How to evaluate the HCV patient in 2015

What Parameters Are Still Important

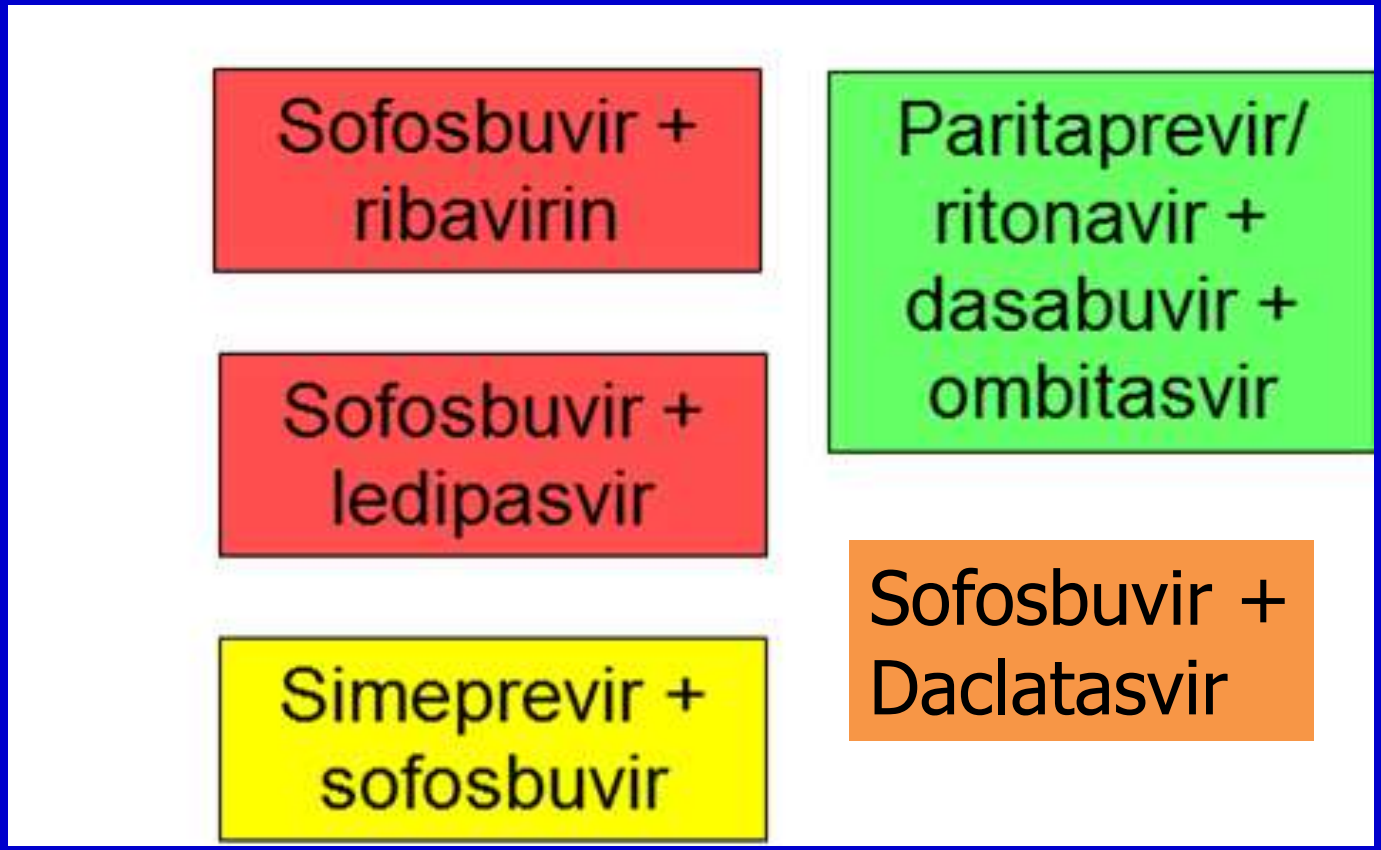
DR. SAMIR R. SHAH

Head , Dept of Hepatology
Institute of Liver Diseases, HPB Surgery and Transplant
Global Hospitals, Mumbai, India
Visiting Consultant, Jaslok and Breach Candy Hospital

Founder Trustee and Hon. Gen. Secretary
National Liver Foundation

Founder Executive Committee Member, CEVHAP

2015 : Interferon Free Regimes for HCV



Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors
- Blood transfusion prior to HCV screening in in Blood Banks
- IVDU
- Sexual exposure MSM

Comorbidities
- Diabetes, obesity
- Thyroid
- Alcohol
- Psychiatric
- HIV, HBV Co-infection

Current Medications

Treatment History

Physical:
- Signs of Cirrhosis/Decompensation
- Extra Hepatic Manifestations

ANTI HCV

Positive	Negative	Positive
Blood donors	Immunocompromised Hemodialysis	High Risk Immunocompetent
Normal SGOT/SGPT	↑SGOT/SGPT	↑SGOT/SGPT
Confirm with HCVRNA	Confirm with HCVRNA	HCVRNA Usually +ve
?FALSE +VE	?FALSE – VE	High + ve Prediction

Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors **Blood transfusion prior to HCV screening in Blood Banks**
IVDU
Sexual exposure MSM

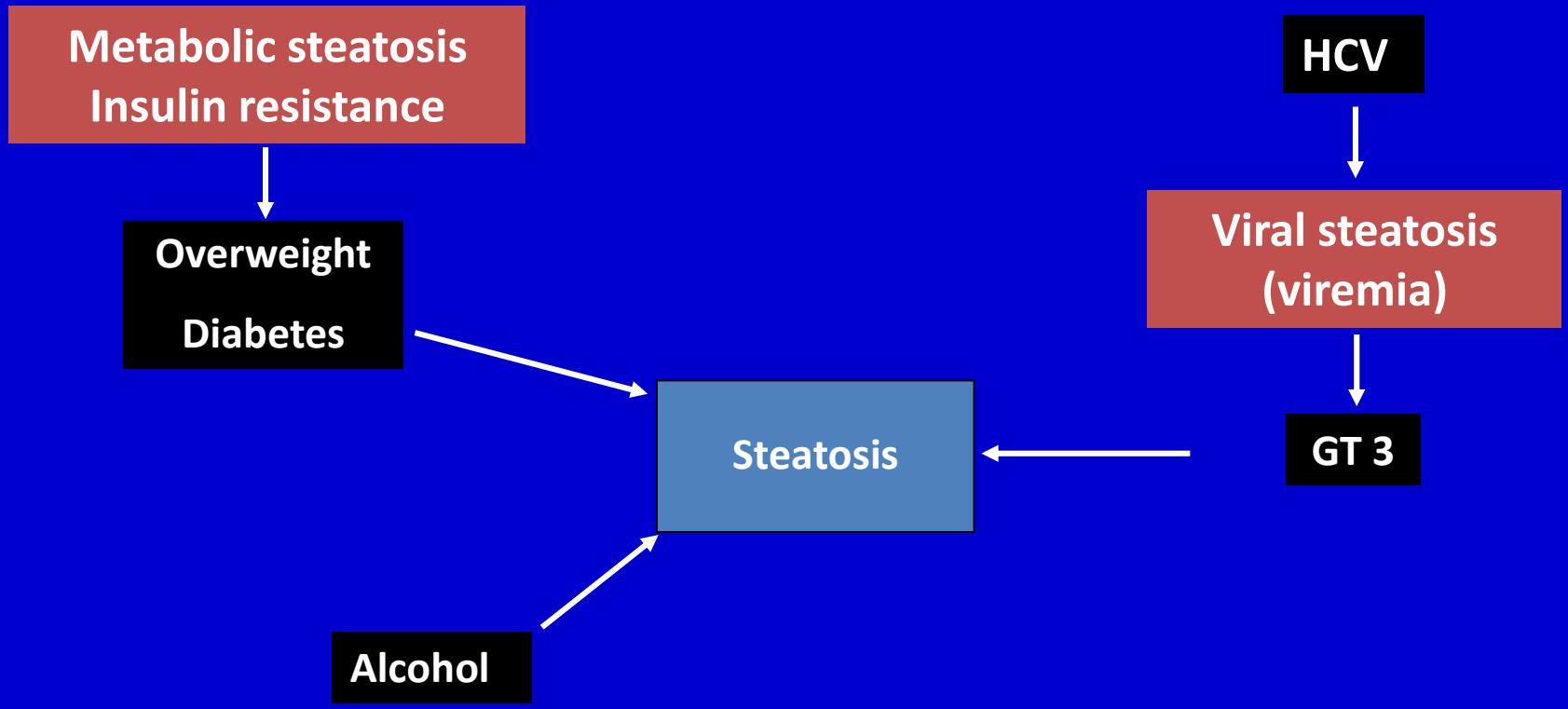
Comorbidities **Diabetes, obesity, Fatty liver**
Thyroid
Alcohol
Psychiatric
HIV, HBV Co-infection

Treatment History

Current Medications

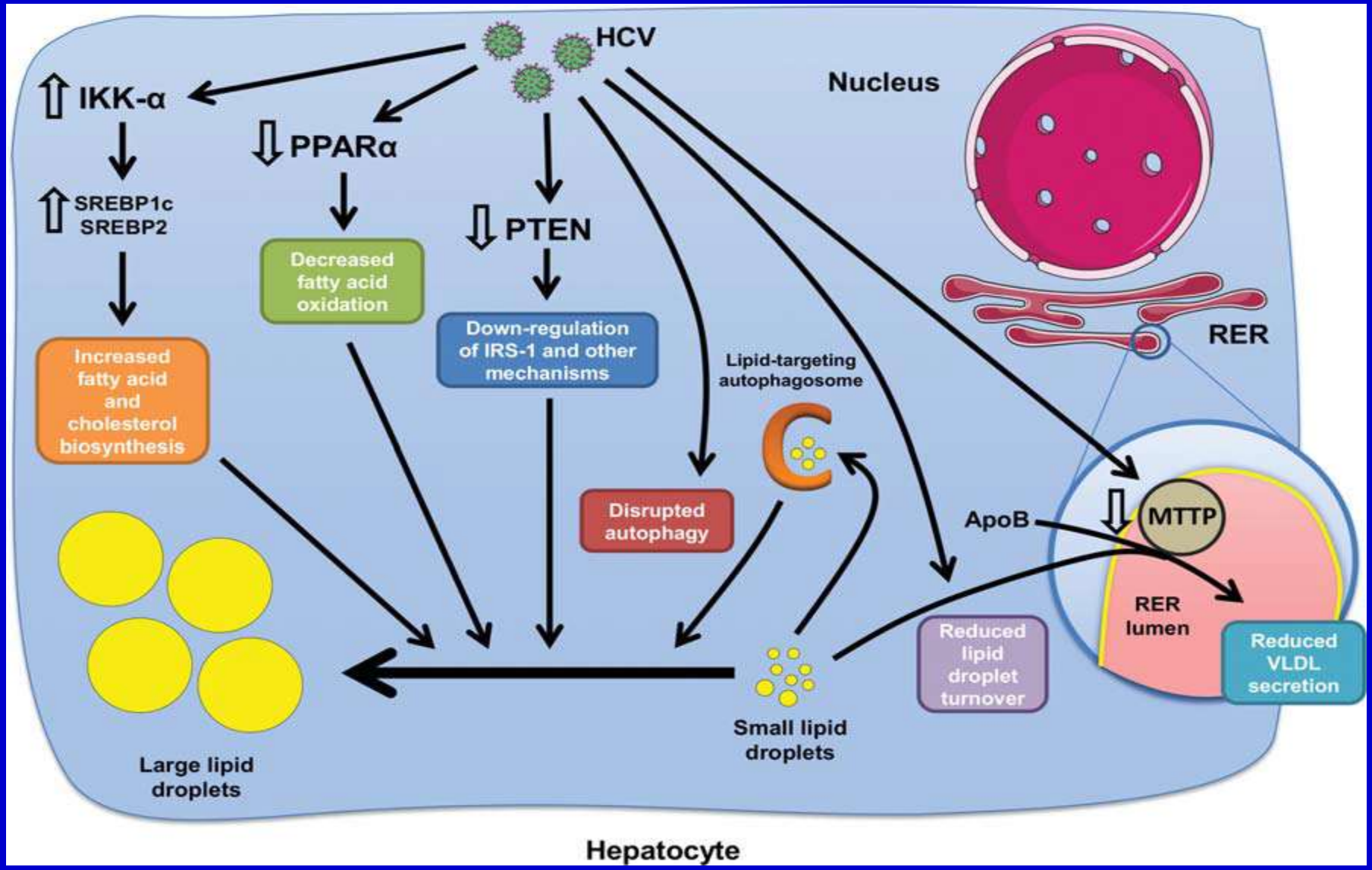
Physical: **Stigmata of CLD/Decompensation**

2 Types of Steatosis in Hepatitis C



Rubbia-Brandt L, et al. J Hepatol. 2000;33:106-115. Adinolfi LE, et al. Hepatology. 2001;33:1358-1364. Serfaty L, et al. Am J Gastroenterol. 2002;97:1807-1812. Monto A, et al. Hepatology. 2002;36:729-736. Poynard T, et al. Hepatology. 2003;38:75-85.

HCV INDUCED STEATOSIS : PROPOSED MECHANISM



Nicolas Goosens etal ,Hepatology 2014;59:2403-2412

Steatosis Is an Independent Predictor of Relapse Following RVR in HCV Geno 3

932 HCV Rx Naïve

Geno 2 : 427

Geno 3 : 505

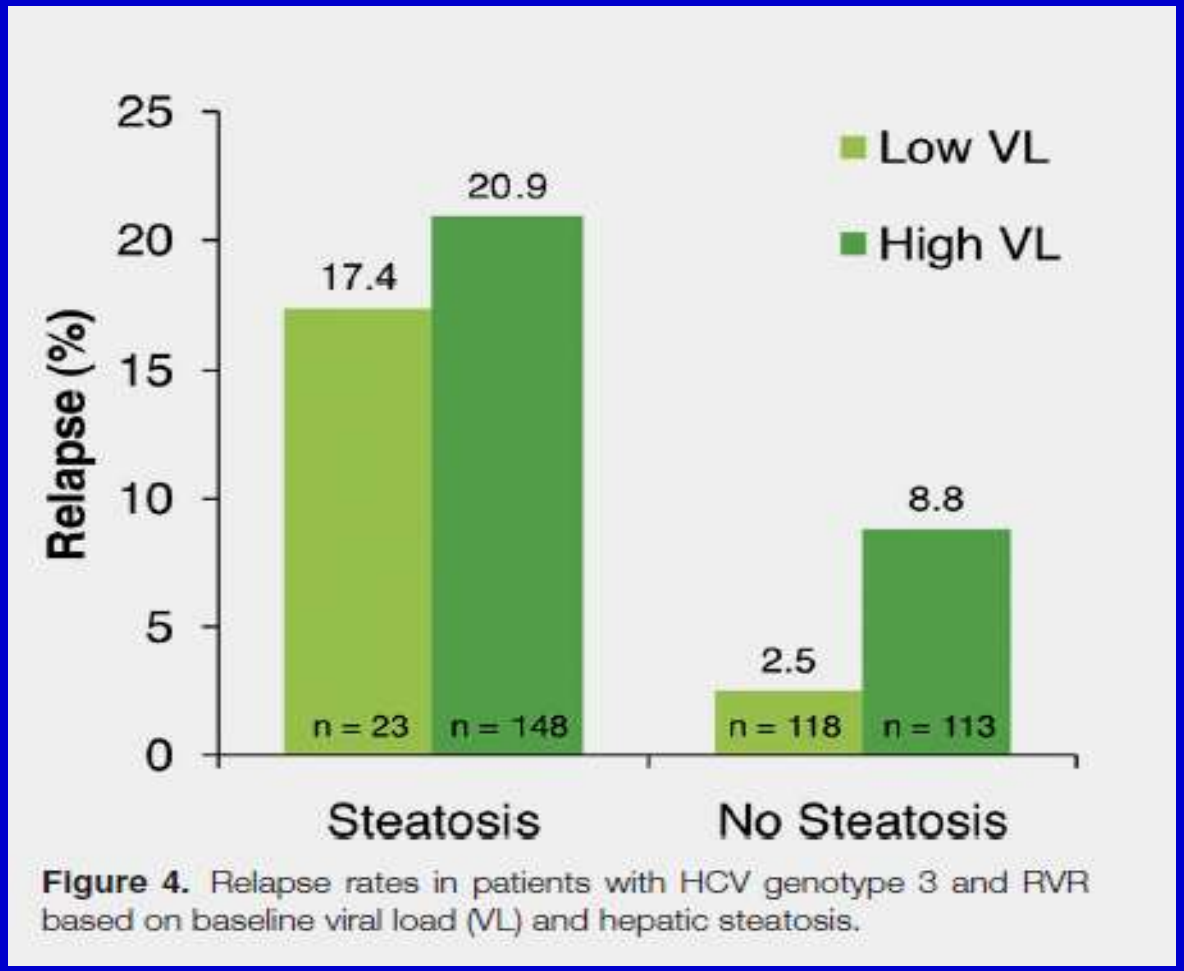


Figure 4. Relapse rates in patients with HCV genotype 3 and RVR based on baseline viral load (VL) and hepatic steatosis.

Clinical Gastroenterol and Hepatology 2011 : Aug 2011

Samir R. Shah, K.Patel, P.Marcellin, G.Foster, M.Manns, S.Kottilil, L.Healey E.Pulkstenis, G.Mani, J.McHutchison, M. Sulkowski, S.Zeuzem and D. Nelson

Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors
- Blood transfusion prior to HCV screening in Blood Banks
- IVDU
- Sexual exposure MSM

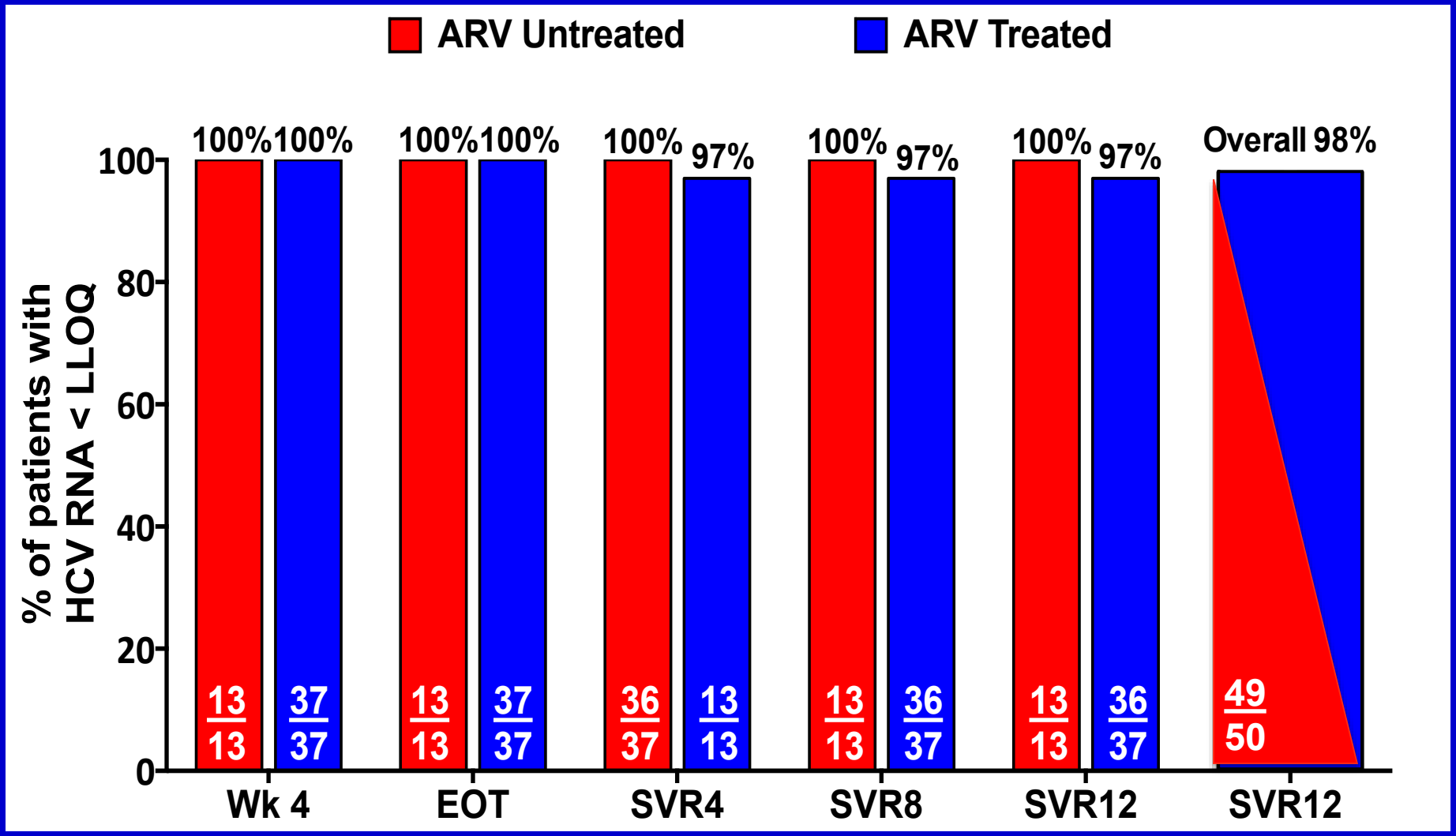
Comorbidities
- Diabetes, obesity
- Thyroid
- Alcohol
- Psychiatric
- HIV, HBV Co-infection

Current Medications

Treatment History

Physical:
- Signs of Cirrhosis/Decompensation
- Extra Hepatic Manifestations

High SVR in HIV-infection



Osinusi A. Kottilil S. JAMA 2015

Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors
- Blood transfusion prior to HCV screening in Blood Banks
- IVDU
- Sexual exposure MSM

Comorbidities
- Diabetes, obesity
- Thyroid
- Alcohol
- Psychiatric
- HIV, HBV Co-infection

Current Medications

Treatment History

Physical:
- Signs of Cirrhosis/Decompensation
- Extra Hepatic Manifestations

Drug– Drug Interactions

Cardiovascular drugs		SIM	DCV	SOF	SOF/ LDV	3D
Antiarrythmics	Amiodarone	•	•	•	•	•
	Digoxin	•	•	•	•	•
	Flecainide	•	•	•	•	•
	Vernakalant	•	•	•	•	•
Antiplatelet and anticoagulants	Clopidogrel	•	•	•	•	•
	Dabigatran	•	•	•	•	•
	Warfarin	•	•	•	•	•
Beta blockers	Atenolol	•	•	•	•	•
	Bisoprolol	•	•	•	•	•
	Propranolol	•	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•	•
	Diltiazem	•	•	•	•	•
	Nifedipine	•	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•	•
	Candesartan	•	•	•	•	•
	Doxazosin	•	•	•	•	•
	Enalapril	•	•	•	•	•

Lipid lowering drugs	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

3D: ombitasvir/paritaprevir/ritonavir plus dasabuvir combination; DCV: daclatasvir; LDV: ledipasvir; SIM: simeprevir; SOF: sofosbuvir; 3D, DCV, LDV, SIM are not licensed for use in HCV in India

EASL. J Hepatol 2015; doi.og/10.1016/j.jhep.2015.03.025

Drug– Drug interactions

CNS drugs		SIM	DCV	SOF	SOF/ LDV	3D
Anti-depressants	Amitriptyline	•	•	•	•	•
	Citalopram	•	•	•	•	•
	Duloxetine	•	•	•	•	•
	Escitalopram	•	•	•	•	•
	Fluoxetine	•	•	•	•	•
	Paroxetine	•	•	•	•	•
	Sertraline	•	•	•	•	•
	Trazodone	•	•	•	•	•
	Trimipramine	•	•	•	•	•
	Venlafaxine	•	•	•	•	•
Anti-psychotics	Amisulpiride	•	•	•	•	•
	Aripiprazole	•	•	•	•	•
	Chlorpromazine	•	•	•	•	•
	Clozapine	•	•	•	•	•
	Flupentixol	•	•	•	•	•
	Haloperidol	•	•	•	•	•
	Olanzapine	•	•	•	•	•
	Quetiapine	•	•	•	•	•
	Risperidone	•	•	•	•	•

Illicit drugs	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

3D: ombitasvir/paritaprevir/ritonavir plus dasabuvir combination;
CNS: central nervous system; DCV: daclatasvir;
LDV: ledipasvir; SIM: simeprevir; SOF: sofosbuvir;
3D, DCV, LDV, SIM are not licensed for use in HCV in India

EASL. J Hepatol 2015; doi.og/10.1016/j.jhep.2015.03.025

Sofosbuvir : Contraindicated Drugs

Class	Contraindicated Medications
Alpha-1-adrenoreceptor antagonist	Alfuzosin HCL
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital
Antihyperlipidemic agent	Gemfibrozil
Antimycobacterial	Rifampin
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine
Ethinyl estradiol-containing products	All EE-containing medications, such as oral contraceptives
Herbal	St John's Wort
HMG CoA reductase inhibitors	Lovastatin, simvastatin
Neuroleptics	Pimozide
NNRTI	Efavirenz
PDE5 inhibitor	Sildenafil when dosed for treatment of PAH
Sedatives/hypnotics	Triazolam, oral midazolam

Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

HCV-HIV Drug Interaction Scorecard

	Simeprevir[1]	Sofosbuvir[2]	Ledipasvir[3,4]	Daclatasvir[5]	AbbVie 3D[6,7]
ATV/r	No data	No data	↑ LDV, ↑ ATV[a]	DCV ↑[b]	ATV ↔; ABT450 ↑
DRV/r	SIM ↑; DRV ↔	SOF ↑; DRV ↔	↑ LDV, ↔ DRV[a]	No data	DRV ↓/↑; 3D ↓
LPV/r	No data	No data	No data	No data	LPV ↔; ABT450 ↑
TPV/r	No data	No data	No data	No data	No data
EFV	SIM ↓; EFV ↔	SOF ↔; EFV ↔	LDV ↓; EFV ↓[a]	DCV ↓[b]	No PK data[c]
RPV	SIM ↔; RPV ↔	SOF ↔; RPV ↔	LDV ↔; RPV ↔	No data	ABT450 ↑; RPV ↑
ETR	No data	No data	No data	No data	No data
RAL	SIM ↔; RAL ↔	SOF ↔; RAL ↔	LDV ↔; RAL ↔	No data	3D ↔; ↑ RAL
EVG/cobi	No data	No data	No data	No data	No data
DTG	No data	No data	No data	No data	No data
MVC	No data	No data	No data	No data	No data
TDF	SIM ↔; TFV ↔	SOF ↔; TFV ↔	LDV ↔; ↑TFV	DCV ↔; TFV ↔	3D ↔; TFV ↔

[a]Watch renal function, TFV levels increased, [b]Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD,
[c]3D + EFV led to premature study discontinuation due to toxicities

[1]Ouwerkerk-Mahadaven S, et al. IDWeek 2012, [2]Kirby AASLD 2012, [3]Harvoni Package Insert, [4]German P, et al. 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, May 19-21, 2014, Washington DC, [5]Bifano M, et al. Antivir Ther. 2013;18(7):931-40, [6]Khatri ICAAC 2014, poster 484, [7]Khatri ICAAC 2014, poster 483.

Slide Courtesy of Jen Kiser, Univ. of Colorado

Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors
- Blood transfusion prior to HCV screening in Blood Banks
- IVDU
- Sexual exposure MSM

Comorbidities
- Diabetes, obesity
- Thyroid
- Alcohol
- Psychiatric
- HIV, HBV Co-infection

Current Medications

Treatment History

Physical:
- Signs of Cirrhosis/Decompensation
- Extra Hepatic Manifestations

Decompensated Liver Disease

Change in MELD	N (%)	Mean age	Mean MELD	Mean platelet (10^9/L)	Mean albumin (g/L)	Ascites N (%)	HE N (%)	Bleeds N (%)
Improve by >2	92 (41.8)	55.2	13.6 *	78	32*	33 (35.9)	18 (19.6)	28 (30.4)
Worse by >2	23 (10.5)	57.5	10.7 *	91	29*	10 (43.5)	2 (8.7)	6 (26.1)

* $p<0.005$

- No significant MELD score change in 105 (47.7%) of patients

ILTS EXPERT PANEL CONSENSUS CONFERENCE GUIDELINES, 2006

Consider Treatment	CTP Score	MELD Score	
Strongly consider	≤7	< 18	Treat
In select cases	8 - 11	18-25	Treat Carefully but Tx planned
Treatment not advised	> 11	> 25	Consider Tx and Rx post Tx

Steven K etal, Int. J. Med. Sci 2006,3- 75-77

Treatment of HCV Pre Transplant

	DDLT	LDLT
MELD <15	Start DAA observe response	Start DAA observe response
MELD >15	If Liver available go ahead with Transplant Treat post Transplant with DAA	Start DAA Time Transplant after 4 weeks

Initial Evaluation of HCV

History : **Confirmation of Diagnosis**

Risk factors
- Blood transfusion prior to HCV screening in Blood Banks
- IVDU
- Sexual exposure MSM

Comorbidities
- Diabetes, obesity
- Thyroid
- Alcohol
- Psychiatric
- HIV, HBV Co-infection

Current Medications

Treatment History

Physical: **Signs of Cirrhosis/Decompensation**

Extra Hepatic Manifestations

Extrahepatic Manifestations

Association defined on the basis of high prevalence and pathogenesis
Mixed cryoglobulinemia (complete or incomplete clinical syndrome)
B-cell non-Hodgkin's lymphoma

Association defined on the basis of higher prevalences than in controls
Monoclonal gammopathies
Porphyria cutanea tarda
Lichen planus
Diabetes mellitus

Associations to be confirmed/characterized
Autoimmune thyroiditis
Thyroid cancer
Sicca syndrome
Alveolitis–lung fibrosis
Noncryoglobulinemic nephropathies
Erectile dysfunctions
Carotid Atherosclerosis
Psychopathological disorders

Anecdotal observations
Psoriasis
Peripheral/central neuropathies
Chronic polyarthritis
Rheumatoid arthritis
Polyarthritis nodosa
Bechet's syndrome
Myositis/dermatomyositis
Fibromyalgia
Chronic urticaria
Chronic pruritus
Kaposi's pseudosarcoma
Vitiligo
Cardiomyopathies
Mooren corneal ulcer
Necrolytic acral erythema

Evaluation : Assessment During Treatment

General	Complete Blood count with platelet
	Liver Profile
	Renal Profile with Estimated Creatinine Clearance
Specific	HCVRNA Quantitative and Genotype
	IL28 B
	HBsAb/IgG anti HAV
	AFP
Assessment of fibrosis	Non invasive methods
	Liver Biopsy

Evaluation : Assessing Disease Status

Gastroscopy

USG/CT/MRI

Anemia and HCV Treatment

- Gene variants leading to ITPA deficiency protects against anemia
- HCV Treatment related anemia associated with higher SVR
- Drop in Hb >3gms% - 43.7% v/s. 29%
- Early onset anemia ≤8 weeks treated with EPO higher SVR 45% v/s. 26% and lower discontinuation 12.6% V/s. 30%
- No impact of EPO on late onset anemia

Sulkowski et al Gastro 2010, Nov 139(5) 1602-11

LDV/SOF ± RBV in Compensated Cirrhosis: Safety Highlights

Pts, n (%)	LDV/SOF 12 and 24 Wks (n = 251)	LDV/SOF + RBV 12 and 24 Wks (n = 262)	Total (N = 513)
AE leading to study drug modification/discontinuation	3 (1)	38 (15)	41 (8)
Hemoglobin < 10 g/dL	1 (< 1)	26 (10)	27 (5)
Hemoglobin < 8.5 g/dL	0	3 (1)	3 (< 1)

- Safety outcomes in pts with cirrhosis similar to those previously reported for pts without cirrhosis
- AEs more frequent in pts who received RBV, including anemia

Bourlière M, et al. AASLD 2014. Abstract 82. Reproduced with permission.

BOSON: Pts Without SVR12 and Safety/Tolerability

Outcome	16 Wks SOF + RBV (n = 196)	24 Wks SOF + RBV (n = 199)	12 Wks SOF + PegIFN/RBV (n = 197)
On-treatment failure, n (%)	0	3 (2)	0
Relapse, n/N (%)	52/195 (27)	24/195 (12)	9/195 (5)
Other,* n (%)	3 (2)	2 (1)	5 (3)
Safety Outcome, n (%)			
▪ AEs	185 (94)	188 (95)	195 (99)
▪ Grade 3/4 AE	11 (6)	7 (4)	15 (8)
▪ Serious AE	8 (4)	10 (5)	12 (6)
▪ Tx discontinuation for AE	3 (2)	2 (1)	1 (<1)
▪ Grade 3/4 lab abnormality	30 (15)	29 (15)	74 (38)
▪ Hemoglobin < 10 g/dL	7 (4)	12 (6)	24 (12)
▪ Hemoglobin < 8.5 g/dL	0	0	2 (1)
▪ Platelets < 50,000 cells/mm^3	1 (1)	0	9 (5)

*Pts who discont. before achieving HCV RNA < LLOQ or did not return for Wk 12 posttreatment visit.

Foster GR, et al. EASL 2015. Abstract LO5. Reproduced with permission.

Early Experience with Sof Based Therapy

Treatment details	Patients	Completed treatment	Response at Wk 4	EOTR	SVR
PegIFN+ Ribavirin+ Sofosbuvir	4	2/4	2/2	2/2	NA
Sofosbuvir+ Ribavirin	41	13/41	27/28	13/13	1/1
Sofosbuvir+ Daclatsvir	6	1/6	4/4	1/1	NA
Harvoni	1	0/2	2/2	-	NA
Sofosbuvir+ Simeprevir	2	2/2	2/2	2/2	2/2
	55	18/55	37/38	18/18	3/3

Early Experience with Sof Based Therapy

	Number of patients	Completed treatment	Dosage of Ribavirin
Non Cirrhotic	**12**	**8/12**	**98.33%**
Cirrhotic	**29**	**5/29**	**<80% 14/29 48%** **<50% 5/29 17%** **10/29 needed blood transfusion** **>80% 15/29 51%**

Evaluation : Assessment During Treatment

General	Complete Blood count with platelet
	Liver Profile
	Renal Profile with Estimated Creatinine Clearance
Specific	HCVRNA Quantitative and Genotype
	IL28 B
	HBsAb/IgG anti HAV
	AFP
Assessment of fibrosis	Non invasive methods
	Liver Biopsy

Evaluation : Assessing Disease Status

Gastroscopy

USG/CT/MRI

Guidance for Renal Impairment

- If CrCl > 30 mL/min, no dosage adjustment needed with
  - LDV/SOF
  - OMV/PTV/RTV + DSV
  - SMV
  - SOF
- If CrCl < 30 mL/min, consult with expert—limited safety and efficacy data available

AASLD/IDSA HCV Guidelines.

Evaluation : Assessment During Treatment

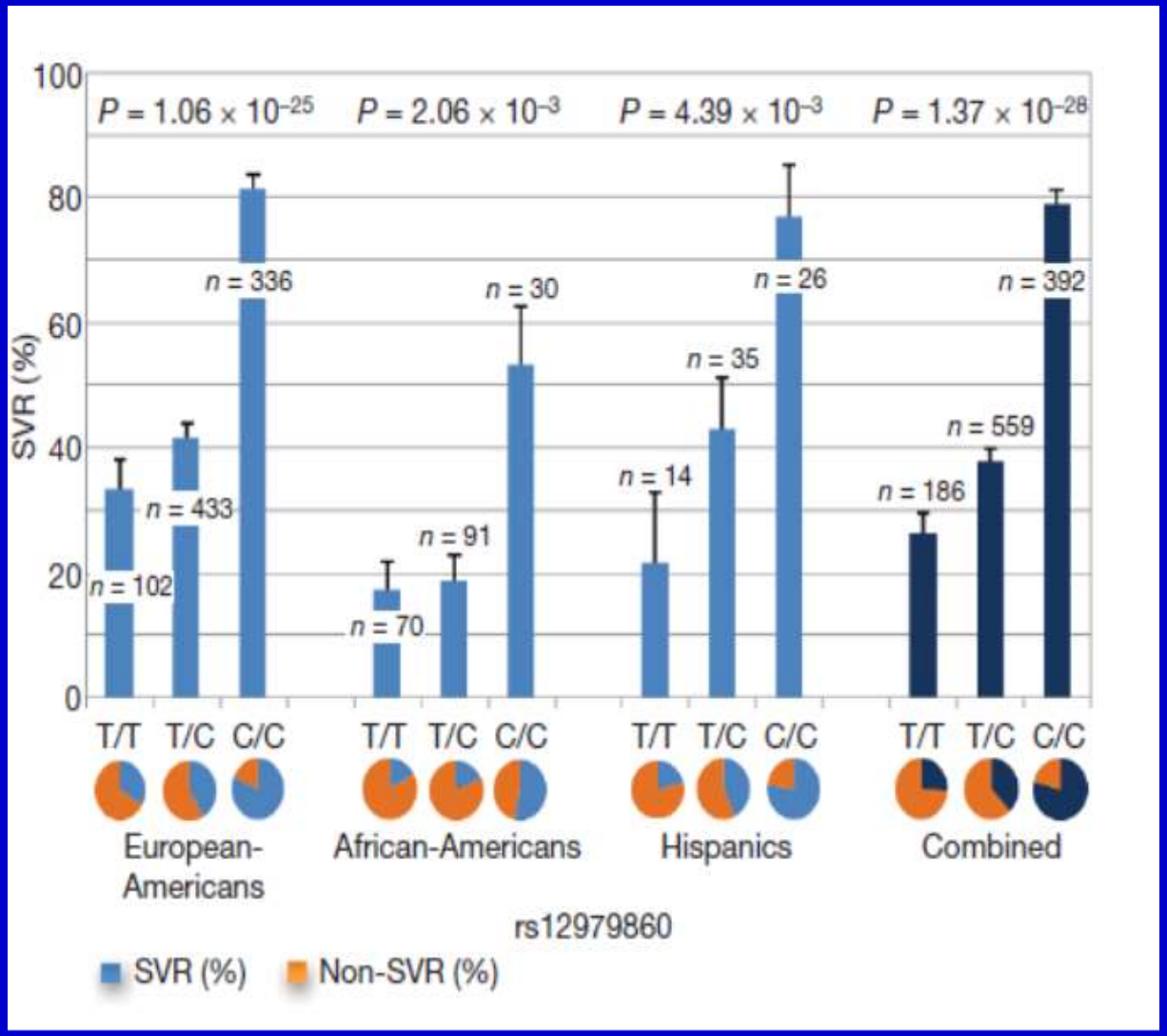
General	Complete Blood count with platelet Liver Profile Renal Profile with Estimated Creatinine Clearance
Specific	HCVRNA Quantitative and Genotype IL28 B HBsAb/IgG anti HAV AFP
Assessment of fibrosis	Non invasive methods
	Liver Biopsy

Evaluation : Assessing Disease Status

Gastroscopy

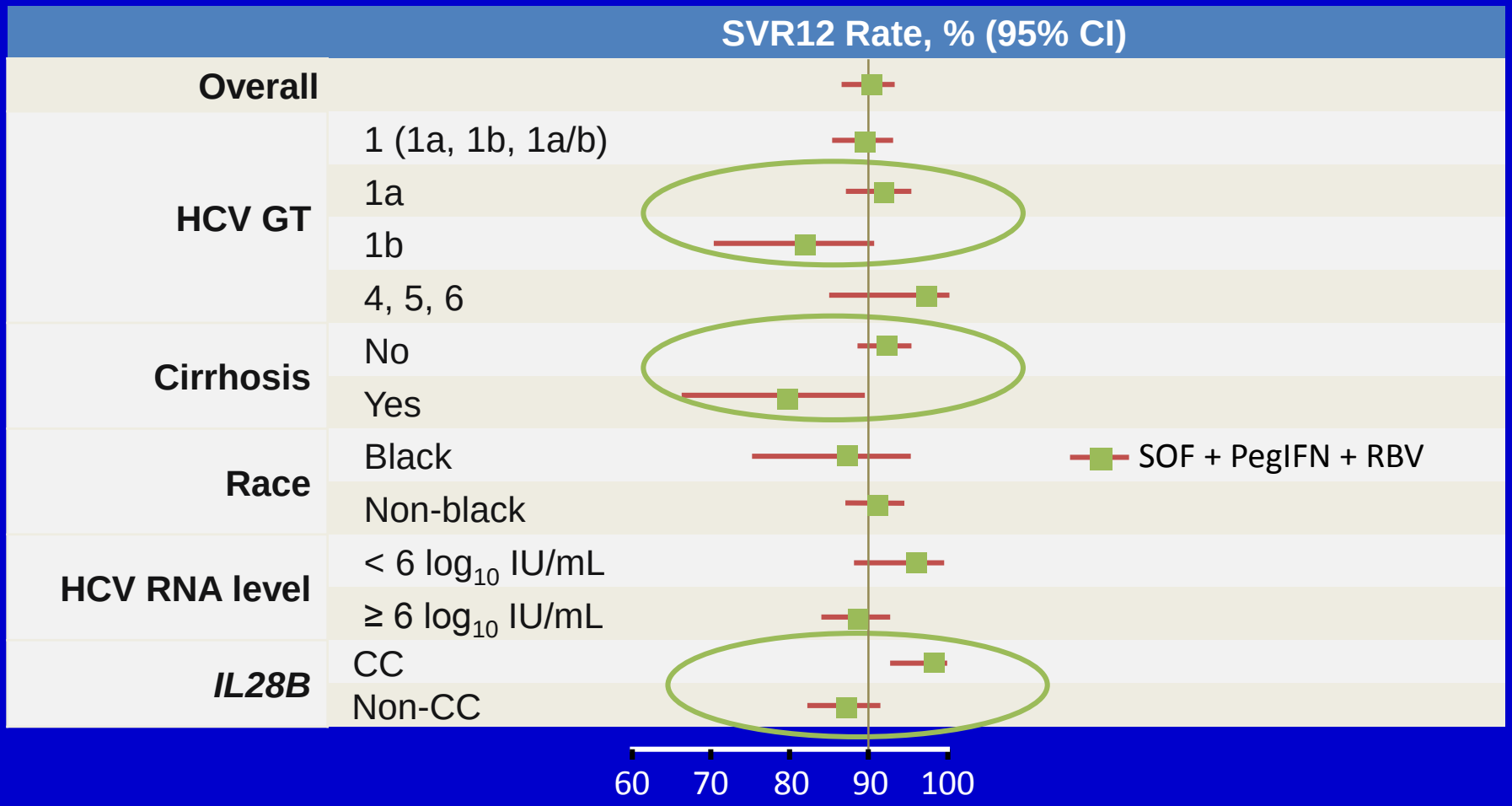
USG/CT/MRI

C allele associated with PegIFN and RBV in IDEAL



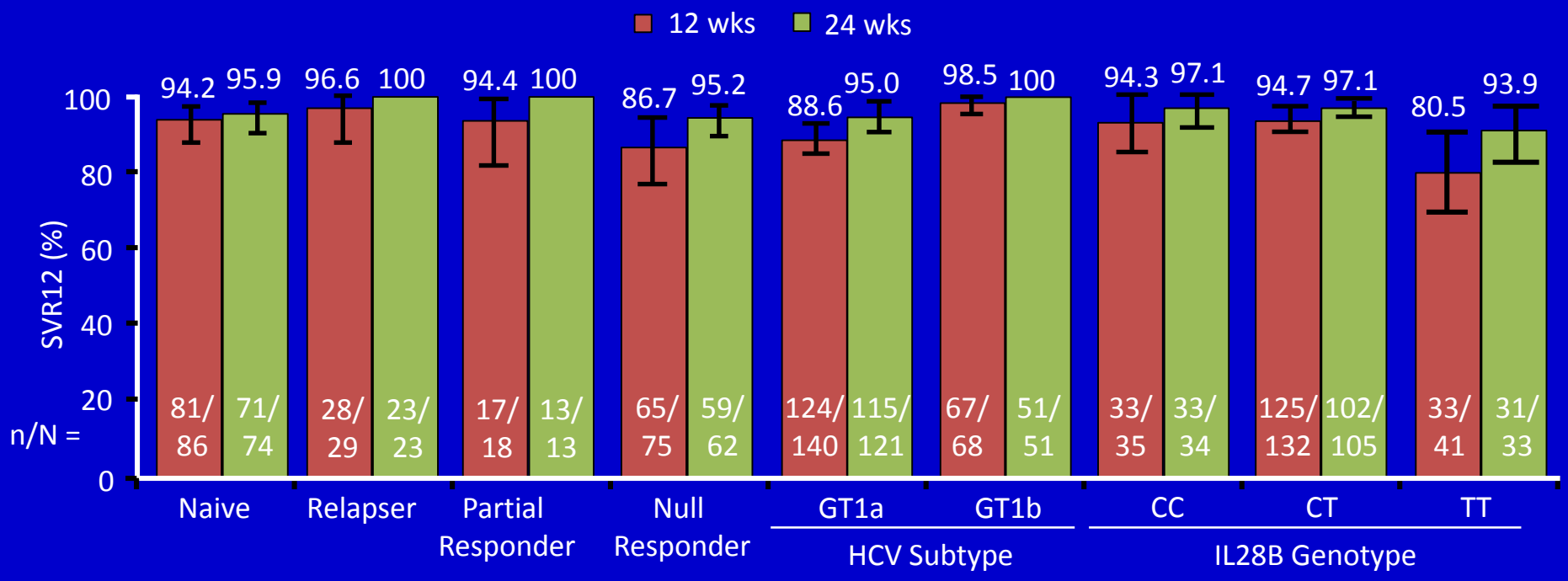
Ge, Nature, 2009

NEUTRINO Study: SVR12 by Prespecified Subgroups



Lawitz E, et al. N Engl J Med. 2013;368:1878-1887.

TURQUOISE II: SVR12 With OMV/PTV/RTV + DSV + RBV in GT1 Cirrhotics



Factor	*P* Value
IL28B TT genotype	.021
Previous null response to pegIFN/RBV	.038
GT1a HCV	.046

Fried MW, et al. AASLD 2014. Abstract 81. Reproduced with permission.

Evaluation : Assessment During Treatment

General	Complete Blood count with platelet Liver Profile Renal Profile with Estimated Creatinine Clearance
Specific	HCVRNA Quantitative and Genotype IL28 B HBsAb/IgG anti HAV AFP
Assessment of fibrosis	Non invasive methods
	Liver Biopsy
Gastroscopy	
USG/CT/MRI	

Assessment Of Fibrosis

- **Liver Biopsy**
- **Non Invasive Methods**
  - **Direct Serum Markers/Panels**
    Directly measure components of extracellular matrix
  - **Indirect Serum Markers/Panels**
    Indirect markers of liver function or inflammation
  - **Imaging Modalities**
    Fibroscan, ARFI, MR Elastography

Fibrosis Assessment

F0 F1 F2 F3 F4 F5 F6

Fibro Test + APRI	≤ 0.48 ≤ 1	>0.75 > 2

Fibro Scan

<12.5 >12.5

Liver Biopsy

Absence Of Cirrhosis

Presence Of Cirrhosis

Predictors of Treatment Response

Pre- Treatment

Host

Non-Modifiable

- Age
- Sex
- Race/IL28B
- Degree of fibrosis

Modifiable

- Alcohol
- Coffee
- Vit D
- Obesity
- Steatosis
- LDL and Statins

Viral

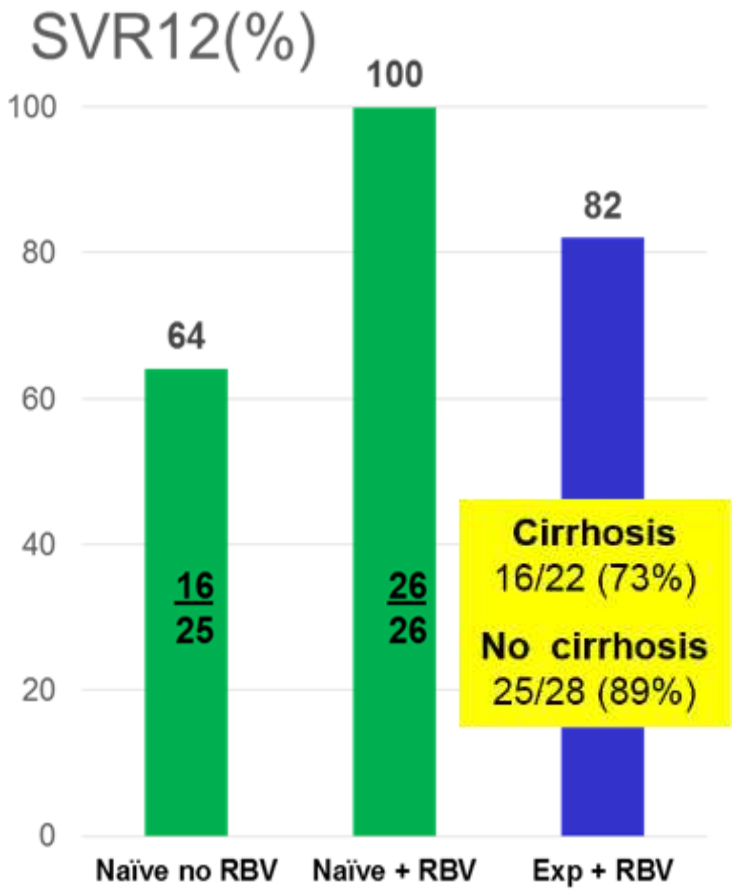
- Genotype
- Viral load

On Treatment

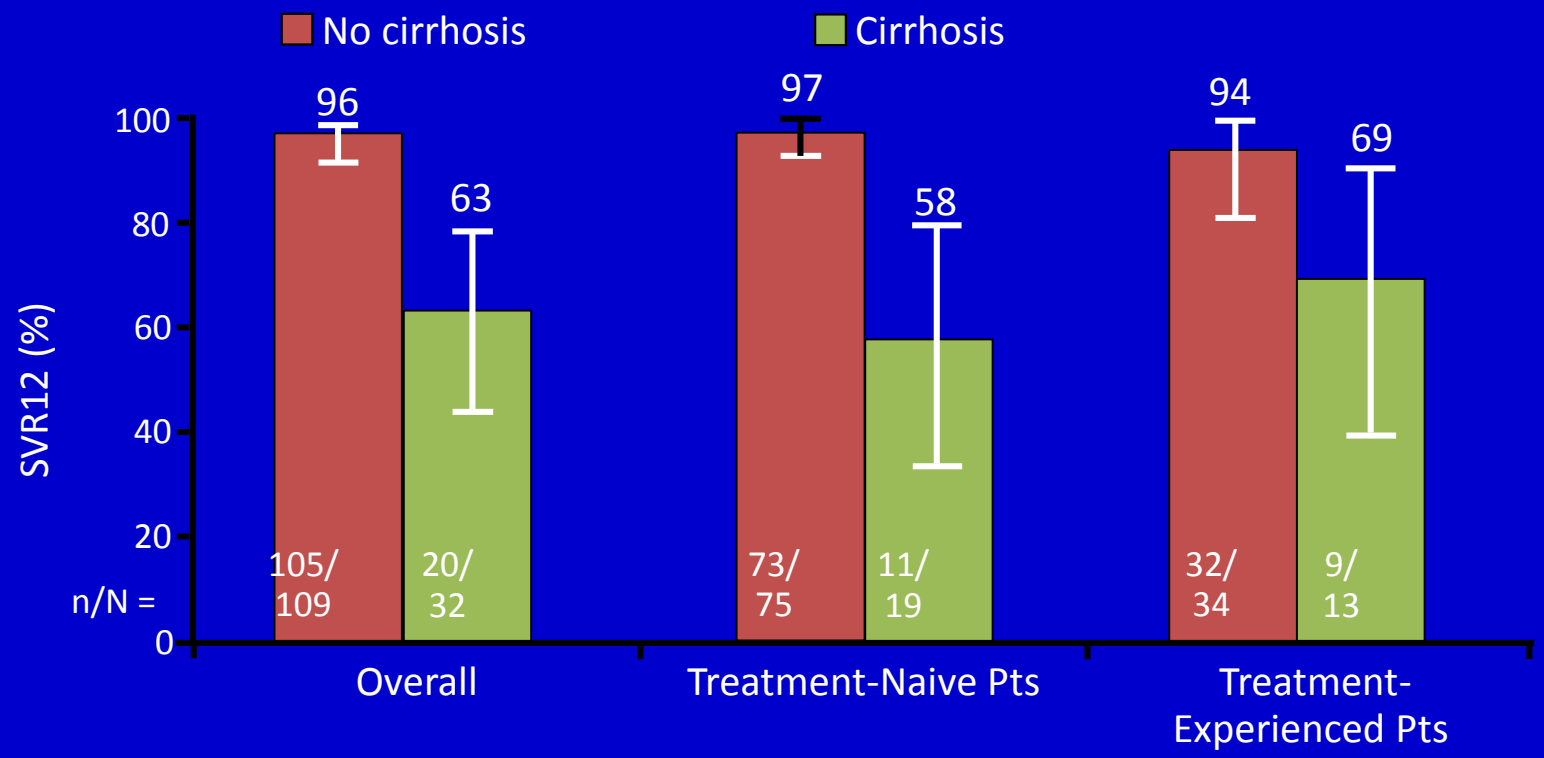
- RVR: Viral Kinetics and Response Guided Therapy
- Degree of Anemia
- Ribavirin Dosage

Genotype 3 Sofosbuvir + Ledipasvir

- ELECTRON2
  - Treatment naïve (EASL)
  - Tx experienced (AASLD)
  - Cirrhosis included
- Design
  - Open label cohort
- Regimen
  - Naïve
    - SOF/LDV
    - SOF/LDV/RBV
  - Treatment experienced
    - SOF/LDV/RBV
- Duration
  - 12 weeks



SOF + DCV for 12 Wks in Pts With GT 3 HCV Infection



- Of 16 pts with relapse, 11 had cirrhosis
- 1 of 16 relapses occurred between posttreatment Wks 4 and 12

Nelson DR, Cooper JN, Lalezari JP, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015;61:1127-1135.

Evaluation of HCV Patient in 2015

- **Initial Evaluation of HCV**
- **Evaluation : Assessment During Treatment**
- **Evaluation : Assessing Disease Status**