بسم الله الرحمن الرحيم

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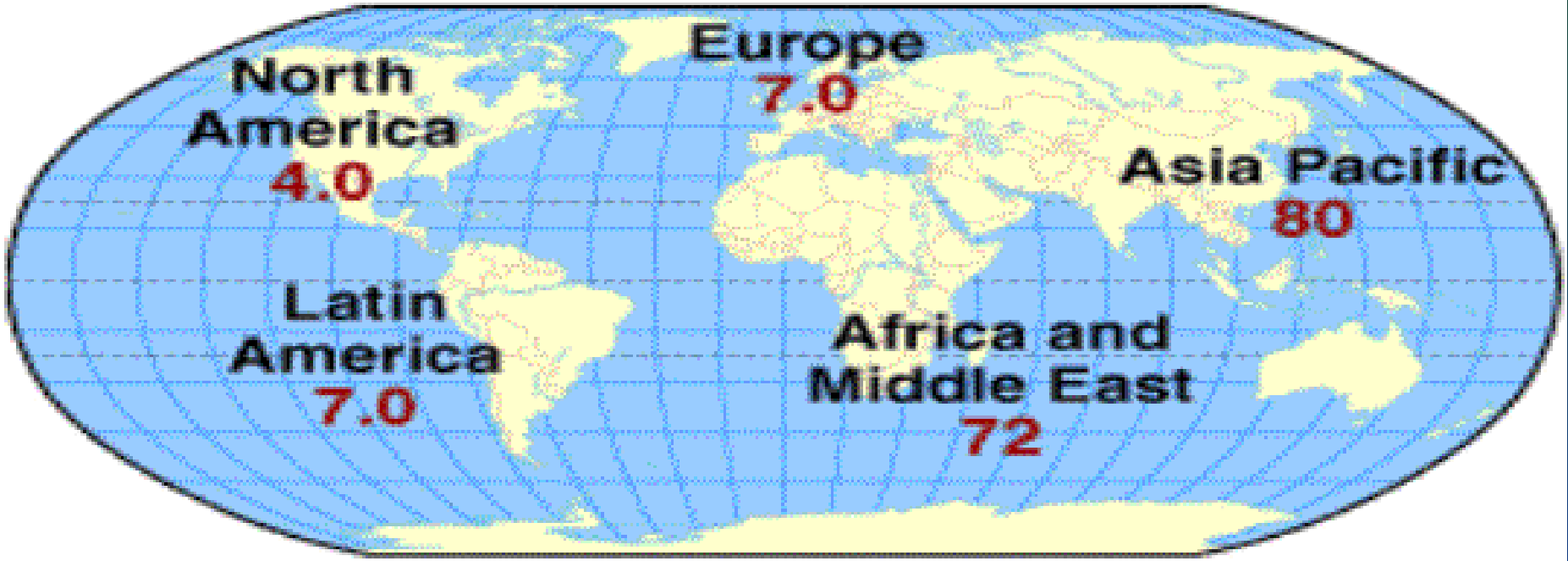
Updating HCV Management in Renal Patients

By

May Hassaballa
Prof. Of Internal Medicine & Nephrology
Cairo University

Global Chronic Hepatitis C Infection

(Millions)



Estimated Total Chronic HCV Infections Worldwide:

170 MILLION

Source: World Health Organization hepatitis C prevalence, 2000 and United Nations global population

Nephrology

Am J Nephrol 2013;38:405–412
DOI: 10.1159/000355615

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Hepatitis C Infection Is Very Rarely Treated among Hemodialysis Patients

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Michel Jadoul[c]

[a]Arbor Research Collaborative for Health, Ann Arbor, Mich., USA; [b]University of Michigan, Ann Arbor, Mich., USA; [c]Cliniques Universitaires St-Luc, Université catholique de Louvain, Brussels, Belgium

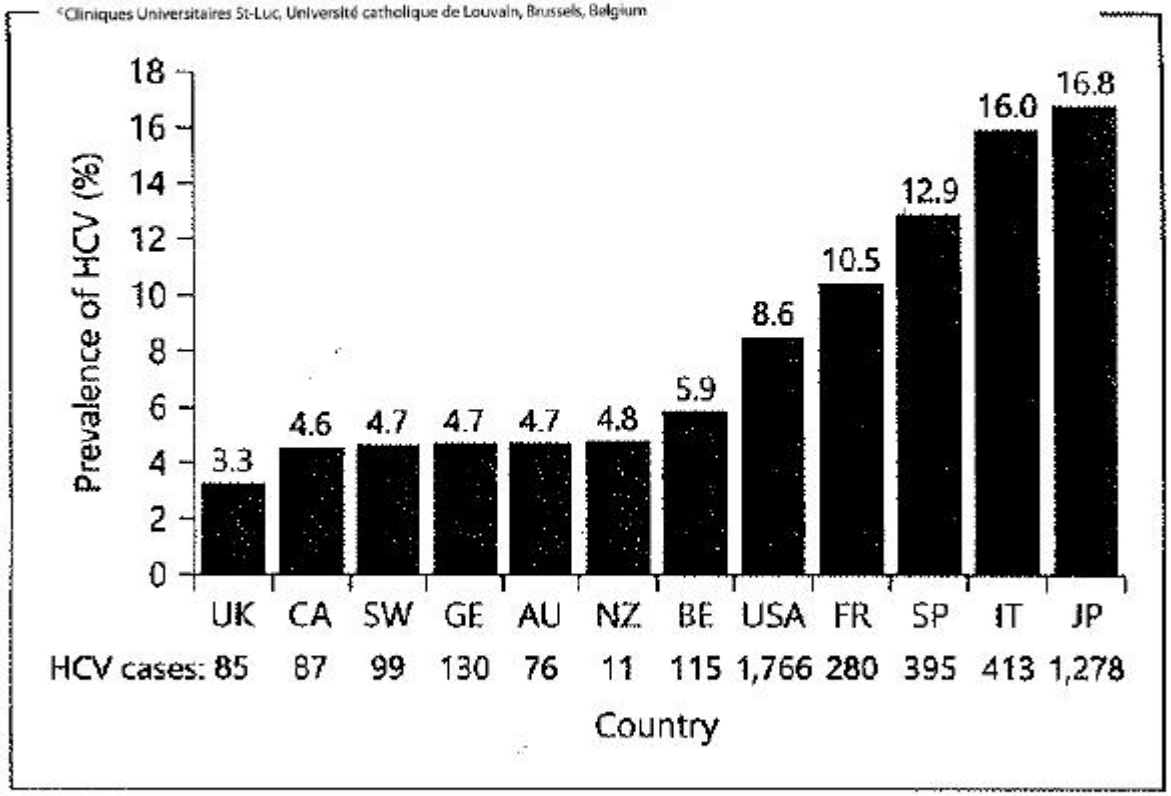
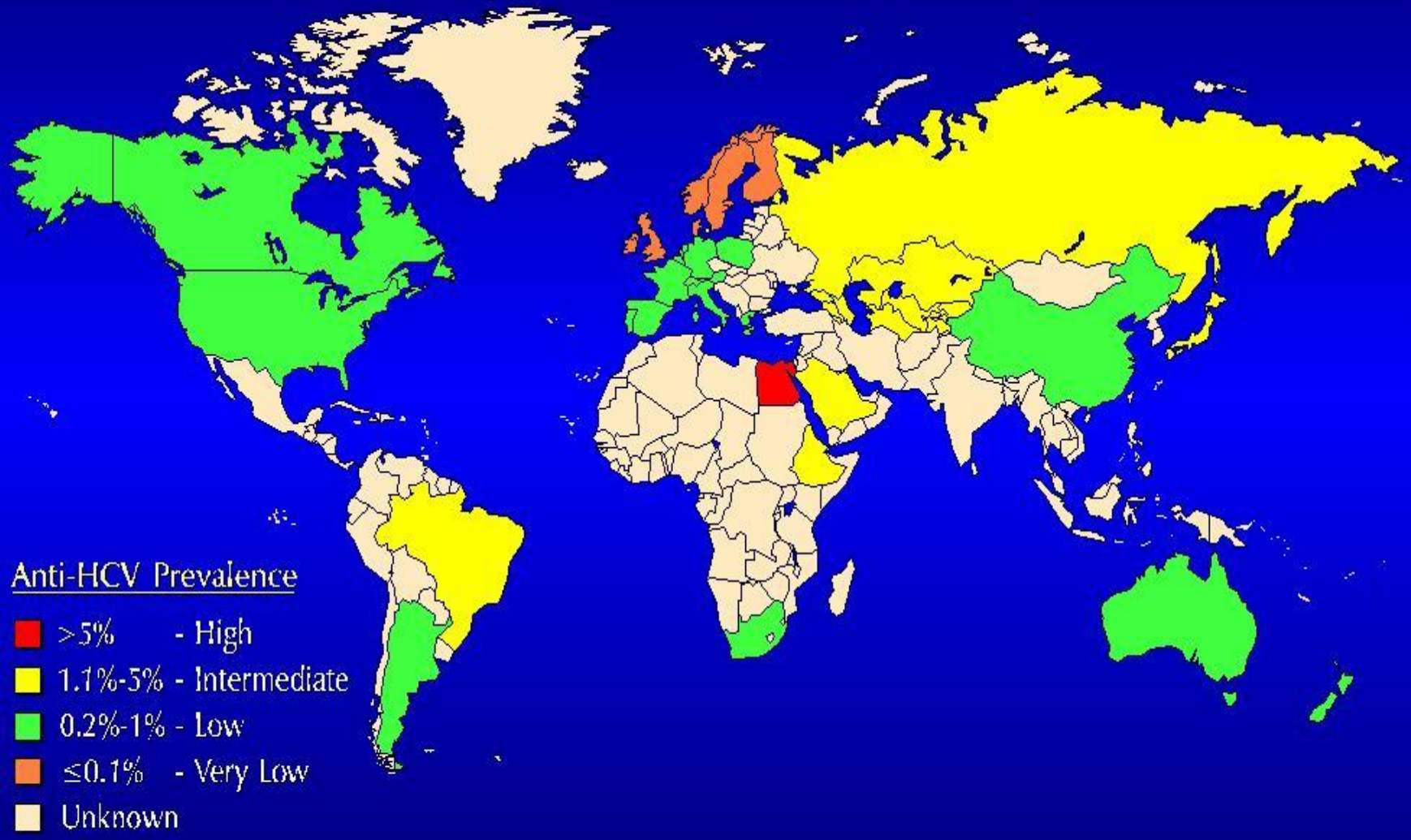


Fig. 3. Prevalence of HCV infection in HD patients, by country. Overall prevalence 9.5% (4,735 of 49,767 patients). CA = Canada; SW = Sweden; GE = Germany; AU = Australia; NZ = New Zealand; BE = Belgium; FR = France; SP = Spain; IT = Italy; JP = Japan.

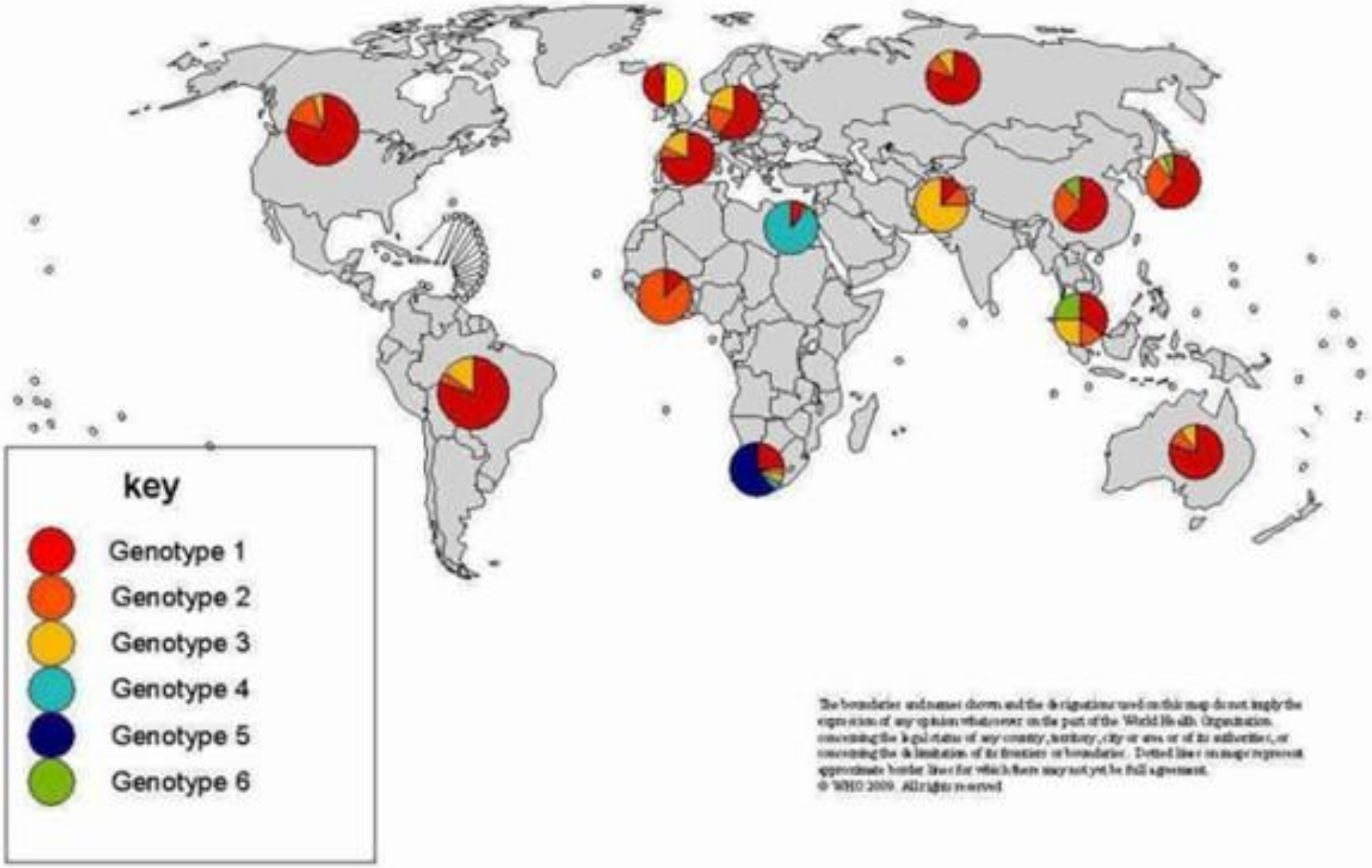
Prevalence of HCV Infection Among Blood Donors*



* Anti-HCV prevalence by EIA-1 or EIA-2 with supplemental testing; based on data available in January, 1995.

CDC

Global distribution of HCV genotypes



Effect of HCV on the the kidney

- Implicated in CKD onset
- Accelerates progression of CKD to ESRD
- Increased risk of mortality in Dx patients
- Reduced long term patient and graft survival after Tx

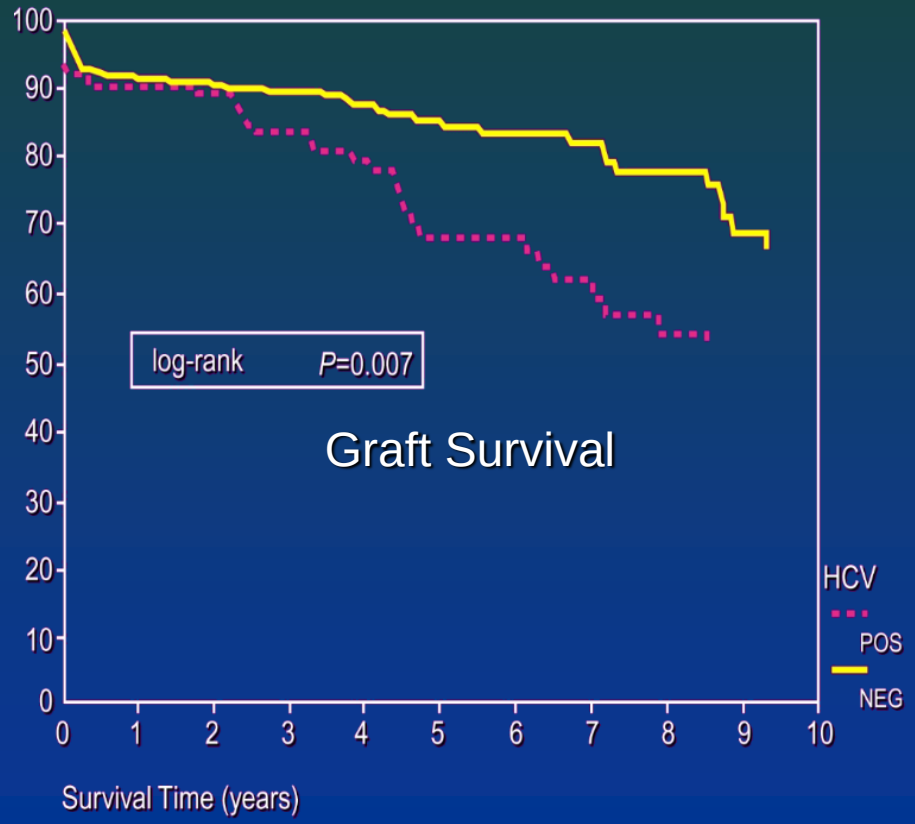
Table 3. Hepatitis C infection among hemodialysis patients is associated with markedly increased risk of mortality (case-mix adjusted)

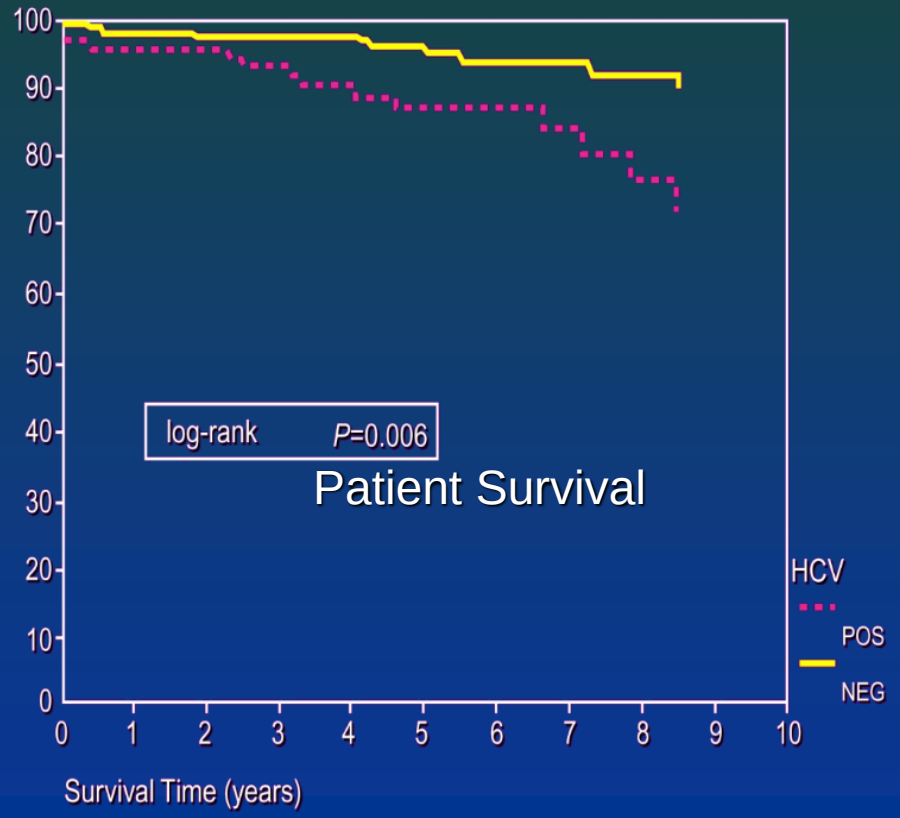
Study	HR mortality	95% CI	Nation
DOPPS[1]	1.22	1.11–1.33	International
Pereira [5]	1.41	1.01–1.97	USA
Stehman-Breen [6]	1.97	1.16–3.33	USA
Nakayama [7]	1.57	1.23–2.00	Japan
Espinosa [8]	1.62	1.05–2.49	Spain
Johnson [9]	1.37	1.15–1.62	Japan
Johnson [9]	1.29	1.05–1.58	Australia/ New Zealand

HRs compare HCV+ patients vs. HCV– patients.
[1] DOPPS phases 1–3 (1996–2008).

HCV: Virologic Status of Renal Transplant Recipients

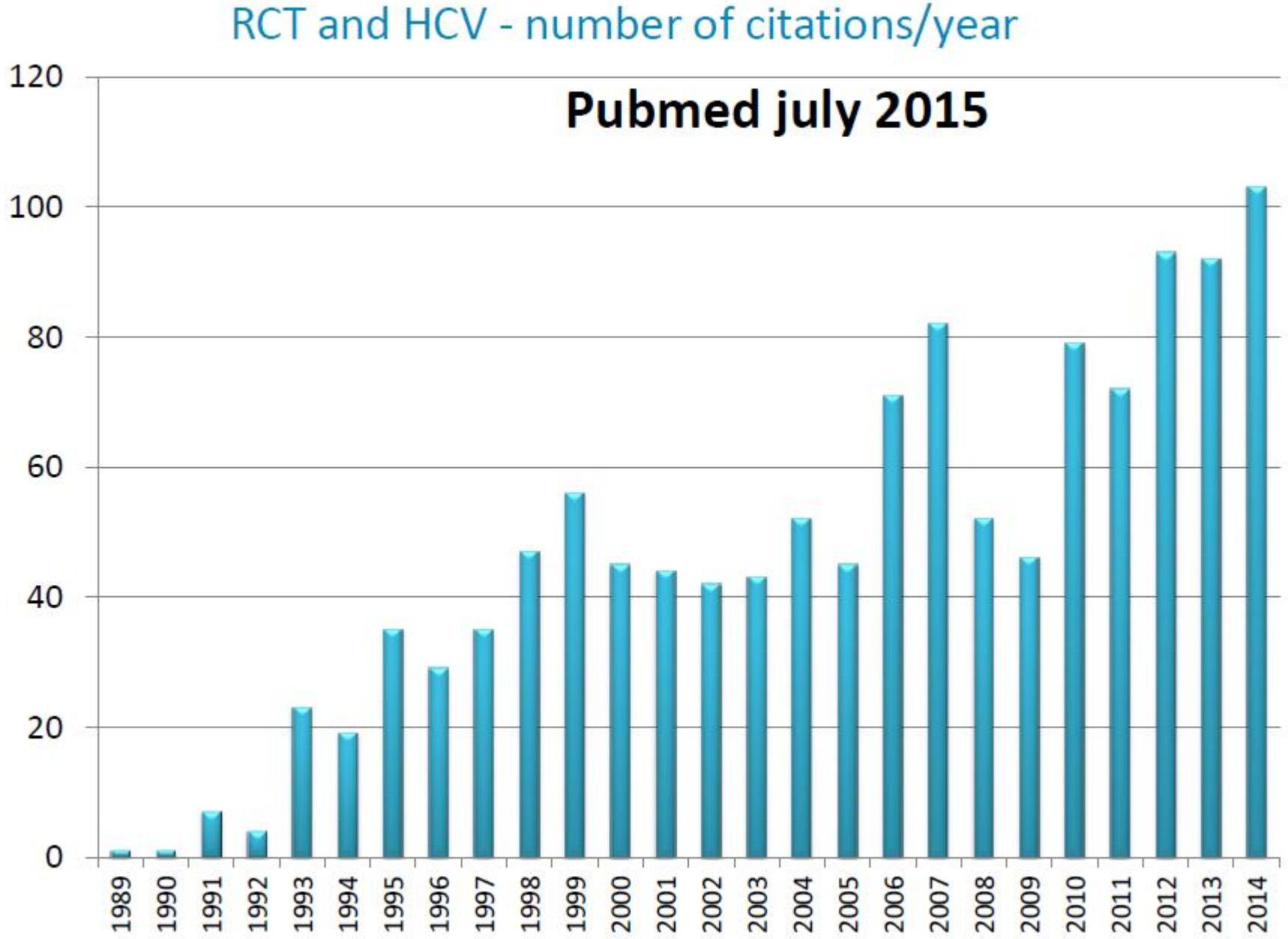
Graft and Recipient Survival





HCV infection is associated with lower graft and recipient survival

Gentil MA et al. Nephrol Dial Transplant. 1999;14:2455-2460.


RCT and HCV - number of citations/year
Pubmed july 2015
120
100
80
60
40
20
0
1989
1990
1991
1992
1993
1994
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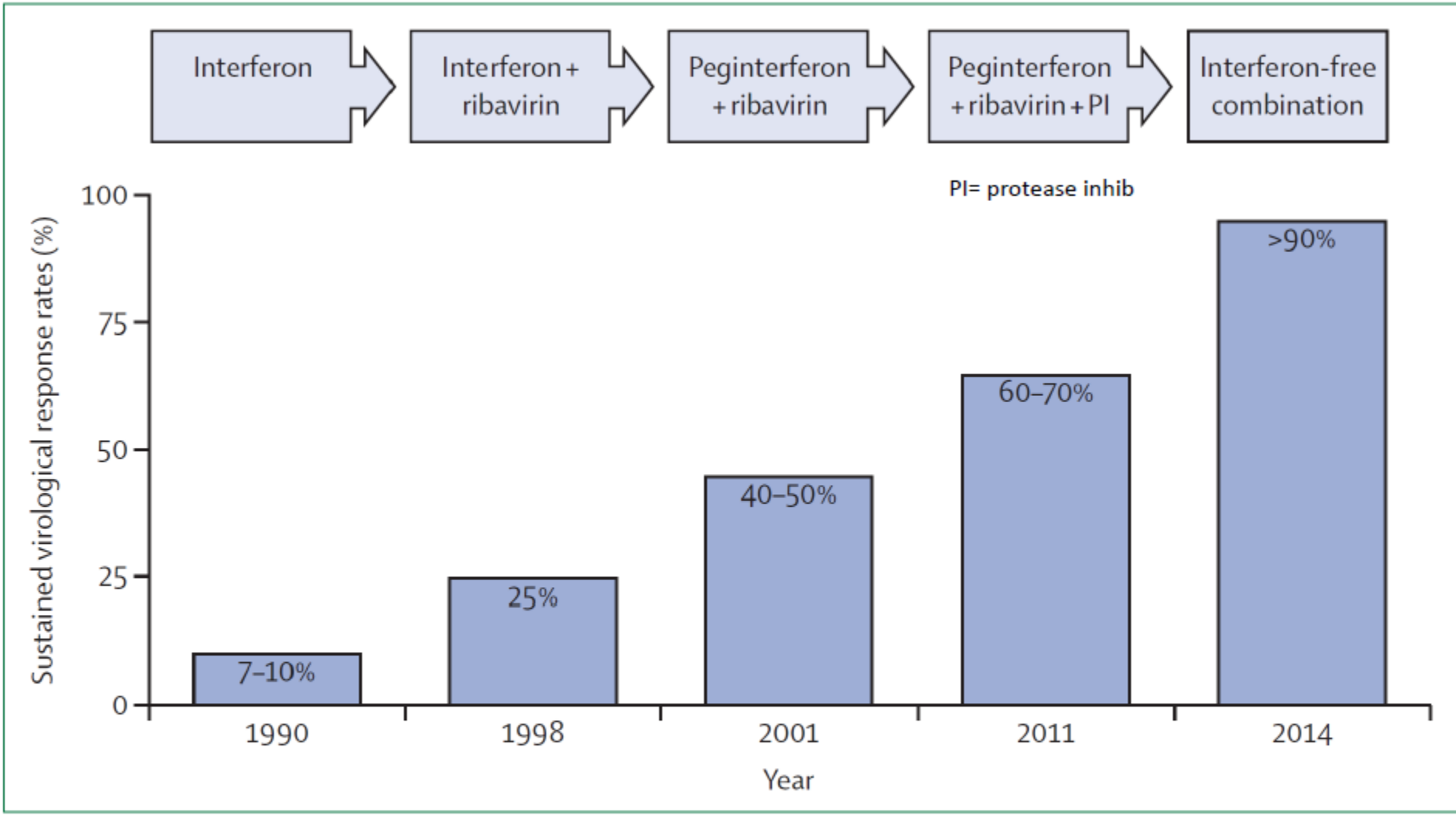


Figure 1: **Changes in standard of care for HCV, and improvements in numbers of sustained virological responses**
Data from references 9–12. PI=protease inhibitor.

Hepatitis C

Lancet 2015; 385: 1124–35

Daniel R Webster, Paul Klenerman, Geoffrey M Dusheiko

Direct-Acting Antivirals

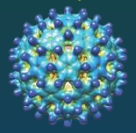
- Host targeting
- IFN free regimens
- Effective (SVR rates 80 – 100%)
- Shorter regiments (12 weeks or even 8 weeks)
- Less side effects
- Many drugs not eliminated by the kidney

HCV Structure and site for DAAs

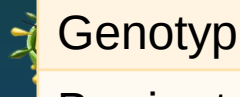
Structural

Non-Structural

Potency	+++	+++	++	++
Genotypic Coverage	++	++	+++	+
Barrier to resistance	++ / +++	+ / ++	+++	+



Capsid shell



A dependent RNA polymerase

CORE | E1 | E2 | P7 | NS2 | NS3 NS4A | NS4B | NS5A | NS5B

- Telaprevir
- Boceprevir
- Simeprevir
- Paritaprevir
- Faldaprevir
- Asunaprevir
- Grazoprevir

- Daclatasvir
- Ledipasvir
- Ombitasvir
- Elbasvir
- MK-8742

Nucleos(t)ides

- Sofosbuvir
- Mericitabine
- VX-135

Non-nucleosides

- Dasabuvir
- Beclabuvir
- GS-9669

HCV Structure and site for DAAs

Structural

Non-Structural

Viral eplication

RNA dependent RNA polymerase

NS5A

NS5B

- Telaprevir
- Boceprevir
- Simeprevir
- previr
- previr
- previr
- Grazoprevir

SBV/RBV
SBV/SMV
SBV/LDV (**Harvoni**)
SBV/DCV
PRV/OBV/r (**Qurevo**) +
DCV/ASV/BCV
GRV/EBV

FDA Approves Zepatier (elbasvir and grazoprevir) for Chronic Hepatitis C Genotypes 1 and 4

s(t)ides
sbuvir
citabine
135

Non-nucleosides
- Dasabuvir
- Beclabuvir
- GS-9669

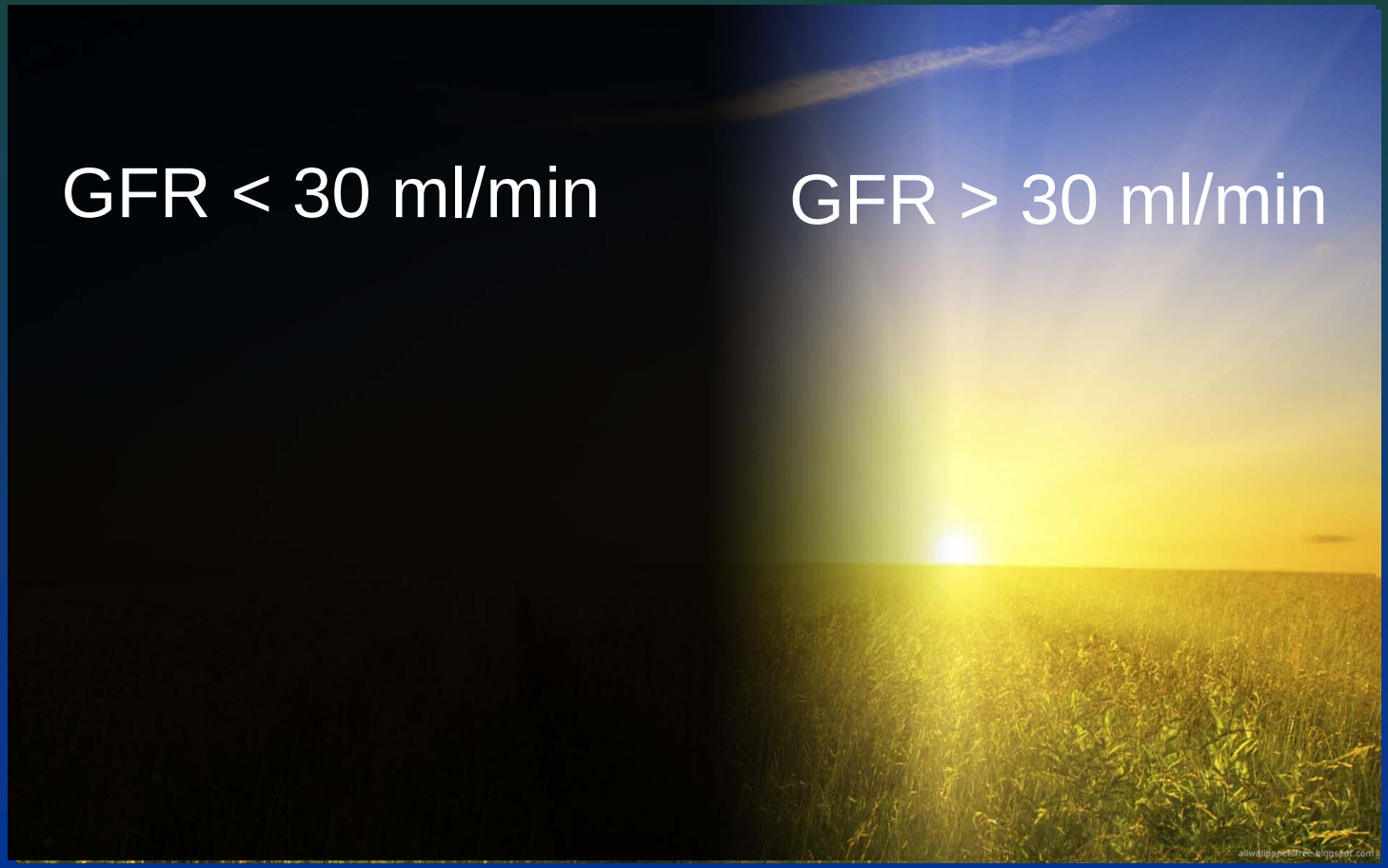
Determining Factors

- **The stage of liver disease [EASL Grade A1]:**
  - Compensated cirrhosis: +RBV 12W / - 24W
  - Decompensated cirrhosis: SBV + DCV / LDV
    - Avoid Qurevo
- **Presence of co-morbid conditions and related chronic drug administration [EASL Grade A1]**
- **Previous antiviral treatment with interferon or direct anti-viral agents**
- **Genotype**

SBV/RBV
SBV/SMV
SBV/LDV (**Harvoni**)
SBV/DCV
PRV/OBV/r (**Qurevo**) +/- DSV
DCV/ASV/BCV
GRV/EBV

X

Directly Acting Antivials

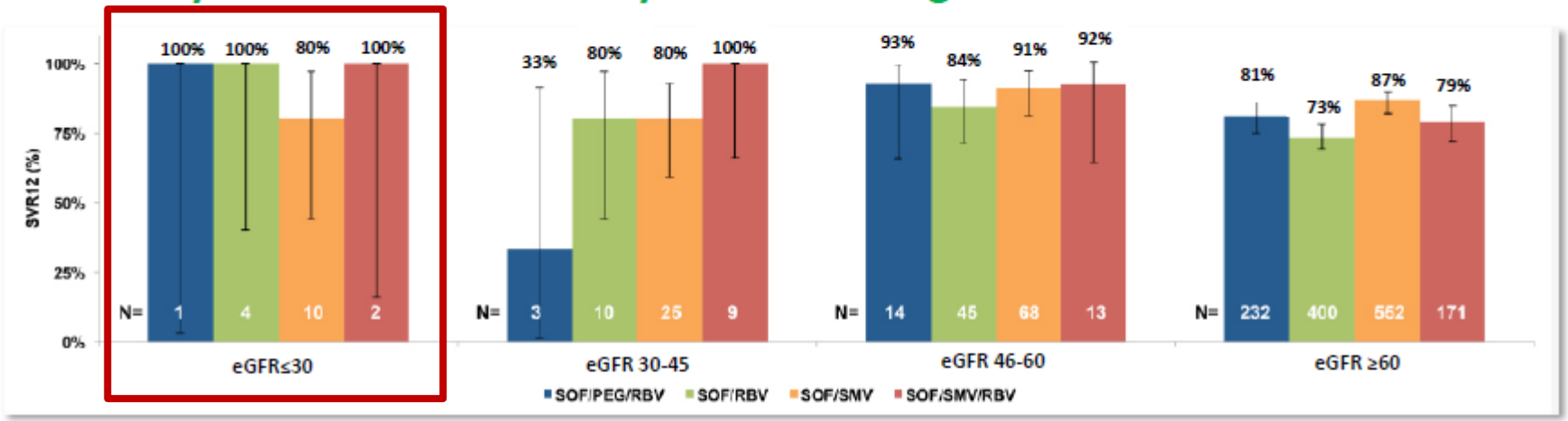


TREATMENT OF HCV IN CKD

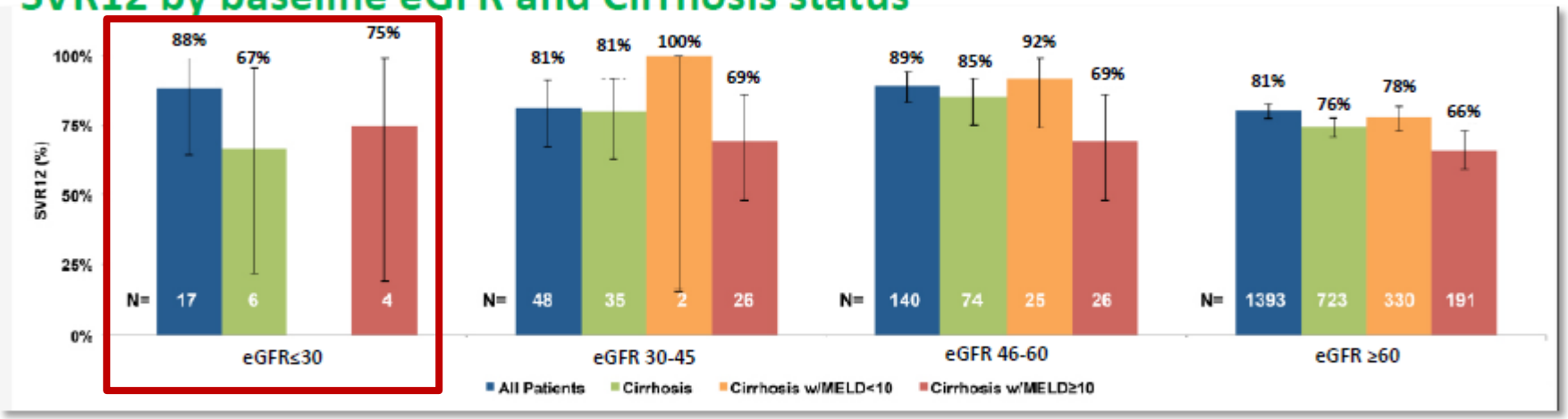
- **Chronic kidney disease**
  - The HCV-TARGET cohort
  - A small US study
  - The Austrian experience
  - RUBY-1
  - Pharmacokinetics: DCV-TRIO
  - C-SURFER

REAL WORLD DATA
SAFETY AND EFFICACY OF SOFOSBUVIR-CONTAINING REGIMENS IN HEPATITIS C INFECTED PATIENTS WITH REDUCED RENAL FUNCTION: HCV TARGET

SVR12 by baseline eGFR and by treatment regimen



SVR12 by baseline eGFR and Cirrhosis status



From: Saxena V. ILC 2015, #LP08

*Among patients with known outcomes

REAL WORLD DATA

SAFETY AND EFFICACY OF SOFOSBUVIR-CONTAINING REGIMENS IN HEPATITIS C INFECTED PATIENTS WITH REDUCED RENAL FUNCTION: HCV-TARGET

Table 2: Safety Outcomes by Baseline eGFR*

Dichotomous = no (%) Continuous = mean (range)	eGFR ≤ 30 (N=17)	eGFR 30-45 (N=56)	eGFR 46-60 (N=157)	eGFR>60 (N=1,559)
Common AEs				
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)
Headache	1 (6)	9 (16)	19 (12)	274 (18)
Nausea	3 (18)	8 (14)	33 (21)	247 (16)
Anemia AE	**6 (35)**	**16 (29)**	**37 (24)**	**246 (16)**
Required Transfusion(s)	2 (12)	5 (9)	3 (2)	31 (2)
Erythropoietin Start on Treatment	1 (6)	8 (14)	14(9)	50 (3)
RBV[§]				
Reduction in RBV due to Anemia	3 (38)	8 (30)	33 (42)	185 (19)
RBV Discontinuation	0 (0)	4 (15)	1 (1)	12 (1)
Worsening Renal Function[✚]	**5 (29)**	**6 (11)**	**4 (3)**	**14 (1)**
Renal or Urinary System AEs[Φ]	**5 (29)**	**6 (11)**	**13 (8)**	**84 (5)**
Any Serious AEs	**3 (18)**	**13 (23)**	**8 (5)**	**100 (6)**
Cardiac Serious AEs	**1 (6)**	**2 (4)**	**8 (5)**	**53 (3)**
Early Treatment Discontinuation	**1 (6)**	**4 (6)**	**6 (4)**	**68 (4)**
Early Treatment Discontinuation AE	**1 (6)**	**2 (3)**	**4 (2)**	**39 (3)**
Death[§]	**1 (6)**	**0 (0)**	**2 (1)**	**10 (1)**

*Among all patients who completed therapy; [§] Among patients treated with RBV; [✚] includes acute on chronic renal insufficiency, outcome abstracted from treatment documentation; [Φ] includes acute renal failure, dysuria, hematuria, urinary retention and other similar renal/urinary problems; [§] eGFR ≤ 30 patient that died: Liver transplant recipient with baseline MELD of 26 who died from worsening renal failure and hepatic decompensation

From: Saxena V, JLC 2015, #LP08

TREATMENT OF HCV IN CKD

- **Chronic kidney disease**
  - The HCV-TARGET cohort
  - A small US study
  - The Austrian experience
  - RUBY-1
  - Pharmacokinetics: DCV-TRIO
  - C-SURFER

Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of Hepatitis C in patients with end stage renal disease

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Journal of Hepatology **2015** vol. 63 | 763–773

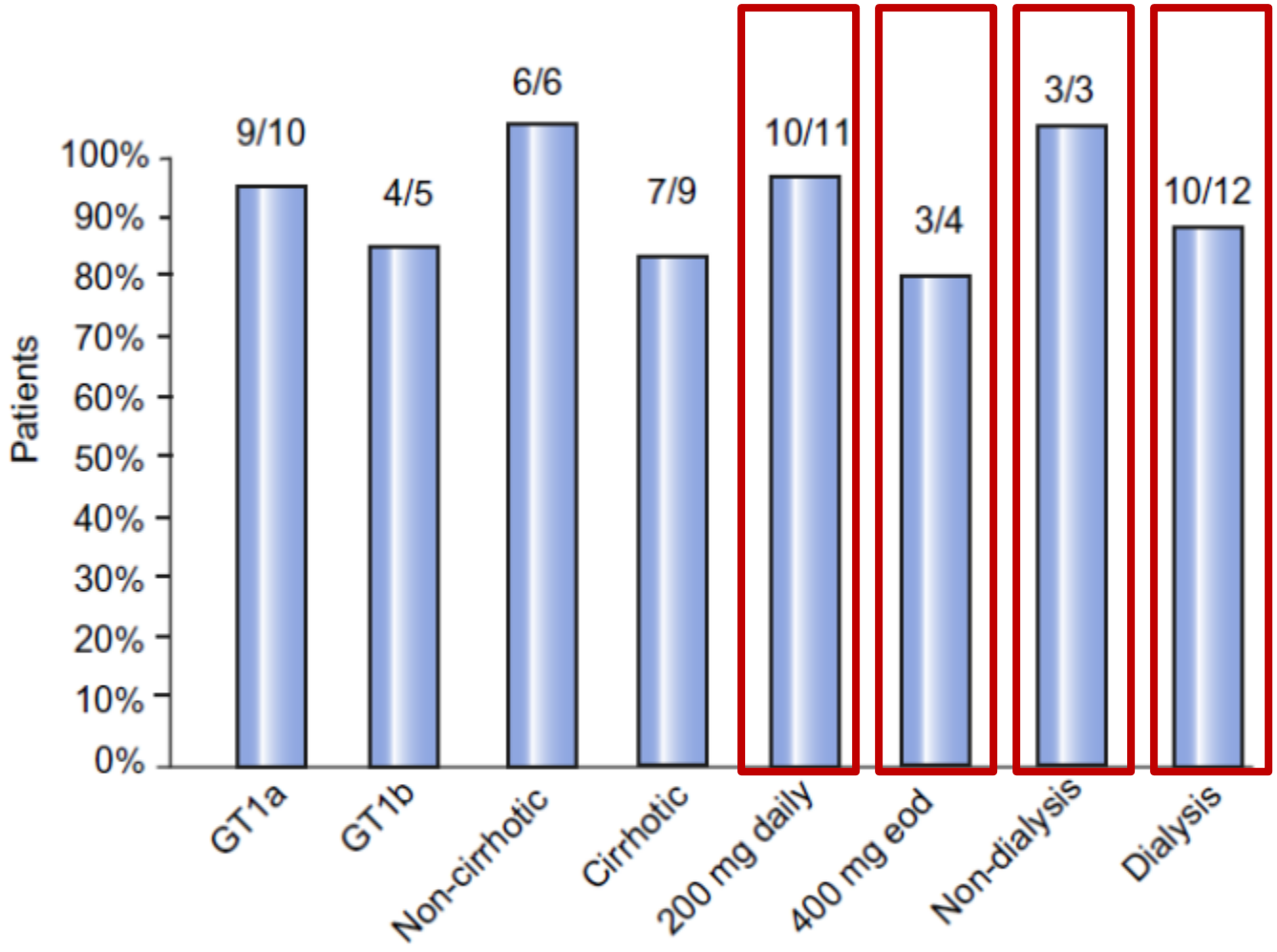
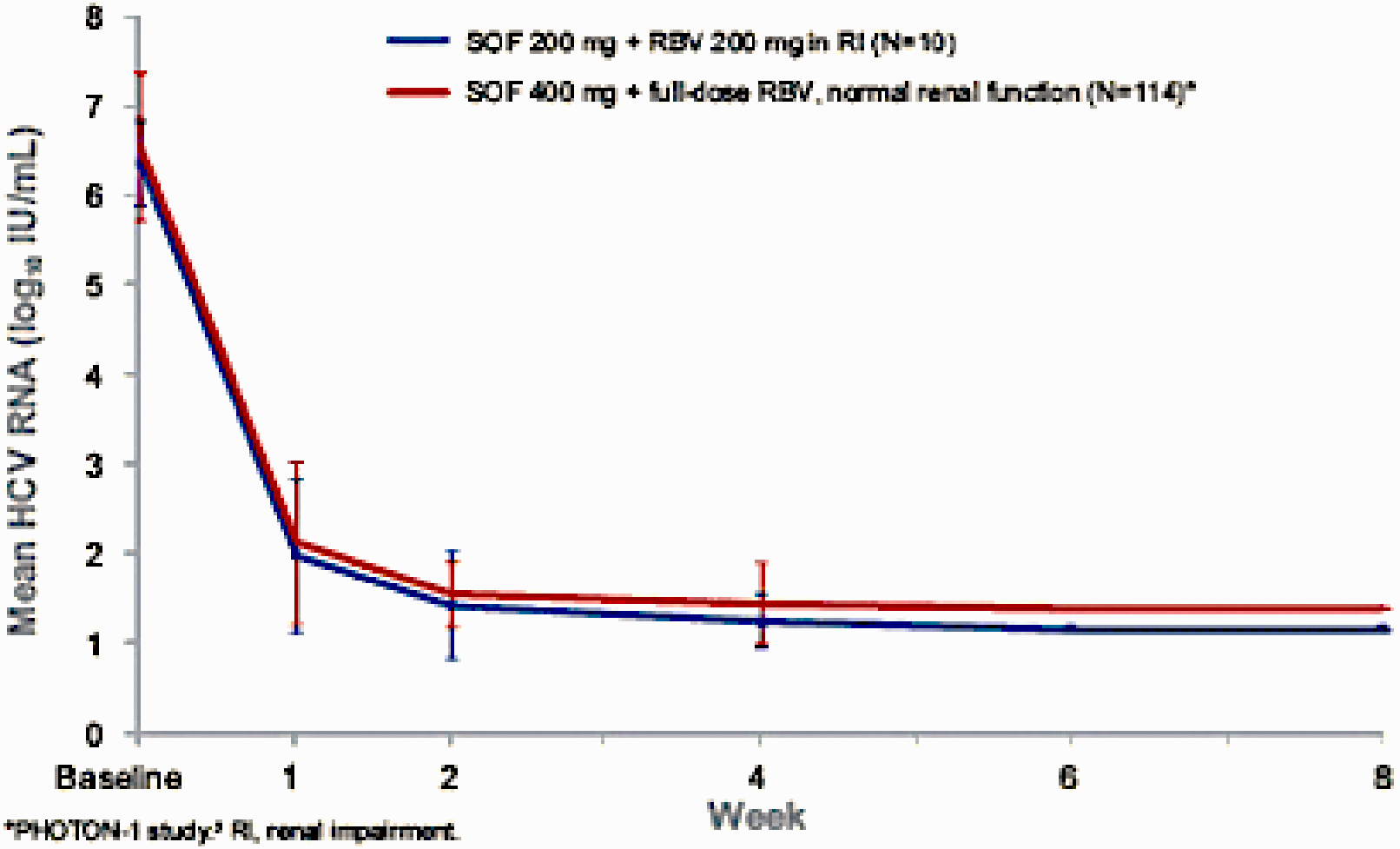


Fig. 1. SVR 12 subgroup analysis.

Viral Kinetics: SOF 200 mg + Reduced RBV in Severe Renal Impairment and SOF 400 mg + Full-Dose RBV in Normal Renal Function



*PHOTON-1 study.[3] RI, renal impairment.

Liver
INTERNATIONAL

Rapid Communication

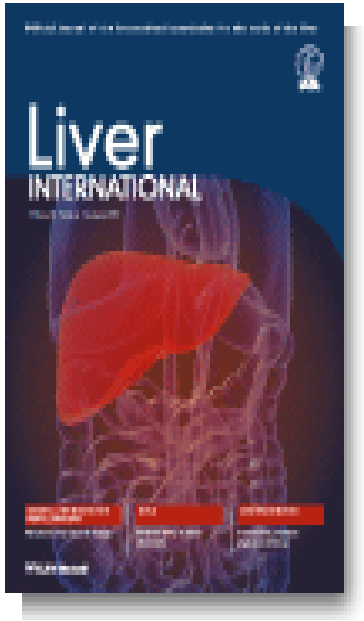
Sofosbuvir and simeprevir in hepatitis C genotype 1-patients with end-stage renal disease on haemodialysis or GFR <30 ml/min

Hector E. Nazario[1,*], Milka Ndungu[1] and Apurva A. Modi[2]

Article first published online: 15 DEC 2015

DOI: 10.1111/liv.13025

Issue



Liver International

Early View (Online Version of Record published before inclusion in an issue)

Table 1. Baseline characteristics

Baseline demographics	All patients (n = 17)
Median age, y (range)	57 (46–69)
Sex, male	14 (82%)
HCV genotype 1a	13 (76%)
HCV RNA level >800 000 IU/ml	13 (76%)
IL28B (non-CC)	10 (59%)
Patients on haemodialysis	15 (88%)
Patients GFR <30 ml/min; no dialysis	2 (12%)
Fibrosis score	
Cirrhosis (F4)	8 (47%)
Fibrosis score 3	4 (24%)
Fibrosis score 0–2	5 (29%)
Treatment naïve	14 (82%)
Treatment experienced	3 (18%)
Peg-INF + RBV NR	2 (67%)
Mean baseline haemoglobin, (range)	11.6 (9.9–13.8)
Median baseline ALT	24
Median baseline AST	33
Median baseline total bilirubin	0.5
Median baseline INR	1.0
Patients on erythropoietin replacement	7 (41%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GFR, glomerular filtration rate; HCV, hepatitis C viruse; NR, non-responder; Peg-INF, peg-interferon; RBV, ribavirin.

Abstract

Background & Aims

Treating chronic hepatitis C (CHC) in patients with end-stage renal disease (ESRD) has suboptimal tolerability and cure rates. Safety and efficacy of sofosbuvir plus simeprevir regimen in CHC-infected patients with ESRD on haemodialysis (HD) or glomerular filtration rate (GFR) <30 ml/min is unknown. We evaluated the safety and efficacy of sofosbuvir and simeprevir in this special patient population.

Methods

All (*n* = 17) patients in the analysis had ESRD on HD or GFR <30 ml/min. All received sofosbuvir 400 mg daily and simeprevir 150 mg *daily*, *without* ribavirin for 12 weeks. Safety and efficacy data were collected; including SVR4 and SVR12 data for all patients after completing therapy.

Results

In this 17 patient cohort, eight (47%) were cirrhotic, four (24%) had stage three liver fibrosis and 13 (76%) were genotype 1A. All 17 have completed 12 weeks of therapy. Treatment was overall well tolerated with no treatment discontinuations reported. Four (24%) patients reported mild adverse events (AE). These AEs were insomnia (*n* = 2), headache (*n* = 1), nausea (*n* = 1) and worsening anaemia requiring blood transfusion (*n* = 1). All 17 patients reached post-treatment week-12 follow-up, and achieved SVR12 or virological cure (100% SVR12).

Conclusions

Daily, full dose of sofosbuvir plus simeprevir for 12 weeks of therapy appears to be well tolerated in patients with ESRD on HD or GFR <30 ml/min. Most common AEs resembled those of healthier CHC patients without significant renal impairment. The cure rates obtained in this cohort treated with sofosbuvir and simeprevir are dramatically superior to any previous treatment regimen studied & published in this special patient population.

Liver INTERNATIONAL

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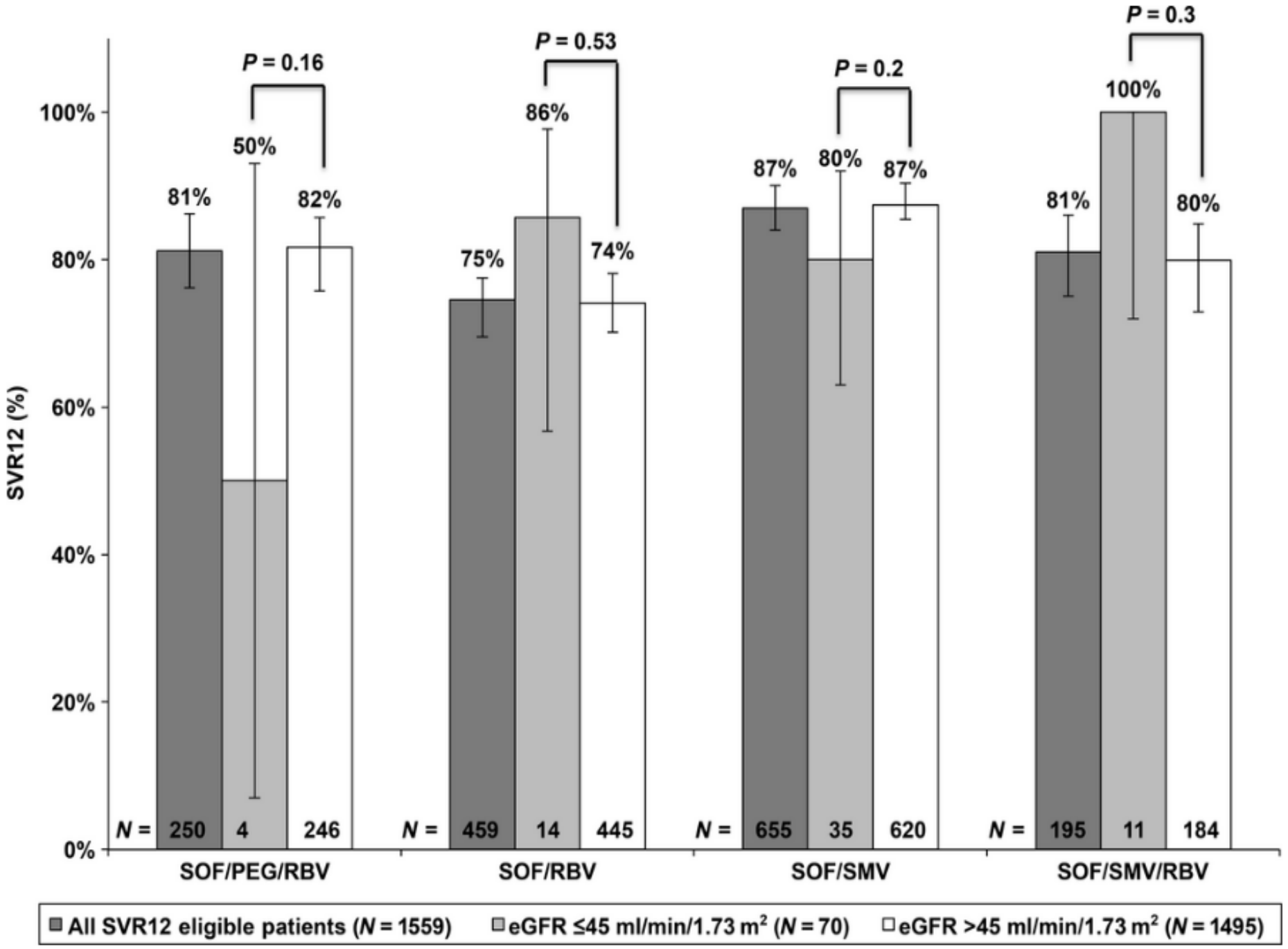
Viral Hepatitis

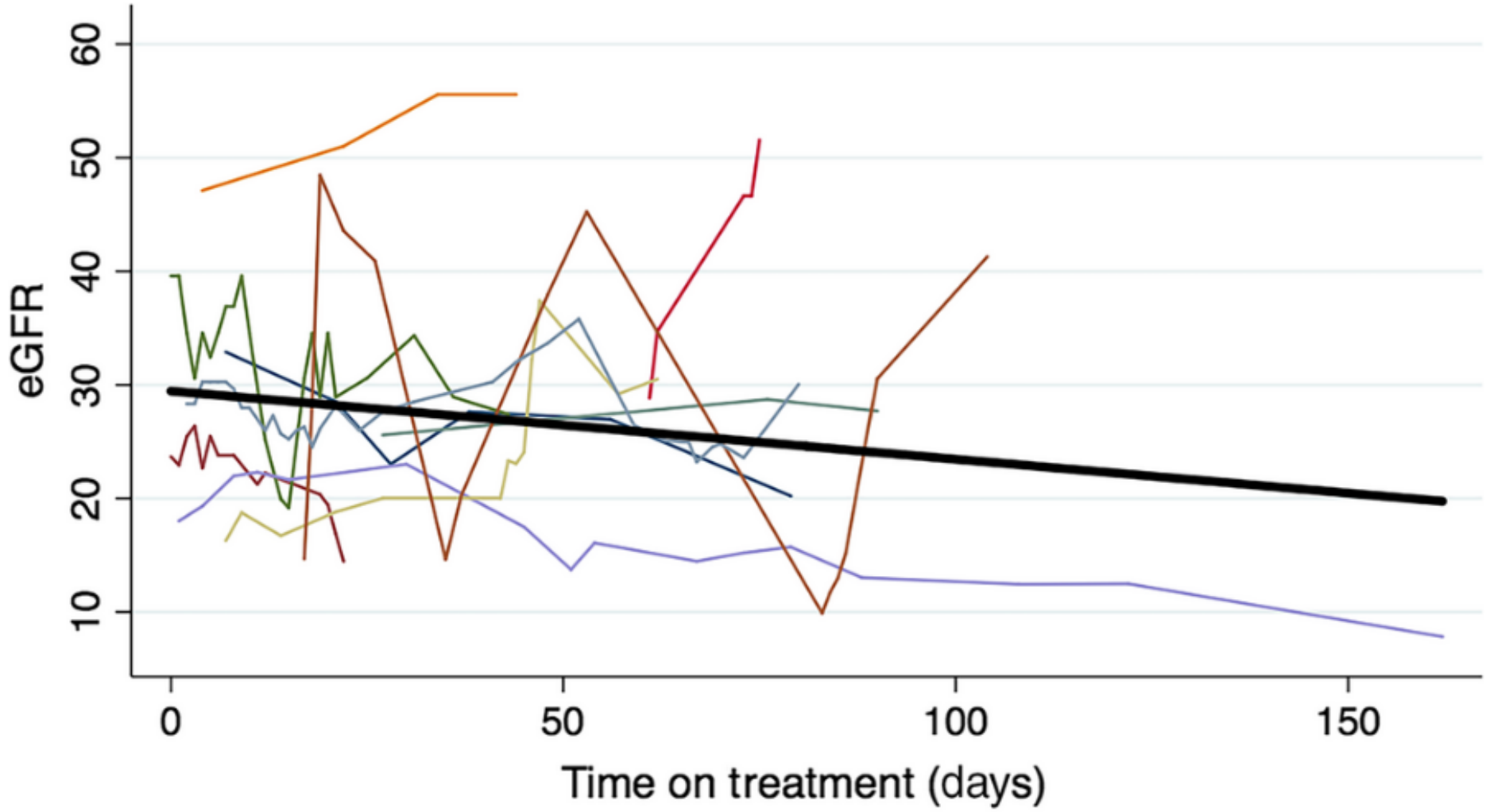
Safety and efficacy of sofosbuvir-containing regimens in hepatitis C-infected patients with impaired renal function

Varun Saxena, Farrukh M. Koraishy, Meghan E. Sise, Joseph K. Lim, Monica Schmidt, Raymond T. Chung, Annmarie Liapakis, David R. Nelson, Michael W. Fried, Norah A. Terrault ✉, HCV-TARGET

First published: 24 March 2016 Full publication history

DOI: 10.1111/liv.13102 View/save citation


P = 0.16
P = 0.53
P = 0.2
P = 0.3
100%
80%
60%
40%
20%
0%
SVR12 (%)
81%
50%
82%
75%
86%
74%
87%
80%
87%
81%
100%
80%
N = 250 4 246
N = 459 14 445
N = 655 35 620
N = 195 11 184
SOF/PEG/RBV
SOF/RBV
SOF/SMV
SOF/SMV/RBV
All SVR12 eligible patients (N = 1559)
eGFR ≤45 ml/min/1.73 m² (N = 70)
eGFR >45 ml/min/1.73 m² (N = 1495)



Those with GFR<45 ml/min had higher rates of worsened renal function

TREATMENT OF HCV IN CKD

- **Chronic kidney disease**
  - The HCV-TARGET cohort
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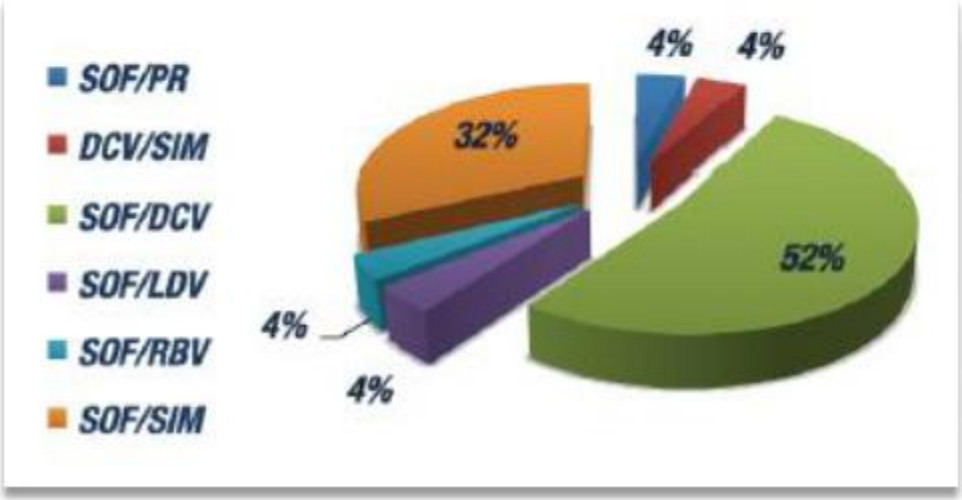
  - The Austrian experience
  - RUBY-1
  - Pharmacokinetics: DCV-TRIO
  - C-SURFER

REAL LIFE EXPERIENCE WITH INTERFERON/RIBAVIRIN-FREE ANTIVIRAL TREATMENT IN RENAL TRANSPLANT RECIPIENTS AND ENDSTAGE RENAL DISEASE-PATIENTS ON DIALYSIS INFECTED WITH HEPATITIS C VIRUS

- 25 patients with chronic HCV infection were evaluated
  - 10 patients were on hemodialysis/peritoneal dialysis
  - 8 patients post NTX (1 OLT at treatment-week 20)
  - 7 experienced combined NTX/OLT

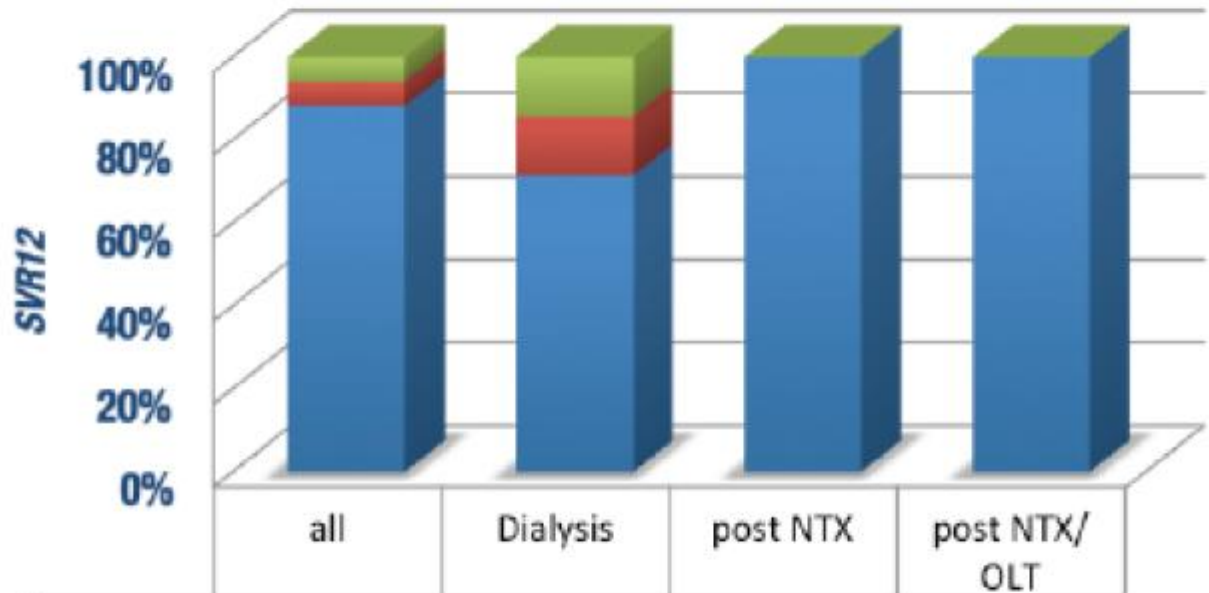
DAA-based treatment regimens



HCV genotype distribution

From: Beinhardt S. ILC 2015, #P0871

REAL LIFE EXPERIENCE WITH INTERFERON/RIBAVIRIN-FREE ANTIVIRAL TREATMENT IN RENAL TRANSPLANT RECIPIENTS AND ENDSTAGE RENAL DISEASE-PATIENTS ON DIALYSIS INFECTED WITH HEPATITIS C VIRUS



	all	Dialysis	post NTX	post NTX/ OLT
no FUP	1	1	0	0
Relapse	1	1	0	0
SVR12	15	5	6	4

FIGURE 4: **no FUP: follow-up not available yet**

From: Beinhardt S. ILC 2015, #P0871

Japanese Studies, 2016 Daclatasvir - Asunaprevir

Therapeutic Apheresis and Dialysis

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Original Article

Effect and Safety of Daclatasvir-Asunaprevir Combination Therapy for Chronic Hepatitis C Virus Genotype 1b -Infected Patients on Hemodialysis

Ryoichi Miyazaki ✉, Kyoko Miyagi

First published: 21 April 2016 Full publication history

DOI: 10.1111/1744-9987.12407 View/save citation

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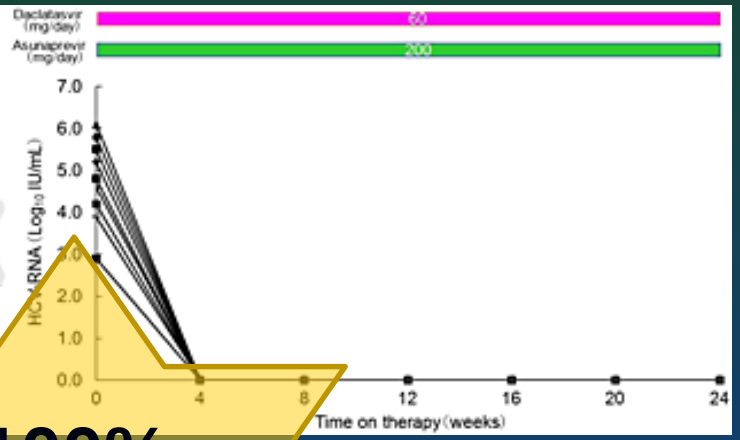
10 Patients



100%

SVR12

Journal of Gastroenterology

July 2016, Volume 51, Issue 7, pp 733–740

Efficacy and safety of daclatasvir and asunaprevir combination therapy in chronic hemodialysis patients with chronic hepatitis C

21 Patients

Authors Authors and affiliations

Goki Suda, Mineo Kudo, Atsushi Nagasaka, Ken Furuya, Yoshiya Yamamoto, Tomoe Kobayashi, Keisuke Shinada, Miki Tateyama, Jun Konno, Yoko Tsukuda, Kazushi Yamasaki, Megumi Kimura, Machiko Umemura, Takaaki Izumi,

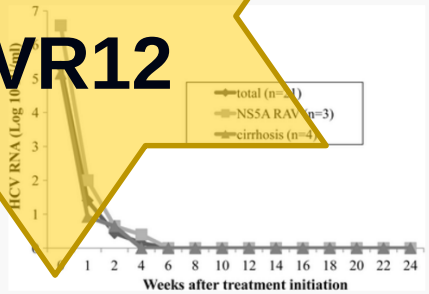


Fig. 1
Mean changes in hepatitis C virus (HCV) RNA during treatment in all patients, patients with resistance-associated variants (RAVs) in NS5A, or patients with liver cirrhosis

Original Article

Pharmacokinetics, efficacy and safety of daclatasvir plus asunaprevir in dialysis patients with chronic hepatitis C: pilot study

Y. Kawakami, M. Imamura, H. Ikeda, M. Suzuki, K. Arataki, M. Moriishi, N. Mori, K. Kokoroishi, Y. Katamura, T. Ezaki, T. Ueno, K. Ide, T. Masaki, H. Ohdan, K. Chayama ✉

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18 Patients

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Pages 850–856

TREATMENT OF HCV IN CKD

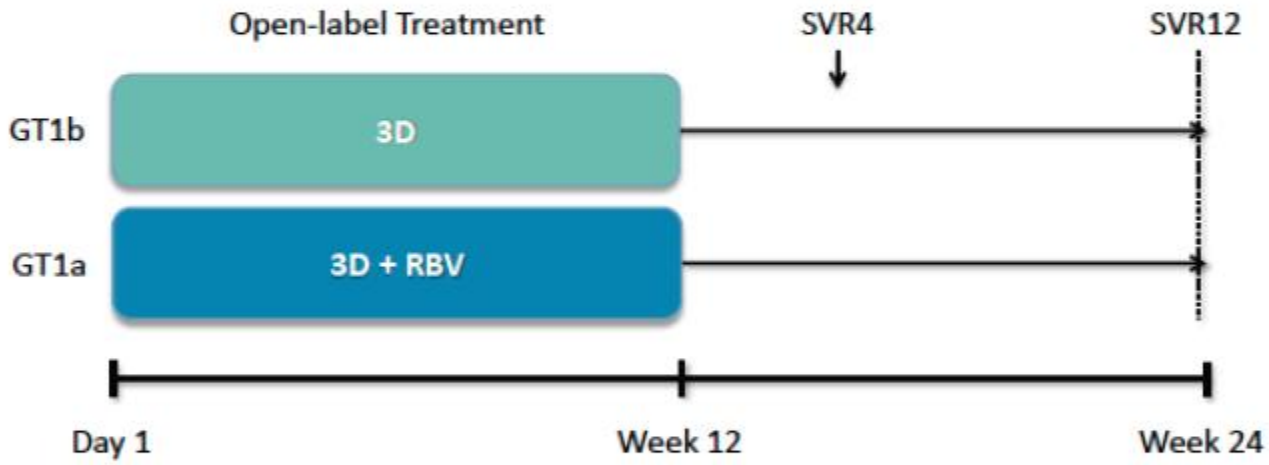
- **Chronic kidney disease**
  - The HCV-TARGET cohort
  - A small US study
  - The Austrian experience
  - RUBY-1
  - Pharmacokinetics: DCV-TRIO
  - C-SURFER

APPROVED AGENTS

SAFETY OF OMBITASVIR/PARITAPREVIR/RITONAVIR PLUS DASABUVIR FOR TREATING HCV GT1 INFECTION IN PATIENTS WITH SEVERE RENAL IMPAIRMENT OR END-STAGE RENAL DISEASE: THE RUBY-I STUDY

Multicenter, Open-label, Phase 3b Study

- 9 sites, all in the United States



- **3D**: Co-formulated OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg BID)
- **For GT1a**: RBV 200 mg QD
- **For GT1b**: No RBV

Patient Status as of 10 April 2015

- 20 patients enrolled
  - 14/20 completed 12 weeks of 3D ± RBV
  - 6/20 remain on treatment

From: Pockros PJ. ILC 2015, #L01

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BASELINE DEMOGRAPHICS

	3D±RBV N=20
Male; n (%)	17 (85)
Black; n (%)	14 (70)
Age, years; median (range)	60 (49-69)
Hispanic or Latino ethnicity; n(%)	3 (15)
Degree of fibrosis*; n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV viral load, log_{10} (IU/mL); median (range)	6.6 (5.5-7.6)
GT1a; n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage; n (%)	
4 (eGFR 15-30 mL/min/1.73m²)	7 (35)
5 (eGFR <15 mL/min/1.73m² or requiring dialysis)	13 (65)
On dialysis; n (%)	13 (65)
eGFR, mL/min/1.73m²; median (range)	10.9 (5.4-29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2-10.8)

*Biopsy: 5 patients; Fibroscan: 10 patients; Fibrotest: 5 patients.

From Pockros PJ. ILC 2015, #L01

SAFETY OF OMBITASVIR/PARITAPREVIR/RITONAVIR PLUS DASABUVIR FOR TREATING HCV GT1 INFECTION IN PATIENTS WITH SEVERE RENAL IMPAIRMENT OR END-STAGE RENAL DISEASE: THE RUBY-I STUDY

SAFETY AND EFFICACY

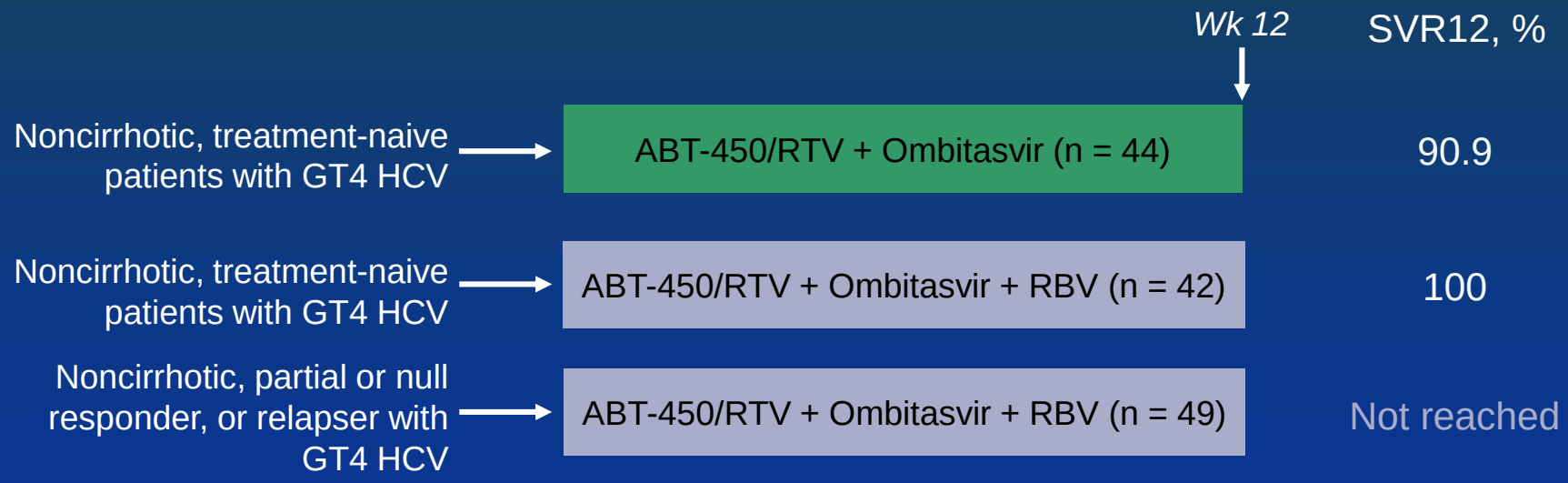
- No discontinuations or treatment-related serious AEs
- All patients completing treatment to date had virologic response

Timepoint	N	Virologic Response (n)	Percent
End of Treatment	14	14	100
Post-treatment Week 4	10	10	100
Post-treatment Week 12	2	2	100

From Pockros PJ. ILC 2015, #L01

PEARL I: ABT-450/RTV + Ombitasvir ± RBV in Tx-Naive Noncirrhotic GT4 Pts

- **Open-label, nonrandomized phase II trial**
- **Primary endpoint: SVR12**
  - **Interim results, SVR12 available for Tx-naive arms only**



ABT-450/RTV 150/100 mg once daily; ombitasvir 25 mg once daily; RBV 1000-1200 mg/day.

Figure shows design of presented arms from Substudy 1 only. Substudy 2 in patients with compensated cirrhosis is ongoing; arms not shown.

Hezode C, et al. EASL 2014. Abstract O58. Reproduced with permission.

TREATMENT OF HCV IN CKD

- **Chronic kidney disease**
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  - RUBY-1
  - Pharmacokinetics: DCV-TRIO
  - C-SURFER

C-SURFER: GRAZOPREVIR PLUS ELBASVIR IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFECTION AND CHRONIC KIDNEY DISEASE

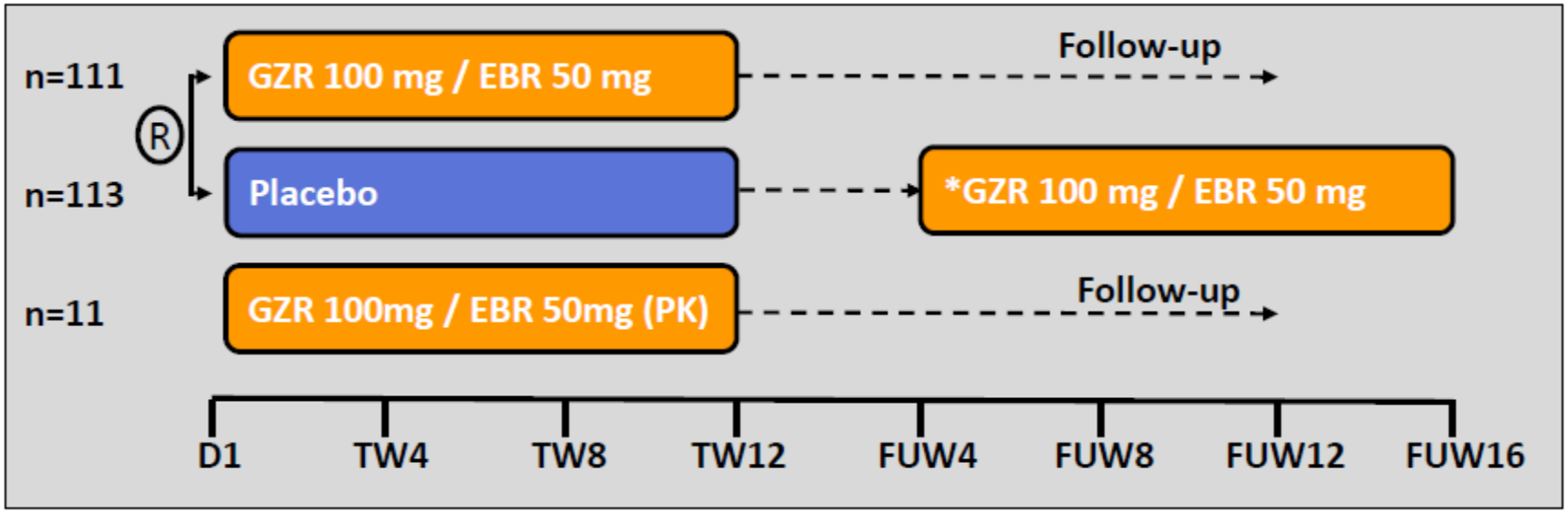
- This study evaluated grazoprevir + elbasvir in HCV-infected patients with CrCl <30 mL/min, including patients on hemodialysis
  - <1% of grazoprevir and elbasvir are renally excreted*
  - Phase 1 trial demonstrated no need for dose adjustments in CKD[1]

From Roth D. ILC 2015, #LP02

*Yeh WW, et al. Hepatology 2014; 60(suppl 4): 1940

CrCL = creatinine clearance (estimated using MDRD-4); CKD = chronic kidney disease

C-SURFER: STUDY DESIGN



- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by diabetes (yes/no) and hemodialysis status (HD/non-HD)
- 224 patients randomized to immediate treatment with GZR/EBR or deferred treatment where patients received placebo for 12 weeks then open-label GZR/EBR starting at FUW4
- 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic sampling

*Deferred open-label treatment arm (all randomized patients remained blinded to treatment until FW4)
GZR and EBR were administered as separate entities in the immediate and PK arms, and as a fixed dose-combination in the deferred arm. CKD = chronic kidney disease; GT = genotype; HD = hemodialysis; R = randomized

From: Roth D. ILC 2015, #LP02

INVESTIGATIONAL AGENTS

C-SURFER: KEY INCLUSION/EXCLUSION CRITERIA

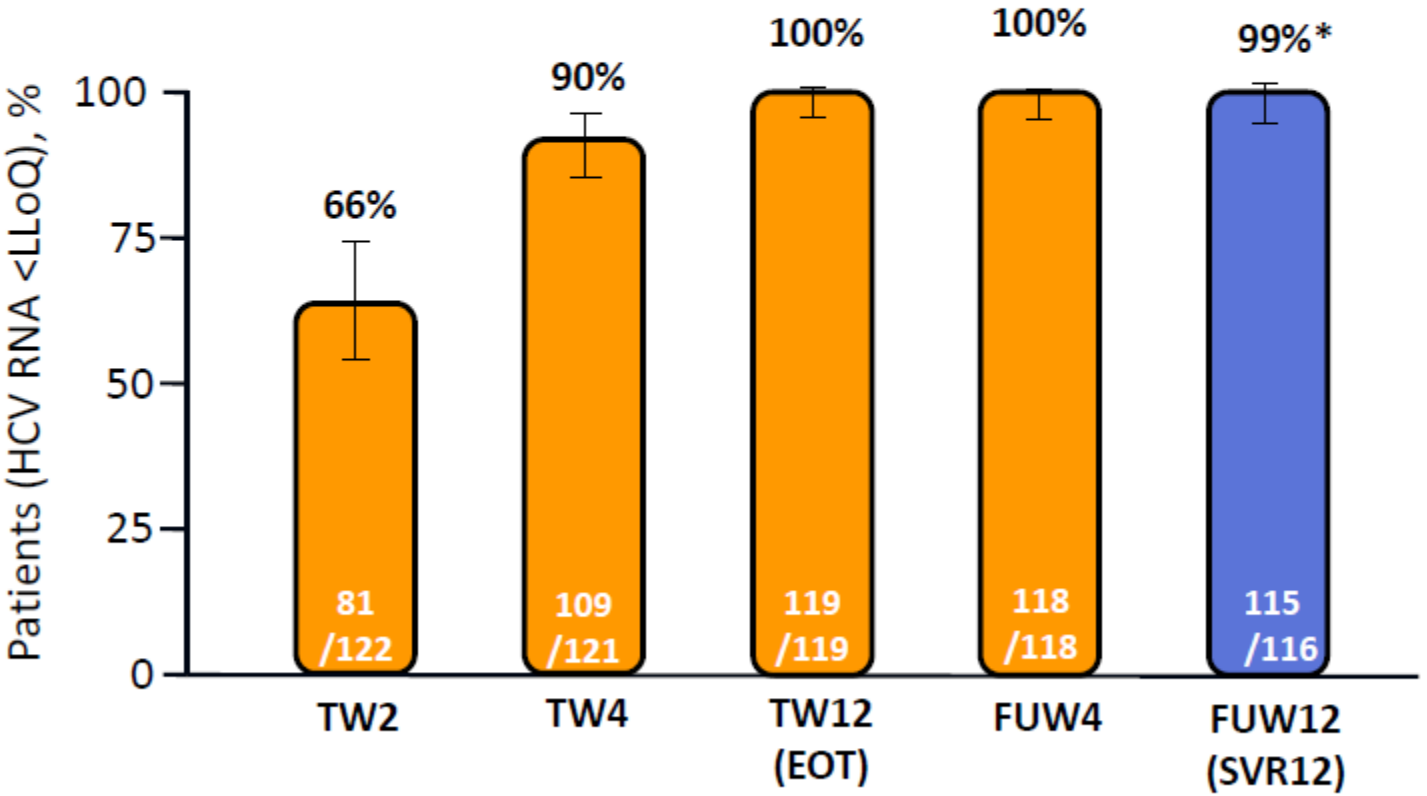
- HCV GT1 infection
- Treatment-naive and treatment-experienced patients
- CKD stage 4/5 (± hemodialysis dependence)
  - CKD stage 4: eGFR 15-29 mL/min/1.73m^2
  - CKD stage 5: eGFR <15 mL/min/1.73m^2 or on dialysis
  - target 20% non-hemodialysis patients
- Compensated cirrhosis allowed
  - Liver staging was based on biopsy within 24 months of enrolment; Fibroscan within 12 months of enrolment; or a combination of Fibrotest score of >0.75 and an AST:platelet ratio index of >2
  - Patients with presence or history of ascites, gastric or variceal bleeding, hepatic encephalopathy, or other signs/symptoms of advanced liver disease were excluded
- HBV and HIV negative

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate

From: Roth D, JLC 2015, #LB02

C-SURFER: ON-TREATMENT VIROLOGIC RESPONSE (ITG)

1 noncirrhotic patient with HCV GT1b infection relapsed at FW12



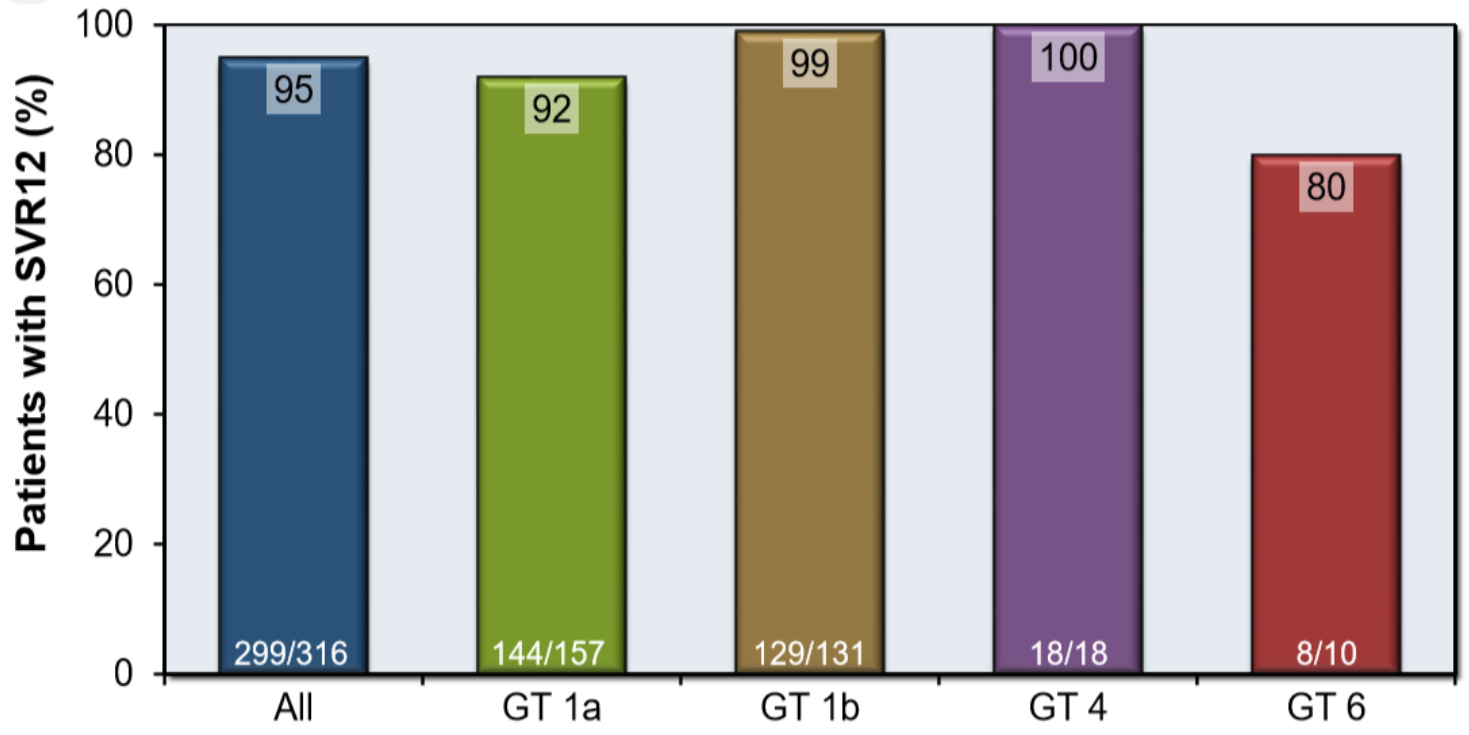
*Efficacy is presented for the modified full analysis set population (mFAS). Full Analysis set: patients with SVR12 94%

6 patients were excluded from the per protocol: lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)

From: Roth D. ILC 2015, #LP02

Elbasvir-Grazoprevir in Treatment-Naïve HCV GT 1, 4 or 6
C-EDGE TN: Results

C-EDGE TN: SVR12 Results by Genotype



Primary efficacy analysis included all patients who received ≥1 dose of drug.

CKD on Conservative Rx

Basic Combination	RBV	Duration (weeks)	GT1 data	GT4 data	eGFR>30 SVR12	eGFR<30 SVR12
Paritaprevir/ Ritonavir+ Ombitasvir **(Qurevo)**	Yes	12	RUBY-1	PEARL-1 Extrapolation	100%	100%
Grazoprevir/ Elbasvir **(Zepatier)**	No	12	C-SURFER	C-EDGE Extrapolation	100%	99%
Sofosbuvir **(Sovaldi)**+ Simeprevir **(Olysio)**	No	12	COSMOS	Bhamidimarri Sofo ½ dose	93%	87%
Daclatasvir Asunaprevir	No	12	Japanese study			100%
Ledipasvir + Sofosbuvir **(Harvoni)**	Yes No	12 12 12	ION-1	GS-US-337-1119, O056 SYNERGY	97.7% 93% 95%	Avoid
Sofosbuvir **(Sovaldi)**	Yes	24		Egypt Ancestry	90%	Avoid

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016☆

European Association for the Study of the Liver*

- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected with HCV genotype 4 should be treated with the combination of ritonavir-boosted paritaprevir and ombitasvir for 12 weeks with daily ribavirin (200 mg/day) if the haemoglobin level is >10 g/dl at baseline, or with the combination of grazoprevir and elbasvir for 12 weeks without ribavirin (**B1**).

Recommended Regimens for Patients with Severe Renal Impairment, Including Severe Renal Impairment (Creatinine Clearance [CrCl] <30 mL/min) or End-Stage Renal Disease (ESRD)

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **For patients with genotype 1a, or 1b, or 4 infection and CrCl below 30 mL/min for whom the urgency to treat is high and kidney transplant is not an immediate option, daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100mg) for 12 weeks is a Recommended regimen.**
  Rating: Class IIb, Level B

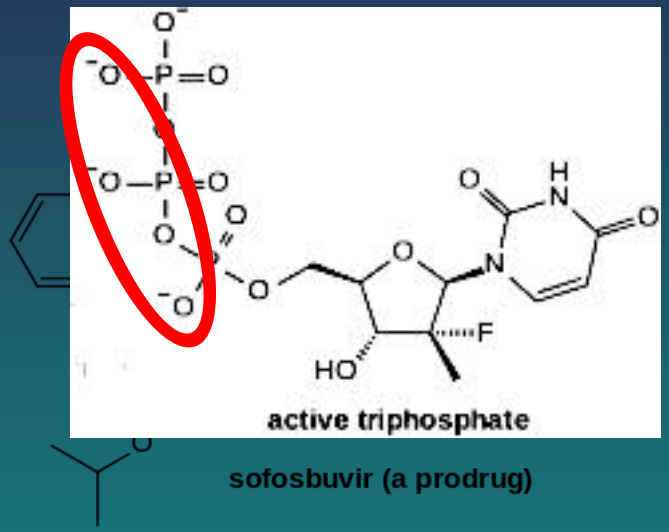
- **For patients with genotype 1b infection and CrCl below 30 mL/min for whom the urgency to treat is high and kidney transplant is not an immediate option, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen.**
  Rating: Class IIb, Level B

Alternative Regimen for Genotype 1a-infected Patients with CrCl Below 30 mL/min

- **For HCV genotype 1a infection, daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and dose-adjusted ribavirin** (200 mg daily) for 12 weeks is an Alternative regimen.**
  Rating: Class IIb, Level B

Dialysis-related Pharmacokinetics

- Protein binding 61%
- Molecular size 529.45
- Molecular charge -ve



- Studies on dialysance PK of different DAAs underway
- Results of Clinical Trials

Table 2. Pharmacokinetics of sofosbuvir 200 mg vs. 400 mg in ESRD.

	Setting	Sofosbuvir AUC	GS-331007 AUC
Sofosbuvir 400 mg	Severe CKD	171%	451%
	1 h pre-HD	28%	1280%
	1 h post-HD	60%	2070%
Sofosbuvir 200 mg	Severe CKD	5-10%	300%
	1 h pre-HD	n.a.	n.a.
	1 h post-HD	n.a.	n.a.

*Adapted from Gane *et al.* [4].

CKD on Dialysis

Basic Combination	RBV	Duration (weeks)	GT1 data	GT4 data	eGFR>30 SVR12	eGFR<30 SVR12
Paritaprevir/ Ritonavir+ Ombitasvir **(Qurevo)**	Yes	12	RUBY-1	PEARL-1 Extrapolation	100%	100%
Grazoprevir/ Elbasvir **(Zepatier)**	No	12	C-SURFER	C-EDGE Extrapolation	100%	99%
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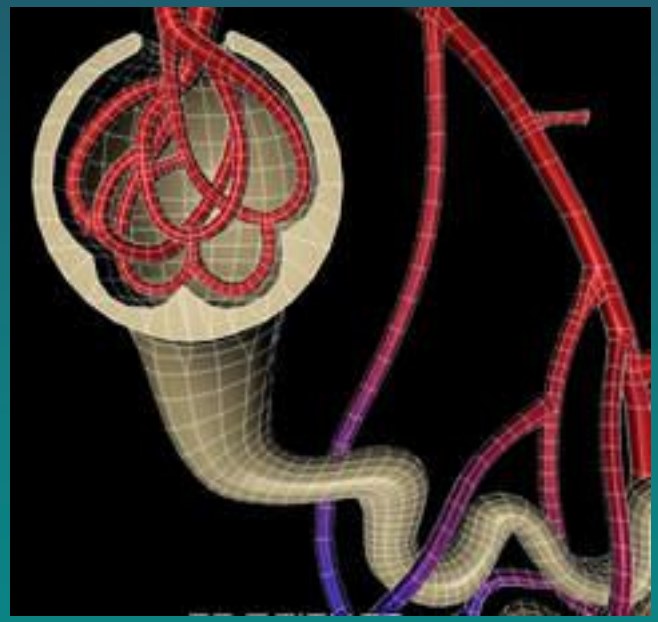
Ledipasvir + Sofosbuvir **(Harvoni)**	Yes No	12 12 12	ION-1	GS-US-337-1119, O056 SYNERGY	97.7% 93% 95%	Avoid

Pharmacokinetics

Interferon – >95%

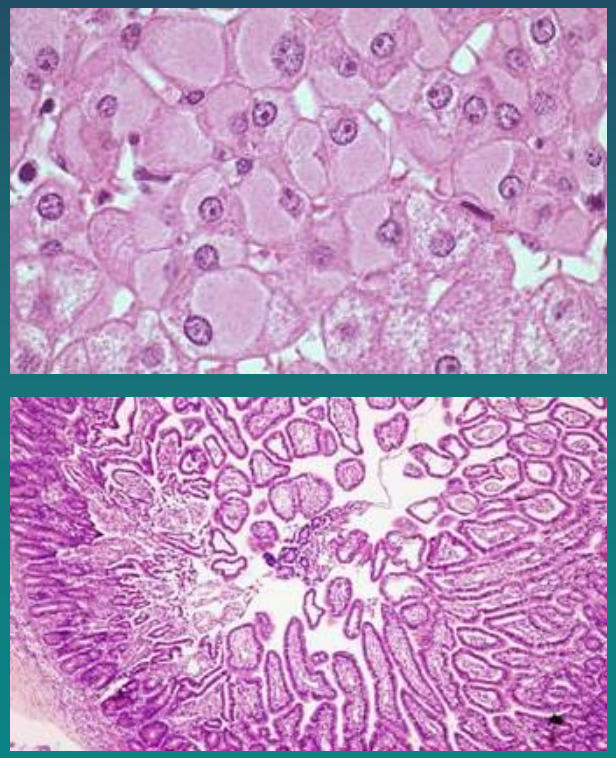
Ribavirin- 61%

2nd wave DAAs- <10%



Proximal Tubules

2nd wave DAAs- >90%



Cytochrome P450

Dose Adjustments in Chronic Kidney Disease

Creatinine Clearance	PEG IFN alfa 2a, µg/wk	PEG IFN alfa 2b, µg/kg/wk	Ribavirin Daily
> 50 ml/min	180	1.5	1000-1200 mg/day
30-50 mL/min	180	1.125	Alternating doses, 200 mg and 400 mg every other day
Less than 30 mL/min	135	0.75	200 mg/day
Hemodialysis	135	0.75	200 mg/day

Kidney Transplantation

[SP747] SUCCESSFUL CONTROL OF FIBROSING CHOLESTATIC HEPATITIS C WITH SOFOSBUVIR IN A KIDNEY TRANSPLANT RECIPIENT.

Alessandra Palmisano[1], Anna Maria Degli Antoni[2], Augusto Vaglio[1], Giovanni Piotti[1], Elena Cremaschi[1], Carlo Buzio[1], Umberto Maggiore[1]

[1]University Hospital of Parma, Parma, Italy[2]University Hospital of Parma, Parma, Italy.

INTRODUCTION AND AIMS: Fibrosing cholestatic (FCH) hepatitis C is characterized by high HCV load causing direct hepatotoxicity, progressive hepatic failure and death. The standard treatment of choice, based on interferon plus ribavirine, is risky in kidney transplant recipients, being associated with steroid-resistant acute rejection and graft loss. Recently, sofosbuvir, a novel oral nucleotide NS5B polymerase inhibitor, has been successfully employed for the treatment of chronic HCV infection in phase III randomized clinical trials. However, there are no published reports documenting the use of sofosbuvir for the treatment of FCH hepatitis C in kidney transplant recipients. Herein, we describe a case of an HCV-HIV positive patient who developed a fibrosing cholestatic hepatitis C after kidney transplantation treated with sofosbuvir.

METHODS: CASE REPORT: A 47-year-old man was admitted because of a progressive deterioration of liver functions tests. He had received a kidney transplant 40 days earlier under standard immunosuppressive therapy (basiliximab induction, maintenance with cyclosporine [average blood trough levels 150, ng/mL], MMF [1g/bid], and methylprednisolone [4mg/day]). The post-operative period was uneventful, and graft function was stable (serum creatinine 1.7mg/dL). His medical history was significant for chronic HCV infection not responsive to the interferon based therapy but with no signs of progressive chronic liver disease, HIV infection on antiretroviral treatment with undetectable viremia since 6 years, and ESRD due to HIV collapsing FSGS 11 years earlier. At the time of transplantation, HCV-RNA levels were 265.400 IU/mL. Total serum bilirubin levels, which were 3.8 mg/dl at the time of admission, increased up to 5.8 mg/dl over the following 2 weeks. Serum gamma-GT and ALT peaked at 461 IU/L and 577 IU/L respectively (day 6 from admission). HCV viremia increased up to 69.326.200 IU/mL, whereas HIV-RNA remained undetectable. Liver biopsy (day 1 from admission) showed FCH with intracellular viral inclusions. MMF treatment was withdrawn and cyclosporine dose was halved. Despite a plateauing of the liver function tests, HCV-RNA viral load did not decline significantly. Two months after admission, we started treatment with sofosbuvir (compassionate use) plus rivabirin.

RESULTS: After four weeks of therapy HCV RNA became undetectable and all the liver function tests returned to the normal range. The patient did not develop treatment side effects a part from anemia requiring Epoetin 40000/IU per week. Three months from admission, the patient underwent a renal graft biopsy that did not show signs of rejection. Cyclosporine dosage was increased to reach to standard blood levels, but MMF was not resumed. At last follow up (6 months from admission), there was no detectable HCV and HIV, liver function tests were normal and renal function was stable (creatinine 1,7 mg/dL).

CONCLUSIONS: The present case shows that IFN free sofosbuvir based therapy may be a safe and effective approach for treatment of fibrosing cholestatic hepatitis C in kidney transplant recipients

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Original Article

Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation

N. Kamar, O. Marion, L. Rostaing, O. Cointault, D. Ribes, L. Lavayssière, L. Esposito, A. Del Bello, S. Métivier, K. Barange, J. Izopet, L. Alric

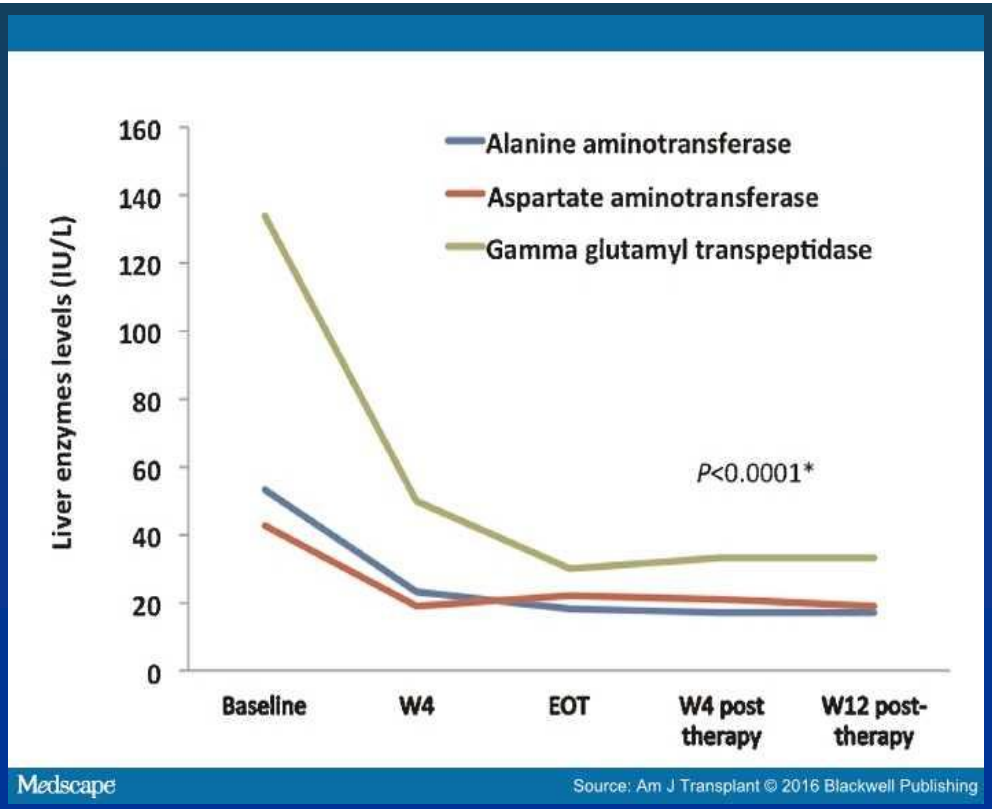
First published: 20 November 2015 Full publication history

25 Patients

- **SBV/RBV 3**
- **SBV/DCV 4**
- **SBV/SMV+- RBV 7**
- **SBV/LDV+- RBV 10**
- **SBV/RBV + PegINF 1**

10 F3-F4

15 F1-F2



Outcomes of liver enzyme parameters during and after antiviral therapy. *Friedman test. EOT, end of therapy

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Brief Communication

Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents

D. Sawinski, N. Kaur, A. Ajeti, J. Trofe-Clark, M. Lim, M. Bleicher, S. Goral, K. A. Forde, R. D. Bloom

First published: 5 February 2016 Full publication history

DOI: 10.1111/ajt.13620 View/save citation

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- **SBV/SMV 9**
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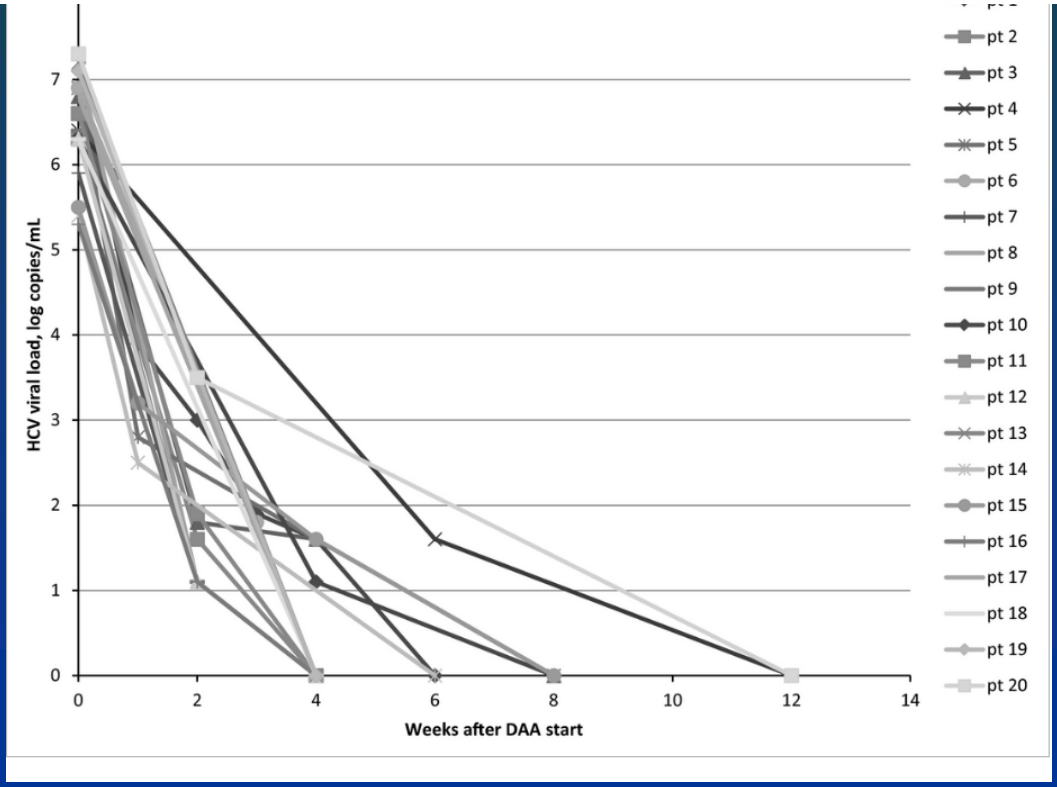
- **SBV/DCV 1**

50% advanced hepatic fibrosis



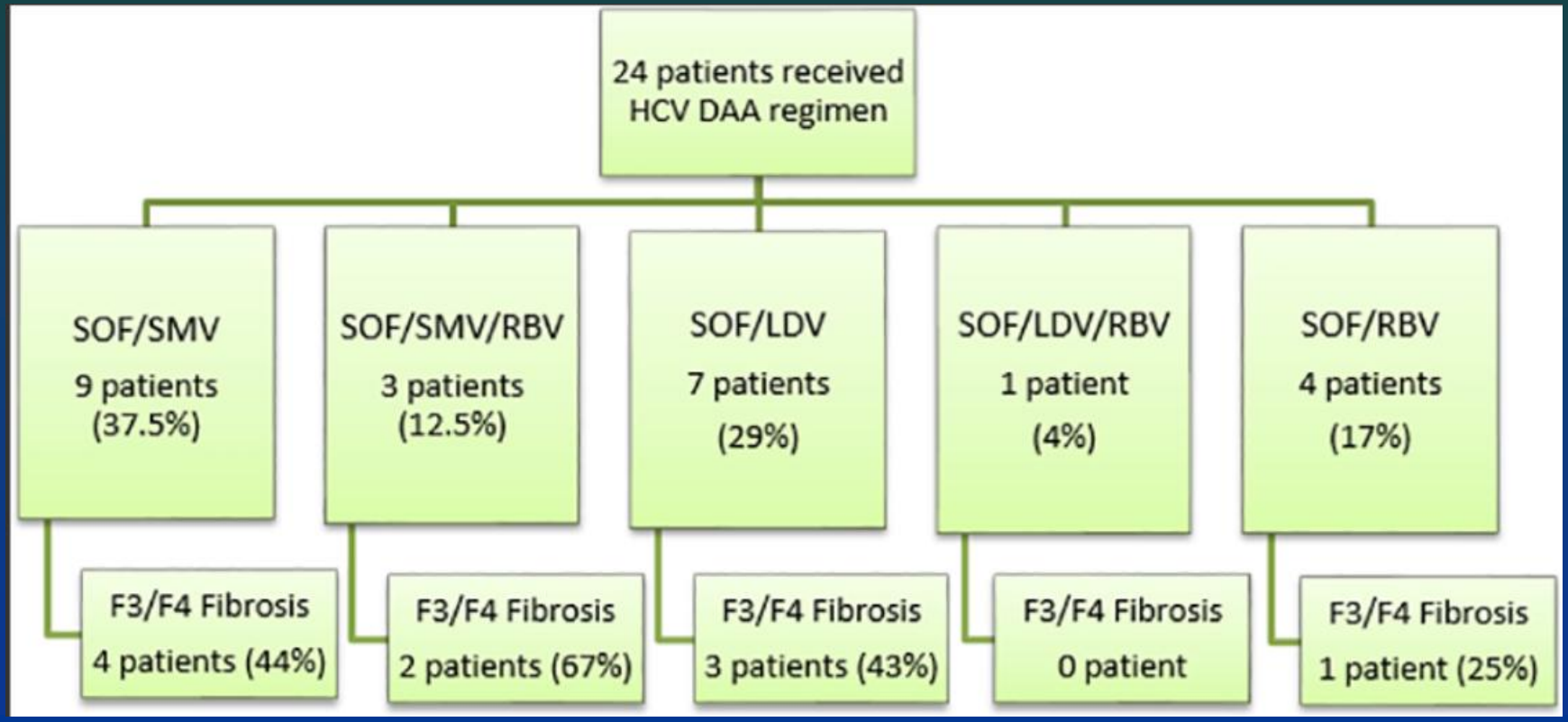
Kinetics of HCV viral load clearance on DAA

Efficacy and Safety of Direct Acting Antivirals in Kidney Transplant Recipients with Chronic Hepatitis C Virus Infection

Ming V. Lin, Meghan E. Sise, Martha Pavlakis, Beth M. Amundsen, Donald Chute, Anna E. Rutherford, Raymond T. Chung, Michael P. Curry, Jasmine M. Hanifi, Steve Gabardi, Anil Chandraker, Eliot C. Heher, Nahel Elias, Leonardo V. Riella

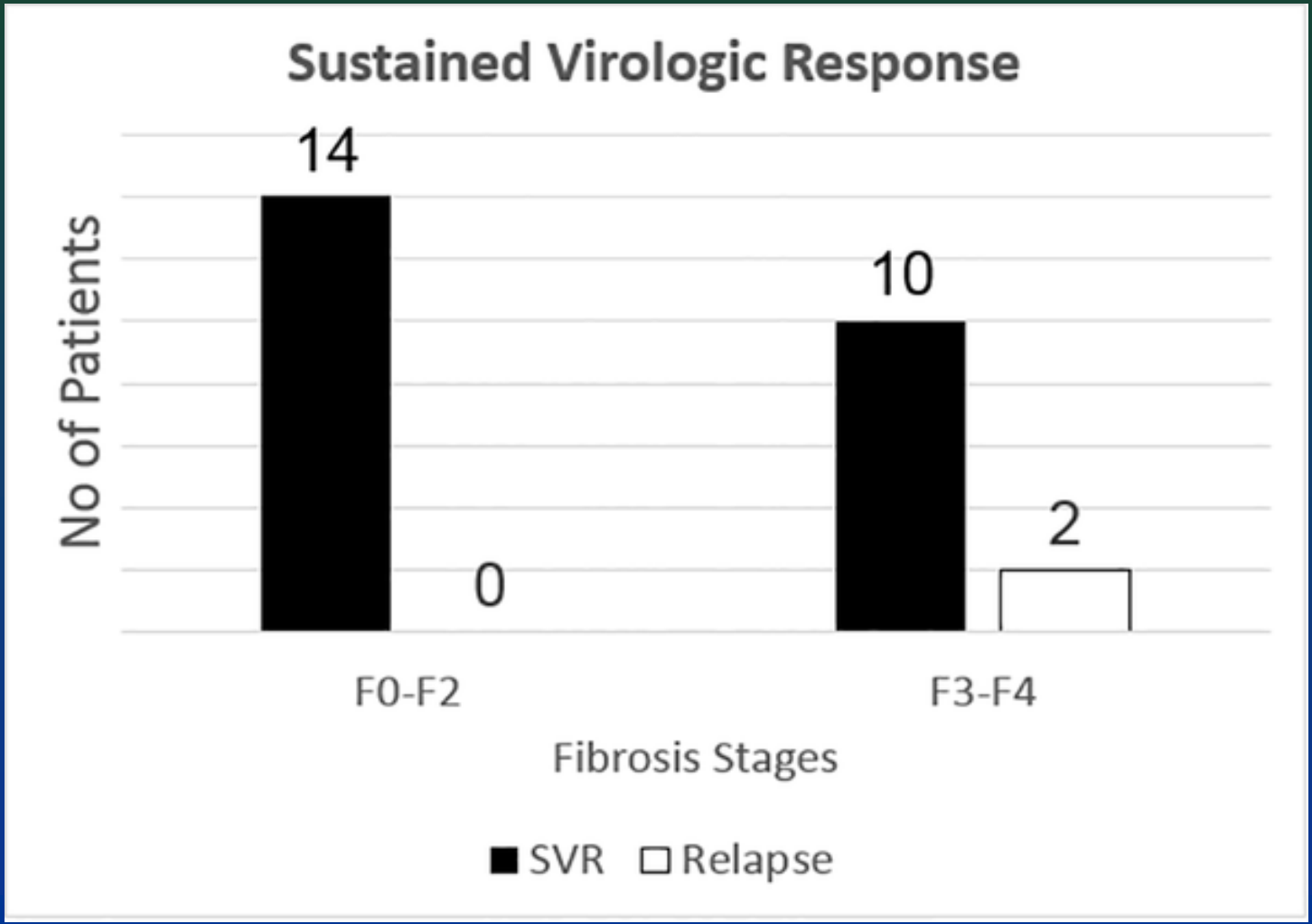
Published: July 14, 2016 • http://dx.doi.org/10.1371/journal.pone.0158431

Study Population



42% advanced fibrosis/cirrhosis

Fig 3. Sustained Virologic Response.



Lin MV, Sise ME, Pavlakis M, Amundsen BM, Chute D, et al. (2016) Efficacy and Safety of Direct Acting Antivirals in Kidney Transplant Recipients with Chronic Hepatitis C Virus Infection. PLOS ONE 11(7): e0158431. doi:10.1371/journal.pone.0158431
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0158431

JOURNAL OF HEPATOLOGY
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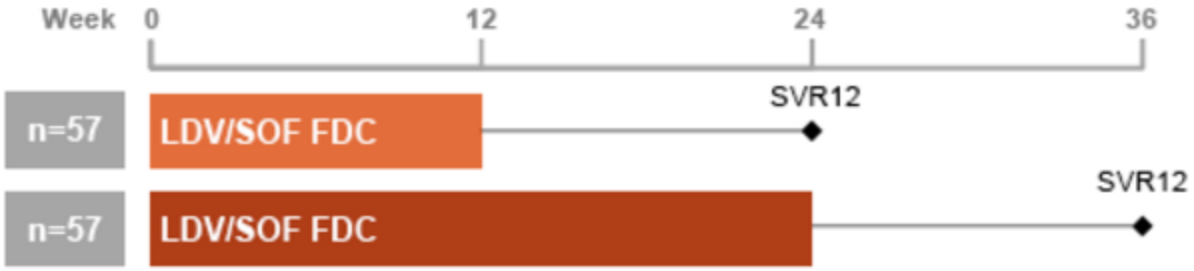
2016 Volume 64, Issue 2, Supplement, Page S183

Ledipasvir/Sofosbuvir for 12 or 24 Weeks Is Safe and Effective in Kidney Transplant Recipients with Chronic Genotype 1 or 4 Hcv Infection

M. Colombo, A. Aghemo, L. Liu, R. Hyland, C. Yun, D. Brainard, J. McHutchison, M. Bourlière, M. Peck-Radosavljevic, M. Manns, S. Pol

Study Design

GT 1 and 4, Post-Kidney Transplant

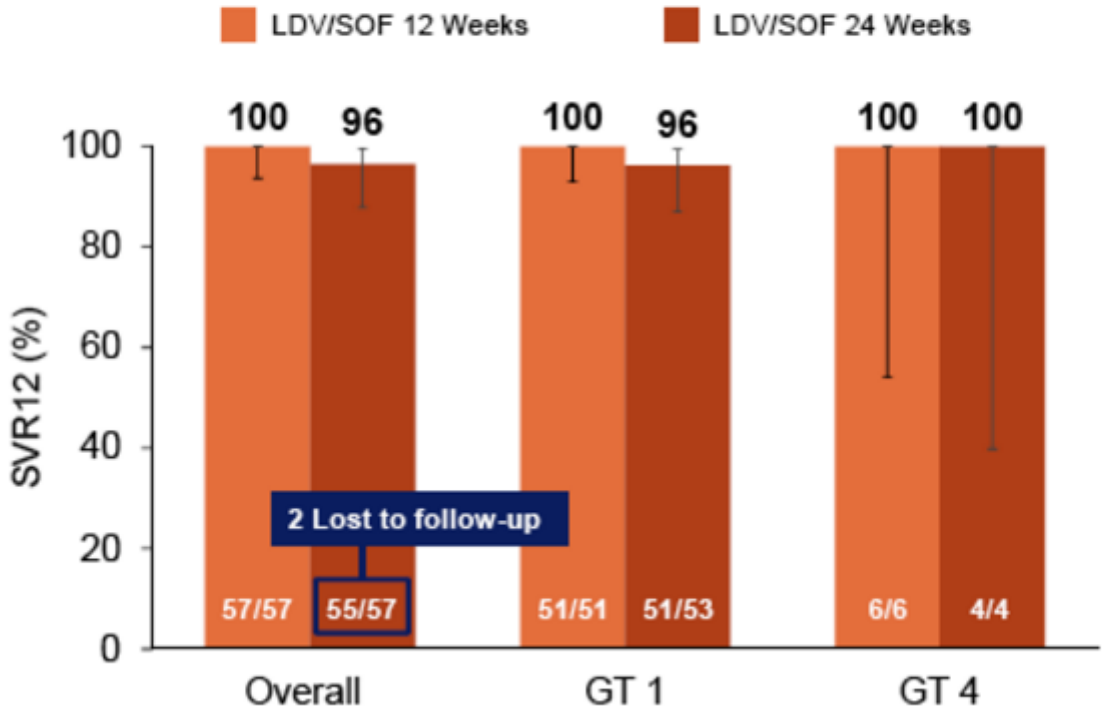


- Phase 2, randomized, open label multicenter study
  - 5 sites in Italy, France, Austria and Germany
- Kidney transplant recipients with HCV GT 1 or 4, treatment-naïve or -experienced, with or without cirrhosis
- Cirrhosis determined by biopsy (Metavir score =4 or Ishak score ≥5), FibroScan® > 12.5 kPa or FibroTest >0.75 + APRI >2
- Key inclusion criteria
  - >6 months from kidney transplant
  - HCV RNA ≥LLOQ (15 IU/mL) at screening
  - Hemoglobin ≥10 g/dL, platelets >50 x 10^3/µL, CL_{cr} ≥40 mL/min

LLOQ, lower limit of quantitation; CL_{cr}, creatinine clearance; APRI, AST: platelet ratio index.

Results: SVR12

GT 1 and 4, Post-Kidney Transplant



Daclatasvir after kidney transplantation

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Original Article

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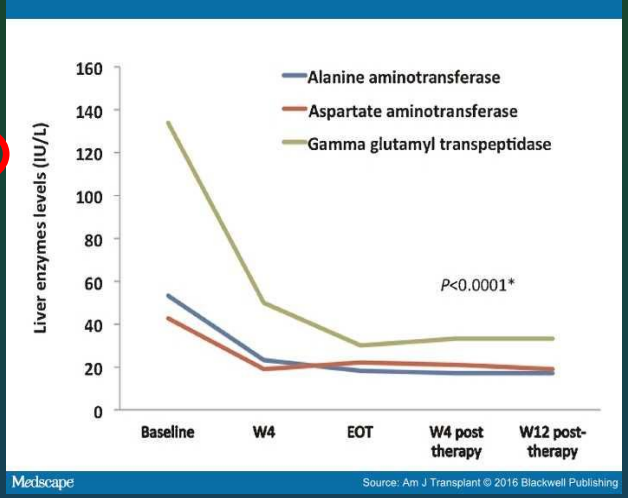

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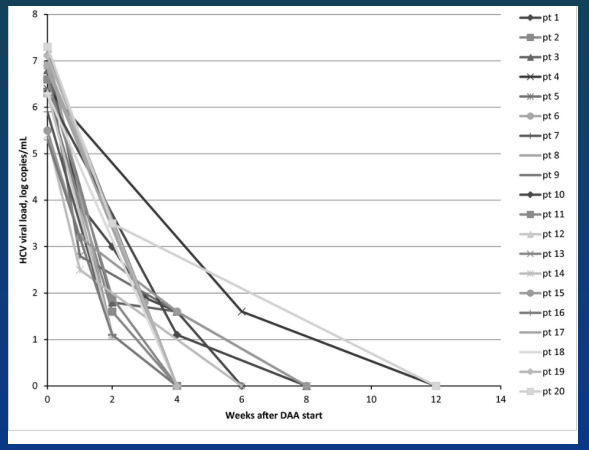
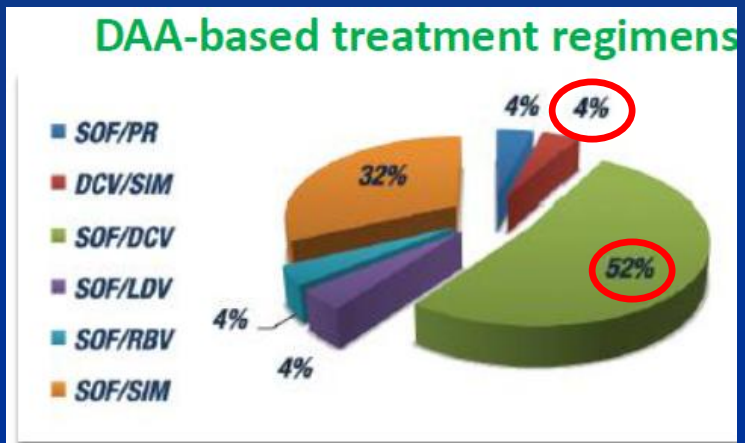
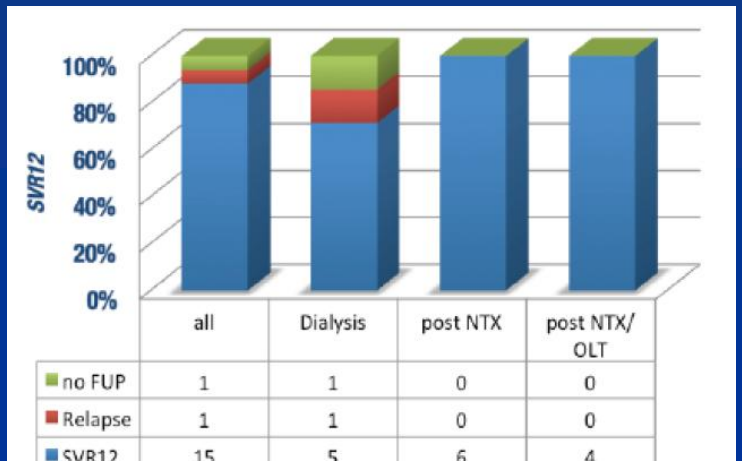


The Austrian Experience



25 Patients



	all	Dialysis	post NTX	post NTX/ OLT
no FUP	1	1	0	0
Relapse	1	1	0	0
SVR12	15	5	6	4

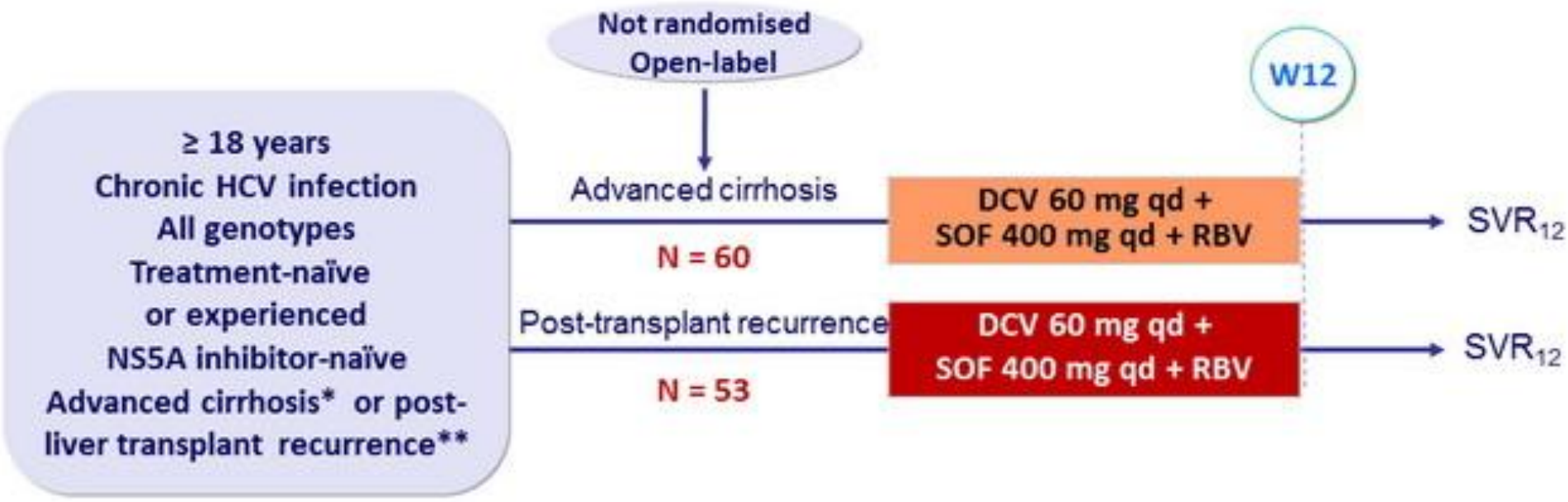
ALLY-1

ALLY-1 Study: DCV + SOF + RBV for advanced liver disease and post-liver transplant recurrence

Daclatasvir, Sofosbuvir, and Ribavirin Combination for HCV Patients with Advanced Cirrhosis or Posttransplant Recurrence: PHASE 3

Poordad F. EASL 2015, Abs. L08

Anti-HCV	Genotype	Cirrhosis	Special population
Daclatasvir	1	Yes	Liver transplantation
Sofosbuvir	1a		
Ribavirin	1b		
	3		



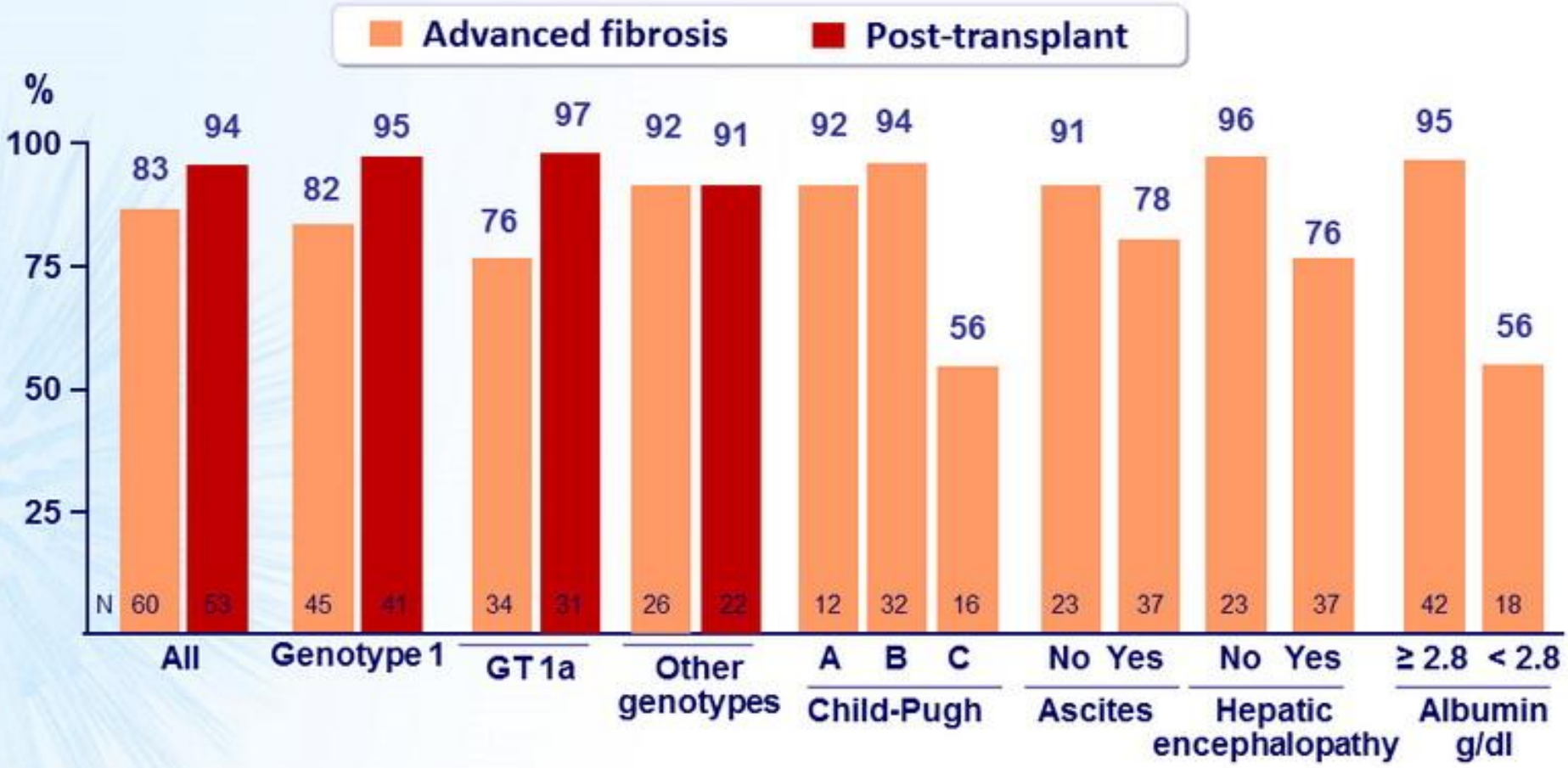
** Child-Pugh A, B or C, MELD score 8-40, hepatocarcinoma allowed*

*** = 3 months post-transplant, no rejection, any immunosuppressive regimen*

RBV : 600 mg/day (bid dosing), adjusted to 1000 mg/day, based on hemoglobin and creatinine clearance

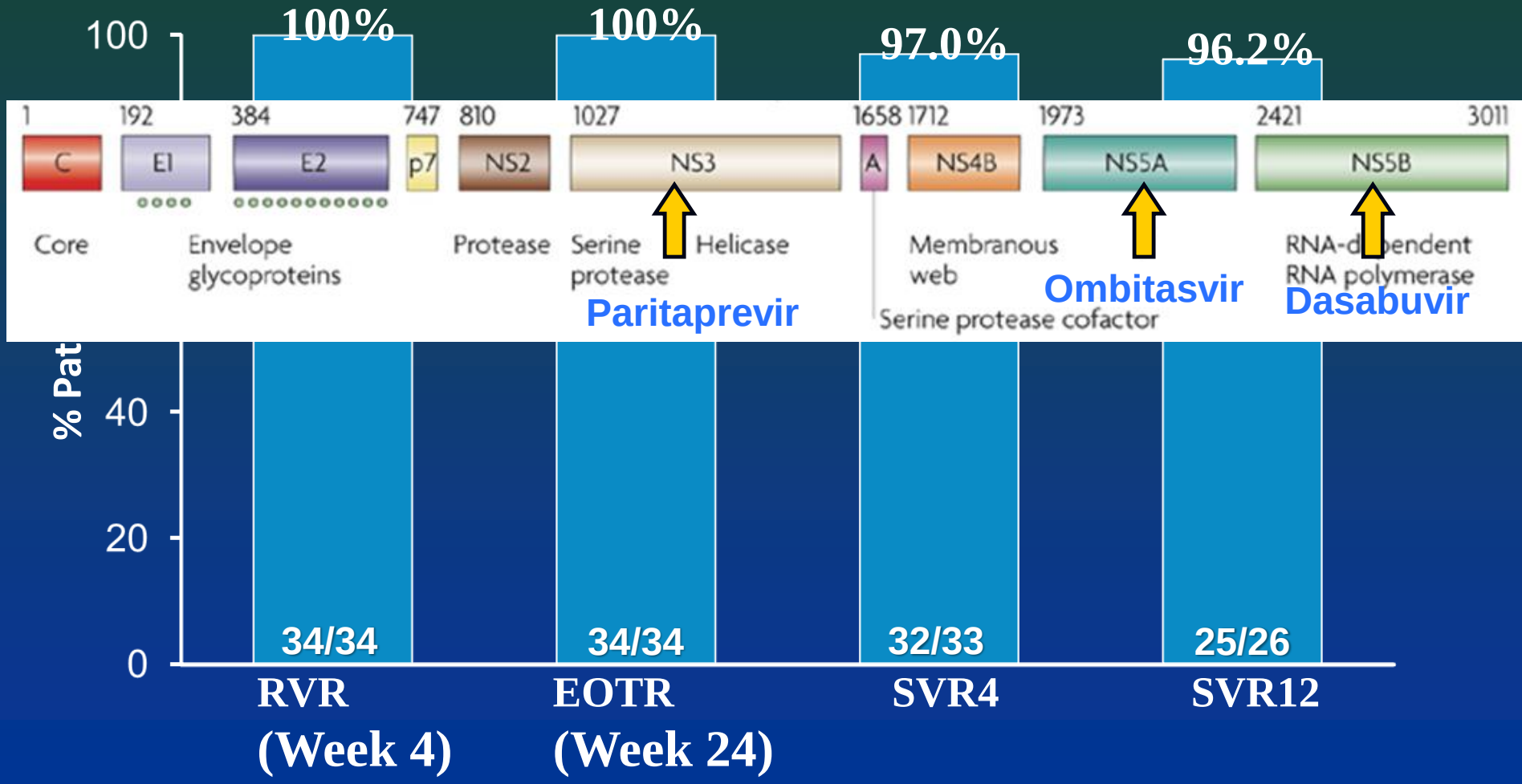
ALLY-1 Study: DCV + SOF + RBV for advanced liver disease and post-liver transplant recurrence

SVR_{12} (HCV RNA < 25 IU/ml)



Poordad F. EASL 2015, Abs. L08

Paritaprevir/Ombitasvir/Dasabuvir/RBV post OLT: Preliminary Efficacy Results



Dose adjustments with tacrolimus and cyclosporin easily addressed

Transplant eGFR>30

Basic Combination	RBV	Duration (weeks)	GT1 data	GT4 data	SVR12
Ledipasvir + Sofosbuvir (**Harvoni**)	No	12 24	Colombo et al.,	Colombo et al.,	100% 98%
Daclatasvir + Sofosbuvir	Yes 600mg	12	ALLY-1	*EASL recommend-ation*	97%
Paritaprevir/ Ritonavir+ Ombitasvir (**Qurevo**)	Yes	12	CORAL-I	PEARL-1 *Extrapolation*	97%

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ORIGINAL ARTICLE

Antiviral treatment prioritization in HCV-infected patients with extrahepatic manifestations – An Egyptian perspective

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EVALUATION & INDICATIONS FOR TREATMENT

Nature and stage of chronic kidney disease

***Compelling Indications*:**

1. **HCV-infected patients who have already received a kidney transplant** [Class I, Level B (AASLD 2015)]

2. **Patients on the waiting list for kidney transplantation**

[Class I, Level B (AASLD 2015)] & [A1 EASL]

➢ *In critical situations where KTx cannot wait, treatment may be postponed to follow the transplant, yet at the expense of increased risk of acute post-transplant complications.*

3. **Mesangiocapillary glomerulonephritis**

[Class IIa, Level B (AASLD 2015)]

4. **Nephrotic syndrome due to any histopathological type of glomerulonephritis** [Class IIa, Level B (AASLD 2015)]

5. **Patients on regular dialysis**

[Class IIa, Level C (AASLD 2015)]

EVALUATION & INDICATIONS FOR TREATMENT

Nature and stage of chronic kidney disease

***Potential Indications*:**

(To be considered on individual case to case basis by a panel of experts; priority to higher severity grades and life threatening co-morbid conditions that are likely to tolerate and benefit from eradication of HCV infection)

1- Patients in CKD stages 3-5 (eGFR < 60 ml/min/1-73sqm), regardless of etiology (not graded)

2- De-novo HCV infection persisting for over 12 weeks in patients with any grade CKD.

[KDIGO 2008 (Weak)]

Scoring of patients with CKD for DAA treatment priority.

Positive points:

Post-renal transplant	5 points
Regular Dialysis	5 points
Cryoglobulinemic vasculitis	5 points
Non-Hodgkin B-cell lymphoma	5 points
Biopsy confirmed MCGN with hypocomplementemia	4 points
Biopsy-confirmed MCGN without hypocomplementemia	3 points
Nephrotic syndrome regardless histological type	2 points
Previous treatment failure	2 points
HBV/HIV/ CMV co-infection	2 points
Stage of kidney disease (MDRD-4)	1 point/stage
Stage of liver disease (Fibroscan)	1 point/stage

Negative points:

Age >70	-1 point/5years
Decompensated cirrhosis	-3 points
Concurrent drug-drug interaction with selected Protocol	-3 points
Concomitant heart disease	-1 point/NYHA score
Concomitant pulmonary disease	-1 point/- 10% FVC1
Concomitant CNS disease	-1 point/10%disability

CONCLUSION

- HCV can now be cured by DAA
- DAA can be used across all genotypes and in all stages of liver and kidney disease
- Where possible, antiviral therapy should be given to potential transplant recipients before listing for renal transplantation.
- Paritaprevir/r/Ombitasvir (Qurevo) & *Grazoprevir/Elbasvir* (Zepatier) are best options for Dx patients, other options include

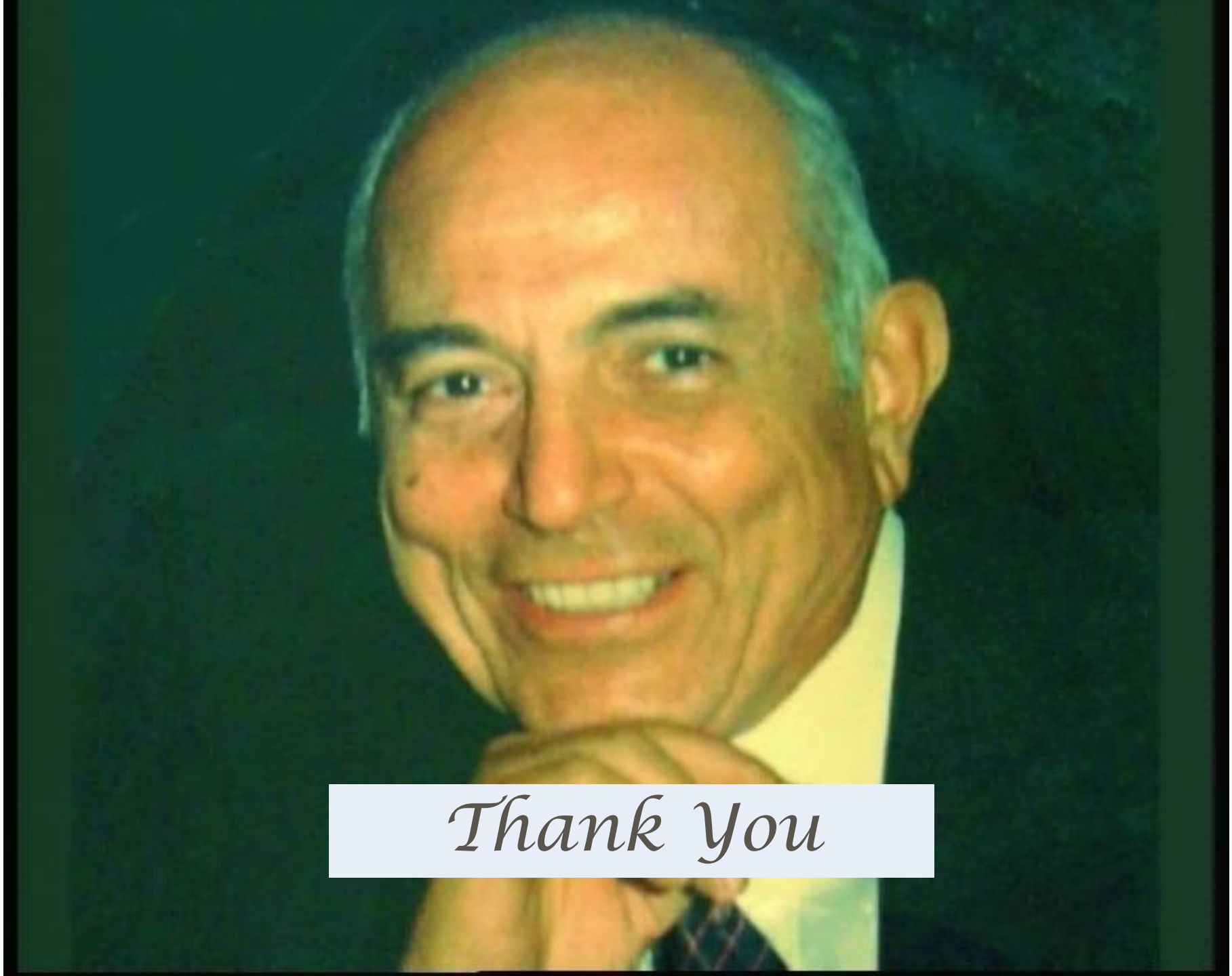
  Sofosbuvir /simeprevir

  Sofosbuvir/daclatasvir

  Sofosbuvir/ RBV

CONCLUSION

- Treatment options in kidney transplant patients include
- *Sofosbuvir / Ladipasvir (Harvoni)*
- *Sofosbuvir/ Daclatasvir*
- *Paritaprevir/Ombitasvir//RBV (Qurevo)*
- *Sofosbuvir /simeprevir*
- *Sofosbuvir/ RBV*
- Interferon should be completely avoided in kidney transplant recipients


Thank You