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10° Challenges in Viral Hepatitis

Lausanne, 18 January 2018

Clinical Challenges in HCV- are there any left?

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Financial Disclosures

Grant and research support:	Gilead Sciences, AbbVie
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Speaking and teaching:	Merck, BMS, Gilead Sciences, Janssen, AbbVie

Clinical Challenges in HCV: 2 Easy Questions

Are there any cases when treatment is unsafe?

Are there any cases when treatment efficacy is impaired?

EASL 2016: IFN-Free Treatment Options

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Yes	No	No	Yes	Yes
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No

EASL HCV Treatment Recommendations 2016

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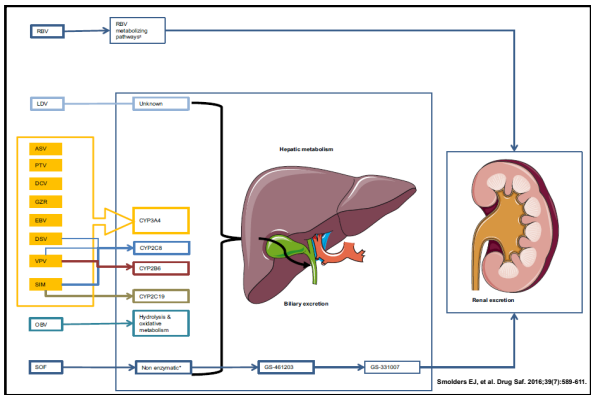
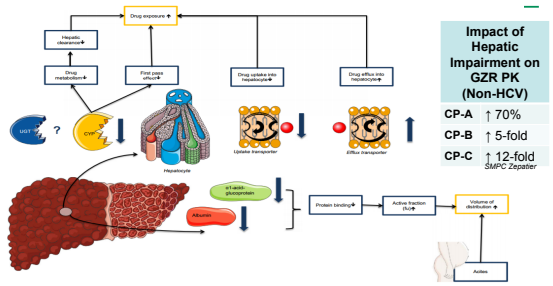
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No
*GLE + PIB	Yes	Yes	Yes	Yes	Yes
*SOF + VEL + VOX	Yes	Yes	Yes	Yes	Yes

EASL HCV Treatment Recommendations 2016 * personal opinion*



Disease Severity Impacts the PK of PIs



Impact of Hepatic Impairment on GZR PK (Non-HCV)	
CP-A	↑ 70%
CP-B	↑ 5-fold
CP-C	↑ 12-fold

SMPC Zepatier

Fig. 2 Overview of the pathophysiological changes in patients with liver cirrhosis that influence drug metabolism and therefore the pharmacokinetics of drugs. *CYP* cytochrome P450, *UGT* uridine diphosphate-glucuronosyltransferase, ↓ indicates decrease, ↑ indicates increase

Drug Saf (2016) 39:589–611

FDA Warning on 3D Regimen

«FDA Drug Safety Communication: FDA warns of serious liver injury with hepatitis C treatments Viekira Pak and Technivie»

«The U.S. Food and Drug Administration (FDA) is warning that hepatitis C treatments with Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, we are requiring the manufacturer to add new information about the safety risk to the drug labels […]. Some of these events resulted in liver transplantation or death. […] at least 26 worldwide cases submitted to FAERS were considered to be possibly or probably related to Viekira Pak or Technivie. In most of the cases, liver injury occurred within 1 to 4 weeks of starting treatment. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended […]»

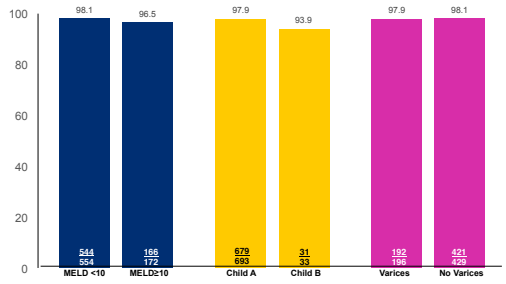
FDA Drug Safety Communication; 22 October 2015

ABACUS Study
Clinical features of the cirrhotic cohort

Variable	Cirrhosis N=762
Total bilirubin – mg/dl	1.1 ± 0.6
INR- %	1.0 ± 0.2
Albumin – g/dl	3.9 ± 0.4
Platelets - mmc	129 ± 74
Child Pugh B	5.1
MELD ≥10	24.3
Esophageal varices Absent/Present/Missing	58.4/27.6/14.0
Genotype 1/1a/1b/4/Unknown	2.1/19.9/75.3/2.2/0.4
HCVRNA >1,000,000 IU	52.5
Naïve to Antiviral Therapy	31

Petta S et al, Lancet Gastroenterology and Hepatology 2017

SVR: Effect of Liver Function
PP Analysis



Petta S et al, Lancet Gastroenterology and Hepatology 2017

Safety Analysis: Death

Gender	Age	Child	Meld	Varices	Ascites	PLT<10000	Albumin <3.5	Time of Death	Cause of death
Female	68	B	13	1	1	No	Si	11 week	Pneumonia→ Hepatopulmonary Syndrome
Female	58	B	11	1	1	Si	Si	3 week	Cholecystitis→sepsis→MOF
Male	46	A5	10	1	0	Si	No	8 week	Car accident
Male	61	A5	10	1	0	-	No	4 month after stop therapy	Stop therapy after 4 weeks for bradicardia→ pace-maker→ after 3 months surgical resection of HCC→ AKI→ MOF
Male	48	A5	8	1	0	Si	No	14 week	Sudden death of unknown etiology
Female	66	A5	6	0	0	Si	No	FU week 4	Progression of lymphoma

Petta S et al, Lancet Gastroenterology and Hepatology 2017

EASL 2018*: IFN-Free Options in Decompensated Cirrhosis

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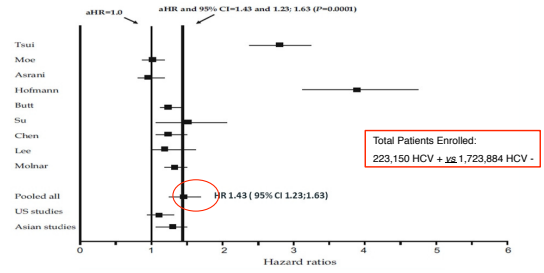
*SOF + VEL + VOX	No	No	No	No	No

EASL HCV Treatment Recommendations 2016 * personal opinion*

HCV Infection Increases the Risk of Developing CKD
A Systematic Review and Meta-Analysis



CKD DEFINED AS REDUCED GLOMERULAR FILTRATION RATE (GFR) AND/OR DETECTABLE PROTEINURIA

Fabrizi F, Dig Dis Sci 2015;60:3801

Impact of Renal Impairment on DAA Pharmacokinetics

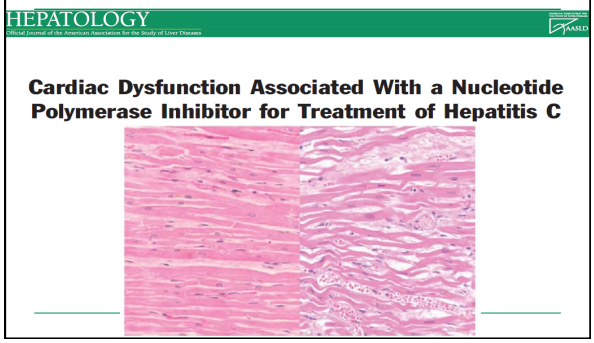
Change in exposure compared to healthy subjects with normal renal function	Mild impairment (eGFR = 60–89 mL/min/1.73m²)	Moderate impairment (eGFR = 30–59 mL/min/1.73m²)	Severe impairment (eGFR = <30 mL/min/1.73m²)
Ombitasvir	↔	↔	↔
Paritaprevir	↑ ≤20%	↑ ≤37%	↑ ≤50%

- Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m² or with end-stage renal disease because no dose recommendation can currently be given for these patients (**B1**).

Elbasvir	NA	NA	↑ 86%

Khatri A, *et al. Hepatology* 2014; 60(Suppl):320A;
Harvoni, (July 2016) Olysio (August 2016) , and Daklinza (October 2016) Summaries of Product Characteristics
Yeh WW, *et al. Hepatology* 2014; 60(suppl 6):1340 (poster presentation).

Unexpected SAEs with DAAs


HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Cardiac Dysfunction Associated With a Nucleotide Polymerase Inhibitor for Treatment of Hepatitis C

EASL 2018*: IFN-Free Treatment Options

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SOF + SIM ± RBV	Suboptimal	No	No	Yes	No
*GLE + PIB	Yes	Yes	Yes	Yes	Yes
*SOF + VEL + VOX	Yes	Yes	Yes	Yes	Yes

EASL HCV Treatment Recommendations 2016 * personal opinion*

EASL 2018*: IFN-Free Treatment Options in CKD Stage 4-5

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Caution	No	No	Caution	Caution
SOF/VEL ± RBV	Caution	Caution	Caution	Caution	Caution
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Caution	Caution	Caution	Caution	Caution
SOF + SIM ± RBV	Suboptimal	No	No	Caution	No
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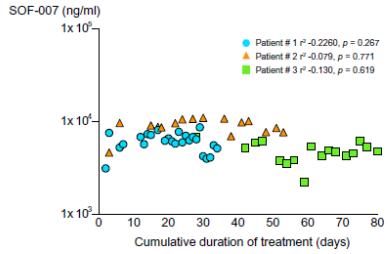
EASL HCV Treatment Recommendations. J Hepatol. 2017;66(1):153-194 ** personal opinion*

EASL 2018*: IFN-Free Treatment Options in CKD Stage 4-5 with CPT B-C Cirrhosis

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Caution	No	No	Caution	Caution
SOF/VEL ± RBV	Caution	Caution	Caution	Caution	Caution
OBV/PTV/r + DSV (3D) ± RBV	No	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	No	No
GZR/EBR ± RBV	No	No	No	No	No
SOF + DCV ± RBV	Caution	Caution	Caution	Caution	Caution
SOF + SIM ± RBV	No	No	No	No	No
*GLE + PIB	No	No	No	No	No
*SOF + VEL + VOX	No	No	No	No	No

EASL HCV Treatment Recommendations. J Hepatol. 2017;66(1):153-194 * personal opinion*

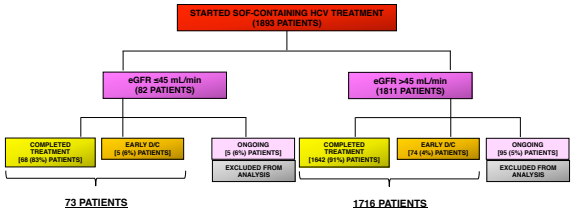
Sofosbuvir Based Regimens in Patients on Hemodialysis



Desnoyer A et al, J Hepatol 2016; 65:40-47

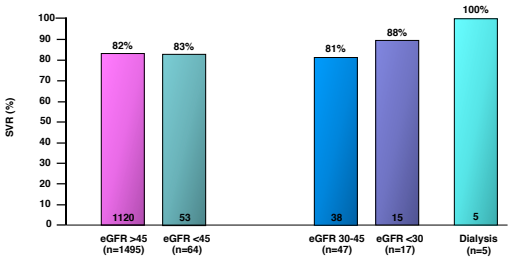
The TARGET Cohort: SOF-Based Regimens to Treat CKD Patients with HCV

- ✓ **SOF (NS5B)**
- ✓ Any HCV genotype
- ✓ Any CKD stage



Saxena V, et al. Liver Int 2016;36:807-816

HCV TARGET: SVR Rates in Patients With Impaired Renal Function



Saxena V, et al. Liver Int 2016;36:807-816

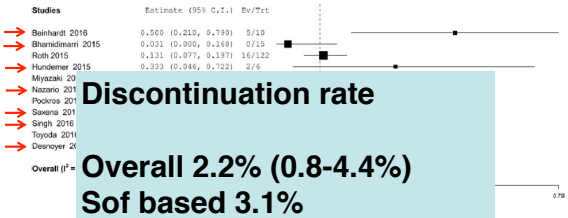
The TARGET Cohort: Low eGFR Values Are Associated with Worsening Renal Function

	eGFR ≤ 30 (N=17)	eGFR 30-45 (N=56)	eGFR 46-60 (N=157)	eGFR>60 (N=1,559)	p-value
Common SOF AEs					
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)	0.54
Headache	1 (6)	9 (16)	19 (12)	274 (18)	0.24
Nausea	3 (18)	8 (14)	33 (21)	247 (16)	0.39
Anemia AE	6 (35)	16 (29)	37 (24)	246 (16)	<0.01
Transfusions	2 (12)	5 (9)	3 (2)	31 (2)	<0.01
Erythropoietin	0 (0)	6 (11)	13 (8)	46 (3)	<0.01
RBV					
Reduction	3 (43)	8 (30)	33 (42)	185 (19)	<0.01
D/C	0 (0)	4 (15)	1 (1)	12 (1)	<0.01
↓ eGFR	5 (29)	6 (11)	4 (3)	14 (1)	<0.01
Renal-Urinary System AE	5 (29)	6 (11)	13 (8)	84 (5)	<0.01
SAEs	3 (18)	13 (23)	8 (5)	100 (6)	<0.01
Early Treatment D/C	1 (5)	4 (6)	6 (4)	68 (4)	0.60
Early Treatment DC (AE)	1 (5)	2 (3)	4 (2)	39 (3)	0.53
Death	1 (5)	0 (0)	2 (1)	10 (1)	0.11

Baseline Characteristic	Univariate IRR (95% CI)	Univariate p-value	Multivariate IRR (95% CI)	Multivariate p-value
Safety Outcome: Worsening Renal Function[1]				
eGFR 5≤5 (vs. eGFR >45)	13.6 (6.5-28.7)	<0.001	4.71 (1.85-12.0)	0.001
Male (vs. female)	0.83 (0.38-1.78)	0.63	1.47 (0.68-3.17)	0.33
Age≥65 (vs. age<65)	1.18 (0.45-3.09)	0.73	1.21 (0.41-3.57)	0.73
Black or AA race (vs. non-Black or non-AA)	0.90 (0.27-2.95)	0.86	0.78 (0.20-3.14)	0.73
Genotype 1 (vs. non-1)	0.67 (0.31-1.45)	0.31	0.45 (0.20-1.02)	0.06
Prior HCV treatment (vs. treatment naïve)	0.52 (0.24-1.13)	0.10	0.50 (0.23-1.07)	0.07
Cirrhosis (vs. no cirrhosis)	3.23 (1.48-2.55)	0.01	1.98 (0.56-6.95)	0.29
MELD ≥ 10 (vs. MELD < 10)	0.46 (0.22-0.98)	0.05	1.11 (0.45-2.77)	0.82
Any transplant[2] (vs. no transplant)	1.70 (0.35-8.31)	0.52	1.28 (0.53-	0.58

Saxena V, et al. Liver Int 2016;36:807-816

Safety of DAAs in HCV Patients with CKD stage 4-5



Discontinuation rate

Overall 2.2% (0.8-4.4%)
Sof based 3.1%

Li T et al, Liver International. 2017;37:974–98

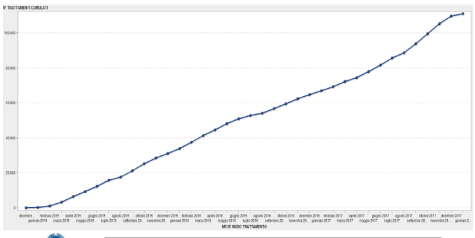
Clinical Challenges in HCV: 2 Easy Questions

Are there any cases when treatment is unsafe?

Are there any cases when treatment efficacy is impaired?

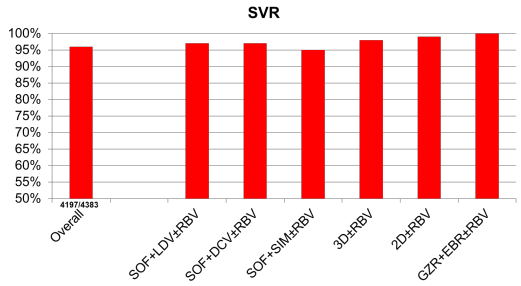
Treatment of HCV in Italy

Trend cumulativo dei trattamenti avviati

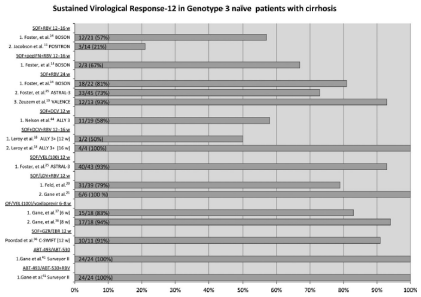


111.058 «avviati» sono i trattamenti (solo pazienti eleggibili) con almeno una scheda di Dispensazione farmaco

Treatment of HCV in Northern Italy

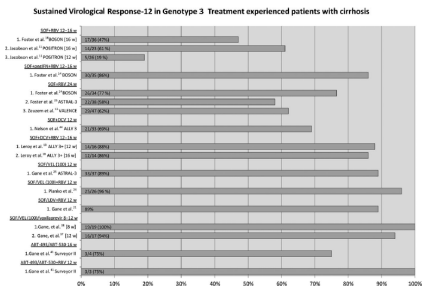


Treatment of HCV-3: Is It Still a Challenge?



Gimeno-Ballester V et al, J Viral Hep 2017

Treatment of HCV-3: Is It Still a Challenge?



Gimeno-Ballester V et al, J Viral Hep 2017

Genotype 3 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/VEL ± RBV	12 wk	12 wk + RBV*¶	12 wk + RBV*¶	12 wk + RBV*¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	24 wk + RBV	24 wk + RBV

*24 wk without RBV if RBV contraindicated or poorly tolerated
¶Only if presence of NS5A RAS Y93H at baseline, if resistance testing available

EASL HCV Treatment Recommendations 2016

Glecaprevir/Pibrentasvir EMA Label

Genotype	Recommended treatment duration	
	No cirrhosis	Cirrhosis
All HCV genotypes	8 weeks	12 weeks

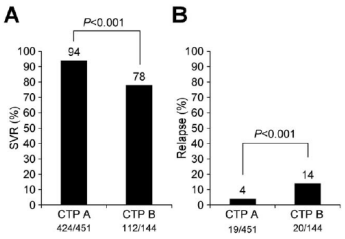
Failures to PegIFN + Riba ± Sofosbuvir or Sofosbuvir + Ribavirin

Genotype	Recommended treatment duration	
	No cirrhosis	Cirrhosis
GT 1, 2, 4-6	8 weeks	12 weeks
GT 3	16 weeks	16 weeks

Sofosbuvir/Velpatasvir/Voxilaprevir EMA Label

Patient population	Treatment duration
DAA naïve patients without cirrhosis	8 weeks
DAA naïve patients with compensated cirrhosis	12 weeks 8 weeks may be considered in genotype 3 infected patients (see section 5.1)
DAA experienced patients* without cirrhosis or with compensated cirrhosis	12 weeks

High Risk Of Post-DAA Relapse In CPT-B&C



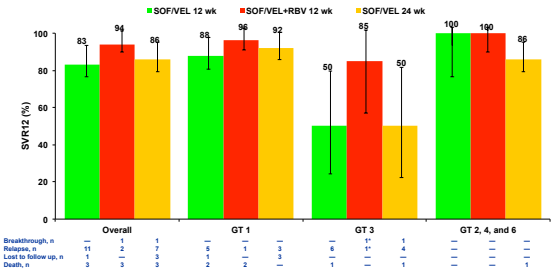
Fernandez Carrillo C et al, Hepatology 2017

Ribavirin is Still Essential in CPT B & C Patients

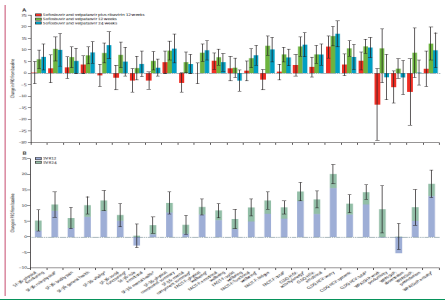
	LDV/SOF (12 wk) N=51	LDV/SOF/RBV (12 wk) N=70	LDV/SOF (24 wk) N=408	LDV/SOF/RBV (24 wk) N=60	TOTAL N=589
Compensated Cirrhosis Overall	100 (92,100) [43/43]	96.1 (86.5,100) [49/51]	96.7 (93.6,98.6) [234/242]	90.9 (70.8,98.9) [20/22]	96.6 (94.2,98.3) [346/358]
Incl. Albumin ≤3.5 and Tbilirubin ≥1.2	100[b] (2.5, 100) [1/1]	100[b] (15.8,100) [2/2]	96.0 (79.7, 100) [24/25]	100[b] (15.8, 100) [2/2]	96.7 (82.8,99.9) [29/30]
Incl. Albumin >3.5 and Tbilirubin <1.2	100 (88.4,100) [30/30]	100 (89.4,100) [33/33]	96.7 (92.4,98.9) [146/151]	91.7 (61.5,99.8) [11/12]	97.3 (94.3,99.0) [220/226]
Decompensated Cirrhosis	87.5 (47.4,99.7) [7/8]	100 (82.4,100) [19/19]	90.4 (84.8, 94.4) [150/166]	97.4 (86.2,99.9) [37/38]	92.2 (88.0,95.3) [213/231]
Post-Liver Transplant	90.9 (58.7,100) [10/11]	96.6 (82.2,100) [28/29]	88.9 (70.8,97.7) [24/27]	93.8 (69.8,99.8) [15/16]	92.8 (84.9,97.3) [77/83]

Lim JK et al , Clinical Gastro Hep in press

ASTRAL-4: SOF/VEL ± RBV in HCV Patients with Decompensated Liver Disease

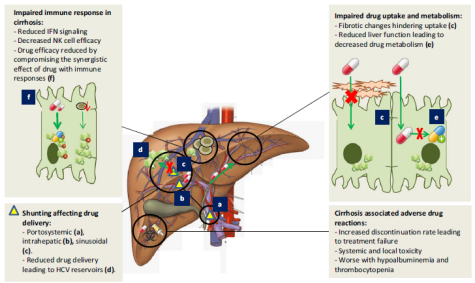


Ribavirin Has a Negative Effect on PRO in HCV Decompensated Patients



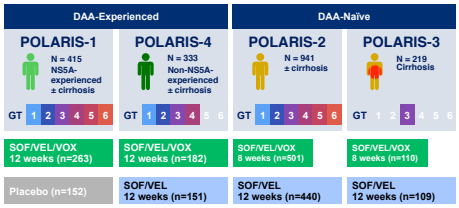
Yonoussi ZM, et al. Lancet Gastroenterology and Hepatology in press

Sorting Out Decompensated Cirrhosis as a Factor Associated with Treatment Failure



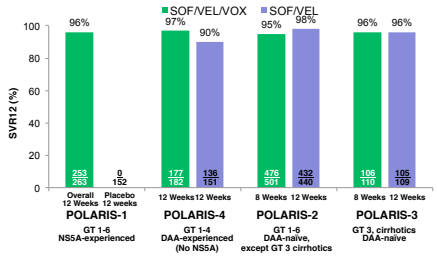
Al Marzooqi & Feld. Liver International 2015

POLARIS Phase 3 Program: SOF/VEL/VOX in DAA Failures



Bourliere M, NEJM 2017 . Jacobson IM, Gastroenterology 2017

Efficacy Summary of the Polaris Phase III Program (ITT Analysis)



*All studies included patients with compensated cirrhosis

Bourliere M, NEJM 2017 . Jacobson IM, Gastroenterology 2017

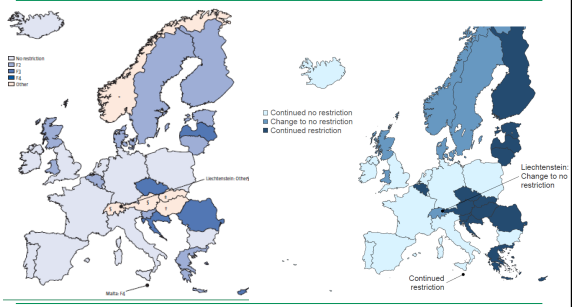
Challenges I Could Not Address

- Treatment of Patients with active HCC
- Treatment of Patients with Extra-hepatic malignancies

- Screening Strategies
- Linkage to care Strategies
- Prevention of reinfection/infection (PrEP?)

- Retreatment of SOF/VEL/VOX falures
- Ultra short treatments

The HCV World is Changing Fast!



Marshall A et al, Lancet Gastroenrology and Hepatology in press

Marshall A et al, J Hep submitted

2016 Lasker~DeBakey Clinical Medical Research Award

Hepatitis C replicon system and drug development

Ralf F.W. Bartenschlager
Heidelberg University

Charles M. Rice
Rockefeller University

Michael J. Sofia
Arbutus Biopharma

For development of a system to study the replication of the virus that causes hepatitis C and for use of this system to revolutionize the treatment of this chronic, often lethal disease.


NOhep