Treatment Algorithm in Chronic Viral hepatitis : An update in 2009

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780-850 A.C. in Baghdat
Mathematician and inventor
af Algebra **(El-Harizmi)**

An **algorithm** is a step by step list of directions that need to be followed to solve a problem.

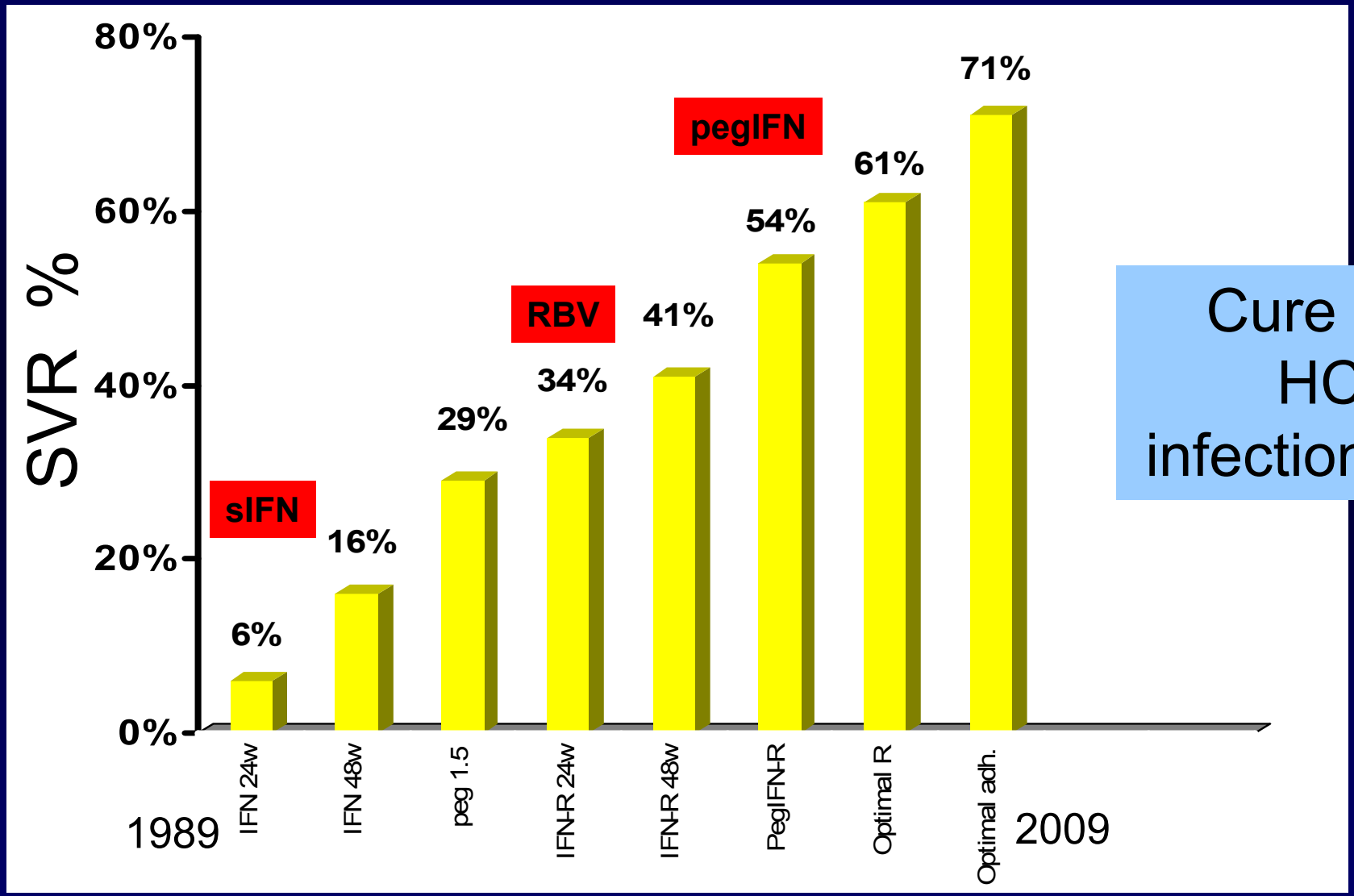
The instructions should be simple enough so that each step can be done without thinking about it.

Wikipedia

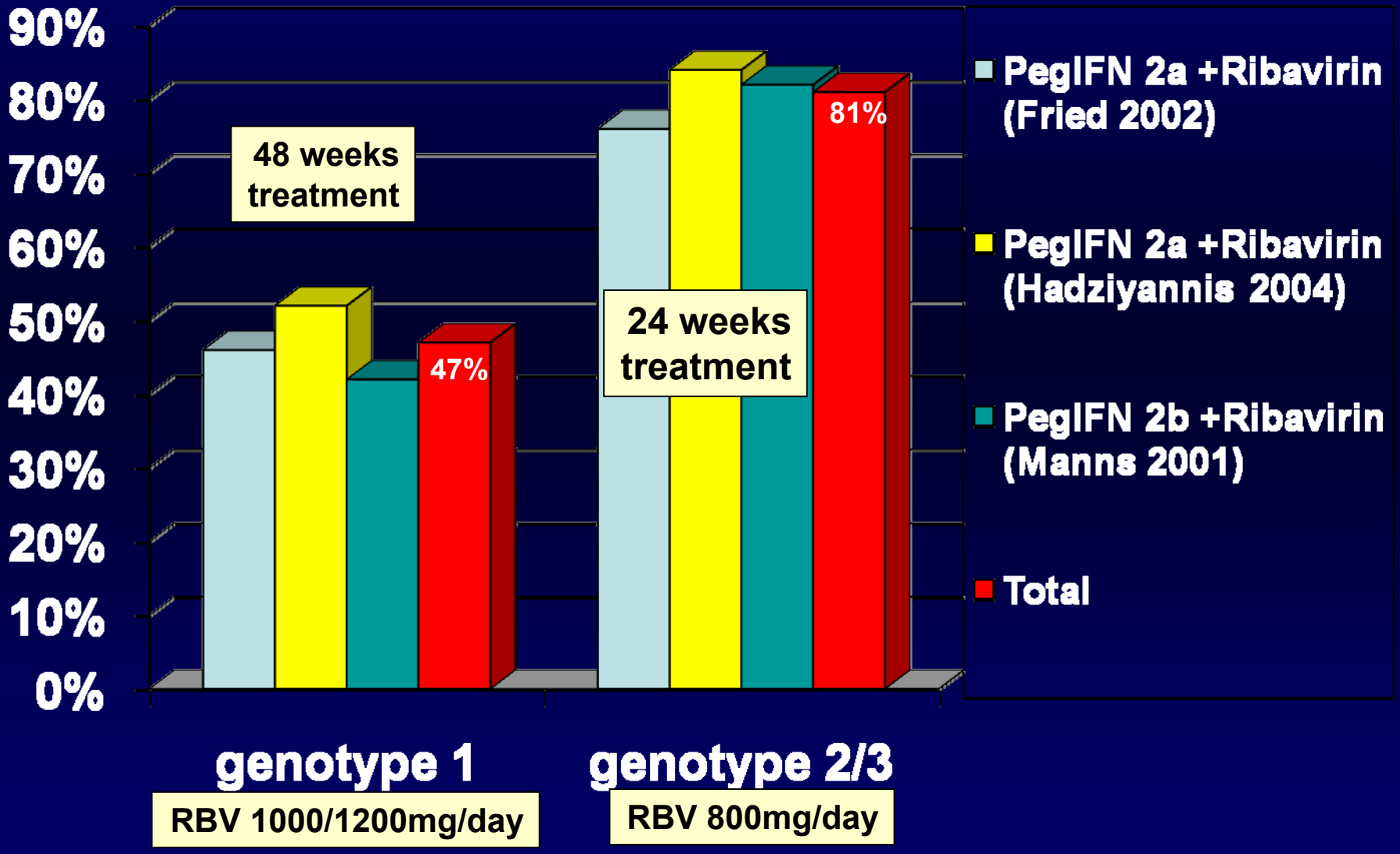
Guidelines for viral hepatitis

- Provide an evidence-based approach to management of patients with chronic viral hepatitis
- Written to assist physicians and other healthcare providers with:
  - Recognition of CVH
  - Diagnosis of CVH
  - Management/treatment of patients with CVH
- International and national guidelines are available

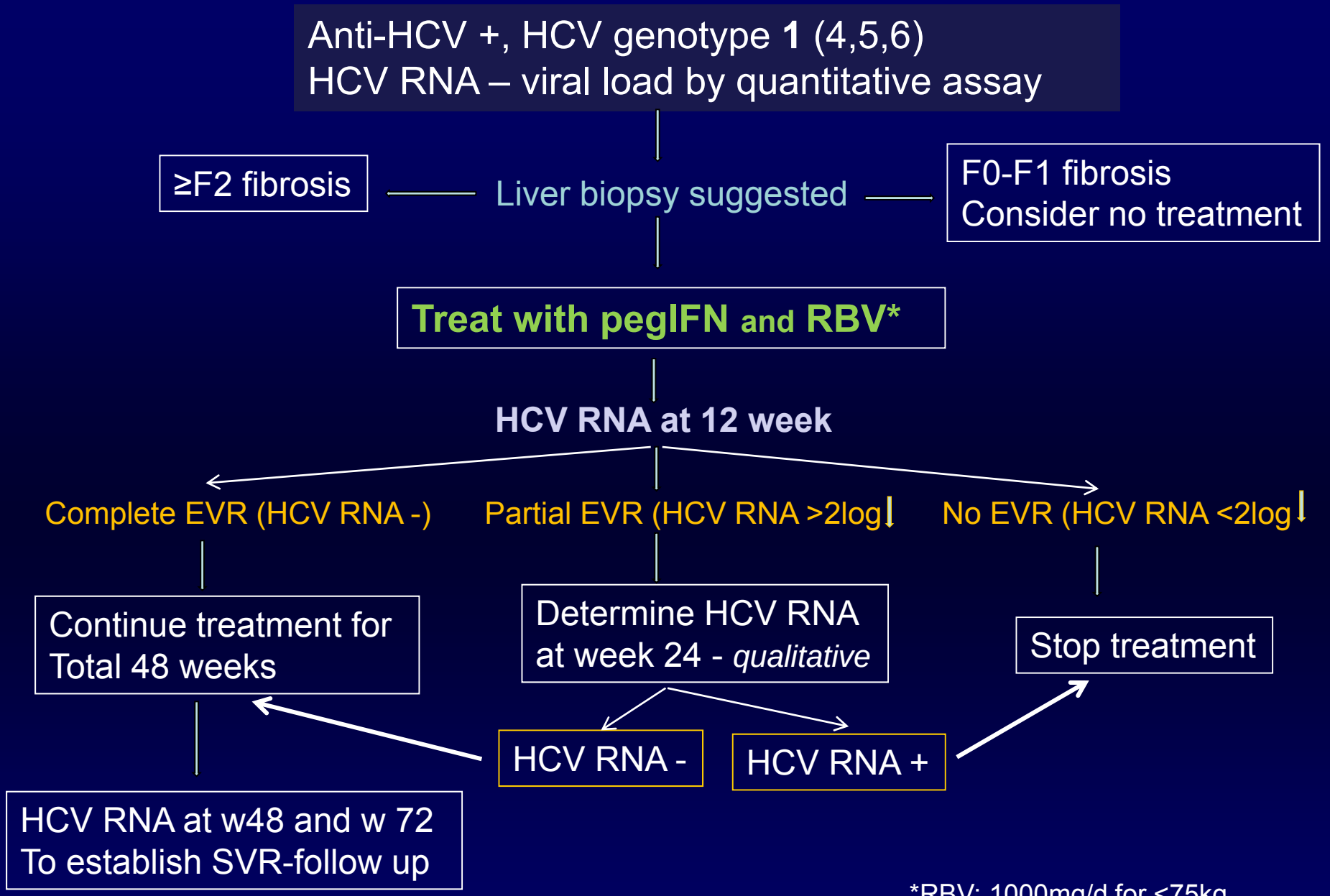
Progress in Chronic Hepatitis C treatment during the last 20 years



Registration trials in chronic hepatitis C treatment-
The rates of sustained viralogical responses*



** HCV RNA negative and ALT normal at 6 months after the treatment*

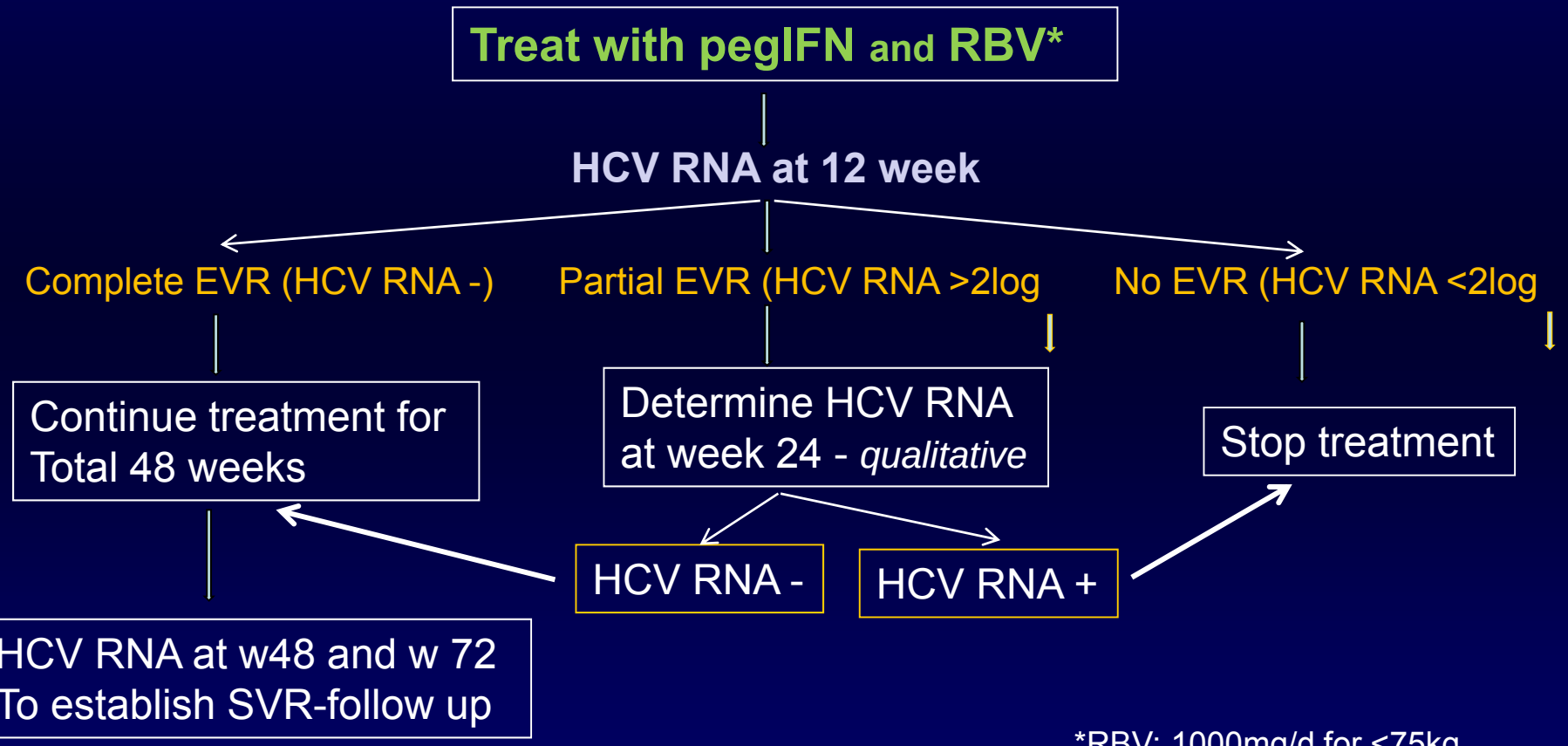


*RBV: 1000mg/d for <75kg,
1200mg/d for >75kg)
EVR: Early viral responsesponse
SVR: Sustained viral re

AASLD Practice Guidelines. Ghany et al. Hepatology 2009.

Anti-HCV +, HCV genotype **1** (4,5,6)
HCV RNA – viral load by quantitative assay

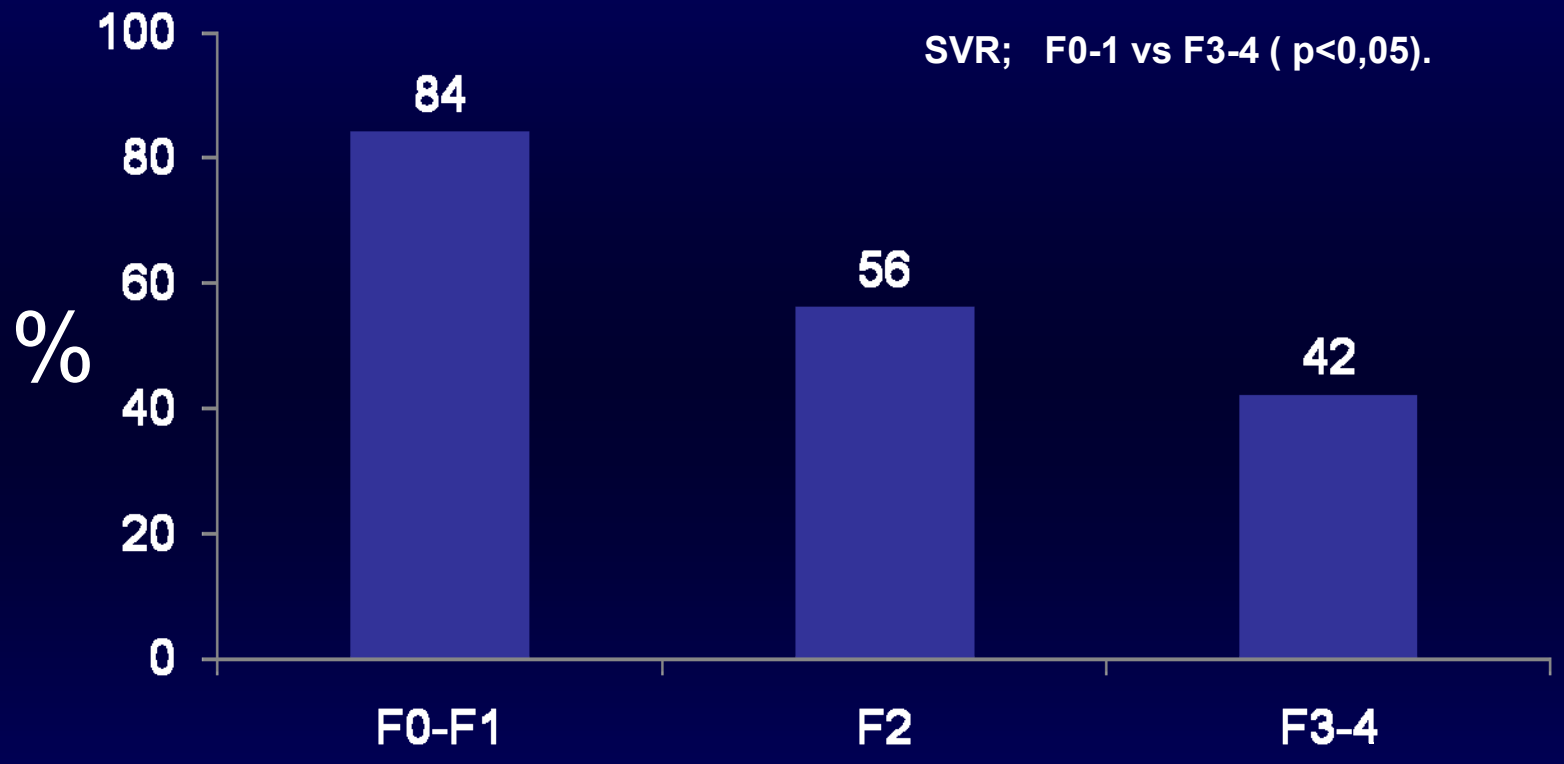
No biopsy – Biopsy is optional.. Treatment can be initiated if there is no contrindications…. ***TASL proposal and Turkish Health Autorithies ("SUT") decision…***



AASLD Practice Guidelines. Ghany et al. Hepatology 2009. TASL modifications 2009…

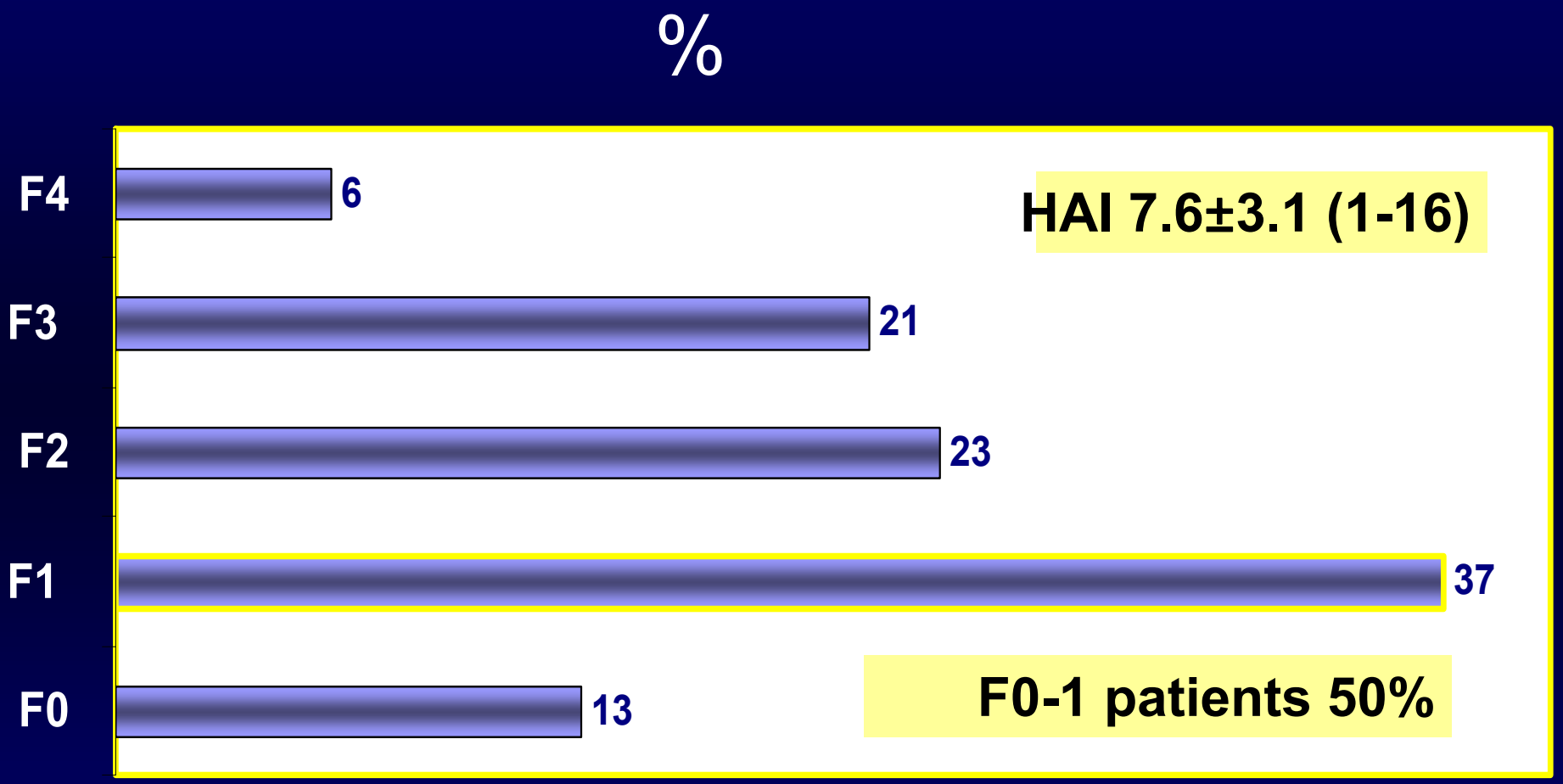
*RBV: 1000mg/d for <75kg, 1200mg/d for >75kg)
EVR: Early viral responsesponse
SVR: Sustained viral re

SVR and baseline fibrosis score (n:242)



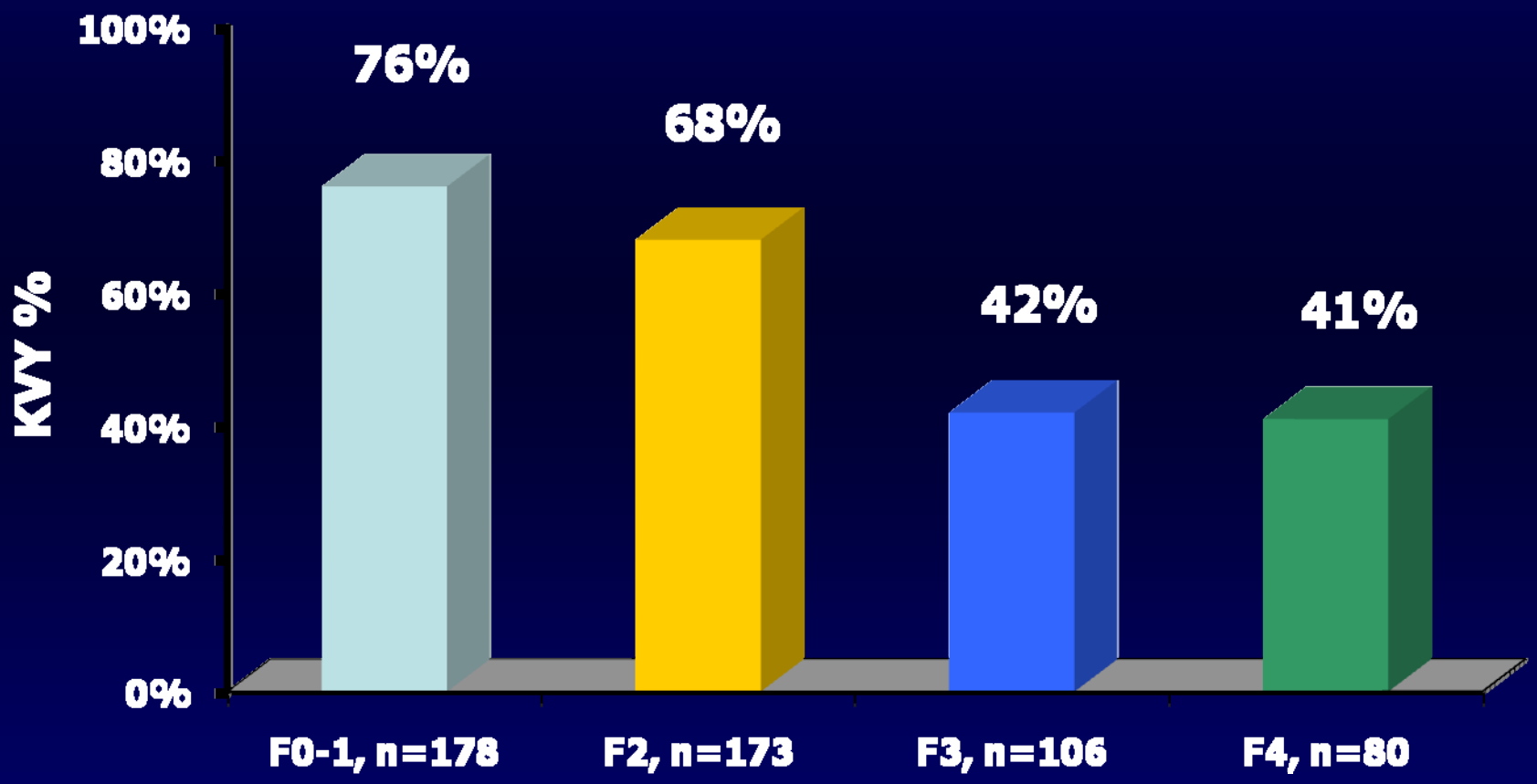
Cakaloglu et al. 2007

Pretreatment liver biopsy findings (n: 492)

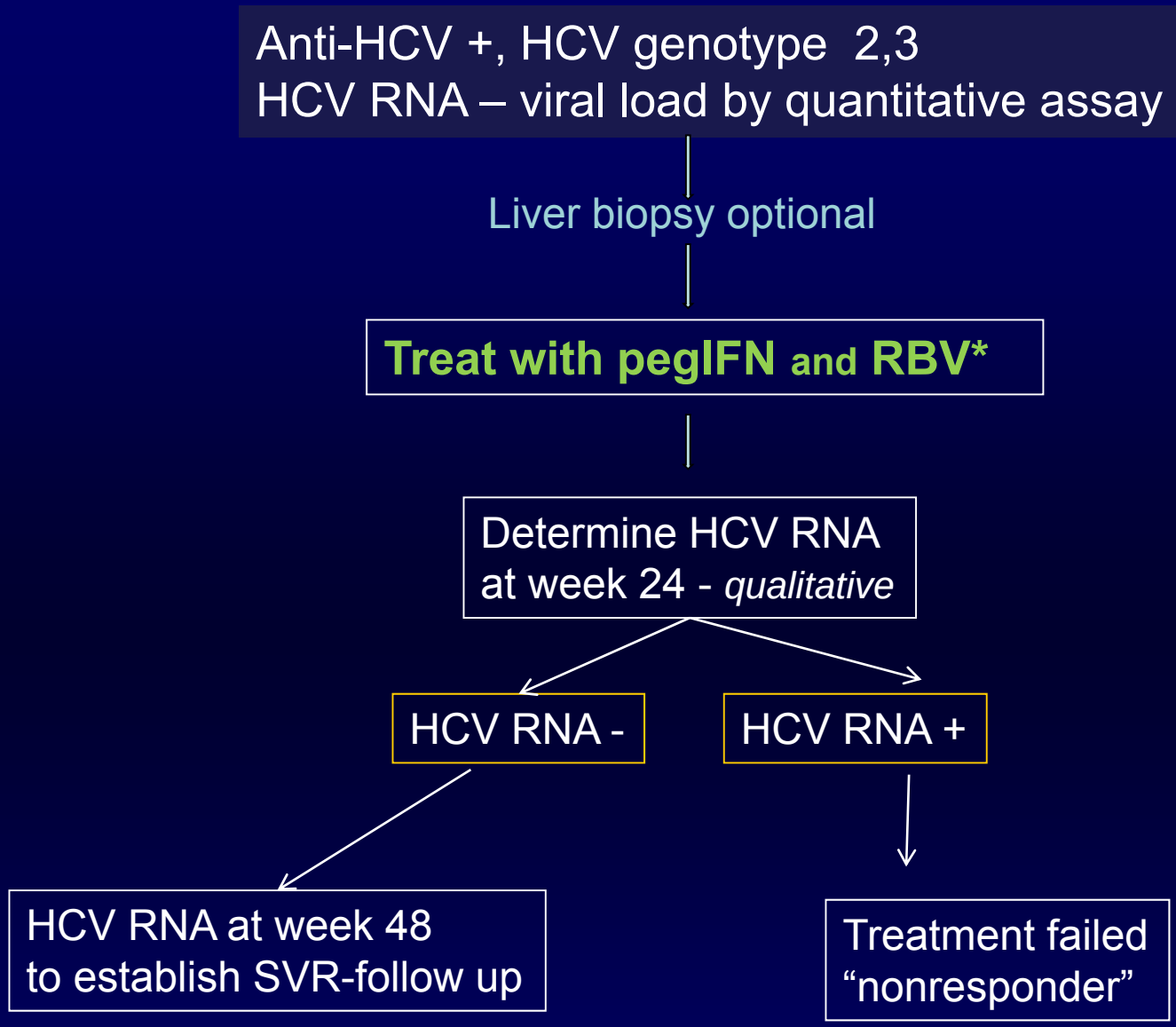


Cakaloglu et al. 2007

Sustained virological response and baseline fibrosis score, N=537



Power; Abadir et al AASLD 2005.

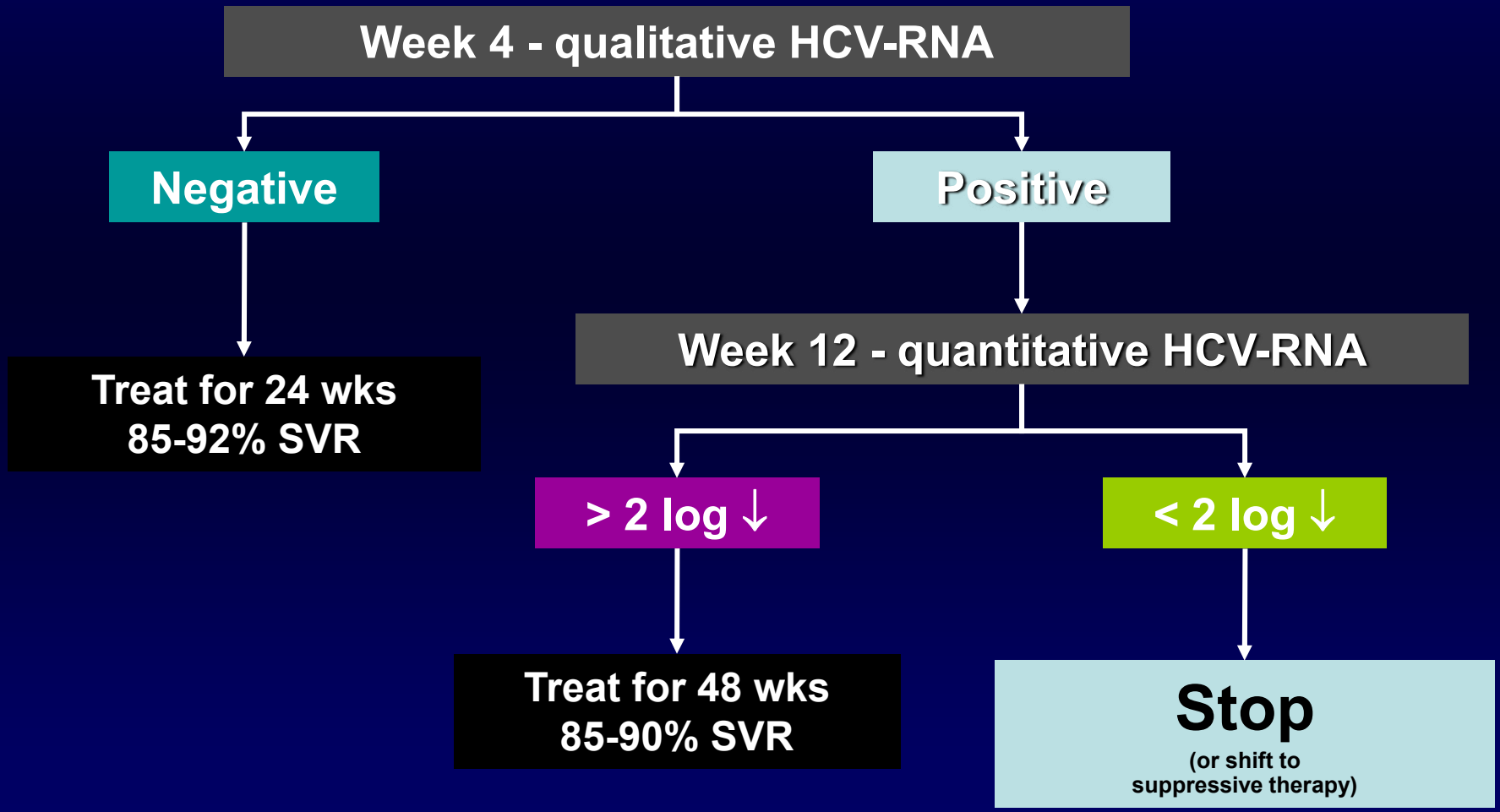


*RBV: 800mg/day
EVR: Early viral responsesponse
SVR: Sustained viralological response

AASLD Practice Guidelines. Ghany et al. Hepatology 2009.

New Schedule for Rapid Responders HCV-1 (Low Viral Load)

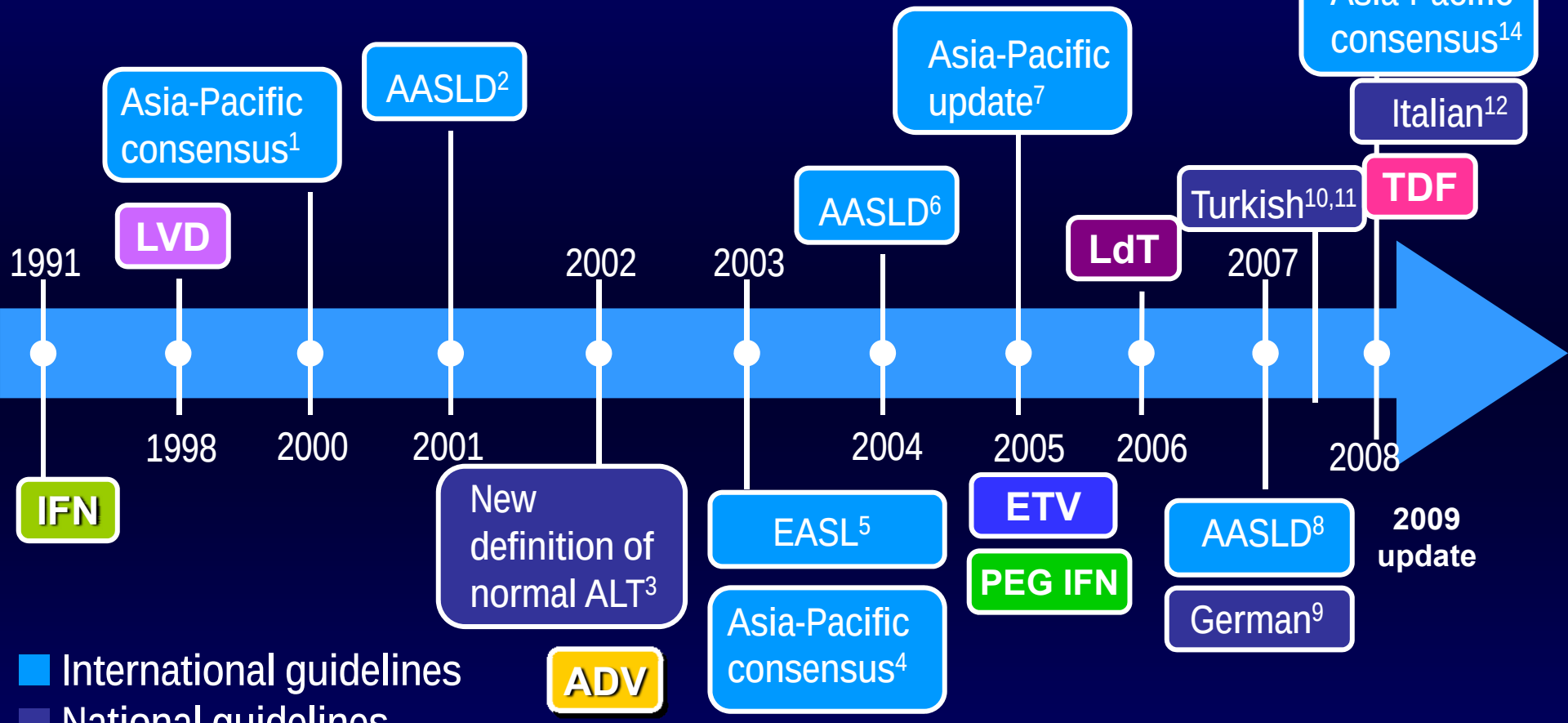
PEG-IFN α-2b 1.5 μg/kg QW + ribavirin 800-1,400 mg/day



EU approvel in 2005

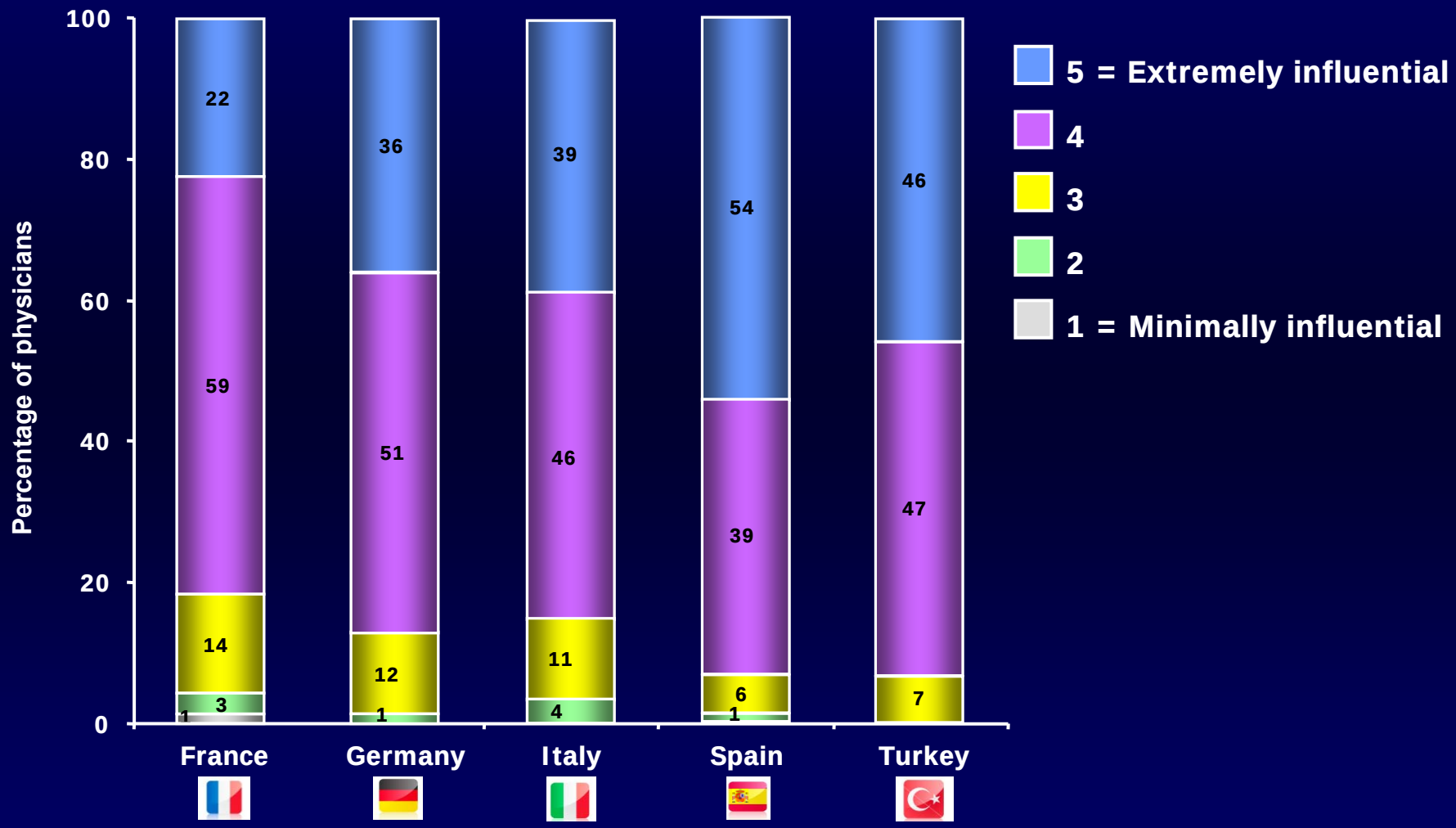
Evolution of CHB guidelines

To provide an evidence-based approach to management of patients with chronic hepatitis B (CHB)…



1. APASL working party. *J Gastroenterol Hepatol*. 2000;15(8):825-41; 2. Lok AS & McMahon BJ. *Hepatology* 2001;34:1225-41; 3. Prati D, et al. *Ann Intern Med.* 2002;237:1-10; 4. Liaw YF, et al. *Liver Int.* 2005;25:472-89; 5. The EASL Jury. *J Hepatol.* 2003;39:S3-25; 6. Lok AS & McMahon BJ. *Hepatology* 2004;39:857-61; 7. Liaw YF, et al. *Liver Int.* 2005;25:472-89; 8. Lok AS & McMahon BJ. *Hepatology* 2007;45:507-39; 9. Cornberg M, et al. *Gastroenterology* 2007;45:1281-328; 10. http://www.tasl.org.tr/UserFiles/File/HBV-kilavuz-13092007.pdf, accessed April 2008; 11. Balik I, Tabak F. Viral Hepatitle Savaşım Derneği (VHSD) Guidelines 2007; 12. Carosi G & Rizzetto M. Italian Guidelines 2008; 13. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol.* 50 (2009), doi: 10.1016/j.jhep.2008.10.001. 14. Liaw YF, et al. *Hepatol Int.* 2008;2(3):263-83.

Do we follow the guidelines?



Goals of therapy

- To improve quality of life and survival by preventing progression to:
  - **Cirrhosis**
  - **Decompensated cirrhosis**
  - **End-stage liver disease**
  - **HCC**
  - **Death**
- Goal can be achieved if HBV replication is suppressed in a sustained manner
  - The accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and HCC
- HBV infection cannot be entirely eradicated due to persistence of intrahepatic cccDNA

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol 50. (2009),

Indication for treatment

- Based mainly on the combination of 3 criteria:
  - **HBV DNA levels**
  - **Serum ALT levels**
  - **Histological grade and stage**
- Patients should be considered for treatment when:
  - HBV DNA levels >2000 IU/mL (10,000 copies/mL) and/or
  - Serum ALT levels are >1 x ULN, and
  - Liver biopsy shows moderate to severe active necroinflammation and/or fibrosis (e.g. at least grade A2, stage F2 by METAVIR scoring)

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Treatment strategies

- **Finite treatment of with PEG IFN-α or nucleoside analogues (NAs)**
  - Intended to achieve sustained off-treatment virological response
  - Mainly recommended for HBeAg(+) patients with greatest chance of seroconversion
    - High baseline ALT >3 x ULN
    - HBV DNA $<10^7$ IU/mL and
    - High HAI score in liver biopsy (≥ Metavir A2-Knodell/Ishak 6-7)
  - 48-week course of PEG IFN-α
  - NA therapy is dependent on time to HBe seroconversion

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

Finite treatment with NAs in HBeAg(+) patients

- Use the most potent agents with the highest genetic barrier to resistance
- NA therapy can be stopped 24 to 48 weeks after HBe seroconversion
- HBsAg should be checked every 6 months following HBe seroconversion
  - HBsAg loss rarely observed in NA-treated patients

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

Long-term therapy with NAs

- HBV DNA levels should be monitored:
  - At Week 12
  - Then every 12 to 24 weeks
- HBV DNA monitoring is critical to detect treatment failure
- HBV DNA reduction to undetectable levels (<10–15 IU/mL) should ideally be achieved to avoid resistance
- NAs are cleared by the kidneys, and appropriate dosing adjustments are recommended for patients with reduced creatinine clearance
  - Intensive monitoring (monthly in the first 3 months) may be required

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Definition of response

Therapy	Response	Definition
NAs	**Primary non-response**	Decrease in serum HBV DNA <1$\log_{10}$ IU/mL from baseline at month 3 of therapy
	Virological response	Undetectable HBV DNA* within 48 weeks of therapy
	Partial virological response	Decrease in serum HBV DNA >1$\log_{10}$ IU/mL from baseline, but detectable HBV DNA*. Partial virological response should be assessed at Week 24 or 48
	Virological breakthrough	On-therapy increase in serum HBV DNA of >1$\log_{10}$ IU/mL compared to nadir
IFN-α	**Primary non-response**	Decrease in serum HBV DNA to <1$\log_{10}$ IU/mL from baseline at month 3 of therapy
	Virological response	HBV DNA <2000 IU/mL at Week 24 of therapy
	Serological response	HBe seroconversion in HBeAg(+) patients

* by real-time PCR.

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

EASL compared to other international guidelines

Criteria	EASL/2009	AASLD/2007-9	APASL/2007
HBV DNA treatment threshold - HBeAg(+) (IU/mL)	2,000	20,000	20,000
- HBeAg(-) (IU/mL)	2,000	2,000–20,000	2,000
ALT treatment threshold	>ULN for the laboratory	>2 x ULN	>2 x ULN
Main factor in decision to treat	HBV DNA, ALT and liver biopsy	ALT	HBV DNA and ALT
Biopsy	● ——	Consider in certain groups	—— ●
Recommended therapy HBeAg(+) patients	PEG IFN-α or NAs (Entecavir or Tenofovir recommended)	**Tenofovir and Entecavir** or PEG IFN-α are preferred as initial treatments	Adefovir, Entecavir, Lamivudine, IFN-α or PEG IFN-α preferred (Entecavir or Lamivudine when ALT >5 x ULN)
Recommended therapy HBeAg(-) patients	As above	As above	As above but Lamivudine not recommended/ cautioned due to high resistance rate

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),
Lok AS & McMahon BJ. Hepatology 2007 and 2009 ;45:507-39. Liaw Y-F, et al. Hepatol Int. 2008;2:263-83.

EASL compared to other international guidelines

Criteria	EASL	Turkish (VHSD)	Turkish (TASL) 2007/8
HBV DNA threshold - HBeAg(+) (IU/mL)	2,000	20,000	2,000-~~20,000~~
- HBeAg(-) (IU/mL)	2,000	2,000	2,000-~~20,000~~
ALT treatment threshold	>ULN for laboratory	–	>ULN for lab.
Main factor in decision to treat	HBV DNA, ALT and liver biopsy	HBV DNA, ALT (only in HBeAg(+)) and biopsy	HBV DNA, ALT and biopsy
Biopsy	Consider in certain groups	Consider in certain groups	**Biopsy evidence needed to treat**
Recommended therapy, HBeAg(+) patients	PEG IFN-α or NAs (Entecavir or Tenofovir recommended)	Tenofovir, Entecavir Lamivudine or PEG IFN-α	NAs or PEG IFN-α Tenofovir and Entecavir superior to ADV and LMV. **PEG IFN-α not preferred if age >50 yrs and ALT<2 x ULN, or HBV DNA >2x10^6 IU/ml**
Recommended therapy, HBeAg(-) patients	As above	As above	As above

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),
Viral Hepatitle Savasim Dernegi (VHSD) Diagnosis and Treatment Guidelines, November 2007.
Turkish Association for the Study of the Liver (TASL). A guideline to diagnosis, approach, management and follow up, 2008/9.

EASL compared to other international guidelines

TASL guideline and "SUT" applications:

Ishak or Metavir
≥ F2 and/or A2 or HAI ≥9 (6)

		Turkish (VHSD)	Turkish (TASL) 2008/9
HB		,000	2,000-20,000
			2,000-20,000
			>ULN for lab.
		ALT Ag(+)) psy	HBV DNA, ALT and biopsy
B		r in certain groups	**Biopsy evidence needed to treat**
Recommended therapy, HBeAg(+) patients	PEG IFN-α or NAs (Entecavir or Tenofovir recommended)	Tenofovir, Entecavir Lamivudine or PEG IFN-α	NAs or PEG IFN-α Tenofovir and Entecavir superior
Recommended therapy, HBeAg(-) patients	As above	As above	

PegIFNs
<50 years of age
ALT>2xULN
HBV DNA <$2x10^6$ IU/ml

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Viral Hepatitle Savasim Dernegi (VHSD) Diagnosis and Treatment Guidelines, November 2007.
Turkish Association for the Study of the Liver (TASL). A guideline to diagnosis, approach, management and follow up, 2008/9.

“SUT” modification in 2009

If HBV DNA $<10^7$ IU/ml

↓

Lamivudine first line medication

↓

At w24 determine HBV DNA (-) continue with lamivudine

↓

HBV DNA detectable by PCR;

-antiviral response failure

-resistance development

↓

“add on” or switch to Tenofovir DF

“SUT” modification in 2009

?

If HBV DNA $<10^7$ copy/ml

↓

Lamivudine first line medication

↓

At w24 determine HBV DNA (-) continue with lamivudine

↓

HBV DNA detectable by PCR;

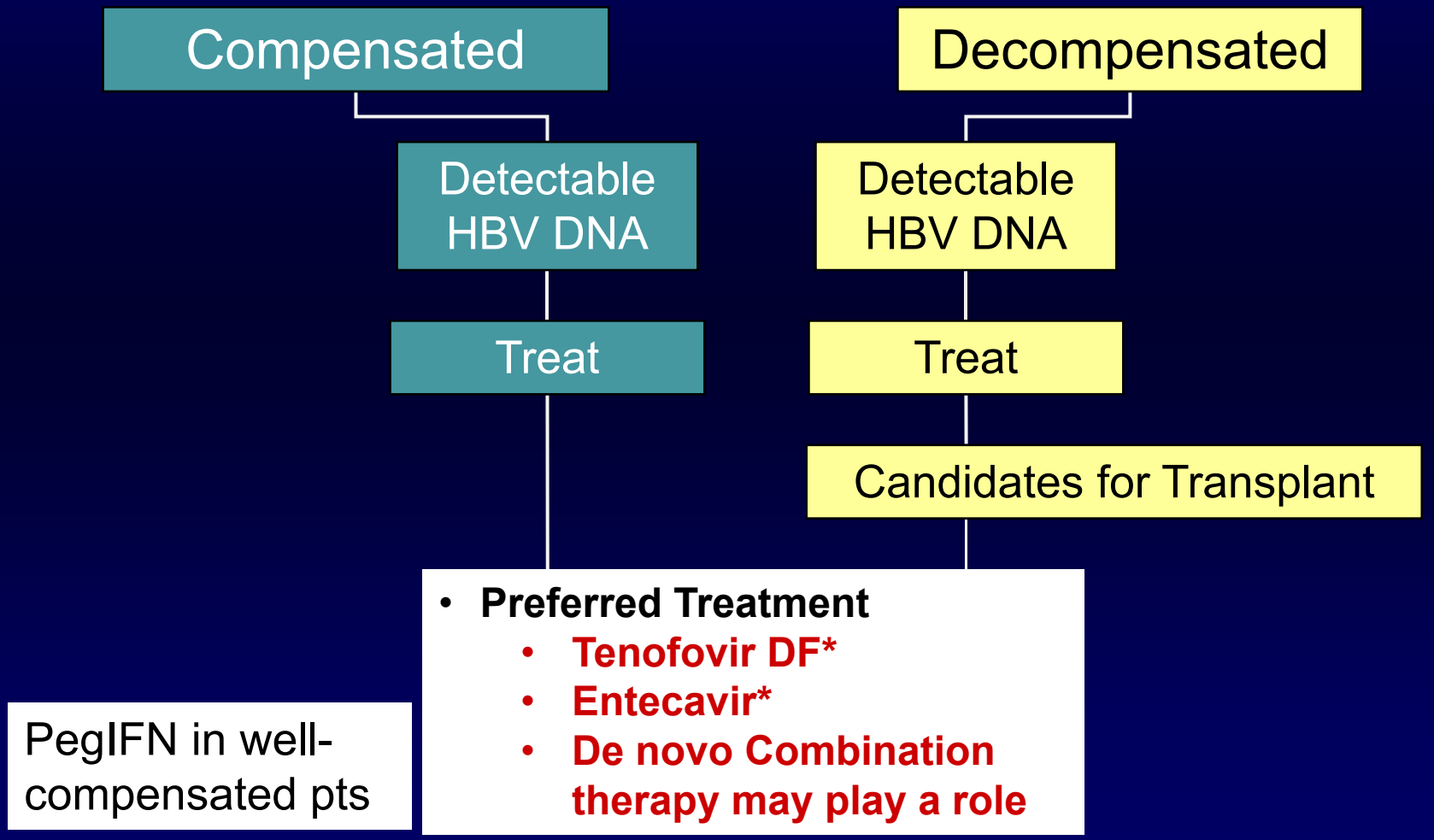
-antiviral response failure

-resistance development

↓

“add on” or switch to Tenofovir DF

Compensated and Decompensated Cirrhosis



EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

Treatment failure

- **Primary non-response**
  - Check compliance
  - In adefovir-treated patients, switch rapidly to Baraclude or tenofovir
  - In compliant patients, check for resistance and formulate a rescue strategy
- **Partial response**
  - Check compliance
  - In patients treated with lower potency drugs switch to a more potent drug, or add a more potent drug without cross-resistance
- **Virological breakthrough**
  - As early as possible, identify viral load increase and adapt treatment
  - Identify resistance profile and adapt treatment accordingly

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

Resistance

In case of resistance, initiate appropriate rescue therapy using:

- The most potent antiviral agent with minimal risk of inducing multiple drug-resistant strains

Adding on a drug without cross-resistance is the only efficient strategy

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

Cross-resistance data (*in vitro*)

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild type	S	S	S	S	S
M204I	R	R	I	S	S
L180M+M204V	R	R	I	S	S
A181T/V	I	S	S	R	S
N236T	S	S	S	R	I
L180M+M204V/I ±I169T±V173L ± M250V	R	R	R	S	S
L180M+M204V/I ±T184G±S202I/G	R	R	R	S	S

Fournier C & Zoulim F. Clin Liv Dis. 2007;11;869-92.
EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009).

Summary

- The new EASL guidelines provide clinicians with best practice on how to treat patients with CHB
- Treatment initiation should be based on:
  - Patient's health
  - HBV DNA and ALT levels
  - Assessment of liver damage
- Use a potent agent with a high barrier to resistance
- Tenofovir and Entecavir are recommended as first-line agents
- HBV treatment knowledge has increased significantly in recent years
- New guidelines recognise that many patients are at significant risk of disease progression – so recommendations have evolved

EASL Clinical Practice Guidelines: Management of chronic hepatitis B. J Hepatol. 50 (2009),

There was an old hepatologist who lived in a shoe
He had so many tests he didn't know what to do
There was e, surface, core and DNA too
But now we have "x", it's there just for you

Koretz RL. Hepatitis: Facts and Fables. In "Current Hepatology" Volume 10, Ed: Gary Gitnick, Year Book Medical Publishers Inc, Chicago 1990,p1-54.

Year 2008;

There was an old hepatologist who lived in a shoe

He had so many medications he didn't know what to do

There was IFN, lamivudine, adefovir, pegIFN and entecavir too

But now we have telbivudine and tenofovir, they'r there just for you.