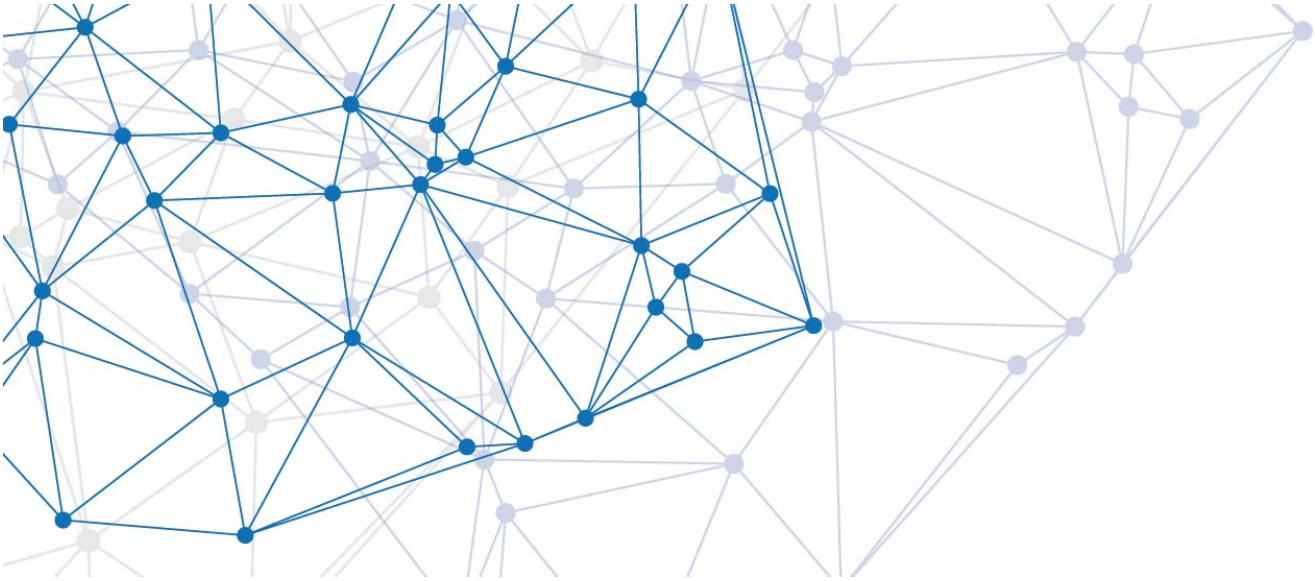

C 型肝炎治療的臨床實務

Chen-Hua Liu, MD, PhD/ 劉振驊 醫師

Hepatitis Research Center, and Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

1. **Global & Taiwan HCV epidemiology, natural history**
2. **Introduction: direct acting antivirals (DAAs)**
3. **Summary of currently reimbursed DAAs in Taiwan**
   - **Daclatasvir/asunaprevir**
   - **Paritaprevir/ombitasvir/dasabuvir ± ribavirin**
   - **Elbasvir/grazoprevir ± ribavirin**
   - **Sofosbuvir + ribavirin**
   - **Sofosbuvir/ledipasvir ± ribavirin**
   - **Glecaprevir/pibrentasvir**
4. **Special Population**
   - **Organ transplantation**
   - **HIV coinfection**
   - **HBV coinfection**
   - **Chronic kidney disease (CKD)**
   - **Adolescents and Children**
   - **Inherited blood disorders**
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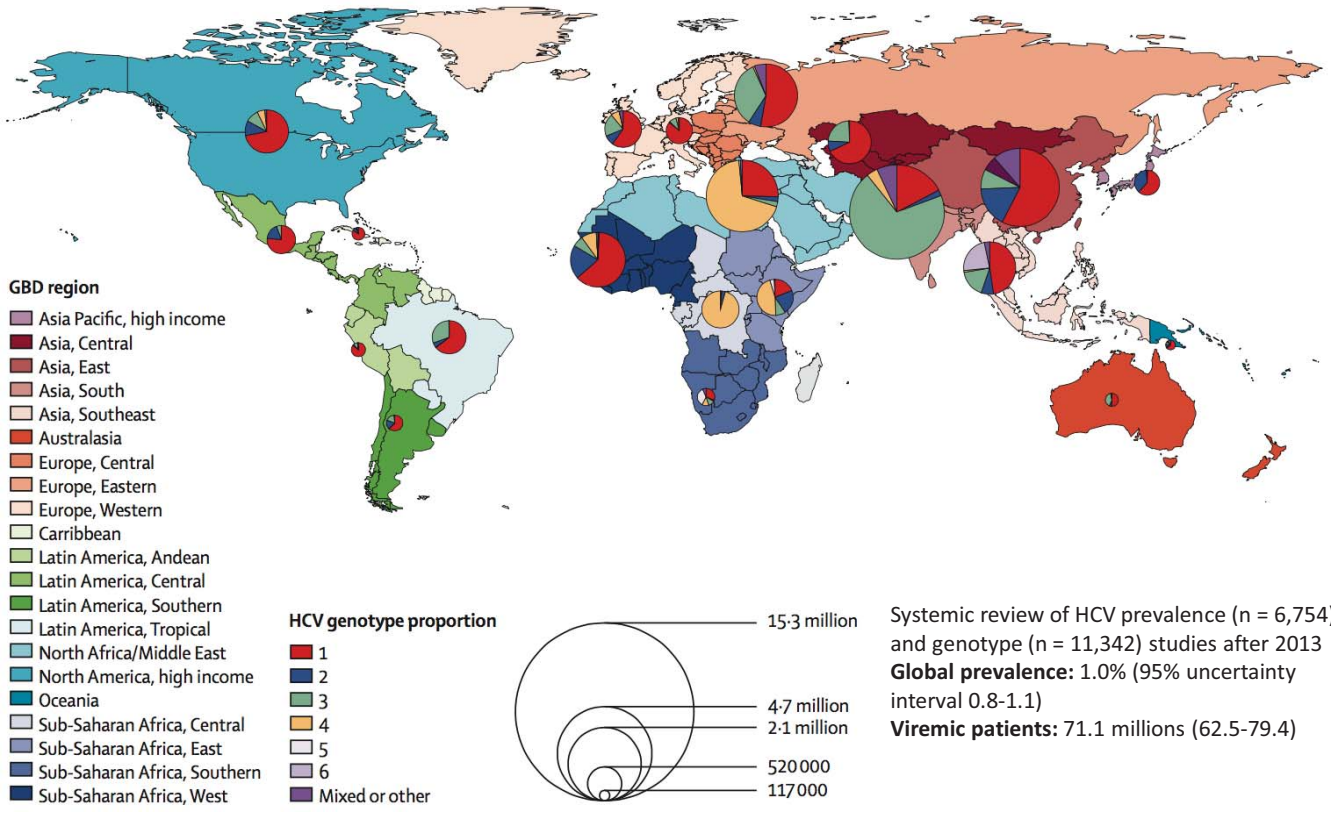
Global Prevalence and Genotype Distribution of HCV in 2015



Systemic review of HCV prevalence (n = 6,754) and genotype (n = 11,342) studies after 2013
Global prevalence: 1.0% (95% uncertainty interval 0.8-1.1)
Viremic patients: 71.1 millions (62.5-79.4)

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-76

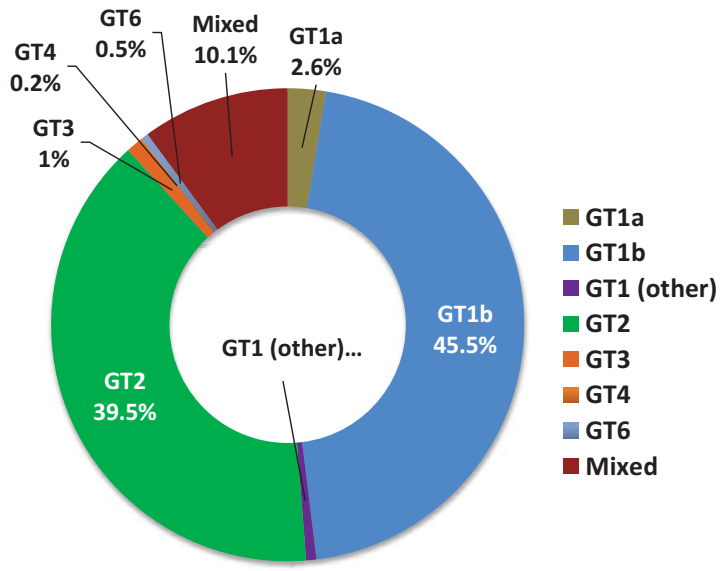
HCV Prevalence and Genotypes Distribution in Taiwan: Global Survey Polaris 2015

Viremic Prevalence
2.1% (1.3-3.7)

Viremic Population
489K (310-877)

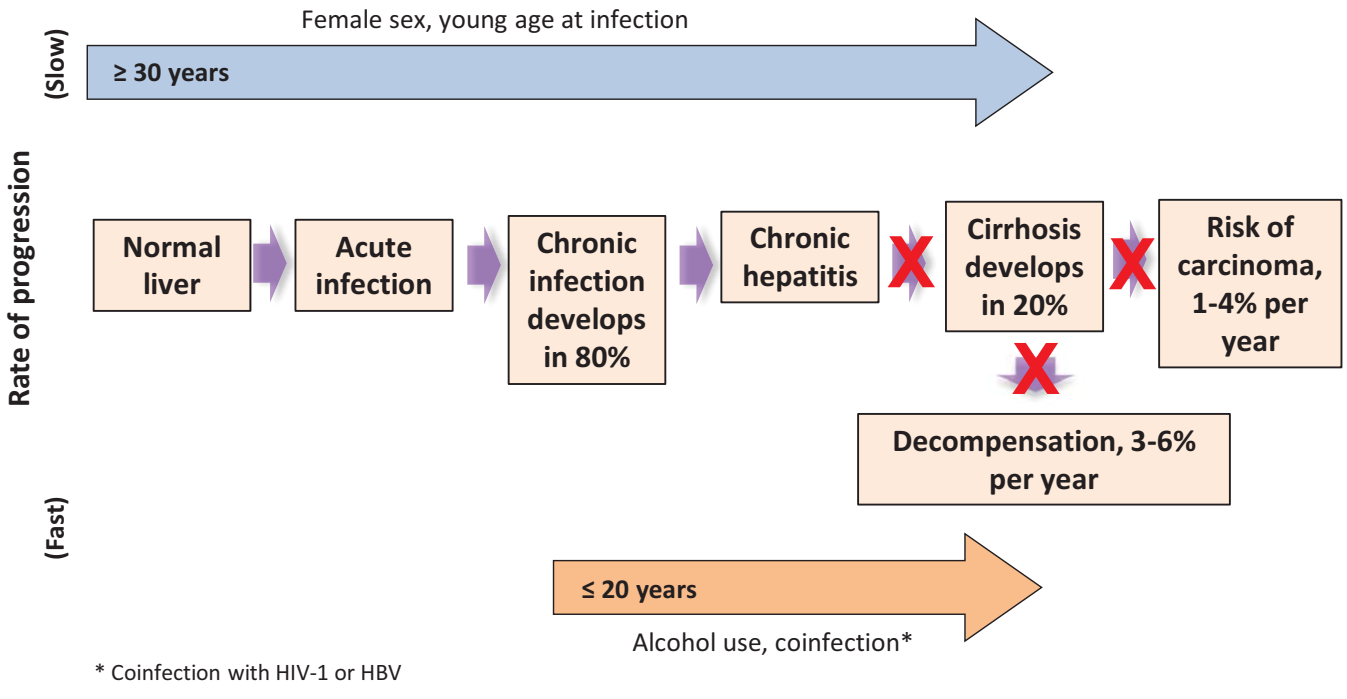
Dominant GT in Taiwan: GT1b & GT2

- Mixed types: 10.1%
- GT6 is increasing due to increasing immigrants



Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-76

Disease Progression in HCV



* Coinfection with HIV-1 or HBV

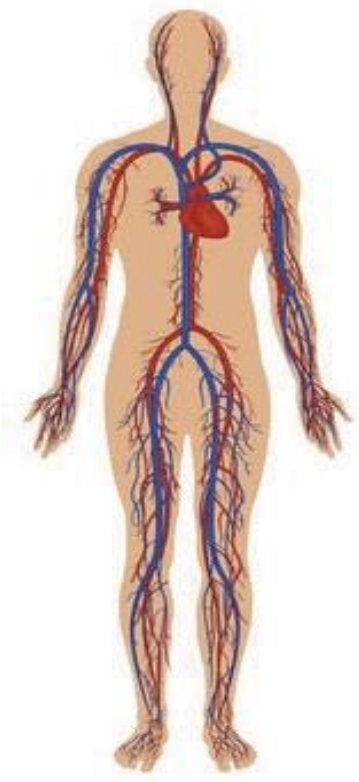
Lauer GM, et al. N Engl J Med 2001;345:41-52

Extrahepatic Manifestation of HCV Infection

CNS disorders
Chronic fatigue, subclinical cognitive impairment, psychomotoric deceleration , symptoms of depression, neurocognitive disorders, peripheral neuropathy, Parkinson's disease

Cardiovascular diseases
Cardiomyopathy, myositis

Rheumatologic disorders
Mixed cryoglobulinemia, , cryoglobulinemic vasculitis, rheumatoid arthritis, oligopolyarthritis, rheumatoid factor positivity, Sicca syndrome, uveitis



Endocrine disorders
Autoimmune thyroidopathies, CREST syndrome, insulin resistance, diabetes mellitus, growth hormone and vitamin D insufficiencies

Renal disorders
Glomerulonephritis, nephrotic syndrome

Hematologic disorders
Lymphoproliferative disorders, non-Hodgkin's lymphoma, immune thrombocytopenic purpura, monoclonal gammopathies, autoimmune hemolytic anemia, aplastic anemia

Dermatologic disorders
Palpable purpura, porphyria cutanea tarda, lichen planus, pruritus, cutaneous necrotizing vasculitis

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Therapeutic Targets for HCV (Licensed and Investigational)

NA3/4A Protease inhibitors

Telaprevir (Incivek)
Boceprevir (Victrelis)
RG7227 (Danoprevir)
TMC435 (Simeprevir)
MK-7009 (Vaniprevir)
MK-5172 (Grazoprevir)
BI201335 (Faldaprevir)
BMS-650032 (Asunaprevir)
ABT-450/r (Paritaprevir)
ABT-493 (Glecaprevir)
GS-9857 (Voxilaprevir)

NS4B inhibitors

Clemizole

NS5A inhibitors

BMS790052 (Daclatasvir)
GS-5885 (Ledipasvir)
ABT-267 (Ombitasvir)
MK-8742 (Elbasvir)
GS-5816 (Velpatasvir)
ABT-530 (Pibrentasvir)
MK-8408 (Ruzasvir)
PPI461
PPI668

NS5B Polymerase inhibitors

Active site (nucleosides)	RG-7128 (Mericitabine) GS-7977 (Sofosbuvir) MK-3682 IDX184	
Non-nucleosides	GS-9190 (Tegobuvir) BI207127 (Deleobuvir) TMC647055 Filibuvir (PF-00868554) VX-222 GS-9669 BMS791325 (Beclabuvir) ANA598 (Setrobuvir) ABT-072 ABT-333 (Dasabuvir)	NNI-site 1 NNI-site 1 NNI-site 1 NNI-site 2 NNI-site 2 NNI-site 2 NNI-site 1 & 2 NNI-site 3 NNI-site 3 NNI-site 4

Host-targeted Antivirals

Debio025 (Alisporivir)
SCY-635
Miravirsen (SPC3649)
ITX-5061
ANA773 (TLR-7)

Classes of HCV Direct Acting Antiviral Agents

HCV DAA class	Nomination	Drugs of class
NS3/4A protease inhibitor (PI)	**PREVIR**	asunaprevir, paritaprevir, grazoprevir, voxilaprevir, glecaprevir
NS5A inhibitor	**ASVIR**	daclatasvir, ombitasvir, elbasvir, ledipasvir, velpatasvir, pibrentasvir
NS5B polymerase inhibitor	**BUVIR**	sofosbuvir (NUC), dasabuvir (non-NUC)

Cocktail combination therapy is required and mandatory !

McCauley JA, et al. Curr Opin Pharmacol 2016;30:84-92
Eltahla AA, et al. Viruses 2015;7:5206-24
Gitto S, et al. J Viral Hepat 2017;24:180-6

Currently Available IFN-free DAA Regimens

Characteristics	DCV/ASV	PrOD	EBR/GZR	SOF-Based					GLE/PIB
				SOF/RBV	LDV/SOF	DCV/SOF	VEL/SOF	VOX/VEL /SOF	
DAA class	NS3 NS5A	NS3 NS5A NS5B non-NUC	NS3 NS5A	NS5B NUC	NS5A NS5B NUC	NS5A NS5B NUC	NS5A NS5B NUC	NS3 NS5A NS5B NUC	NS3 NS5A
Genotype coverage	1b	1, 4	1, 4	2, 3	1, 4, 5, 6	1-6	1-6	1-6	1-6
Treatment duration (wk)	24	12-24	12-16	12-16	12-24	12-24	12-24	8-12	8-16
Daily pills	3	4	1	1	1	2	1	1	3
Ribavirin	-	1a	1a (RAS) 1a/1b (PI failure) 4 (prior on-Tx failure)	+	1 (TE, cirrhosis) 1/4 (Child B/C, post-LTx)	3 (cirrhosis) Post-LTx	Child B/C	-	-
NS5A RAS test	+ (1b)	-	+ (1a)	-	-	-	-	-	-
FDA/EMA approval	-	+	+	+	+	+	+	+	+
Available in Taiwan	+	+	+	+	+	+	-	-	+

DAA: direct acting antiviral agent, DCV: daclatasvir, ASV: asunaprevir, PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir, EBR: elbasvir, GZR: grazoprevir, SOF: sofosbuvir, RBV: ribavirin, LDV: ledipasvir, VEL: velpatasvir, VOX: voxilaprevir, GLE: glecaprevir, PIB: pibrentasvir, NS: non-structural, NUC: nucleoside analogue, wk: week, RAS: resistance associated substitution, CKD: chronic kidney disease, DDI: drug-drug interaction

Currently Reimbursed IFN-free DAA Regimens

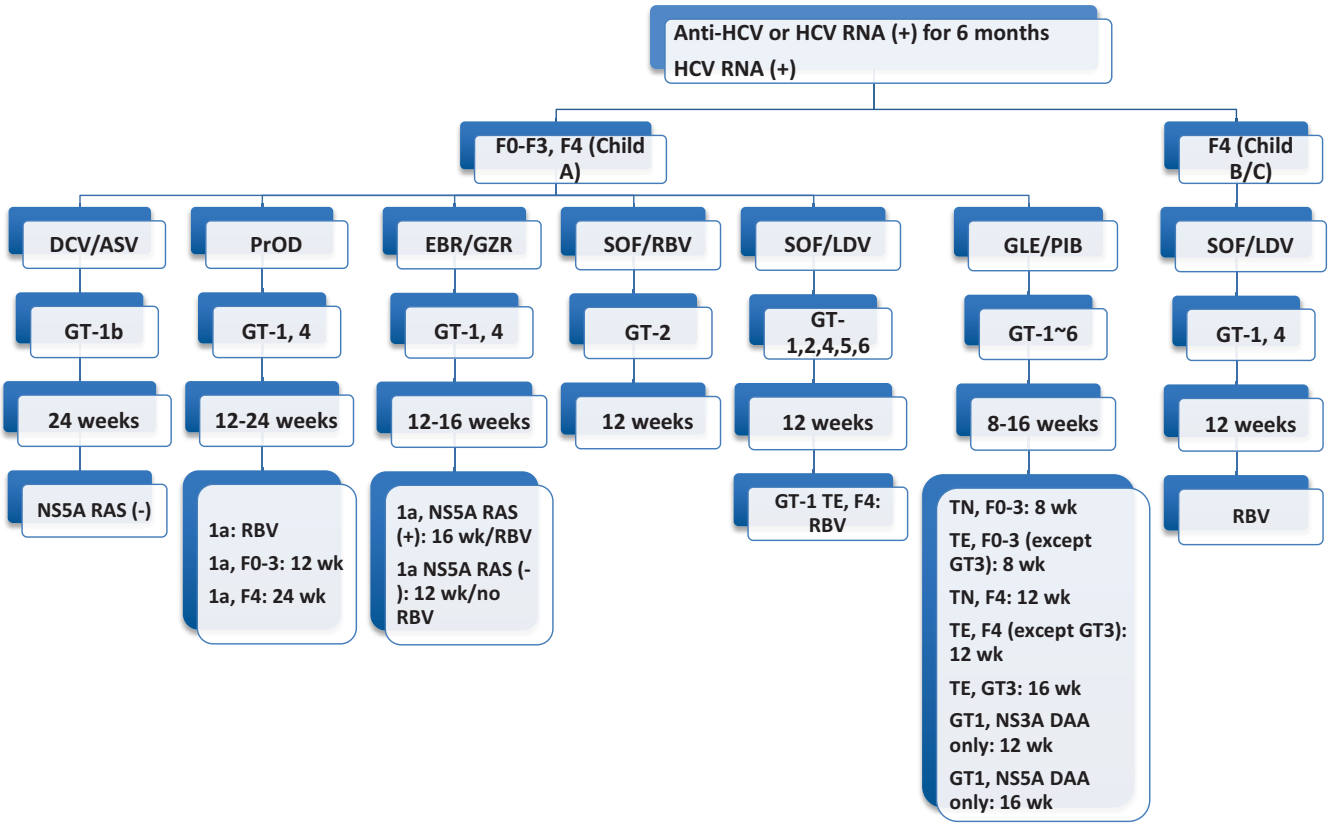
Characteristics	DCV/ASV	PrOD	EBR/GZR	SOF-Based		GLE/PIB
				SOF/RBV	LDV/SOF	
DAA class	NS3 NS5A	NS3 NS5A NS5B non-NUC	NS3 NS5A	NS5B NUC	NS5A NS5B NUC	NS3 NS5A
Genotype coverage	1b	1, 4	1, 4	2, 3	1, 4, 5, 6	1-6
Treatment duration (wk)	24	12-24	12-16	12-16	12-24	8-16
Daily pills	3	4	1	1	1	3
Ribavirin	-	1a	1a (RAS) 1a/1b (PI failure) 4 (prior on-Tx failure)	+	1 (TE, cirrhosis) 1/4 (Child B/C, post-LTx)	-
NS5A RAS test	+ (1b)	-	+ (1a)	-	-	-
FDA/EMA approval	-	+	+	+	+	+
Available in Taiwan	+	+	+	+	+	+

DAA: direct acting antiviral agent, DCV: daclatasvir, ASV: asunaprevir, PrOD: paritaprevir/ritonavir/ombitasvir/dasabuvir, EBR: elbasvir, GZR: grazoprevir, SOF: sofosbuvir, RBV: ribavirin, LDV: ledipasvir, VEL: velpatasvir, VOX: voxilaprevir, GLE: glecaprevir, PIB: pibrentasvir, NS: non-structural, NUC: nucleoside analogue, wk: week, RAS: resistance associated substitution, CKD: chronic kidney disease, DDI: drug-drug interaction

Spectrum of Genotype/Subtype Coverage for Various Reimbursed IFN-free DAAs (Taiwan)

DAA regimen	HCV Genotype Coverage						
Daclatasvir Asunaprevir	1a	1b	2	3	4	5	6
Paritaprevir/ritonavir Ombitasvir Dasabuvir	1a	1b	2	3	4	5	6
Grazoprevir Elbasvir	1a	1b	2	3	4	5	6
Sofosbuvir Ribavirin	1a	1b	2	3	4	5	6
Sofosbuvir Ledipasvir	1a	1b	2	3	4	5	6
Glecaprevir Pibrentasvir	1a	1b	2	3	4	5	6

慢性C肝患者符合健保給付條件 (2019)



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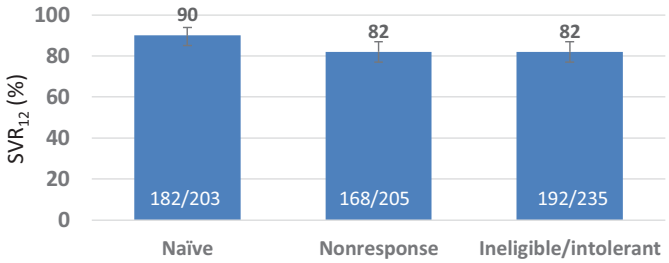
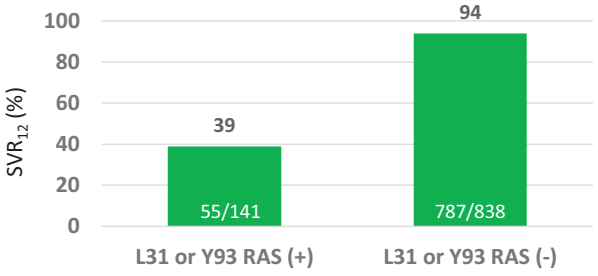
Daclatasvir/Asunaprevir for HCV-1b Patients (with/without NS5A RASs)

HALLMARK-DUAL

- Phase 3 study
- HCV-1b patients (treatment-naïve, prior non-responders, relapsers)
- Treatment: daclatasvir/asunaprevir (DCV/ASV) for 24 weeks
- Fibrosis: F0-4, Child A cirrhosis

HALLMARK-DUAL
Treatment-naïve/experienced
Non-cirrhotic/cirrhotic





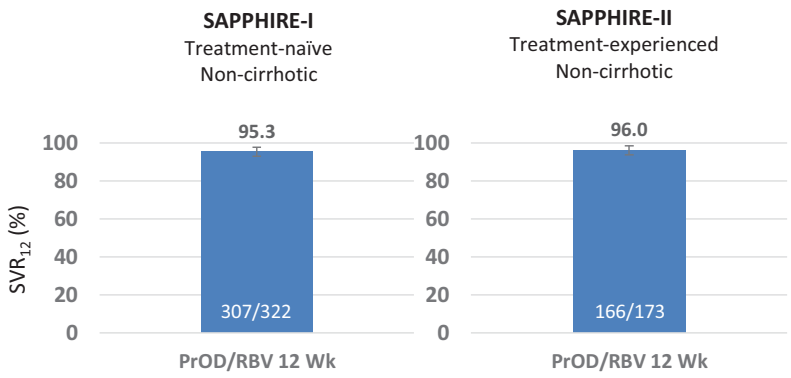
* NS5A RAS evaluated by population sequencing with a cutoff value of 15-20%

Manns M, et al. Lancet 2014;384:1597-605
McPhee F, et al. Adv Ther 2015;32:637-49

Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir + RBV for HCV-1a Patients

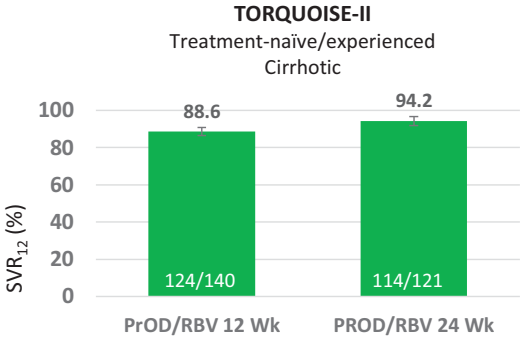
SAPPHIRE-I & II

- Phase 3 study
- HCV-1a patients (treatment-naïve or experienced)
- Treatment: PrOD + RBV for 12 weeks
- Fibrosis: F0-3



TURQUOISE-II

- Phase 3 study
- HCV-1 patients (treatment-naïve and experienced)
- Treatment: PrOD + RBV for 12 or 24 weeks
- Fibrosis: F4, Child A

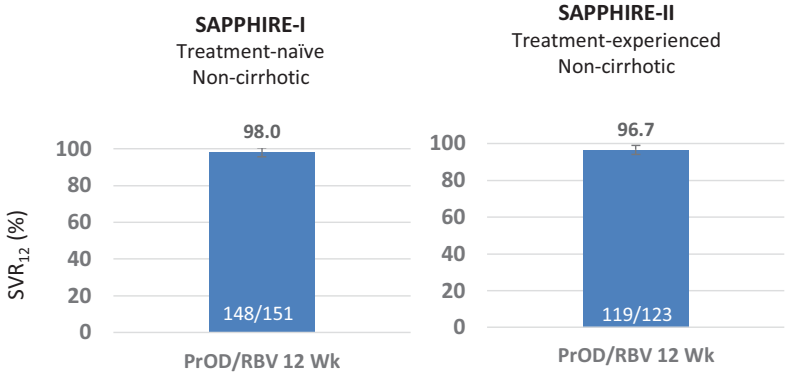


Poordad F, et al. N Engl J Med 2014;370:1973-82
Feld J, et al. N Engl J Med, 2014;370:1594-603
Zeuzem S, et al. N Engl J Med, 2014;370:1604-14

Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir ± RBV for HCV-1b Non-Cirrhotic Patients

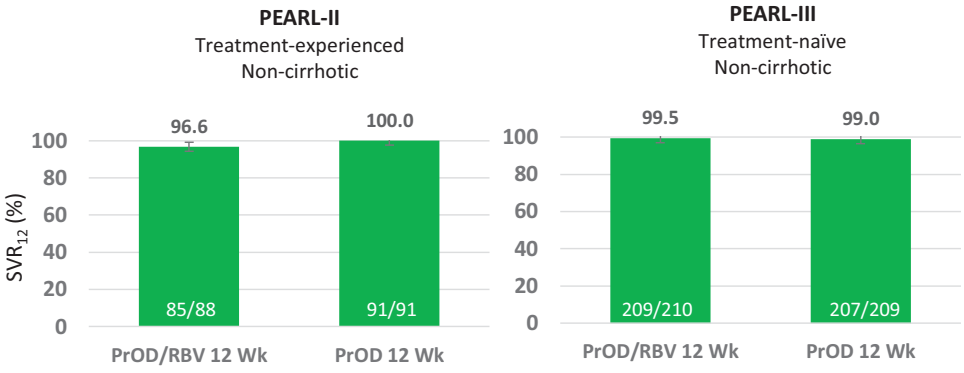
SAPPHIRE-I & II

- Phase 3 study
- HCV-1b patients (treatment-naïve or experienced)
- Treatment: PrOD + RBV for 12 weeks
- Fibrosis: F0-3



PEARL-II & III

- Phase 3 study
- HCV-1b patients (treatment-naïve or experienced)
- Treatment: PrOD ± RBV for 12 weeks
- Fibrosis: F0-3

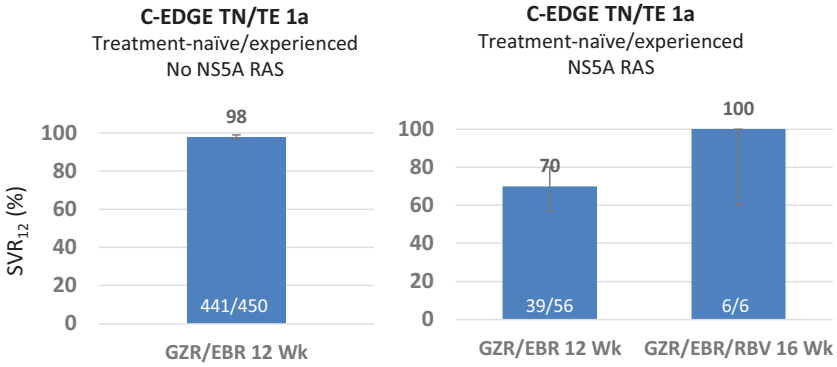


Feld J, et al. N Engl J Med, 2014;370:1594-603
Zeuzem S, et al. N Engl J Med, 2014;370:1604-14
Ferenci P, et al. N Engl J Med 2014;370:1983-92
Andreone P, et al. Gastroenterology 2014;147:359-65

Grazoprevir/Elbasvir ± Ribavirin for HCV-1 Patients (with/without NS5A RASs)

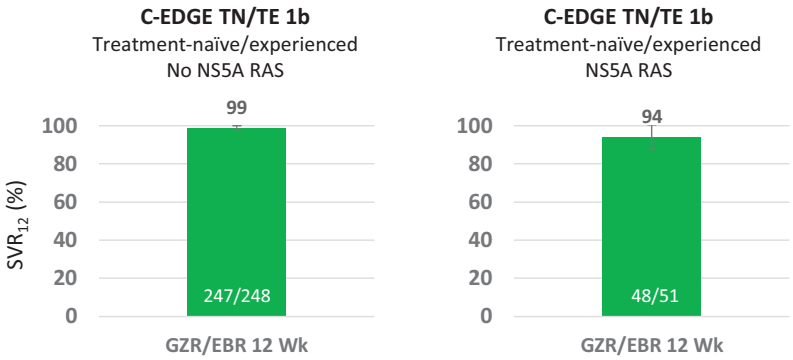
C-EDGE TN/TE-1a

- Phase 3 study
- HCV-1a patients (treatment-naïve and experienced)
- Treatment: GZR/EBR ± RBV for 12 or 16 weeks
- Fibrosis: F0-F4, Child A



C-EDGE TN/TE-1b

- Phase 3 study
- HCV-1b patients (treatment-naïve and experienced)
- Treatment: GZR/EBR ± RBV for 12 weeks
- Fibrosis: F0-F4, Child A



Zeuzem S, et al. Ann Intern Med 2015;163:1-13

Kwo P, et al. Gastroenterology 2017;152-164-75

Sofosbuvir/Ribavirin for HCV-2 Patients

Lawitz E, et al. N Engl J Med 2013;368:1878-87

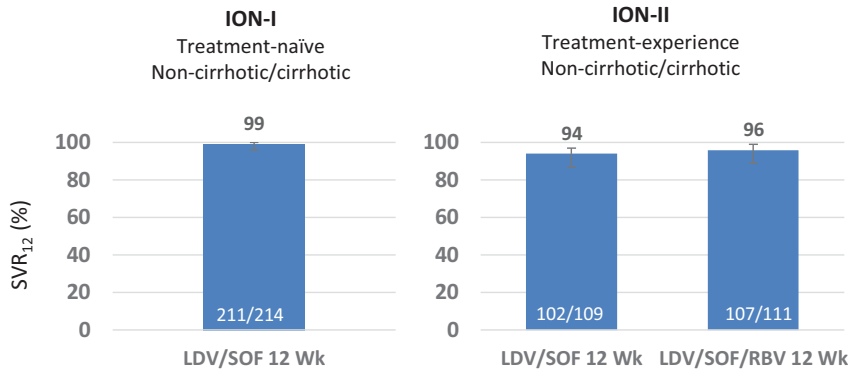
Jacobson IM, et al. N Engl J Med 2013;368:1867-77

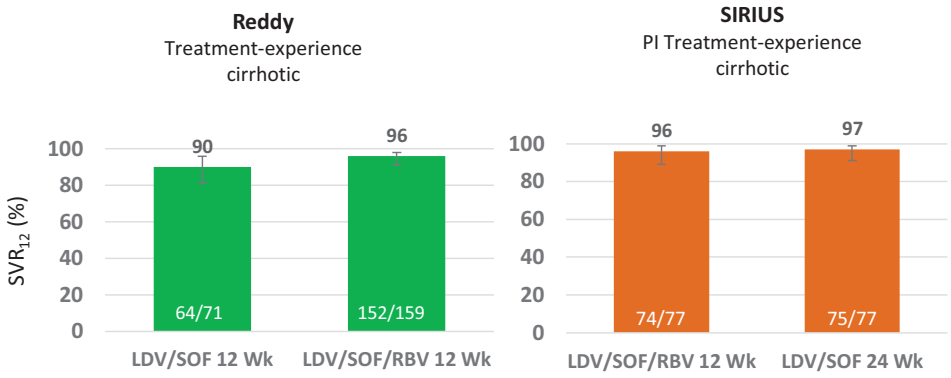
Zeuzem S, et al. N Engl J Med 2014;370:1993-2001

Ledipasvir/Sofosbuvir ± RBV for HCV-1 Patients

ION I & II

- Phase 3 study
- HCV-1 patients (treatment-naïve or experienced)
- Treatment: ledipasvir/sofosbuvir ± RBV for 12-24 weeks
- Fibrosis: F0-4, Child A cirrhosis





Afdhal N, et al. N Engl J Med 2014;370:1889-98

Afdhal N, et al. N Engl J Med 2014;370:1483-93

Reddy KR, et al. Hepatology 2015;62:79-86

Bourlière M, et al. Lancet Infect Dis 2015;15:397-404

Ledipasvir/Sofosbuvir for HCV-2 Patients

LEPTON

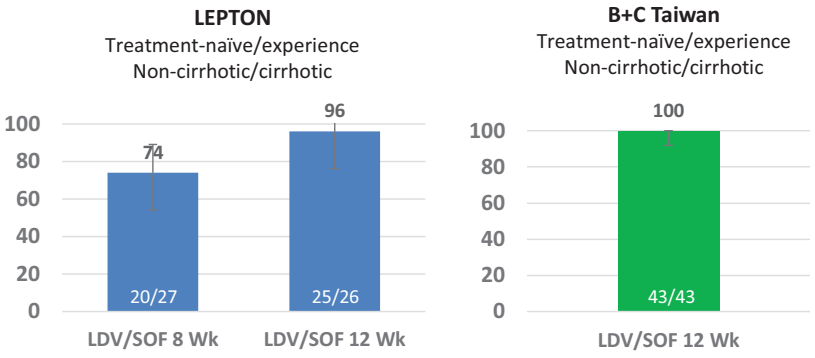
- Phase 2 study
- HCV-2 patients (TN/TE)
- Treatment: ledipasvir/sofosbuvir for 8 or 12 weeks
- Fibrosis: F0-4, Child A cirrhosis

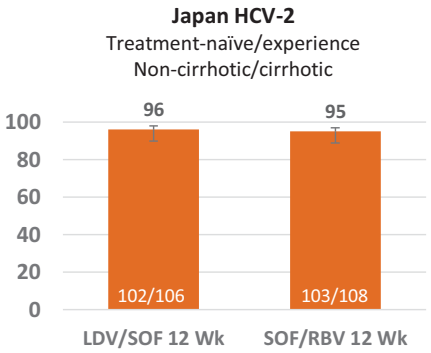
B+C Taiwan

- Phase 3 study
- HCV-2 patients (TN/TE)
- Treatment: ledipasvir/sofosbuvir for 12 weeks
- Fibrosis: F0-4, Child A cirrhosis

Japan HCV-2

- Phase 3 study
- HCV-2 patients (TN/TE)
- Treatment: ledipasvir/sofosbuvir or sofosbuvir/ribavirin for 12 weeks
- Fibrosis: F0-4, Child A cirrhosis





Gane EJ, et al. Gastroenterology 2017;152:1366-71

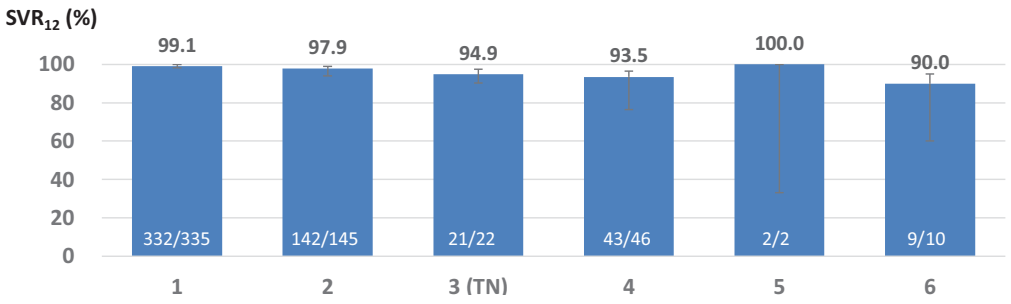
Liu CJ, et al. Gastroenterology 2018;154:989-97

Asahina Y, et al. Liver Int 2018;38:1552-61

Glecaprevir/Pibrentasvir for HCV-1 to 6

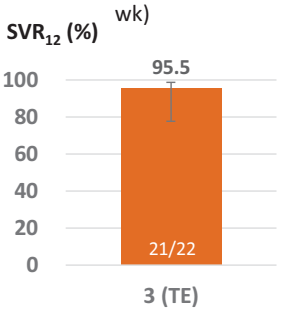
ENDURANCE-1, 3; SURVEOR-II [Part 4]

No LC; HCV-1, 2, 4, 5, 6 (TN/TE) and HCV-3 (TN) (G/P 8 wk)



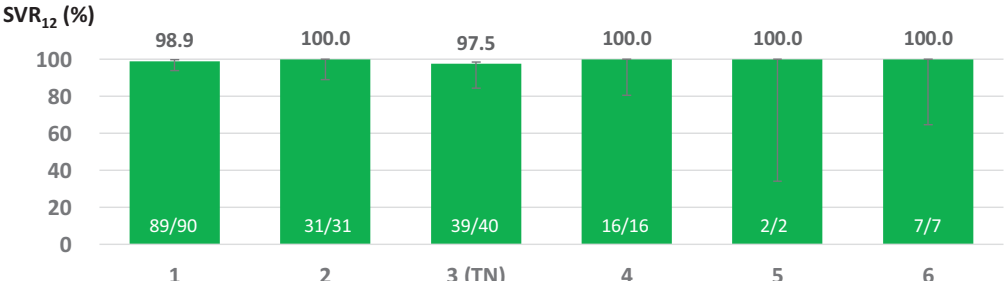
SURVEOR-II [Part 3]

No LC; HCV-3 (TE) (G/P 16 wk)



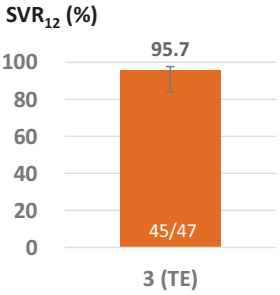
EXPEDITION-1; SURVEOR-II [Part 4]

LC; HCV-1, 2, 4, 5, 6 (TN/TE) and HCV-3 (TN) (G/P 12 wk)



SURVEOR-II [Part 3]

LC; HCV-3 (TE) (G/P 16 wk)



Zeuzem S, et al. New Engl J Med 2018;378:354-69

Asselah T, et al. Clin Gastroenterol Hepatol 2018;16:417-26

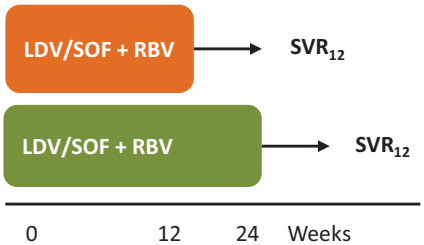
Wyles D, et al. Hepatology 2018;67:514-23

Ledipasvir/Sofosbuvir with Ribavirin for HCV-1/4 Patients with Advanced Liver Disease: SOLAR-1 & 2

- **Design:** phase 2b, open-label study in 29 sites in US (SOLAR-1) and in EU (SOLAR-2)
- **Intervention:** LDV/SOF + RBV for 12 or 24 weeks for HCV-1/4 patients with decompensated cirrhosis (pre-transplantation) and various stage of hepatic fibrosis, including compensated/decompensated cirrhosis (post-transplant)

Pre-transplant	**CPT B (7-9)** **CPT C (10-12)**
Post-transplant	**Fibrosis (F0-F3)** **CPT A (5-6)** **CPT B (7-9)** **CPT C (10-12)** **FCH ***

* No FCH enrolled in SOLAR-2

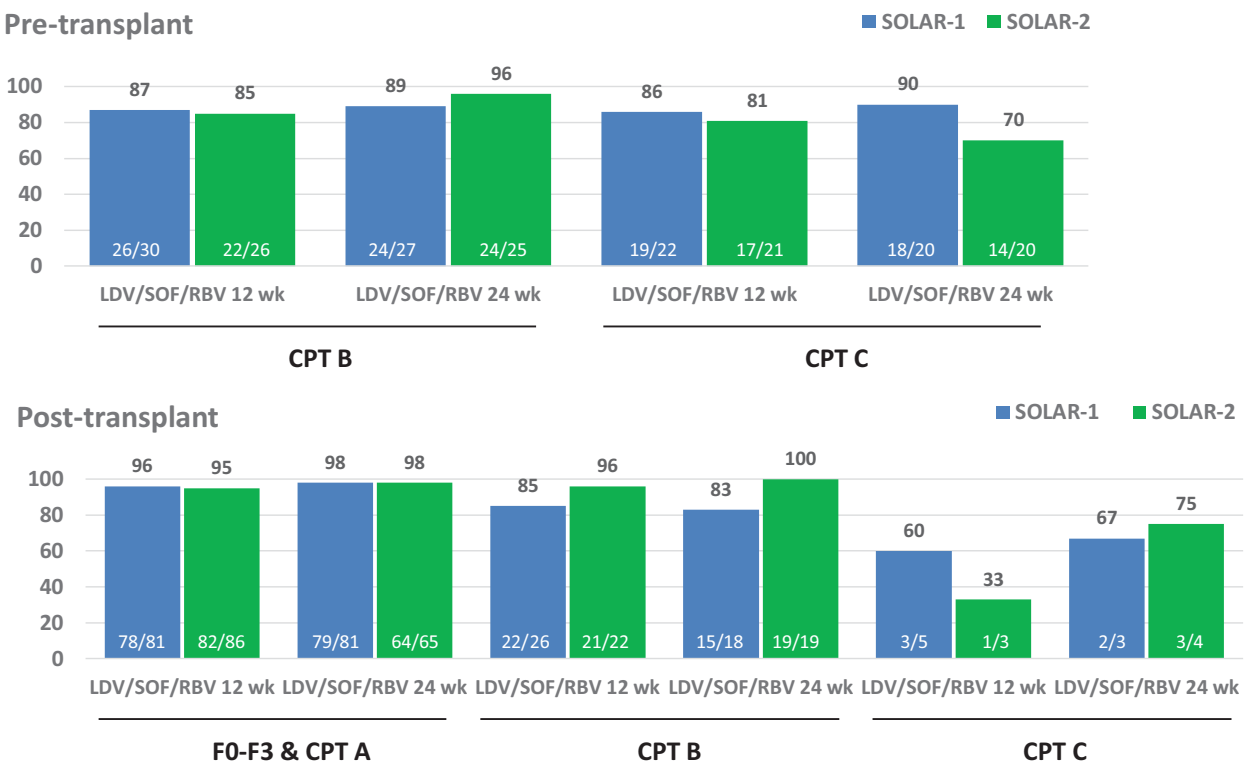


- **Broad inclusion criteria:**
  - No hepatocellular carcinoma (HCC)
  - Total bilirubin ≤ 10 mg/dL (except FCH), haemoglobin ≥ 10 g/dL, AST/ALT < 10X ULN
  - Creatinine < 2.5 X ULN (CrCl > 40 ml/min), platelets > 30,000/mL, CPT ≤ 12
- **RBV dosing**
  - F0–F3 and CTP A cirrhosis: weight-based (< 75 kg , 1000 mg; ≥ 75 kg, 1200 mg)
  - CTP B and C cirrhosis: dose escalation, 600–1200 mg/d (initial 600 mg/day, subsequent dose escalation)

Charlton M, et al. Gastroenterology 2015;149:649-59

Manns M, et al. Lancet Infect Dis 2016;16:685-97

Ledipasvir/Sofosbuvir with Ribavirin for HCV-1/4 Patients with Advanced Liver Disease: SOLAR-1 & 2



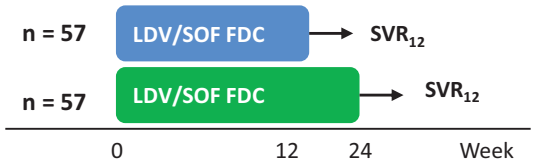
Charlton M, et al. Gastroenterology 2015;149:649-59

Manns M, et al. Lancet Infect Dis 2016;16:685-97

1. **Global & Taiwan HCV epidemiology, natural history**
2. **Introduction: direct acting antivirals (DAAs)**
3. **Summary of currently reimbursed DAAs in Taiwan**
   - **Daclatasvir/asunaprevir**
   - **Paritaprevir/ombitasvir/dasabuvir ± ribavirin**
   - **Elbasvir/grazoprevir ± ribavirin**
   - **Sofosbuvir + ribavirin**
   - **Sofosbuvir/ledipasvir ± ribavirin**
   - **Glecaprevir/pibrentasvir**
4. **Special Population**
   - **Organ transplantation**
   - **HIV coinfection**
   - **HBV coinfection**
   - **Chronic kidney disease (CKD)**
   - **Adolescents and Children**
   - **Inherited blood disorders**
5. **Drug drug interaction (DDI)**
6. **Perspectives**

Ledipasvir/Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients with HCV Genotype 1 or 4 Infection

- **Objective:** HCV is associated with poor outcomes in KT recipients, and effective and safe IFN-free treatment options are needed in these patients
- **Design:** phase 2, randomized, open-label, multicenter study at 5 sites in Italy, Austria and Germany
- **Patients:** KT recipients with HCV GT 1 or 4 infection, TN or TE, with/without cirrhosis [liver biopsy F4 or Ishak ≥ 5, Fibroscan > 12.5 kPa or Fibrotest > 0.75 + APRI > 2]



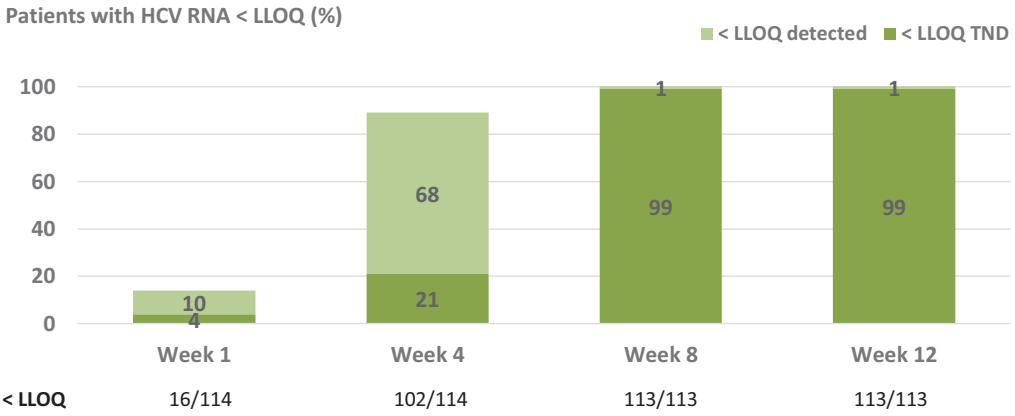
Key inclusion criteria
- > 6 months from kidney transplant
- HCV RNA ≥ LLOQ (15 IU/mL) at screening
- Hb > 10 g/dL, PLT > 50K/µL, Ccr ≥ 40 mL/min

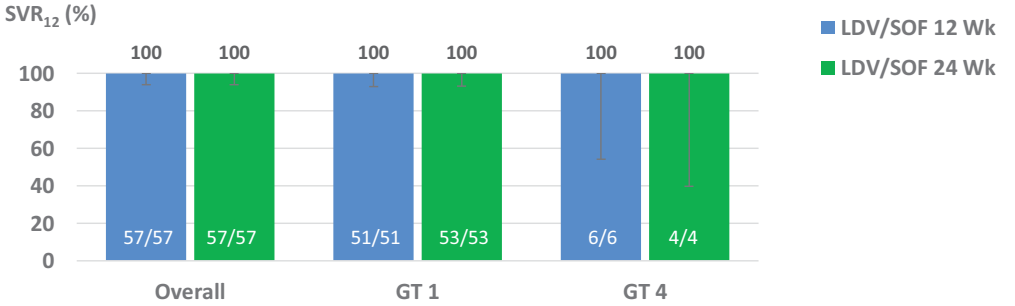
	12 wk (n = 57)	24 wk (n = 57)
Age, yr, median (range)	53 (31-72)	53 (25-75)
Male, n (%)	33 (58)	33 (58)
White, n (%)	54 (95)	53 (93)
BMI, kg/m², median (range)	23 (18-43)	24)20-39)
IL28B CC, n (%)	14 (25)	18 (32)
GT 1, no confirmed subtype, n (%)	2 (4)	0 (0)
GT 1a/1b, n (%)	7/42 (12/74)	10/43 (18/75)
GT4, n (%)	6 (11)	4 (7)
Prior HCV Tx, n (%)	17 (30)	18 (32)
HCV RNA, log_{10} IU/mL, median (range)	6.4 (4.5-7.6)	6.2 (4.7-7.0)
Cirrhosis, n (%)	8 (14)	9 (16)

	12 wk (n = 57)	24 wk (n = 57)
eGFR, mL/min, median (range)	50 (37-135)	60 (35-130)
Creatinine, mg/dL, median (range)	1.3 (0.5-2.7)	1.3 (0.8-2.4)
From transplant, y, median (range)	10 (0.5-40)	12 (0.8-42)
Immunosuppressant, n (%)		
Corticosteroid	39 (68)	42 (74)
Tacrolimus	25 (44)	30 (53)
Mycophenolate	38 (67)	31 (54)
Cyclosporine	23 (40)	21 (37)
Azathioprine	6 (11)	8 (14)
Number of immunosuppressant, n (%)		
1	6 (11)	5 (9)
2	23 (40)	22 (39)
≥ 3	28 (49)	28 (49)

Colombo M, et al. Ann Intern Med 2017;166:109-17

Ledipasvir/Sofosbuvir for 12 or 24 Weeks in Kidney Transplant Recipients with HCV Genotype 1 or 4 Infection



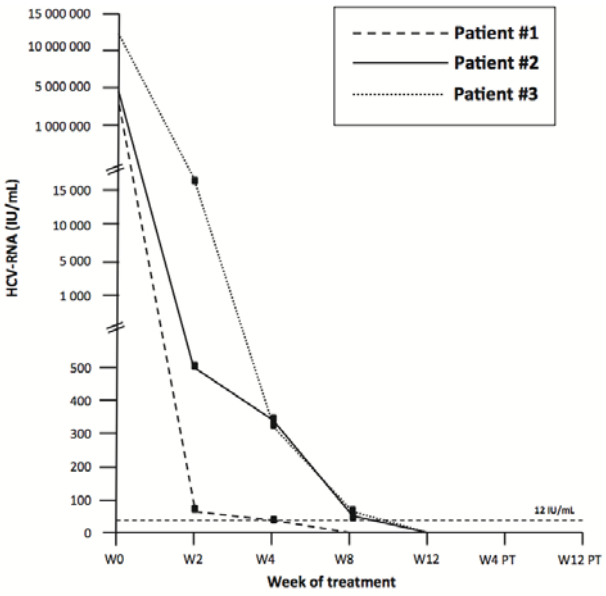


Colombo M, et al. Ann Intern Med 2017;166:109-17

Sofosbuvir-based Regimens for HCV Patients who Underwent Lung Transplant

- **Design:** case report (n = 3) for patients underwent lung transplant and received SOF-based DAAs

Characteristic	Patient 1	Patient 2	Patient 3
Gender	F	F	F
Age, y	29	38	47
BMI, kg/m^2	21.1	24.2	23.4
HCV GT	2a/c	1b	1a
HCV RNA, IU/mL	2.71 x 10^6	4.74 x 10^6	1.14 x 10^7
eGFR, mL/min	48	99	64
LSM, kPa	11.2	8.8	8.9
Pulmonary disease	cystic fibrosis	cystic fibrosis	cystic fibrosis
Time from lung transplant, m	17	11	22
Immunosuppressant	TAC, steroid	TAC, steroid	TAC, steroid
Steroid dose, mg	7.5	10	5
TAC dose, mg	7.5	6.5	1
TAC range, ng/mL	6-8	8-10	6-8
Immunosuppressant dose adjustment	None	None	None
DAA	SOD/RBV	SOF/LDV	SOF/LDV
Tx duration, week	12	12	12
SVR	Yes	Yes	Yes

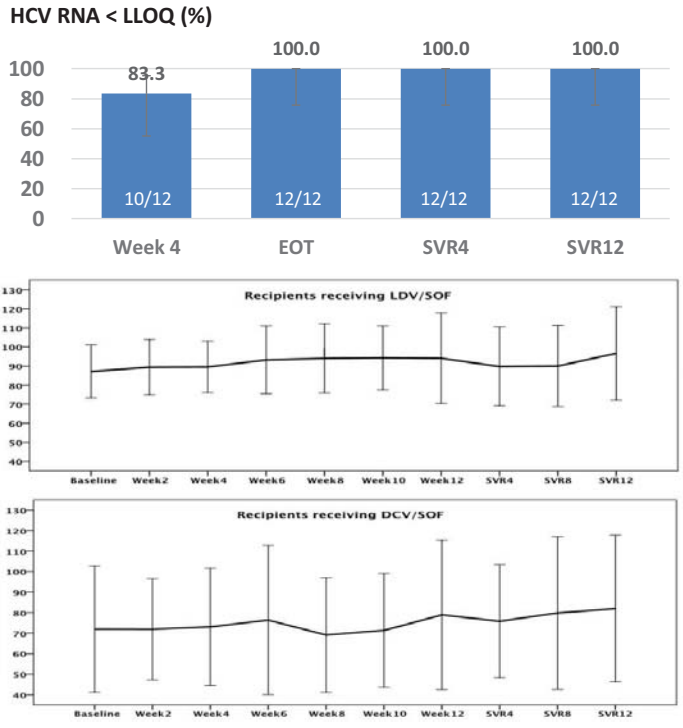


D'Ambrosio R, et al. Liver Int 2016;36:1585-9

Sofosbuvir-Based IFN-free DAAs for Heart Transplant Recipients with Chronic Hepatitis C Virus Infection

- **Design (N = 12):** prospective cohort study in heart transplant recipients treated by SOF/LDV (HCV-1) or SOF/DCV (HCV-2 or 6) for 12 weeks

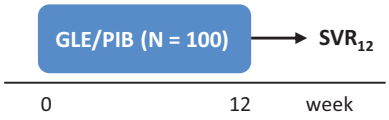
Characteristic	Patients (N = 12)
Age, years, median (range)	55 (38, 62)
Male, n (%)	7 (58.3)
Treatment-naïve, n (%)	10 (83.3)
HCV infection, n (%)	
Prior to heart transplantation	7 (58.3)
De novo infection	5 (41.7)
HCV genotype 1b/2/6, n (%)	7/4/1 (58.3/33.3/8.3)
HCV RNA, $\log_{10}$ IU/mL, median (range)	6.34 (4.68, 7.59)
Hepatic fibrosis (METAVIR), n (%)	
F0-1/F2	5/3 (41.7/25.0)
F3/F4	1/3 (8.3/25.0)
Immunosuppressant	
Prednisone	6 (50.0)
Cyclosporine	1 (8.3)
Tacrolimus	9 (75.0)
Sirolimus	2 (16.7)
Mycophenolate mofetil	8 (66.7)
Everolimus	5 (41.7)



Liu CH, et al. Clin Infect Dis 2018;66:289-92

Glecaprevir/Pibrentasvir for Liver or Renal Transplant Adults with HCV Genotype 1-6 Patients: MAGELLAN-2

- **Design:** open-label, multicenter, phase 3 study; efficacy and safety of G/P for 12 weeks in liver and renal transplant adults conducted in Australia, Canada, New Zealand, Italy, Puerto Rico, Spain, Taiwan, UK and US



Single liver or renal transplant recipient ≥ 3 months prior to screening
On a stable IS regimen based on tacrolimus, sirolimus, everolimus, mycophenolate mofetil (MMF), azathioprine, cyclosporine and/or mycophenolic acid
- Prednisone/prednisolone permitted at ≤ 10 mg/day at time of screening
- Cyclosporine permitted at ≤ 100 mg/day at time of screening

Exclusion: AST/ALK > 10X ULN, PLT < 70K, Ccr < 30, Alb < 3.5, ARF within 3 months, re-transplantation or dual transplantation, steroid-resistant rejection within 3 months, experienced with DAA other than SOF

Characteristics	G/P 12 wk (N = 100)
Male, n (%)	75 (75)
Age, y, median (range)	60 (39, 78)
White, n (%)	78 (78)
BMI, kg/m², median (range)	26.0 (17.4, 42.5)
HCV RNA, log_{10} IU/mL, median (range)	6.5 (4.0, 7.6)
Fibrosis, n (%)	
F0-1	80 (80)
F2	6 (6)
F3	14 (14)
HCV GT, n (%)	
1	57 (57)
2	13 (13)
3	24 (24)
4	4 (4)
5	0 (0)
6	2 (2)

Characteristics	G/P 12 wk (N = 100)
Tx experience, n (%)	34 (34)
IFN-based	32 (32)
SOF-based	1 (1)
TE, pre-transplant	24 (24)
TE, post-transplant	10 (10)
Liver transplant	80 (80)
Kidney transplant	20 (20)
Immunosuppression	
Tacrolimus	68 (68)
MMF	30 (30)
Cyclosporine	13 (13)
Prednisone	13 (13)
Prednisolone	11 (11)
Everolimus	8 (8)
Azathioprine	6 (6)
Sirolimus	7 (7)

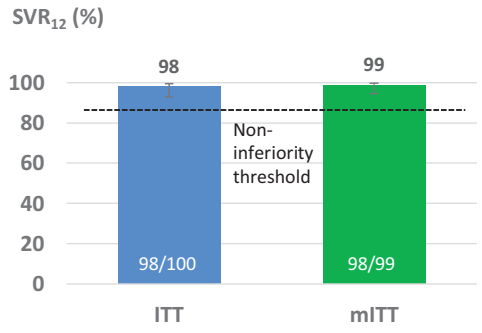
Characteristics	G/P 12 wk (N = 100)
Time since transplant, m, median (range)	55.6 (4.2, 545.3)
eGFR, mL/min/1.73m², median (range)	62.3 (28.7, 132.2)

Baseline RASs	G/P 12 wk (N = 98)
None	66 (67)
NS3 only	0 (0)
NS5A only	32 (33)
NS3 + NS5A	0 (0)

NS3: 155, 156, 168
NS5A: 24, 28, 30, 31, 58, 92, 93

Reau N, et al. Hepatology 2018;68:1298-307

Glecaprevir/Pibrentasvir for Liver or Renal Transplant Adults with HCV Genotype 1-6 Patients: MAGELLAN-2



- One GT3a relapsed at PTW4
- One patient LTFU
- mITT: excludes non virologic failure

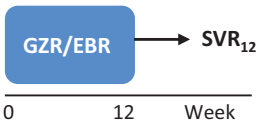
Events, n (%)	G/P 12 wk (N = 100)
Any AE	85 (85)
AE leading to drug DC*	1 (1)
Serious AE	8 (8)
DAA-related serious AE**	2 (2)
DAA-related AE leading to drug DC	0 (0)
Death	0 (0)
AE occurring in ≥ 10% of patients	
Headache	22 (22)
Fatigue	22 (22)
Nausea	12 (12)
Pruritus	12 (12)
Diarrhea	10 (10)
Transplant rejection***	1 (1)
AST, grade ≥ 3 (> 5X ULN)	0 (0)
ALT, grade ≥ 3 (> 5X ULN)†	1 (1)
T-Bil, grade ≥ 3 (> 3X ULN)‡	1 (1)
CLCr, grade ≥ 3 (< 30 mL/min/1.73m²)	2 (2)

* Cerebrovascular accident unrelated to G/P week 6, SVR_{12} achieved.
** Sinusitis (day 2), abnormal hepatic function (PTW4).
*** Patient with non-serious AE of mild liver transplant rejection at week 10 unrelated to DDIs; did not lead to Tx interruption; treated with short course of steroid and increase IS dose.
† Isolated grade 3 elevation on Day 3 without concomitant bilirubin elevation; ALT declined to normal and remained normal.
‡ Grade 3 bilirubin elevation on Day 46 in patients with renal impairment; due to DDI between tacrolimus and clarithromycin. Resolved on Day 85 without treatment interruption; patient achieved SVR_{12}.

Reau N, et al. Hepatology 2018;68:1298-307

Grazoprevir/Elbasvir in for with HIV/HCV Coinfection: C-EDGE Coinfection

- **Design:** phase III, open-label, single arm study to evaluate safety and efficacy of GZR/EBR for 12 weeks in TN HIV/HCV GT 1/4/6 infection (N = 218)



Patients:

- Treatment-naïve with/without cirrhosis
- GT1, 4, or 6 infection (Abbott RealTime Genotype II assay)
- Co-infection with HIV-1: naïve to ART with CD4 > 500 cells/mm^3 and HIV RNA < 50,000 copies/mL; on stable ART for ≥ 8 weeks with CD4 count > 200 cells/mm^3 and undetectable HIV RNA

Resistance analysis:

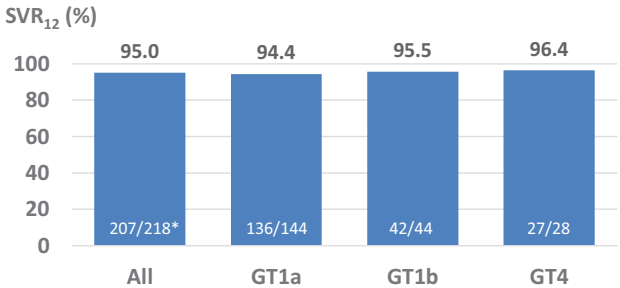
- Population sequencing with a detection of limit of variants of ~25% prevalence

Demographics	GZR/EBR (N = 218)
Age, y, mean (SD)	48.7 (8.9)
Male, n (%)	183 (83.9)
Race*, n (%)	
Black	38 (17.4)
White	167 (76.6)
Asian	6 (2.8)
Other	7 (3.2)
HCV genotype, n (%)	
1a	144 (66.1)
1b	40 (20.2)
1 (other)	1 (0.5)
4	28 (12.8)
6	1 (0.5)
Baseline HCV RNA > 800K IU/mL, n (%)	130 (59.6)
Cirrhosis, n (%)	35 (16.1)
IL28B CC, n (%)	77 (35.3)

Demographics	GZR/EBR (N = 218)
ART, n (%)	
Receiving ART with undetectable HCV RNA	211 (96.8)
Naïve to ART	7 (3.2)
ART regimen , n (%)	
Abacavir-containing regimen	47 (21.6)
Tenofovir-containing regimen	164 (75.2)
Raltegravir	113 (51.8)
Dolutegravir	59 (27.1)
Rilpivrine	38 (17.4)
Baseline CD4 count cells/µL	
Mean (SD)	613 (57)
Median (1st – 3rd quartile)	568 (424-766)

Rockstroh J, et al. Lancet HIV 2015;2:e319-27

Grazoprevir/Elbasvir in for with HIV/HCV Coinfection: C-EDGE Coinfection



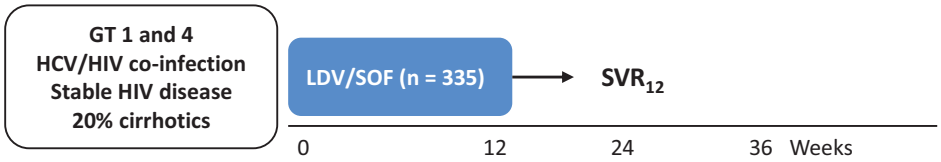
	All	GT1a	GT1b	GT4
LTFU or DC unrelated to VF	4	3	1	0
Breakthrough	0	0	0	0
Relapse	6	4	1	1
Reinfection	1	1	0	0

LTFU: lost to follow-up, DC: discontinue, VF: virologic failure
* One patients with genotype 6 and one with genotype 1 not-otherwise subtyped were also included, both patients achieved SVR$_{12}$

Variable	n/M	SVR$_{12}$ % [95% CI]
All	207/218	95.0 [91.2, 97.5]
Sex		
Male	172/183	94.0 [89.5, 97.0]
Female	35/35	100.0 [90.0, 100.0]
Age		
< 65 yr	201/212	94.8 [90.9, 97.4]
≥ 65 yr	6/6	100.0 [54.1, 100.0]
Race		
White	158/167	94.6 [90.9, 97.5]
African American	36/38	94.7 [82.3, 99.4]
Asian	6/6	100 [54.1, 100.0]
IL28B SNP		
CC	74/77	96.1 [89.0, 99.2]
Non-CC	133/141	94.3 [89.1, 97.5]
Cirrhosis		
No	172/183	94.0 [89.5, 97.0]
Yes	35/35	100.0 [90.0, 100.0]
Baseline VL		
≤ 800,000 IU/mL	84/88	95.5 [88.8, 98.7]
> 800,000 IU/mL	123/130	94.6 [89.2, 97.8]
ART regimen		
Abacavir-containing	43/47	91.5 [79.6, 97.6]
Tenofovir-containing	158/164	96.3 [92.2, 98.6]
ART third agent		
Raltegravir	107/113	94.7 [88.8, 98.0]
Dolutegravir	58/59	98.3 [90.9, 100.0]
Rilpivrine	36/38	94.7 [82.3, 99.4]

Rockstroh J, et al. Lancet HIV 2015;2:e319-27

Ledipasvir plus Sofosbuvir for HIV-HCV Co-Infected Patients (ION-4)



Characteristic	LDV/SOF (N = 335)
Male, n (%)	276 (82)
Median age, yrs (IQR)	52 (48-58)
Race, n (%)	
White	203 (61)
Black	115 (34)
Asian	6 (2)
Other or unknown	11 (3)
Mean BMI (IQR)	27 (24-30)
IL28B, n (%)	81 (24)
CC	81 (24)
CT	185 (55)
TT	69 (21)
Genotype 1, n (%)	327 (98)
1a	250 (75)
1b	77 (23)
4	8 (2)
Cirrhosis, n (%)	67 (20)
Mean HCV RNA, log_{10} IU/mL (IQR)	6.7 (6.3-7.2)

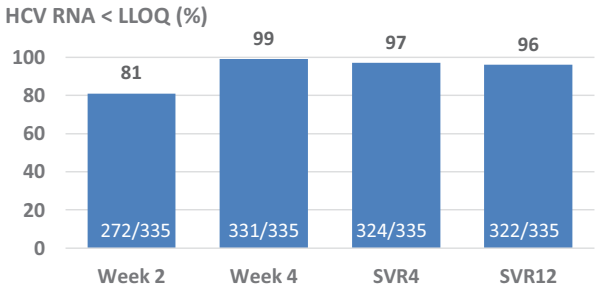
Characteristic	LDV/SOF (N = 335)
HCV treatment experience, n (%)	
Naïve	150 (45)
Experienced	185 (55)
Median CD4+ cell count, cells/mm³ (IQR)	628 (469-823)
ARV regimen (+ TDF/FDC), n (%)	
Efavirenz	160 (48)
Raltegravir	146 (44)
Rilpivirine	29 (9)

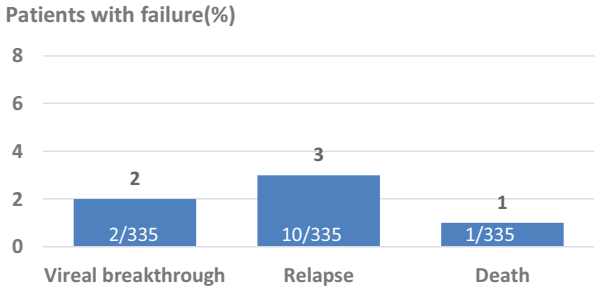
Inclusion Criteria:

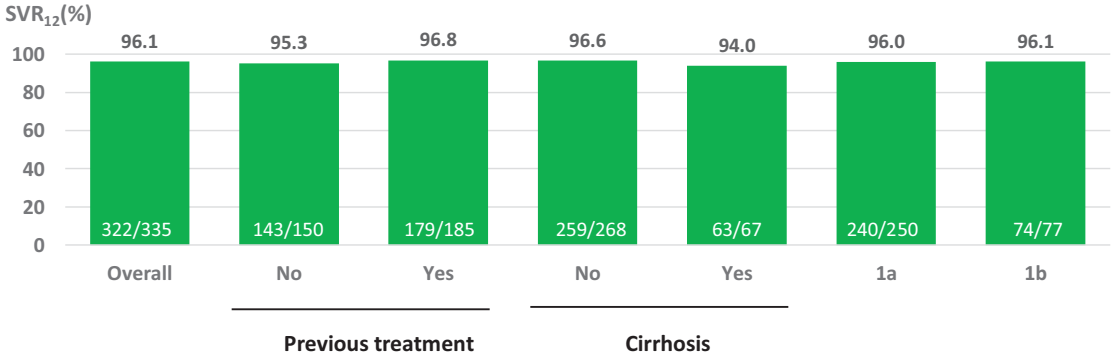
- HCV treatment naïve and experienced (including PI failures)
- HCV GT 1 and 4
- With or without compensated cirrhosis
- Platelet ≥ 50,000 cells/mm³, hemoglobin ≥ 10 g/dL
- Creatinine clearance ≥ 60 mL/min
- HIV positive with stable virologic suppression on ART
  - HIV-1 RNA < 50 copies/mL
  - CD4 T-cell count > 100 cells/mm³
  - ART regimen: could include FTC/TDF plus EFV or RPV or RAL
- US, Canada, New Zealand

Naggie s, et al. N Engl J Med 2015;373:705-13

Ledipasvir plus Sofosbuvir for HIV-HCV Co-Infected Patients (ION-4)



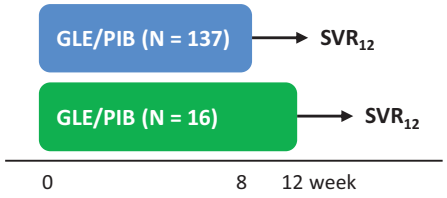




Naggie s, et al. N Engl J Med 2015;373:705-13

Glecaprevir/Pibrentasvir for HCV GT 1-6/HIV-1 Co-Infected Patients: EXPEDITION-2

- **Design:** phase 3, multicenter evaluating 8 or 12 week G/P in HCV/HIV-1 patients with and without compensated cirrhosis, respectively



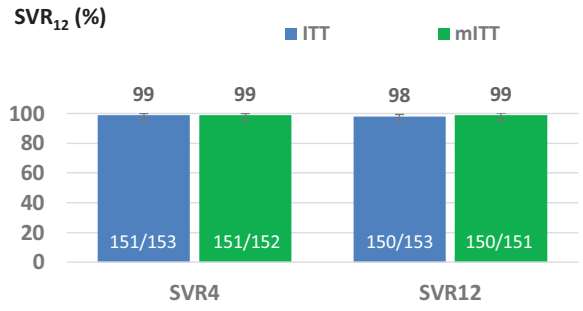
- Non-cirrhosis: 8 wk; cirrhosis: 12 wk
- ART naïve with CD4 count ≥ 500 cells/mm3 or ≥ 29% or on a stable ART regimen for at least 8 weeks prior to screening with CD4 count ≥ 200 cells/mm3 or ≥ 14%, and plasma HIV-1 RNA < LLOQ

Characteristics	G/P 8 wk (N = 137)	G/P 12 wk (N = 16)
Male, n (%)	113 (82)	15 (94)
Age, y, median (range)	45 (23, 74)	50 (35, 62)
White, n (%)	106 (77)	15 (94)
Black, n (%)	24 (18)	1 (6)
BMI, kg/m^2, median (range)	25.0 (18.1, 40.6)	27.6 (21.6, 38.2)
HCV RNA, log$_{10}$ IU/mL, median (range)	6.2 (4.0, 7.4)	6.1 (4.4, 7.0)
Treatment-naïve, n (%)	111 (81)	14 (88)
Treatment-experienced, n (%)	26 (19)	2 (13)
IFN-based	23 (17)	2 (13)
SOF-based	3 (2)	0 (0)
Fibrosis stage, n (%)		
F0-1	120 (88)	0 (0)
F2	2 (1)	0 (0)
F3	15 (11)	0 (0)
F4	0 (0)	16 (100)

Characteristics	G/P 8 wk (N = 137)	G/P 12 wk (N = 16)
HCV GT, n (%)		
1	87 (64)	10 (63)
1a	66 (48)	5 (31)
1b	21 (15)	5 (31)
2	9 (7)	1 (6)
3	22 (16)	4 (25)
4	16 (12)	1 (6)
5	0 (0)	0 (0)
6	3 (2)	0 (0)
No ART therapy, n (%)	9 (7)	0 (0)
CD4, cells/mm^3, median (range)	588 (154, 2103)	545 (222, 1806)
PPI use, n (%)	11 (8)	1 (6)
IDU within 12 months, n (%)	12 (9)	1 (6)
IDU > 12 months before screening, n (%)	62 (45)	10 (63)
on OST, n (%)	11 (8)	2 (13)

Rockstroh JK, et al. Clin Infect Dis 2018;67:1010-7

Glecaprevir/Pibrentasvir for HCV GT 1-6/HIV-1 Co-Infected Patients: EXPEDITION-2



- **Non-SVR$_{12}$:** breakthrough (1), missing data (1), discontinued (1)
- **SVR$_{12}$:** 136/136 (100%) for non-cirrhosis; 14/15 (93%) for cirrhosis
- **Breakthrough:** GT-3a cirrhosis on-treatment week 8 VF
  - NS3: no RAS at baseline; Y56H at failure
  - NS5A: A30V at baseline; S24F and M28K (not A30V) at failure

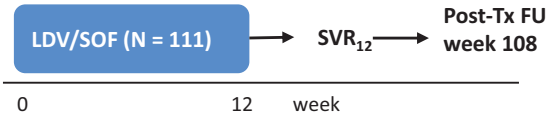
Events, n (%)	G/P 8 wk (N = 137)	G/P 12 wk (N = 16)
Any AE	86 (63)	8 (50)
Grade 1 (mild)	52 (60)	3 (38)
Serious AE	3 (2)*	1 (6)**
DAA-related	0 (0)	0 (0)
AE leading to drug DC	0 (0)	1 (6)**
AEs occurring in ≥ 5% of patients		
Fatigue	18 (13)	0 (0)
Nausea	12 (9)	1 (6)
Headache	12 (9)	0 (0)
Nasopharyngitis	12 (9)	0 (0)
Laboratory abnormalities		
ALT > 5X ULN (≥ Grade 3)	0 (0)	0 (0)
AST > 5X ULN (≥ Grade 3)	0 (0)	0 (0)
T-Bil > 3X ULN (≥ Grade 3)	1 (0.7)***	0 (0)

* Upper GI hemorrhage, obliterating arteriopathy, and urolithiasis in 1 patient each, all unrelated to G/P ** One patient with cerebrovascular accident and cerebral hemorrhage, both unrelated to G/P. *** One patient had grade 3 total bilirubin elevation on Day 10 that continued through Day 31; levels normalized by Day 59 without treatment interruption.

Rockstroh JK, et al. Clin Infect Dis 2018;67:1010-7

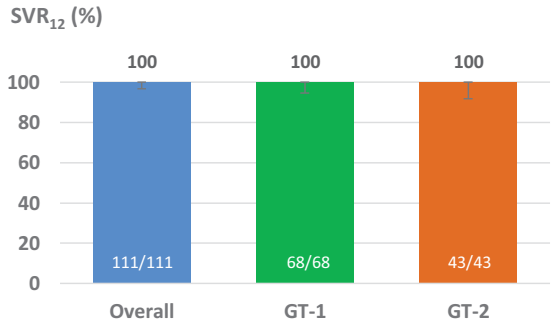
Ledipasvir/Sofosbuvir for 12 Weeks in Patients with Chronic Hepatitis C and B Coinfection: Phase 3 Study in Taiwan

- **Design:** multicenter, open label study at 14 sites in Taiwan to evaluate the efficacy and safety of LDV/SOF for 12 weeks in HBsAg (+) patients with HCV-1 or 2 infection (N = 111)



	Characteristics	Patient (N = 111)
HCV	Age, y, mean (range)	55 (36, 76)
	Male, n (%)	42 (38)
	BMI, kg/m2, mean (range)	25 (17, 34)
	IL28B CC, n (%)	85 (77)
	GT-1/GT-2, n (%)	66/43 (61/39)
	HCV RNA, log_{10} IU/mL, mean (range)	5.9 (3.8, 7.1)
	Cirrhosis, n (%)	18 (16)
	ALT, U/L, mean (range)	68 (17, 281)
HBV	HBsAg (+), n (%)	110 (99)*
	HBeAg (+), n (%)	1 (< 1)
	GT B/GT C**	33/5 (33/5)
	HBV Tx experienced, n (%)	5 (4)
	HBV DNA, log10IU/mL, mean (range)	2.1 (1.3, 5.8)
	HBV DNA < LLOQ, n (%)	37 (33)

* 1 patient changed HBsAg status between screening and baseline.
** HBV genotype could not be determined if HBV DNA < 5,000 IU/mL (N = 68, 62%)



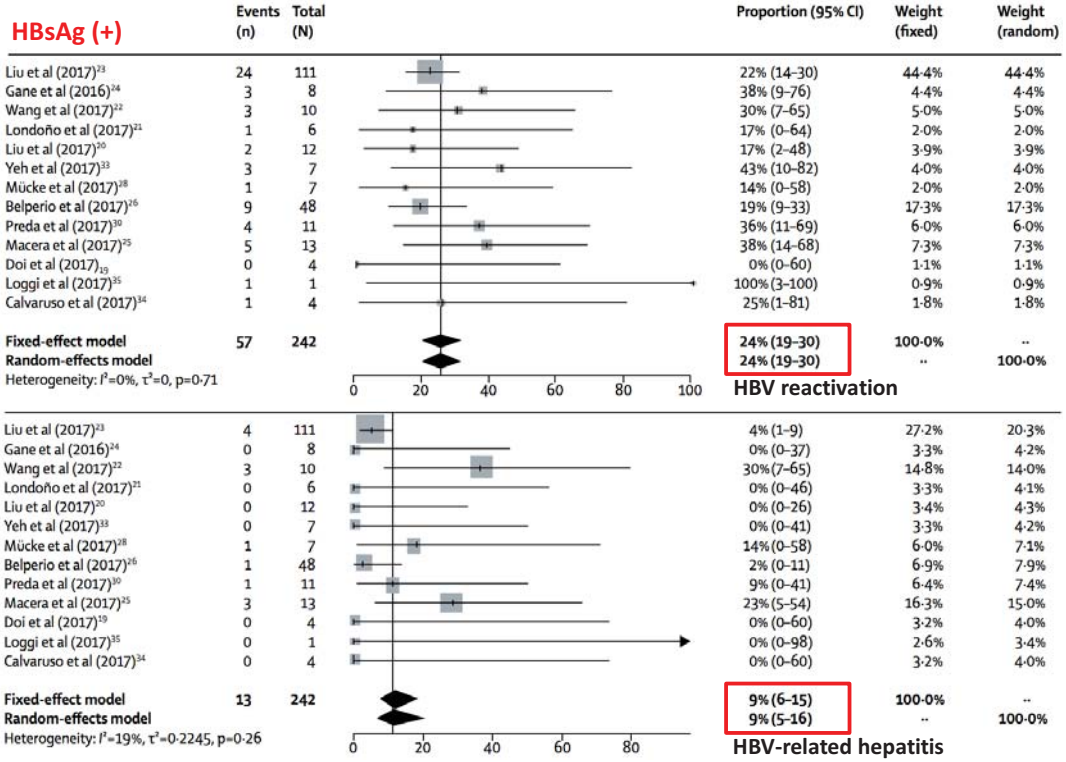
	Patients, n (%)	Patient (N = 111)
Overall safety	Any AE	66 (60)
	Grade 3-4 AE	1 (< 1)
	Serious AE	4 (4)*
	Tx DC due to AE	0 (0)
Laboratory abnormalities	Grade 3-4	1 (< 1)**

* Optic neuritis (G3), post-polypectomy hemorrhage (G2), duodenal ulcer (G1), meniscus injury (G2).
** 44 year old male with transient, asymptomatic G4 lipase at week 4.
All grade 3-4 AEs or SAEs were assessed by the investigator as unrelated to LDV/SOF.

Liu CJ, et al. EASL 52nd Annual Meeting, Amsterdam, Netherland, 2017

HBV Reactivation during DAA Therapy for Hepatitis C: Systemic Review and Meta-Analysis

- **Design:** meta-analysis of 17 studies and 1,621 patients [chronic: 242, resolved: 1,379] between Oct 1, 2010 and Sep 30, 2017



HBV reactivation:

HBsAg (+)
- Increase ≥ $2log_{10}$ HBV DNA
- > 100 IU/mL with baseline undetectable level

HBsAg (-)/anti-HBc (+)
- Reverse HBsAg seroconversion
- Detectable HBV DNA

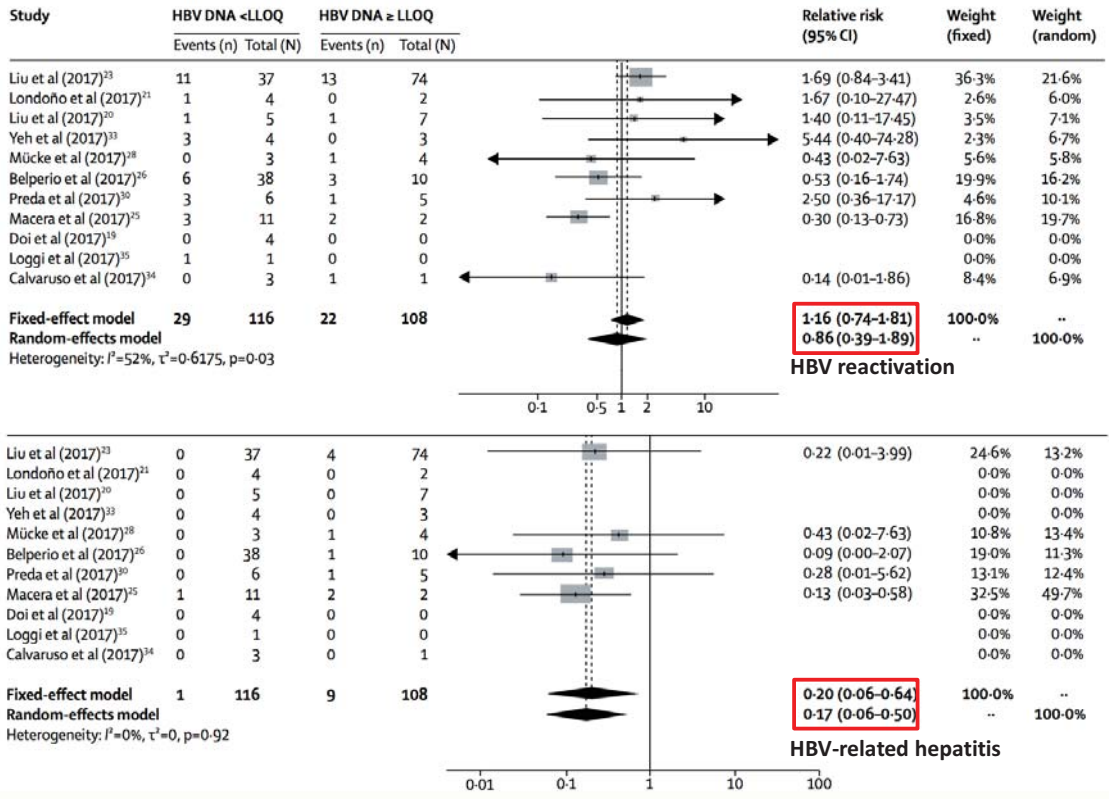
HBV-related hepatitis
- ALT ≥ 2X ULN in combination with molecular reactivation

Liver events
- Liver failure
- Transplantation
- Death

Mücke MM, et al. Lancet Gastroenterol Hepatol 2018;3:172-80

HBV Reactivation during DAA Therapy for Hepatitis C: Systemic Review and Meta-Analysis

HBsAg (+), relative risk for baseline HBV DNA <LLOQ or ≥ LLOQ



Mücke MM, et al. Lancet Gastroenterol Hepatol 2018;3:172-80

Direct Acting Antiviral Agents (DAAs) for CKD patients

Stage of CKD	DCV	SMV	SOF	SOF/LDV	PTV/r/OBV +DSV	GZR/EBR
Stage 1 GFR > 90 ml/min	O	O	O	O	O	O
Stage 2 (mild) GFR 60–89 ml/min	O	O	O	O	O	O
Stage 3 (moderate) GFR 30–59 ml/min	O	O	O	O	O	O
Stage 4 (severe) GFR 15–29 ml/min	O	O	N	N	O	O
Stage 5 (renal failure) GFR<15 ml/min or dialysis	O	N	N	N	O	O

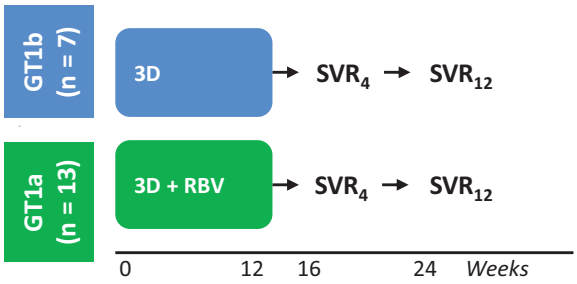
O: No dosage adjustment. N: No dose recommendation can be given.

CLCr	RBV
GFR > 50 ml/min	1,000-1,200 mg/day
GFR 30–50 ml/min	200/400 mg/day at alternative dose
GFR < 30 ml/min	200 mg/day
Hemodialysis	200 mg/day

Kwo PY, Badshah MB. Curr Opin Organ Transplant 2015;20:235-41

Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for HCV-1 Patients with Severe Renal Impairment or End-Stage Renal Disease: RUBY-I

- **Background:**
  - Safety and efficacy of interferon-free DAA regimens have not been adequately studied in this population
  - 3D regimen is metabolized in the liver and does not require dose-adjustment in patients with CKD
- **RUBY-I study:** to evaluate 3-DAA combination of paritaprevir/ritonavir, ombitasvir, and dasabuvir (3D) with or without RBV in treatment-naïve patients with HCV-1nfection and CKD stage 4 or 5, including those on H/D; 9 sites in US, open-label study



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

- RBV: started at 200 mg QD for all GT1a-infected patients
- GT1a patients on hemodialysis, RBV was dosed 4 hours prior to start of hemodialysis
- Hemoglobin: at weeks 1, 2, 3, 4, 6, 8, and 12 end of treatment)
- RBV was interrupted if: decrease of > 2 g/dL in < 4 weeks or value < 10 g/dL
- RBV could be resumed at discretion of investigator if hemoglobin decrease resolved

Inclusion: HCV GT 1, with HCV RNA > 1,000 IU/mL at screening; treatment-naïve adults; chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2; negative for Hepatitis B and HIV
Exclusion: clinically significant comorbidity; hemoglobin < 10 g/dL
Disease Stage: non-cirrhotic*

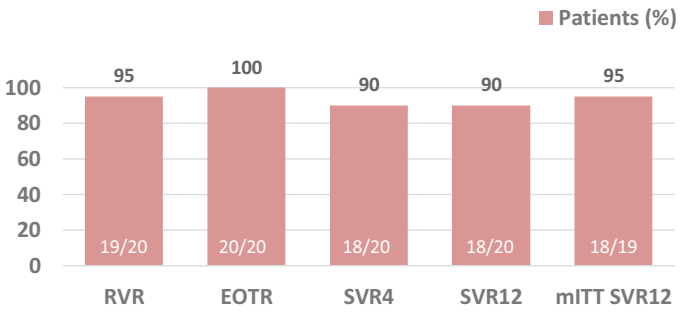
*Histologic diagnosis (Metavir Score ≤ 3, Ishak score ≤ 4), or Screening FibroScan score < 14.6 kPa or FibroTest ≤ 0.72 and APRI ≤ 2

Pockros PJ, et al. Gastroenterology 2016;150:1590-8

Ombitasvir/Paritaprevir/Ritonavir plus Dasabuvir for HCV-1 Patients with Severe Renal Impairment or End-Stage Renal Disease: RUBY-I

Patient Characteristics	3D ± RBV (N=20)
Age, years, median (range)	60 (49-69)
Male, n (%)	17 (85)
Black race, n (%)	14 (70)
Hispanic or Latino ethnicity, n(%)	3 (15)
BMI, median, kg/m^2 (range)	30.5 (20.3-37.1)
GT1a; n (%)	13 (65)
IL28B non-CC, n (%)	14 (70)
Hemoglobin, g/dL, median (range)	12.0 (9.5-16.6)
History of DM, n (%)	11 (55)
HCV RNA, log$_{10}$ (IU/mL), median (range)	6.6 (5.5-7.6)
Fibrosis stage*, n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
CKD stage, n (%)	
4 (eGFR 15-30 mL/min/1.73m^2)	7 (35)
5 (eGFR <15 mL/min/1.73m^2 or requiring dialysis)	13 (65)
On dialysis, n (%)	13 (65)
eGFR, mL/min/1.73m^2, 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.

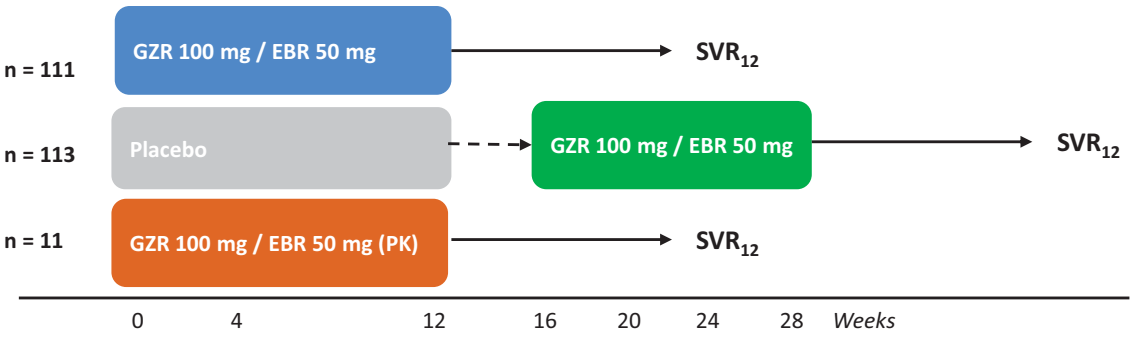


2 patients failed to achieve SVR12
- 1 GT1a patients died 14 days after the EOT due to LV systolic dysfunction, which was not attributed to DAA or RBV
- 1 GT1a patients relapsed at PTW4
  - 49 y/o, black male, on dialysis [F3 fibrosis, IL28B CT, BMI: 37 kg/m^2]
  - Compliance: < 92% for OBV/PTV/r, DSV
  - RAVs: no [at baseline], NS3 (D168V) and NS5A (Q30R) [at relapse]

Pockros PJ, et al. Gastroenterology 2016;150:1590-8

Grazoprevir/Elbasvir in Treatment-Naïve and Treated-Experienced Patients with HCV-1 Infection and Chronic Kidney Disease: C-SURFER

- **Aim:** to evaluate grazoprevir (GZR) + elbasvir (EBR) in HCV-infected patient with Ccr < 30 mL/min, including patients on hemodialysis [< 1% of GZR and EBR is renally excreted]



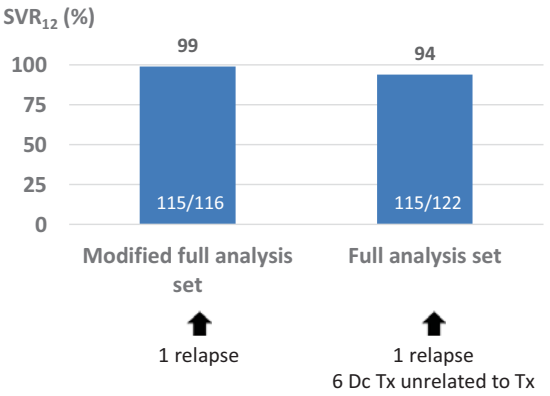
Design: randomized, parallel-group, placebo-controlled trial; stratified by DM and hemodialysis

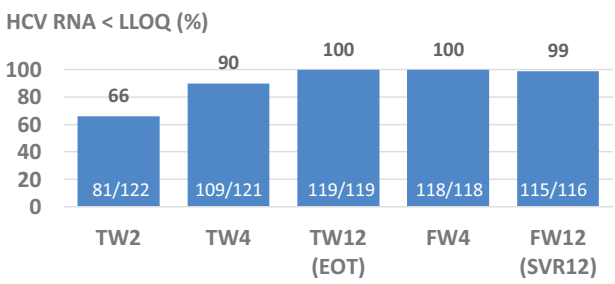
Inclusion: HCV GT1, treatment-naïve or experienced, CKD stage 4/5 (± hemodialysis dependence)

- CKD stage 4: eGFR 15-29 mL/min/1.73 m^2
- CKD stage 5: eGFR < 15 mL/min/ 1.73 m^2
- Target 20% non-hemodialysis patients
- Compensated cirrhosis allowed

Roth D, et al. Lancet 2015;386:1537-45

Grazoprevir/Elbasvir in Treatment-Naïve and Treated-Experienced Patients with HCV-1 Infection and Chronic Kidney Disease: C-SURFER





Relapse: GT1b; BL NS5A RAV (L31M); at failure NS3 RAV (V170I), NS5A RAV (L31M, Y93H)

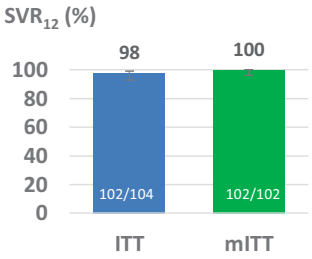
Character	n/N	SVR_{12} (%) [95% CI]
All patients	115/116	99.1 [95.3, 100]
Cirrhosis		
Yes	6/6	100 [54.1, 100]
No	109/110	99.1 [95.0, 100]
HCV genotype		
1a	61/61	100 [94.1, 100]
1b	54/55	98.2 [90.3, 100]
Race		
White	58/59	98.3 [90.9, 100]
African American	51/51	100 [93.0, 100]
Asian	5/5	100 [47.8, 100]
Previous treatment		
Naïve	96/96	100 [96.2, 100]
Experienced	19/20	95.0 [75.1, 100]
CKD stage		
4	22/22	100 [84.6, 100]
5	93/94	98.9 [94.2, 100]
Hemodialysis		
Yes	86/87	98.9 [93.8, 100]
No	29/29	100 [88.1, 100]

Roth D, et al. Lancet 2015;386:1537-45

Glecaprevir/Pibrentasvir (G/P) for HCV GT 1-6 Patients with Renal Impairment: EXPEDITION-4

- **EXPEDITION-4:** phase 3, multicenter, open-label study for treatment-naïve or -experienced (SOF/PR also included) patients with chronic HCV GT1-6 infection with/without cirrhosis (Child-Pugh A) and CKD stage 4 or 5

Characteristic	G/P N = 104
Male, n (%)	79 (76)
Black, n (%)	25 (24)
Age, median years (range)	57 (28 – 83)
BMI, median kg/m^2 (range)	26 (18 – 45)
HCV RNA, median log$_{10}$ IU/mL (range)	5.9 (3.4 – 7.5)
PPI use, n (%)	43 (41)
HCV genotype	
1a/1b/other	23 (22)/29 (28)/2 (2)
2	17 (16)
3	11 (11)
4/5/6	20 (19)/1 (1)/1 (1)
Prior treatment history	
Naïve	60 (58)
IFN/Peg-IFN ± RBV	42 (40)
SOF + RBV ± Peg-IFN	2 (2)
Compensated cirrhosis	
Yes	20 (19)
No	84 (81)
CKD stage	
Stage 4	14 (13)
Stage 5	90 (87)
Hemodialysis	85 (82)
Polymorphism	
Any	28/96 (29)
NS3 or NS5A	1/96 (1), 24/96 (25)
NS3 and NS5A	0/96 (0)



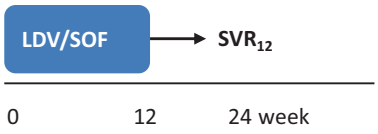
mITT: ITT population excluding 2 non-virologic failure (1 discontinuation, 1 LTFU)

Event, n (%)	G/P (N = 121)
Any AE	74 (71)
AEs leading to study drug discontinuation	4 (4)
Serious AEs	25 (24)
Serious AEs related to DAA	0
Death	1 (1)
AEs occurring in ≥ 10% total patients	
Pruritus	21 (20)
Fatigue	15 (14)
Nausea	12 (12)
Hemoglobin Grade ≥ 3 (6.5-8.0 g/dL)	5 (5)
AST Grade ≥ 2 (3-20X ULN)	0
ALT Grade ≥ 2 (3-20X ULN)	0
Total bilirubin Grade ≥ 3 (3-10X ULN)	1 (1)

Gane E, et al. N Engl J Med 2017;377:1448-55

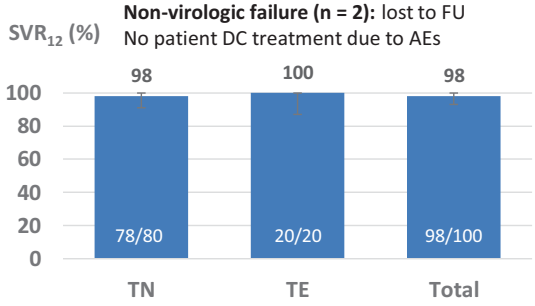
Ledipasvir/Sofosbuvir for HCV GT1 Adolescents 12-17 Years Old

- **Design:** phase 2, multicenter, open-label study
- **Patients (N = 100):** HCV GT-1, naïve or experienced, with/without cirrhosis, age 12-17 yr, Hb > 11 g/dL, ANC > 1500 cells/mm^3, eGFR > 90 mL/min/1.73m$_2$, Cre < 1.5 mg/dL



	TN (n = 80)	TE (n = 20)	Total (N = 100)
Age, y, median (range)	15 (12, 17)	15 (12, 17)	15 (12, 17)
Female, n (%)	50 (63)	13 (65)	63 (63)
White, n (%)	71 (89)	19 (95)	90 (90)
BMI, kg/m2, median (range)	21 (13, 37)	22 (18, 32)	21 (13, 37)
Genotype 1a/1b, n (%)	66/14 (83/18)	15/5 (75/25)	81/19 (81/19)
HCV RNA ≥ 800K IU/mL, n (%)	44 (55)	11 (55)	55 (55)
IL28B CC, n (%)	20 (25)	4 (20)	24 (24)
Cirrhosis, n (%)	1 (1)	0 (0)	1 (1)
ALT, U/L, mean (SD)	54 (56.2)	50 (36.2)	53 (52.7)
eGFR, mL/min/1.73m^2, mean (SD)	153.6 (36.9)	144.9 (33.0)	151.9 (36.1)

Non-virologic failure (n = 2): lost to FU
No patient DC treatment due to AEs



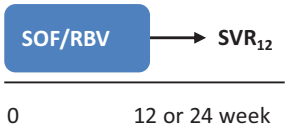
	Adolescents vs. Adults % GMR (90% CI)
SOF	
AUC$_{tau}$ (ng.h/mL)	160 (138, 185)
C$_{max}$ (ng/mL)	156 (127,190)
GS-331007	
AUC$_{tau}$ (ng.h/mL)	105 (91, 122)
C$_{max}$ (ng/mL)	139 (120, 161)
LDV	
AUC$_{tau}$ (ng.h/mL)	127 (95, 170)
C$_{max}$ (ng/mL)	162 (125, 209)
C$_{tau}$ (ng/mL)	128 (95, 172)

* 10 adolescents in the study; 2113 adults in PK comparison; all ranges between 50-200%

Balistreri WF et al. Hepatology 2017;66:371-8

Sofosbuvir/Ribavirin for HCV GT2/3 Adolescents 12-17 Years Old

- **Design:** phase 2, multicenter, open-label study
- **Patients (N = 52):** HCV GT-2/3, naïve/experienced, with/without cirrhosis, age 12-17 yr, Hb > 11 g/dL for female and > 12 g/dL for male, ANC > 1500 cells/mm^3, eGFR > 90 mL/min/1.73m$_2$, Cre < 1.5 mg/dL

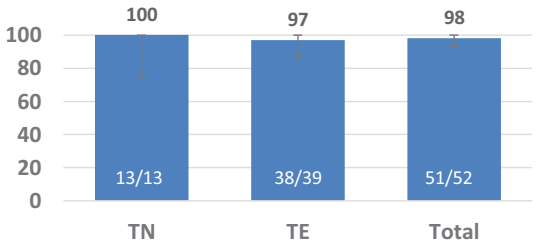


GT2: 12 wks; GT3: 24 wks
RBV: 15 mg/kg (< 47 kg), 600 mg (47-49 kg), 800 mg (50-65 mg), 1000 mg (66-80 kg), 1200 mg (81-105 kg), 1400 mg (> 105 kg)

	HCV-2 (n=13)	HCV-3 (n = 39)	Total (N = 52)
Age, y, median (range)	14 (12, 17)	15 (12, 17)	15 (12, 17)
Male, n (%)	8 (62)	23 (59)	31 (60)
White, n (%)	11 (85)	36 (92)	47 (90)
BMI, kg/m2, median (range)	21 (16, 28)	22 (16, 32)	22 (16, 32)
Genotype , n (%)			
2/2b/2a or 2c	6/5/2 (46/39/15)	0/0/0 (0/0/0)	6/5/2 (12/10/4)
3/3a	0/0 (0/0)	1/38 (3/97)	1/38 (2/73)
HCV RNA ≥ 800K IU/mL, n (%)	8 (62)	26 (67)	34 (65)
IL28B CC, n (%)	3 (23)	16 (47)	19 (37)
No cirrhosis, n (%)	4 (31)	17 (44)	21 (40)
ALT, U/L, mean (SD)	37 (25.1)	60 (57.5)	54 (52.2)
eGFR, mL/min/1.73m^2, mean (SD)	147.5 (25.2)	151.3 (25.4)	150.3 (25.1)

SVR$_{12}$ (%)

Non-virologic failure (n = 1): LTFU PTW4



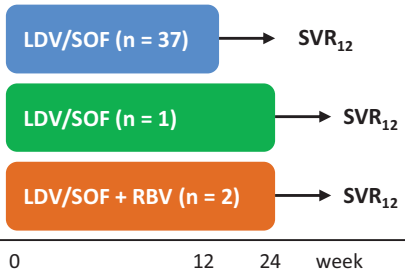
	Adolescents vs. Adults % GMR (90% CI)
SOF	
AUC$_{tau}$ (ng.h/mL)	109.7 (98.4, 122.3)
C$_{max}$ (ng/mL)	98.5 (86.7, 111.9)
GS-331007	
AUC$_{tau}$ (ng.h/mL)	111.5 (103.5, 120.1)
C$_{max}$ (ng/mL)	105.5 (96.2, 115.6)
C$_{tau}$ (ng/mL)	128 (95, 172)

* 28 adolescents in the study; 838 adults in PK comparison; all ranges between 50-200%

Wirth S, et al. Hepatology 2017;66:1102-10

Ledipasvir/Sofosbuvir ± RBV for 12 or 24 Weeks in Children 6-11 Years Old with Chronic Hepatitis C Infection

- **Prevalence of HCV in children:** 0.4% in Europe and USA and up to 6% in resource-limited countries
- **FDA approval:** SOF and LDV/SOF for children ≥ 12 years of age or ≥ 35 kg for HCV
- **Design:** open-label in children aged 6-11 years in 31 sites in Australia, New Zealand, UK, and US



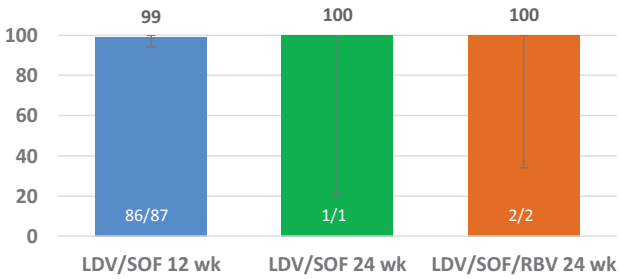
- Half-strength LDV/SOF 45/200 mg FDC, RBV dosed using a weight-based algorithm
- 24 weeks: GT-1 TE (n = 1) and GT-3 (n = 2)
- Diagnosis of cirrhosis based on cirrhosis, but not required for enrollment

- **PK study: :**LDV/SOF 45/200 mg results in plasma concentration in children 6-11 years old generally within range of those observed in adults.

Characteristics	Patients (N = 90)
Male, n (%)	53 (59)
Age, y, mean (range)	9 (6, 11)
White, n (%)	71 (79)
Weight, kg, mean (range)	33 (18, 76)
BMI, kg/m^2, mean (range)	18 (13, 31)
Treatment experienced, n (%)	18 (20)
Cirrhosis, n (%)*	2 (2)
IL28B CC, n (%)	23 (26)
HCV GT, n (%)	
1	86 (96)
3	2 (2)
4	2 (2)
Vertical transmission, n (%)	87 (97)

Cirrhosis status unknown in 63 (70%) patients

SVR$_{12}$ (%)

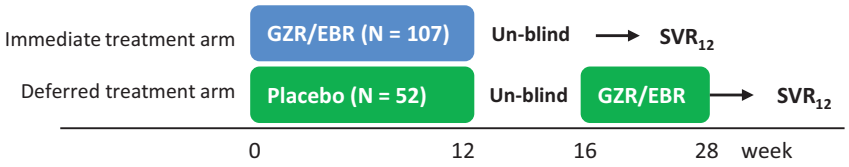


1 GT-1a patient with cirrhosis relapsed at PTW4

Murray KF, et al. EASL 52nd Annual Meeting, Amsterdam, Netherland, 2017

Elbasvir/Grazoprevir in Treatment-Naïve and Experienced HCV GT-1,4,6 Infection and Inherited Blood Disorders

- **Background:** treatment of HCV infection in patients with inherited blood disorders (IBLD) is complex [historically, the risk of hemolytic anemia from ribavirin and frequent comorbidities limited use of interferon-based HCV therapy in patients with inherited bleeding disorders]
- **Aim:** to assess the safety and efficacy of EBR/GZR in patients with sickle cell anemia, thalassemia, or hemophilia / von Willebrand disease and HCV infection
- **Design:** randomized, parallel-group, multi-site, placebo-controlled trial; stratification by cirrhosis (yes/no) and disease status (sickle cell anemia versus thalassemia versus hemophilia/von Willebrand disease)



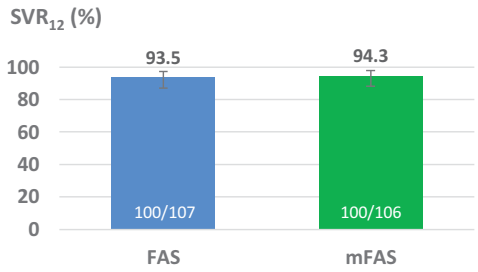
Key Inclusion Criteria

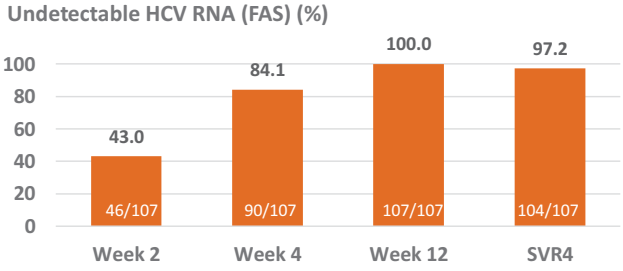
- HCV GT1, 4 & 6 infection
- Treatment-naive and treatment-experienced patients
- Inherited blood disorder (IBLD) : sickle cell anemia, β-thalassemia, hemophilia A/B, von Willebrand disease
- Patients with sickle cell anemia and β-thalassemia were required to have hemoglobin levels >7.0 g/dL
- Compensated cirrhosis allowed
- Patients with HIV/HCV co-infection were enrolled, provided they were receiving stable antiretroviral therapy using tenofovir or abacavir and either emtricitabine or lamivudine plus raltegravir, dolutegravir, or rilpivirine for ≥8 weeks prior to study entry, and had a CD4+ T-cell count >200 cells/mm^3 and undetectable plasma HIV-1 RNA.

Hezode C, et al. Hepatology 2017;66:736-45

Elbasvir/Grazoprevir in Treatment-Naïve and Experienced HCV GT-1,4,6 Infection and Inherited Blood Disorders

Characteristic	Immediate Tx (N = 107)	Deferred Tx (N = 52)
Age, y, mean (SD)	44.2 (11.2)	42.5 (9.8)
Male, n (%)	80 (74.8)	39 (75.0)
Race		
White	81 (75.7)	40 (76.9)
Black/African American	19 (17.8)	9 (17.3)
Asian/other	7 (6.5)	3 (5.8)
BMI, kg/m^2, mean	24.97	24.44
IL28B non-CC, n (%)	78 (72.9)	42 (80.8)
HCV RNA > 800K IU/mL, n (%)	68 (63.6)	27 (51.9)
Cirrhosis, n (%)	26 (24.3)	12 (23.1)
Treatment-experienced, n (%)	54 (50.5)	25 (48.1)
HIV coinfection, n (%)	6 (5.6)	4 (7.7)
HCV genotype		
1a	47 (43.9)	18 (34.6)
1b	46 (43.0)	27 (51.9)
1 other	2 (1.9)	0 (0.0)
4	12 (11.2)	6 (11.5)
6	0 (0.0)	1 (0.9)
Bleeding disorder, n (%)		
Sickle cell anemia	19 (17.8)	10 (19.2)
β-thalassemia	41 (38.3)	20 (38.5)
Hemophilia A/B von Willebrand disease	47 (43.9)	22 (42.3)





Relapse rate: 6/107 (5.6%)

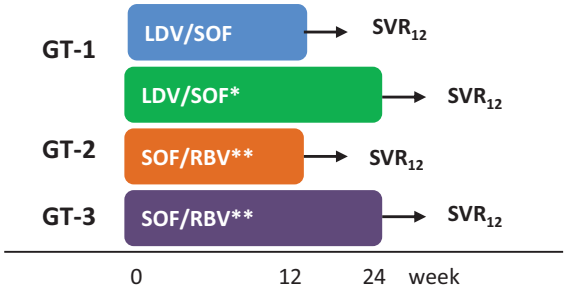
SVR$_{12}$ (%) [95% CI]

- HCV-1a: 91.5 [79.6-97.6] (41/45)
- HCV-1b: 95.7 [85.2-99.5] (44/46)
- HCV-4: 91.7 [61.5-99.8] (11/12)

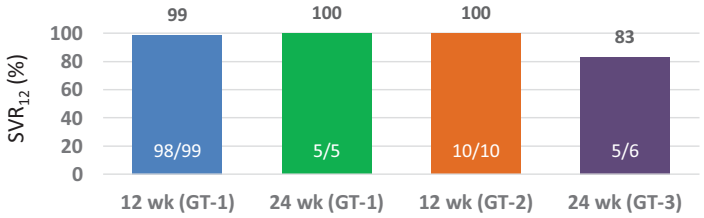
Hezode C, et al. Hepatology 2017;66:736-45

Sofosbuvir/Ledipasvir or Sofosbuvir/Ribavirin in HCV-Infected Patients with Bleeding Disorders

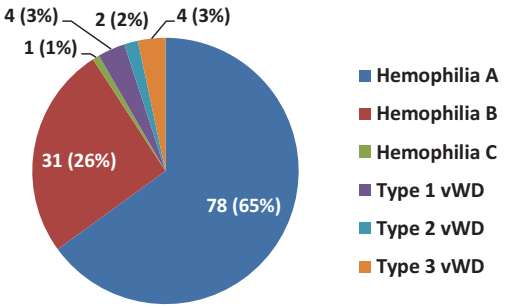
- **Aim:** to evaluate the safety and efficacy of LDV/SOF (GT-1 and 4), and SOF/RBV (GT-2, and 3) in patients with bleeding disorder, including those with HIV infection
- **Design:** phase 2b, multicenter, open-label study in US



* GT-1 patients with cirrhosis were treated for 24 weeks
** Weight-based RBV at a cutoff value of 75 kg (1,000 or 1,200 mg/day)



- One GT-1 patients lost to FU following week 4 visit
- One of 6 (17%) with GT-3 relapse (patient had cirrhosis)



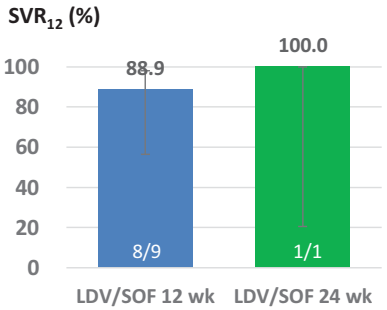
	LDV/SOF		SOF/RBV	
	12 wk (n = 99)	24 wk (n = 5)	12 wk (n = 10)	24 wk (n = 6)
Any bleeding AE	19 (19)	1 (20)	1 (10)	1 (17)
Hemoarthrosis	10 (10)	0	1 (10)	0
Muscle hemorrhage	5 (5)	0	0	0
Epistaxis	2 (2)	0	0	1 (17)

Walsh CE, et al. Haemophilia 2017;23:198-206

Ledipasvir/Sofosbuvir for HCV-Infected Patients with Sickle Cell Disease

- **Design:** open-label, single center study in US, HCV-1/4 patients receiving LDV/SOF for 12 (non-cirrhosis) or 24 (cirrhosis) weeks
- **Patients (N = 10):** sickle cell disease (SCD), Hb > 6 g/dL, PLT > 50K/mL, HCV-1 or 4, compensated liver disease

Characteristic	LDV/SOF 12 wk (n = 9)	LDV/SOF 24 wk (n = 1)
Male, n (%)	6 (67)	0 (0)
Age, y, mean (range)	43 (22, 62)	44
Black or AA, n (%)	9 (100)	1 (100)
BMI, kg/m², median (range)	22.0 (18.7, 27.7)	45.2
HCV genotype		
1a/1b/4	5/1/3 (56/11/33)	1/0/0 (100/0/0)
Treatment-naive	7 (78)	0 (0)
HCV RNA > 800K IU/mL, n (%)	3 (33)	1 (100)
eGFR, mean	116.4	194.4
iron, µg/dL, mean (SD)	113 (71.3)	81
Ferritin, ng/mL, mean (SD)	890.7 (844.5)	197.8
Hb S, mean (%) (SD)	72 (27)	45.4
Hb F, mean (%) (SD)	4.6 (4.8)	2.0

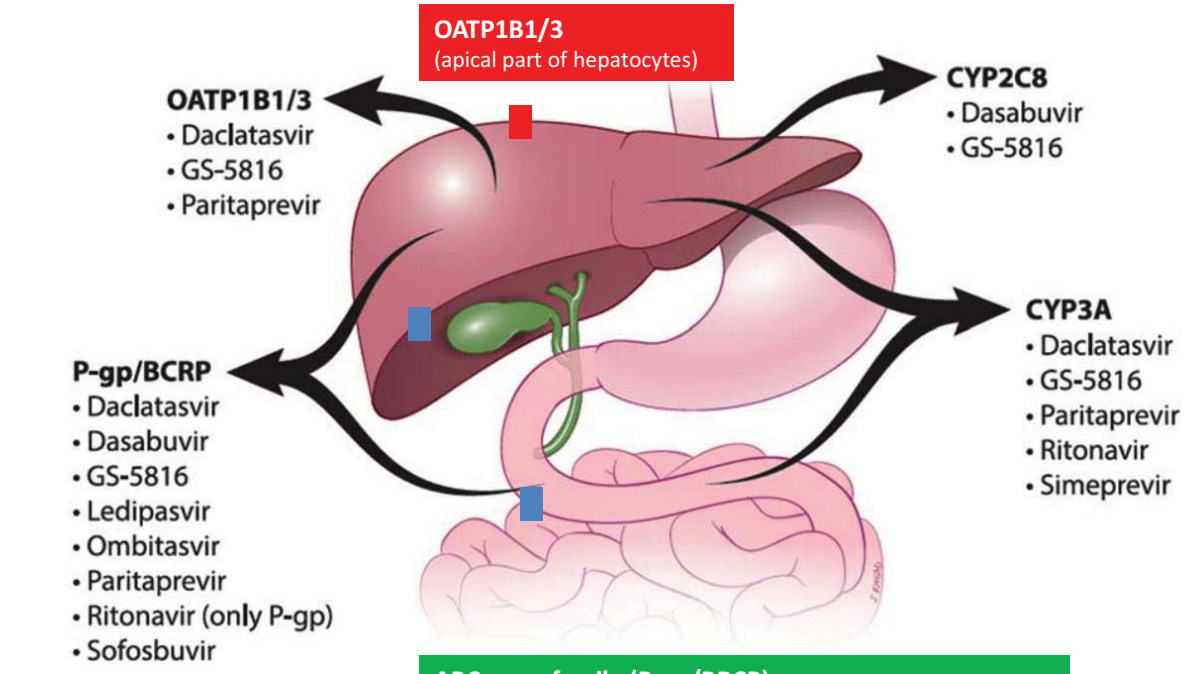


- 1 patient relapse (poor adherence: low plasma concentration of LDV and GS-331007)

Moon J, et al. Clin Infect Dis 2017;65:864-6

1. Global & Taiwan HCV epidemiology, natural history
2. Introduction: direct acting antivirals (DAAs)
3. Summary of currently reimbursed DAAs in Taiwan
   - Daclatasvir/asunaprevir
   - Paritaprevir/ombitasvir/dasabuvir ± ribavirin
   - Elbasvir/grazoprevir ± ribavirin
   - Sofosbuvir + ribavirin
   - Sofosbuvir/ledipasvir ± ribavirin
   - Glecaprevir/pibrentasvir
4. Special Population
   - Organ transplantation
   - HIV coinfection
   - HBV coinfection
   - Chronic kidney disease (CKD)
   - Adolescents and Children
   - Inherited blood disorders
5. Drug drug interaction (DDI)
6. Perspectives

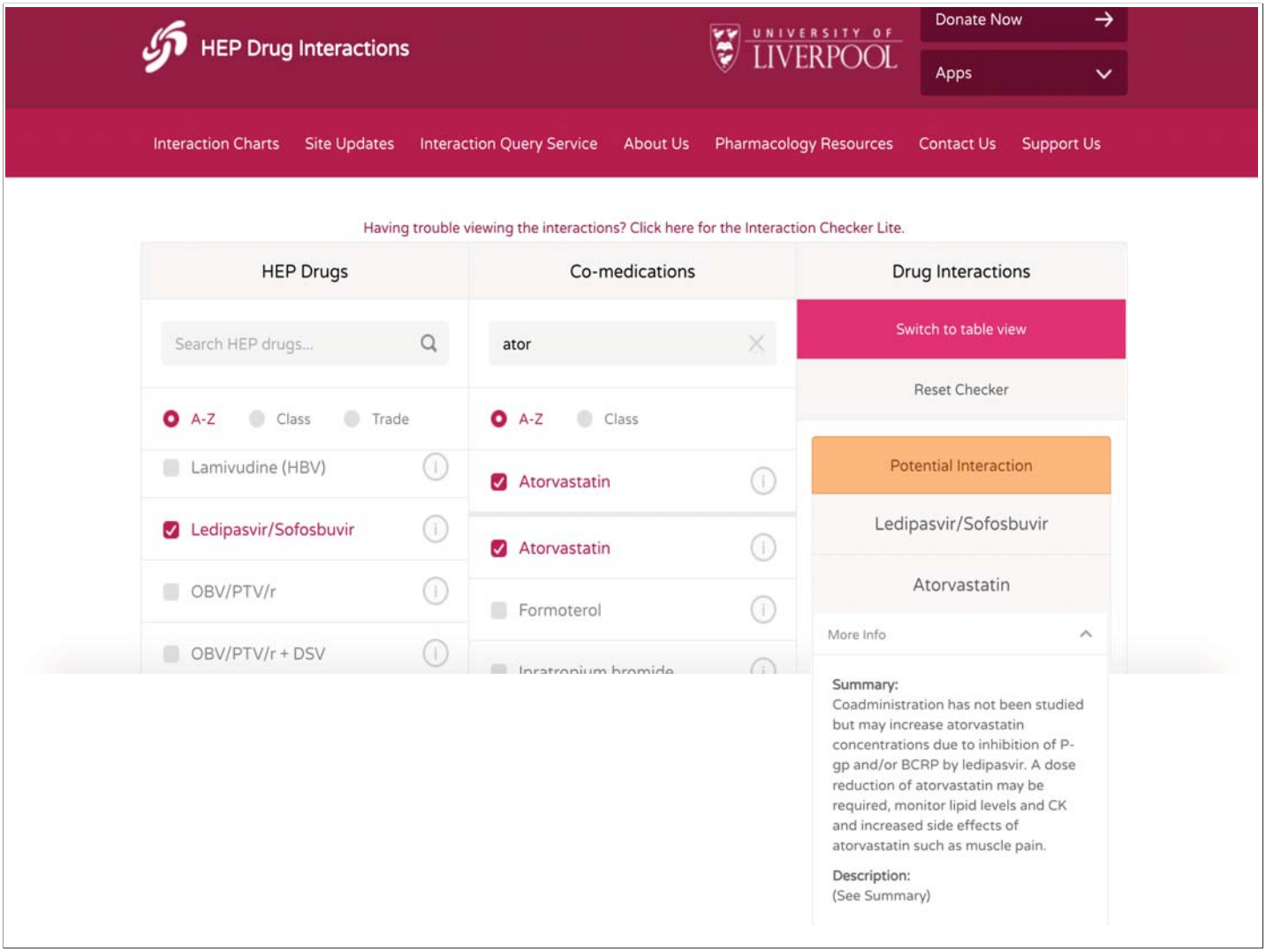
Metabolic Pathways of Potential Drug-Drug Interactions for Direct Acting Antivirals



P-gp/BRCP
(apical part of enterocytes and basolateral parts of hepatocytes)

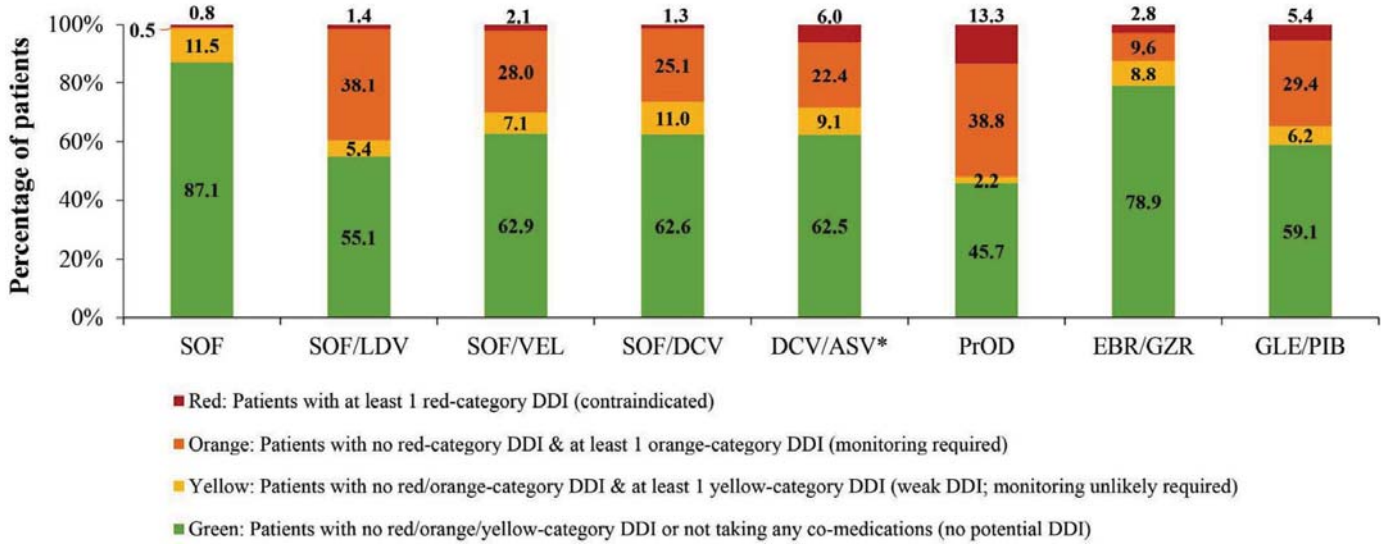
ABC superfamily (P-gp/BRCP)
- Export drugs back to intestine and from the liver to the bile
- Trying to decrease the body drug concentration

Dick TB, et al. Hepatology 2016;63:634-43



Co-morbidities, Concomitant Medications and Potential Drug-Drug Interactions in HCV Patients: INITIATE Study

Patient without cirrhosis or with compensated cirrhosis (N = 762)

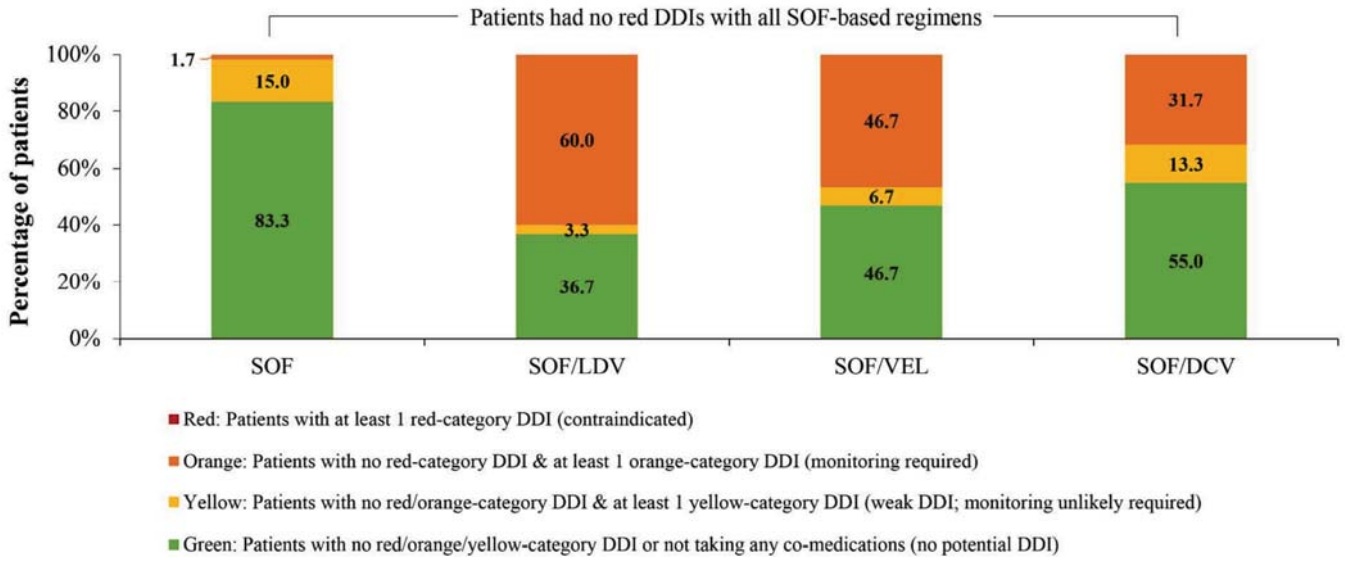


- Red: Patients with at least 1 red-category DDI (contraindicated)
- Orange: Patients with no red-category DDI & at least 1 orange-category DDI (monitoring required)
- Yellow: Patients with no red/orange-category DDI & at least 1 yellow-category DDI (weak DDI; monitoring unlikely required)
- Green: Patients with no red/orange/yellow-category DDI or not taking any co-medications (no potential DDI)

Liu CH, et al. Aliment Pharmacol Ther 2018;48:1290-300

Co-morbidities, Concomitant Medications and Potential Drug-Drug Interactions in HCV Patients: INITIATE Study

Patient with decompensated cirrhosis (N = 60)



Liu CH, et al. Aliment Pharmacol Ther 2018;48:1290-300

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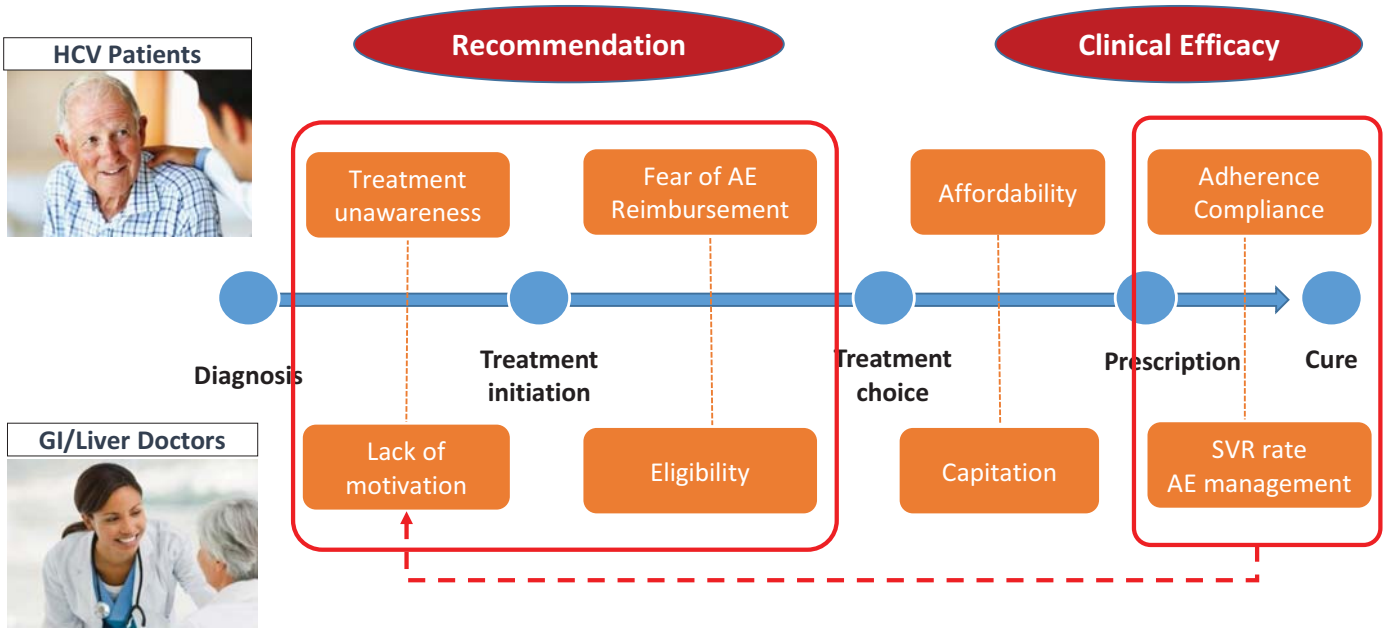
Factors Impacting the Recommendation and Clinical Efficacy



Definition of Public Health Interventions of Infectious Diseases and WHO Target for HCV Elimination 2015-2030

Control	Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level following deliberate efforts with ongoing intervention measures to maintain this reduction.
Elimination of disease	Reduction to zero the incidence of a specific disease in a defined geographical area as a result of deliberate efforts with ongoing intervention measures.
Elimination of infections	Reduction to zero the incidence of infection caused by a specific agent in a defined geographical area as a result of deliberate efforts with continued measures to prevent re-establishment of transmission.
Eradication	Permanent reduction to zero of the worldwide incidence of infection caused by the specific agent as a result of deliberate efforts.
Extinction	The specific infectious agent no longer exists in nature or in the laboratory.

Target Area	Baseline 2015	2020 target	2030 target
Service coverage			
Prevention			
Blood safety: donations screened with quality assurance	89%	95%	100%
Injection safety: use of engineered devices	5%	50%	90%
Harm reduction (sterile syringe/needle set distributed per person per year for people who inject drugs)	20	200	300
Treatment			
Diagnosis of HCV (coverage %)	<5%	30%	90%
Treatment of HCV (coverage %)	<1%	3 million	80% eligible treated
Impact leading to elimination			
Incidence of chronic HCV infections	5-10 million	30% reduction	90% reduction
Mortality from chronic HCV infection	0.70 million	10% reduction	65% reduction

Peltekian KM. Ann Hepatol 2017;16:696-8

Thank You for Your Attention