Update on hepatitis C: treatment and care and future directions

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Hepatitis C update

- Liver disease progression
- Staging of liver disease
- Current therapeutic issues
- Future directions in therapy

Hepatitis C natural history

Determinants of liver disease progression

Prior evidence

- ALT level
- Alcohol intake
- Age at infection
- Co-infection (HIV or HBV)
- Gender
- Stage of fibrosis

New evidence

- Obesity/hepatic steatosis
- Smoking
- Cannabis

No/limited evidence

- HCV genotype
- HCV viral load

Hepatitis C liver disease staging

Methods

- Clinical examination
- Serum transaminases (ALT, AST)
  - Poor correlation with fibrosis
  - Normal in 25% (of whom 30-35% progress to significant fibrosis)
- Surrogate markers
  - Albumin, prothrombin time, bilirubin
- Liver biopsy (current gold standard)

Hepatitis C liver disease staging

Cause

Viral - HBV and HCV

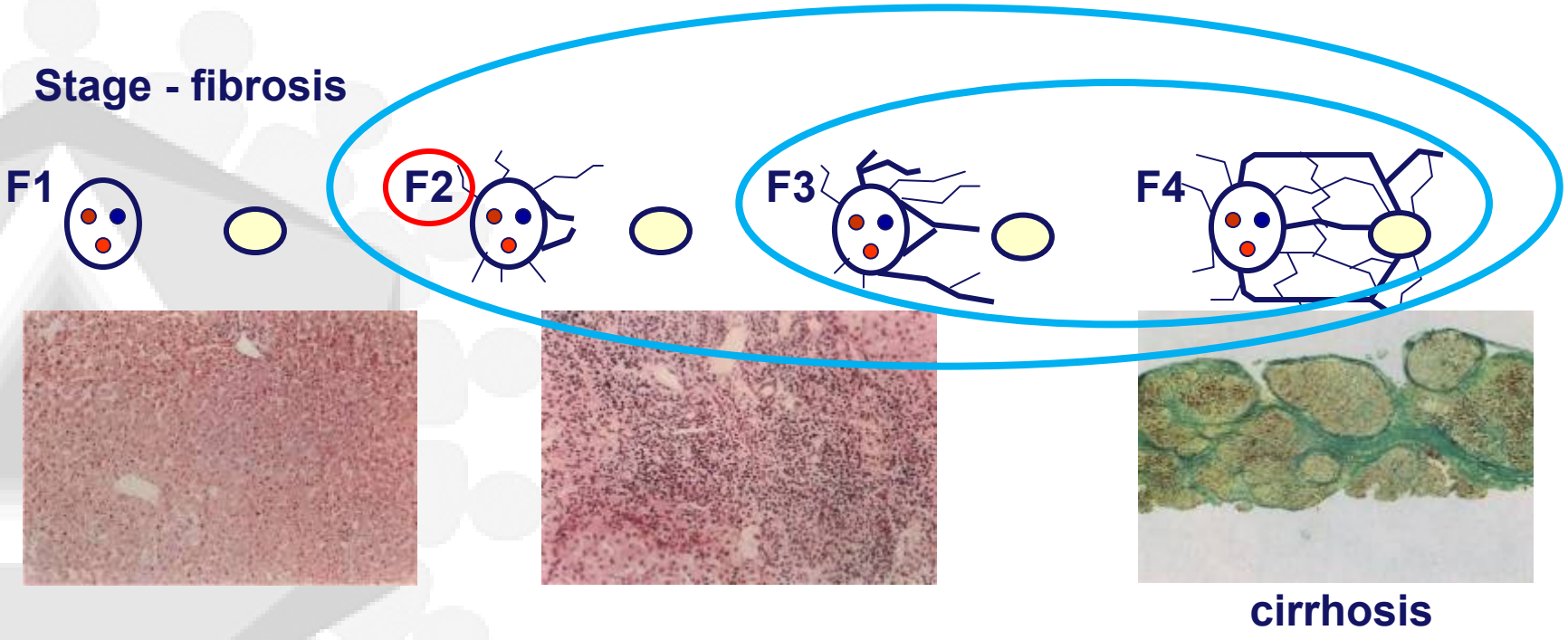
Immune - Autoimmune, PBC, PSC

Toxic - Alcohol

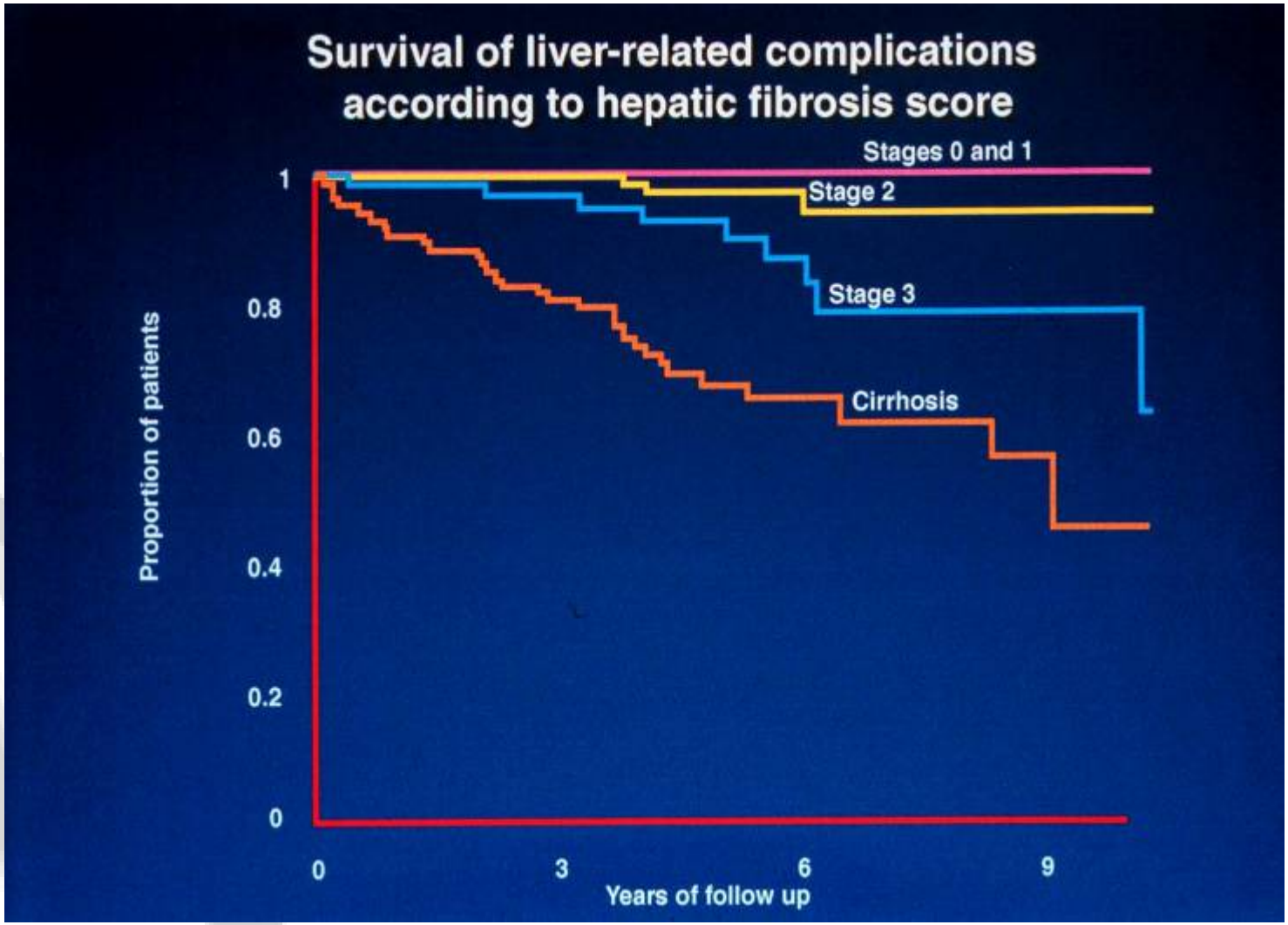
Metabolic - Nonalcoholic fatty liver disease (NAFLD)

Genetic - Haemochromatosis

Stage - fibrosis



Hepatitis C liver disease staging



Hepatitis C liver disease staging

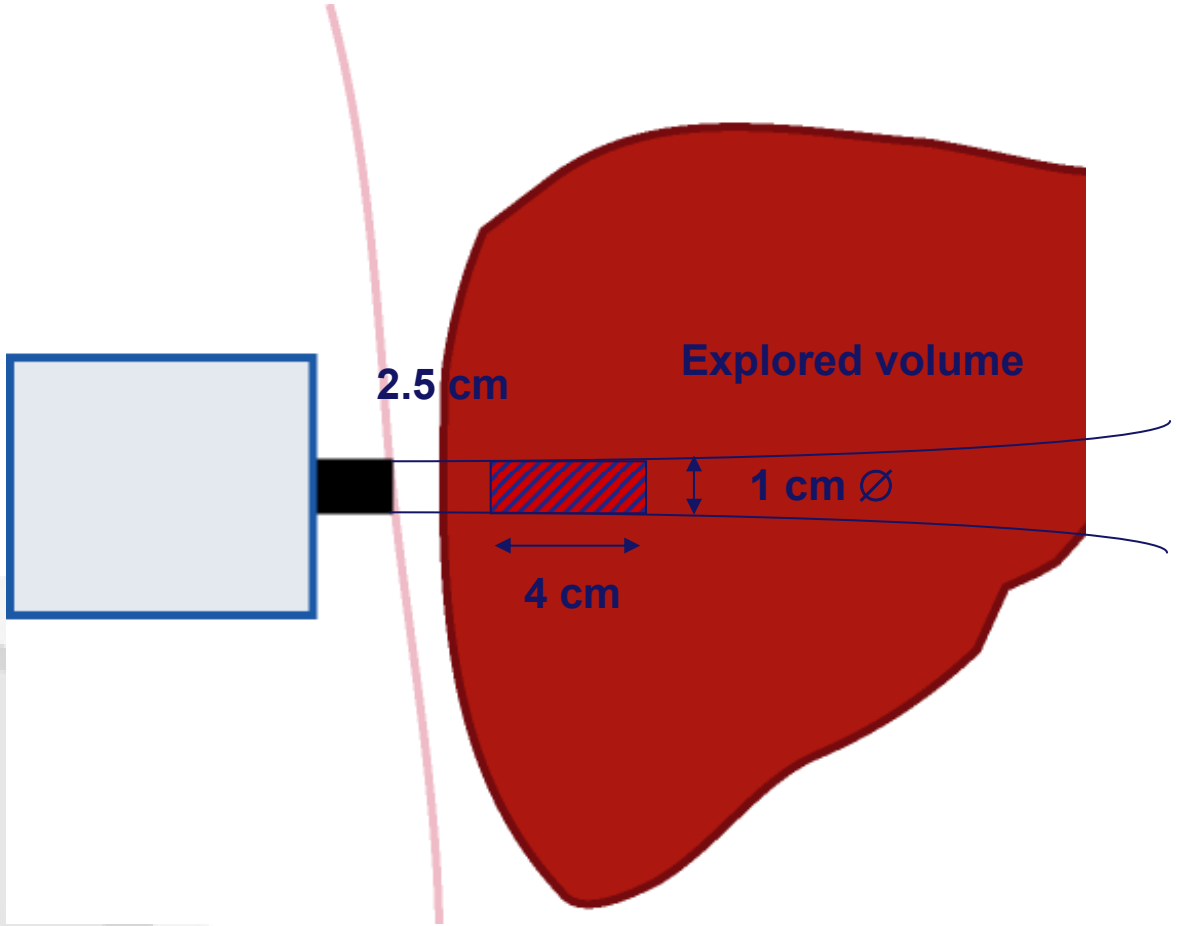
Alternative methods

- **Biochemical surrogate markers**
  - **APRI (AST/platelet ratio)**
  - **FIB-4 (age, AST, platelet, bilirubin)**
  - **Fibrotest**
  - **Hepascore**

- **Transient Elastography (Fibroscan)**

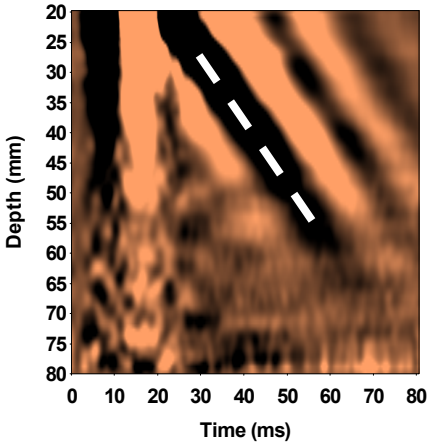
Hepatitis C liver disease staging: fibroscan

Hepatitis C liver disease staging: fibroscan



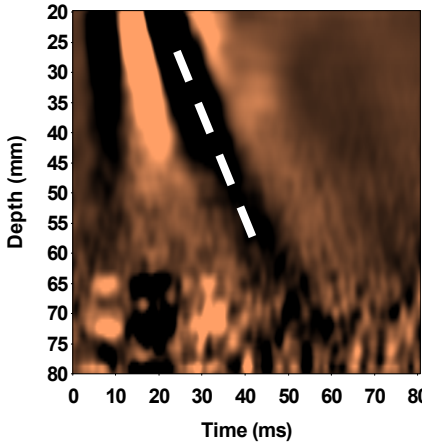
Hepatitis C liver disease staging: fibroscan

Range 2.5 kPa – 75 kPa



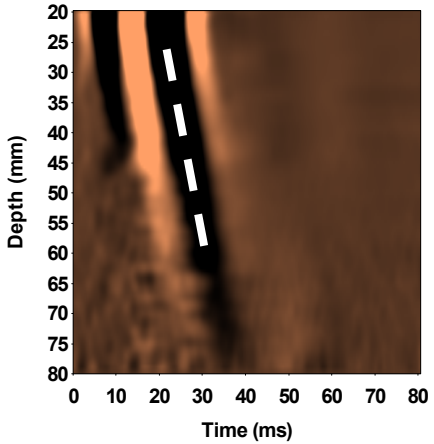
V_S = 1.1 m/s

E ~ 3 kPa



V_S = 1.6 m/s

E ~ 8 kPa



V_S = 3.0 m/s

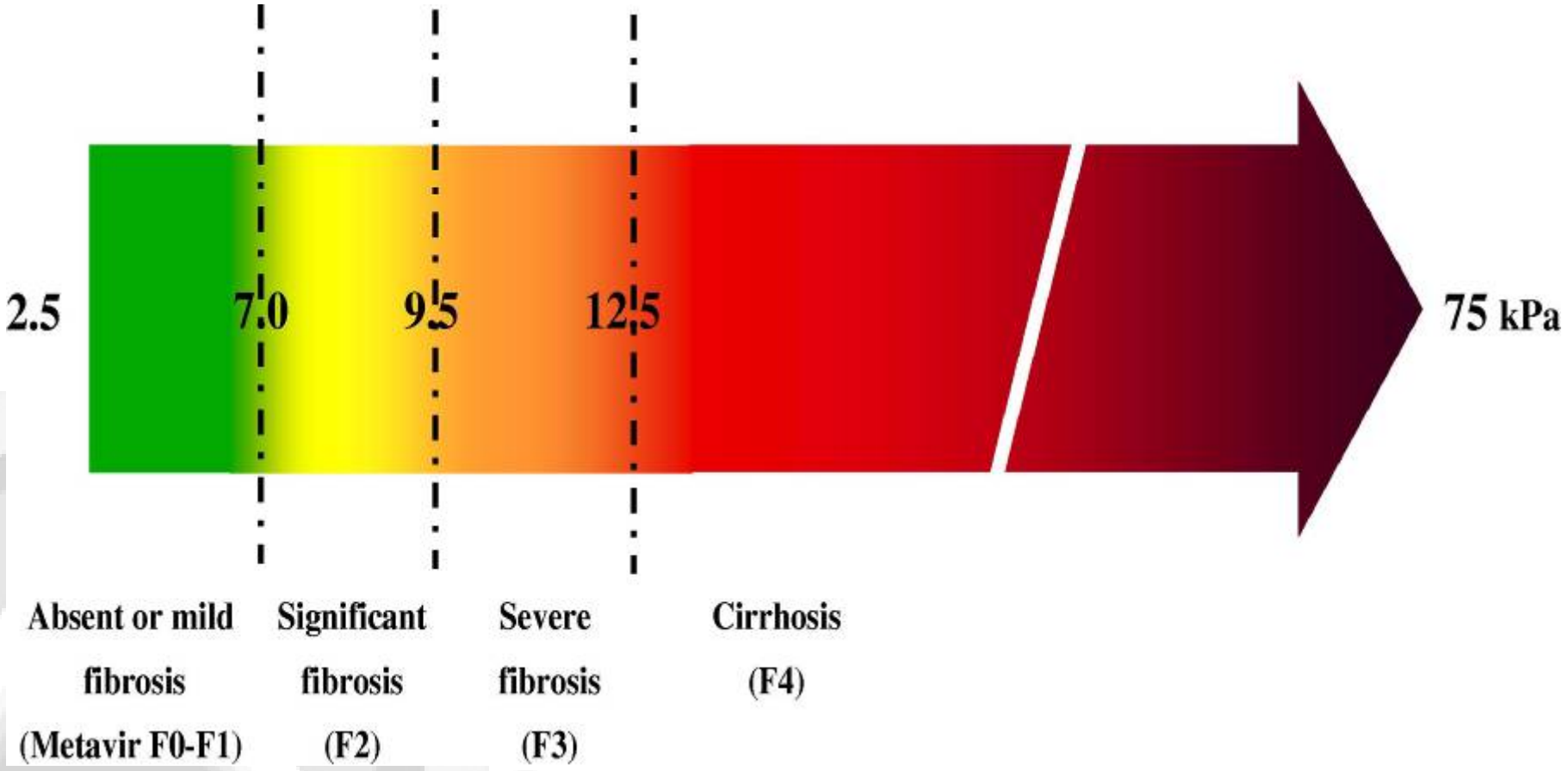
E ~ 27 kPa

F0 F1 F2 F3 F4

Multiple measurements : success rate should be at least 60%

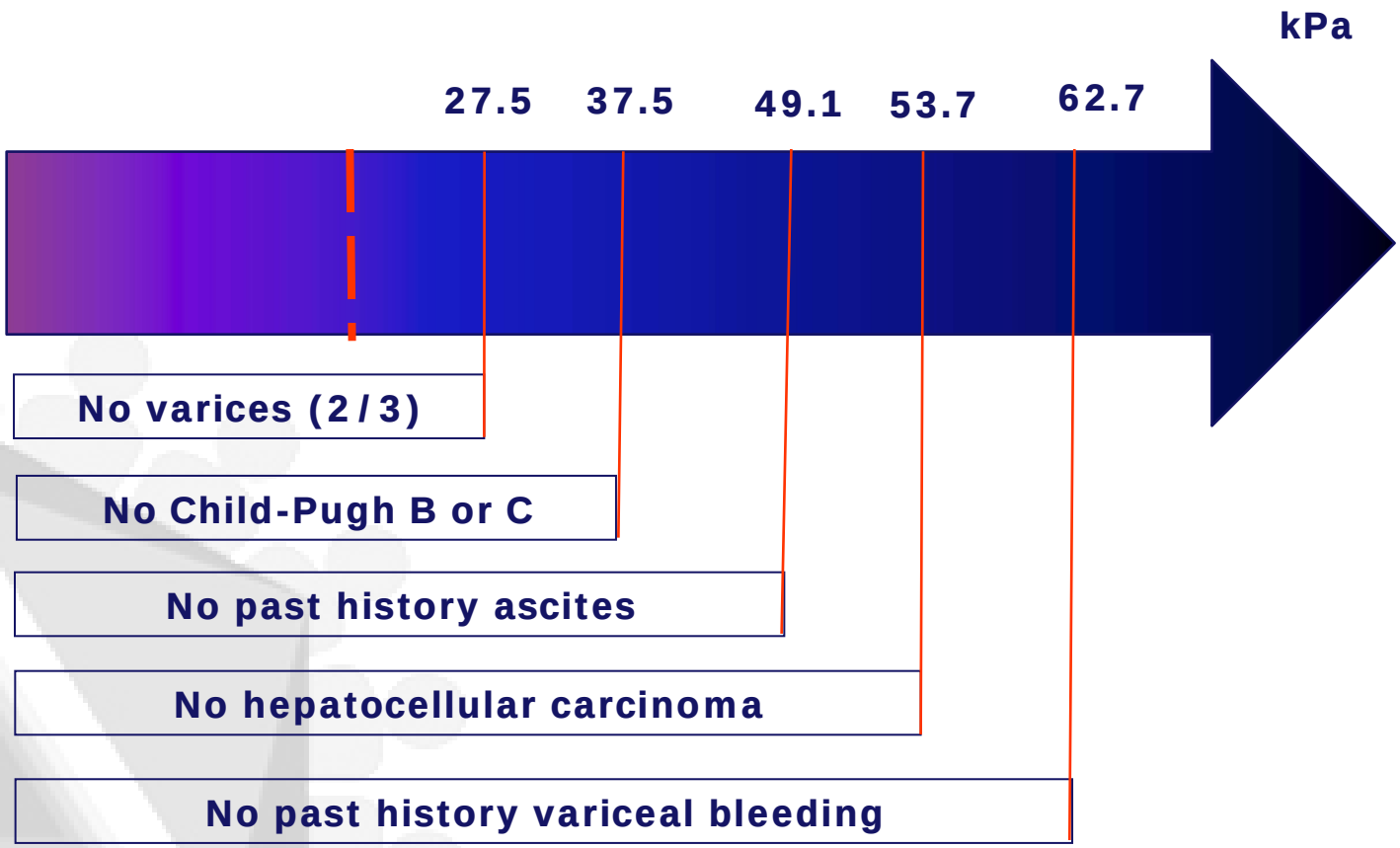
IQR should not be >30% of median value

Hepatitis C liver disease staging: fibroscan



Hepatitis C liver disease staging: fibroscan

711 subjects – 95 with cirrhosis

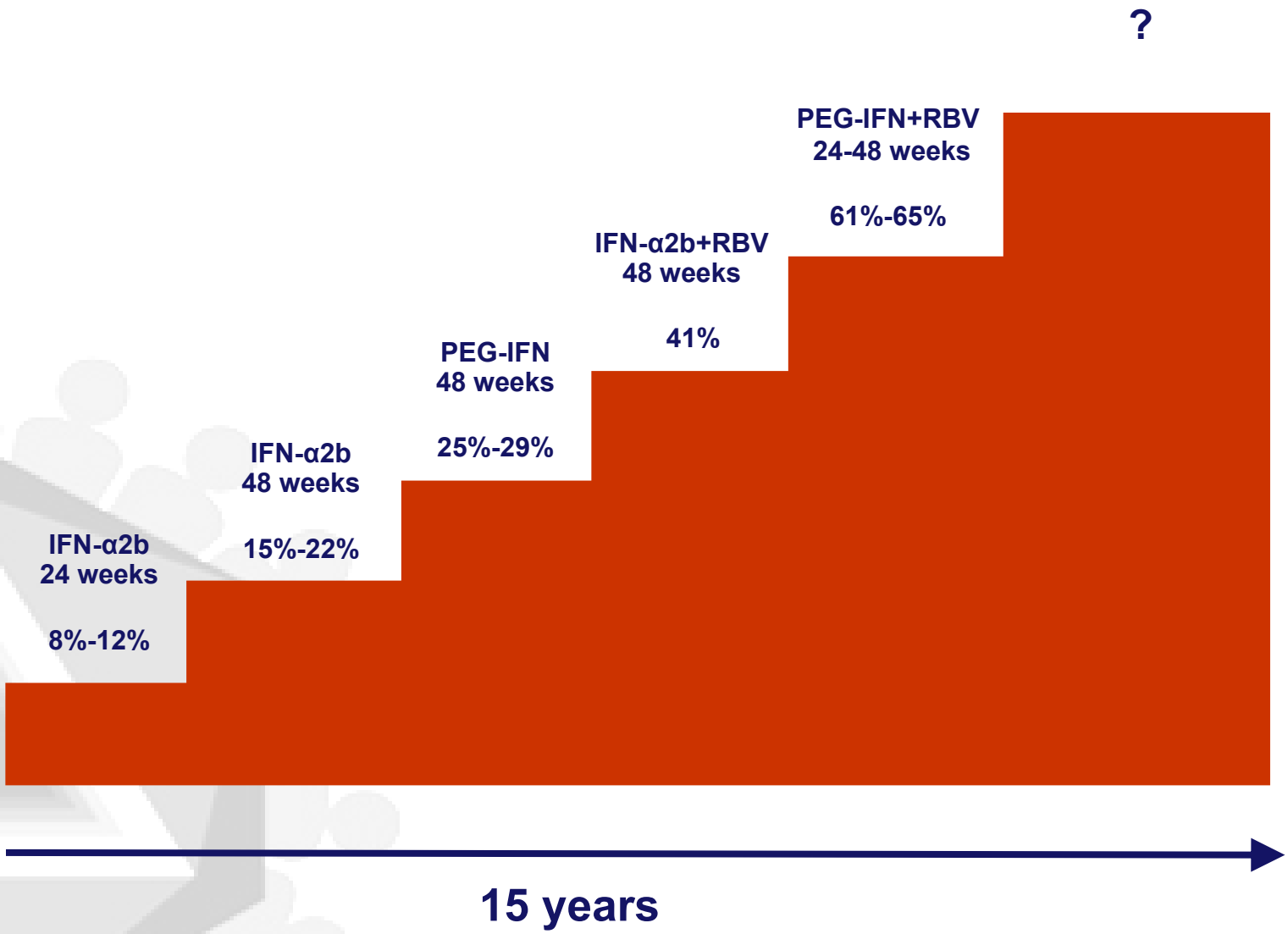


>90% NPV for above complications

Foucher et al 2006

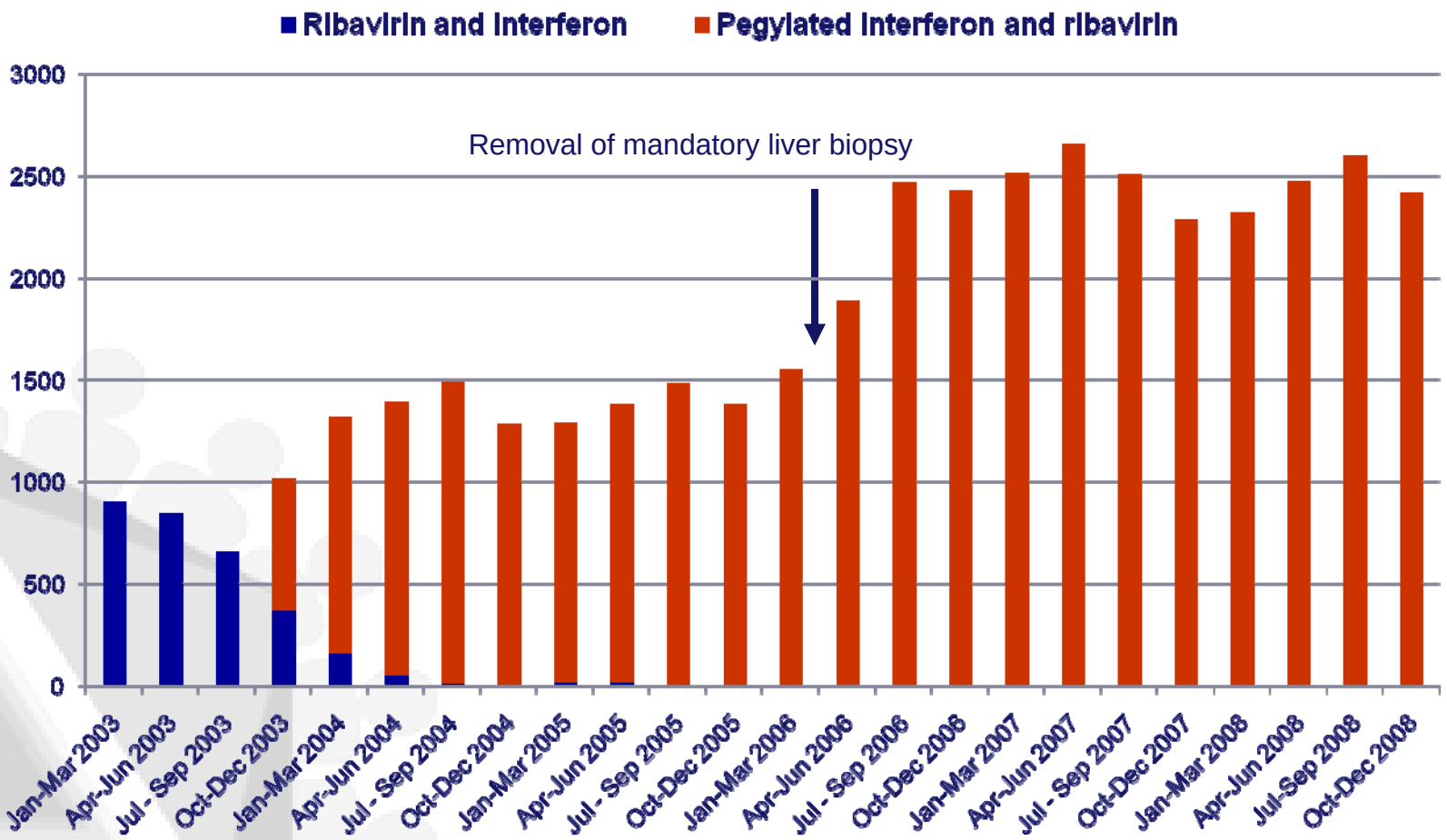
Hepatitis C treatment

Sustained Virological Response



Hepatitis C treatment

HCV treatment through HSD: 2003 – 2008



NCHECR 2009

Hepatitis C treatment

Issues

Positive

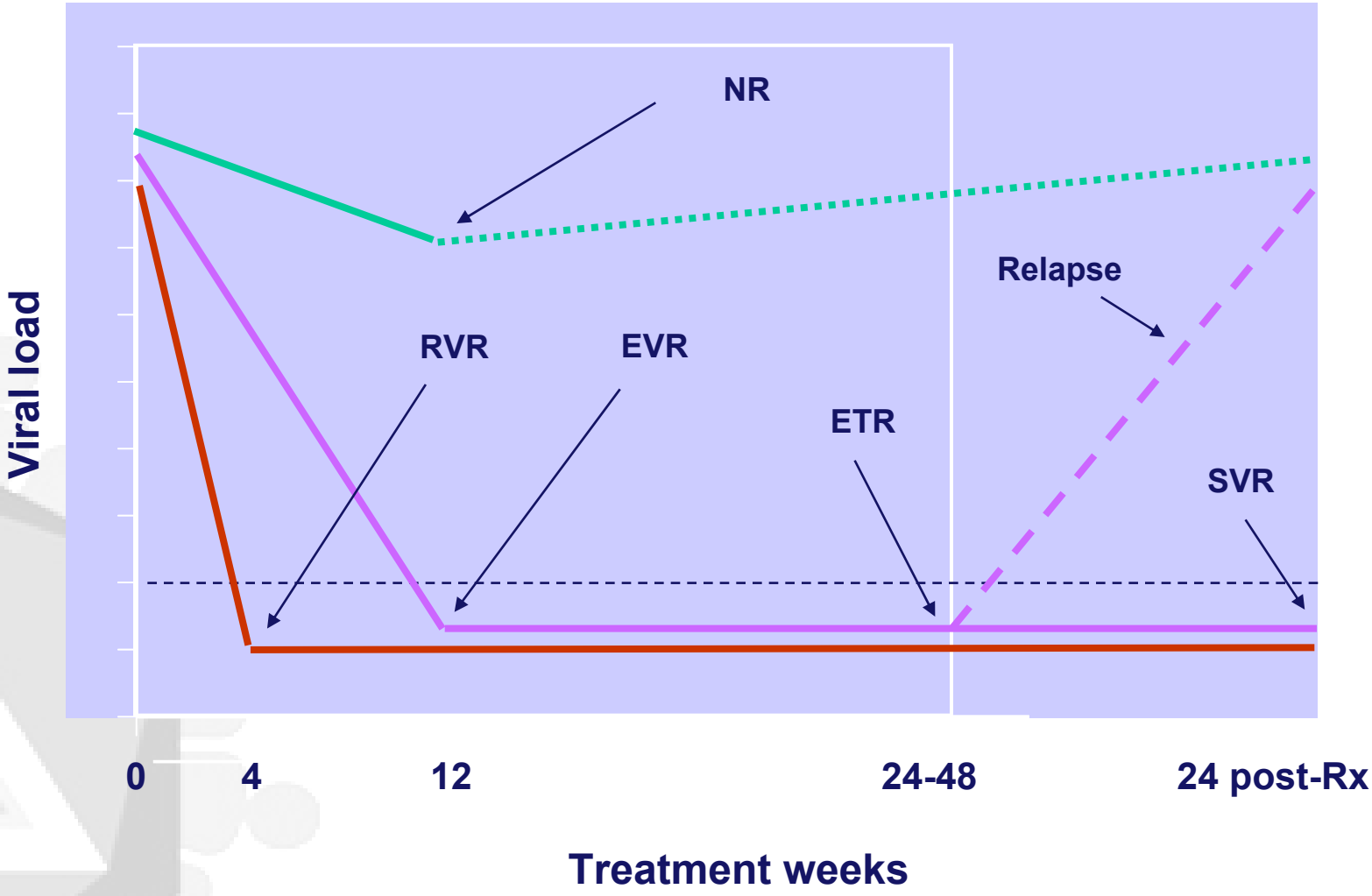
- Curative potential (50 – 80%)
- Improving response rates and clinical experience
- Government-subsidized
- Some expansion of access – removal of liver biopsy

Negative

- Toxicity: flu-like symptoms, depression, anaemia, lethargy
- Requirement for contraception during and 6 months following
- Tertiary hospital – focused

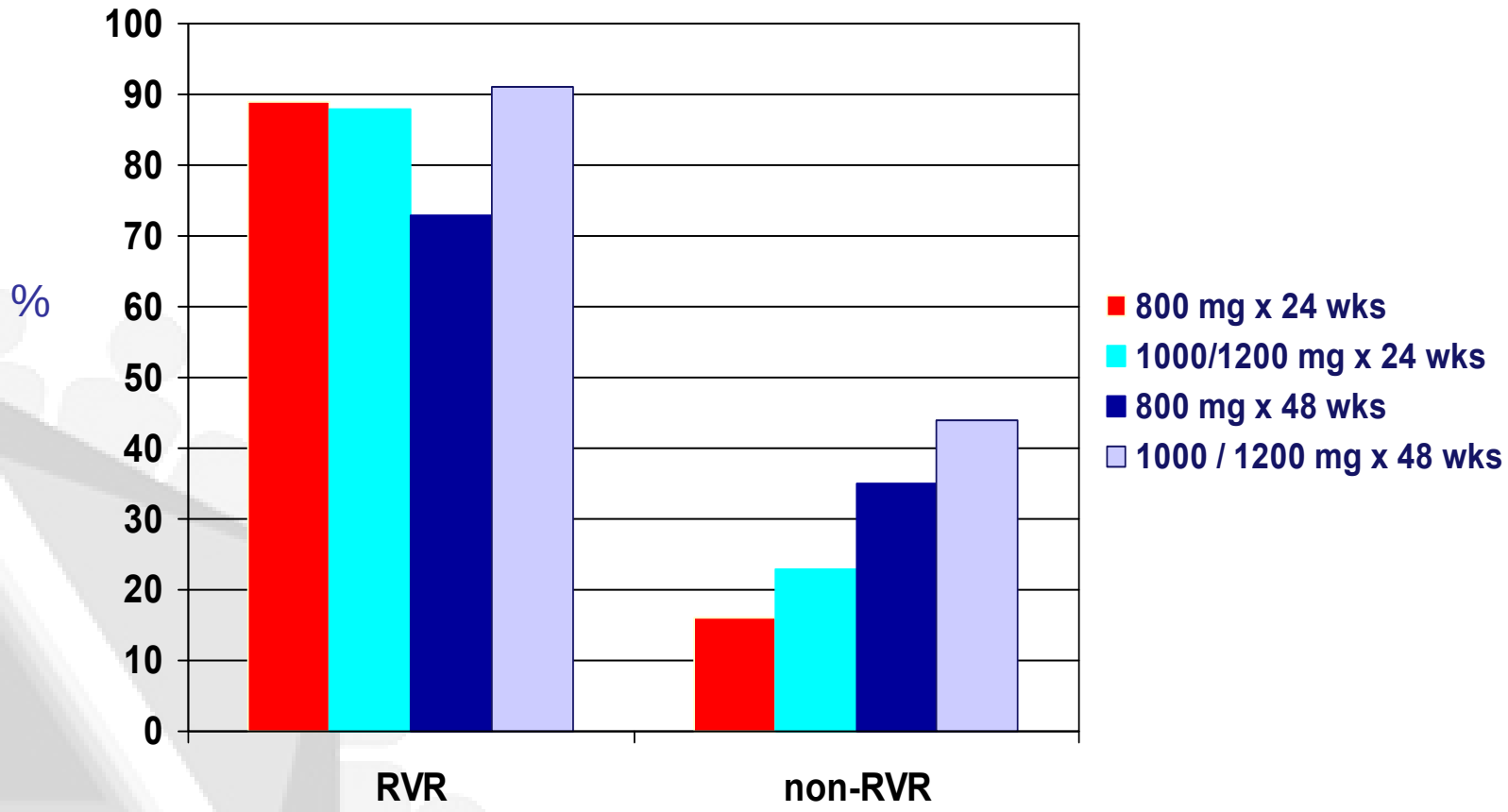
Hepatitis C treatment

HCV treatment response definitions



Hepatitis C treatment

SVR in RVR HCV genotype 1: PEG-IFN2a/RBV

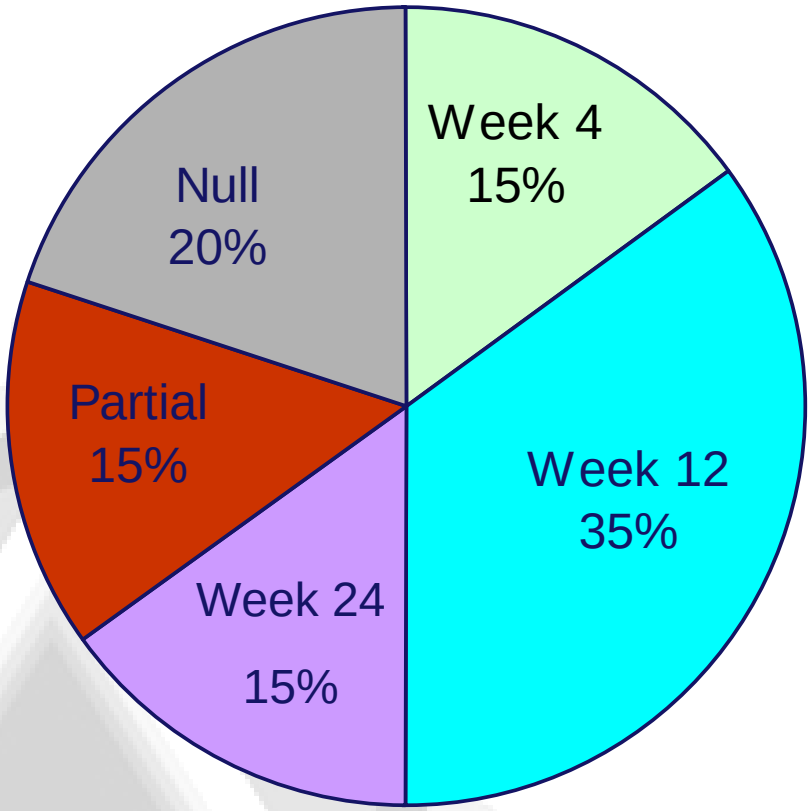


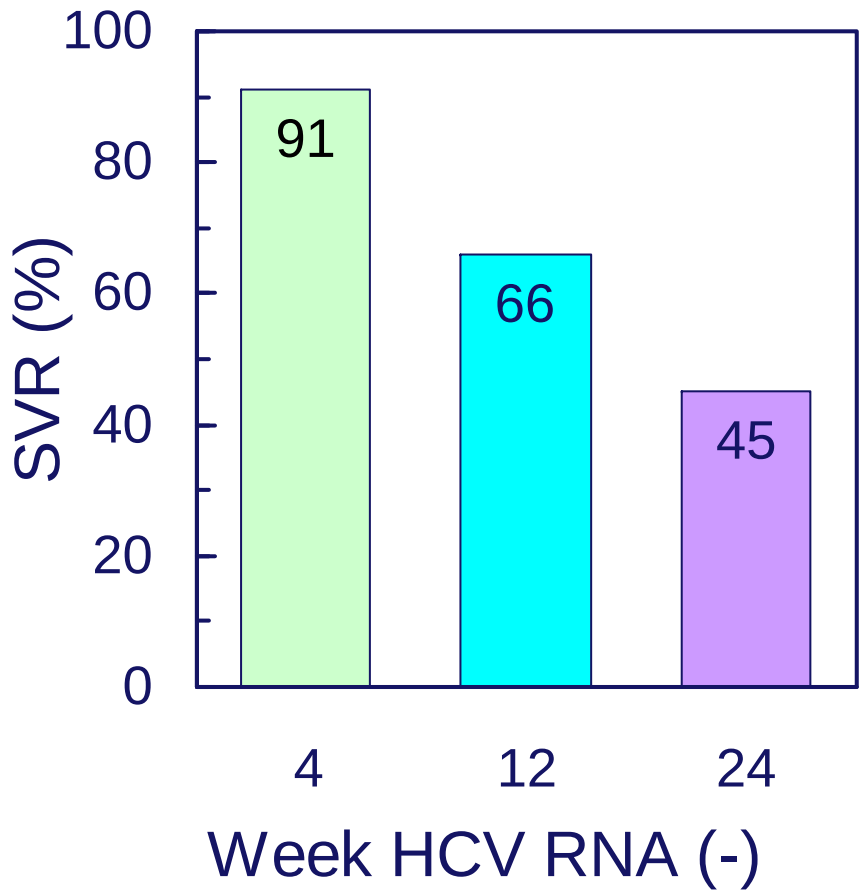
Jensen et al Hepatology 2006

RVR = < 50 IU/ml at week 4; 20%

Hepatitis C treatment

Time to respond and SVR: genotype 1





Ferrenci et al. J Hepatology 2005

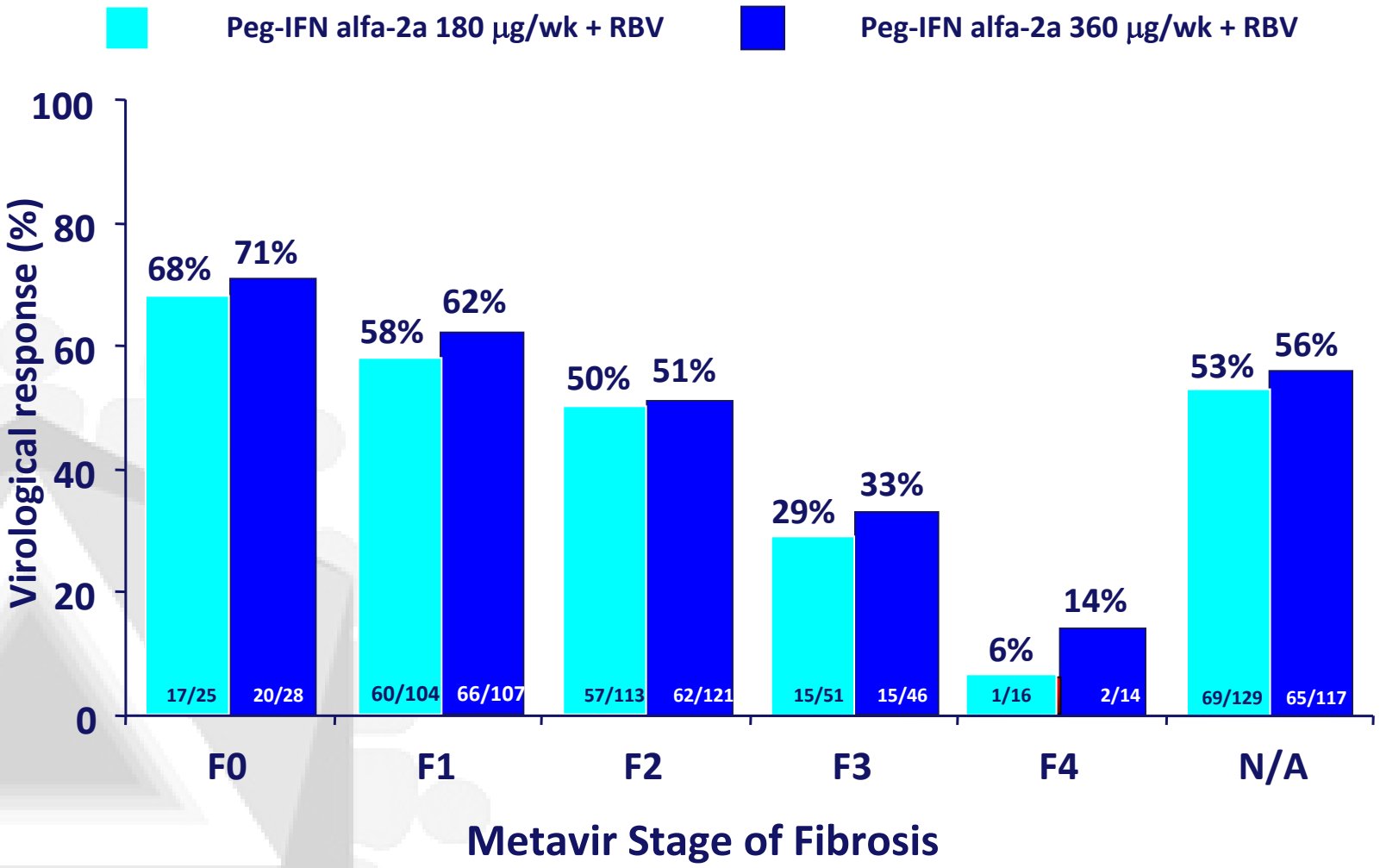
Hepatitis C treatment

Factors associated with poorer SVR

- HCV genotype 1
- HCV viral load (genotype 1)
- Severe fibrosis – cirrhosis
- High body weight
- Insulin resistance
- Age > 40 years
- African American ethnicity
- HIV coinfection
- < 80% adherence (RBV > PEG-IFN)

Hepatitis C treatment

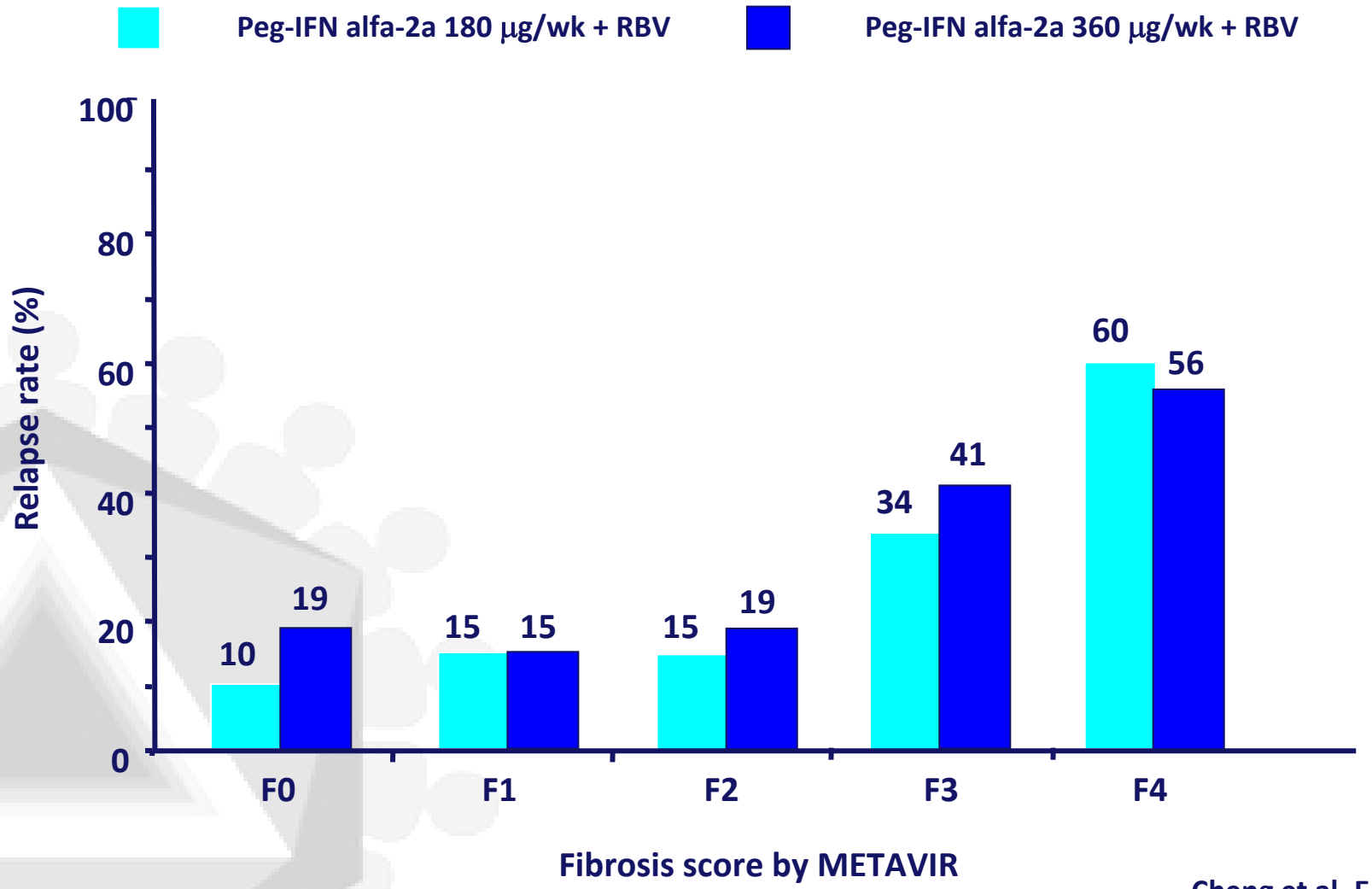
SVR rates by fibrosis stage: CHARIOT study (genotype 1)



Cheng et al. EASL 2009

Hepatitis C treatment

Relapse rates by fibrosis stage: CHARIOT study (genotype 1)



Cheng et al. EASL 2009

Hepatitis C treatment

Re-treatment considerations

- **Factors associated with non-response:**
  - Unable to alter: genotype, HCV viral load, disease stage
  - Some ability to alter: obesity, alcohol intake, adherence

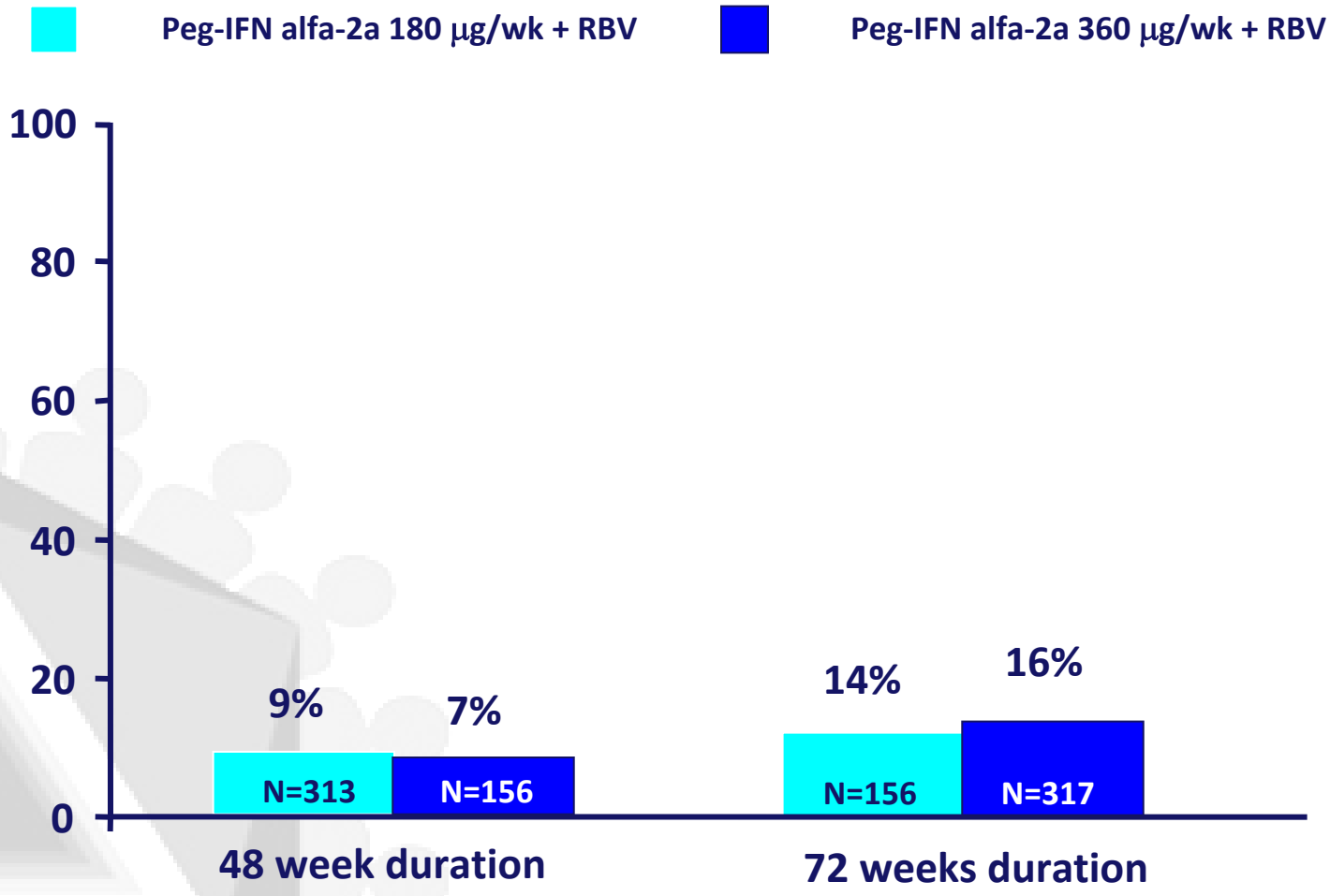
- **Prior virological response best predictor of future response:**
  - Relapsers > Non-responders (<2 log) > Null responders (<0.5 log)

- **Some indications:**
  - prior therapy with IFN monotherapy or IFN/RBV
  - PEG-IFN/RBV genotype 2/3 relapsers (if treated for 24 weeks)
  - heavy alcohol intake or poor adherence

- **Staging of liver disease:**
  - crucial to determine ongoing management strategy
  - stronger consideration for re-treatment if F3/4
  - HCC screening if F4

Hepatitis C treatment

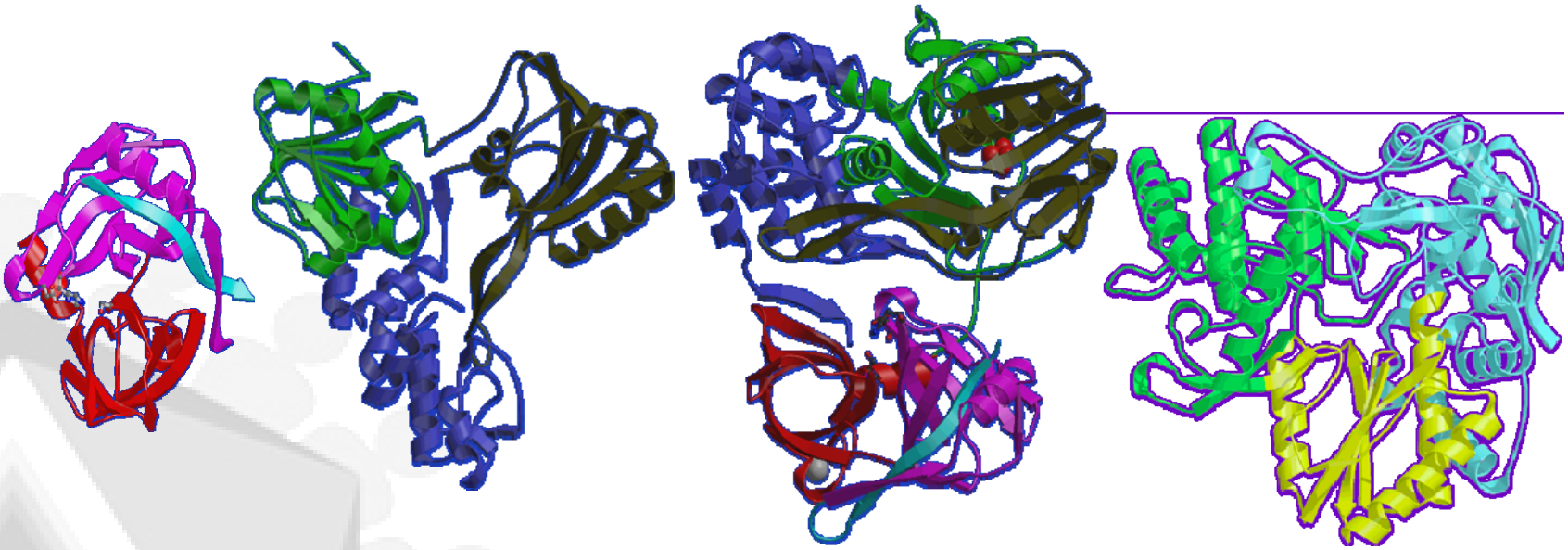
REPEAT study: genotype 1 NR to PEG-IFN-2b/RBV



Jensen DM et al. AIM 2009

Hepatitis C treatment

HCV enzymes are targets for new therapies



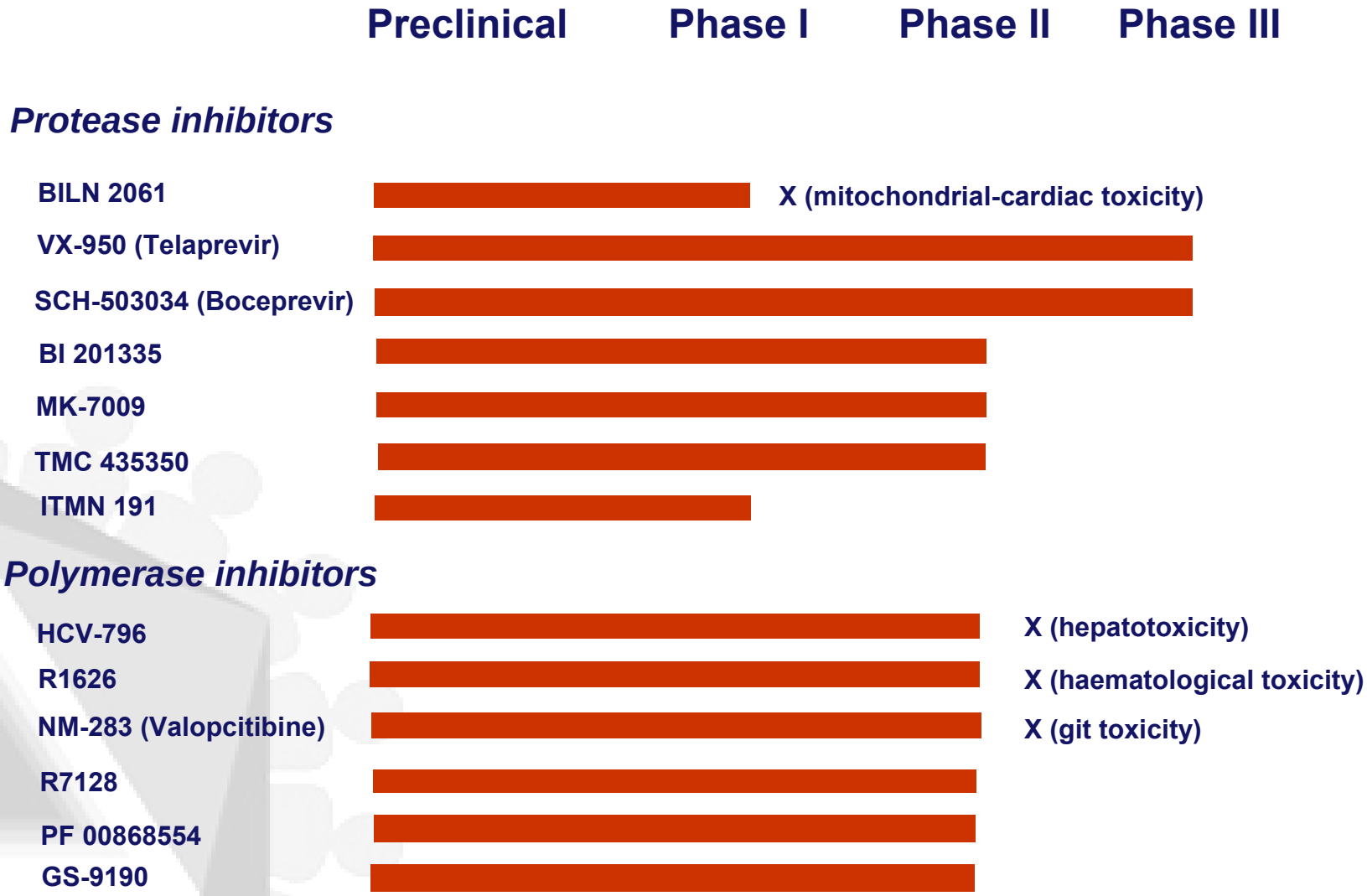
NS3 Protease domain

NS3 Helicase domain

NS3 Bifunctional protease / helicase

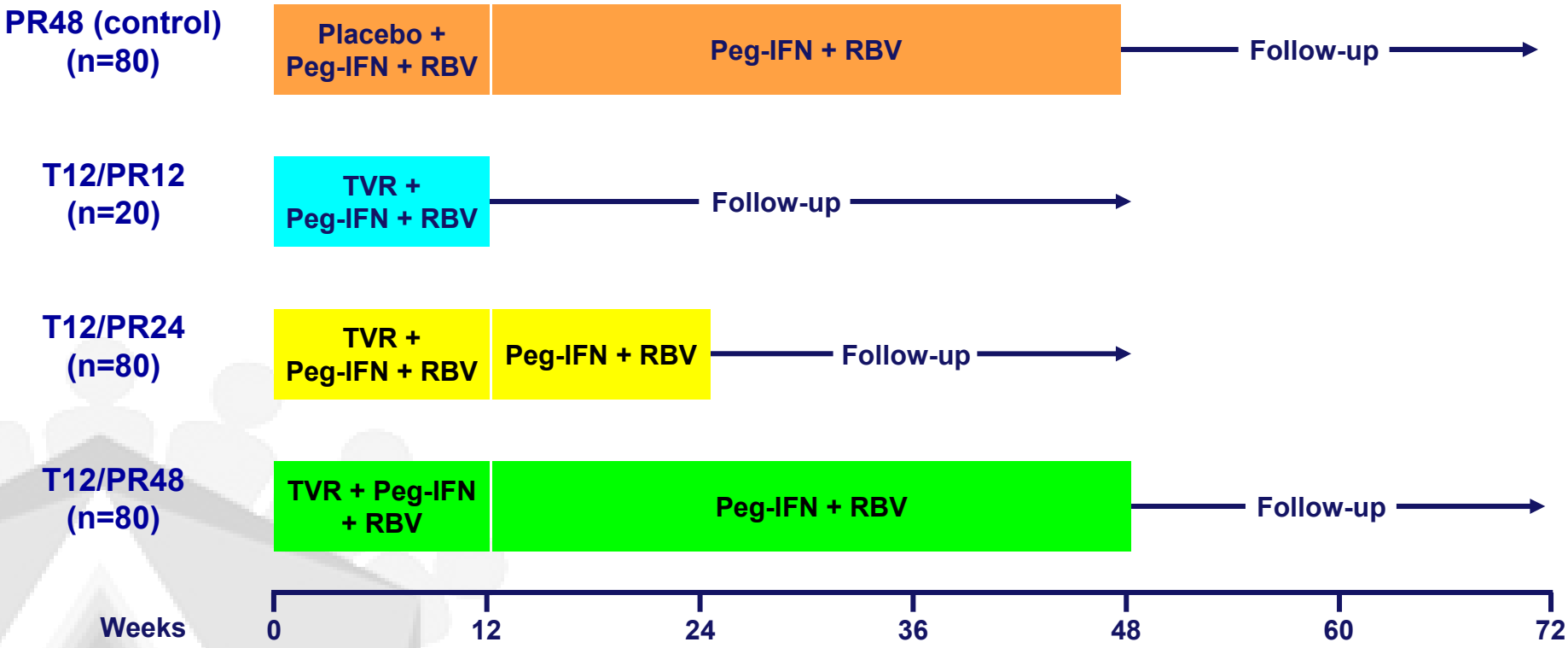
NS5B RNA-dependent RNA polymerase

Hepatitis C treatment



PROVE 1: Telaprevir

Study design: Phase II, genotype 1, treatment naive

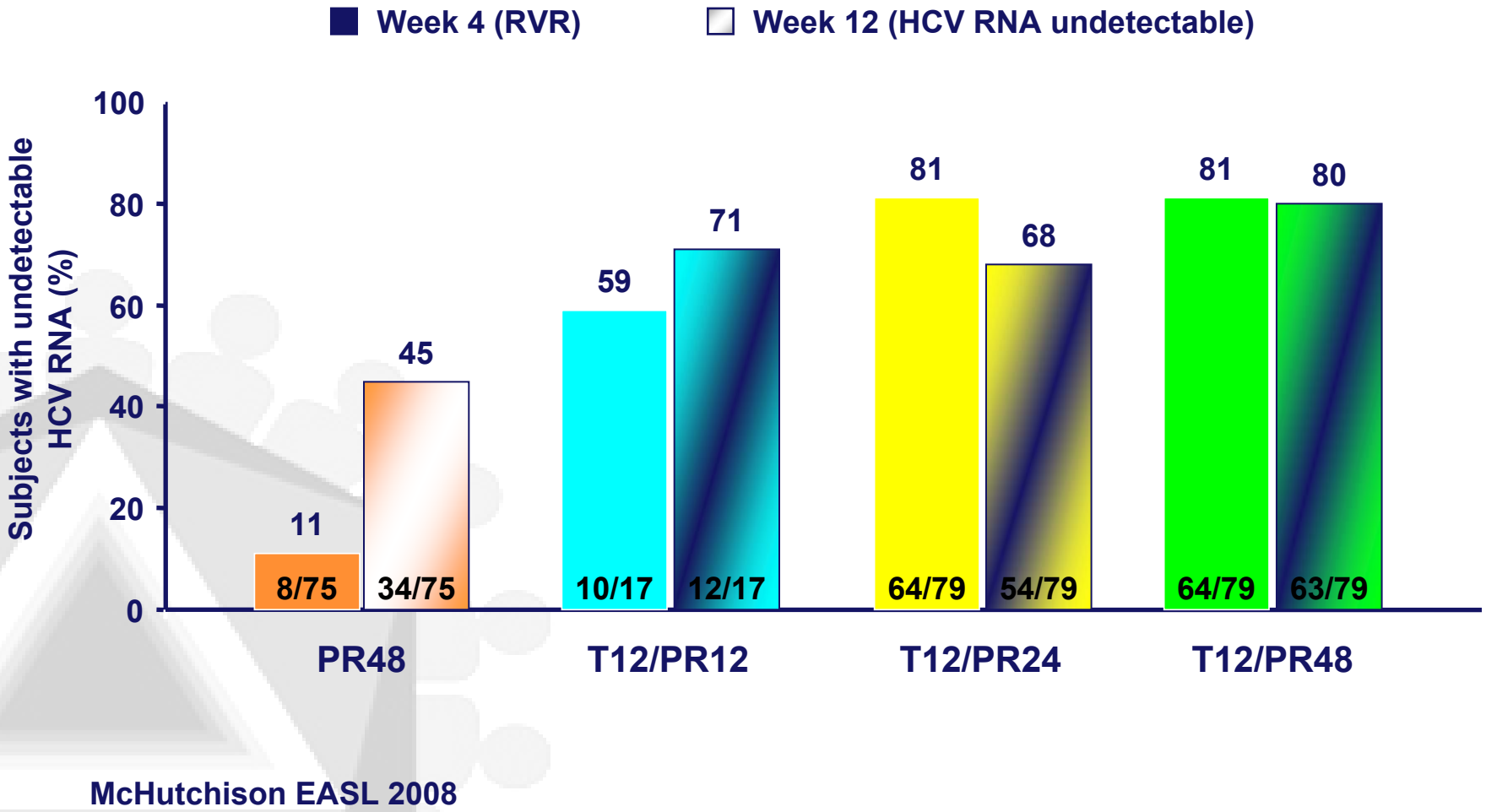


Dosing: Peg-IFN = Peg-IFN alfa-2a 180 µg/week, RBV = RBV 1,000 or 1,200 mg/day, TVR = TVR 750 mg q8h

McHutchison EASL 2008

PROVE 1

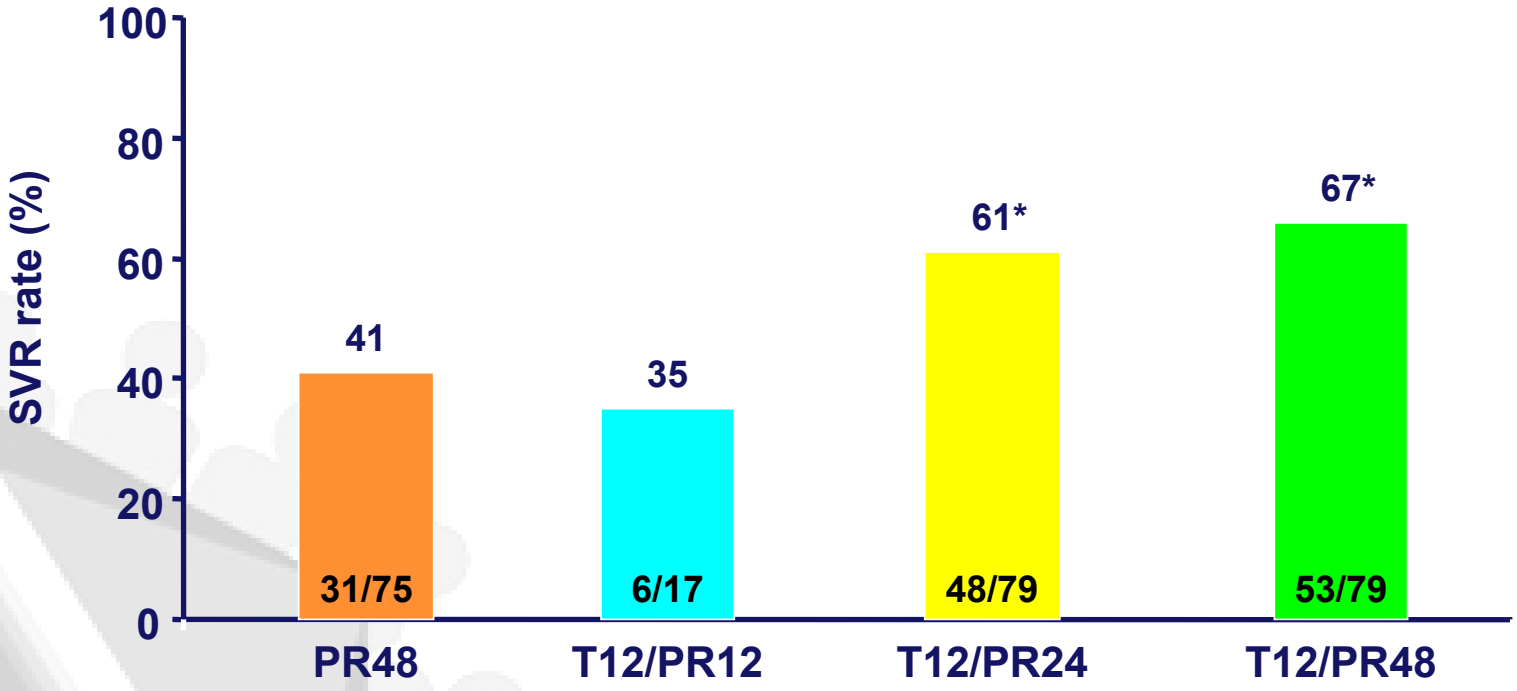
Early virological responses



McHutchison EASL 2008

PROVE 1

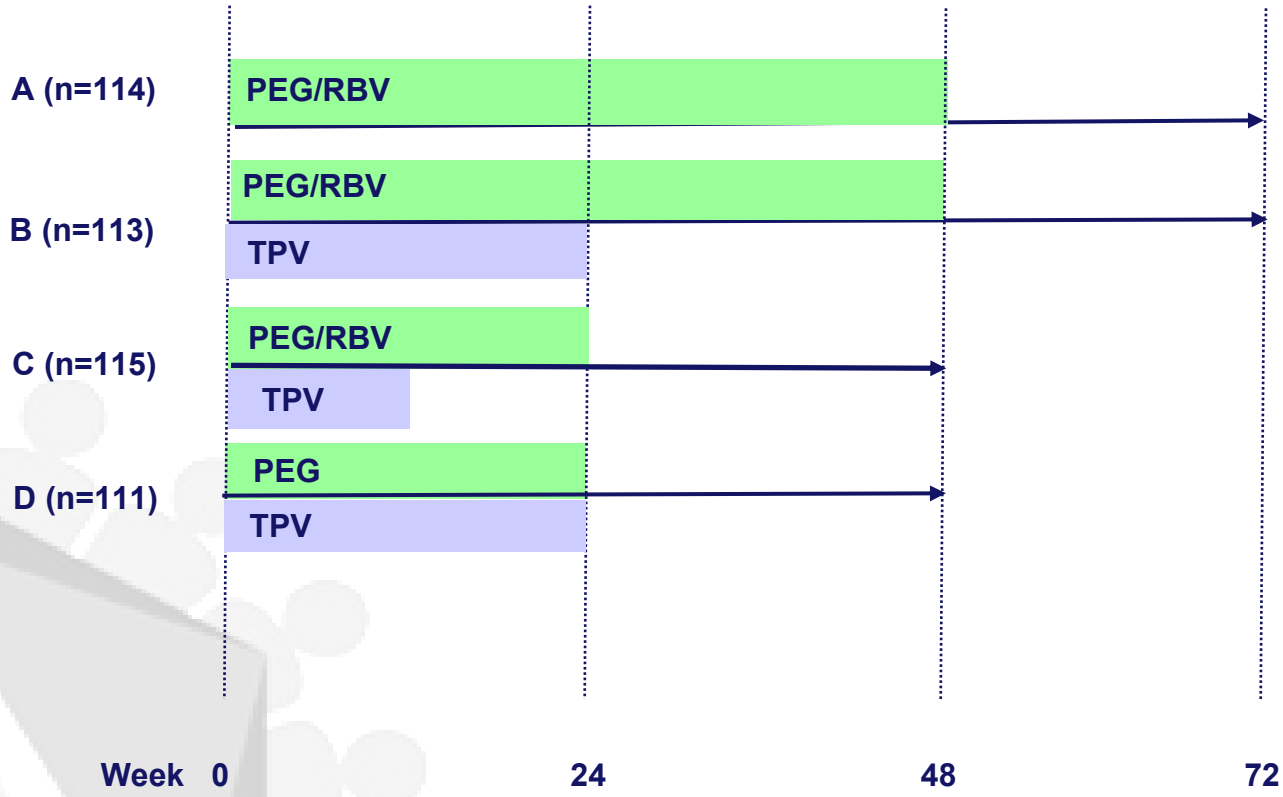
Sustained virological response



McHutchison EASL 2008

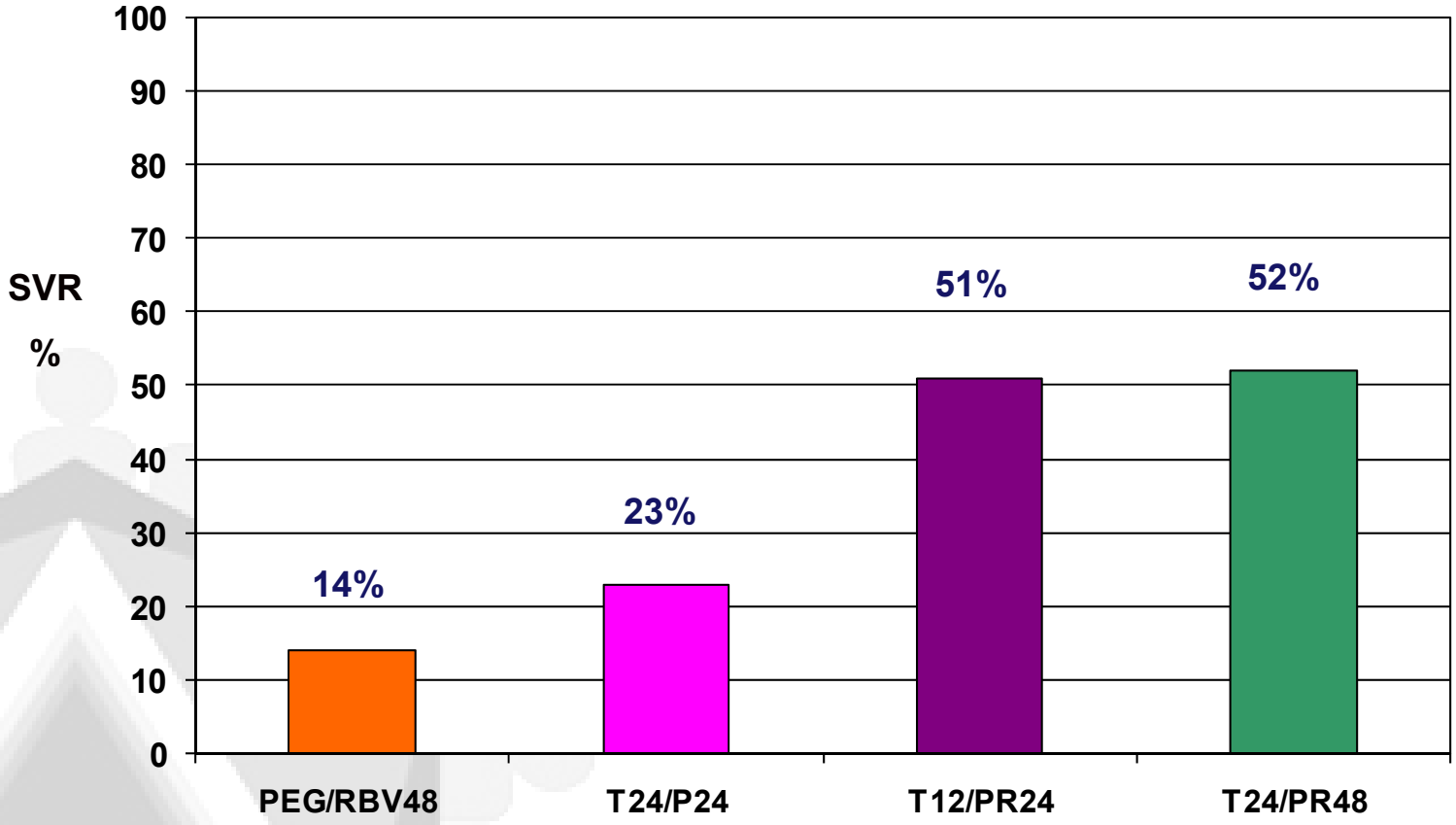
PROVE 3: Telaprevir

Study design: Phase II, PEG-IFN/RBV NRs or relapsers



PROVE-3

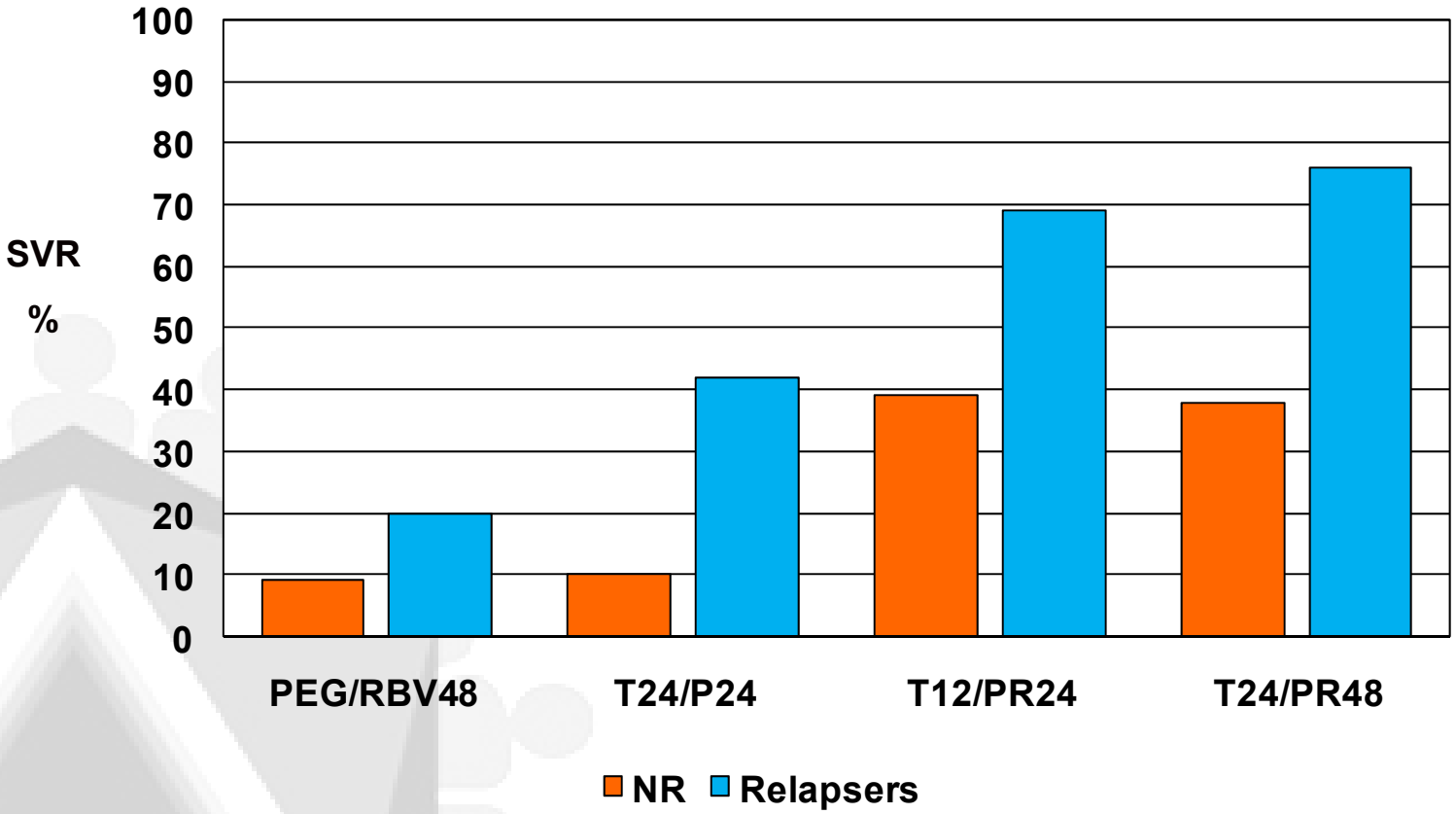
Sustained virological response



Manns et al EASL 2009

PROVE-3

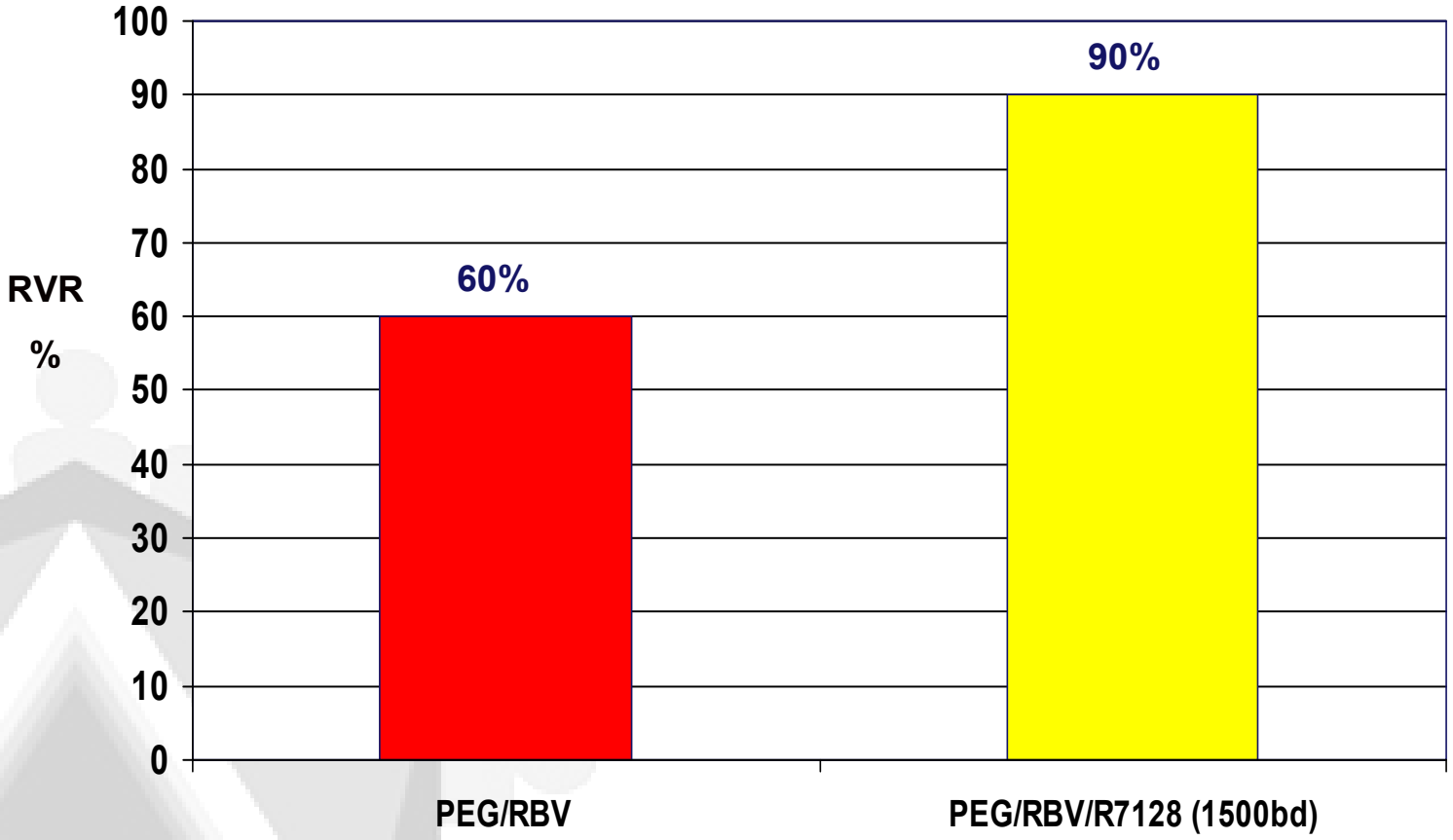
Sustained virological response



Manns et al EASL 2009

Polymerase Inhibitor (R7128): phase II

Week 4 RVR (Gen 2/3, Rx experienced)



Gane et al AASLD 2008

Hepatitis C treatment

Dosing regimens for STAT-C agents

	Phase	Dosing
Protease inhibitors		
Telaprevir	III	750 mg q 8 hrly (1250 mg q 12 hrly – phase II)
Boceprevir	III	800 mg tds
MK 7009	II	300 – 600 mg bd
BI 2100335	II	120 – 240 mg daily
TMC 435350	II	25 – 200 mg daily
Polymerase inhibitors		
R7128	II	500 – 1500 mg bd
PF 00868554	II	200 – 500 mg bd

Hepatitis C update

Conclusions

- Lifestyle factors important to potentially modify: alcohol, diet, smoking
- Liver disease staging crucial for treatment-decision making
- HCV genotype 1 response rates remain sub-optimal, particularly in context of advanced disease, high HCV viral load, HIV coinfection
- Many people should defer to await new therapies, particularly those with genotype 1 (esp high VL) and early liver disease
- Initial protease inhibitors will have significant additional toxicity, but 2nd generation should be much more tolerable