

How to optimize treatment of G1 naïve patients ?

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How to optimize treatment ?

- **Strategy 1**

- Treatment option with highest efficacy (SVR)
- Treatment option with the best cost-efficiency

- **Strategy 2**

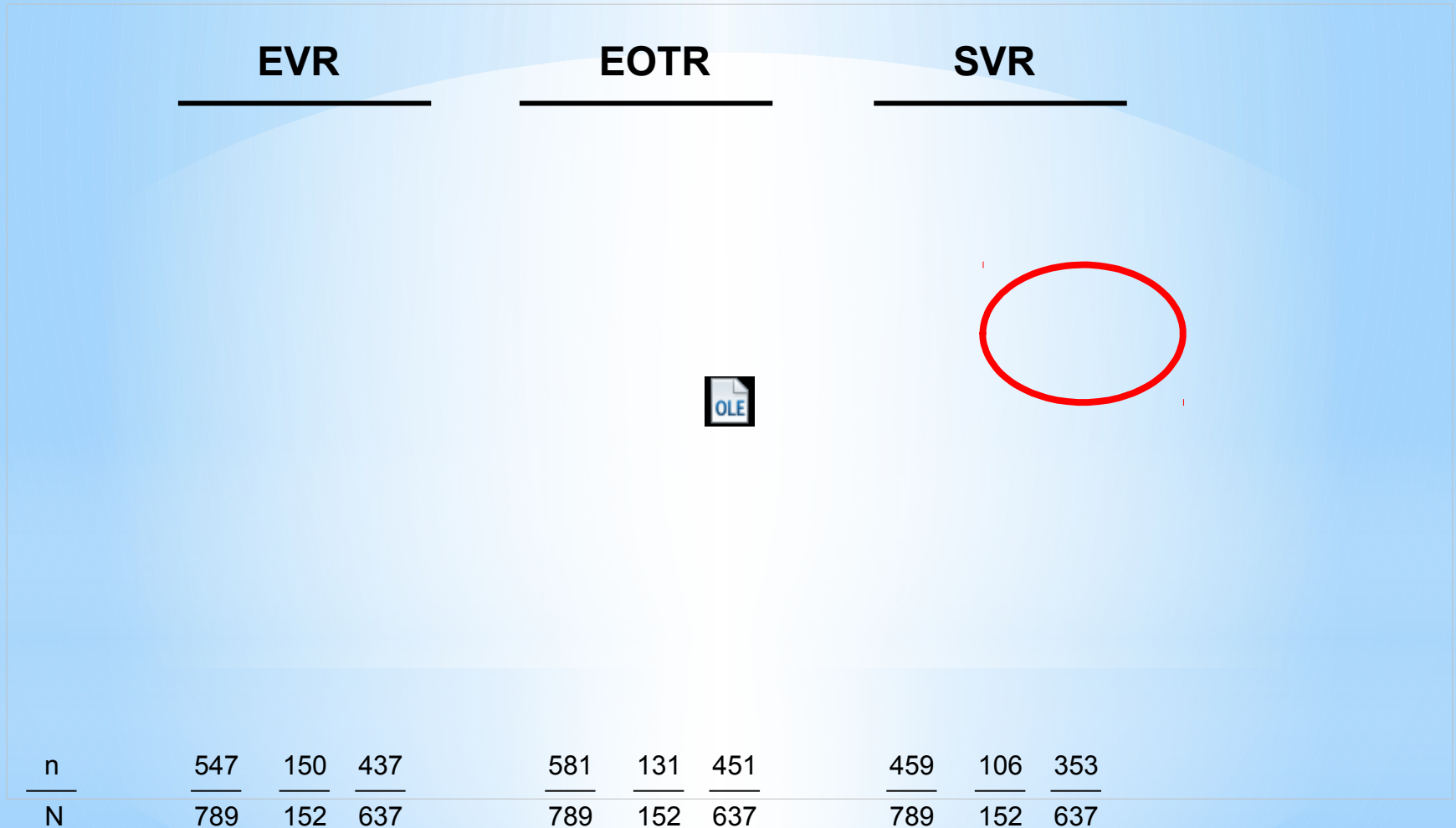
- Optimize efficacy of treatment option with lower efficacy (SVR)

Case report

- male, 54 yrs
- RF: appendectomy in 1978 (TRF not clear)
- ↑ ALT since 1984; max ALT 4xULN
- anti-HCV + 1994
 - GP: past infection
- 1998 Chronic HCV infection
 - HCV RNA positive (VL not known, serotype 1)
 - Liver biopsy - mild chronic hepatitis
 - Concomitant disease absent
 - SOC: rIFN+RBV
 - refused by patient due to fear of AE
- Regular Follow up
 - Annually Blood count, ALT, AST, AFP,
 - Abdominal Sonography
- 2005 DM type II.
 - metformine
- 2007 Central Military Hospital
 - Liver Biopsy G10 S3 (Ishak)
 - HCV RNA 1 650 000 IU/mL
 - HCV Genotype 1b
 - Anti-HBc pos./anti-HBs neg.
 - BMI 35.6 (120kg/183cm)
 - Alcohol intake 4x500mL beer (lager)
 - SOC: PEG-IFN + RBV
 - Married
 - 1 son, 23 years living abroad
 - Small private company

Responses to PEG-IFN α -2a + RBV

„Real life“ data, Central and Eastern Europe



Urbanek, P., Oltman, M., Ivanovski, L., et al. Efficacy and safety of peginterferon α -2a (40KD) plus ribavirin in treatment-naive chronic hepatitis C patients in Central and Eastern Europe. *European Journal of Gastroenterology and Hepatology*, 2011; 11:1004-1010.

Baseline predictors of response to PEG-IFN +RBV

Host related

- Age, Sex, Race

- Useful for advising patients on their likelihood of an SVR
- Most of them are fixed predictors
- No baseline predictor has sufficient negative predictive value to deny treatment

- Fatty liver

disease

- Fibrosis/cirrhosi

Virus related

- HCV genotype

Demografic predictors of SVR

Age	Nr. of pts.	Genotype	Single p value	Odds ratio	Therapy	Author
Younger age	1530	1-6	< 0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	<i>Manns et al. 2001</i>
<40 years	1744	1-6	0.005	1.4 (1.1.-1.9)	IFN/IFN 2b + RBV	<i>Poynard et al. 2000</i>
	1121	1-6	< 0.001	2.60 (1.72-3.95)	PEG IFN 2a+/-RBV/IFN 2b + RBV	<i>Fried et al. 2002</i>
< 45 vs. >45 years	1463	2,3	0.002	1.5 (1.17-1.93)	PEG IFN 2a + RBV	<i>Shiffman et al. 2007</i>
Body weight/BMI						
Lower weight	1530	1-6	<0.0001	No data	IFN 2b + RBV/PEG IFN 2b + RBV	<i>Manns et al. 2001</i>
< 75 kg	1121	1-6	0.002	1.91 (1.27-2.89)	PEG IFN 2a+/-RBV/IFN 2b + RBV	<i>Fried et al. 2002</i>
Lower BMI	455	1	<0.05	No data	PEG IFN 2a + RBV	<i>Berg et al. 2006</i>
< 80 kg vs. > 80 kg	1463	2,3	<0.001	1.75 (1.37-2.24)	PEG IFN 2a + RBV	<i>Shiffman et al. 2007</i>
Body weight	224	2,3	n.s.	No data	PEG IFN 2b + RBV	<i>Zeuzem et al. 2004</i>
	4913	1,2,3	n.s.	No data	PEG IFN 2b + RBV	<i>Jacobson et al., 2007</i>

Kau A, Vermehren J, Sarrazin C. Treatment predictors of a sustained virologic response in hepatitis B and C. J Hepatol, 2008; 49:634-651.

Modifiable pretreatment predictors

- **Body weight**
 - Weight loss if BMI > 30 prior treatment initiation
- **Substance abuse**
 - Treatment of drug or alcohol abuse prior to treatment initiation
- **Psychiatric disease**
 - Effective depression treatment

Berg T, et al. Gastroenterology 2006;130:1086-1097.

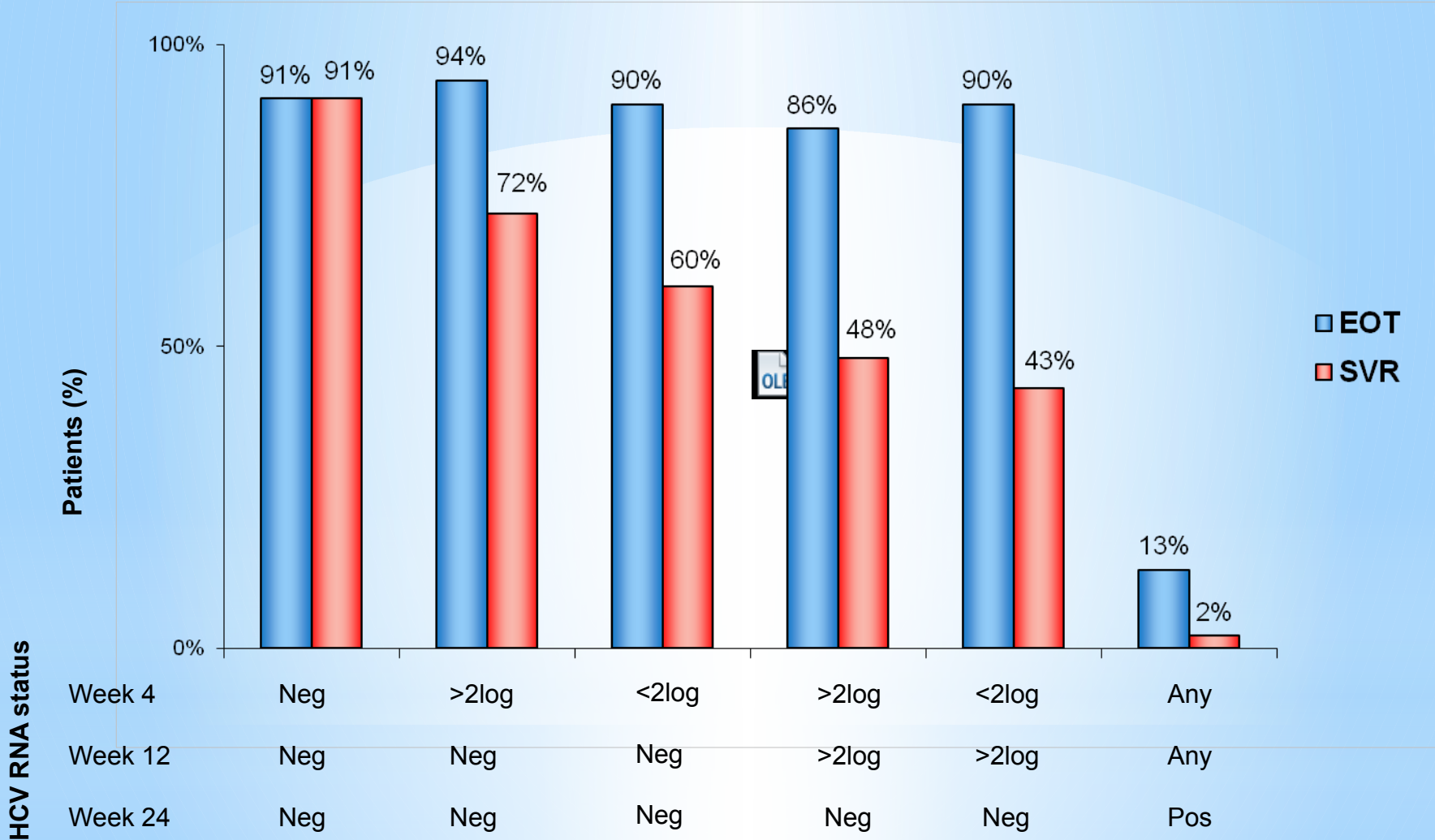


On treatment predictors of response to PEG-IFN + RBV

- **Type of viral response**
- **Adherence to therapy**



Viral kinetics allows to predict SVR



Ferenci P, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2α (40 KD)/ribavirin. *J Hepatol.* 2005; 43(3):425-33.

How to improve adherence to therapy ?

Patient preparation BEFORE treatment

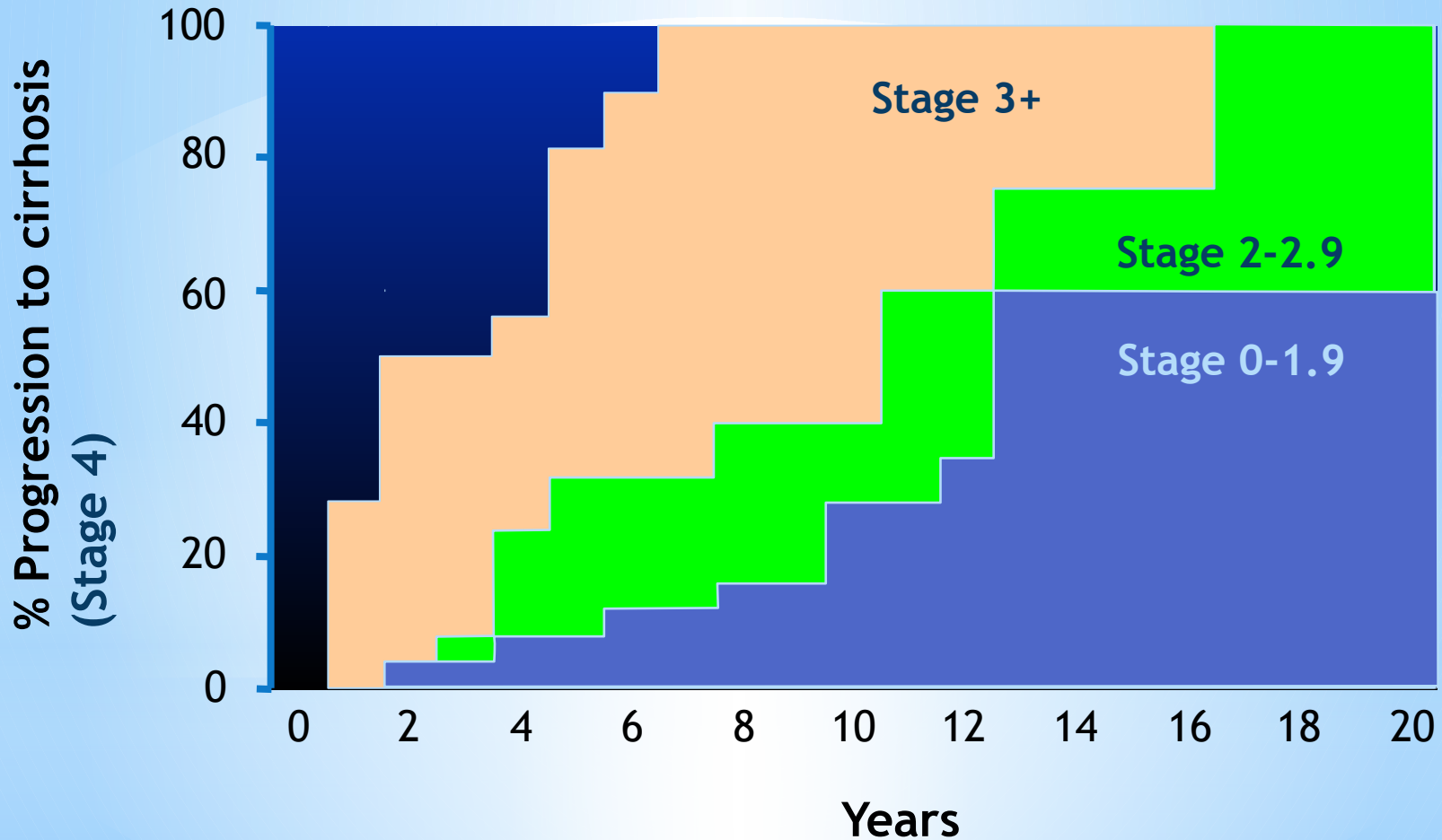
- Topics for discussion
 - Current stage of liver disease
 - Methods for liver disease severity assesment (liver biopsy vs. *non-invasive* procedures)
 - Prognosis
 - Need for effective contraception
 - Treatment options (currently available vs. upcoming combinations vs. clinical trials)
 - Predictors of response to therapy - likelihood of SVR
 - Importance of medication adherence, need for visits/lab follow-ups

- Methadon setting: more visits associated with higher SVR rate

- ADVERSE EVENTS MANAGEMENT during the therapy
- TIMING OF TREATMENT INITIATION
- Job and family - related issues

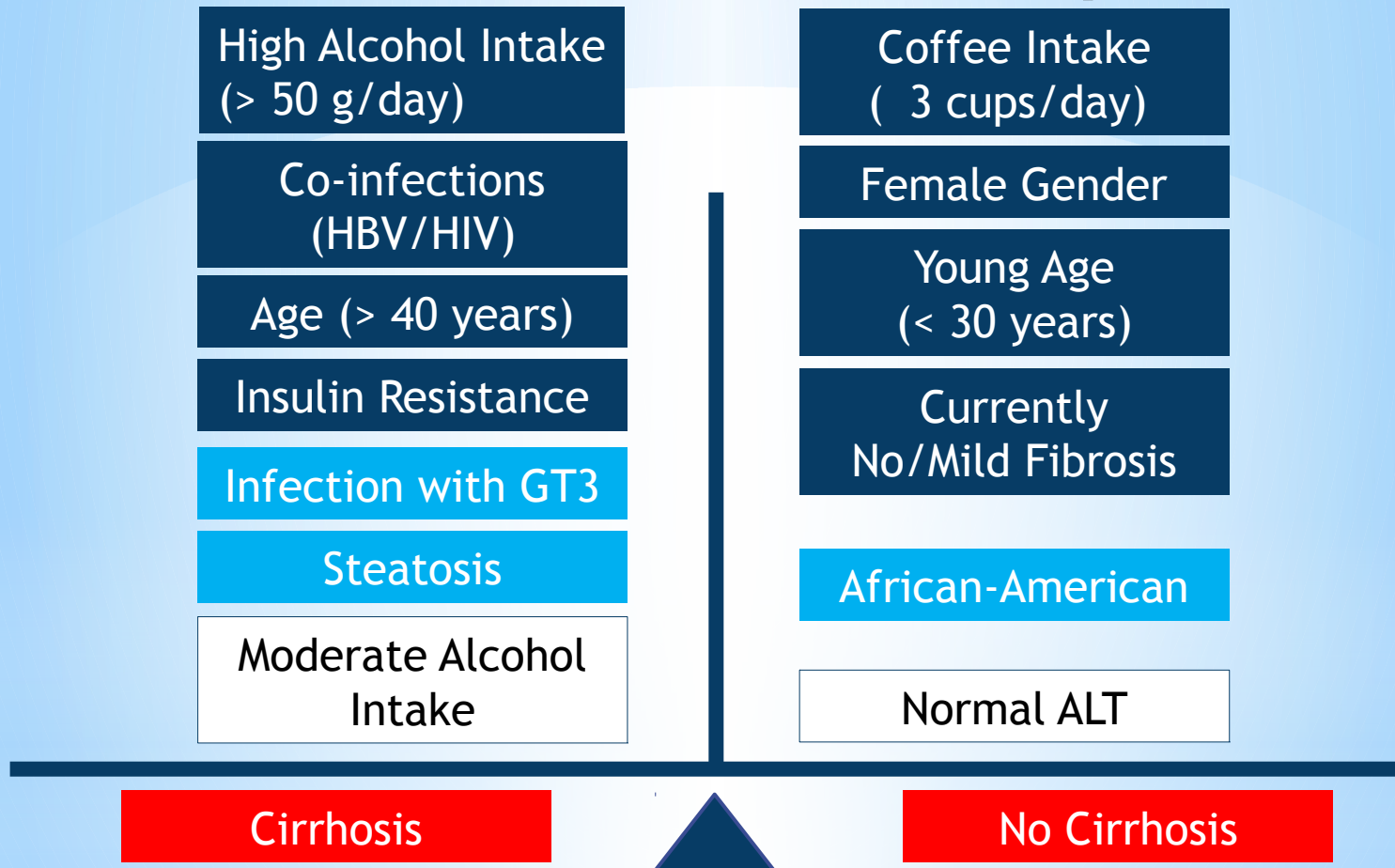


Prediction of liver disease progression based on initial liver histology



Yano, M., et. al. *Hepatology*, 1996; 23: 1334 - 1340

Factors that influence the progression to liver cirrhosis in chronic hepatitis C



■ Strong association

■ Likely associated

□ Further investigations needed

Maasoumy B, Wedemeyer H: *Best Practice & Research Clinical Gastroenterology*, 2012; 26:401-412

DM T2 and HCV

- * HCV is associated with higher incidence of DM T2 in persons >40yrs
 - OR for DM 3.77 (95% CI: 1.8.-7.87)

Mehta et al. Ann Intern Med, 2000; 133: 592-599

- * DM increases the risk of HCC development in HCV+ pts with advanced fibrosis
 - 5yrs incidence of HCC
 - DM : 11.3% (95% CI: 3.0-19.8)
 - No DM: 5.0% (95% CI:2.2-7.8)

Veldt et al. Hepatology 2008;47:1856-1862

Recommendations

1. To lose the weight (10-15%)
2. To initiate treatment

3 months later

1. Body weight 110 Kg (-10kg) BMI 32.8 (-2.8)
2. Antiviral therapy postponed by the patient's decision due to divorce proceedings

Next visit after 6 months

Patient returned after 4 years, june 2011

New situation, new parameters

- 2007 Central Military Hospital
 - Liver Biopsy G10 S3 (Ishak)
 - HCV RNA 1 650 000 IU/mL
 - HCV Genotype 1b
 - Anti-HBc positive/anti-HBs negative
 - BMI 35,6 (120kg/183cm)
 - SOC: PEG-IFN + RBV

 - Married
 - 1 son, 23 years living abroad
 - Small private company
- 2011 Central Military Hospital
 - Liver Biopsy not performed
 - Non-invasive methods routinely not available

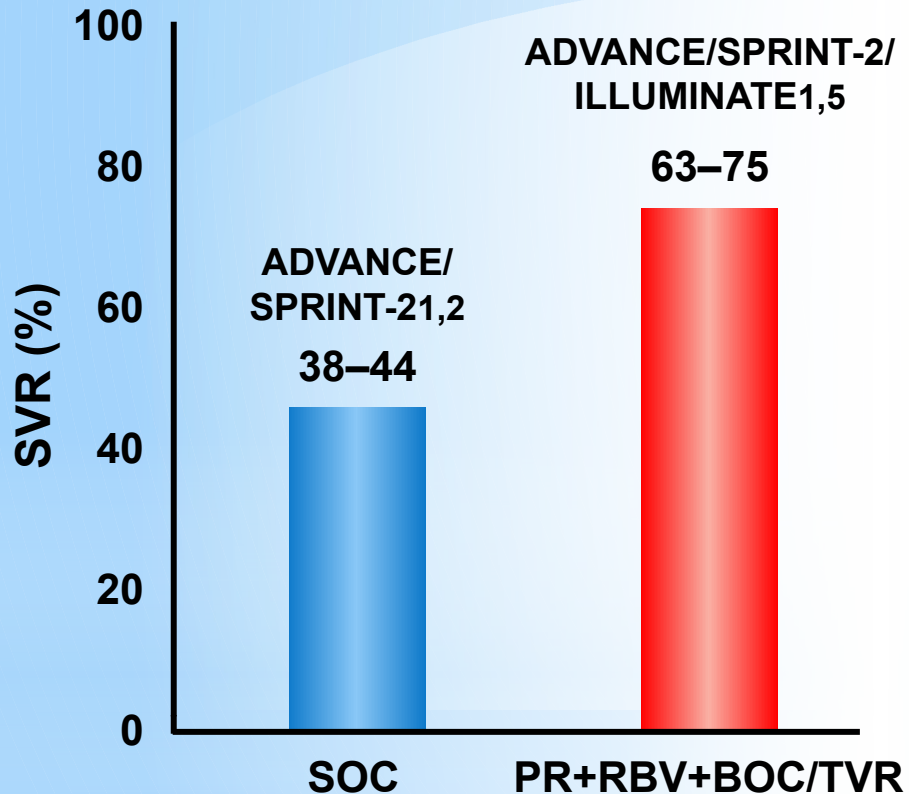
 - HCV RNA 1 300 000 IU/mL
 - HCV Genotype 1b
 - Anti-HBc positive/anti-HBs negative
 - BMI 29.9 (100kg/183cm)
 - rs12979860 IL28B CC

 - SOC: PEG-IFN + RBV
 - Clinical trials: 1 phase III study

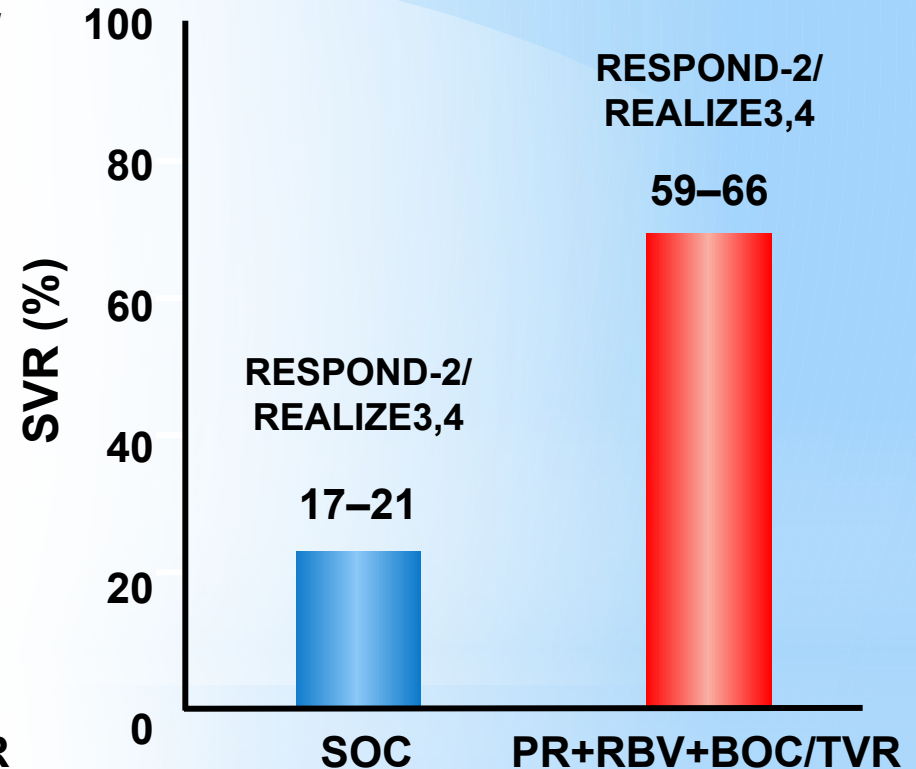
 - Recently married
 - 1 kid / 6 months
 - New stable and perspective job
 - Position: Head of department – 20 people

PEG-IFN + RBV + BOC/TVR

Naïve patients



Non responders



1. Poordad F, et al. *N Engl J Med.* 2011;364:1195-1206.
2. Bacon BR, et al. *N Engl J Med.* 2011;364:1207-1217.
3. Jacobson IM, et al. *N Engl J Med.* 2011;364:2405-2416.

4. Sherman KE, et al. 2010 AASLD. Abstract LB2.
5. Zeuzem S, et al. *N Engl J Med.* 2011;364:2417-2428.

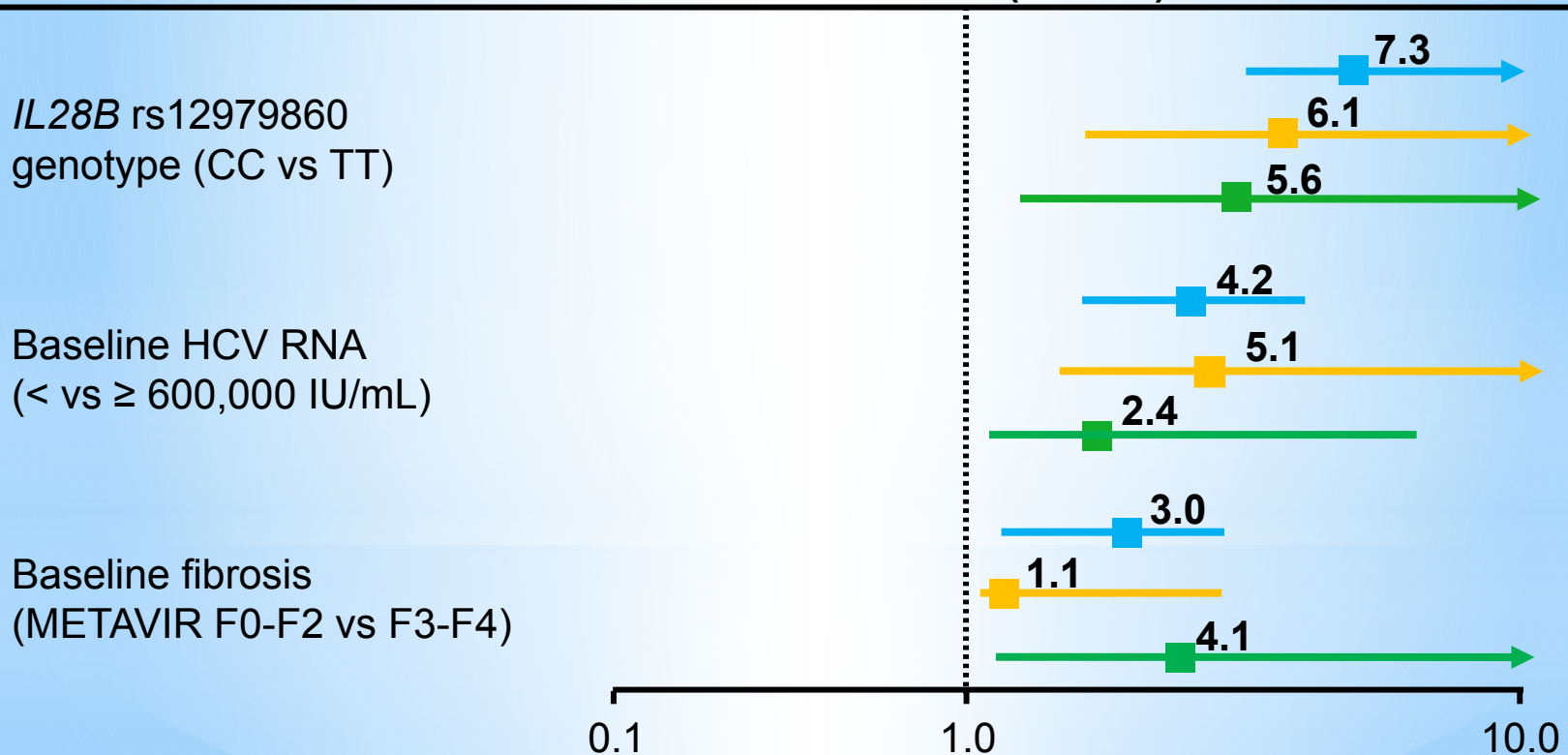
IL28B (rs12979860) Genotype as Predictor of SVR

PEG-IFN + RBV, G1 HCV

■ Whites (n = 871)
 ■ Blacks (n = 191)
 ■ Hispanics (n = 75)

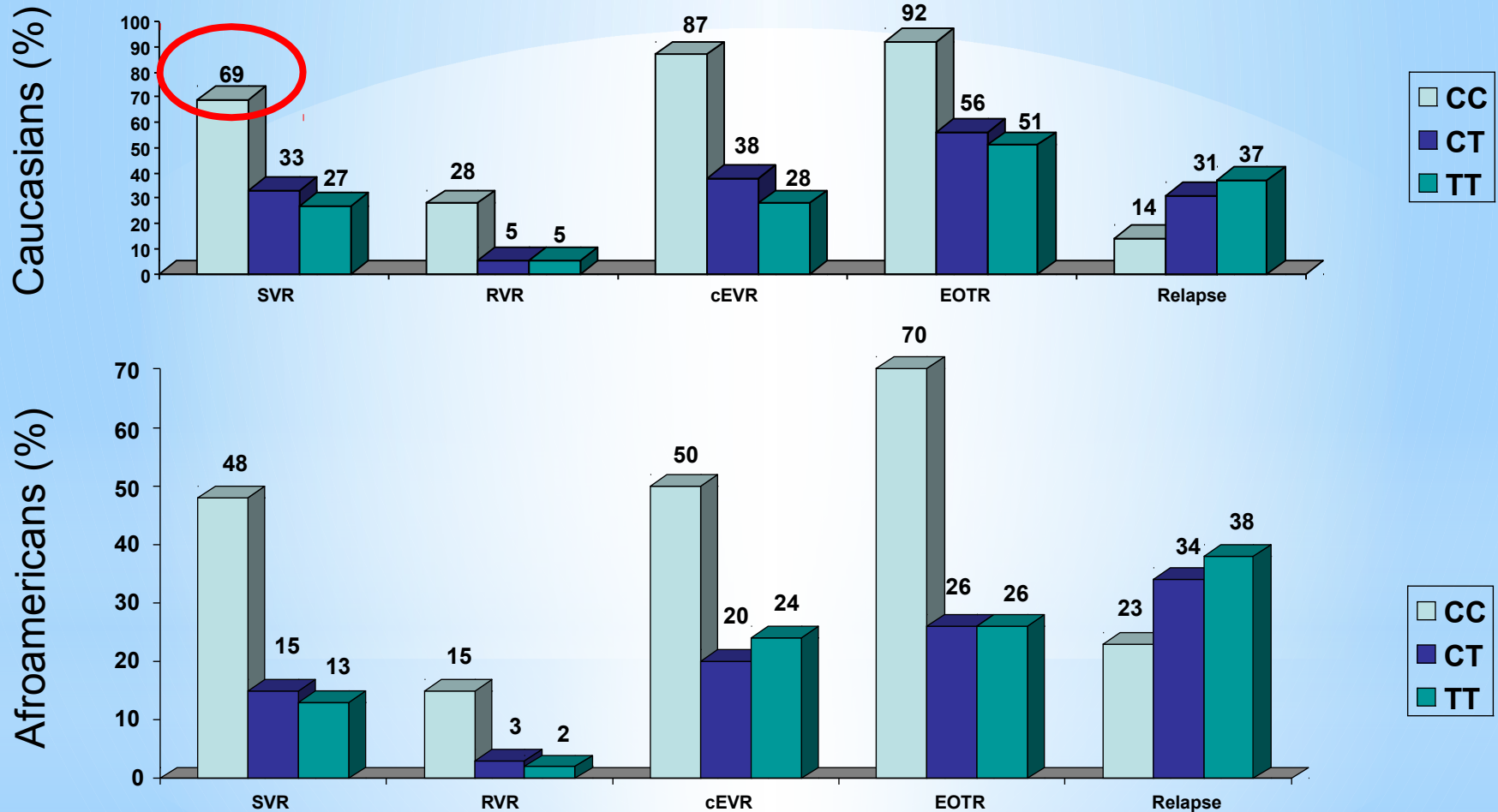
Factor Associated With SVR

Odds Ratio (95% CI)



Ge D, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009;461:399-401.

IL28B (rs12979860) genotype is associated with early viral response to PEG-IFN + RBV



Thompson AJ, et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology*, 2010; 139(1):120-129

Higher Adherence is Associated with Higher SVR Rate

- Adherence to therapy demonstrates higher SVR when patient
 - Takes 80% of the prescribed IFN dose
 - Takes 80% of the prescribed RBV dose
 - Completes 80% the prescribed duration of therapy
 - Quality of life may determine patient adherence

McHutchison JG, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. 2002;123:1061-1069.

Patient's Decision

- Initiate antiviral treatment ASAP
 - Standard of care
 - PEG-IFNalpha2a 180 μ g weekly + RBV 1200mg daily

How to improve adherence to therapy ?

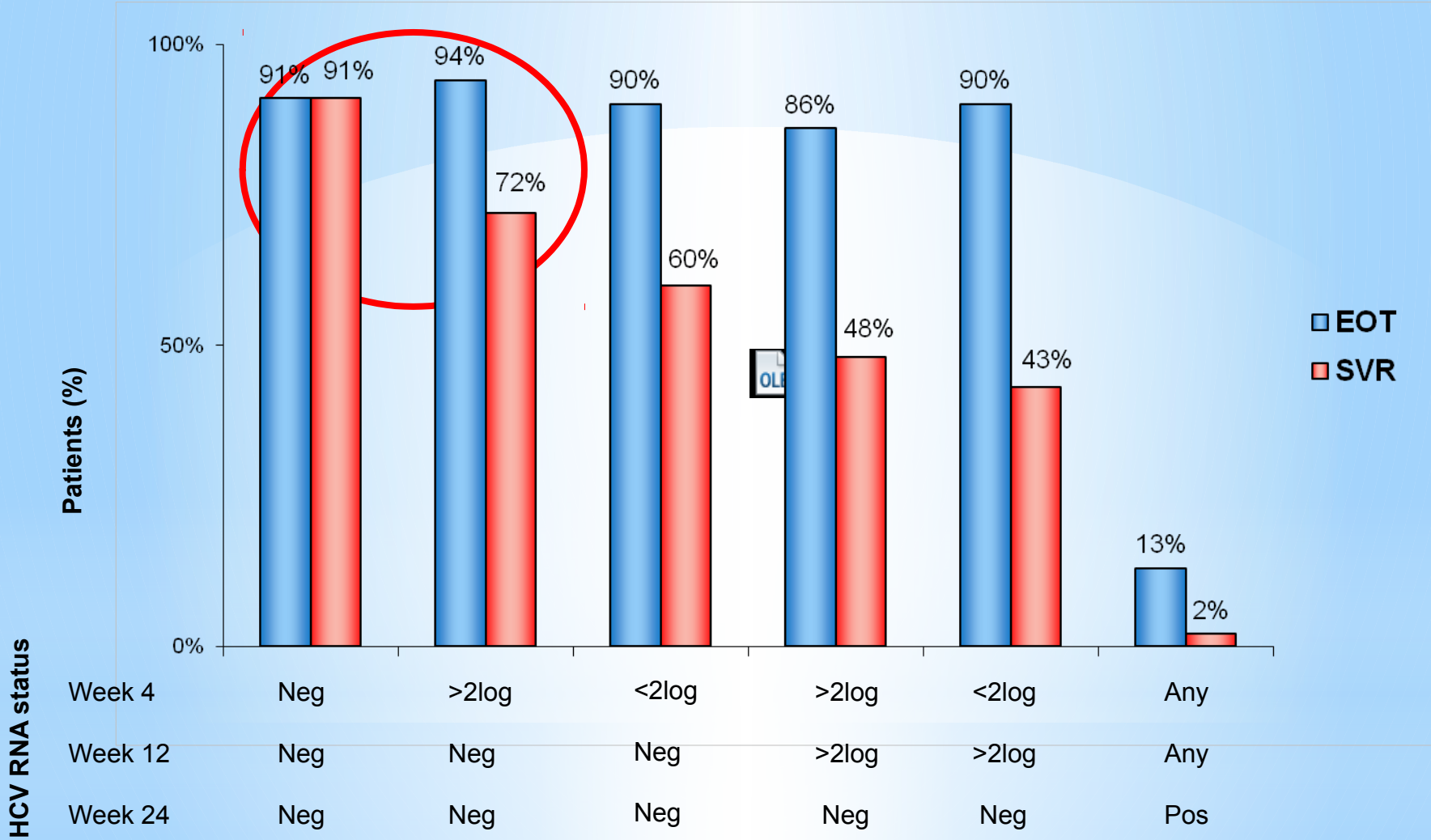
Patient management DURING treatment

- Topics for discussion
 - Viral response
 - Side effects, adverse reactions
 - Active search for EA
 - Preparation for EA development in time manner
 - ADVERSE EVENTS MANAGEMENT during the therapy
 - Enhance patient 's motivation
 - Discuss type of viral response
 - Response Guided Therapy

Viral response

	Day 0	Week 2	Week 4	Week 8	Week12	Week 24	Week 48	FU 24
HCV RNA (IU/mL)	1650000	3100	80	Negative				
log	6,22	3,49	1,9					
Δ log		2,73	4,32					

Viral kinetics allows to predict SVR



Ferenci P, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2 α (40 KD)/ribavirin. *J Hepatol.* 2005; 43(3):425-33.

More precise prediction ?

Christensen PB; Krarup HB; Laursen AL; Madsen PH; Pedersen C;
Schlichting P; Orholm M; Ring-Larsen H; Bukh J; Krogsgaard K

Negative HCV-RNA 2 weeks after

**initiation of treatment predicts sustained virological response to
pegylated interferon alfa-2a and ribavirin in patients with chronic
hepatitis C.**

Scand J Gastroenterol 2012 Sep;47(8-9):1115-9

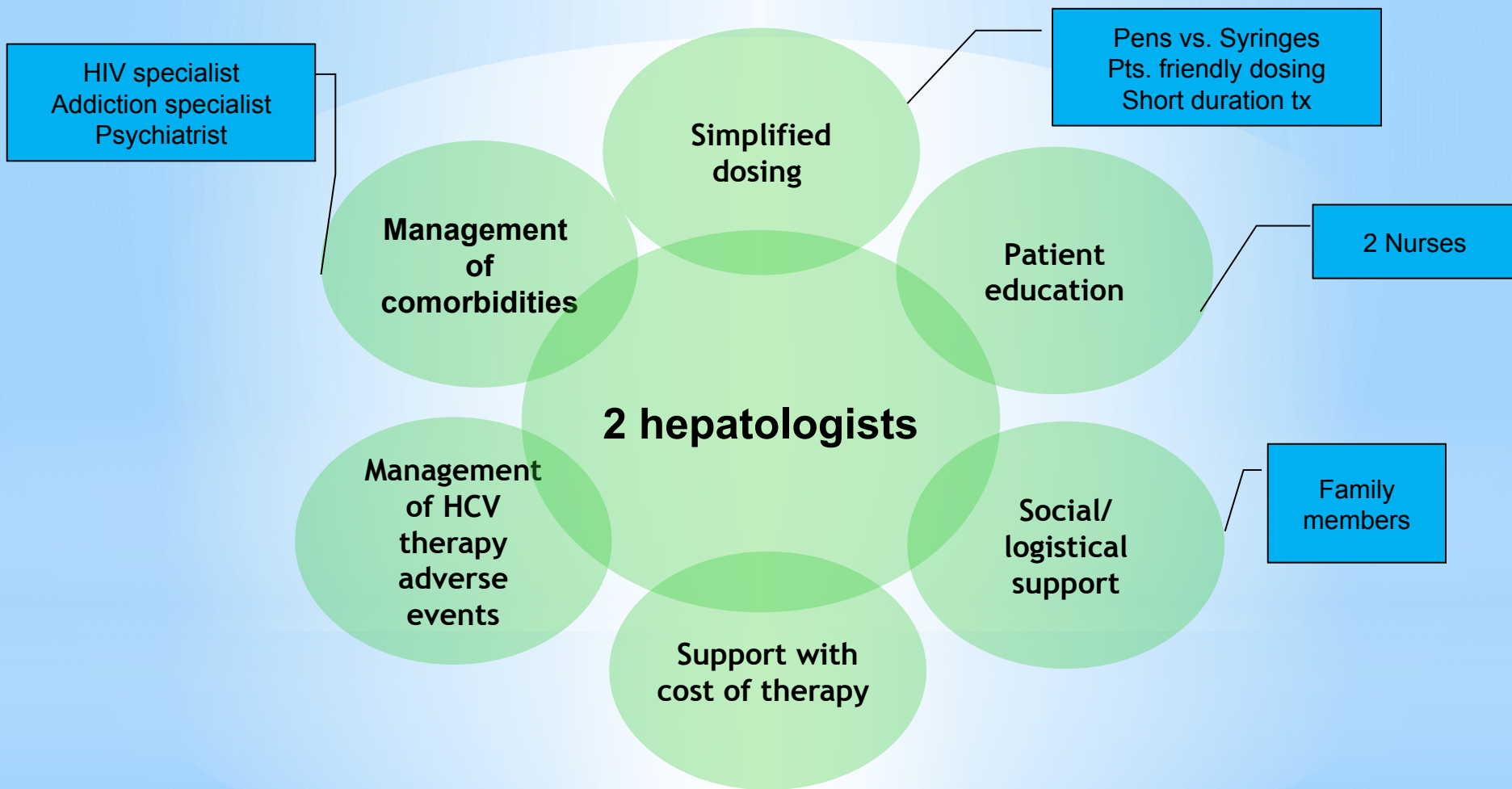
Week 1	HCV RNA < 1000 IU/mL	SVR 93%
Week 1	$\Delta\log < 1$	SVR 75%
Week 2	HCV RNA negative	SVR 100%

Viral response

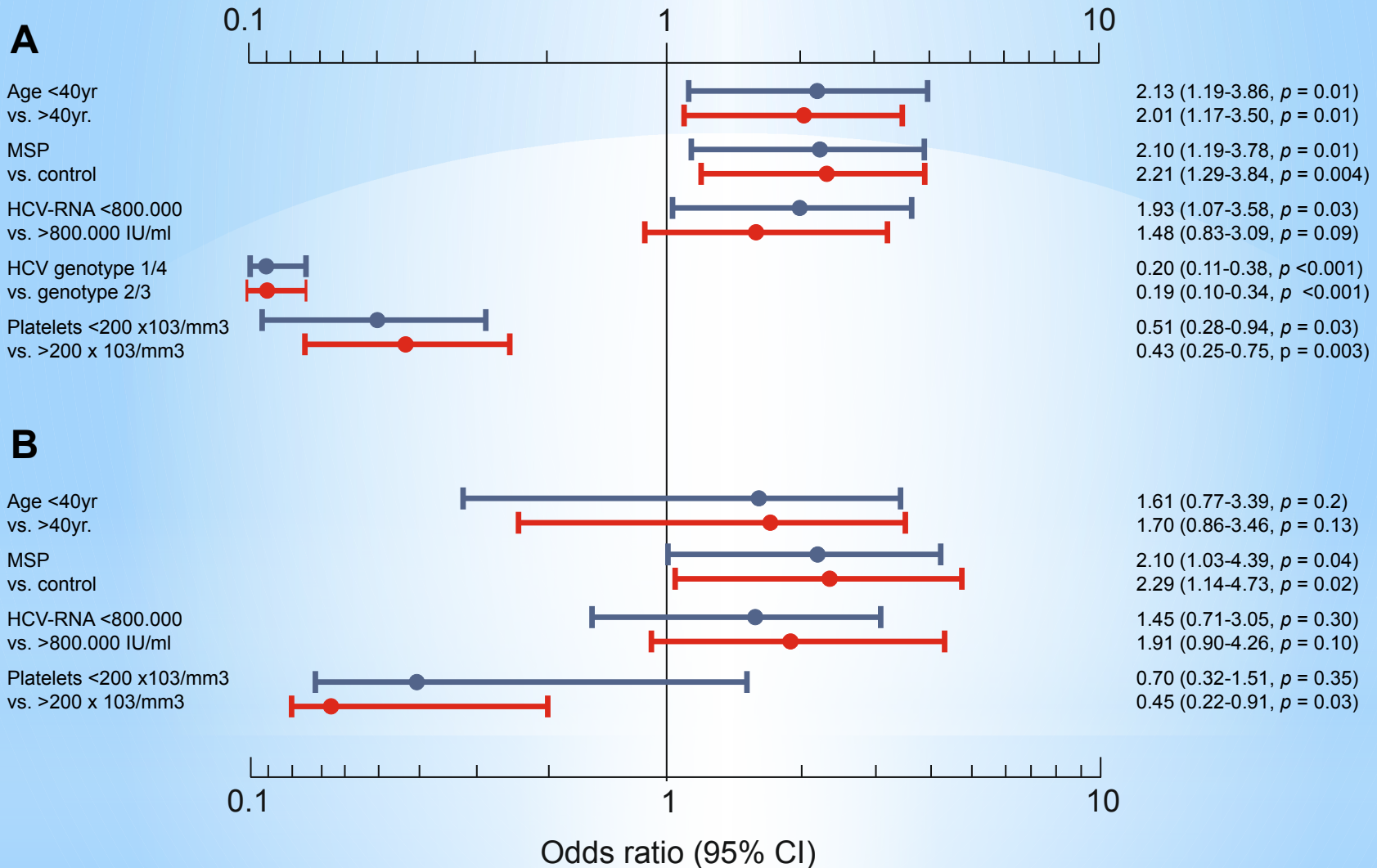
SVR

	Day 0	Week 2	Week 4	Week 8	Week12	Week 24	Week 48	FU 24
HCV RNA (IU/mL)	1650000	3100	80	Negative	Negative	Negative	Negative	negative
log	6,22	3,49	1,9					
Δ log		2,73	4,32					

A Multimodal Approach Central Military Hospital

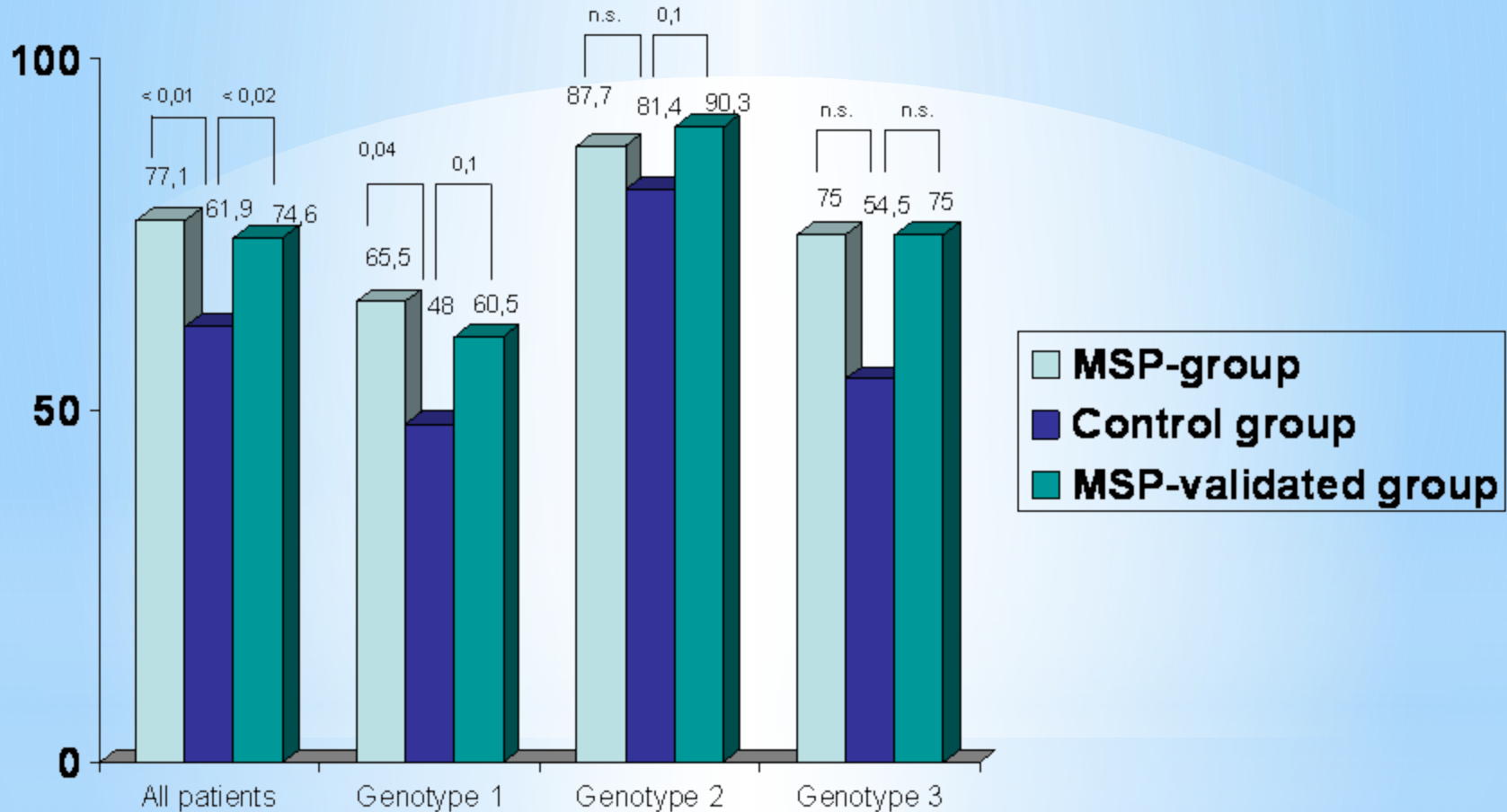


Multidisciplinary Support Programme



Carrion JA, et al. A multidisciplinary support programme increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. *Journal of Hepatology*, 2013; 59(5): p. 926-933

Multidisciplinary Support Programme



Carrión JA, et al. A multidisciplinary support programme increases the efficiency of pegylated interferon alfa-2a and ribavirin in hepatitis C. *Journal of Hepatology*, 2013; 59(5): p. 926-933

Summary

- * Time may be not only the negative factor
 - New treatment options with higher SVR rate
 - Better prediction based on new parameters
- * Adherence to treatment plays a key role for the treatment succes
 - Close detailed discussion with pt
 - Multimodal approach, multidisciplinary team