Εξελίξεις στη θεραπεία της CHC

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Γ’ Παθολογική Κλινική ΑΠΘ

Νοσοκομείο «Γ’ Παπαγεωργίου»

CHC
AASLD-IDSA 2015

Recommendation for treatment

Goal of treatment

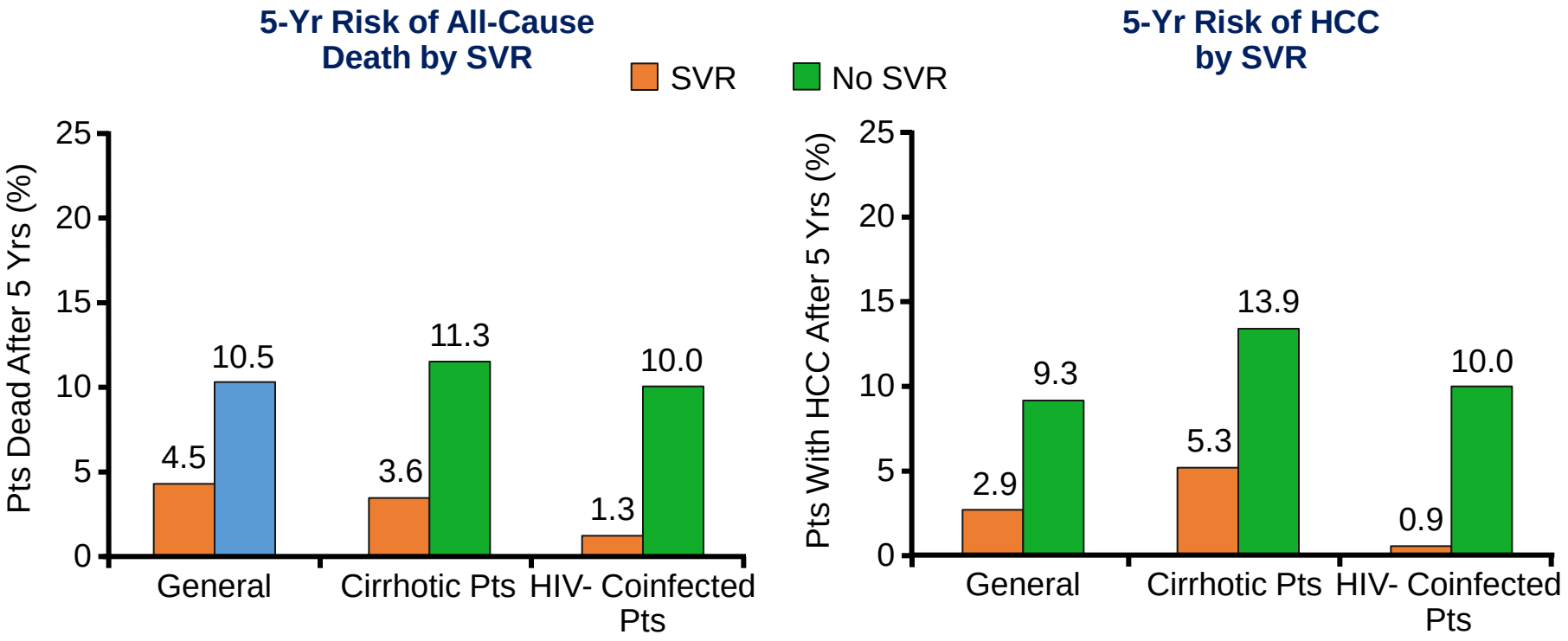
The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by an SVR.

Rating: Class I, Level A

SVR: Sustained Virological Response

SVR Associated With Reduced 5-Yr Risk of Death and HCC in All Populations

- SVR on IFN-based therapy was associated with substantial benefit vs no SVR
  - 62% to 84% reduction in all-cause mortality, 90% reduction in liver transplantation, 68% to 79% reduction in HCC



Hill AM, et al. AASLD 2014. Abstract 44.

Ποιούς θεραπεύουμε

When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications
Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
Organ transplant
Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

High Priority for Treatment Owing to High Risk for Complications

Fibrosis (Metavir F2)

HIV-1 coinfection

Hepatitis B virus (HBV) coinfection

Other coexistent liver disease (eg, [NASH])

Debilitating fatigue

Type 2 Diabetes mellitus (insulin resistant)

Porphyria cutanea tarda

Table 2. Persons At Elevated Risk of HCV Transmission* and in Whom HCV Treatment May Yield Transmission Reduction Benefits

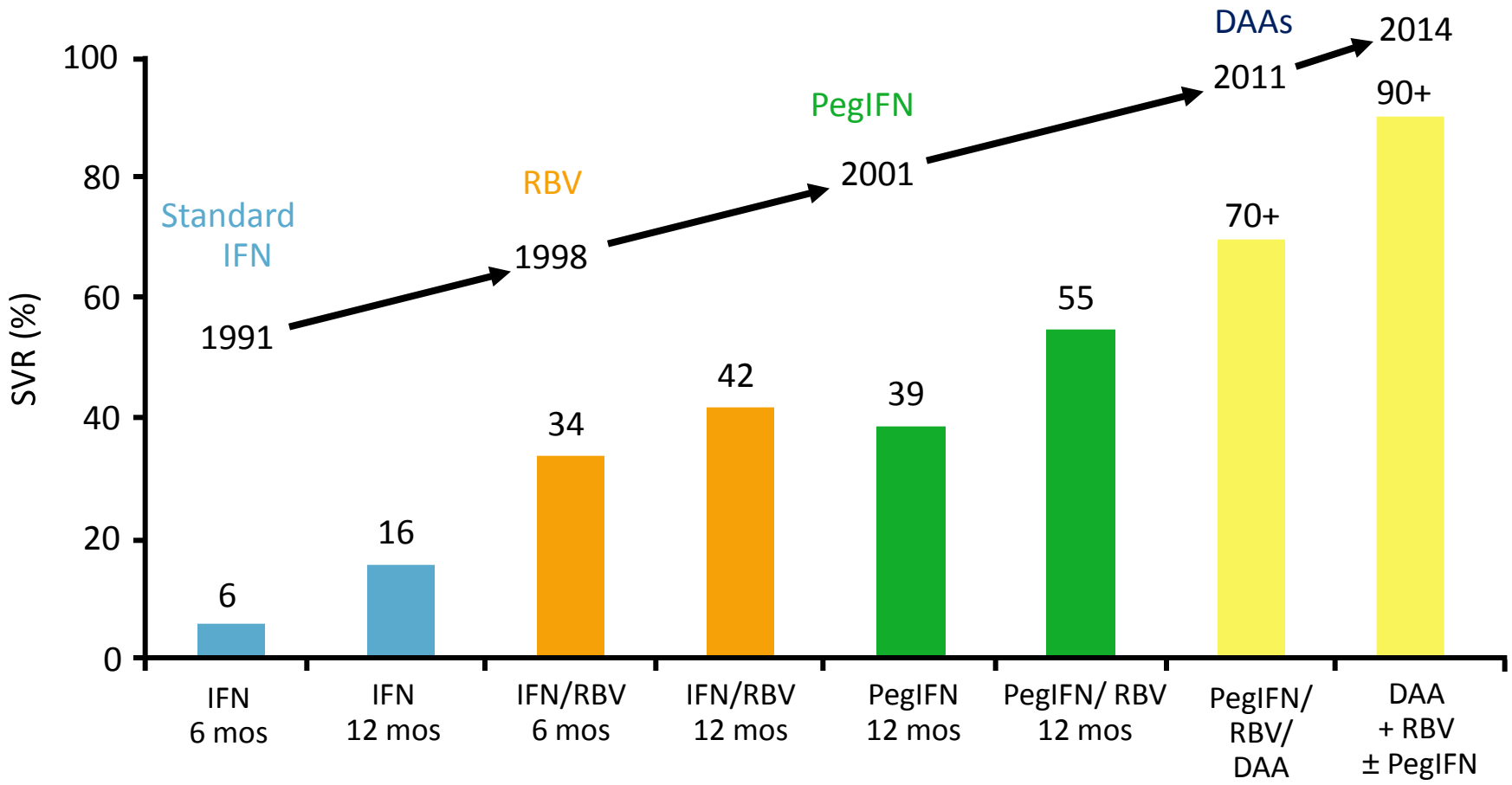
Men who have sex with men (MSM) with high-risk sexual practices
Active injection drug users
Incarcerated persons
Persons on long-term hemodialysis
HCV-infected women of child-bearing potential wishing to get pregnant

Recommendations for pretreatment assessment

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

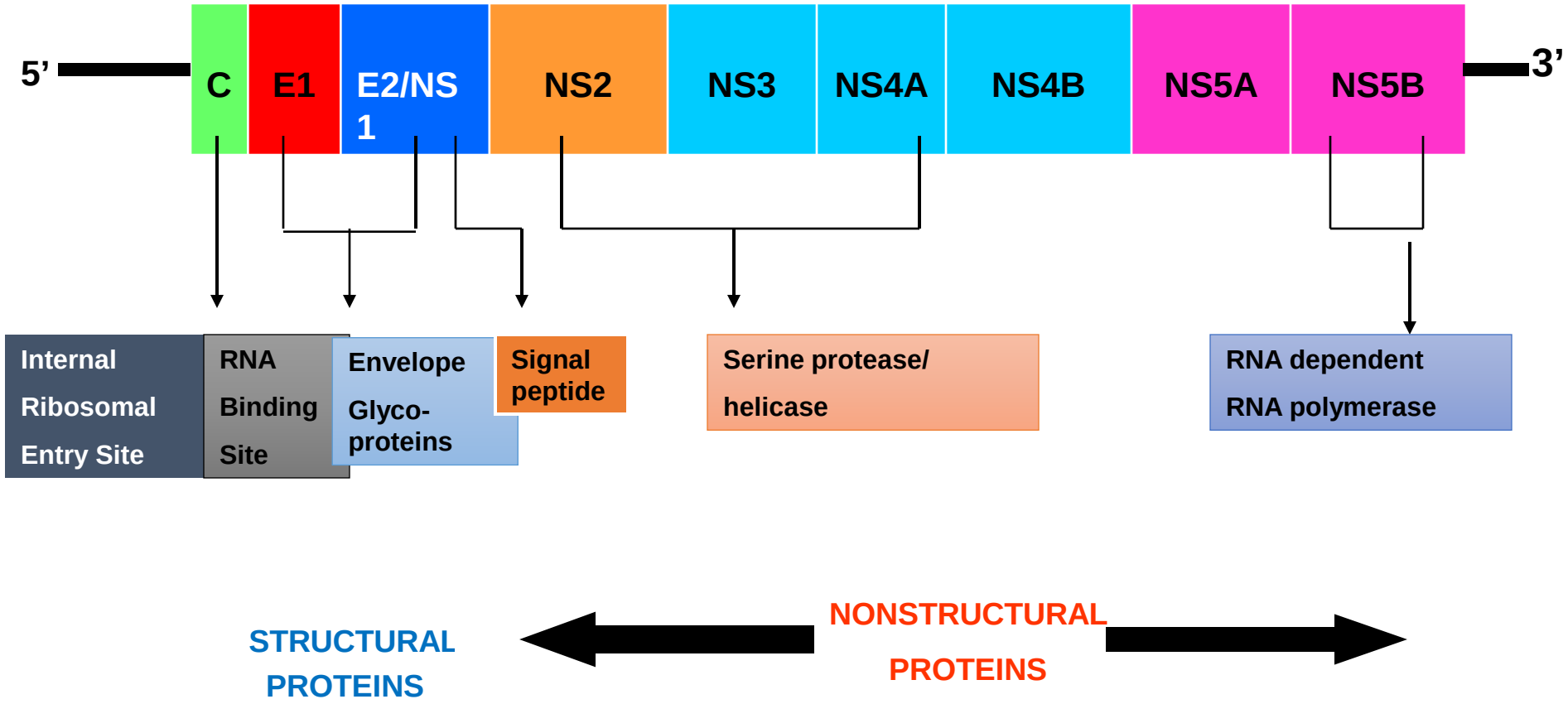
TREATMENT naïve CHC patients

The Good News

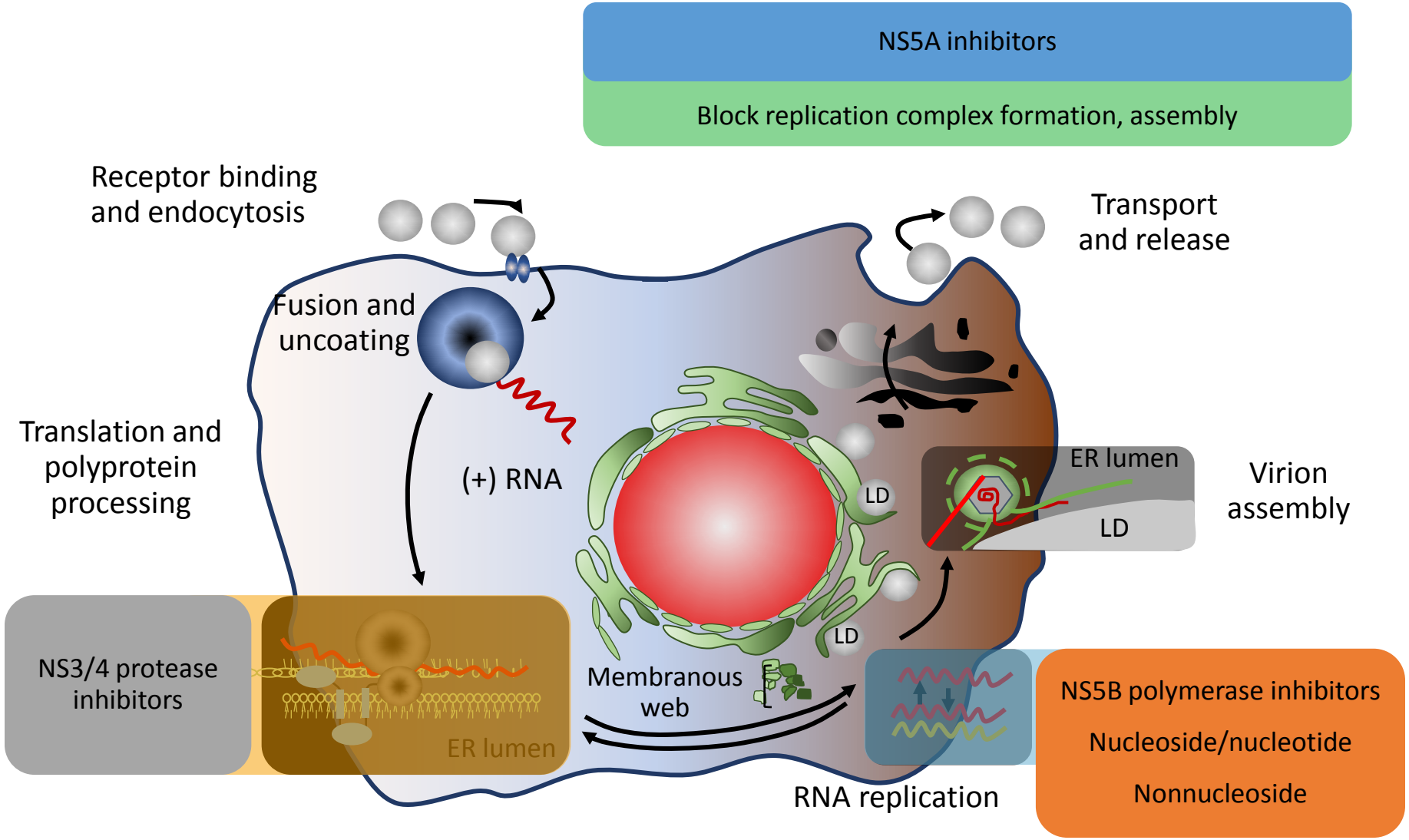


HEPATITIS C VIRUS

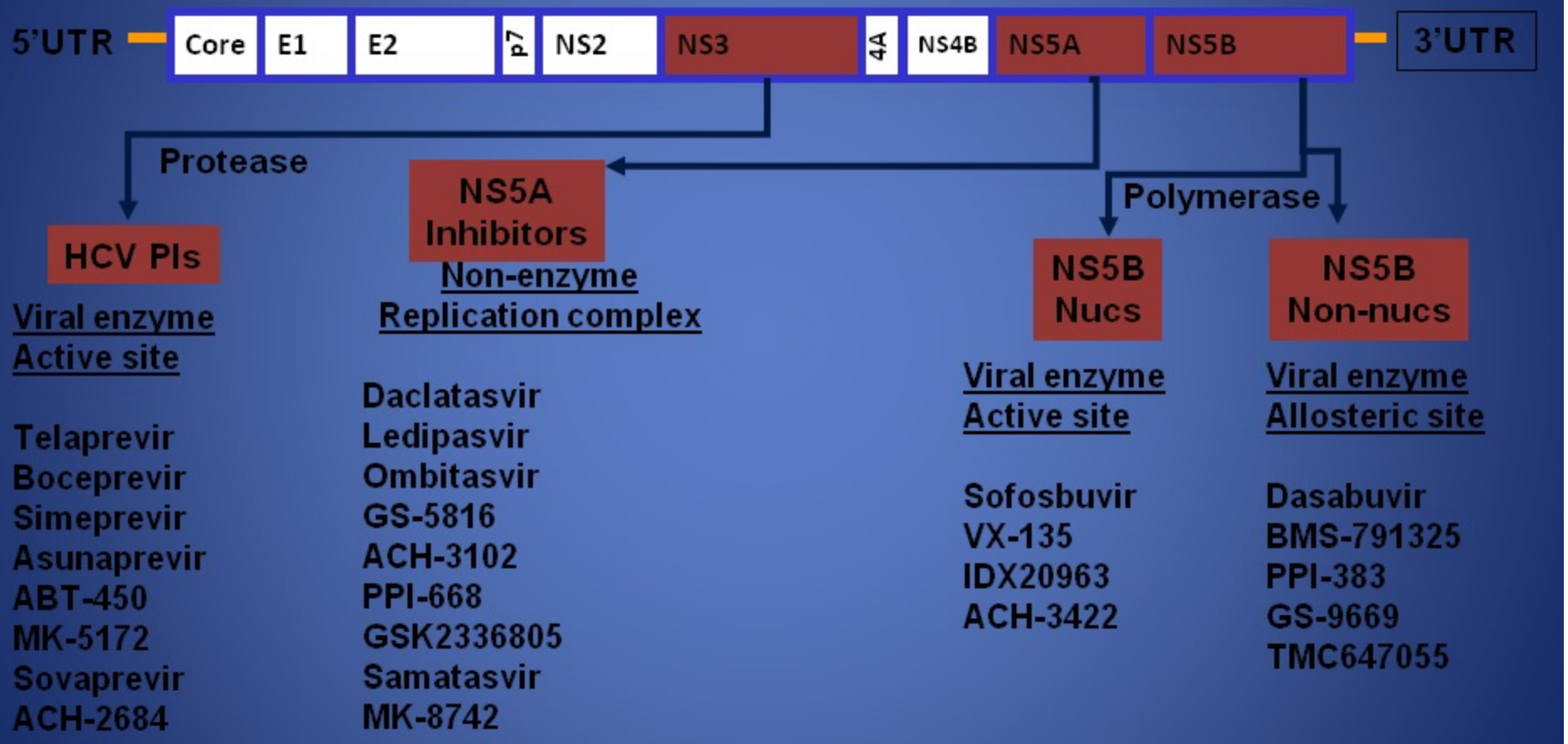
Genome



HCV Life Cycle and DAA Targets



The New Era of HCV Therapy
Multiple Direct Acting Antivirals



Courtesy of David Nelson, M.D.

Agents and regimens

Protease inhibitors	Polymerase inhibitors		NS5A inhibitors	Other
	Nucleotide	Non-nucleoside		
Simeprevir	Sofosbuvir		Ledipasvir	Ribavirin
Paritaprevir/ ritonavir		Dasabuvir	Ombitasvir	
			Daclatasvir	

Genotype 1 Treatment Options
Phase 3 Landscape

2014 (now)	SVR (est)
SOF + LPV	> 94%
PEG/RBV + SOF	90%
SOF + SMV	> 90%
SOF + RBV (select populations)	60-70%

0 — 24-48

2014-2015 — 12 weeks

ABT-450+ 333 + 267 ± RBV	>94%
SOF + DCV	> 94%
DCV + ASU + BMS-791235	90%

HCV genotype 1 regimens

Sofosbuvir, ledipasvir	Simeprevir, sofosbuvir
Paritaprevir/ritonavir, ombitasvir, dasabuvir, ribavirin	Sofosbuvir, daclatasvir

- SVR rates > 90% in genotype 1
  - No head to head trials

Lawitz E. *Lancet* 2014; Afdhal N. *NEJM* 2014; Ferenci P. *NEJM* 2014; Zeuzem S. *NEJM* 2014; Poordad F. *NEJM* 2014; Sulkowski M *NEJM* 2014.

What do I offer…
genotype 1, treatment naïve, non-cirrhotic

Regimen	Weeks	Study	SVR
Sofosbuvir + ledipasvir (HCV RNA < 6 M IU/ml)	8	ION-3	119/123 (97%)
Sofosbuvir + ledipasvir (HCV RNA > 6 M IU/ml)	12	ION-3	206/216 (95%)
Simeprevir + sofosbuvir	12	COSMOS	20/21 (95%)
Paritaprevir/r, dasabuvir, ombitasvir (genotype 1b)	12	PEARL III	207/209 (99.5%)
Paritaprevir/r, dasabuvir, ombitasvir, ribavirin (genotype 1a)	12	PEARL IV	97/100 (97%)
Sofosbuvir + daclatasvir	12		41/41 (100%)

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Kowdley K. NEJM 2014; OLYSIO FDA package insert Nov 2014; Ferenci P. NEJM 2014; Sulkowski M. NEJM 2014

What do I offer…
genotype 1, treatment experienced
Protease inhibitor failures

Regimen	Cirrhosis	Weeks	Study	SVR
Sofosbuvir + ledipasvir	No	12	ION-2	50/52 (96%)
Sofosbuvir + ledipasvir	Yes	24	ION-2	14/14 (100%)
Sofosbuvir + ledipasvir	Yes	24	Late breaker 6	75/77 (97%)
Sofosbuvir, ledipasvir, ribavirin	Yes	12	Late breaker 6	74/77 (96%)
Sofosbuvir + daclatasvir	Mix	24		21/21 (100%)
Sofosbuvir, daclatasvir, ribavirin	Mix	24		20/20 (100%)

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Afdhal N. NEJM 2014; Bourliere M. Liver Meeting 2014 LB-6; Sulkowski M. *NEJM* 2014.

Genotype 2

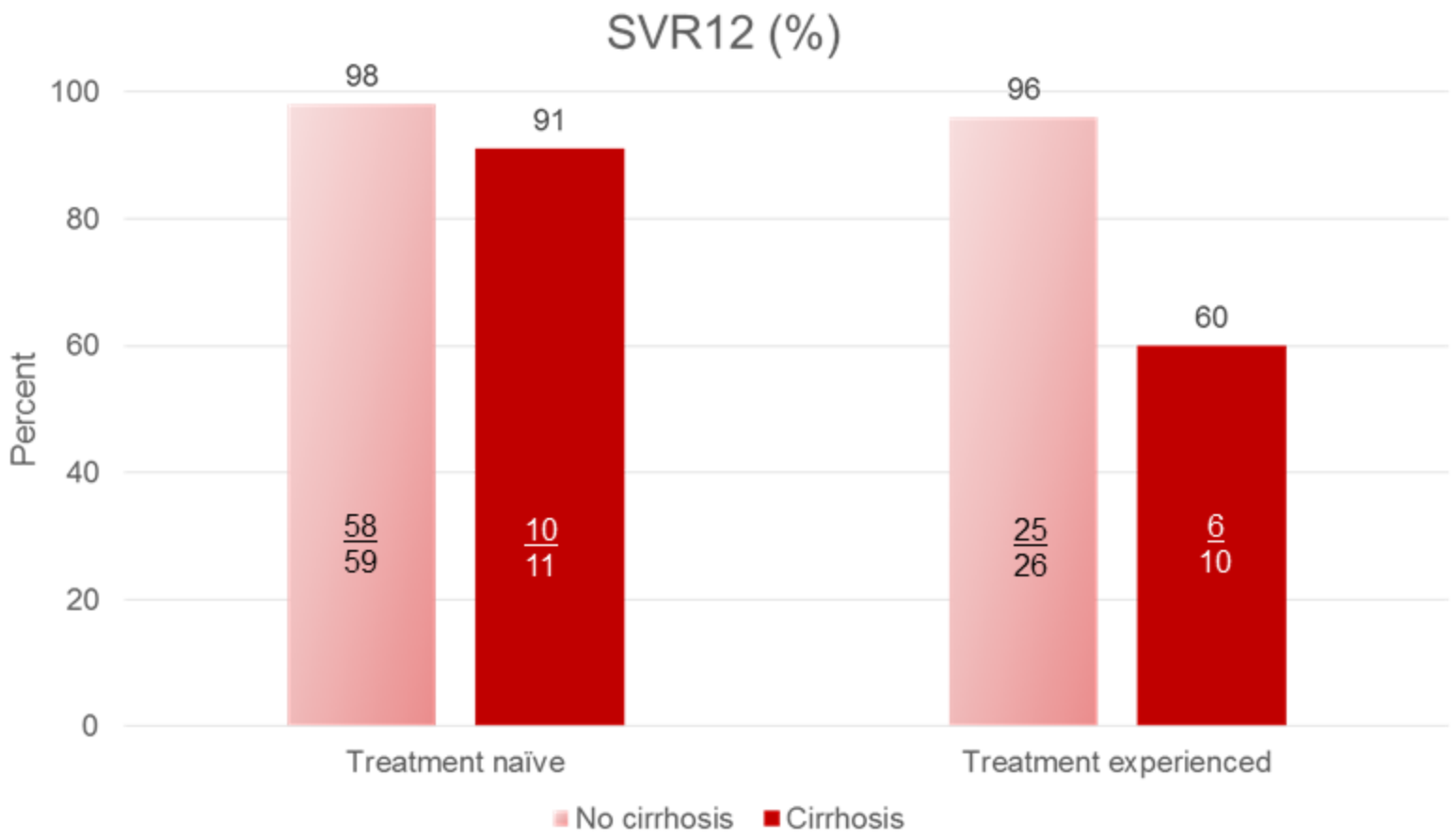
- AASLD-IDSA guidelines
  - www.hcvguidelines.org

American Association for the Study of Liver Diseases
AASLD
IDSA
Infectious Diseases Society of America

	Sofosbuvir + ribavirin x 12 weeks	Peginterferon-α, ribavirin + sofosbuvir
Treatment naive	Recommended	
PEG/RBV nonresponders	Recommended*	Alternative

* Patients with cirrhosis may benefit by extension of treatment to 16 weeks.

Genotype 2 sofosbuvir + ribavirin



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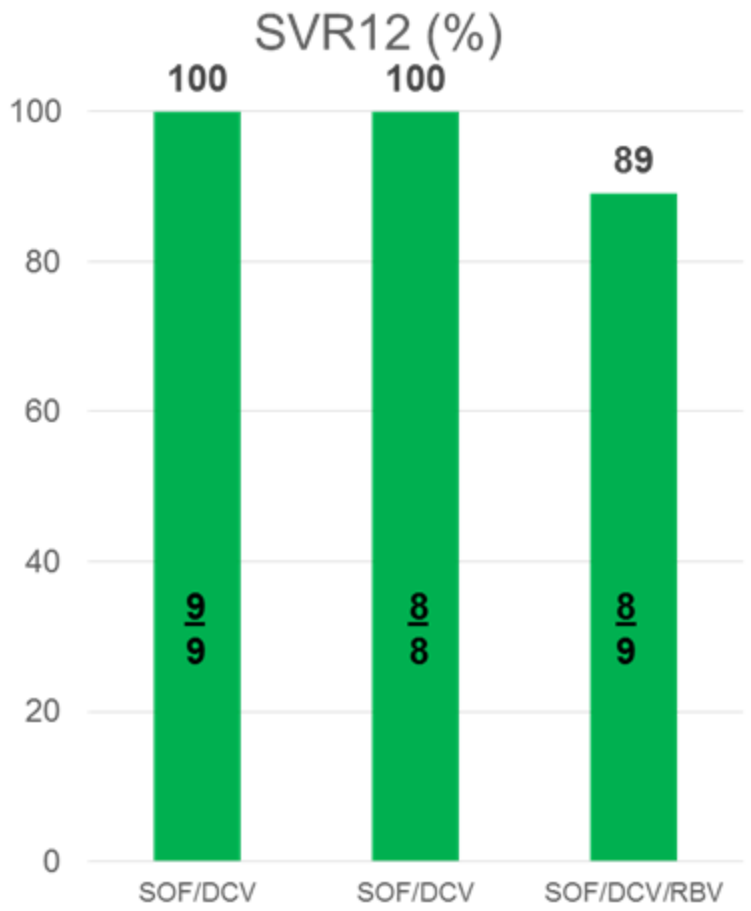
Lawitz E. *NEJM* 2013
Jacobson IM. *NEJM* 2013

Genotype 2 daclatasvir + sofosbuvir

- Patients
  - Genotype 2
  - Treatment naïve
  - Cirrhosis included
- Regimen
  - SOF x 7 days, then SOF/DCV x 23 wks
  - SOF/DCV 24 weeks
  - SOF/DCV/RBV 24 wks
- Benefit
  - Ribavirin free



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Sulkowski M. *NEJM* 2014

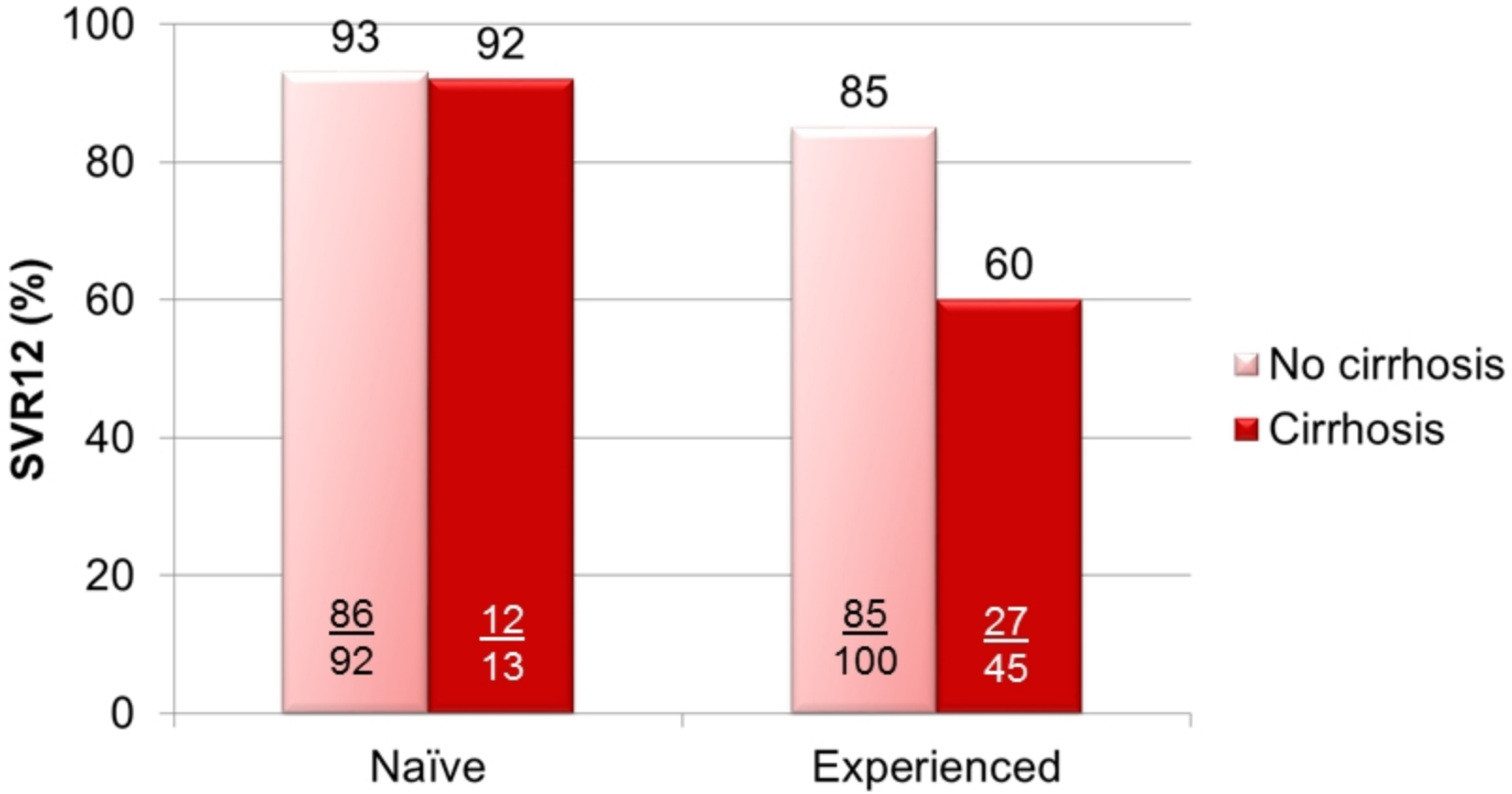
Genotype 3

- AASLD-IDSA guidelines
  - www.hcvguidelines.org

	Sofosbuvir + ribavirin x 24 weeks	Peginterferon-α, ribavirin + sofosbuvir
Treatment naive	Recommended	Alternative
PEG/RBV nonresponders	Recommended	Alternative

Genotype 3 sofosbuvir and ribavirin

VALENCE: 24 weeks duration

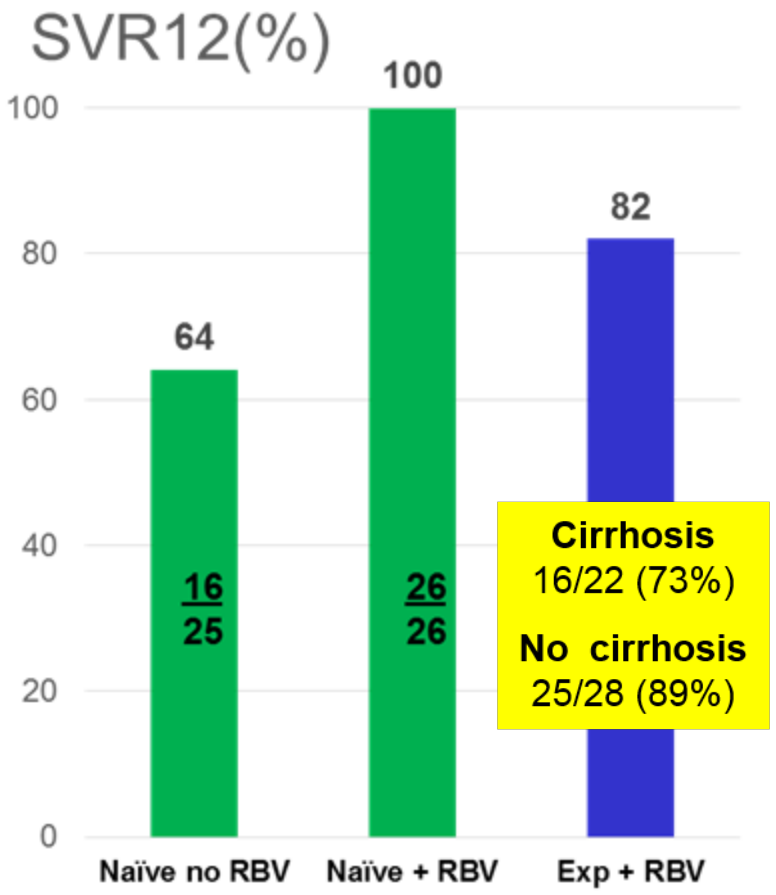


DukeMedicine

Zeuzem S. AASLD 2013

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

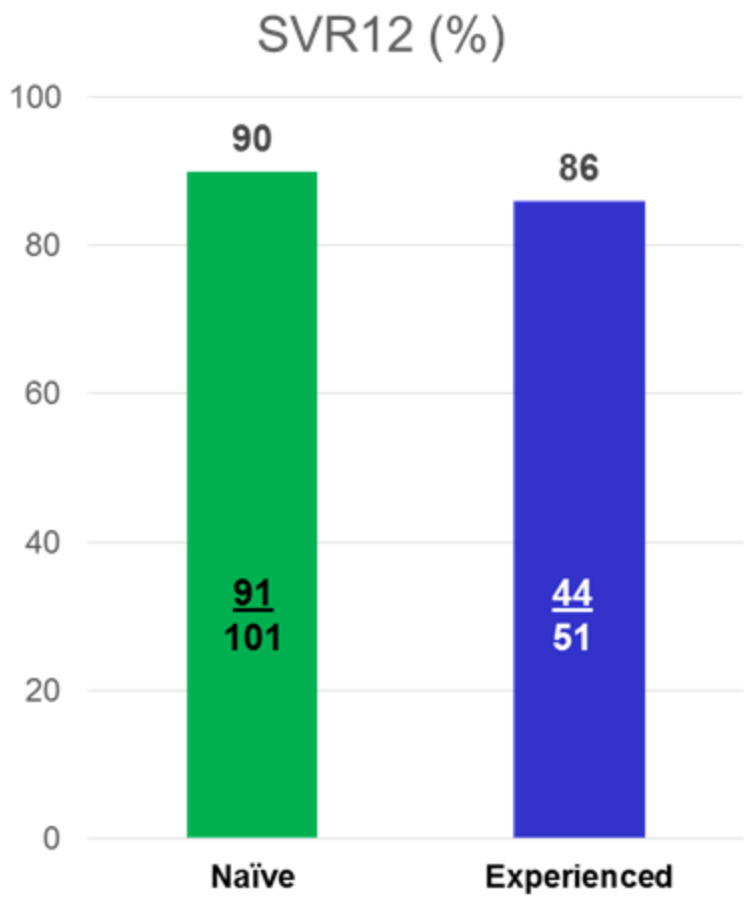


Gane EJ. EASL 2014
Gane EJ. Liver Meeting 2014; LB-11

DukeMedicine

Genotype 3 daclatasvir + sofosbuvir

- Study: ALLY 3
- Patients: 152
  - Genotype 3
  - Treatment naïve (101) and experienced (52)
    - Sofosbuvir and alisporivir included
  - Cirrhosis 21%
- Design
  - Open label cohorts
- Regimen
  - SOF + DCV x 12 weeks



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Nelson DR.. Liver Meeting 2014; abstract LB-3.

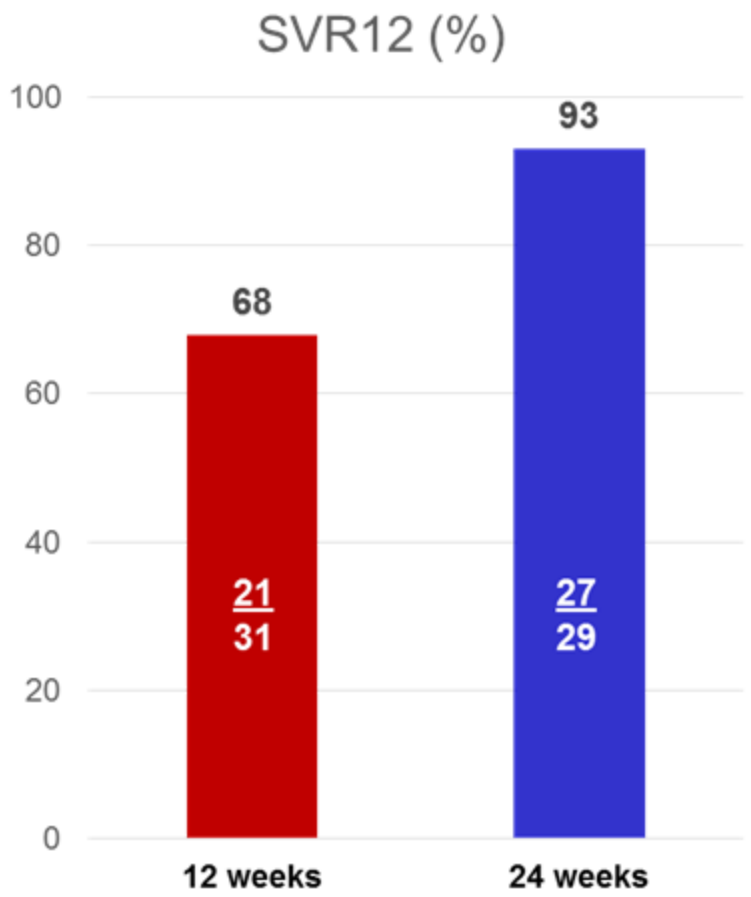
Genotype 4

- AASLD-IDSA guidelines
  - www.hcvguidelines.org

	Sofosbuvir + ribavirin x 24 weeks	Peginterferon-α, ribavirin + sofosbuvir
Treatment naive	Interferon ineligible	Interferon eligible
PEG/RBV nonresponders	Interferon ineligible	Interferon eligible

Genotype 4 sofosbuvir + ribavirin

- Patients
  - Genotype 4
  - Treatment naïve
  - Treatment experienced
  - Cirrhosis 20%
- Design
  - RCT, single center
- Regimen
  - SOF + RBV 12 weeks
  - SOF + RBV 24 weeks

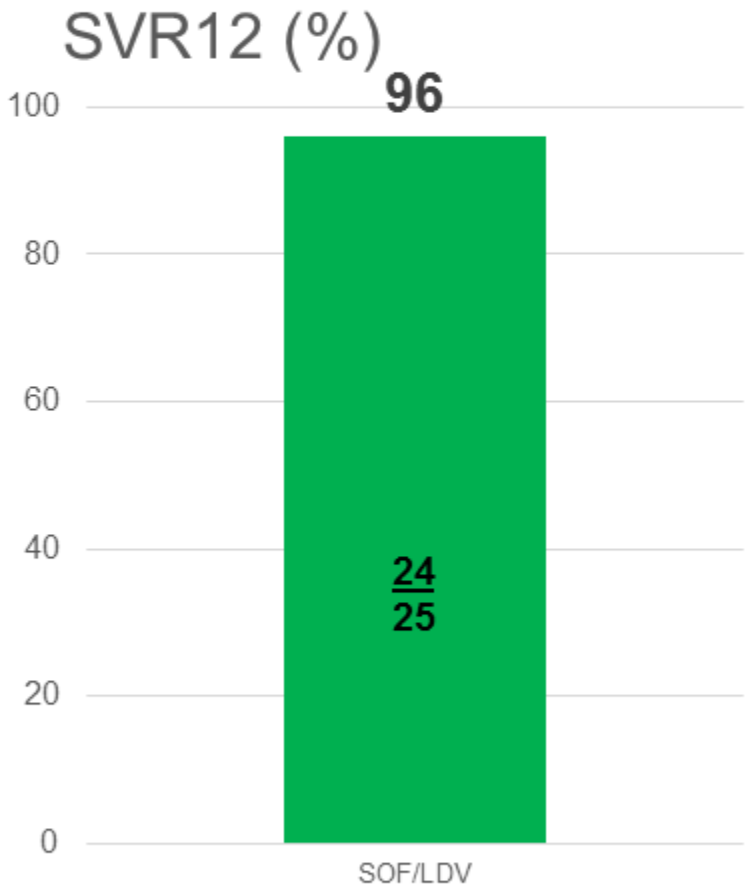


DukeMedicine

Ruane PJ. EASL 2014

Genotype 6 sofosbuvir + ledipasvir

- ELECTRON2
- Patients: 25
  - Treatment naïve
  - Treatment experienced
  - Cirrhosis included
- Design
  - Open label cohort
- Regimen
  - SOF/LDV
- Duration
  - 12 weeks



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Gane EJ. Liver Meeting 2014; LB-11

How to Use Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir

Recommended Regimen Design According to Patient Population

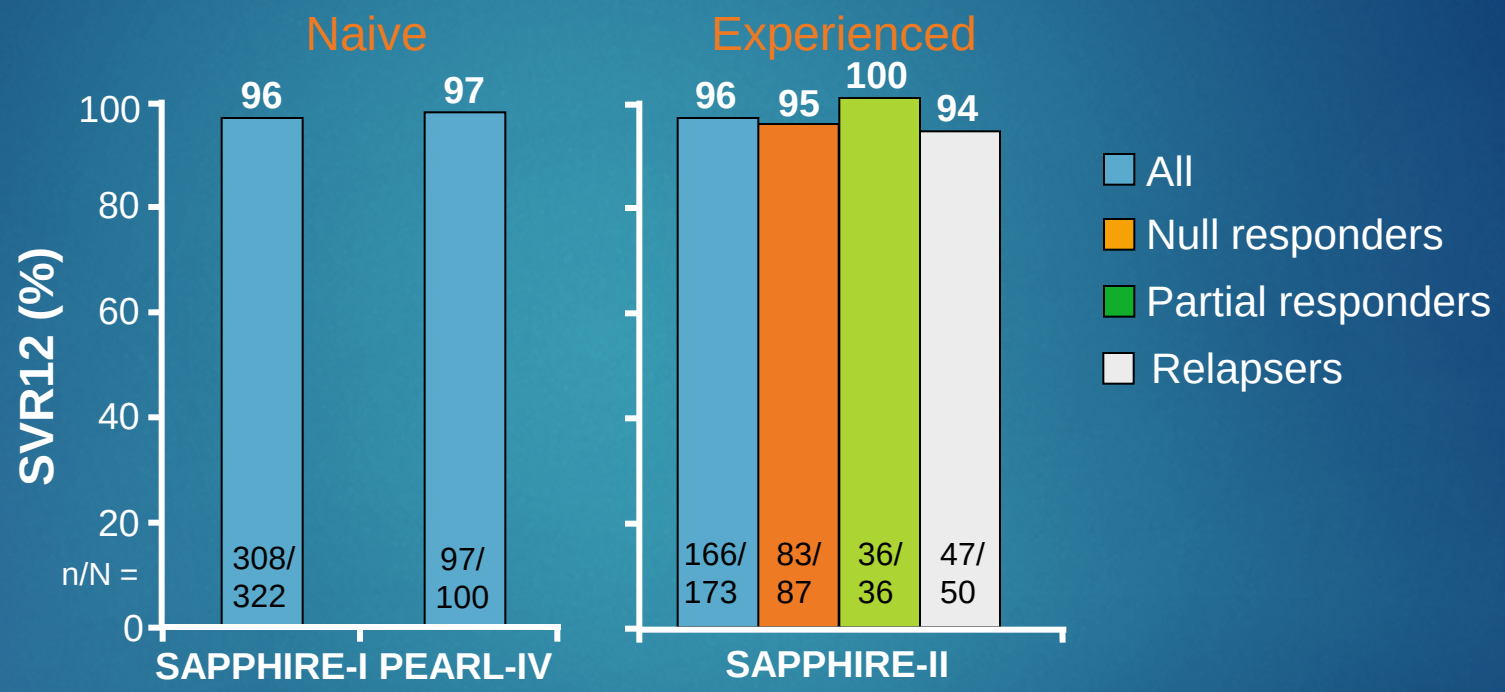
- Duration and inclusion of ribavirin vary according to patient population
  - GT1 subtype, presence of cirrhosis
  - If subtype is unknown or is mixed, use as described for GT1a
- HIV coinfection: use regimen and duration as described for HCV monoinfection

Population	Regimen	Duration
GT1a, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV + RBV	12 wks
GT1a, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV	24 wks*
GT1b, TN or TE, noncirrhotic	OMV/PTV/RTV + DSV	12 wks
GT1b, TN or TE, cirrhotic	OMV/PTV/RTV + DSV + RBV	12 wks
GT1, post-OLT (Metavir ≤ 2)	OMV/PTV/RTV + DSV + RBV	24 wks

*12-wk course may be considered for some patients based on previous treatment history.

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

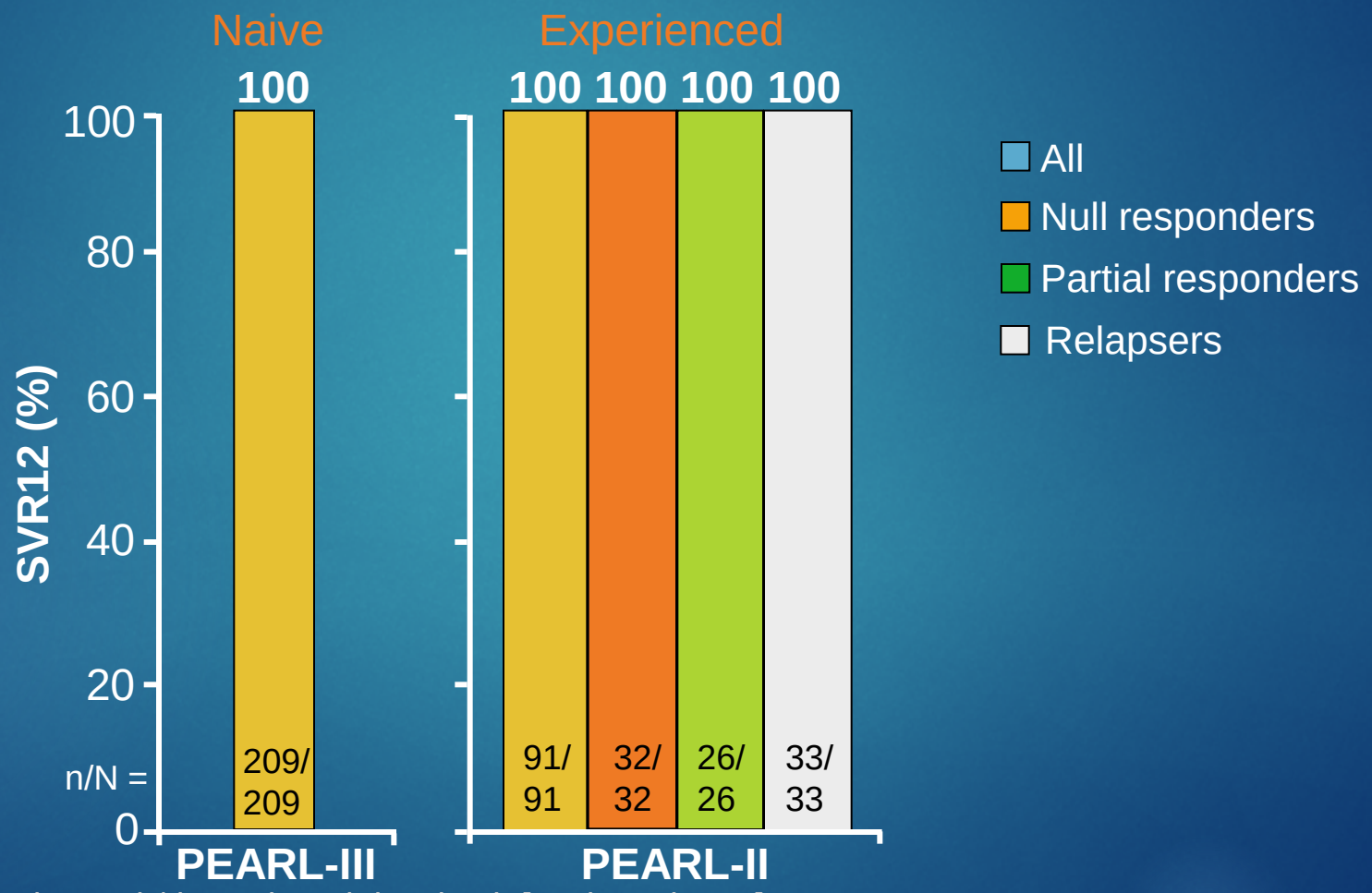
12 Wks of OMV/PTV/RTV + DSV + RBV in Noncirrhotic GT1a Pts



Outcome for Subjects Without SVR12, %	SAPPHIRE-I	PEARL-IV	SAPPHIRE-II
Virologic failure	< 1	1	0
Relapse	2	1	3
Other	2	1	1

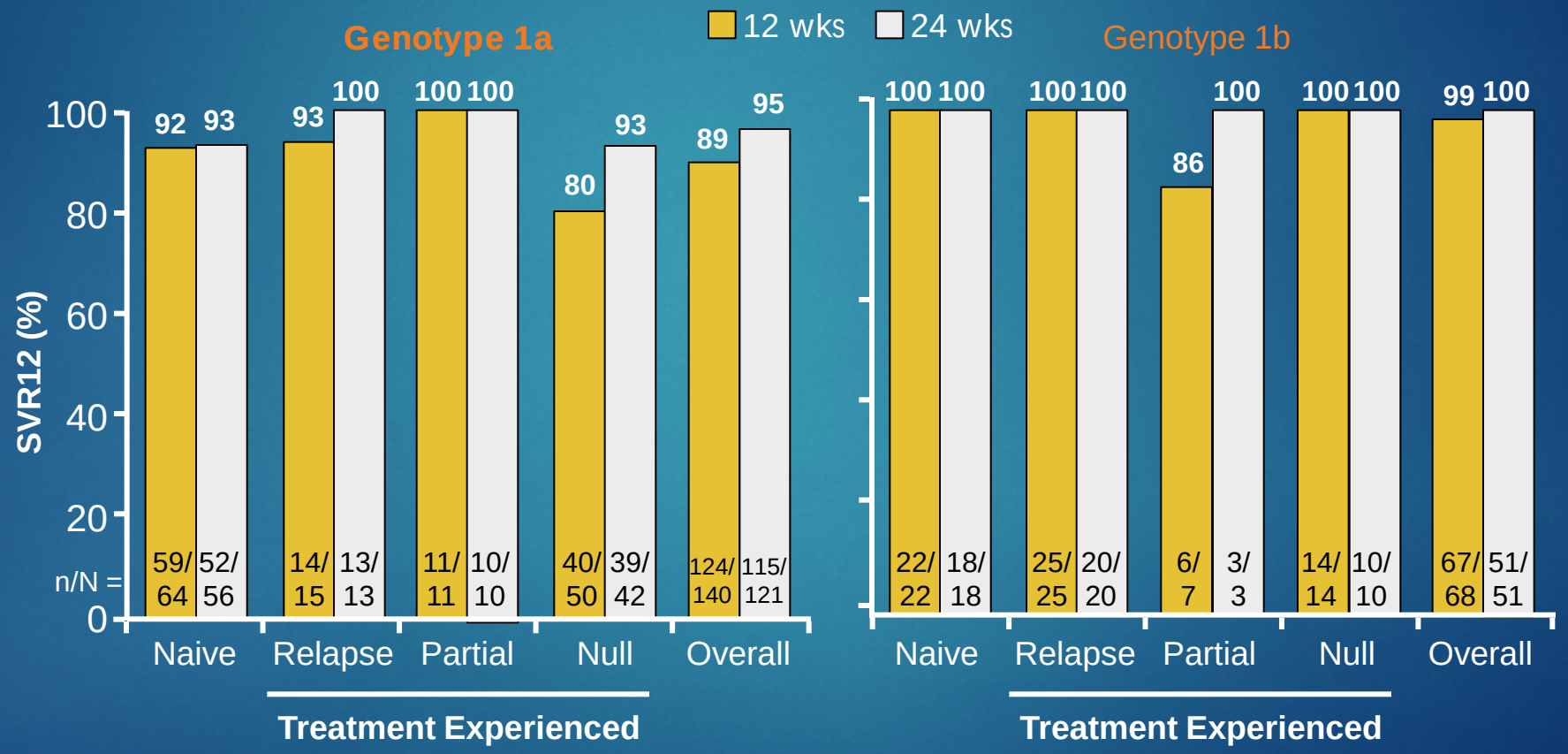
Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

12 Wks of OMV/PTV/RTV + DSV Without RBV in Noncirrhotic GT1b Pts



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

TURQUOISE II: 12 vs 24 Wks of OMV/PTV/RTV + DSV + RBV in Cirrhotics



Poordad F, et al. EASL 2014. Abstract O163. Poordad F, et al. N Engl J Med. 2014;370:1973-1982. Ombitasvir/paritaprevir/ritonavir and dasabuvir [package insert].

All-Oral Regimens for Other Populations

Population	Regimen	Duration
GT2	SOF + RBV[1]	12 wks
GT3	SOF + RBV[1]	24 wks
GT1/2/3/4 HCC pre-OLT	SOF + RBV[1]	48 wks*
GT1, post-OLT (Metavir ≤ 2)	OMV/PTV/RTV + DSV + RBV[2]	24 wks
GT1/4 decompensated cirrhosis (CTP B or C)	SOF/LDV + RBV†[3]	12 wks‡
GT2/3 decompensated cirrhosis (CTP B or C)	SOF + RBV†[3]	Up to 48 wks

*Up to 48 wks or until transplantation, whichever occurs first. †Not FDA approved but recommended in AASLD/IDSA guidance. ‡24 wks of SOF/LDV if anemia or RBV intolerance; 24 wks of SOF/LDV + RBV (600 mg/day with increasing dose if tolerated) if prior SOF failure.

Refer to www.hcvguidelines.org for further information on how to use these therapies

1. Sofosbuvir [package insert]. 2. Ombitasvir/paritaprevir/ritonavir plus dasabuvir [package insert].
3. AASLD/IDSA HCV Guidelines. Accessed January 5, 2015.

Πίνακας 2. Προτεινόμενα θεραπευτικά σχήματα για ασθενείς με χρόνια HCV λοίμωξη ανάλογα με το γονότυπο.

	Γονότυπος 1	Γονότυπος 2	Γονότυπος 3	Γονότυπος 4	Γονότυπος 5 ή 6
Peg-IFNα+RBV (PR)	x24 ή 48 εβδ.	x12-16 ή 24 εβδ.	x16 ή 24 εβδ.	x24 ή 48 εβδ.	x24 ή 48 εβδ.
SOF+PR	x12 εβδ.		x12 εβδ.	x12 εβδ.	x12 εβδ.
SMV+PR / PR*	x12 / 12 ή 36 εβδ. (όχι σε 1a με Q80K)			x12 / 12 ή 36 εβδ.	
DCV+PR / PR				x12 ή 24 / 12 ή 0 εβδ.	
PR / BOC+PR /PR*	x4 / 24 ή 44 / 0 ή 20 ή 0 εβδ.				
TPV+PR / PR*	x12 / 12 ή 36 εβδ.				
SOF+RBV*	x24 εβδ.	x12 εβδ.	x24 εβδ.	x24 εβδ.	x24 εβδ.
SOF+SMV*	x12 εβδ.			x12 εβδ.	
SOF+DCV	x12 ή 24 εβδ.		x12 εβδ. (όχι κίρρωση) ή 24 εβδ. (κίρρωση)	x12 ή 24 εβδ.	
SOF/LDV SOF/LDV+RBV	x12 εβδ. (x8 εβδ. για πρωτοθεραπευόμενους χωρίς κίρρωση, x12 εβδ. (για επαναθεραπευόμενους με κίρρωση)		x12 εβδ.	x12 εβδ.	
PRV/r/OBV+DSV+RBV* PRV/r/OBV+DSV*	x12 εβδ. για 1a x12 εβδ. για 1b				
PRV/r/OBV±RBV				x12 εβδ.	

Το κόστος των νεότερων φαρμάκων

- SOVALDI: 12600 Euro/Bt
- OLYSIO : 7500 Euro/Bt
- DACLATASVIR: 8000 Euro/Bt
- HARVONI(sofosbuvir+ledipasvir): 17131 Euro/Bt

Sovaldi (sofosbuvir) in the News

"New hepatitis C drugs' price prompts an ethical debate: Who deserves to get them?"

Washington Post

"How Much Should Hepatitis C Treatment Cost?"

New York Times

"Prices of new hepatitis C drugs are tough to swallow for insurers."

Los Angeles Times

"Hepatitis C breakthrough drug Sovaldi promises high cure rates, costs."

Denver Post

"$1,000 hepatitis C pill a tough miracle to swallow."

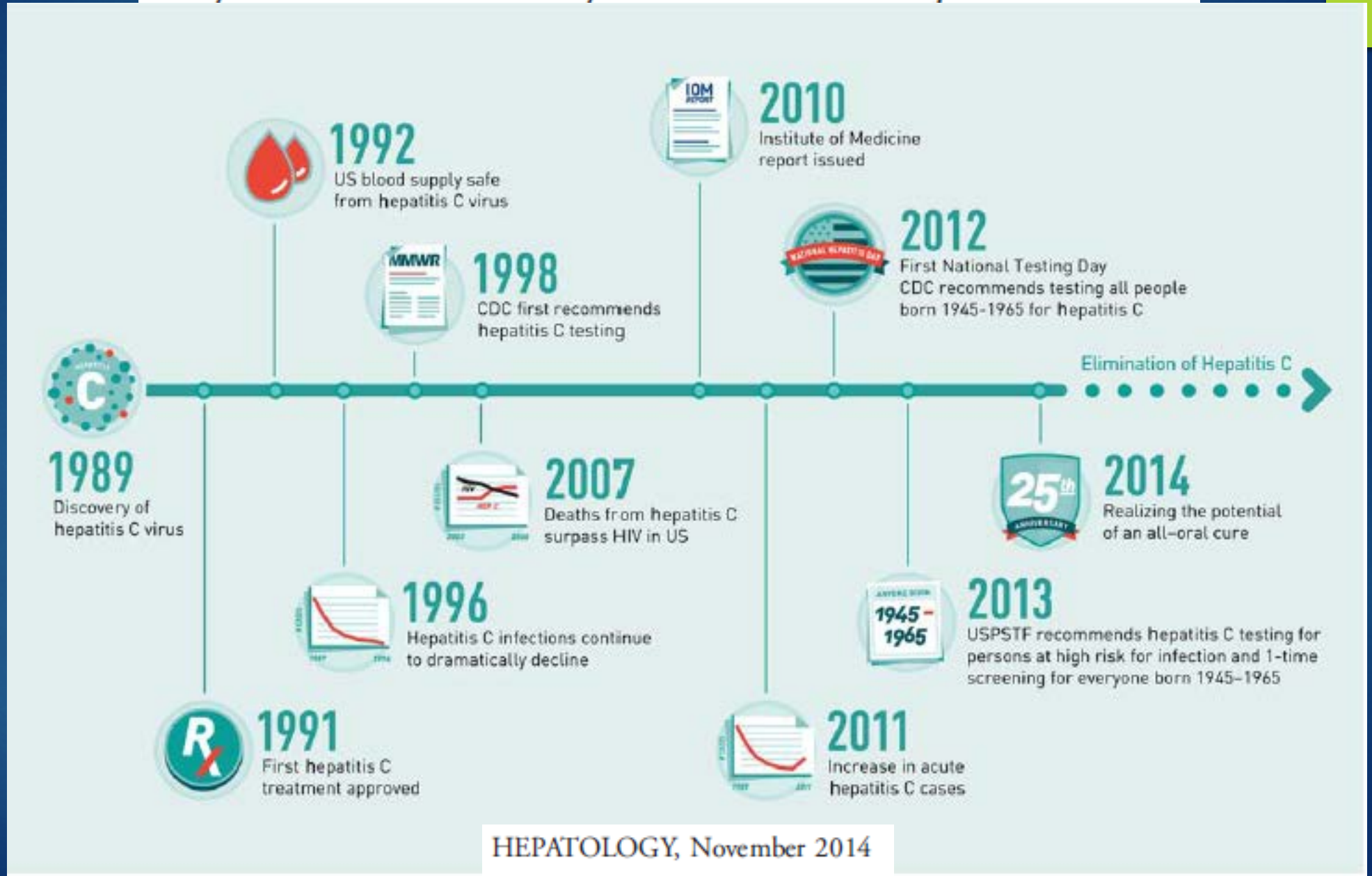
San Francisco Chronicle

The Price of NOT Treating Chronic Hepatitis C

- Study of economic burden of chronic hepatitis C in the US, stratified by disease severity, based upon a large health insurance claims database.
- Based on data from 53,796 patients with chronic hepatitis C – 78% without cirrhosis, 7% with compensated cirrhosis, 15% with ESLD
- Overall Annual Healthcare Costs per Patient: $24,176
- Annual Costs per Patient Without Cirrhosis: $17,277
- Annual Costs per Patient With Compensated Cirrhosis: $22,752
- Annual Costs per Patient With ESLD: $59,995
- Estimated US Average Charges per LTx in 2011: $577,100

Reau N, Jensen D. Review/Editorial HEPATOLOGY 2014;59:1246-1249.
Gordon SC, et al. Disease Burden in Patients with chronic hepatitis C in US .....2003 to 2010. Presented at AASLD 2011.
http://digestive.niddk.nih.gov/ddiseases/pubs/livertransplant/
http://digestive.niddk.nih.gov/before-the-transplant/financing-a-transplant/the-costs/

25 years since discovery: a timeline of major milestones.



HEPATOLOGY, November 2014

HEPATOLOGY, November 2014

ΕΥΧΑΡΙΣΤΩ ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ