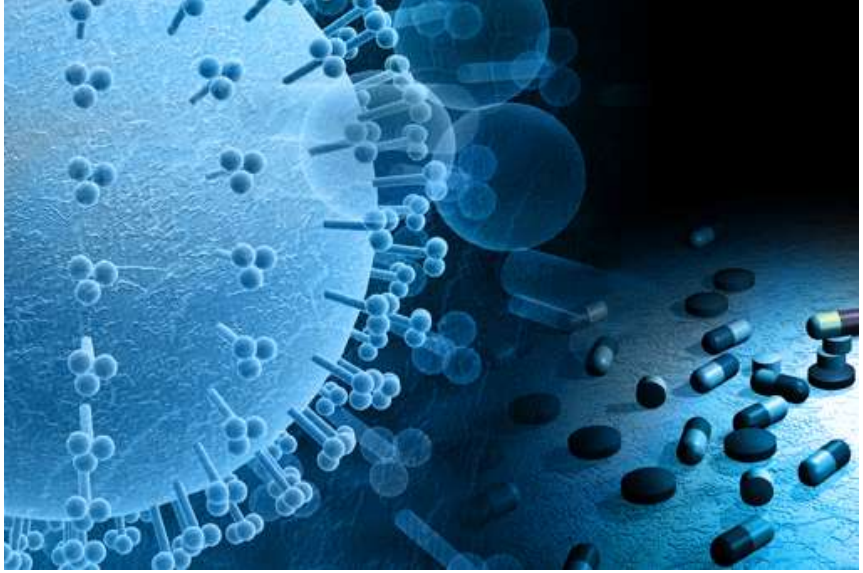


Clinical Studies and Recent Real-World Data with Sofosbuvir/Ledipasvir

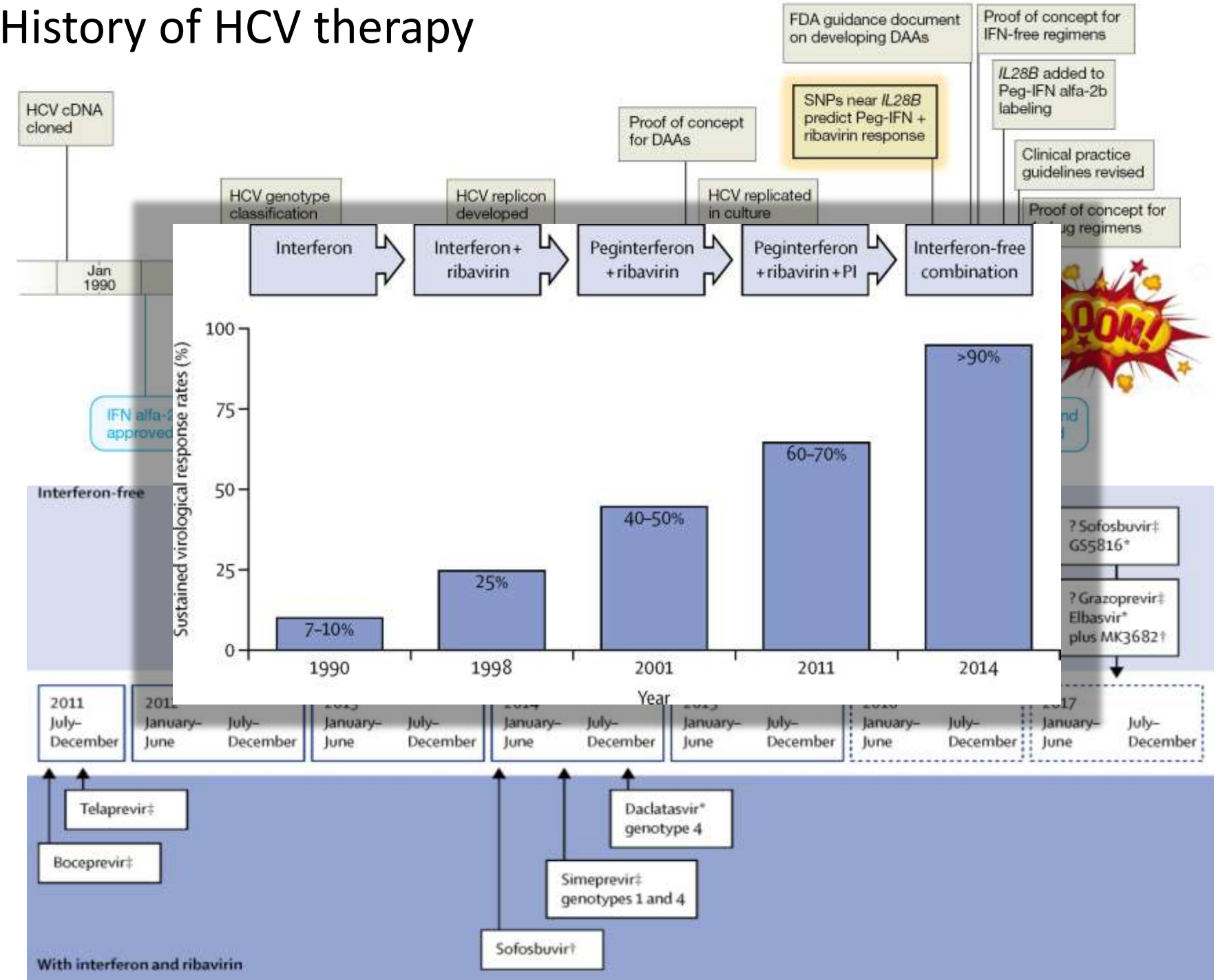
Kalliopi Zachou
Assistant Professor of Medicine
University of Thessaly

Disclosures

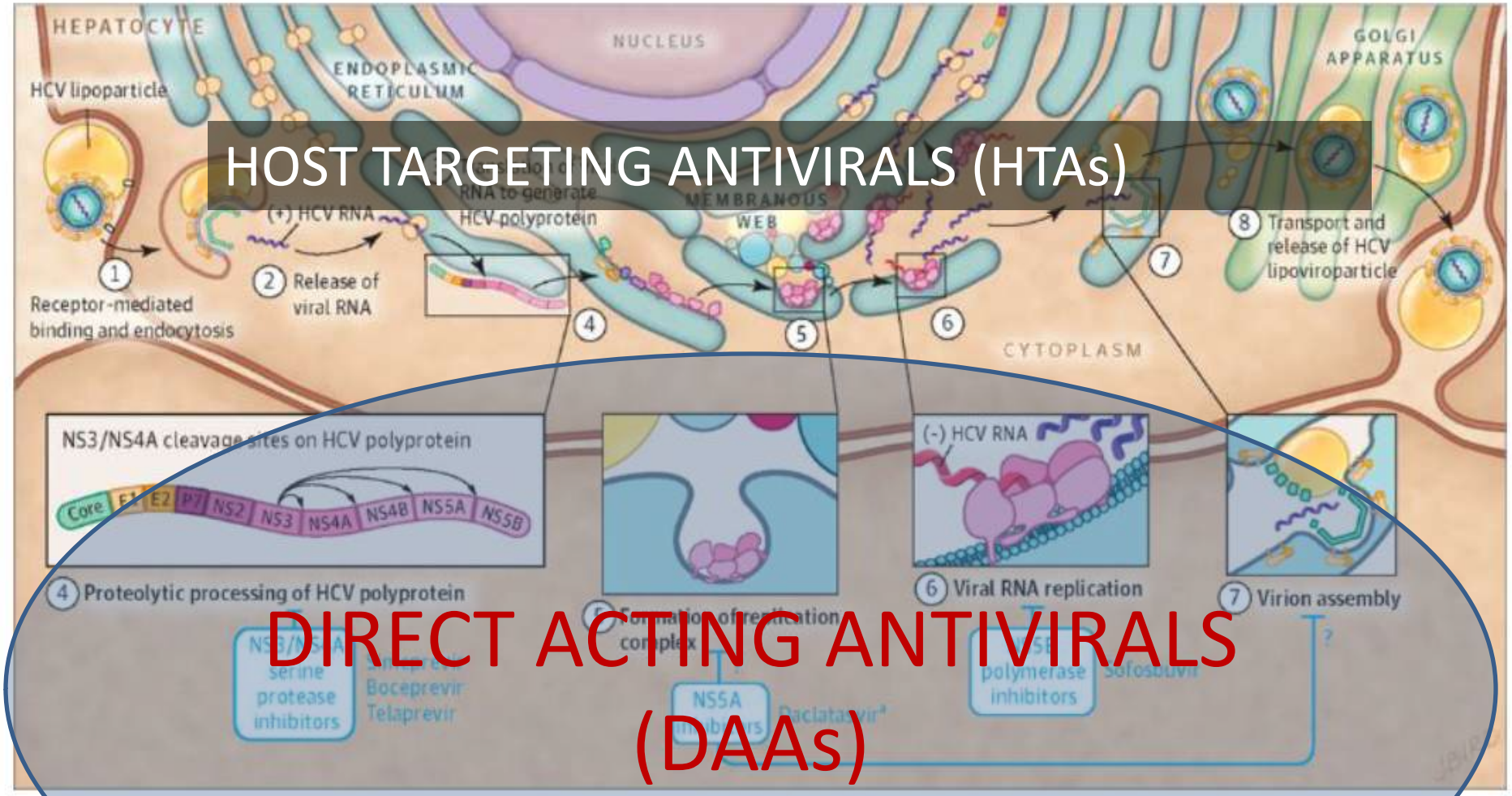
Speaker’s bureau and advisory:

- Gilead
- Bristol

History of HCV therapy

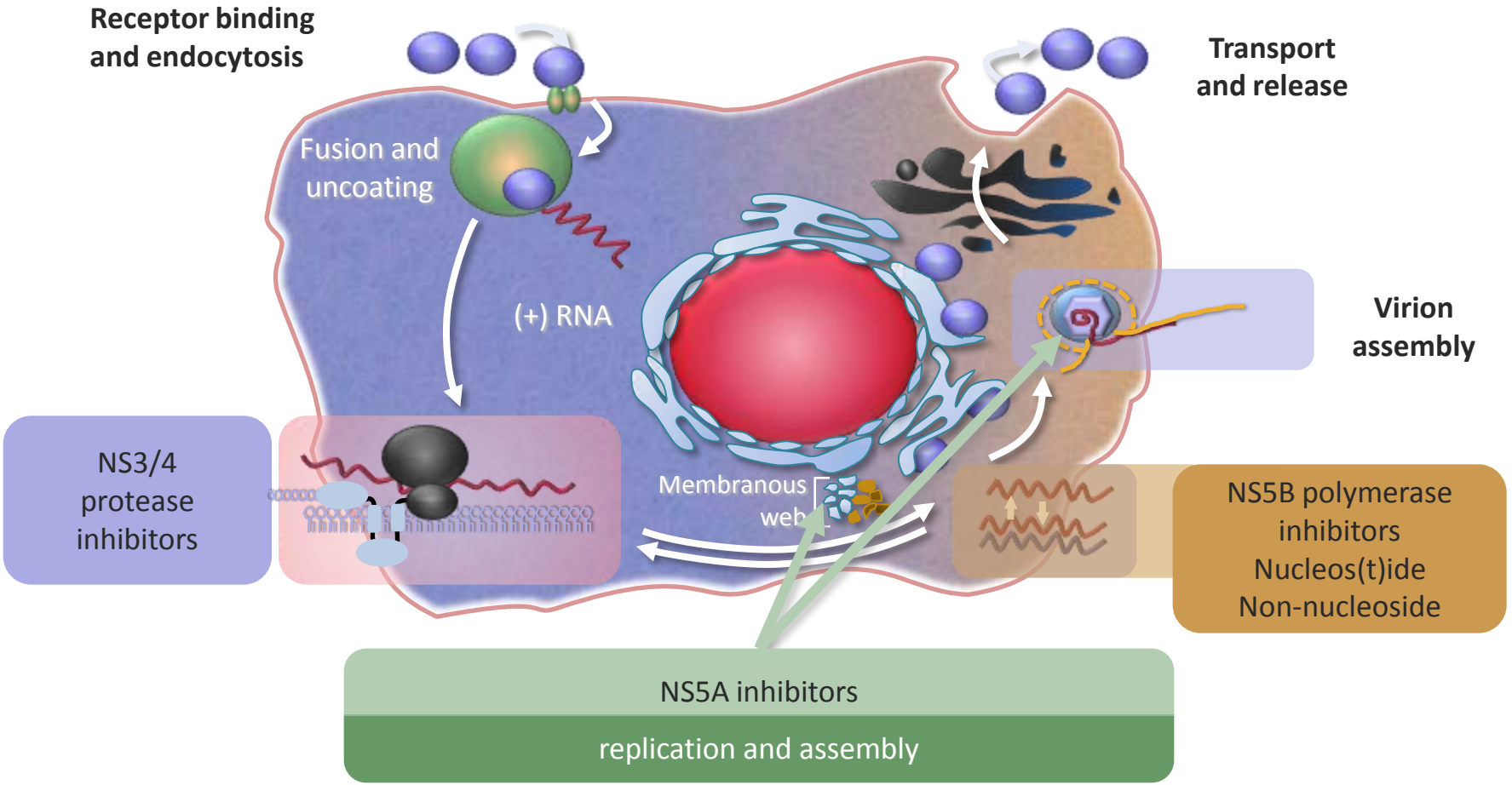


Overview of the hepatitis C virus (HCV) lifecycle and antiviral targets



Kohli A et al *JAMA*. 2014;312:631–40.

HCV Life Cycle and Targets for Direct-Acting Antivirals (DAAs)



Manns MP, et al. *Nat Rev Drug Discov*. 2007

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Recommendations for Testing, Managing, and Treating Hepatitis C

Updated February 24, 2016

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

J Hepatol2015 vol. 63 : 199–236

EASL Recommendations on Treatment of Hepatitis C 2015

European Association for the Study of the Liver *

ΚΑΤΕΥΘΥΝΤΗΡΙΕΣ ΟΔΗΓΙΕΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΠΑΡΕΜΒΑΣΗΣ ΣΕ ΑΣΘΕΝΕΙΣ ΜΕ ΛΟΙΜΩΞΗ ΜΕ ΤΟΝ ΙΟ ΤΗΣ ΗΠΑΤΙΤΙΔΑΣ C

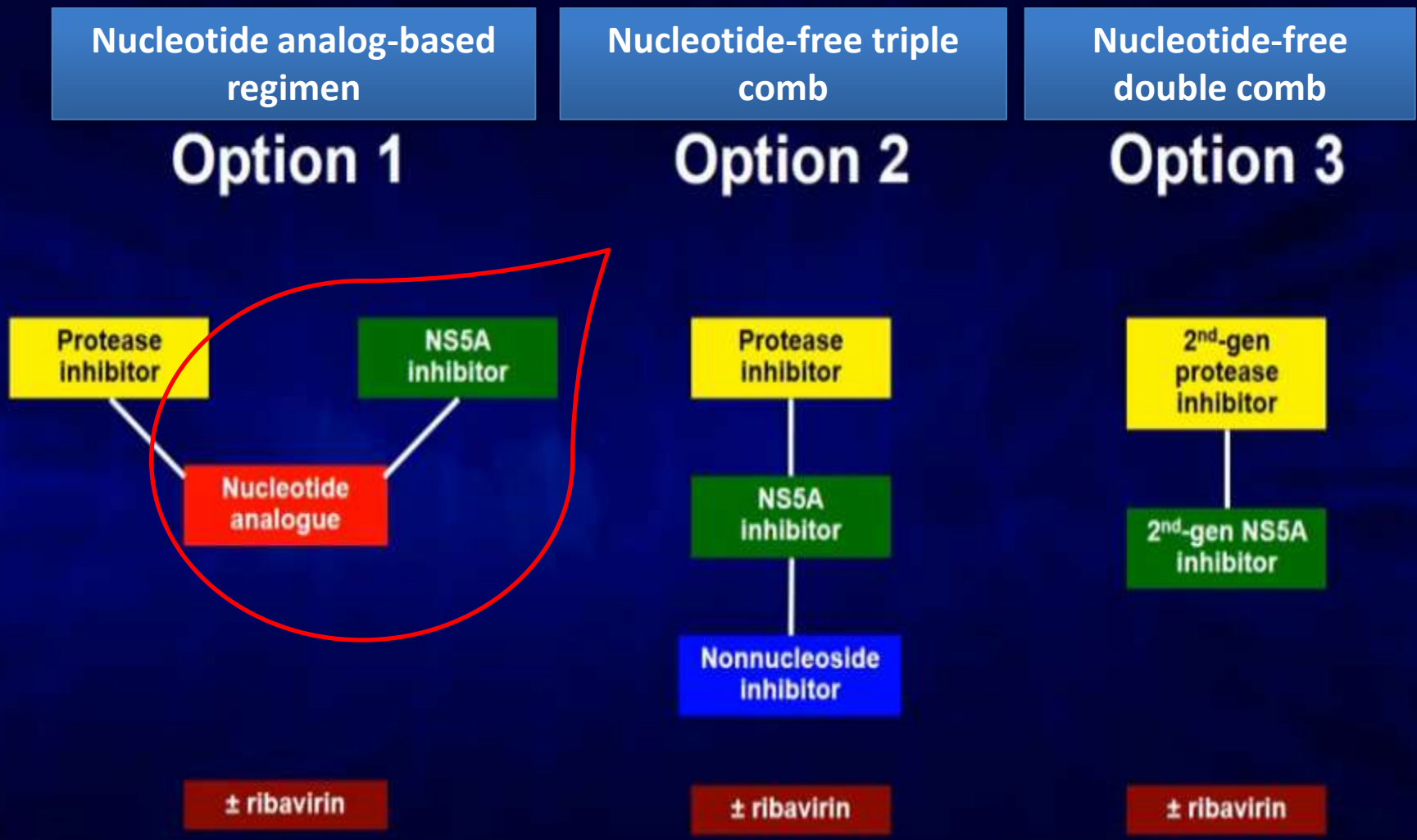
ΚΕΕΛΠΝΟ

Ομάδα Εργασίας ΚΕ.ΕΛ.Π.ΝΟ.
Γ. Παπαθεοδωρίδης, Γ. Γερμανίδης, Γ.Ν. Νταλέκος

Δεκέμβριος 2015

Επιστημονικός Σύμβουλος: Σ.Ι. Χατζηγιάννης

IFN-Free Strategies (2015-2016)



Pawlotsky Gastroenterology 2015

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SMV+PR / PR*	x12 / 12 ή 36 εβδ. (όχι σε 1a με Q80K)			x12 / 12 ή 36 εβδ.	
SOF+RBV*	x24 εβδ.	x12 εβδ.	x24 εβδ. (όχι σε επαναθεραπευόμενους κιρρωτικούς)	x24 εβδ.	x24 εβδ.
SOF+SMV*	x12 εβδ. (όχι σε 1a με Q80K)			x12 εβδ.	
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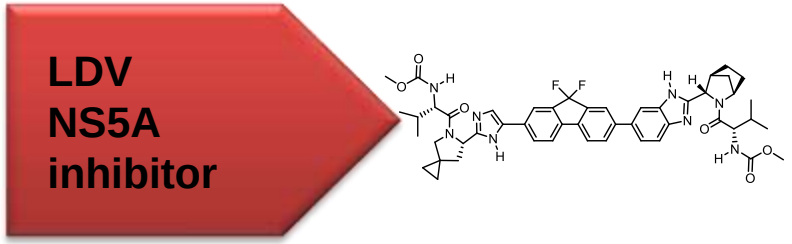
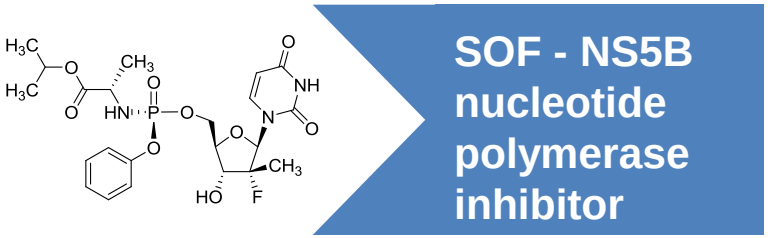
SOF/LDV SOF/LDV+RBV	x12 εβδ. (x8 εβδ. για πρωτοθε-ραπευόμενους χωρίς κίρρωση, x12 εβδ. (για επαναθεραπευ-όμενους με κίρρωση)		x12 εβδ. (δεν συστήνεται λόγω περιορισμένων δεδομένων)	x12 εβδ.	
PRV/r/OBV+DSV+RBV* PRV/r/OBV+DSV*	x12* εβδ. για 1a x12 εβδ. για 1b				
PRV/r/OBV+RBV				x12 εβδ.	

Ledipasvir/Sofosbuvir: A Single Tablet Regimen (STR)

- **Ledipasvir (LDV)**
  - Picomolar potency against HCV GT 1a and 1b
  - Effective against NS5B RAV S282T
  - Once-daily, oral, 90 mg



- **Sofosbuvir (SOF)**
  - Potent antiviral activity against HCV GT 1–6
  - Effective against NS5A RAVs
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



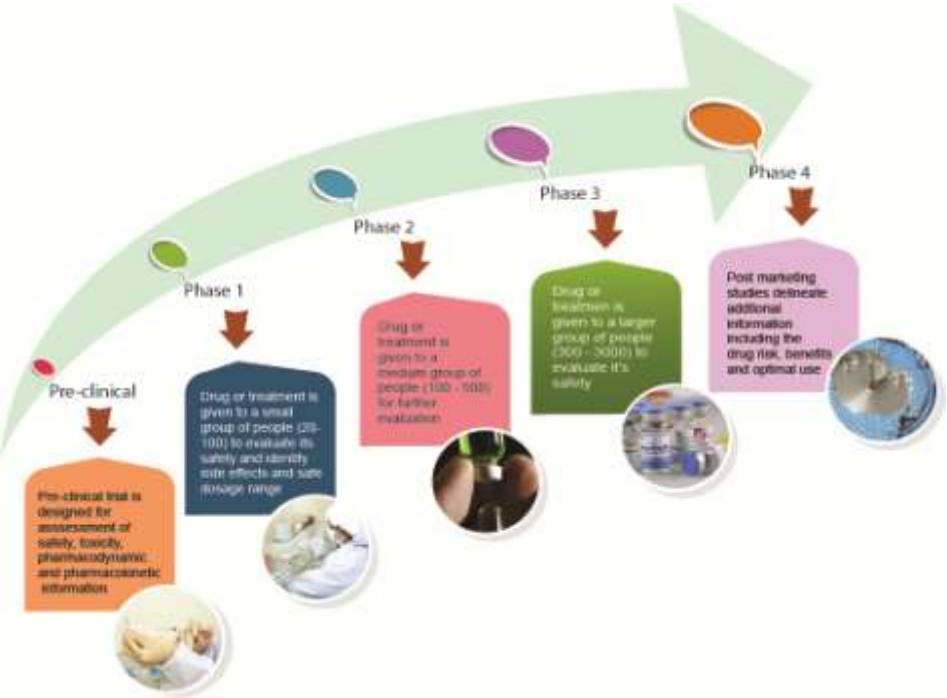
- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet, RBV-free
  - Limited DDIs, no food effect
  - **>2000 patients treated in clinical trials**

FDA Approval 10 October 2014
European Approval 18 November 2014

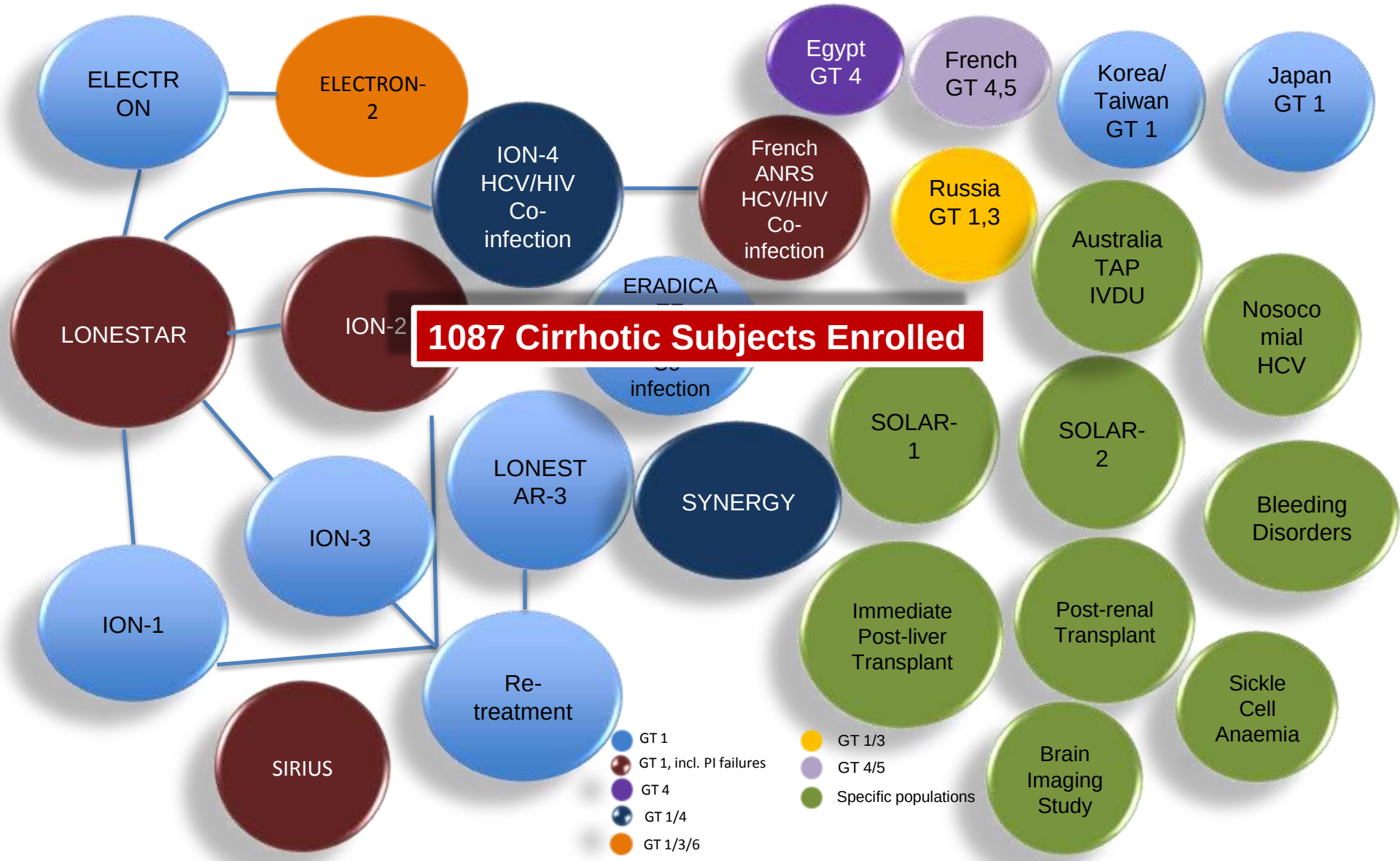
Lawitz E, et al. EASL 2011, poster 1219; Cheng G, et al. EASL 2012, poster 1172; HARVONI▼ (ledipasvir/sofosbuvir), Gilead Sciences International Ltd. SmPC,.

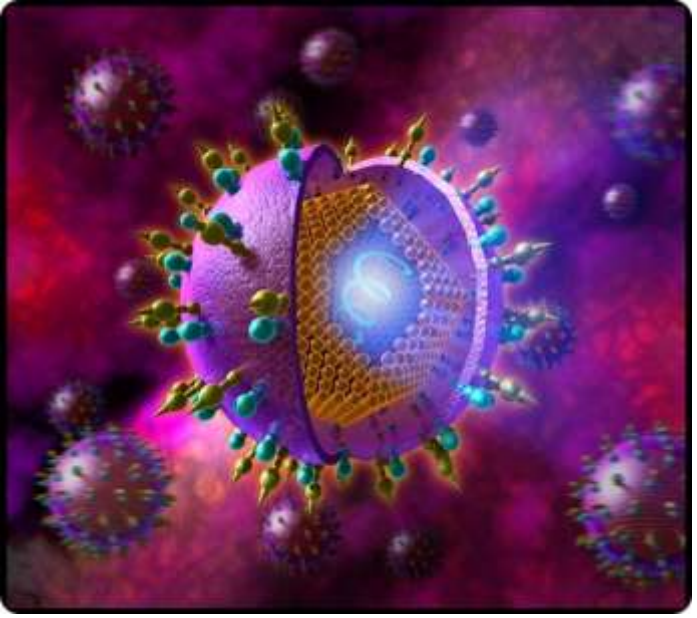

CLINICAL
TRIAL


Real-World Data


Pre-clinical
Phase 1
Phase 2
Phase 3
Phase 4
Post marketing studies delineate additional information including the drug risk, benefits and optimal use

LDV/SOF Clinical Development Program





HCV GEN 1

LDV/SOF: phase 3

ION-1

- N = **865**
- Treatment naïve
- 16% cirrhotic

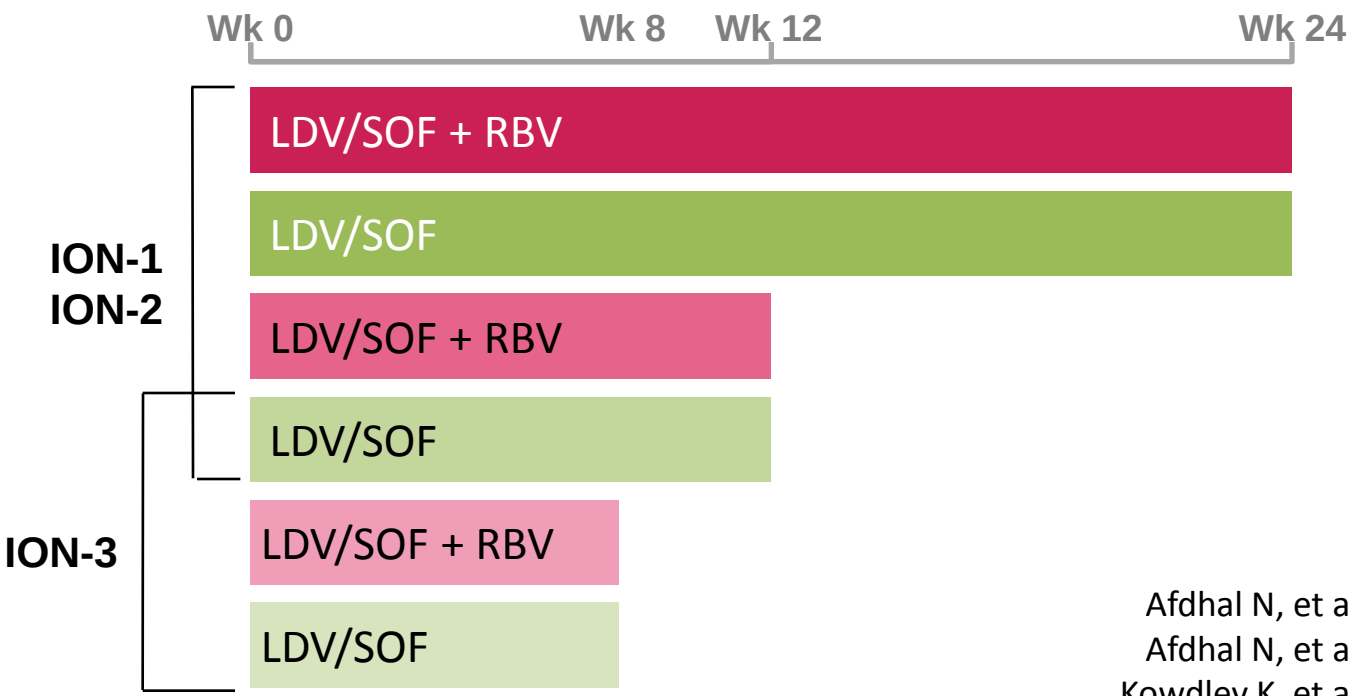
ION-2

- N = **440**
- Treatment experienced
- 20% cirrhotic;

ION-3

- N = **647**
- Treatment naïve
- Non-cirrhotic

1952 total patients (224 cirrhotics)



Afdhal N, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014

Overall Demographics

	Total N=1952		n (%)
Mean age, y (range)	53 (18–80)	Age ≥ 65 yrs, n (%)	152 (8)
Male, n (%)	1175 (60)	Female	777 (40)
Black, n (%)	308 (16)		
Hispanic, n (%)	181 (9)		
Mean BMI, kg/m^2 (range)	27 (18–56)	BMI ≥ 30, n (%)	501 (26)
IL28B non-CC, n (%)	1469 (75)		
GT 1a, n (%)	1443 (74)		
Cirrhosis, n (%)	224 (12)		
Prior PI+PEG+RBV failures	231 (12)		

Afdhal N, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014

LDV/SOF: phase 3 endpoints

ION-1

Primary endpoint:
- SVR 12

Secondary endpoints:
- SVR 4, SVR 24
- Safety and tolerability
- Relapse
- Viral resistance to LDV and SOF during and after treatment

ION-2

Primary endpoint:
- SVR 12

Secondary endpoints:
- SVR 4, SVR 24
- Safety and tolerability
- Relapse
- Viral resistance to LDV and SOF during and after treatment

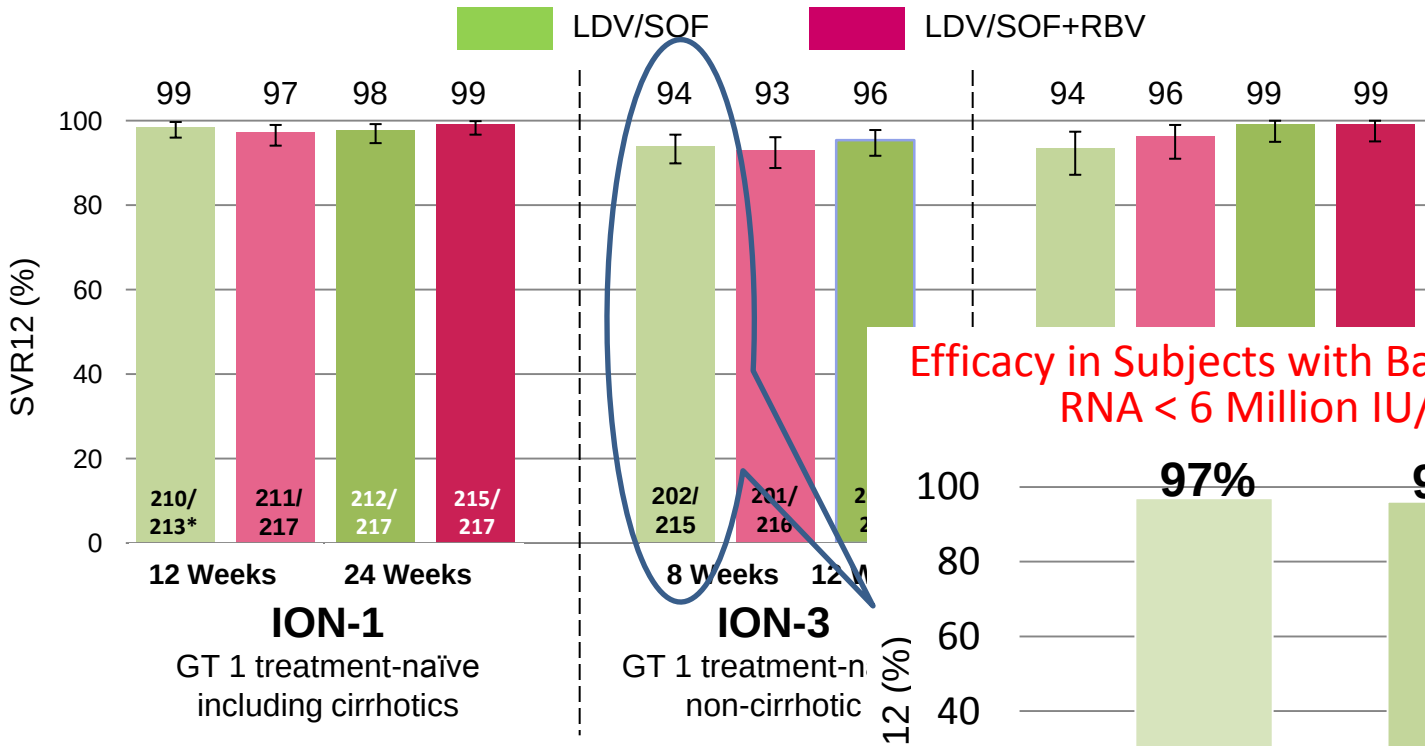
ION-3

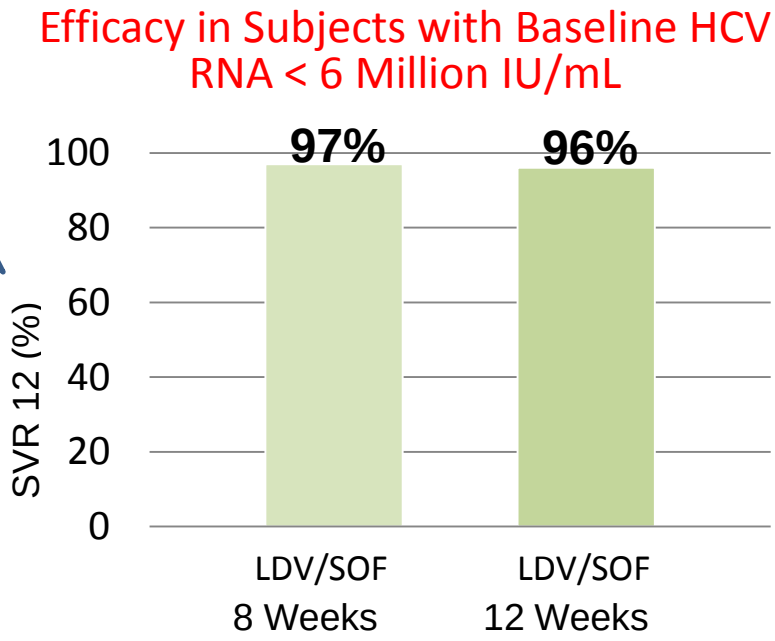
Primary endpoint:
SVR 12

Secondary endpoints:
- Non-inferiority of 8 weeks of LDV/SOF to the other treatment groups
- SVR 4, SVR 24
- Safety and tolerability
- Relapse
- Viral resistance to LDV and SOF during and after treatment

Afdhal N, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014

Results: efficacy summary (ITT Analysis)



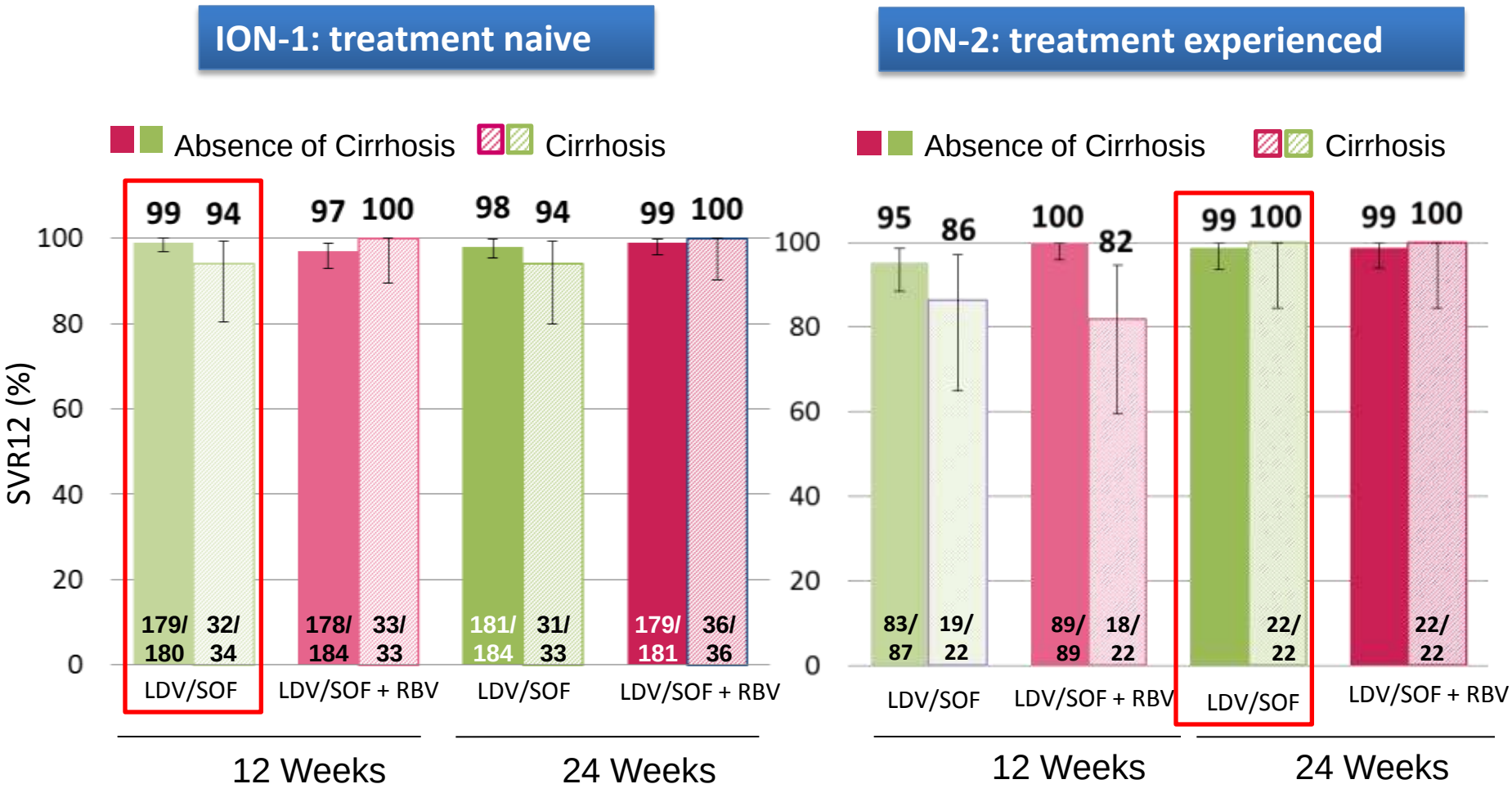


- 97% (1886/1951) overall SVR rate
  - Similar efficacy was observed between the RBV-free and RBV-conta
- 3% (65/1951) did not achieve SVR
  - 1.8% (36) relapsed
  - 1.4% (27) were either lost to follow up or withdrew consent
  - 0.1% (2) virologic breakthrough (both due to non-adherence)

*excluding one subject with genotype 4 infection
Error bars represent 95% confidence intervals.

Afdhal N, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014

Results: SVR12 by presence of cirrhosis (ITT)
ION-1/ -2



Sulkowski M, IAC 2014, LBPE16

Pooled Safety

n (%)	LDV/SOF (N=1080)	LDV/SOF+RBV (N=872)
Adverse Event	800 (74%)	745 (85%)
Treatment Related AEs	484 (45%)	617 (71%)
Grade ≥3 AE	46 (4%)	45 (5%)
SAE	34 (3%)	17 (2%)
Treatment-Related SAE	4 (<1%)	1 (<1%)
AEs Leading to Study Drug Modification/Interruption	6 (1%)	118 (14%)
Treatment DC due to AE	6 (1%)	7 (1%)
Death	0	0

The most common adverse reactions (≥10%) were fatigue and headache in subjects treated with 8, 12, or 24 weeks of LDV/SOF.

Sulkowski M, IAC 2014, LBPE16

Pooled Summary of Adverse Events

n (%)	LDV/SOF 8 Weeks (N = 215)	LDV/SOF 12 Weeks (N = 539)	LDV/SOF 24 Weeks (N = 326)	LDV/SOF+ RBV 8 Weeks (N = 216)	LDV/SOF+ RBV 12 Weeks (N = 328)	LDV/SOF+ RBV 24 Weeks (N = 328)
Fatigue	45 (21%)	116 (22%)	79 (24%)	75 (35%)	124 (38%)	132 (40%)
Headache	30 (14%)	113 (21%)	79 (24%)	54 (25%)	75 (23%)	99 (30%)
Nausea	15 (7%)	61 (11%)	36 (11%)	38 (18%)	57 (17%)	57 (17%)
Insomnia	11 (5%)	41 (8%)	30 (9%)	26 (12%)	63 (19%)	66 (20%)
Diarrhoea	15 (7%)	40 (7%)	33 (10%)	13 (6%)	23 (7%)	31 (10%)
Irritability	3 (1%)	22 (4%)	21 (6%)	29 (13%)	30 (9%)	36 (11%)
Rash	3 (1%)	23 (4%)	21 (6%)	19 (9%)	32 (10%)	43 (13%)
Arthralgia	9 (4%)	32 (6%)	27 (8%)	11 (5%)	27 (8%)	28 (9%)
Cough	3 (1%)	18 (3%)	21 (6%)	12 (6%)	37 (11%)	41 (13%)
Pruritus	2 (1%)	21 (4%)	10 (3%)	16 (7%)	32 (10%)	30 (9%)

Sulkowski M, IAC 2014, LBPE16

Conclusions

- **LDV/SOF for 12 w achieved an SVR12 rate of 99% in treatment-naive GT 1 patients without cirrhosis** (addition of RBV did not increase SVR12 rates)
- Patients with **compensated cirrhosis achieved SVR12 of 94% with 12 or 24 w** of treatment with LDV/SOF
- **LDV/SOF for 8 or 12 weeks** resulted in high SVR12 rates in GT 1 treatment-naïve patients without cirrhosis
- **LDV/SOF for 12 w resulted in SVR12 of 94% in GT 1 patients who had failed PegIFN+RBV±PI** (addition of RBV did not increase SVR12 rates)
  - ✓ Patients who were **treatment experienced and were non-cirrhotic** had SVR12 rate of **95%** with LDV/SOF for **12 weeks**
  - ✓ Patients who were **treatment experienced and were cirrhotic** had SVR12 rate of **100%** with LDV/SOF for **24 weeks**
- Host and viral factors traditionally associated with lower SVR rates did not affect SVR12 rates
- Baseline NS5A polymorphisms did not impact SVR rate
- LDV/SOF STR was well tolerated
  - Addition of RBV contributed to a higher incidence of SAEs and laboratory abnormalities

Afdhal N, et al. *N Engl J Med* 2014
Afdhal N, et al. *N Engl J Med* 2014
Kowdley K, et al. *N Engl J Med* 2014

Greek guidelines for treatment of CHC

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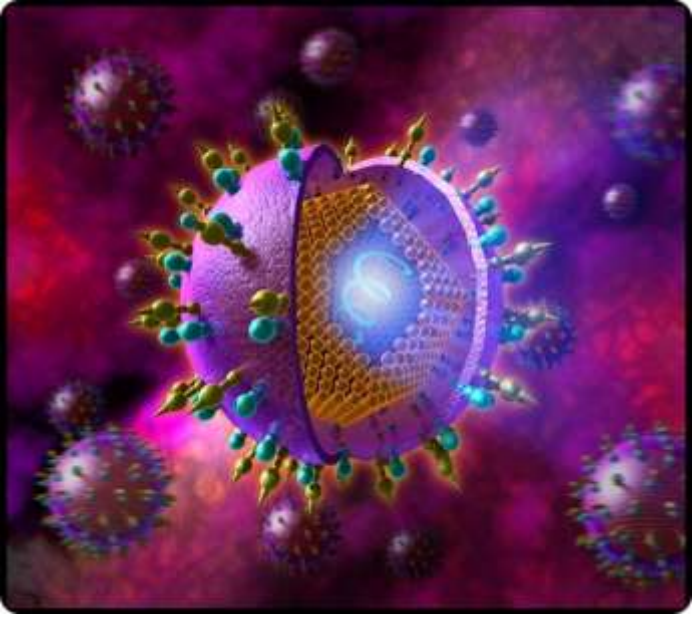
PRV/r/OBV+DSV+RBV* PRV/r/OBV+DSV*	x12* εβδ. για 1a x12 εβδ. για 1b				
PRV/r/OBV+RBV				x12 εβδ.	

EASL (cirrhosis)
12 wk with RBV, or
24wk without RBV, or
24wk with RBV (if negative predictors of response)



HCV GEN 3

The clinical data to support the use of Harvoni in patients infected with HCV genotype 3 are limited. The relative efficacy of a 12 week regimen consisting of ledipasvir/sofosbuvir + ribavirin, compared to a 24 week regimen of sofosbuvir + ribavirin has not been investigated. A conservative 24 weeks of therapy is advised in all treatment-experienced genotype 3 patients and those treatment-naïve genotype 3 patients with cirrhosis (Harvoni SmPC, Dec 2015).

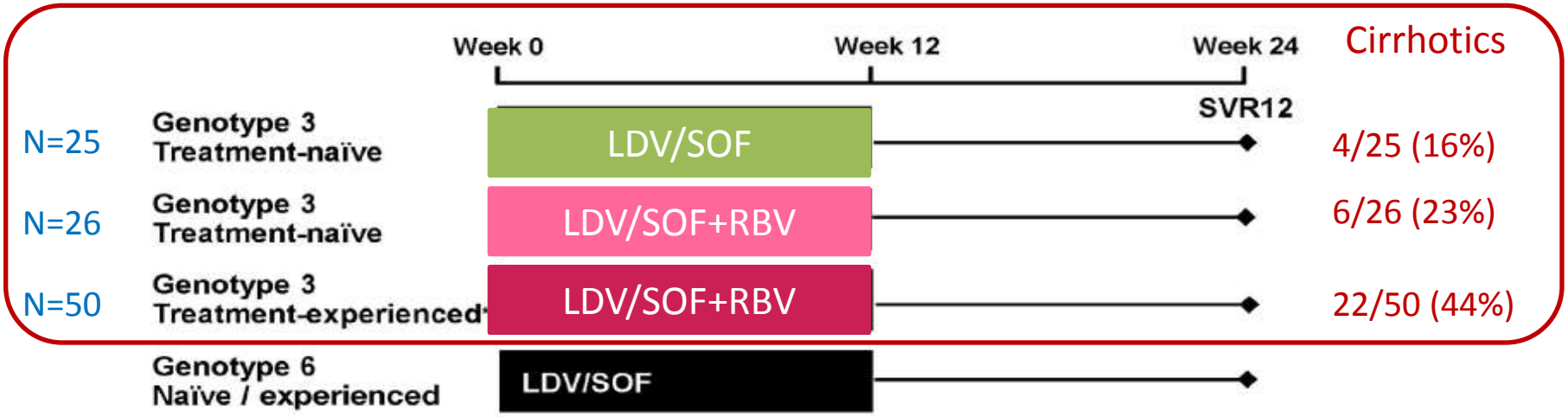
ELECTRON-2 (LDV/SOF±RBV)

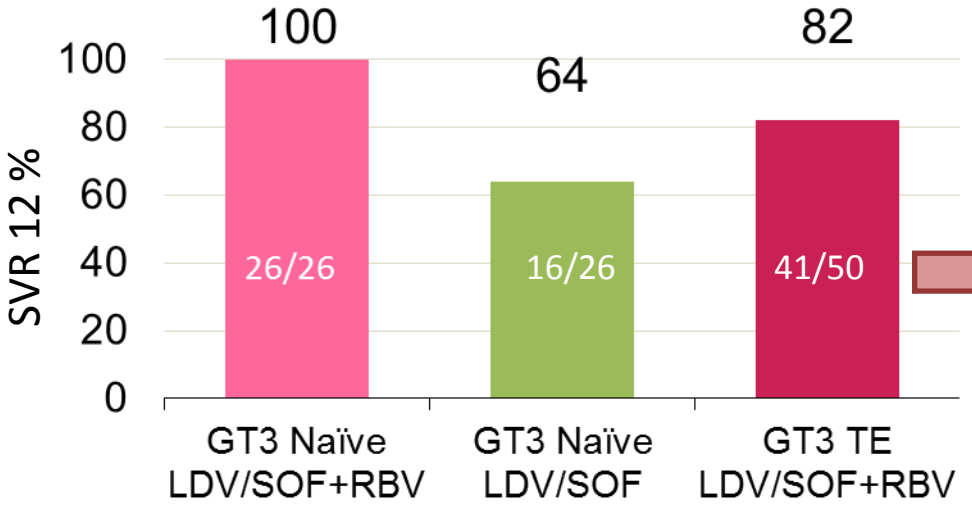
Gastroenterology 2015;149:1454–1461

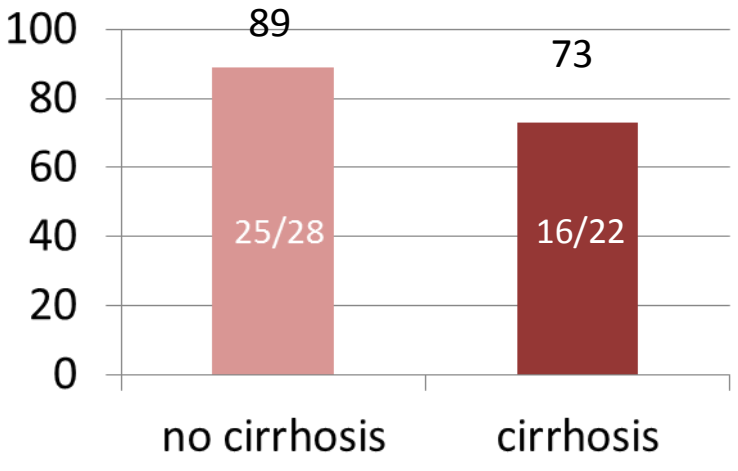
CLINICAL—LIVER

Efficacy of Ledipasvir and Sofosbuvir, With or Without Ribavirin, for 12 Weeks in Patients With HCV Genotype 3 or 6 Infection

Edward J. Gane,[1] Robert H. Hyland,[2] Di An,[2] Evguenia Svarovskaia,[2] Phillip S. Pang,[2] Diana Brainard,[2] and Catherine A. Stedman[3]







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SOF+DCV SOF+DCV+RBV	x12 x12 εβδ. (για επαναθερα-πευόμενους με κίρρωση)		x12 εβδ. (όχι κίρρωση) x12-24 εβδ. (κίρρωση)	x12 ή 24 εβδ.	
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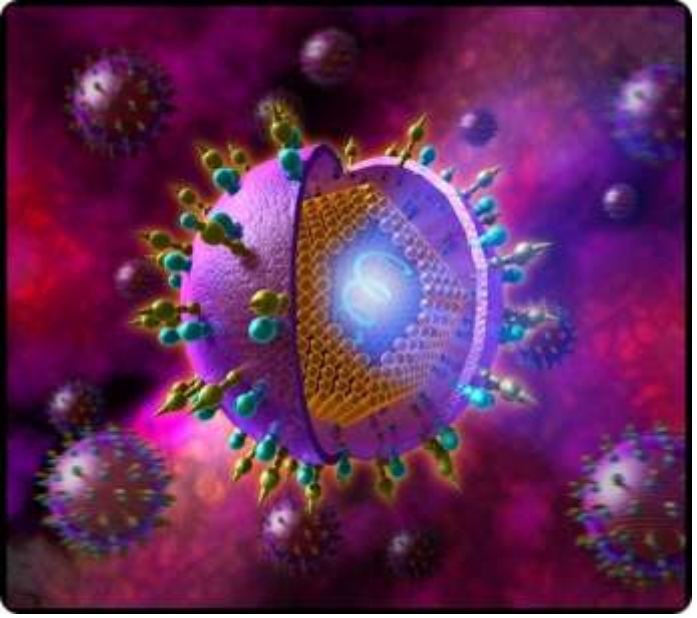
PRV/r/OBV+DSV+RBV* PRV/r/OBV+DSV*	x12* εβδ. για 1a x12 εβδ. για 1b				
PRV/r/OBV+RBV				x12 εβδ.	

Η εγκεκριμένη διάρκεια θεραπείας με Harvoni + RBV στο γονότυπο 3 είναι 24 εβδομάδες

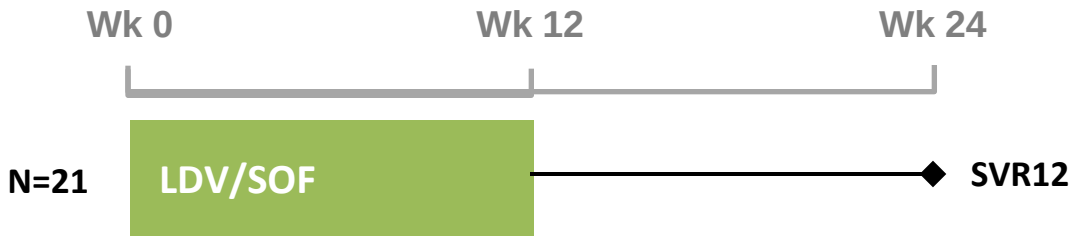


HCV GEN 4

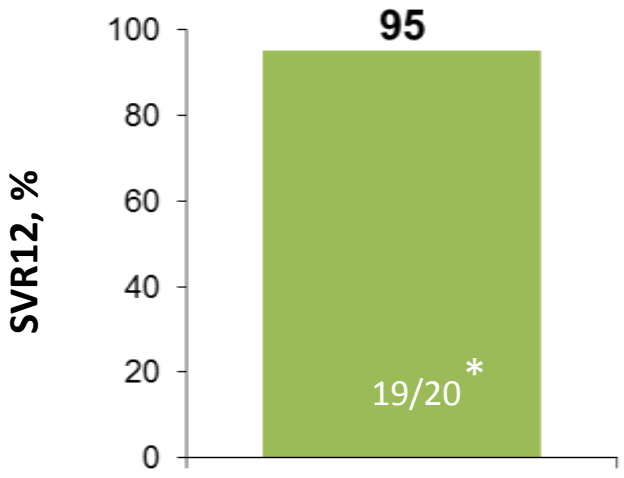
Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study

Lancet Infect Dis 2015; 15: 1049–54

Anita Kohli, Rama Kapoor, Zayani Sims, Amy Nelson, Sreetha Sidharthan, Brian Lam, Rachel Silk, Colleen Kotb, Chloe Gross, Gebeyehu Teferi, Kate Sugarman, Phillip S Pang, Anu Osinusi, Michael A Polis, Vinod Rustgi, Henry Masur, Shyam Kottilil



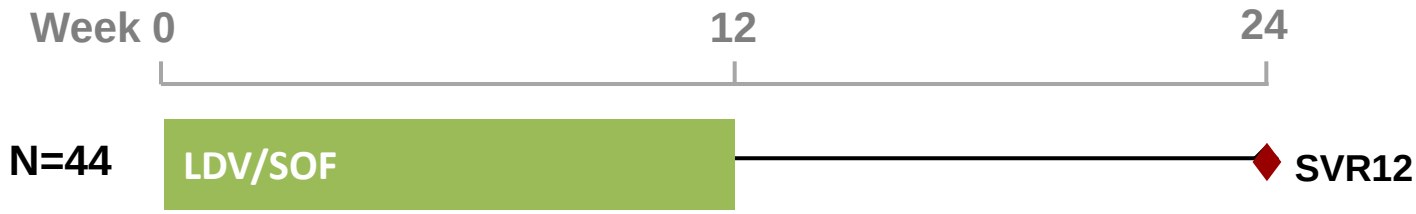
Demographics	
Age	55 ± 10
Male, n (%)	14 (67)
Black, n (%)	9 (43)
Country of Origin	
Egypt, n (%)	6 (29)
United States, n (%)	5 (24)
Ethiopia, n (%)	4 (19)
Cameroon, n (%)	3 (14)
HCV RNA > 800,000 IU/mL, n (%)	13 (62)
Treatment Experienced, n (%)	8 (38)
Cirrhotic, n (%)	7 (33)



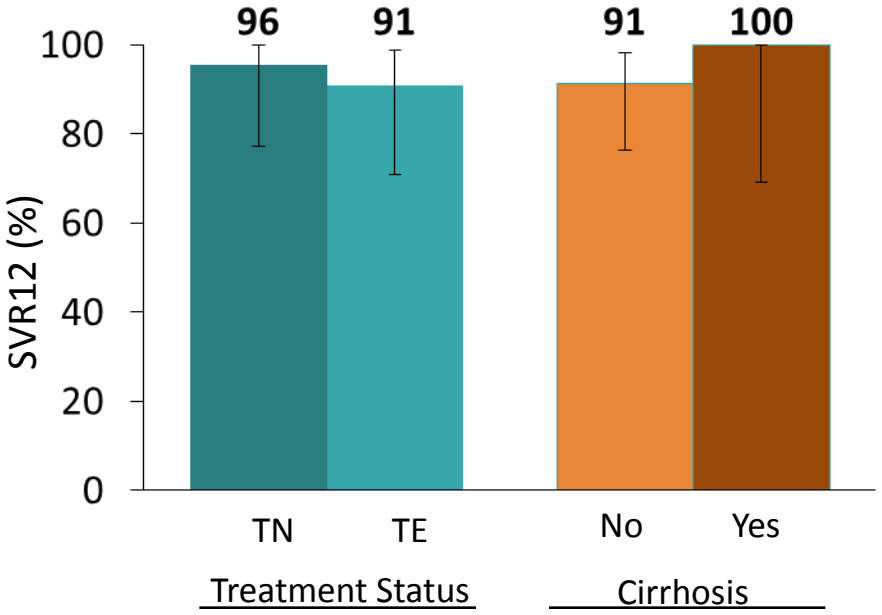
95% SVR12 with LDV/SOF for GT 4 HCV
No subject discontinued due to an AE

LDV/SOF in GT 4 Patients

Multicenter study in GT 4 patients in France



	Naïve n=22	Experienced n=22
Mean age, years (range)	52 (21–69)	50 (30–62)
Male, n (%)	11 (50)	17 (77)
White, n (%)	19 (86)	17 (77)
Cirrhosis, n (%)	1 (5)	9 (41)
IL28B non-CC, n (%)	15 (68)	21 (95)
Mean HCV RNA, log_{10} IU/mL (range)	6.0 (5.1–6.8)	6.3 (5.6–7.5)
GT 4a, n (%)	13 (59)	12 (55)
GT 4d, n (%)	5 (23)	5 (23)
GT 4b, 4f, 4m, 4o, 4r, n (%)	4 (18)	5 (23)



No subjects D/C study due to AEs

LDV/SOF for 12 weeks was highly effective and well tolerated, without the need for RBV

Abergel, EASL, 2015, O056

Greek guidelines for treatment of CHC

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.	
SOF+RBV*	x24 εβδ.	x12 εβδ	(όχι σε ...νους	x24 εβδ.	x24 εβδ.
SOF+SMV*	x12 εβδ. (όχι σε 1a με Q80K)			x12 εβδ.	
SOF+DCV SOF+DCV+RBV	x12 x12 εβδ. (για επαναθερα-πευόμενους με κίρρωση)			x12 ή 24 εβδ.	
SOF/LDV SOF/LDV+RBV	x12 εβδ. (x8 εβδ. για πρωτοθε-ραπευόμενους χωρίς κίρρωση, x12 εβδ. (για επαναθεραπευ-όμενους με κίρρωση)		x12 εβδ. (δεν συστήνεται λόγω περιορισμένων δεδομένων)	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.	

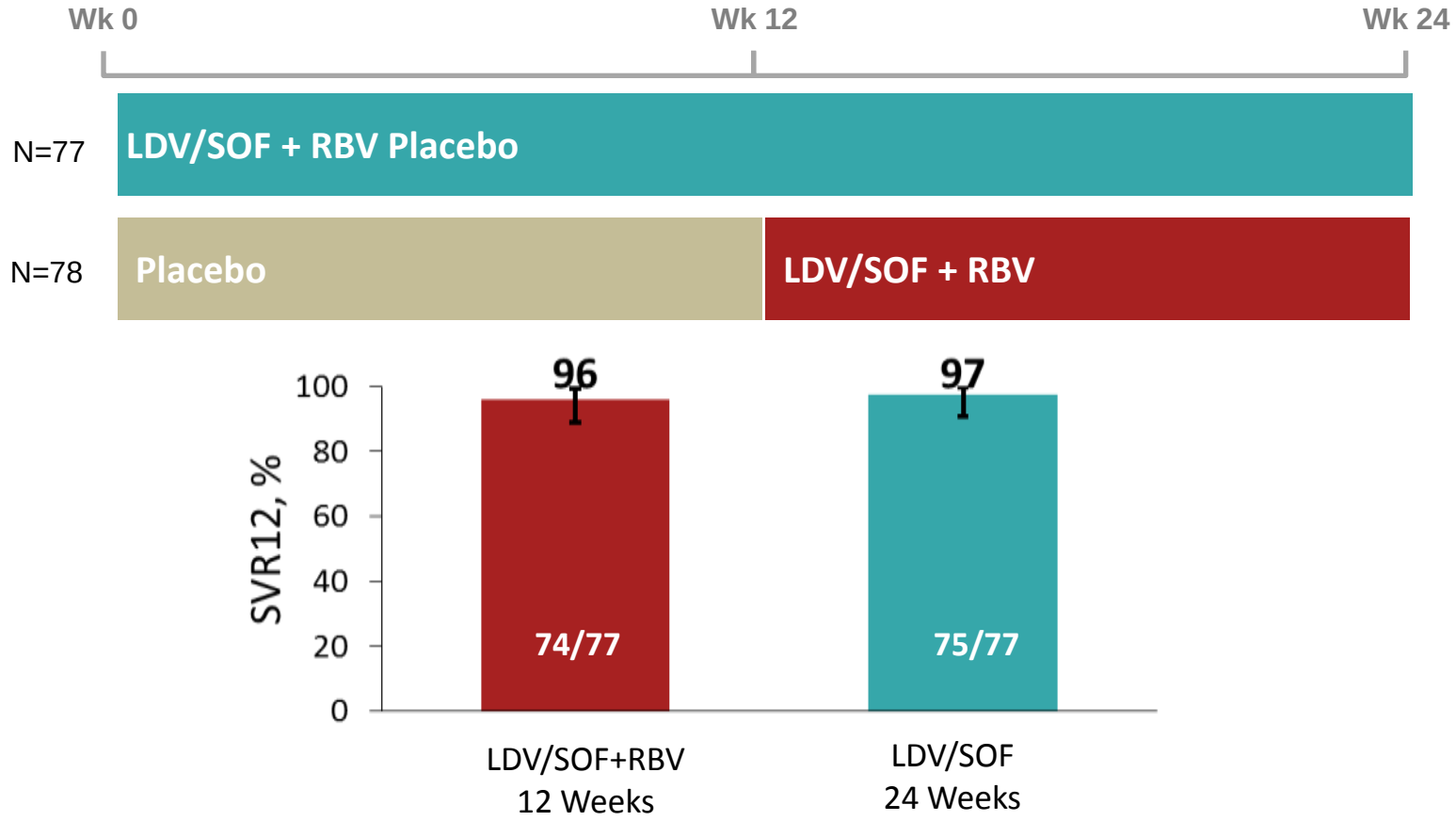
EASL (cirrhosis)
12 wk with RBV, or
24wk without RBV, or
24wk with RBV (if negative predictors of response)

SPECIAL POPULATIONS

- Failure to prior treatment with DAAs
- HCV/HIV co-infection
- Advanced cirrhosis/ post transplant
- Patients with hemoglobulinopathies

LDV/SOF in cirrhotic patients Gen 1 who previously failed PI-Based triple therapy (SIRIUS)

Double-blind, placebo-controlled study in cirrhotic GT1 subjects who failed both PegIFN+RBV and PI+PegIFN+RBV regimens in France (null or partial responders)



TE cirrhotics had a similar response to LDV/SOF+RBV for 12 weeks and LDV/SOF for 24 weeks

Bourliere et al, Lancet Inf Dis 2015

Results: Adverse Events ≥15%

	Placebo 12 Wk → LDV/SOF + RBV 12 Wk			LDV/SOF 24 Wk	
Preferred term, n (%)	**Placebo 12 Wk n=77**	**Second 12 Wk n=76**	**Overall Period n=77**	**First 12 Wk n=78**	**Overall Period n=78**
Asthenia	24 (31)	29 (38)	45 (58)	28 (36)	35 (45)
Headache	16 (21)	13 (17)	21 (27)	27 (35)	31 (40)
Pruritus	14 (18)	11 (14)	22 (29)	4 (5)	7 (9)
Insomnia	9 (12)	7 (9)	17 (22)	11 (14)	13 (17)
Nausea	8 (10)	8 (11)	14 (18)	7 (9)	8 (10)
Fatigue	3 (4)	5 (7)	7(9)	13 (17)	15 (19)
Dry skin	6 (8)	5 (7)	12 (16)	4 (5)	4 (5)
Arthralgia	5 (6)	0	6 (8)	6 (8)	12 (15)
Bronchitis	1 (1)	4 (5)	4 (5)	4 (5)	13 (17)

- Most AEs mild or moderate in severity

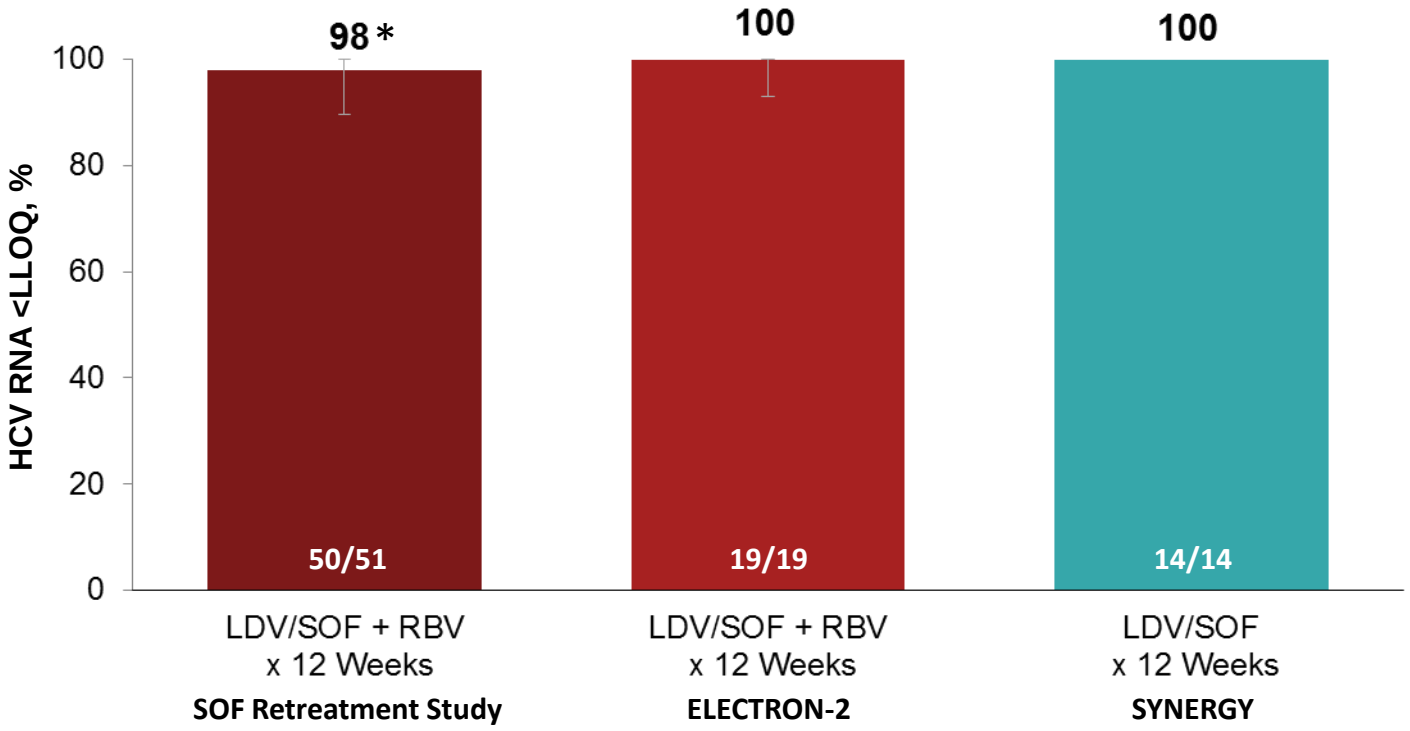
Bourliere et al, Lancet Inf Dis 2015

Conclusions

- 97% of prior PI-failure subjects with cirrhosis achieved SVR12
  - Similar SVR12 rates after 12 weeks of LDV/SOF with RBV compared with 24 weeks of LDV/SOF
- LDV/SOF with and without RBV was well tolerated
  - Only two AEs (headache and fatigue) occurred at a higher frequency with LDV/SOF compared with placebo
  - The majority of these AEs were mild to moderate in severity
- **12 weeks of LDV/SOF with RBV results in high SVR rates among treatment-experienced subjects with cirrhosis who have failed a prior PI-based regimen**

Bourliere et al, Lancet Inf Dis 2015

LDV/SOF ± RBV in treatment experienced GT 1 HCV (SOF Study Retreatment/ ELECTRON-2/ SYNERGY

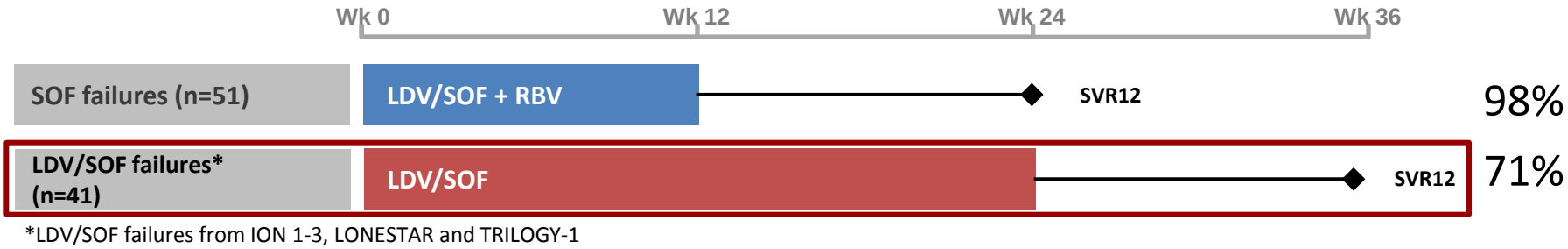


*One subject who relapsed had GT 3a infection

LDV/SOF ± RBV for 12 weeks achieved 100% SVR in GT 1 subjects who failed prior SOF-based therapy

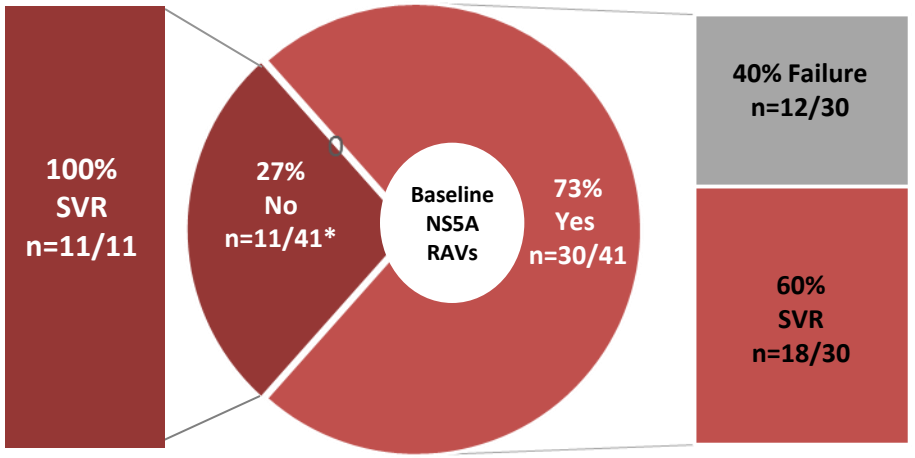
Wyles, AASLD, 2014, Oral #235
Gane, EASL, 2014, Oral #6
Osinusi, et al. *Ann Intern Med.* 2014

Retreatment of Patients Who Failed 8 or 12 Weeks of LDV/SOF-Based Regimens With LDV/SOF for 24 Weeks



*LDV/SOF failures from ION 1-3, LONESTAR and TRILOGY-1

	GT 1 (n=41)
Mean age, years (range)	58 (35-71)
Male, n (%)	34 (83)
Black, n (%)	10 (24)
Cirrhosis, n (%)	19 (46)
IL28B non-CC, n (%)	38 (93)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.2 (4.5-7.4)



*All 11 had failed 8 weeks of LDV/SOF

- No NS5B SOF-associated variants (S282T, L159F, V321A) detected at baseline
- Of 12 patients with NS5A RAVs at baseline who failed treatment, NS5B and NS5A variants were detected in 4 and 12 patients, respectively

Wyles, AASLD, 2014, Oral #235
Lawitz, et al. EASL 2015, O005

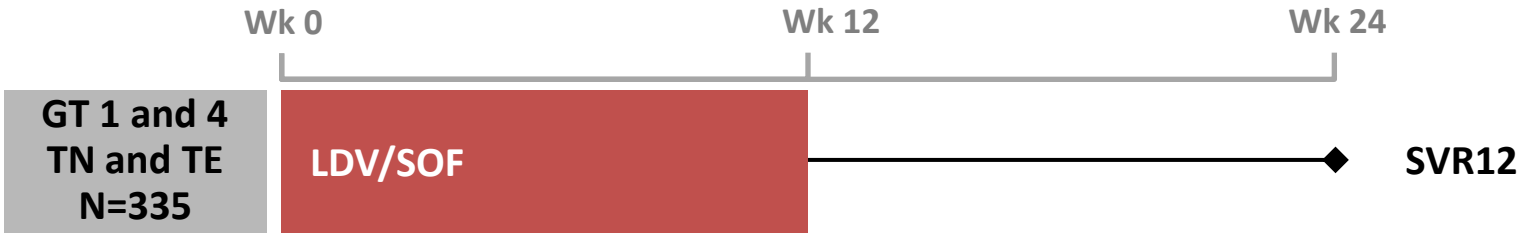
SPECIAL POPULATIONS

- Failure to prior treatment with DAAs
- HCV/HIV co-infection
- Advanced cirrhosis/ post transplant
- Patients with hemoglobulinopathies

ION-4

Study Design

- Phase 3, multicenter, open-label study in US, PR, Canada, and New Zealand



- HIV-1 positive, HIV RNA <50 copies/mL; CD4 cell count >100 cells/mm^3

Demographics

Mean age, y (range)	52 (26-72)
Male, n (%)	276 (82)
Black, n (%)	115 (34)
Hispanic or Latino, n (%)	56 (17)
Mean BMI, kg/m^2 (range)	27 (18-66)
IL28B CC, n (%)	81 (24)
GT 1, n (%)	327 (98)
HCV treatment experienced, n (%)	185 (55)
Cirrhosis, n (%)	67 (20)

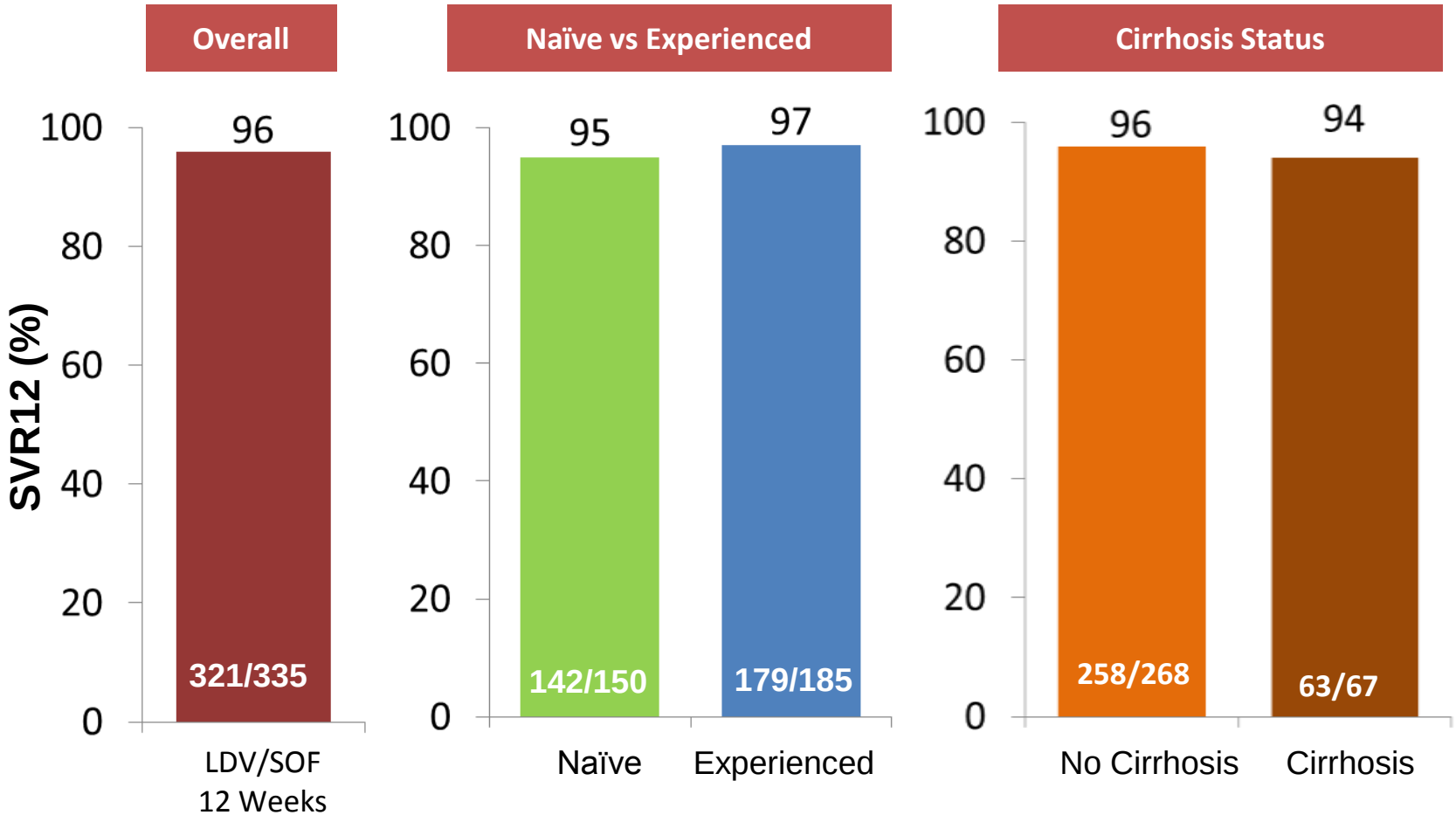
Demographics

Mean HCV RNA, $\log_{10}$ IU/mL ± SD	6.7 ± 0.6
Median CD4 cell count, cells/µL (range)	628 (106-2069)
HIV ART, n (%)	
Efavirenz + FTC + TDF	160 (48)
Raltegravir + FTC + TDF	146 (44)
Rilpivirine + FTC + TDF	29 (9)

FTC, emtricitabine; TDF, tenofovir disoproxil fumarate

Naggie et al, NEJM 2015

Results



- Among those who were treatment-experienced with cirrhosis, 98% (46/47) achieved an SVR12

Naggie et al, NEJM 2015

Safety Summary

	Patients, n (%)	LDV/SOF 12 Weeks N=335
Overall safety	AEs	257 (77)
	Grade 3–4 AE	14 (4)
	Serious AE	8 (2)*
	Treatment D/C due to AE	0
	Death	1 (<1)†
	Grade 3–4 laboratory abnormality	36 (11)

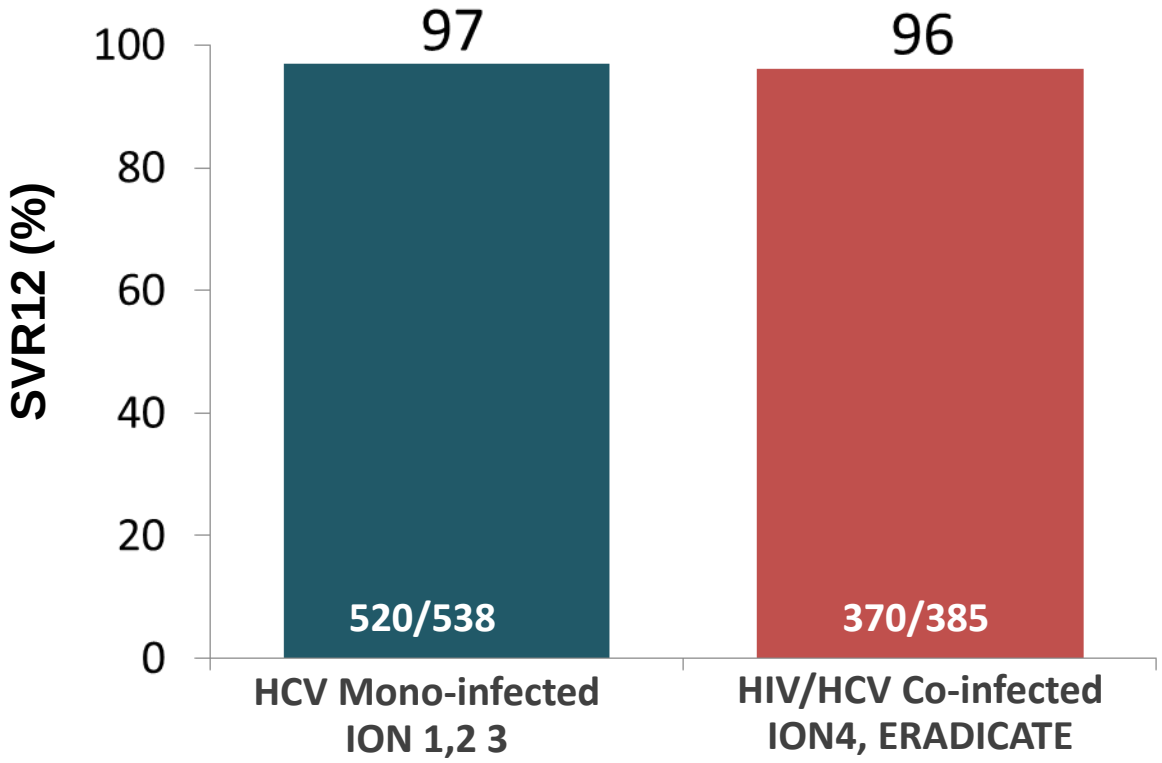
Adverse Events (≥ 5%)

Patients, n (%)	LDV/SOF 12 Weeks N=335
Headache	83 (25)
Fatigue	71 (21)
Diarrhea	36 (11)
Nausea	33 (10)
Arthralgia	22 (7)
Upper respiratory tract infection	18 (5)

*Serious AEs in >1 patient were hepatocellular carcinoma (n=2) and portal vein thrombosis (n=2) in patients with cirrhosis.
†Confirmed IV drug user developed *Staphylococcus aureus* sepsis, endocarditis with associated embolic brain abscesses, and multi-organ system failure.

Naggie et al, NEJM 2015

LDV/SOF x 12 Weeks
SVR12 in HCV Mono-infected and HCV/HIV Co-infected



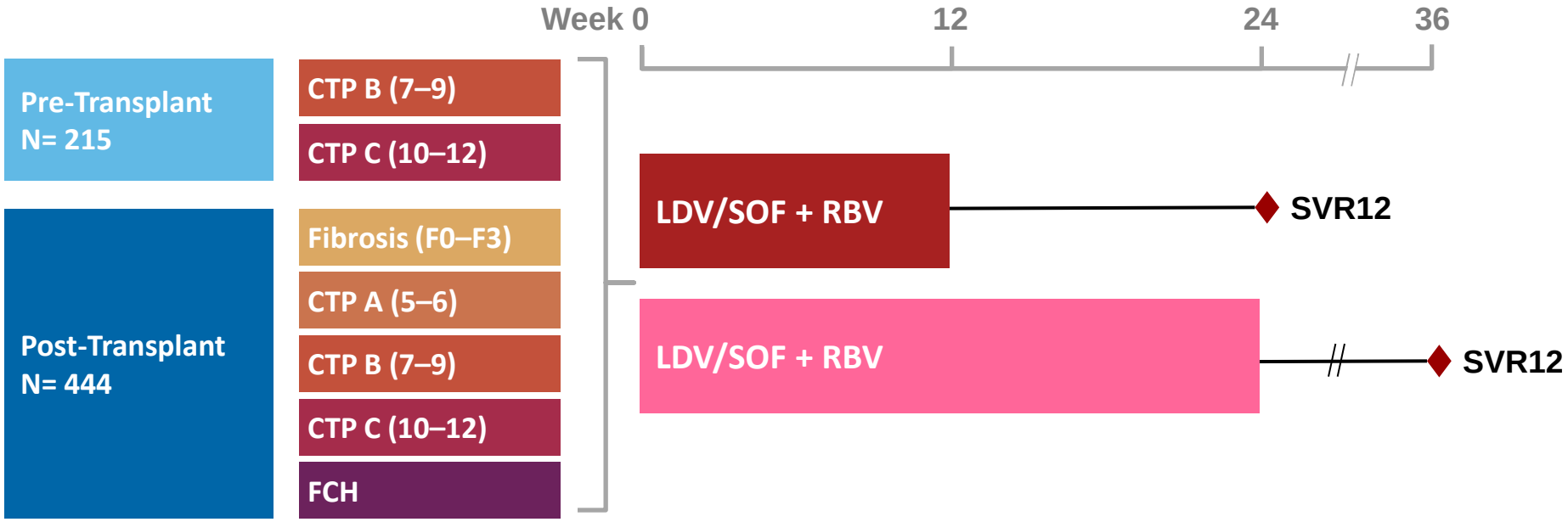
Similar response rates in HCV/HIV co-infected patients compared to HCV mono-infected patients

Afdhal N, et al. *N Engl J Med* 2014; 370: 1889-98; Afdhal N, et al. *N Engl J Med* 2014; 370: 1483-93; Kowdley K, et al. *N Engl J Med* 2014; 370: 1879-88; Naggie et al, CROI 2015, Oral #LB-152; Osinusi A, et al *JAMA* Published online February 23, 2015

SPECIAL POPULATIONS

- Failure to prior treatment with DAAs
- HCV/HIV co-infection
- Advanced cirrhosis/ post-transplant
- Patients with hemoglobulinopathies

LDV/SOF+RBV for 12 or 24 Weeks in 659 Decompensated and Post-Liver Transplant HCV GT 1 and GT 4 Patients



- Broad inclusion criteria:
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤ 10 mg/dL, Haemoglobin ≥ 10 g/dL
  - CrCl ≥ 40 mL/min, Platelets > 30,000/mL
- RBV dosing
  - FCH, Metavir F0–F3 and CTP A cirrhosis: weight-based (1000 mg or 1200 mg)
  - CTP B and C cirrhosis (pre- and post-transplant: dose escalation, 600–1200 mg/d

Charlton et al, Gastroenterology 2015
Manns et al, Lancet Infect Dis 2016

Demographics

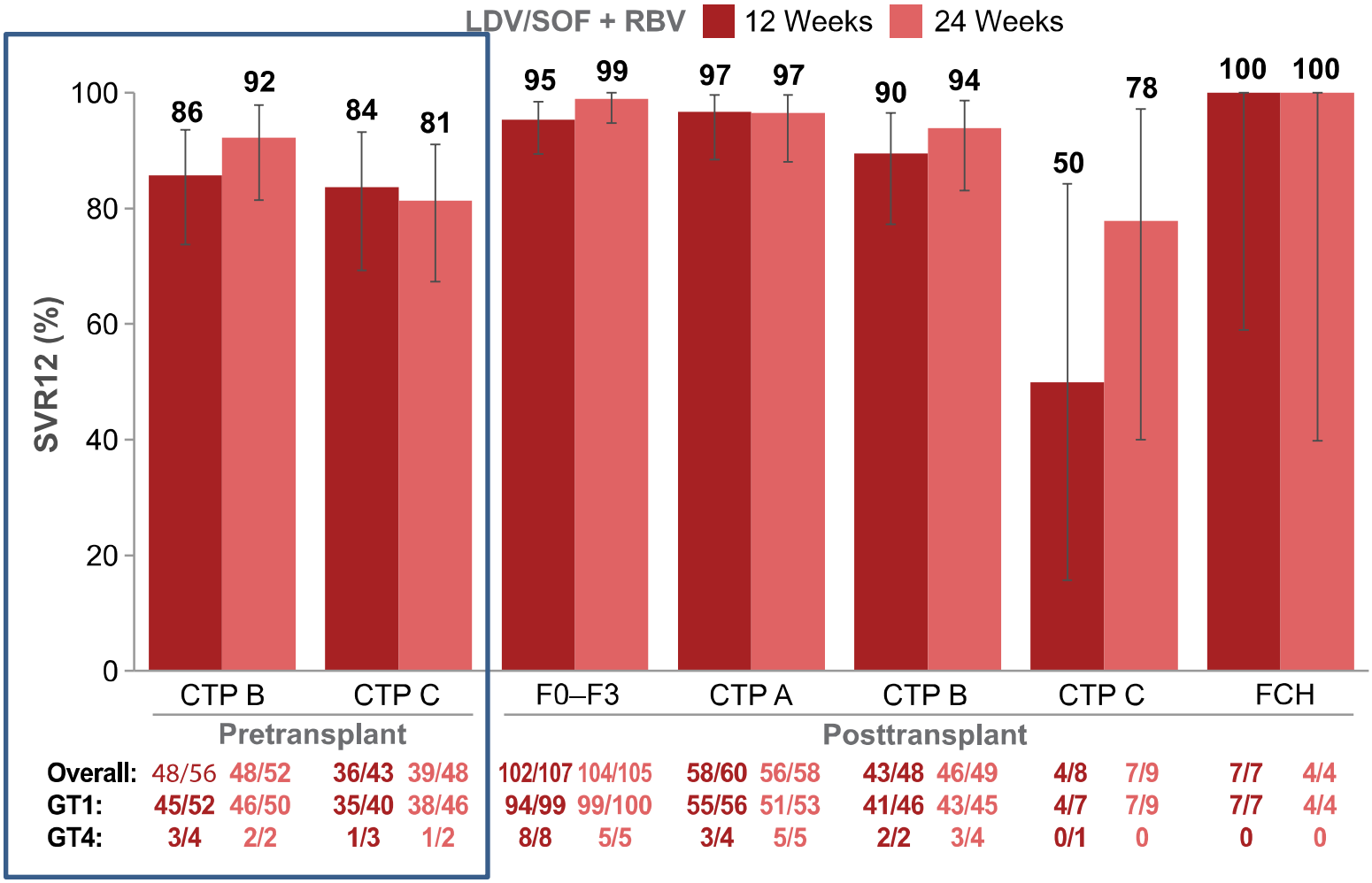
	Pre-Transplant	Post-Transplant		
Patients, n (%)	**CTP B + C n=215**	**F0–3 + CTP A n=330**	**CTP B + C n=114**	**Total n=659**
HCV GT, n (%)				
1a	124 (58)	197 (60)	71 (62)	392 (59)
1b	78 (36)	111 (34)	36 (32)	225 (34)
4	13 (6)	22 (7)	7 (6)	42 (6)
IL28B non-CC, n (%)	167 (77)	272 (83)	92 (81)	431 (81)
Prior HCV treatment, n (%)	150 (70)	270 (82)	96 (84)	516 (78)
Cirrhosis, n (%)	215 (100)	118 (36)	114 (100)	447 (68)
Median eGFR, mL/min/1.73 m^2 (range)	84 (34–224)	63 (20–132)	64 (29–124)	69 (20–224)
MELD, n (%)				
<10	24 (11)	64 (54)	26 (23)	114 (26)
10-15	132 (61)	51 (43)	69 (61)	252 (56)
16–20	54 (25)	3 (3)	16 (14)	73 (16)
21–25	5 (2)	0	3 (3)	8 (2)
Median albumin, g/dL (range)	2.8 (1.6–4.0)	3.9 (2.4–4.8)	3.0 (1.6–4.2)	NR
Median platelets, x 10^3/µL (range)	76 (27–212)	136 (35–434)	90 (32–237)	NR
Ascites, n (%)	163 (76)	9 (3)	83 (73)	NR
Encephalopathy, n (%)	140 (65)	4 (1)	53 (46)	NR

NR, not reported

Charlton et al, Gastroenterology 2015
Manns et al, Lancet Infect Dis 2016

SOLAR-1 and SOLAR-2

Results



Analysis excluded 13 patients transplanted prior to posttreatment Week (FU) 12 with HCV RNA <LLOQ at last measurement prior to transplant, and 3 pretransplant patients who were CTP A at baseline. *Error bars* represent 95% confidence intervals (CIs).

Charlton et al, Gastroenterology 2015
Manns et al, Lancet Infect Dis 2016

Safety Summary

	Pre-Transplant	Post-Transplant		
Patients, n (%)	**CTP B + C n=215**	**F0–3 + CTP A n=330**	**CTP B + C n=114**	**Total n=659**
Any AE	208 (97)	316 (96)	109 (96)	633 (96)
Grade 3–4 AE	51 (24)	76 (23)	33 (29)	160 (24)
Serious AE	61 (28)	49 (15)	34 (30)	144 (22)
Serious treatment-related AE	5 (2)	10 (3)	4 (4)	19 (3)
AE leading to D/C of LDV/SOF	9 (4)	5 (2)	5 (4)	19 (3)
Death	10 (5)	4 (1)	6 (5)	20 (3)
Rejection episode	0	1	0	1
Graft loss	1	1	0	2
Liver transplantation	11	0	0	11

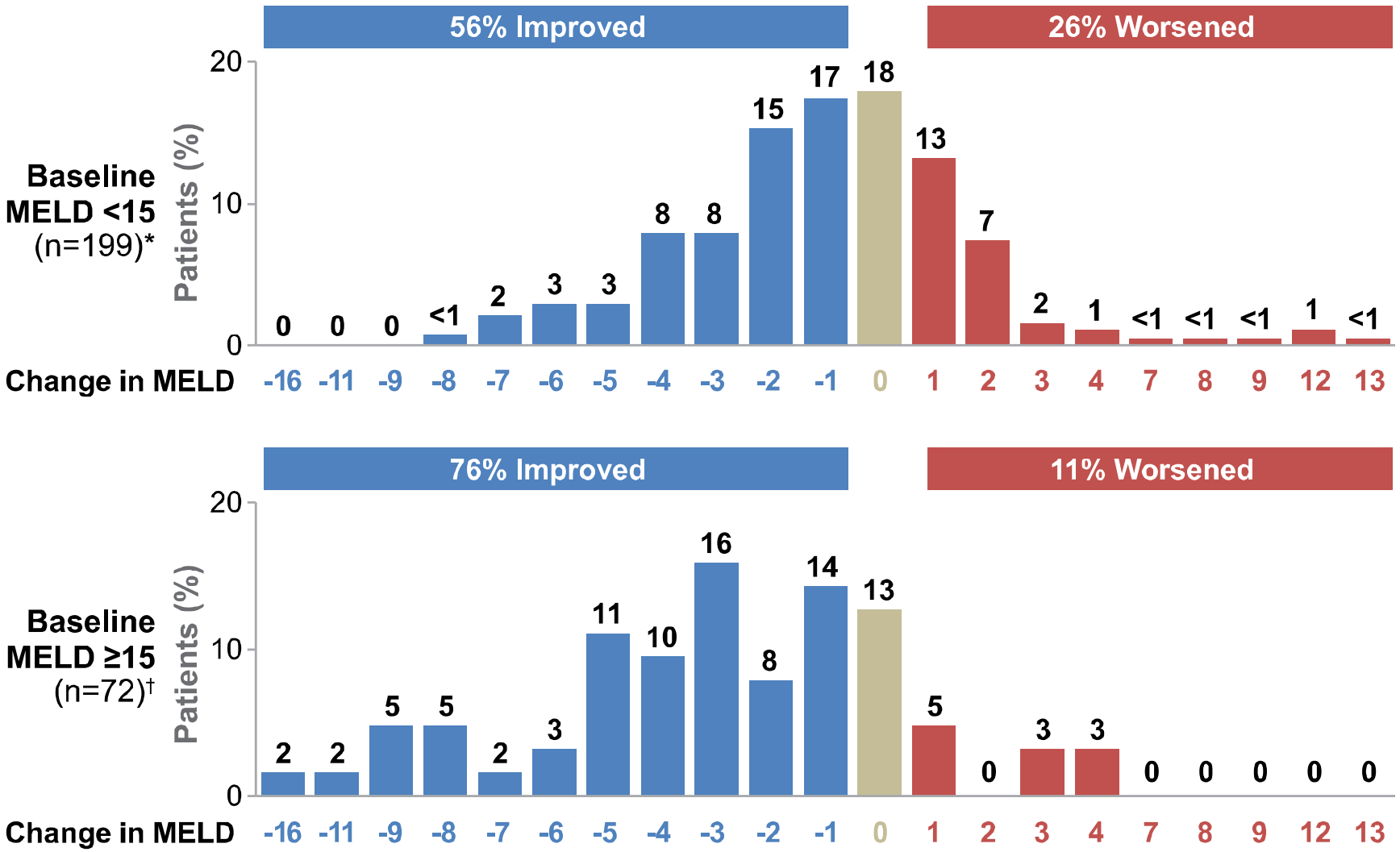
- Treatment-related SAEs were mostly related to RBV treatment
- Deaths and AEs that led to D/C of LDV/SOF were not attributed to study treatment

LDV/SOF+RBV was well tolerated in decompensated cirrhosis and post-transplantation

Charlton et al, Gastroenterology 2015
Manns et al, Lancet Infect Dis 2016

SOLAR-1 and SOLAR-2

MELD Score Change from Baseline to FU-24 in CTP B/C Patients Who Achieved SVR12



Gane, AASLD, 2015, 1049

No FU-24 assessment for *9 patients, †9 patients.

SPECIAL POPULATIONS

- Failure to prior treatment with DAAs
- HCV/HIV co-infection
- Advanced cirrhosis/ post-transplant
- Patients with hemoglobulinopathies

Abstract ID: 1037 **AASLD 2015**

Sofosbuvir and Ledipasvir in attainment of SVR12 in sickle cell disease (SCD) sub-population with chronic hepatitis C (CHC). a single center prospective open label clinical pilot study - SLASH C Trial

P. Basu, Columbia University School of Physicians and Surgeons, Forest hills, New York, UNITED STATES; P. Basu, N. John, M. Aloysius, King's County Hospital Medical Center, NY, New York, New York, UNITED STATES; N.J. Shah, James J. Peters VA Medical Center, Icahn School of Medicine at Mount Sinai, NY , New York, New York, UNITED STATES; R. Brown, Weill Cornell Medical College, New York, New York, UNITED STATES

Patients	N= 24
Genotype	
1a	9
1b	11
1a/4c	1
1a/1b	2
1a/3	1
Stage (metavir)	
F0-F1	9
F2	7
F3/F4	8

All Sofosbuvir /Ledipasvir 12w

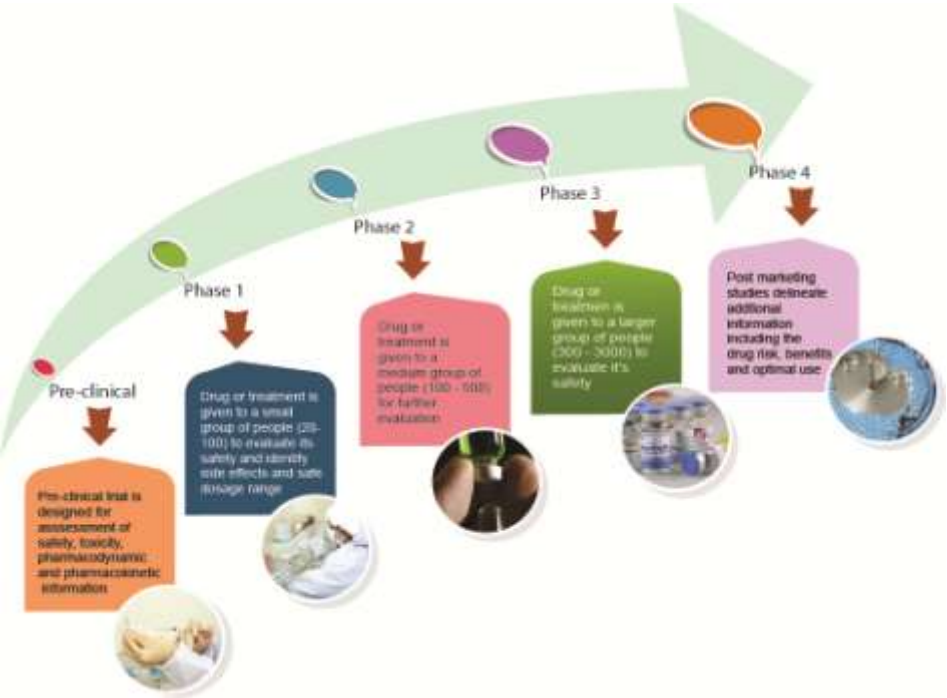
SVR 12: 22/24 (91.7%)

Failure: 2/24 (gen 1a/4c and 1a/3)

Side effects: mild (gastrointestinal 17/24, headache 6/24, insomnia 8/24, anemia 2/24, urinary tract infection 3/24)

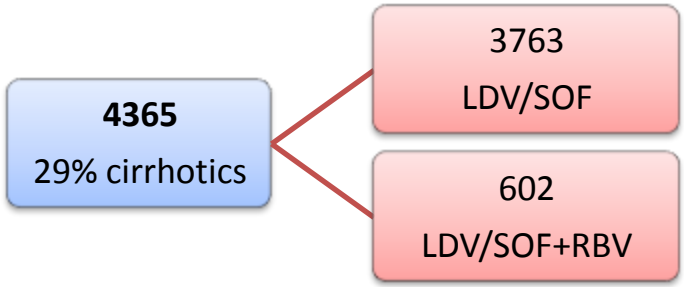

CLINICAL
TRIAL


Real-World Data

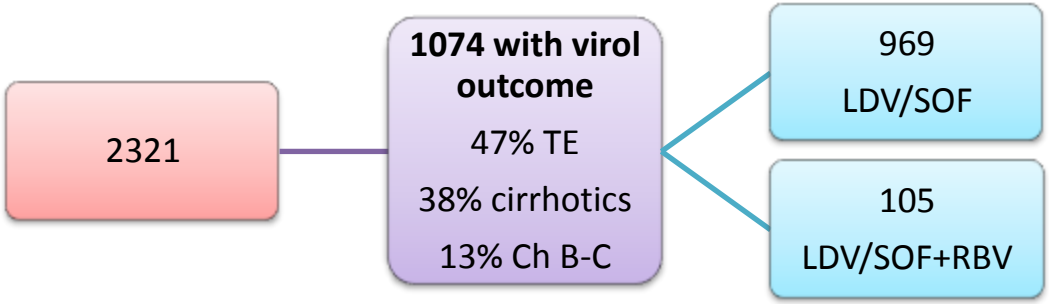

Pre-clinical
Phase 1
Phase 2
Phase 3
Phase 4
Post marketing studies delineate additional information including the drug risk, benefits and optimal use

Real life data LDV/ SOF: 3 large studies in AASLD 2015

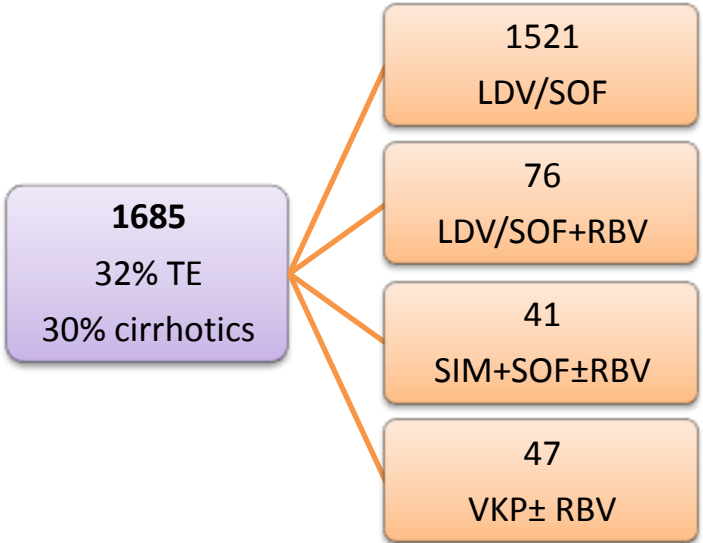
(VA)- Effectiveness of Ledipasvir/ Sofosbuvir in Treatment Naïve Genotype 1 Patients Treated in Routine Medical Practice; Backus Abst 93



(HCV-TARGET) -Treatment Outcomes With 8, 12 and 24 Week Regimens of Ledipasvir/Sofosbuvir for the Treatment of Hepatitis C Infection: Analysis of a Multicenter Prospective, Observational Study; Terrault Abst 94

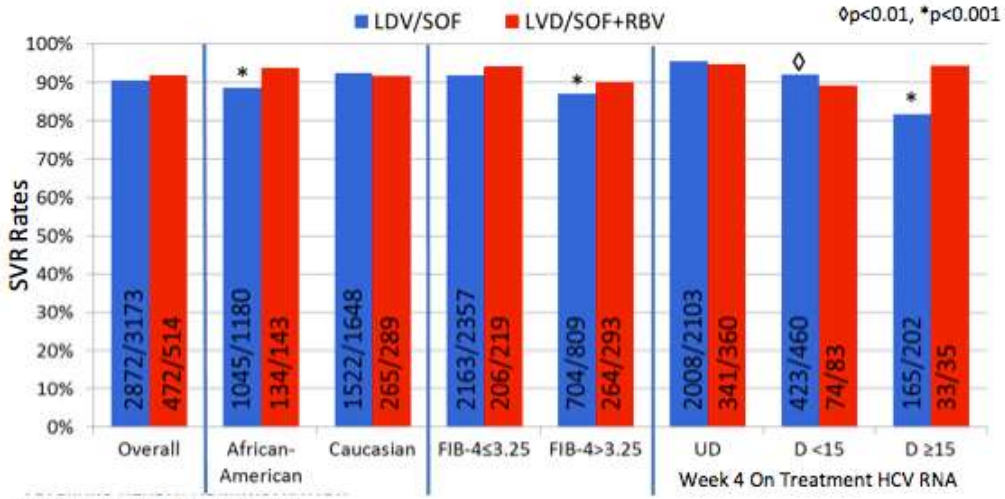


(Trio)- Failure with All-Oral DAA Regimens:Academic and Community Treatment of a Real-World Popu-lation from the TRIO Network; Afdhal Abst LB17; Curry Abst 1108



SVR Rates: Treatment Naïve, GT1

No significant differences in unadjusted SVR rates based on age, sex, decompensated liver disease, diabetes, HIV coinfection, BMI, baseline HCV RNA, subtype and IL28B polymorphism.

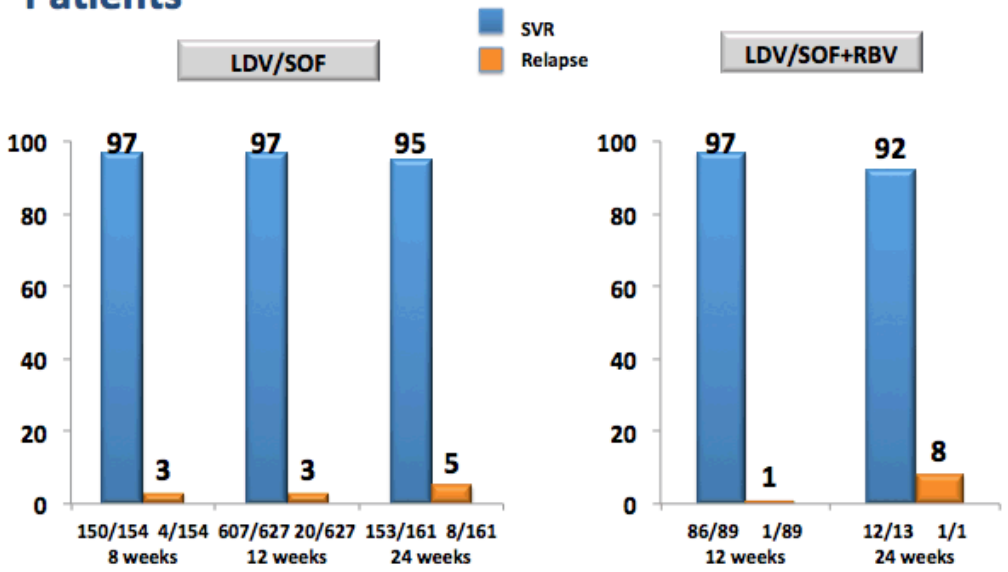


L. Backus et al, AASLD 2015

VA (Backus, abstr 93)

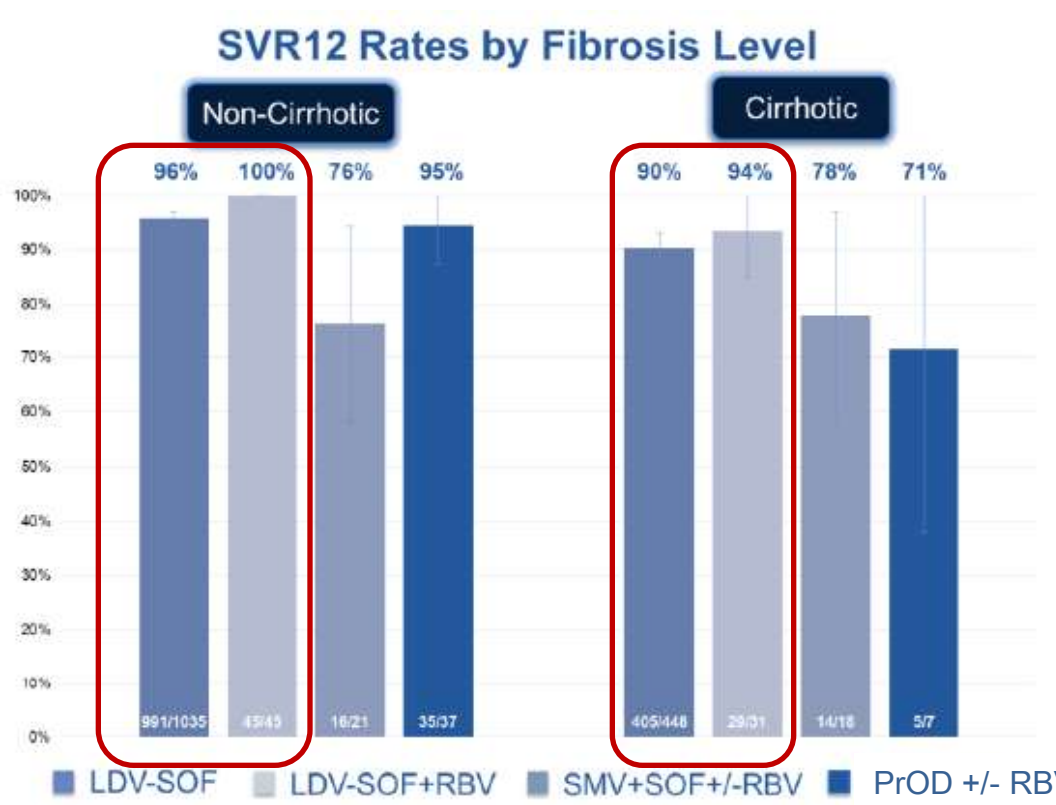
HCV-TARGET (Terrault, abstr 94)

HCV-TARGET: SVR12 and Relapse Rates for LDV/SOF ± RBV by Treatment Duration in HCV G1 Patients

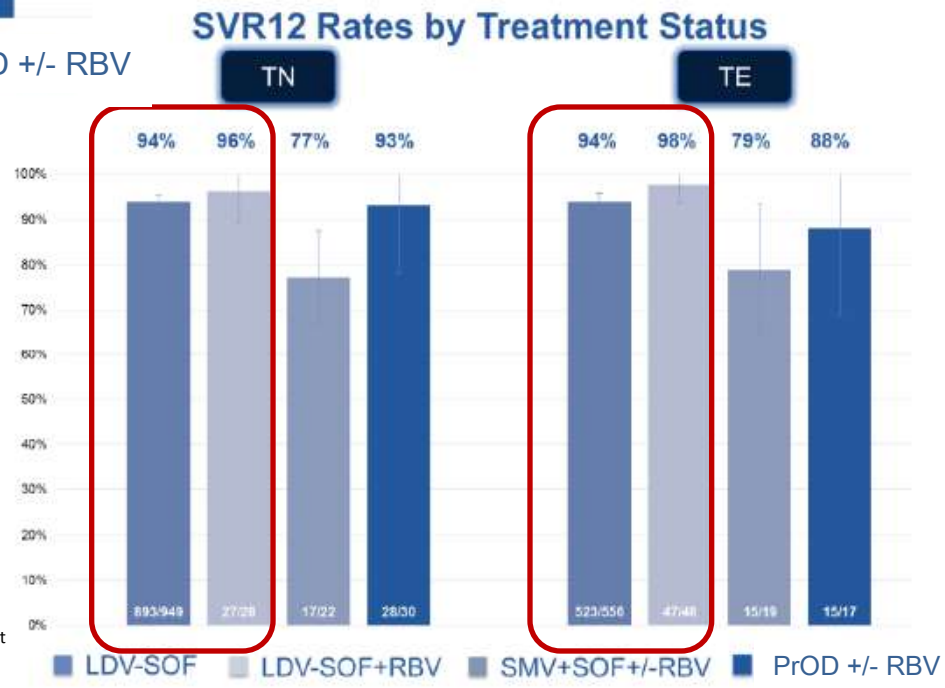


SVR12: SVR at 12 (±1) weeks post treatment

HCV-TARGET

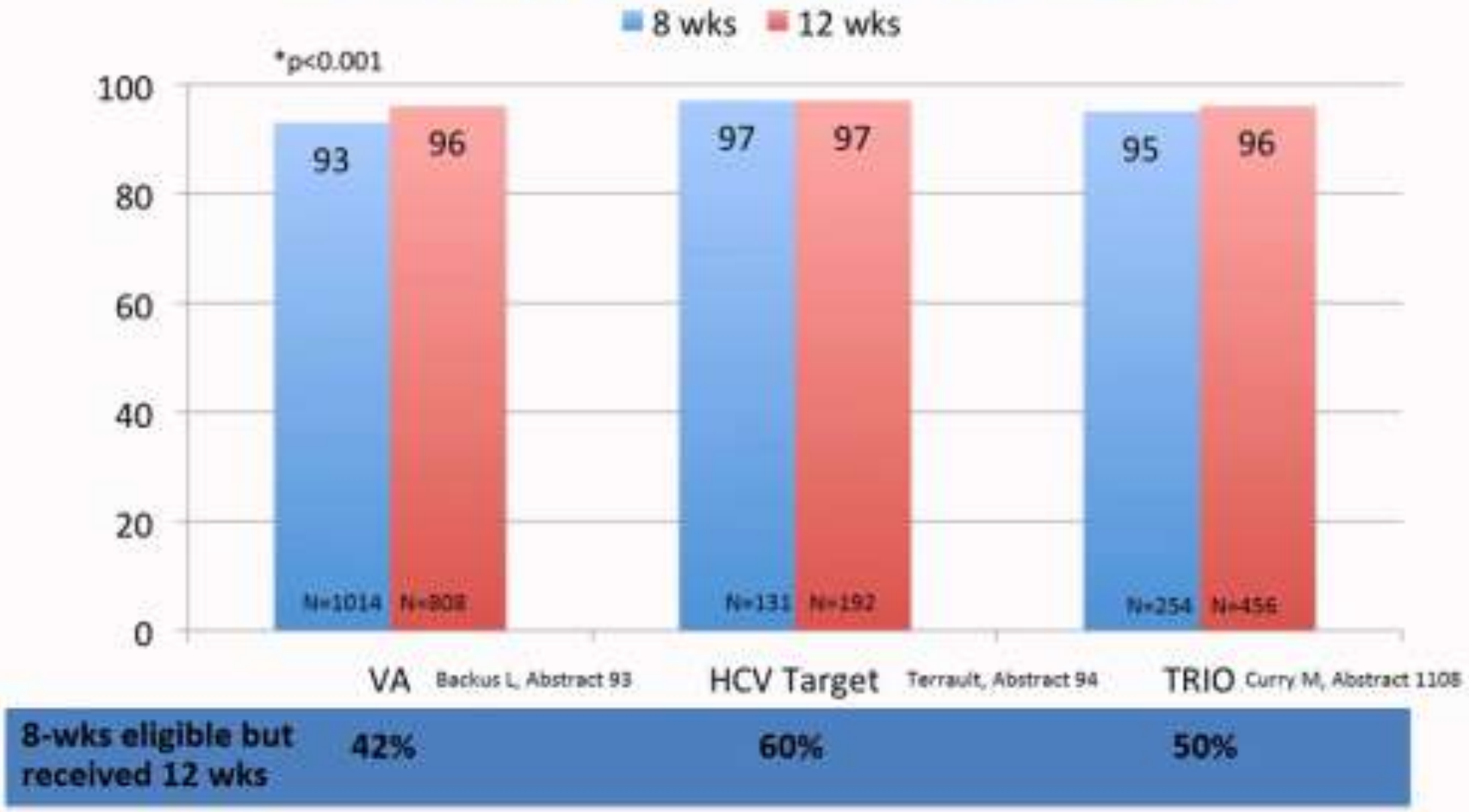


TRIO (Afdhal abstr LB17)



The results shown here have been derived from a real life patient cohort and not from a randomised trial involving direct comparison of therapeutic factors, therefore they do not suggest such comparison.
PrOD: paritaprevir, ritonavir, ombitasvir, dasabuvir, SMV: Simeprevir

Real-World Experience with LDV-SOF of Genotype 1 Treatment Naïve, Non-Cirrhotics with HCV VL <6 million IU/mL



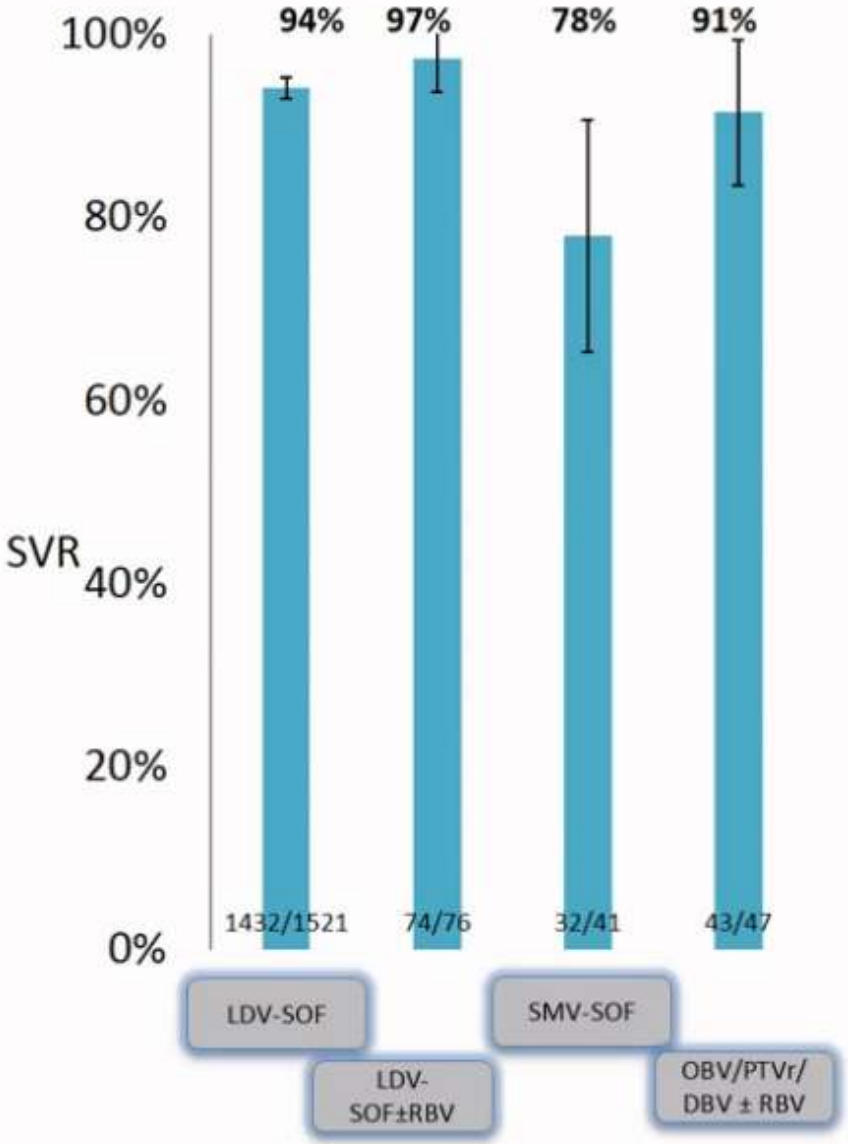
AASLD, 2015

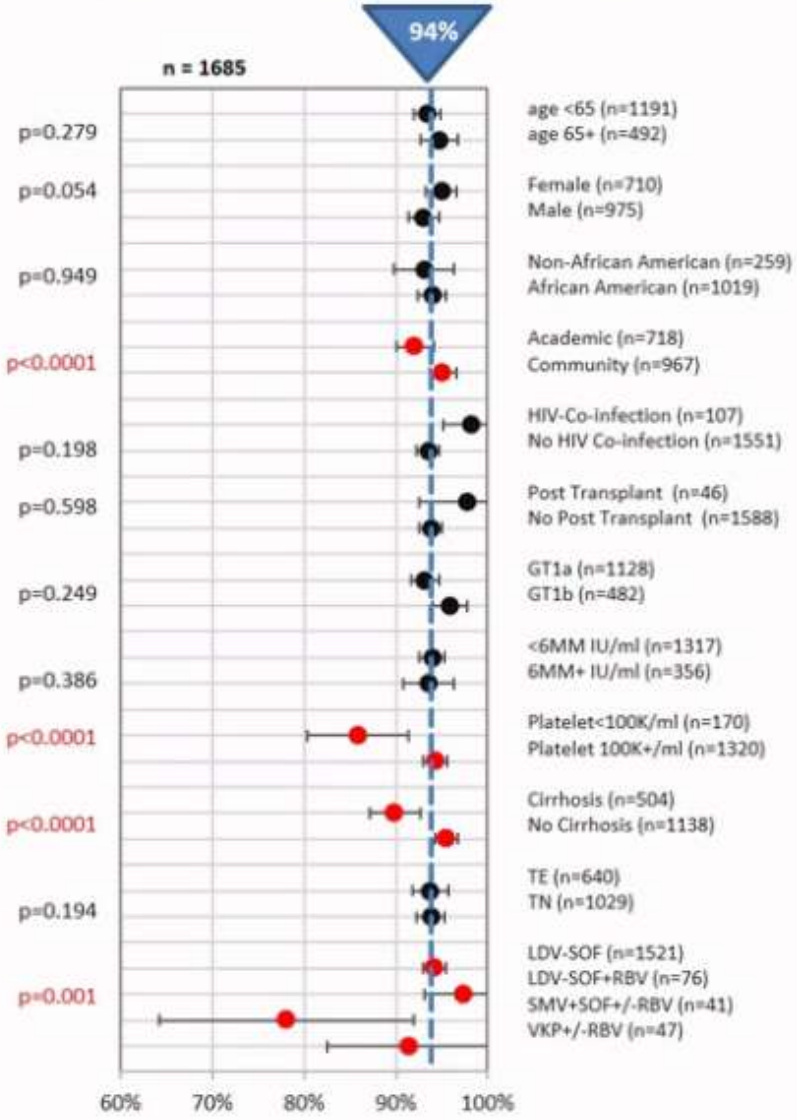
VA: Significant Predictors of SVR in Treatment Naïve GT1 who Completed 8 or 12 Weeks of LDV/SOF

Model	SVR OR (95% CI)
<55 years (ref. 55-64)	1.10 (0.68-1.85)
≥65 years (ref. 55-64)	1.20 (0.86-1.69)
Female (ref. Male)	3.04 (1.12-12.50)
African-American (ref. Caucasian)	0.60 (0.44-0.83)◊
BMI<25 kg/m^2 (ref. 25-29)	0.91 (0.63-1.33)
BMI≥30 kg/m^2 (ref. 25-29)	0.79 (0.56-1.11)
Diabetes	0.98 (0.71-1.35)
FIB4 >3.25 (ref. ≤3.25)	0.47 (0.33-0.65)*
h/o decompensation (ref. no)	0.86 (0.38-2.31)
Subtype 1b (ref. 1a)	1.54 (1.08-2.25)
8 weeks duration (ref. 12 weeks)	0.54 (0.40-0.74)*

◊p<0.01, *p<0.001

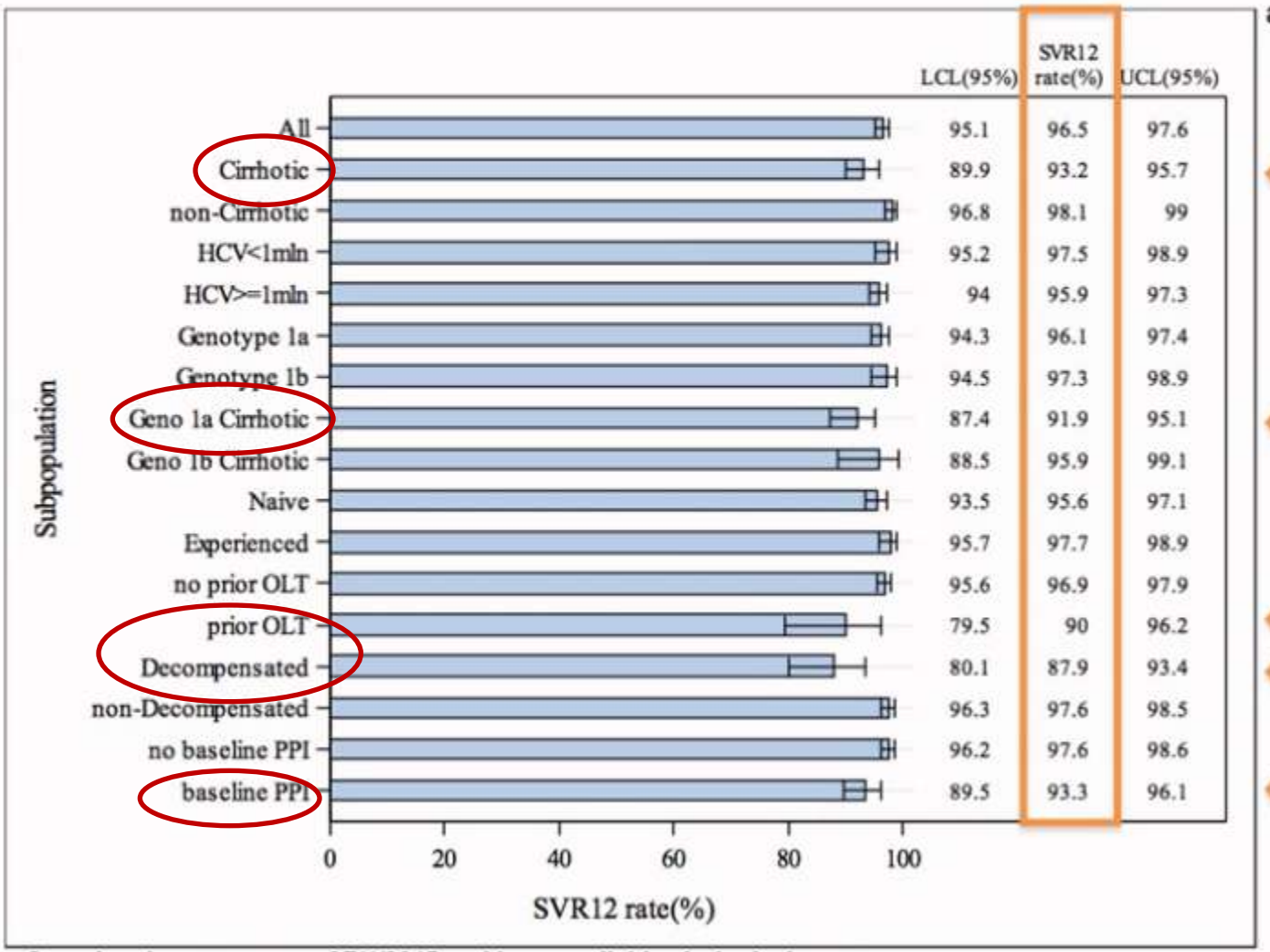
TRIO: SVR12 Influenced by Type of Treatment, Presence of Cirrhosis (platelet count <100K) and Treatment Setting





Afdhal N, AASLD 2015, LB17

HCV-TARGET: SVR12 with LDV/SOF Therapy by Subgroups



Completed treatment as of 7/1/2015 and have available virological outcomes.
Patients who discontinued due to AE or were lost to follow-up are excluded.

SVR12: SVR at 12 (±1) weeks post treatment

HCV-TARGET

Implications: Treating Genotype 1

- SVR results mirror those in clinical trials --> high rate of success
- 8-wk treatment among treatment-naïve, non-cirrhotic, genotype 1 patients with VL <6 million IU/mL is underutilized
- Cirrhosis/Advanced disease associated with lower SVR rates
- Use of PPI is associated with lower SVR rates
  - Potentially modifiable factor to maximize SVR rates
- African-Americans may have lower response rates
  - Reasons unclear

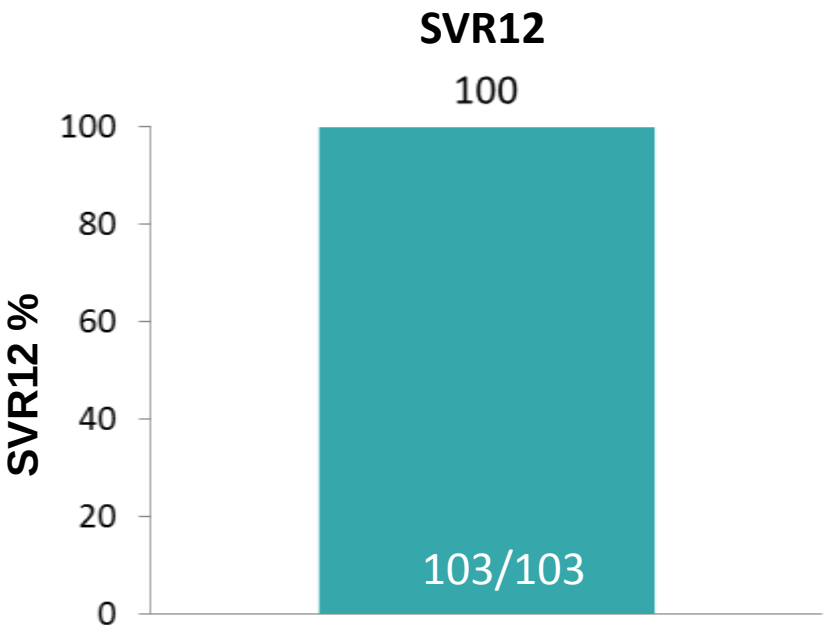
N. Terrault, Debrief AASLD 2015

German Real-World LDV/SOF for 8 Weeks

Single center German study of 103 primarily naïve, non-cirrhotic patients with baseline HCV RNA < 6 million IU/mL treated with LDV/SOF for 8 weeks

Baseline Demographics

	N=103
Median (range) age, years	50 (22–77)
Male gender, n (%)	43 (42)
Caucasian, n (%)	103 (100)
Genotype, n (%)	
GT 1a	49 (46)
GT 1b	52 (51)
GT 4	2 (2)
Metavir stage, n (%)	
F0	56 (54)
F1	25 (24)
F2	17 (17)
F3	5 (5)
Median baseline HCV RNA, IU/mL*	870,964
Treatment-naïve, n (%)†	100 (97)
HIV/HCV coinfection, n (%)	3 (3)
At least one comorbidity, n (%)	94 (91)



LDV/SOF for 8 weeks resulted in high rates of SVR12 and was well tolerated

- 2.3% (n=2) had Grade 3 or 4 AEs
- No AE led to treatment discontinuation or death

*Roche COBAS® AmpliPrep/COBAS® TaqMan®, cut-off < 12 IU/mL † including 3 PegIFN+RBV Relapsers
Fibrosis was measured by FibroScan® with cut-off values for METAVIR stage F3 or less of ≤12.3kPa.

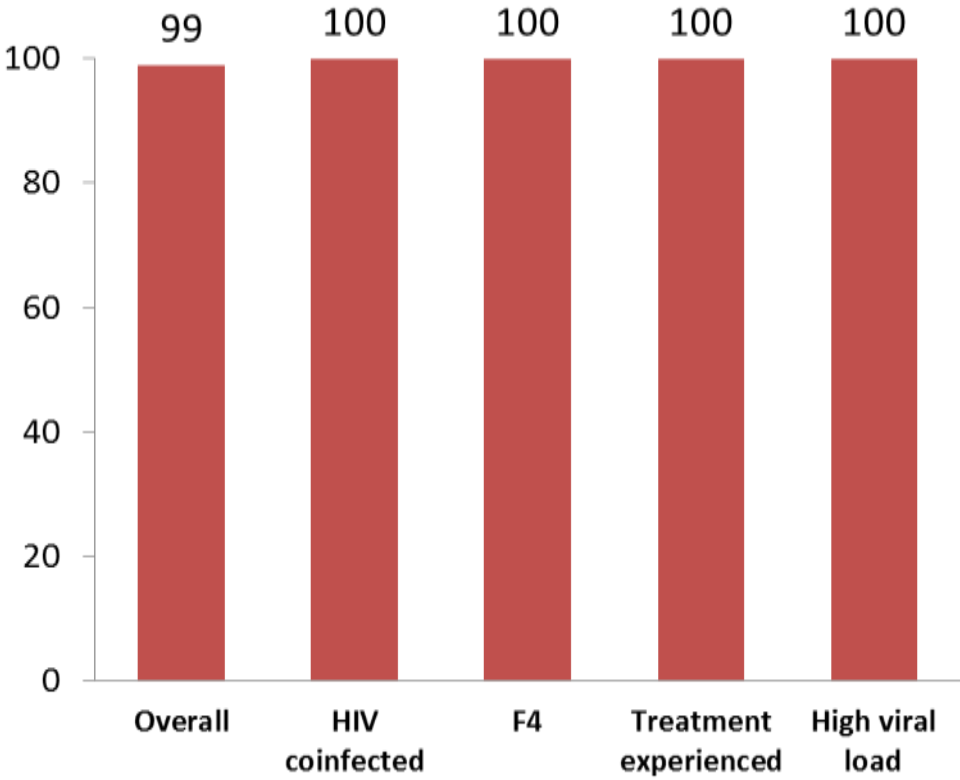
Buggisch, AASLD, 2015, 1205.

LDV/SOF for 8 Weeks in HCV-Monoinfected and HIV/HCV-Coinfected Patients: Interim Analysis

Real-world data from Germany on 148 GT 1 and 4 HCV patients receiving LDV/SOF for 8 weeks

Baseline Demographics

Patients	n=148
Male, n (%)	72 (49)
Median age, years (IQR)	52 (44–58)
GT 1, n (%)	144 (97)
GT 4, n (%)	3 (2)
HIV/HCV coinfection, n (%)	28 (19)
Prior HCV treatment, n (%)	26 (18)
FibroScan >12.5 kPa or APRI >2, n (%)	5 (3)
Median HCV viral load, IU/mL (IQR)	8.1×10^5 ($2.5 \times 10^5 – 1.7 \times 10^6$)
High viral load*	13 (8.8)

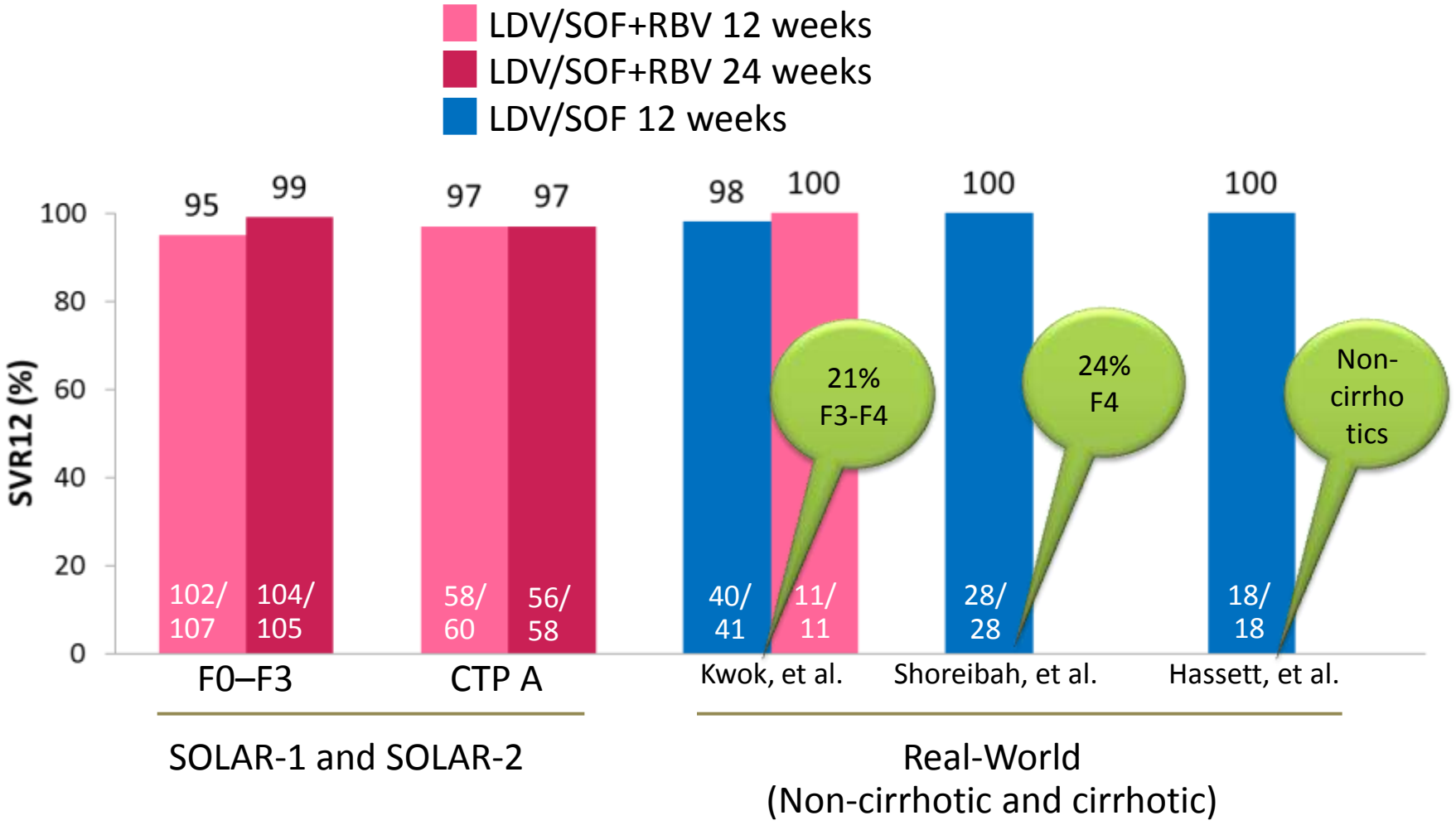


*1 patient relapsed

†High viral load defined as >6M IU/mL (Roche) or >2M IU/mL (Abbott) at baseline

Christensen, AASLD, 2015, 1081

SVR12 Rates Among Patients with Recurrent HCV Post-Liver Transplant



Gane, AASLD, 2015, 1049; Kwok, AASLD 2015, 1101; Shoreibah, AASLD 2015, 1174; Hassett, AASLD, 2015, LB-28

Conclusions

- Clinical trials found high SVR12 rates of LDV/SOF in patients with Gen 1 (and 4) in different groups of patients with CHC
- Real world data support the high SVR12 rates of LDV/ SOF found in clinical trials in Gen 1 HCV patients

THANK YOU

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