYO CLINIC**  
PEG-IFN/RBV: Factors Associated with Successful Therapy of HCV
- Genotypes 2 or 3\*
  - Lower baseline viral levels\*
  - Less fibrosis on liver biopsy\*
  - Lower body weight\*
  - Caucasian race
  - Non-insulin resistant
- \*Adapted from Nation Institutes of Health Consensus Development Conference Statement: Management of Hepatitis C-2002. Hepatology 2002;36:S3-S20.

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**MAYO CLINIC**

**How do we approach treatment?**

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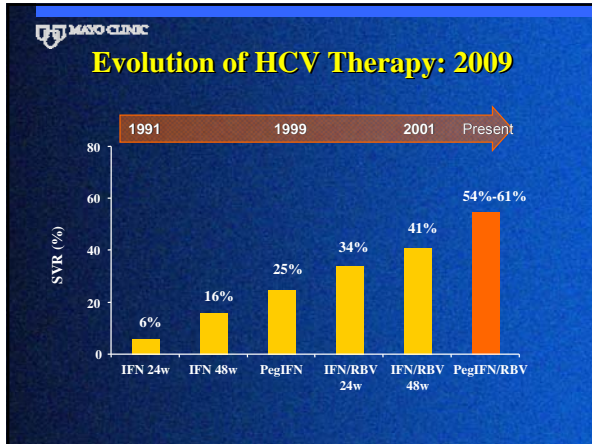
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# Treatment of Hepatitis C 2009: What Are the Options?



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**DEFINITIONS**

- **RVR, Rapid Virological Response**  
HCV-RNA not detectable in blood **4 weeks** after antiviral therapy onset
- **EVR, Early Virological Response**  
HCV-RNA not detectable in blood **12 weeks** after therapy onset
- **EOT, End Of Treatment Response**  
HCV-RNA not detectable after discontinuation of therapy
- **SVR, Sustained Viral Response**  
HCV-RNA not detectable in blood **6 months** after the completion of antiviral therapy

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**Why should you care?**

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# Treatment of Hepatitis C 2009: What Are the Options?

**SVR is Durable and Constitutes a CURE**

	PegIFN $\alpha$ -2a	PegIFN $\alpha$ -2b
No. of patients	997	492
Follow-up, years	4.1	5-6
HCV-RNA negative, %	99.2	99
Relapse	9 (.9%)	5 (1%)
Time to relapse, years	2	>2

Swain et al. DDW 2007

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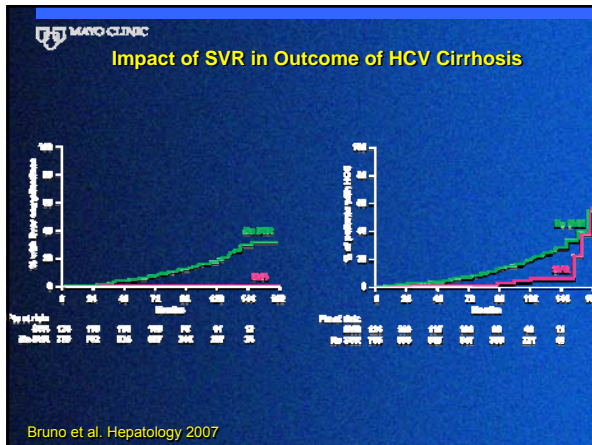
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- Therapy of Chronic HCV in 2009: What is new?**
- Tailoring treatment to individual patients: “A la carte management”
  - STAT-C (**S**pecifically **T**argeted **A**ntiviral **T**herapy for Hepatitis **C**)

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# Treatment of Hepatitis C 2009: What Are the Options?

MAYO CLINIC

- Tailoring treatment to individual patients

Short

Extended

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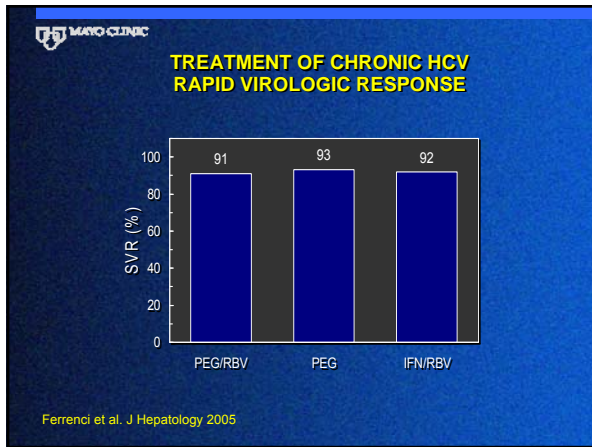
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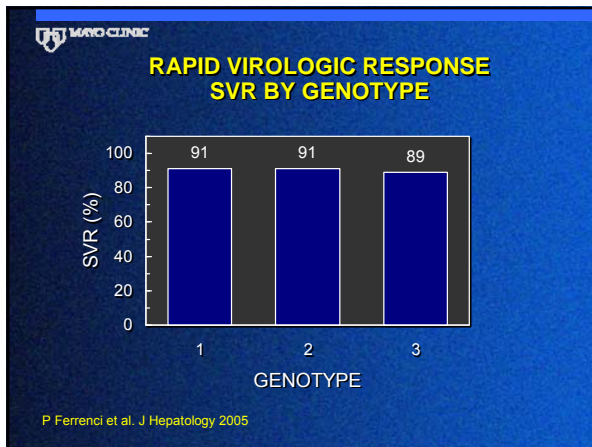
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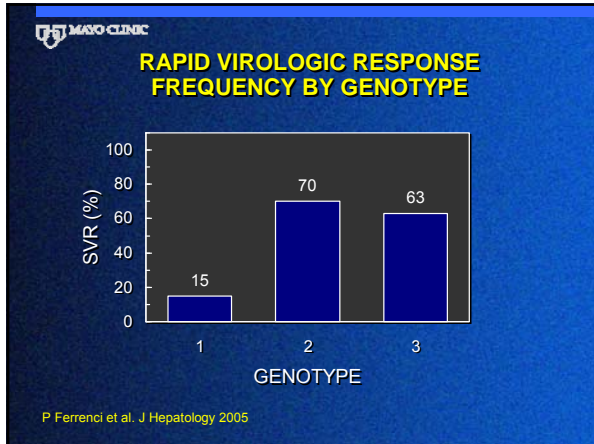
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# Treatment of Hepatitis C 2009: What Are the Options?




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**The case for shorter treatment**

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**Patients Responding to 24-Week Therapy: Independent Factors Predictive of RVR among Patients Treated for 24 Weeks**

Patients	Factor	OR	95% CI	P
All	Baseline HCV RNA <200,000 vs >600,000 IU/mL	9.7	4.2-22.5	<.0001
All	Baseline HCV RNA 200,000-600,000 vs >600,000 IU/mL	3.6	1.5-9.1	.0057
All	HCV subtype: 1b vs 1a	1.8	0.9-3.7	.095
Subtype 1a	Baseline HCV RNA ≤200,000 vs >200,000 IU/mL	5.9	2.0-17.6	.0015
Subtype 1b	Baseline HCV RNA ≤600,000 vs >600,000 IU/mL	10.3	3.6-29.4	<.001

Jensen et al., Hepatology 2006

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# Treatment of Hepatitis C 2009: What Are the Options?

**Early Identification of HCV-1 Patients Responding to 24-Week Therapy**

- 24% of patients infected with HCV genotype 1 and treated with PEGIFN alfa-2a/RBV had a RVR
  - 89% of these patients had SVR after 24-weeks of treatment
- **RVR and HCV-RNA <200,000 IU/ml** are predictors of SVR in patients treated for 24 weeks

Jensen et al., Hepatology 2008

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**SVR in Patients with RVR according to Pretreatment HCV RNA Levels — HCV-2 and HCV-3**

**SVR**

Genotype	HCV RNA at week 4	Group	Weeks	SVR (n/N)	SVR (%)
HCV-2 (n=38)	≤800,000 IU/ml	Group A (16 wks)	6/6	100%	
		Group B (24 wks)	6/6	100%	
	>800,000 IU/ml	Group A (16 wks)	12/13	93%	
		Group B (24 wks)	12/13	93%	
HCV-3 (n=103)	≤800,000 IU/ml	Group A (16 wks)	27/29	93%	
		Group B (24 wks)	21/25	84%	
	>800,000 IU/ml	Group A (16 wks)	12/22	54%	
		Group B (24 wks)	18/27	67%	

Von Wagner et al., Gastroenterology, 2005

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- In HCV-2 and HCV-3 (≤800,000 IU/ml) infected patients who have a RVR, treatment for **16 weeks** with PegIFN alfa-2a and RBV is **sufficient**
- In patients infected by HCV-3 (>800,000 IU/ml), **longer treatment may be necessary**

Von Wagner et al., Gastroenterology, 2005

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# Treatment of Hepatitis C 2009: What Are the Options?

**MAYO CLINIC**

## Peginterferon Alfa-2a and Ribavirin for 16 or 24 Weeks in HCV Genotype 2 or 3

Mitchell L. Shiffman, MD; Fredy Suter, MD; Bruce R. Bacon, MD; David Nelson, MD; Hugh Harley, MB, BS; Ricard Solà, MD; Stephen D. Shafran, MD; Karl Barange, MD; Amy Lin, MS; Ash Soman, MB, BS; Stefan Zeuzem, MD; for the ACCELERATE Investigators

N Engl J Med  
Volume 357(2):124-134  
July 12, 2007

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**MAYO CLINIC**

## Study Overview

- In patients with chronic hepatitis C virus **genotype 2 or 3** participating in this randomized trial, **SVR was higher with 24 weeks of PegIFN and RBV** than with 16 weeks of treatment (70% vs 62%,  $P < 0.001$ )
- In the subgroup of patients with a **RVR**, **SVR rates were 85% in the 24 week group and 79% in the 16-week group** ( $P = 0.02$ )

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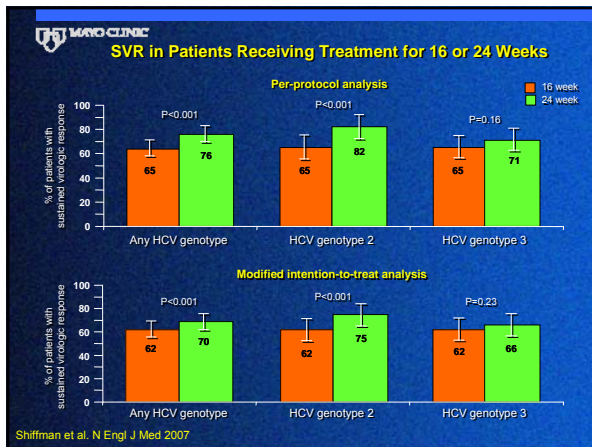
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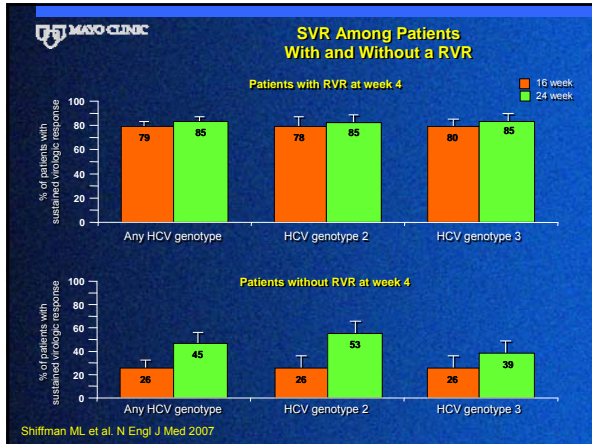
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# Treatment of Hepatitis C 2009: What Are the Options?



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## Conclusion

- Treatment with PegIFN and RBV for 16 weeks in patients infected with HCV genotype 2 or 3 results in a lower overall SVR than the standard 24 week regimen

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## Approach

- HCV Genotype 1 patients should be treated for 48 weeks, those with RVR are more likely to have an SVR
- HCV genotype 2 patients with low HCV RNA **may** reach SVR with 16 weeks
- HCV genotype 3 with higher HCV RNA need to be treated with at least 24 weeks

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 **What about HCV 1 who are slow responders?**

*A majority of patients*

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 **Extended Treatment for HCV-1:  
48 vs 72 Weeks of PegIFN alfa-2a  
and RBV**

- PegIFN alfa-2a, 180µg/week
- RBV 800 mg/day
- 48 vs. 72 weeks

Berg et al. Gastroenterology 2006

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 **Results**

- EOT and SVR rates
  - 71% vs 63% and 53% vs 54%, respectively
- Patients with RVR
  - 76 % vs 84%
- Patients without EVR
  - 17% vs 29% (p = .04)
- AEs were similar in both groups

Berg et al. Gastroenterology 2006

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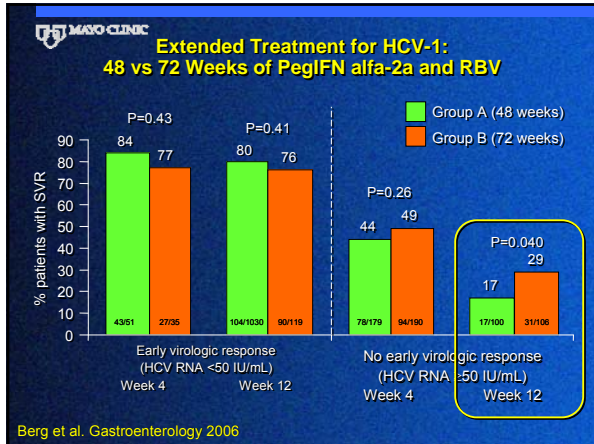
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# Treatment of Hepatitis C 2009: What Are the Options?




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**What to do with the treatment failures?**

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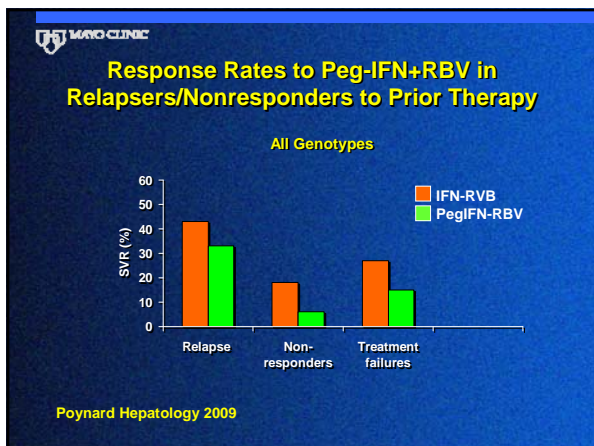
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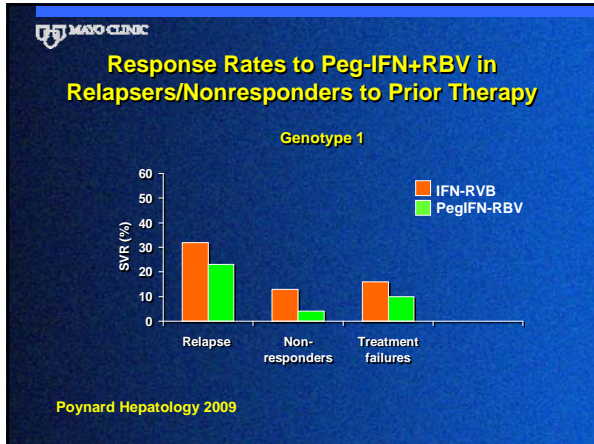
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# Treatment of Hepatitis C 2009: What Are the Options?




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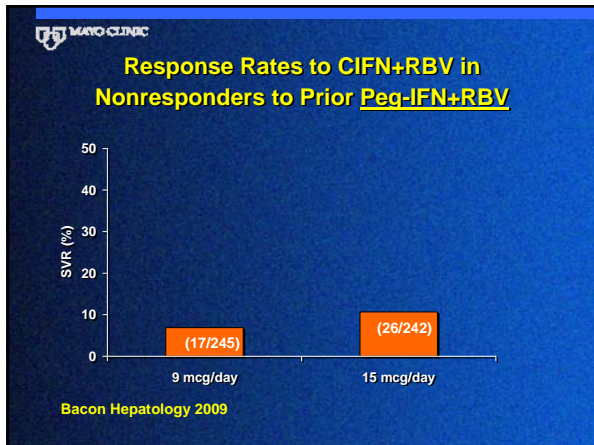
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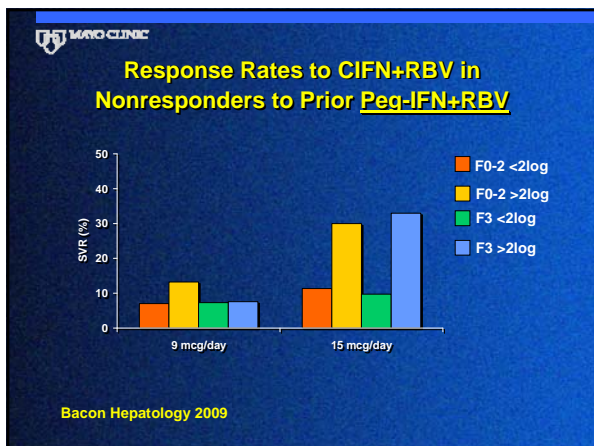
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 **Cirrhotics and "Nearly There"**

- 3 pivotal Maintenance trials:
  - HALT-C
  - EPIC
  - Co-PILOT
- All failed to show decrease in
  - Death
  - HCC
  - LT
- Decrease in PHTN events may be of importance

DI Blasciegla NEJM 2008  
Bruta J Hepatology 2009  
Aldhal J Hepatology 2008

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 **What to do with the treatment failures?**

- Document prior treatment behavior very carefully
- Motivated patients with lower fibrosis and lower counts should be retreated
  - Relapsers
  - Strong IFN response
  - Pts who have not seen PegIFN

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 **HCV therapy in 2009 and beyond:**

- Tailoring treatment to individual patients:  
Shorter vs. extended programs
- **STAT-C (Specifically Targeted Antiviral Therapy for Hepatitis C)**

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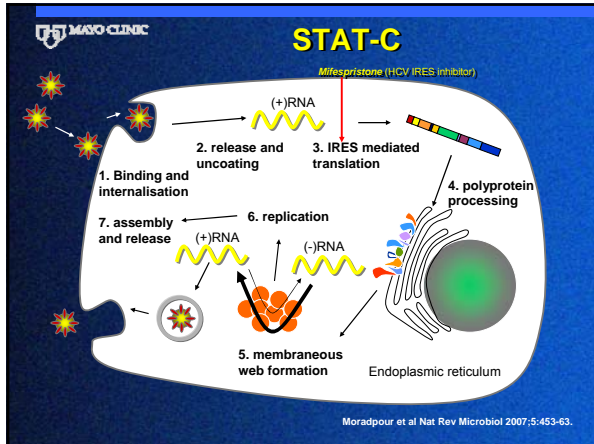
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# Treatment of Hepatitis C 2009: What Are the Options?




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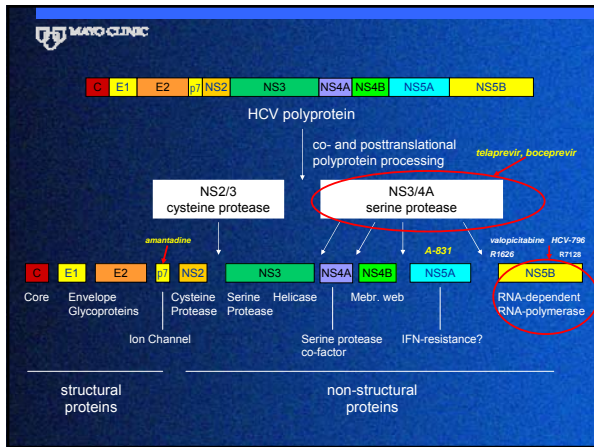
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**STAT-C**

- *Post Translational Processing Inhibitors*

**NS3/4A serine proteinase inhibitors**

TMC 435

ITMN 191 \*

VX-950 (telaprevir) \*

SCH-503034 (boceprevir) \*

ACH-806/GS-9132

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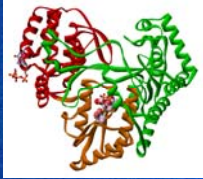
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# Treatment of Hepatitis C 2009: What Are the Options?

**STAT-C**

- HCV Replication Inhibitors
  - NS5B Polymerase inhibitors**
  - MK-0608
  - HCV-796 \*
  - R1626 \*
  - JTK-003
  - NM-283 (valopicitabine) \*
  - XTL 2125 \*
  - R7128 \***




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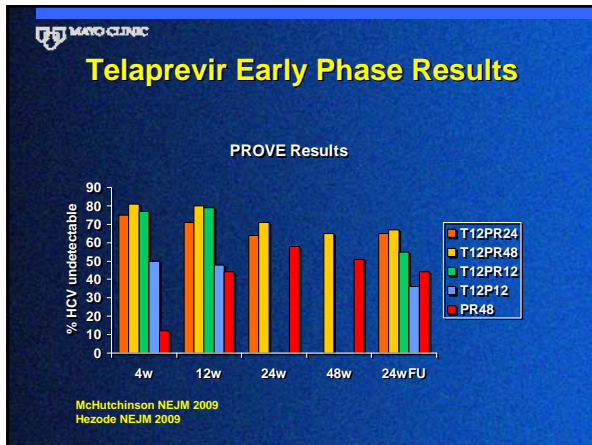
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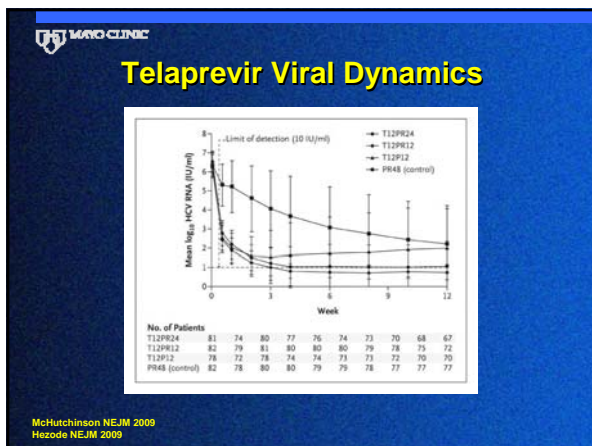
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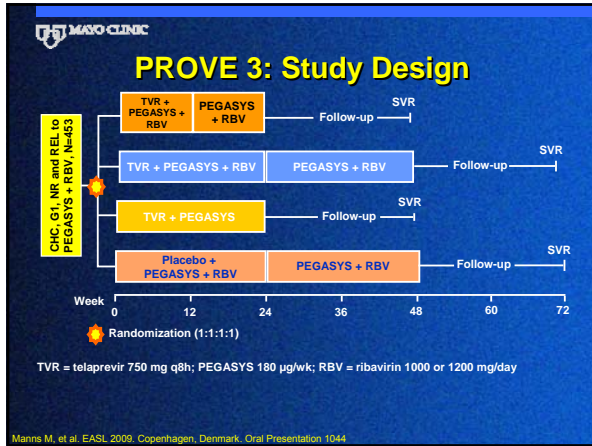
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# Treatment of Hepatitis C 2009: What Are the Options?




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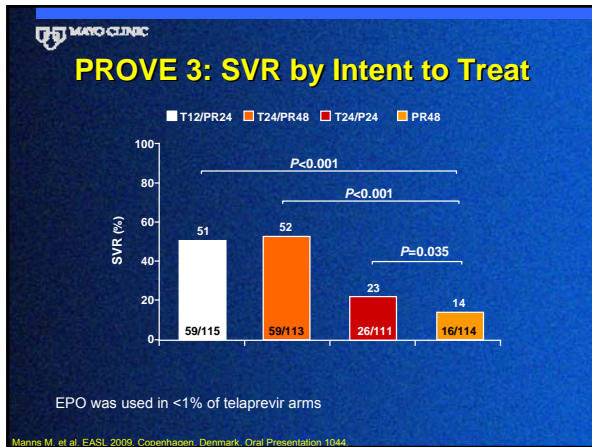
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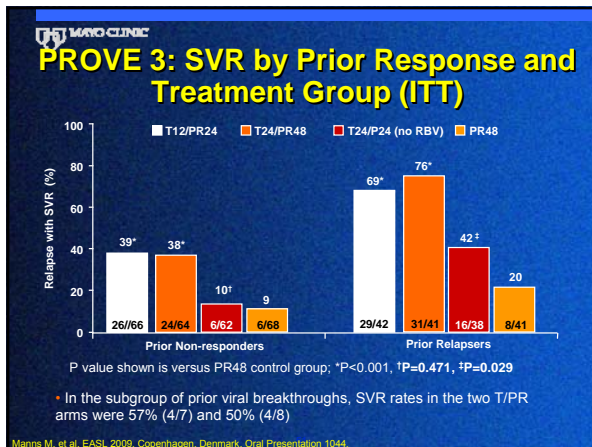
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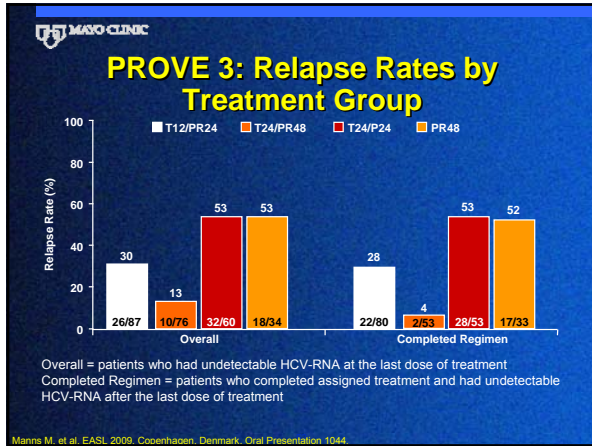
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# Treatment of Hepatitis C 2009: What Are the Options?




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- Telaprevir: Adverse Events**
- Rash present in 6-7% vs 3% in controls
  - Asthenia reported in 4% vs 1% in controls
  - 22 patients had viral breakthrough on TLV, 55% had NS3 mutations that rendered the virus resistant to TLV

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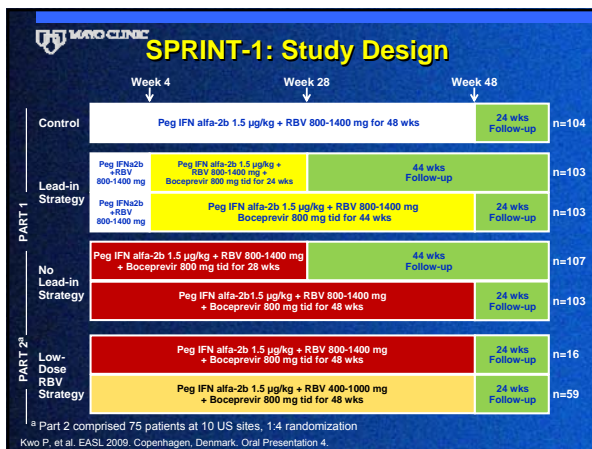
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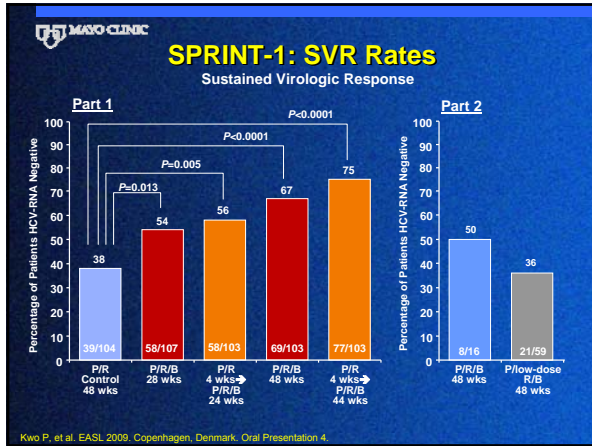
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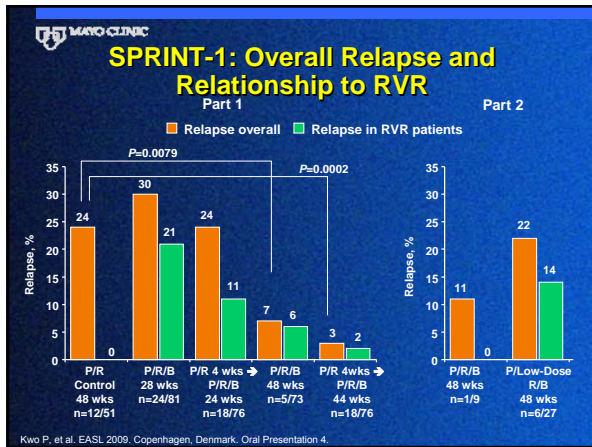
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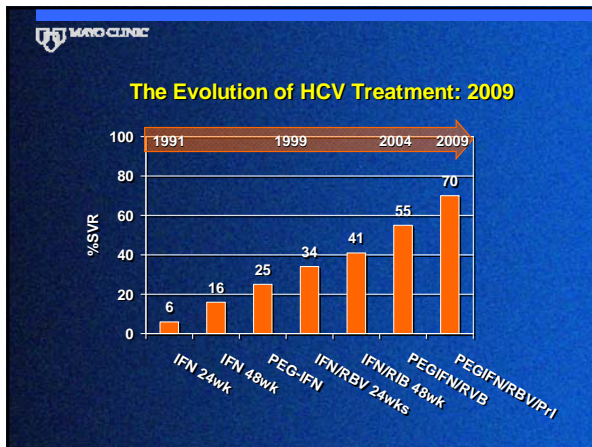
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