Optimal Therapy in Hepatitis C Genotype 4

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HCV Genotype 4
True or False

- HCV-G4 is limited to Africa and the Middle East
- HCV-G 4 is difficult to treat
- Therapy of chronic HCV G 4 has been optimized
- Individuals infected with HCV-G4 respond similarly to therapy
- Triple therapy would improve the response of patients with HCV-G4

Case # 1

- Mr. A, a 29 y old engineer, was informed during his pre-employment physical that his liver enzymes were elevated (ALT: 175 U/L).
- He had no symptoms and his physical examination revealed no abnormalities.
- He could not recall how, when or where he got the infection
- No history of drugs or alcohol
- Positive antibodies to HCV, HCV-PCR: 850, 000 IU/L, HCV genotype 4.
  - Treat or not to treat? Treat for how long?
  - Do we need to know Mr. A's ethnic background or HCV subtype?

Case # 2

- Mr. T
- A 38-year-old Italian
- 2005: Diagnosed with HIV
- Doing well on HAART
- 2008: Diagnosed with HCV
- 2008: Stopped using drugs (heroin)
- 2009: ALT: 126 U/L, HCV-PCR: 1,564,000 I.U.; Liver biopsy: Grade 8, stage 2, CD4+: 520

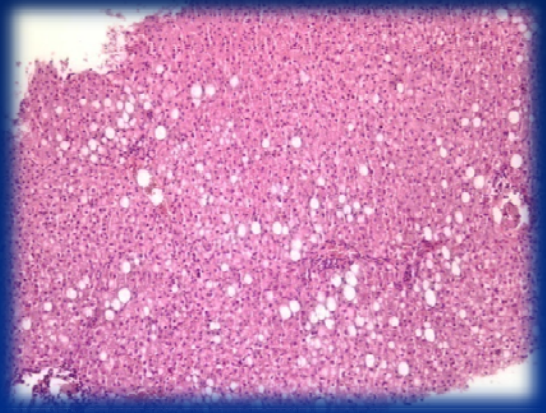
- Treat or not to treat?
- Treat for how long?

Case # 3

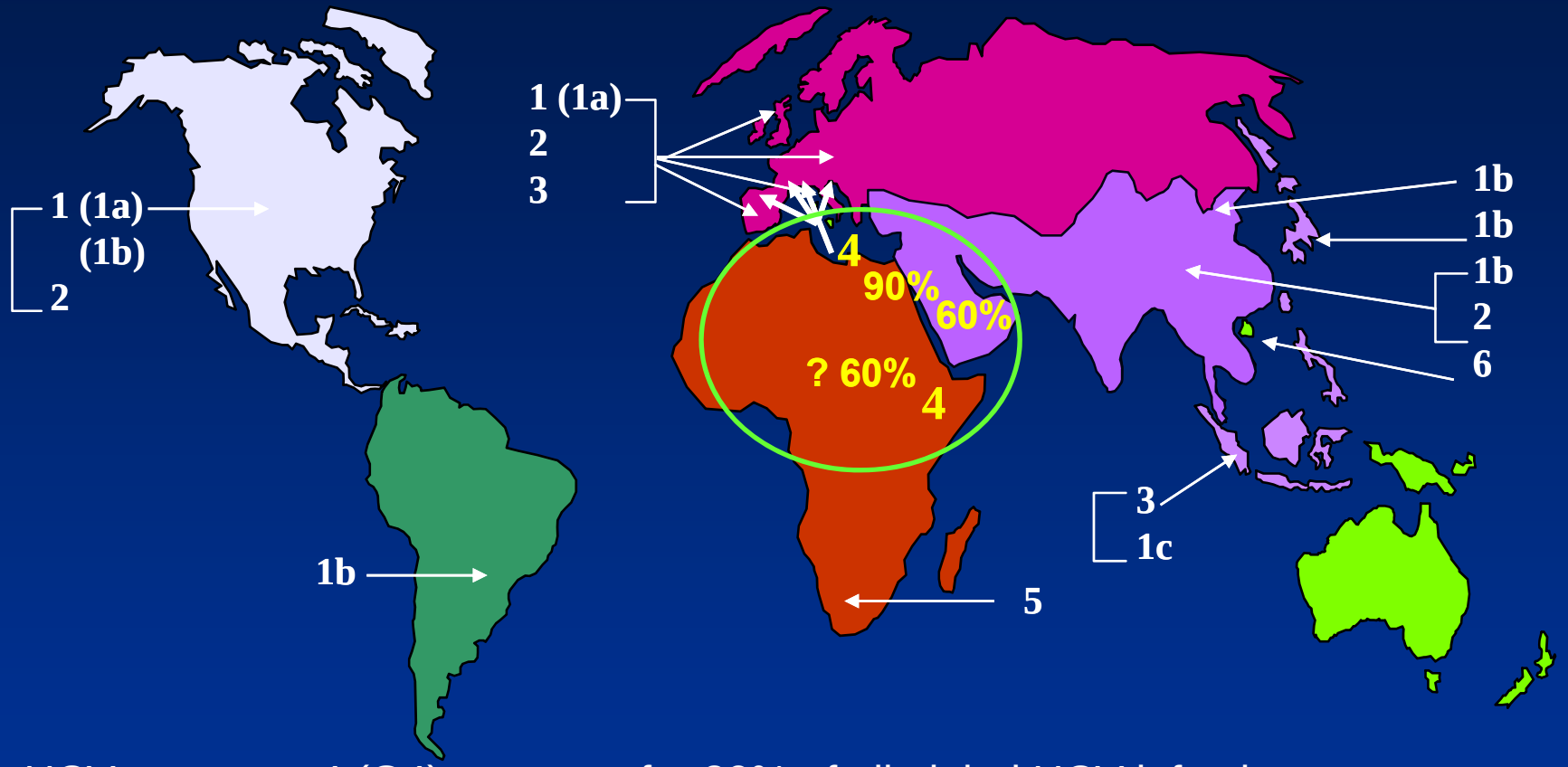
- Ms. H, a 21 y old African American woman accidentally discovered elevated liver enzymes and positive antibodies to HCV during check-up.
- She spent 2 years as volunteer in a peace keeping mission in Rwanda. Her liver was enlarged.
- ALT: 84 U/L; HCV-PCR: 1,240,000 IU, HCV genotype 4K
- Her blood picture, renal profile, thyroid profile were within normal.

Case # 4

- 27-year-old young man was diagnosed with chronic hepatitis C, genotype 4
- Baseline labs:
  - Hb 12.5 g/dL
  - HCV-RNA 650,000 IU/mL
  - ALT/AST 76/87
  - Bilirubin 1.2 mg/dL
  - INR 1.2
- Liver biopsy reveals grade 9, stage 3, steatosis



Worldwide Distribution of Genotypes



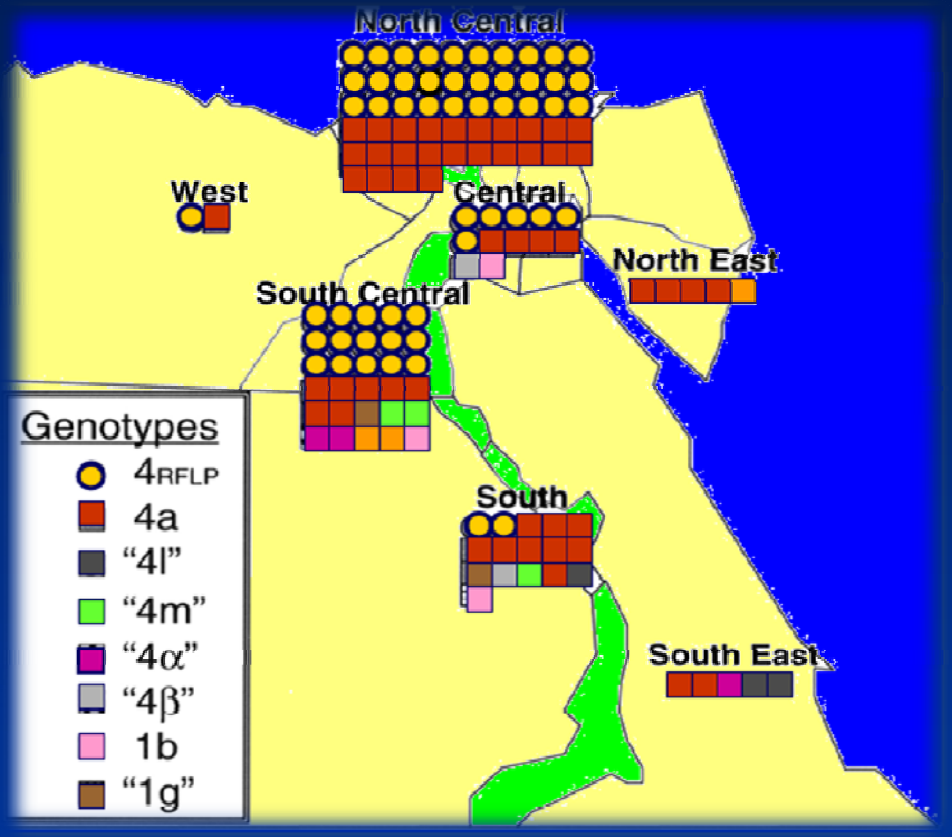
- HCV genotype 4 (G4) accounts for 20% of all global HCV infections
- Hepatitis C genotype 4 has started to spread beyond it strongholds in Africa and the Middle East to Western countries
- HCV genotype 4 is extremely variable, not only in terms of sequence but also in terms of functional and immunological determinants.

Epidemiology of Genotype 4

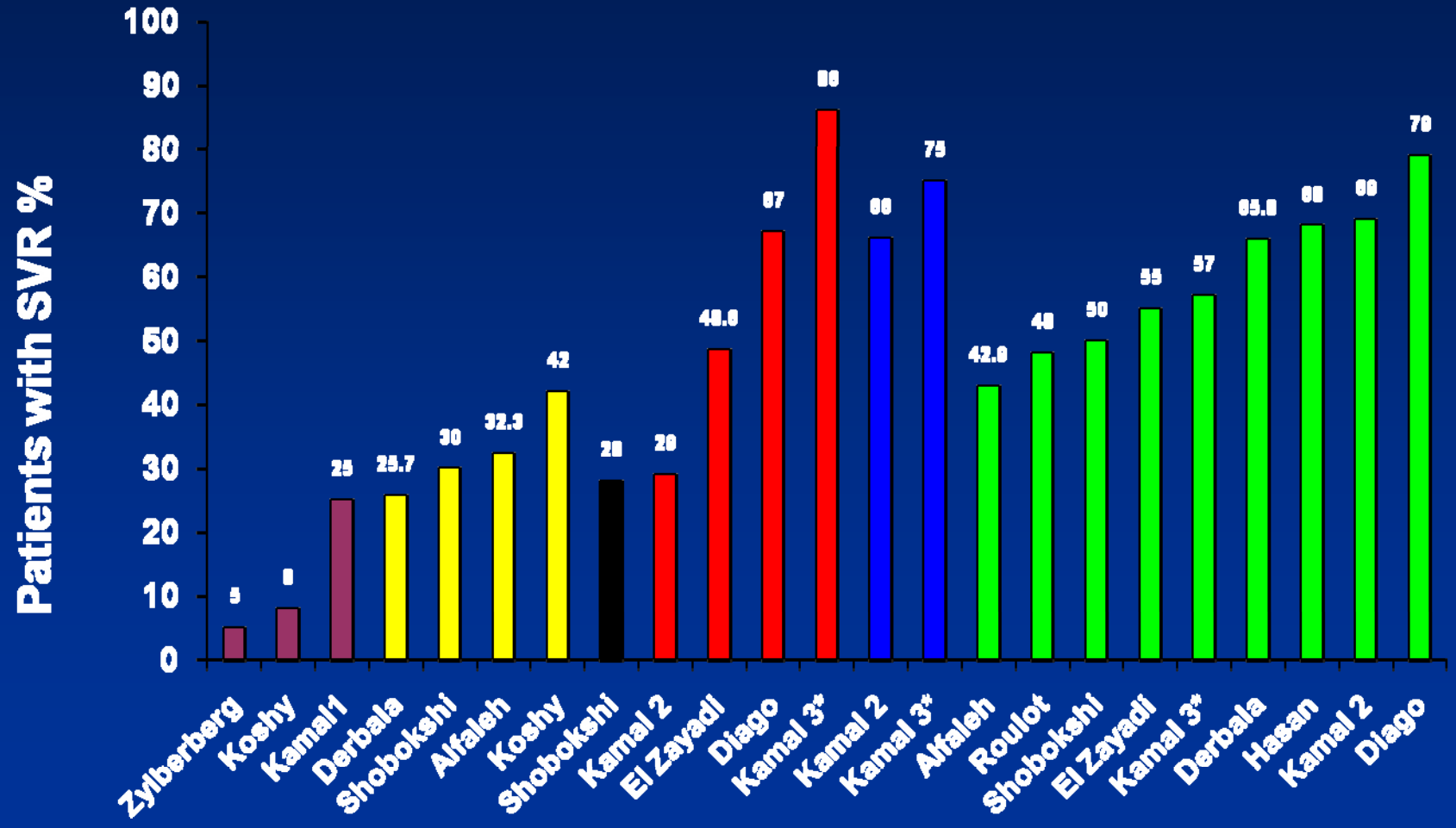
Country	% of HCV-G 4	Subtypes
Egypt	90%	4a (55),4 (24), 4o (7), 4m (3),4l (3), 4n (2)
Gabon	97%	4c (36%),4h (15), 4e (13),4 (13),4g(13),4f (5),4a (2.6)
Central African Republic	100%	4 (66.7), 4k (33.3)
Congo	100%	4 (30), 4c (30), 4k (24), 4r (14), 4a (5).
Cameroon	36%	4f (22), 4 (5), 4t (5), 4k (5), 4e (1.4), 4o (1), 4p (1),
Liberia	100%	4 (100)
Uganda	100%	4 (66.7),4r (33.3)
Tanzania	50%	4d
Rwanda	100	4k (100)
Sudan	5%	4, 4e, and 4c/4d
Tunisia	11%	4k (5), 4a (3.6), 4 (2.6)
Saudi Arabia	60%	**4d (60), 4a (40)**
France	4-10%	4d (2.3), 4a (2.2)
Italy	8.3%	4d (5.9), 4 (2.4)
Spain	3-10%	4c/4d (76.8%), 4 (11.5%), 4a (7.2%), 4e(4.3%)
Greece	13.2%	4a (78%)

Genotype 4 in Egypt

Hepatitis C infection in Egypt is unique due to the high incidence and prevalence rates, various risk factors, predominance of genotype 4 that represents more than 90% of HCV isolates from Egyptian patients and the association of HCV with the parasitic infection, schistosomiasis



SVR Genotype 4
PEG-IFN alfa- + ribavirin

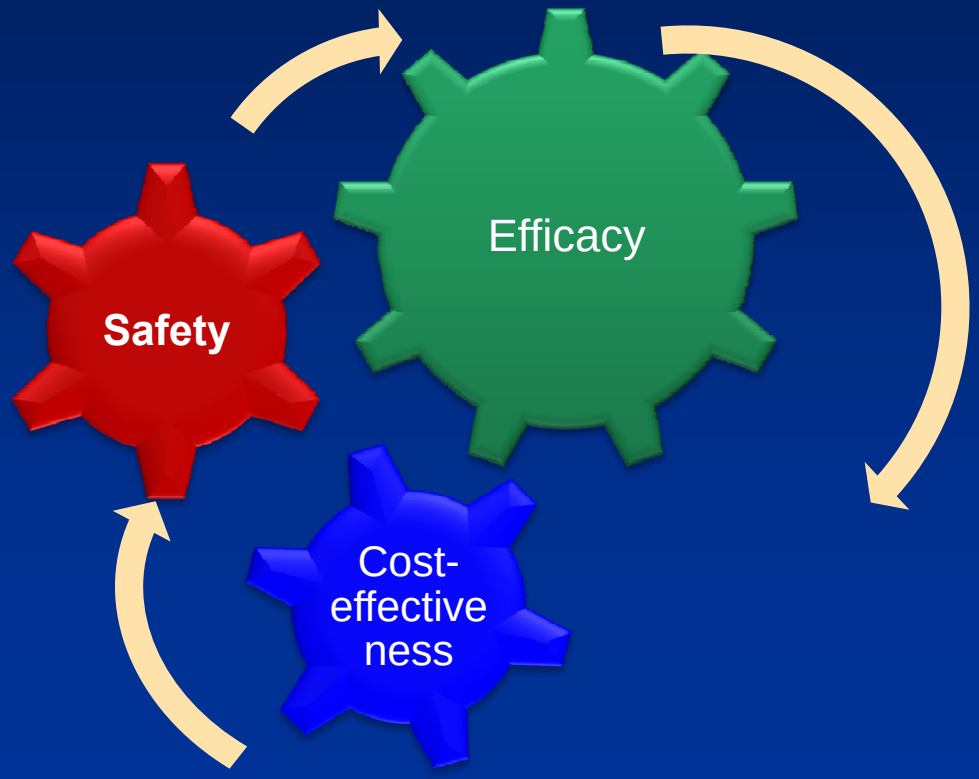


Personalized therapy for chronic hepatitis C genotype 4

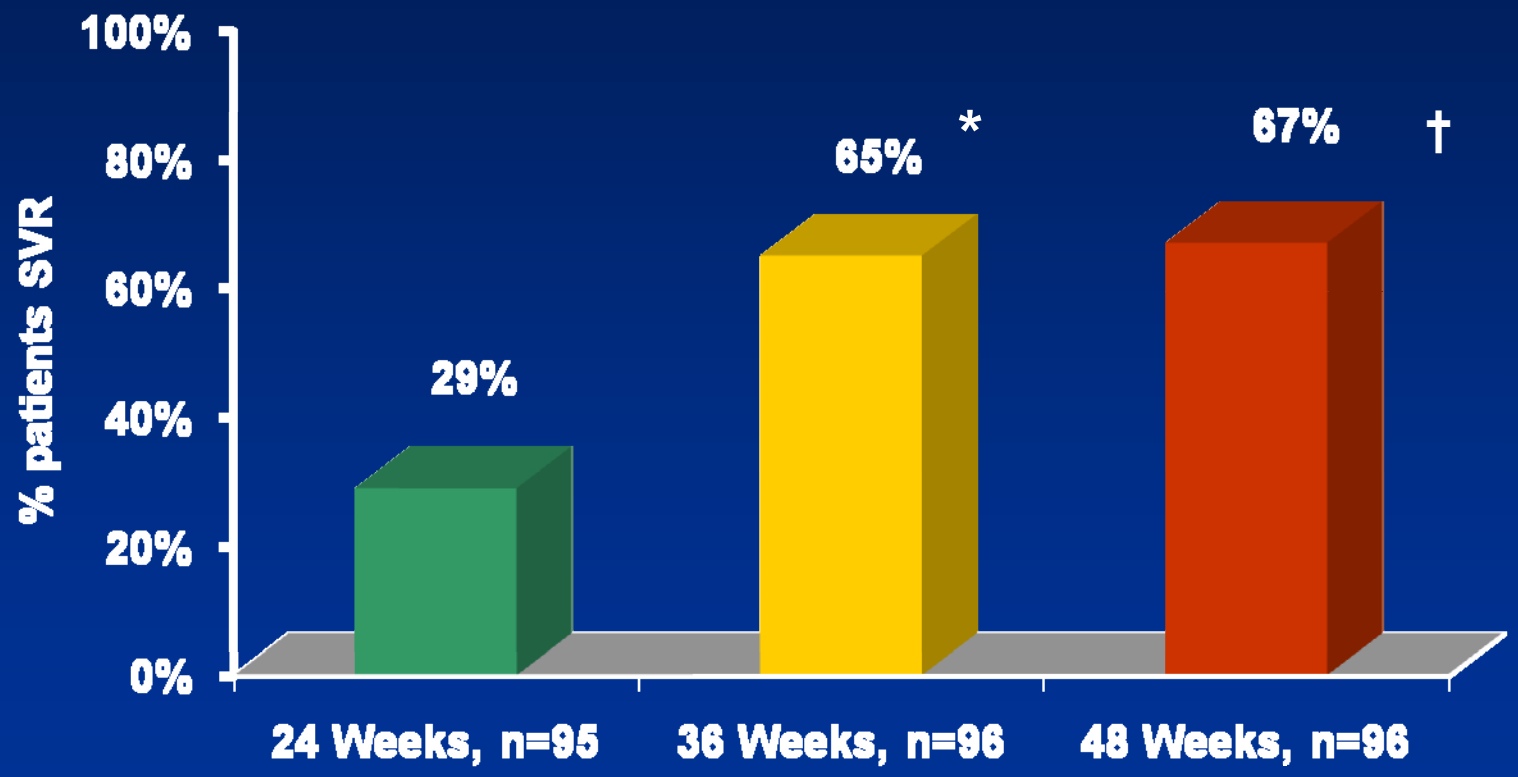
Why?

What?

How?



Personalized therapy for chronic HCV-G4 according to on-treatment viral kinetics (EVR)



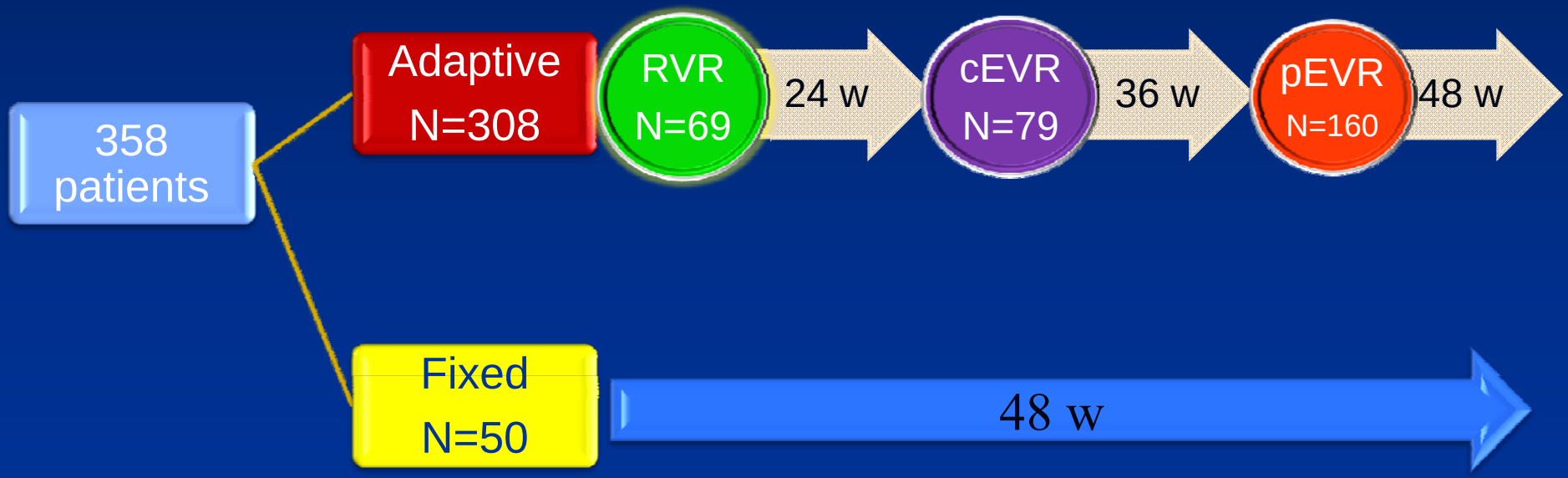
PEG-IFN α-2b 1.5 µg/kg QW + ribavirin 1,000–1,200 mg/day

Kamal S, et al, Gut 2005;54:858–866.

* p= 0.02 for 36 vs. 24 weeks
† p= 0.5 for 48 vs. 36 weeks
‡ p= 0.01 for 48 vs. 24 weeks

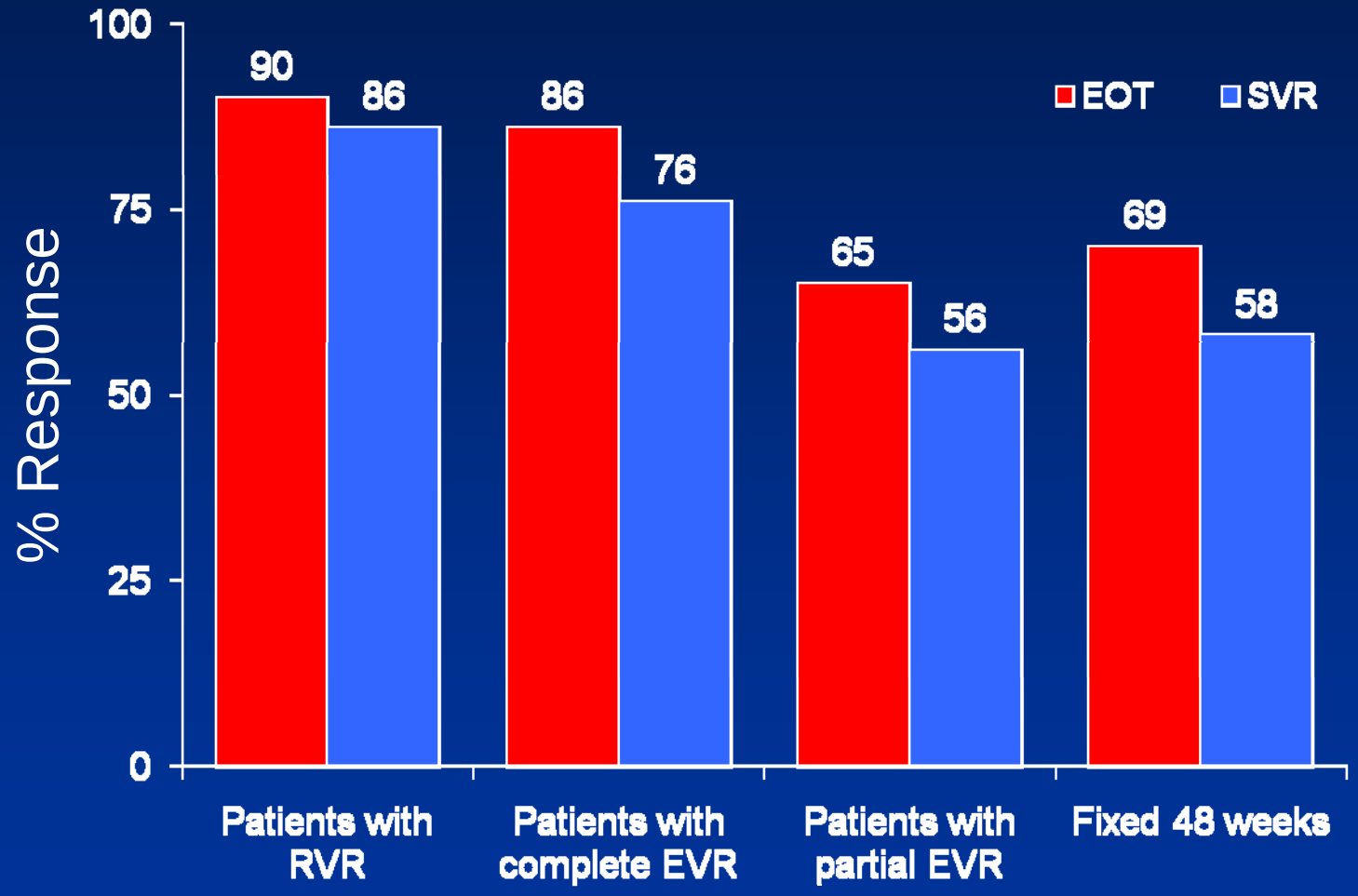
Personalized therapy for chronic HCV-G4 according to RVR and pre-treatment HCV-RNA

RVR, EVR as a guide for 24 w, 36 w or 48w



Kamal et al, Hepatology. 2007 Dec;46(6):1732-40

EOT and SVR rates in HCV-G4 patients with RVR & EVR

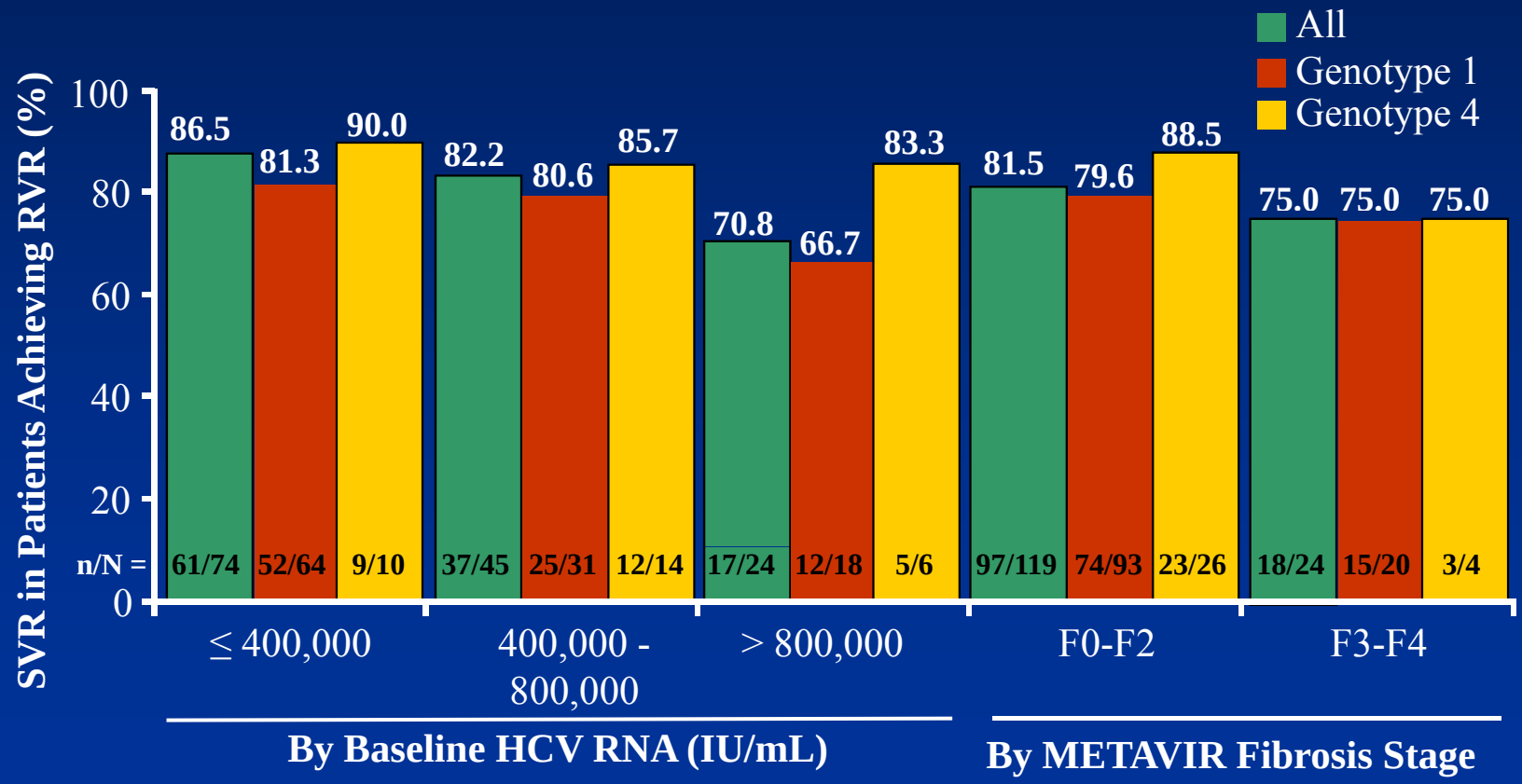


Kamal et al, Hepatology. 2007 Dec;46(6):1732-40

SVR rates in HCV-G4 patients with RVR & EVR

Ferenci P, et al. Gastroenterol. 2008;135:451-458

- **In per-protocol analysis, 80.4% SVR rate in patients with RVR (115/143)**



Ferenci P, et al. Gastroenterol. 2008;135:451-458.

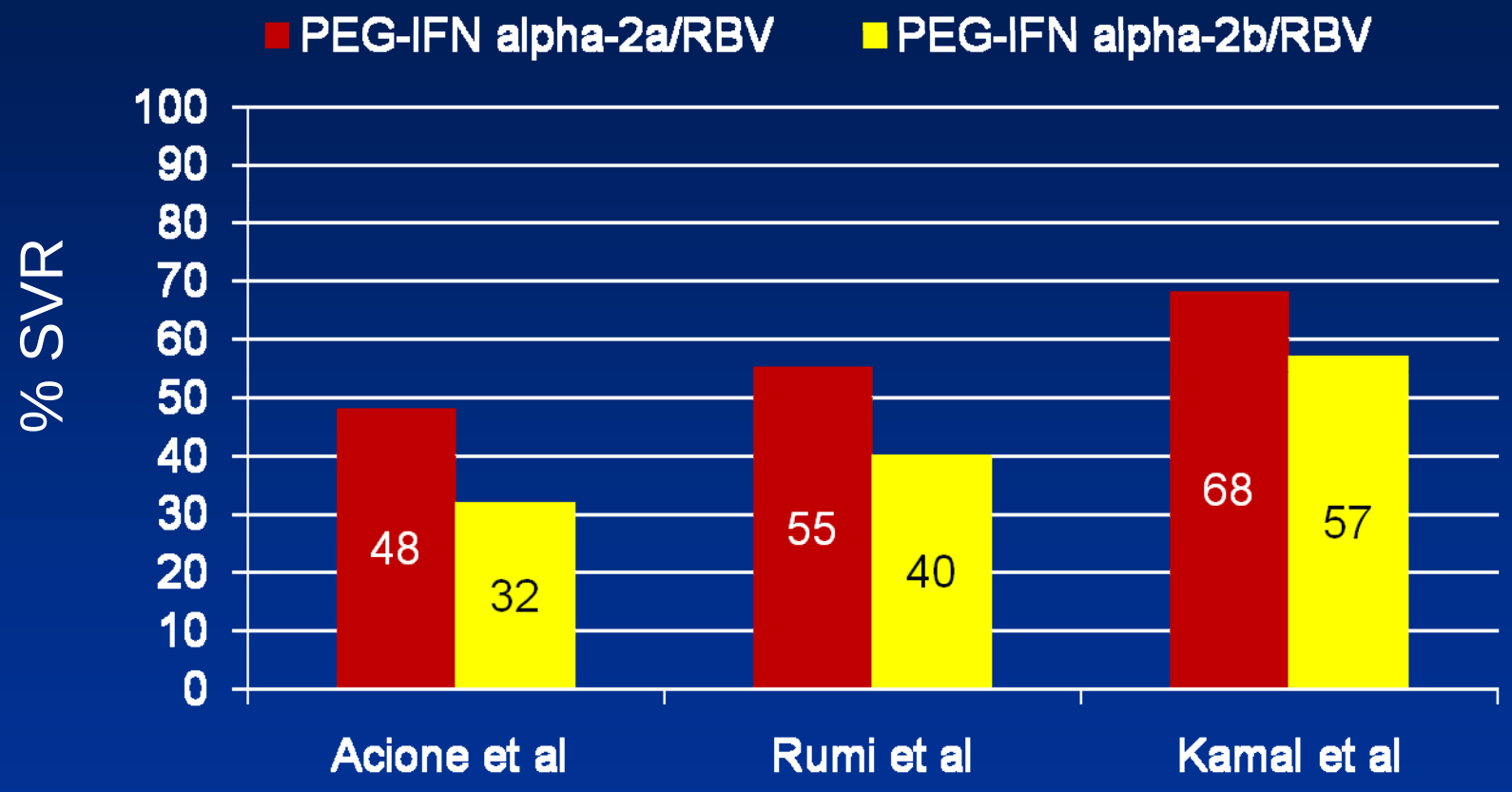
RVR in HCV Genotype 4

	SVR	No SVR	p value	Sensitivity	Specificity	PPV	NPV
RVR + -	72 (97.30) 2 (2.70)	3 (3.70) 78 (96.30)	*<0.0001*	0.96	0.98	0.97	0.96
cEVR + -	43 (97.72) 1 (2.28)	8(9.88) 73 (90.12)	*<0.0001*	0.84	0.99	0.98	0.90
pEVR + -	17 (94.44) 1 (5.56)	32 (39.51) 49 (60.49)	*<0.0001*	0.35	0.78	0.64	0.60

A shortened course of treatment according to RVC could minimize adverse effects and costs without compromising efficacy.

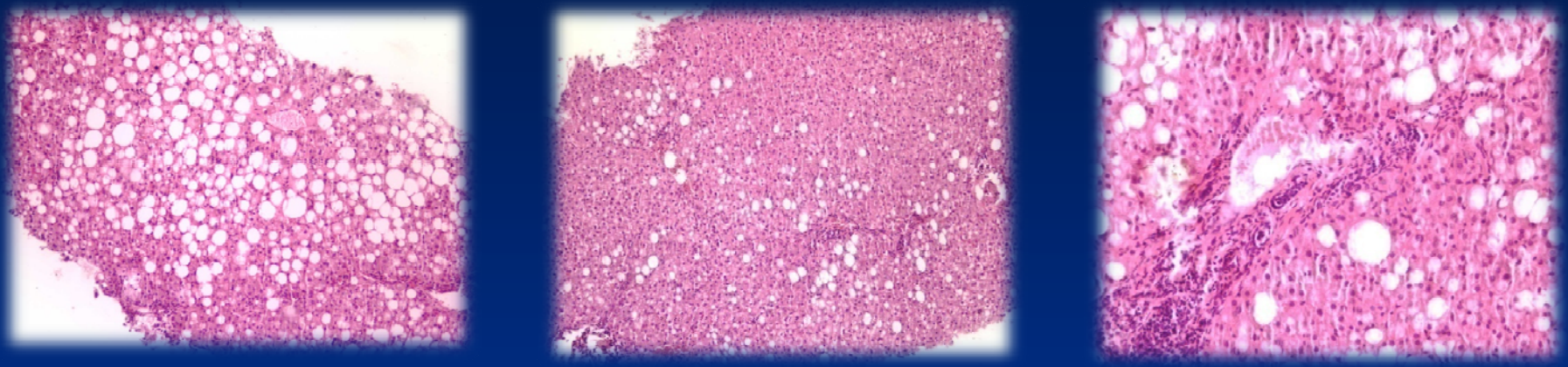
Kamal et al. Liver International, 2011

Higher SVR rates with PEG-IFN α-2a/RBV therapy in chronic HCV-G4



Ascione et al, Gastroenterology, 2010; Rumi et al, Gastroentrology;
Kamal et al, liver International, 2011

Genotype 4: Impact of hepatic fibrosis and cirrhosis



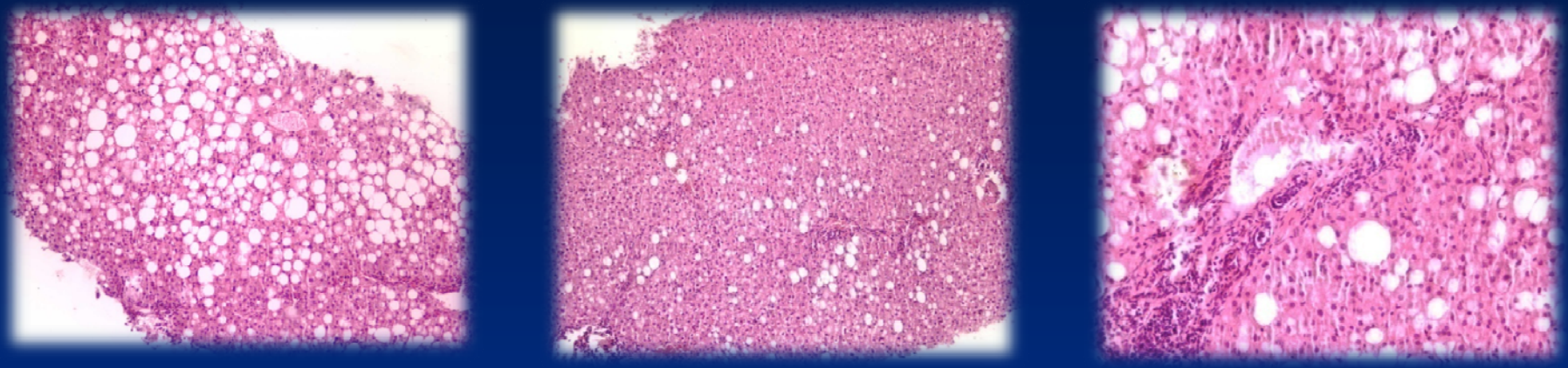
Does Liver histology differ?

HCV-4 features:

- Steatosis which can vary from mild to severe and with no associated sinusoidal fibrosis.
- Nodules in cirrhosis appear to be on the smaller size compared to other types of post-necrotic cirrhosis.

Kamal et al, Hepatology 2011 (in press)

Genotype 4: Impact of hepatic fibrosis and cirrhosis



- Low baseline fibrosis and steatosis is associated with SVR

- In patients with chronic HCV-G4, lower baseline fibrosis stage and steatosis were associated with higher odds of RVR, SVR than those with more advanced histologic disease (OR: 1.27 for each unit difference; 95% CI: 1.15–1.39; *P* <0.0001).

Kamal et al, Hepatology. 2007 Dec;46(6):1732-40, EL Zayadi et al, Gut, 2008; Esmat et al, 2009

Individualization of HCV-G4 therapy according to individuals' genetics, race and ethnicity

- 242 naïve French, Egyptian and (subsaharan) African patients with chronic HCV-4 received peginterferon plus ribavirin for 48 weeks.
- Liver fibrosis was significantly less severe in patients infected in France and Africa
- An overall better response was observed in patients infected with the 4a subtype.
- In multivariate analysis, two factors were associated independently with SVR: the Egyptian origin of transmission and the absence of severe fibrosis
- Why was the response different?

Roulot et al, J Viral Hepat. 2007 Jul;14(7):460-7.

Individualization of HCV-G4 therapy according to host genetics, race and ethnicity

- Pharmacogenomics could be a major step in personalized medicine for optimizing HCV therapy and explaining how individuals' genetic make up influence response to therapy.

- Pharmacogenomics could provide tools to individualize therapy, adjust dosages, reduce the likelihood of adverse effects and therapeutic costs.

IL-28 an individualization of HCV-G4 therapy

- IL28B is located on chromosome 19

- Interleukin-28B belongs to a novel family of type I IFN-like cytokines that has been described independently as IFN-lambda which consists of IL-28A/B and IL-29

- Stättermayer et al. correlated rs12979860 C/C genotype, lower age with SVR in 102 European individuals with HCV genotype 4 and HIV coinfecton.

- RVR and EVR were more likely among carriers of IL-28 polymorphisms rs12979860 C/C and rs8099917 T/T

- The positive predictive value of rs12979860 C/C for SVR was higher than that of rs8099917 T/T.

Stättermayer et al, Clin Gastroenterol Hepatol. 2010

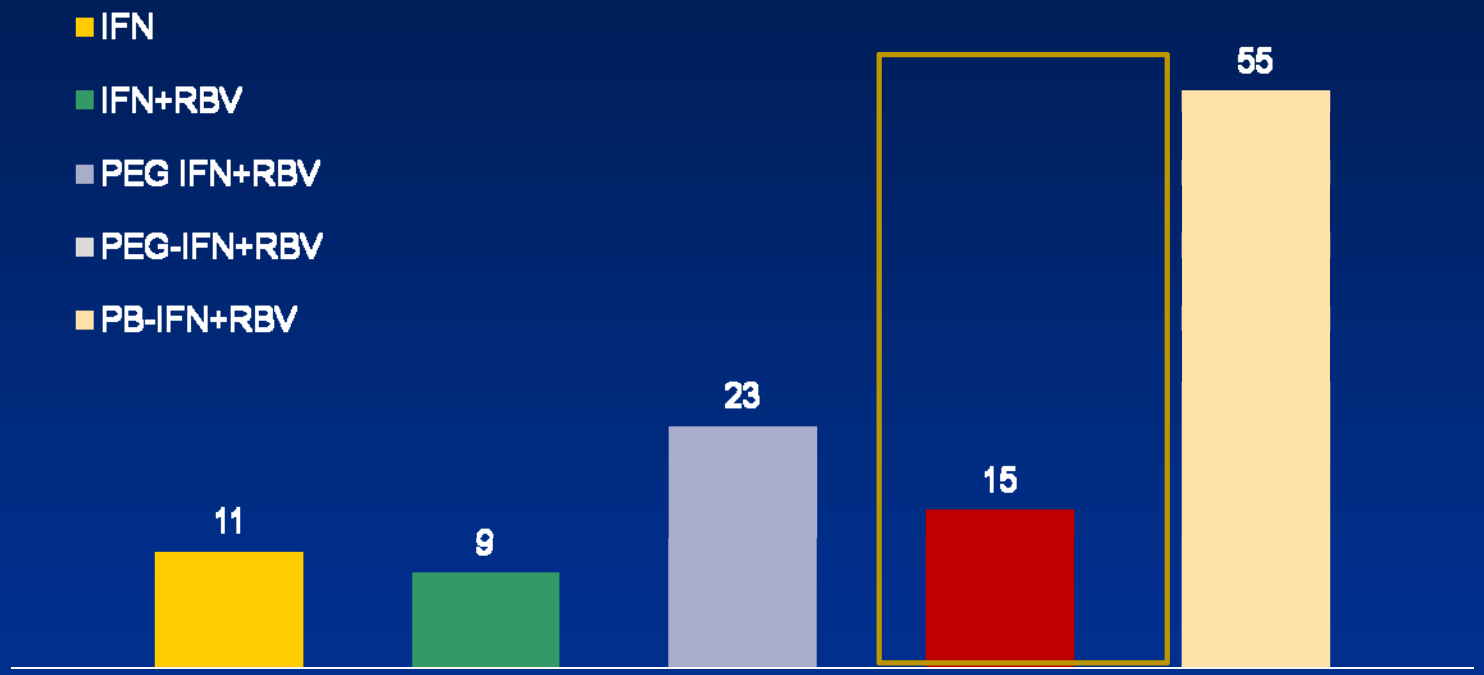
IL-28 an individualization of HCV-G4 therapy

- Despite the advantages of pharmacogenomics in improving the outcome of HCV infection, several barriers may delay the adoption of treatment algorithms based on genetic profiling of patients with HCV.

- Detecting gene variations is a complicated time-consuming, expensive process that might not be easily available in developing countries with heavy burden of HCV.

- Simpler affordable tests for detecting genetic variations are thus required for maximizing the benefit of this technology.

HCV-G4/HIV Coinfection



Soriano et al, Antiviral Ther 2005;10:167-170.
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Legrand-Abravane et al, J Med Virol 2005;77:66-69

Mart´ın- Carbonero et al J Viral Hep, 2008

Predictors of Low SVR

- Age??
- Gender??
- BMI [1,4]
- Fibrosis [6]
- Steatosis [1,6]
- No RVR or EVR[1,2,3,4]
- HCV G 4 non a subtypes ?? [5]
- Coinfections[7]
- IL-28 B
- Higher AFP??[6]rs8099917 T/T??

[1]Kamal et al, GUT; [2]Kamal et al, Hepatology 2007; [3]Kamal et al 2007; [4]Ferenci et al, 2008; [5]Roulot et al 2006; [6]*Gad et al, Liv Int 2008, 28 (8): 1112-1119;* [7]*Legrand-Abravane et al, J Med Virol 2005;77:66-69., Stättermayer et al, Clin Gastrol & Hepatol, 20101*

Improved Virologic Response in Chronic Hepatitis C Genotype 4 Patients Given Nitazoxanide, Peginterferon, and Ribavirin

A phase II, randomized, double-blind, placebo-controlled study of nitazoxanide treatment for 24 weeks

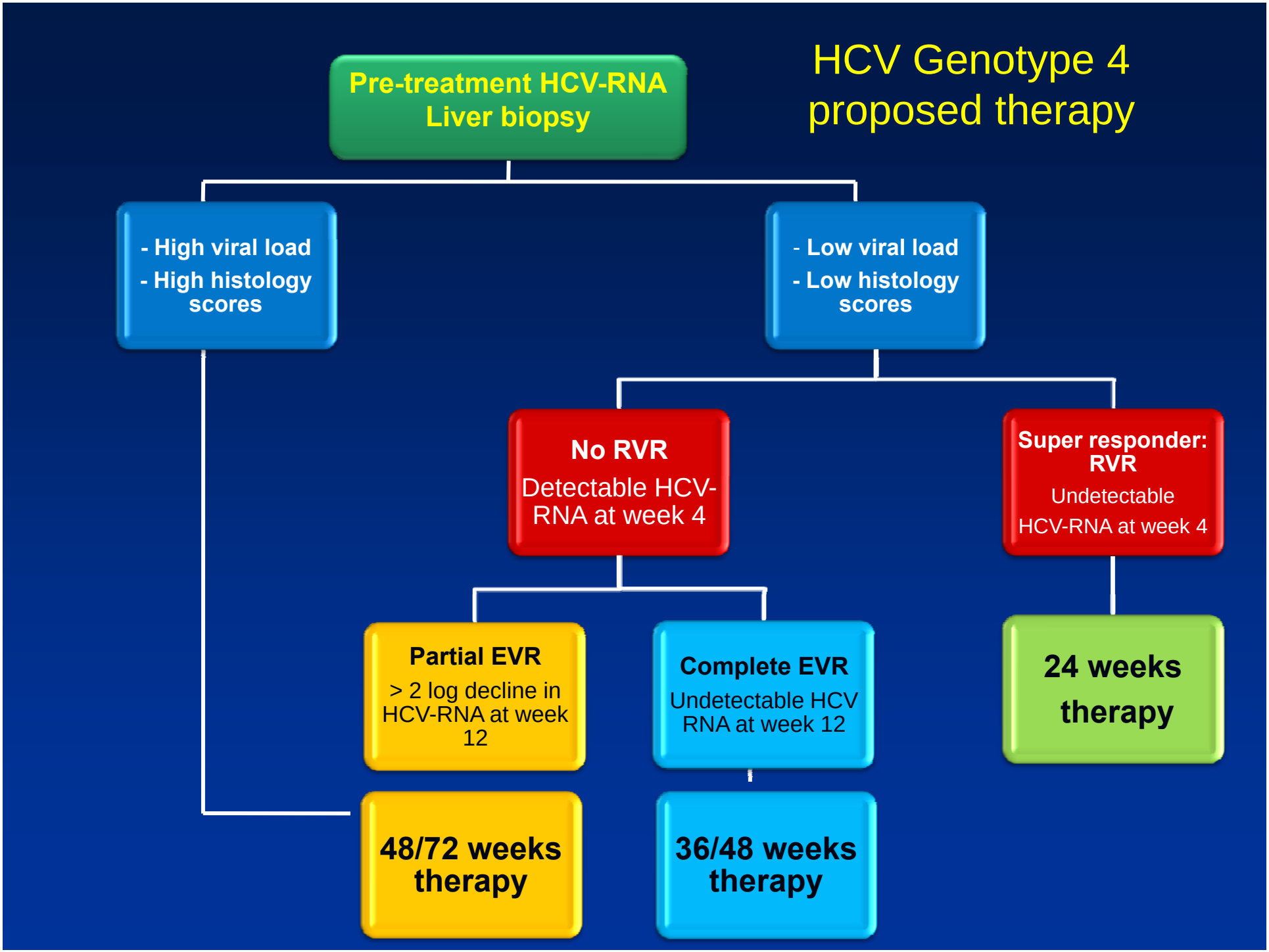
	Peg-IFN/RBV 48 wk (n 40)	**Peg-IFN/NTZ 12 36 wk (n 28)**	**Peg-IFN/NTZRBV 12 36 wk (n 28)**
RVR	15 (38%)	15 (54%)	18 (64%)*
cEVR	28 (70%)	19 (68%)	24 (86%)
EOT	30 (75%)	20 (71%)	23 (82%)
SVR	20 (50%)	17 (61%)	*22 (79%)#*

*

**P .048, compared with Peg-IFN/RBV.*
#P .023, compared with PegIFNRBV.

Rossignol et al., Gastroenterology, 2009

Any Roadmap?


HCV Genotype 4
proposed therapy
Pre-treatment HCV-RNA
Liver biopsy
- High viral load
- High histology scores
- Low viral load
- Low histology scores
No RVR
Detectable HCV-RNA at week 4
Super responder: RVR
Undetectable HCV-RNA at week 4
Partial EVR
> 2 log decline in HCV-RNA at week 12
Complete EVR
Undetectable HCV RNA at week 12
24 weeks therapy
48/72 weeks therapy
36/48 weeks therapy

What we do not know

Non-responders

Renal Disease

HCV-G4/HIV

HCV-G4 Hemophiliacs

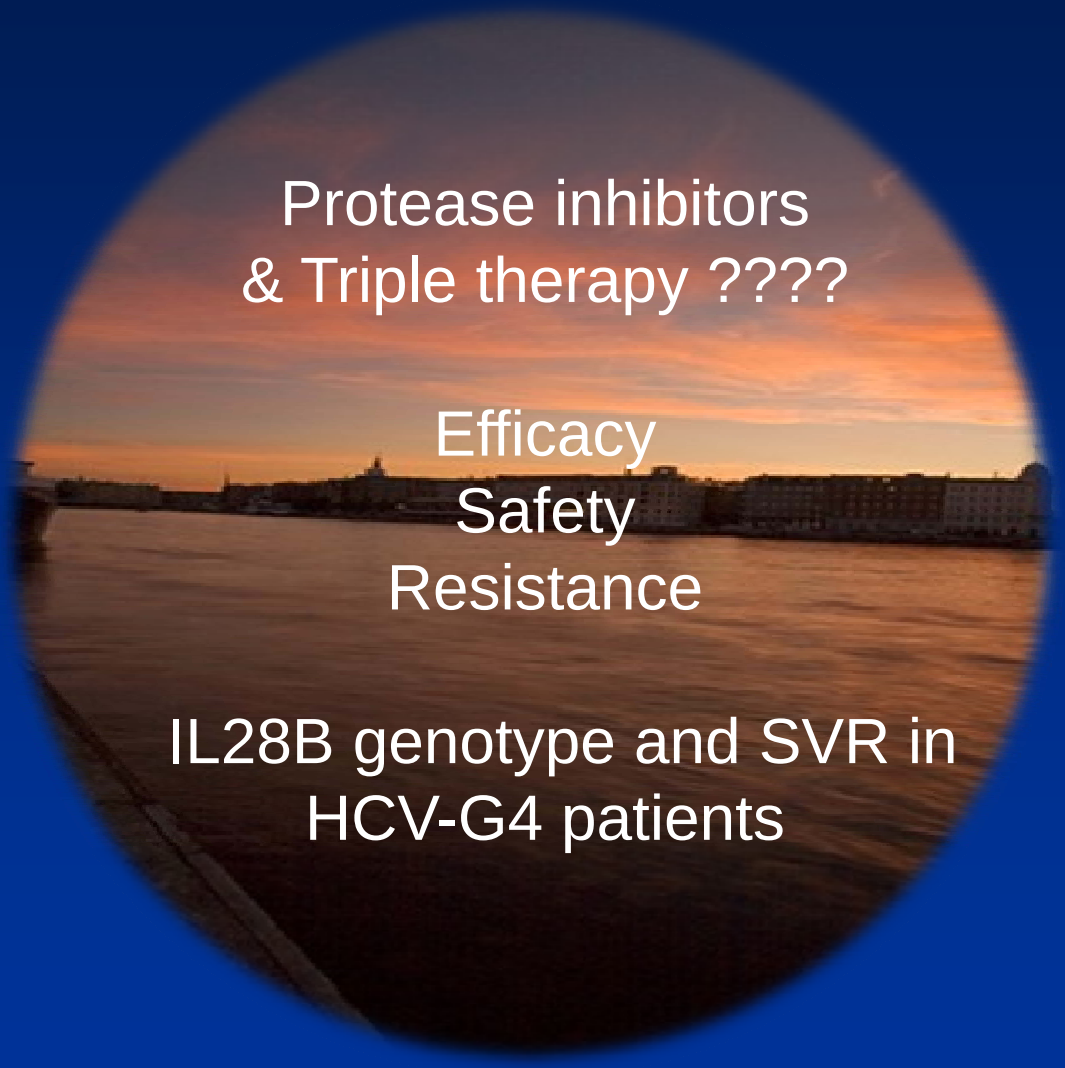
HCV/Schisto

HCV/HBV

Neuro-pshychiatric

Diabetics

What is in the Horizon?



Protease inhibitors
& Triple therapy ????

Efficacy
Safety
Resistance

IL28B genotype and SVR in
HCV-G4 patients

Summary

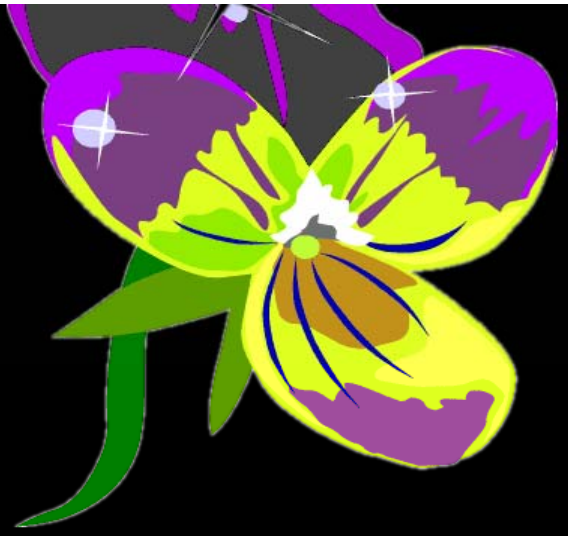
- Hepatitis C genotype 4 has started to spread beyond it strongholds in Africa and the Middle East to Western countries.

- Recent clinical data have provided new insights on hepatitis C genotype 4 infections and have started to refine the treatment strategies.

- Baseline viremia, early viral kinetics, treatment duration, and stage of liver disease represent important considerations that can be used to individualize therapy.

- Further studies are needed to investigate the response of naïve and treatment experiences HCV-G4 patients to triple therapy.

- Further studies are needed to investigate the impact of genetic make-up and IL28B genotype on response rates of HCV-G4 patients



Thank you

Merci

What we have??

HCV-G4 Clinical trials

- 26 published clinical trials on HCV-G4 therapy (PEG-IFN/RBV therapy) with 1385 patients
- 12 registered ongoing trials
- Five randomized clinical trials
- Four trials on duration of therapy
- Enrolled patients: Egyptians, Saudis, French, Spanish, Greek, Italian, Africans

HCV-G4 Clinical trials

- Three trials on HCV-G4/HIV coinfected patients
- Two trials on HCV-G4 heamophliacs
- One trial on non-responders
- One trial on extended therapy.

Case 1

- Mr. A, a 29 y old engineer, was informed during his pre-employment physical that his liver enzymes were elevated (ALT: 175 U/L).
- He had no symptoms and his physical examination revealed no abnormalities and his liver was not enlarged.
- He could not recall how, when or where he got the infection
- No history of drugs or alcohol
- Positive antibodies to HCV, HCV-PCR: 850, 000 IU/L, HCV genotype 4.

Treat? Wait?

Is it important to know Mr. A's ethnic background?

Mr. A's Questions

- He was recently married.
- He is frustrated
- He will be subjected to another medical examination after 3 months.
- He could not recall how, when or where he got the infection

Mr. A's labs

- ALT: 175 U/L
- HCV-PCR: 650, 000 IU/L
- Genotype 4

Mr. M's questions:

- Is treatment possible?
- Is there a possibility of transmitting the infection to his wife?
- What are the odds for having normal liver enzymes and negative HCV values after 3 months of therapy?
- If treatment is considered will he be able to fly? When?

What to do at this time?

- Request a liver biopsy
- Do an ultrasound only
- Request more investigations
- Wait and see

Case Presentation 3

Case Study #4

- 38-year-old Greek man
- Diagnosed with HIV since 2005
- Doing well on HAART
- He stopped using drugs (heroin).
- He has recently separated from a partner of 3 years.

Case Presentation 3

- Mr. H, a 21 y old man accidentally discovered elevated liver enzymes and positive antibodies to HCV during check-up.
- His physical examination revealed no abnormalities and his liver was not enlarged.
- His blood picture, renal profile, thyroid profile were within normal
- He had no symptoms

History:

- Depression since 5 years
- Tri-cyclic antidepressant: 4 years
- History of IDU for 3 years
- Admitted to rehab for 6 months with withdrawal
- Relapse after 3 months.
- Readmitted to rehab and abstained for 1 year.

Lab:

- ALT: 215 U/L
- HCV-PCR: 850, 000 IU/L
- Genotype 4

A liver biopsy was performed revealing

A2 and S 0

based on the METAVIR scoring system

Case Study #4

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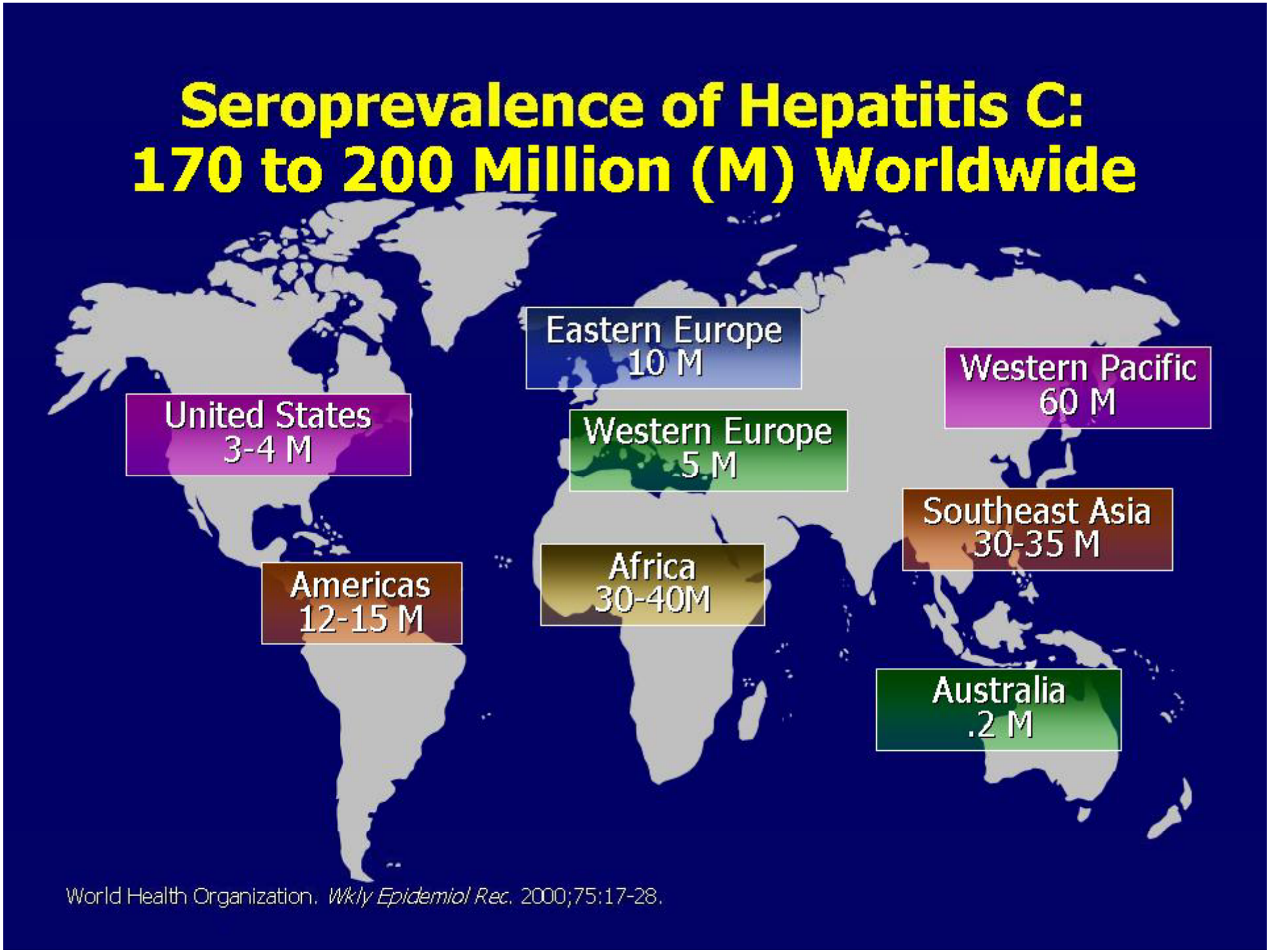
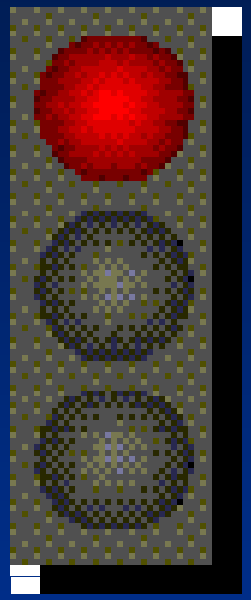
Seroprevalence of Hepatitis C: 170 to 200 Million (M) Worldwide



World Health Organization. *Wkly Epidemiol Rec.* 2000;75:17-28.

- Treat or not to treat?
- Treat for how long?
- What about his depression?
- What about his addiction problem?



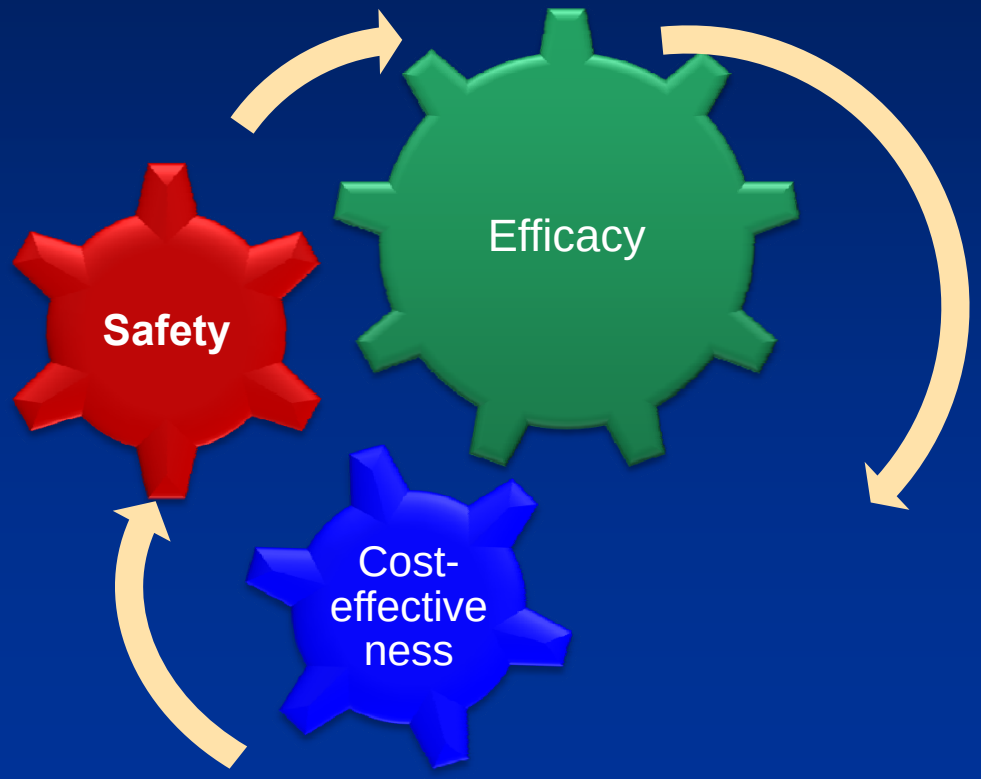
Case Study # 4

July 2007

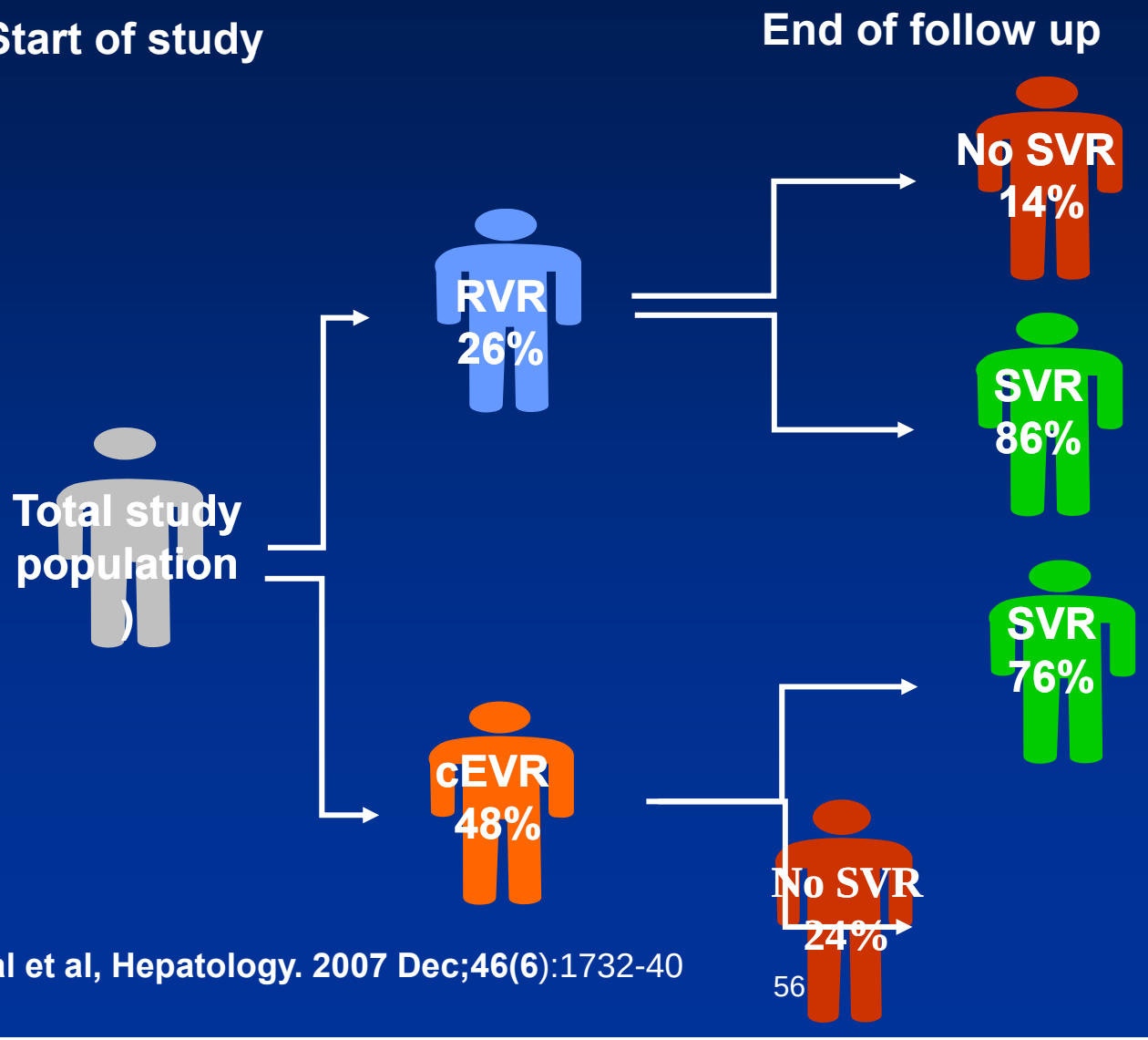
- **ALT: 217 U/L**
- **HCV-AB positive**
- **HCV RNA: 1.2 M U/ml**
- **Genotype 4**
- **Liver biopsy: Grade 8, stage 2**
- **CD4+: 520**

What do you want to know?

Personalized therapy for chronic HCV-G4 according to on-treatment viral kinetics

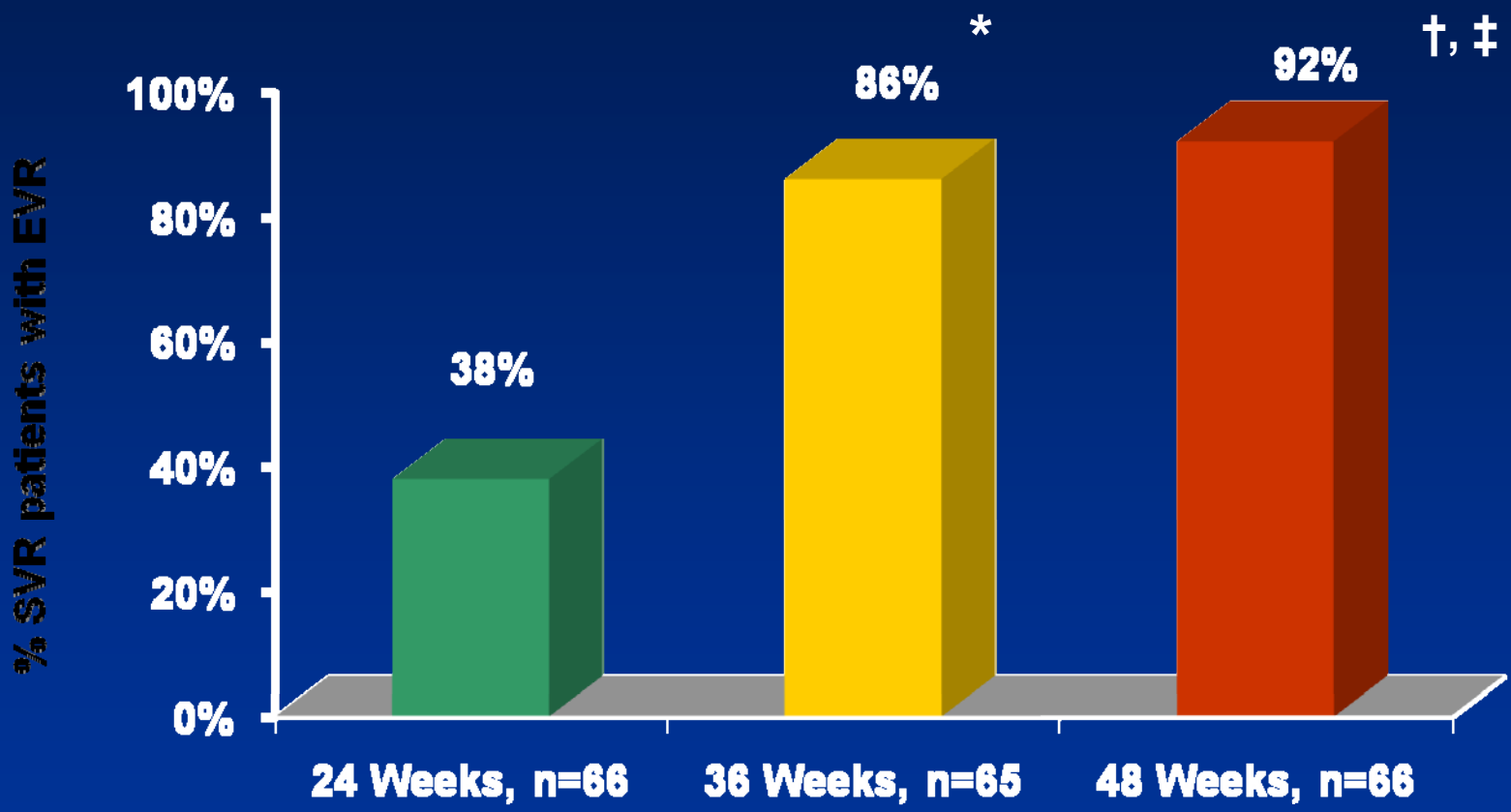


Role of RVR in Determining Treatment Duration of Peginterferon /ribavirin in Chronic Hepatitis C Genotype 4



Kamal et al, Hepatology. 2007 Dec;46(6):1732-40

Sustained Virologic Response in Patients with EVR



* p= 0.002 for 36 vs. 24 weeks
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