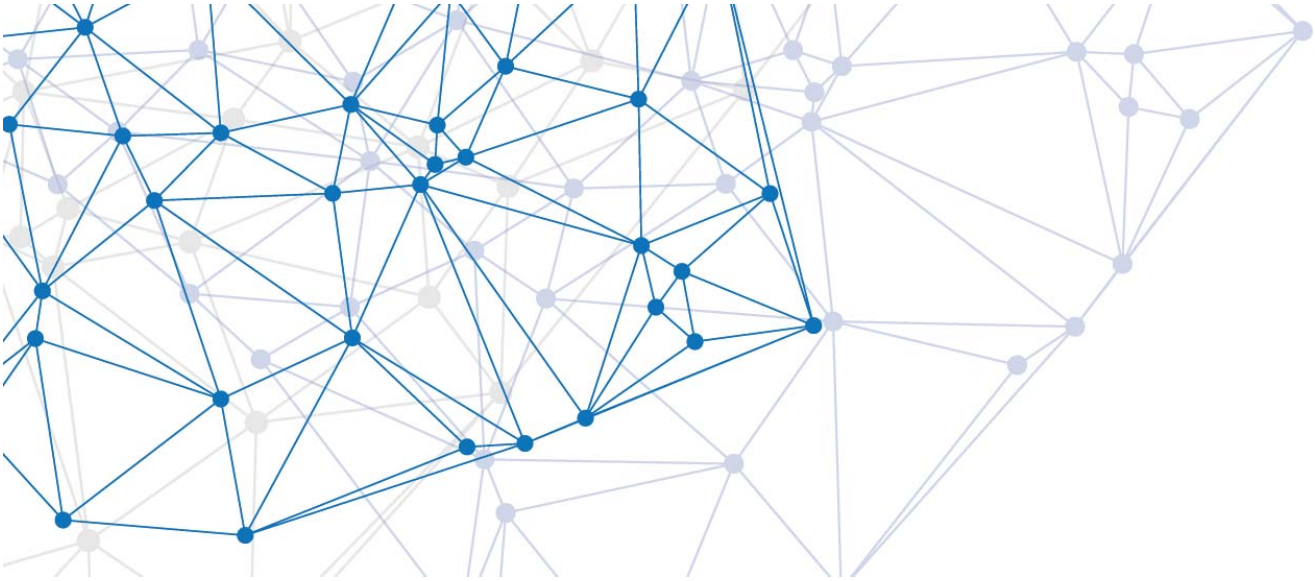

C 型肝炎治療的臨床實務

Chen-Hua Liu, MD, PhD/ 劉振驊 醫師

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

HCV (Epidemiology, Natural History, Treatment, Public Health Issue)

1. **HCV epidemiology and natural history: Global & Taiwan's view**
2. **Introduction: direct acting antivirals (DAAs)**
3. **DAA in usual population: pangenotypic regimens**
   - **Glecaprevir/pibrentasvir**
   - **Sofosbuvir/velpatasvir**
4. **Special Population**
   - **Severe renal impairment (RI)**
   - **Organ transplantation: chronic and de novo**
   - **HIV coinfection**
   - **HBV coinfection**
   - **Adolescents and Children**
5. **Drug drug interaction (DDI), pill characters**
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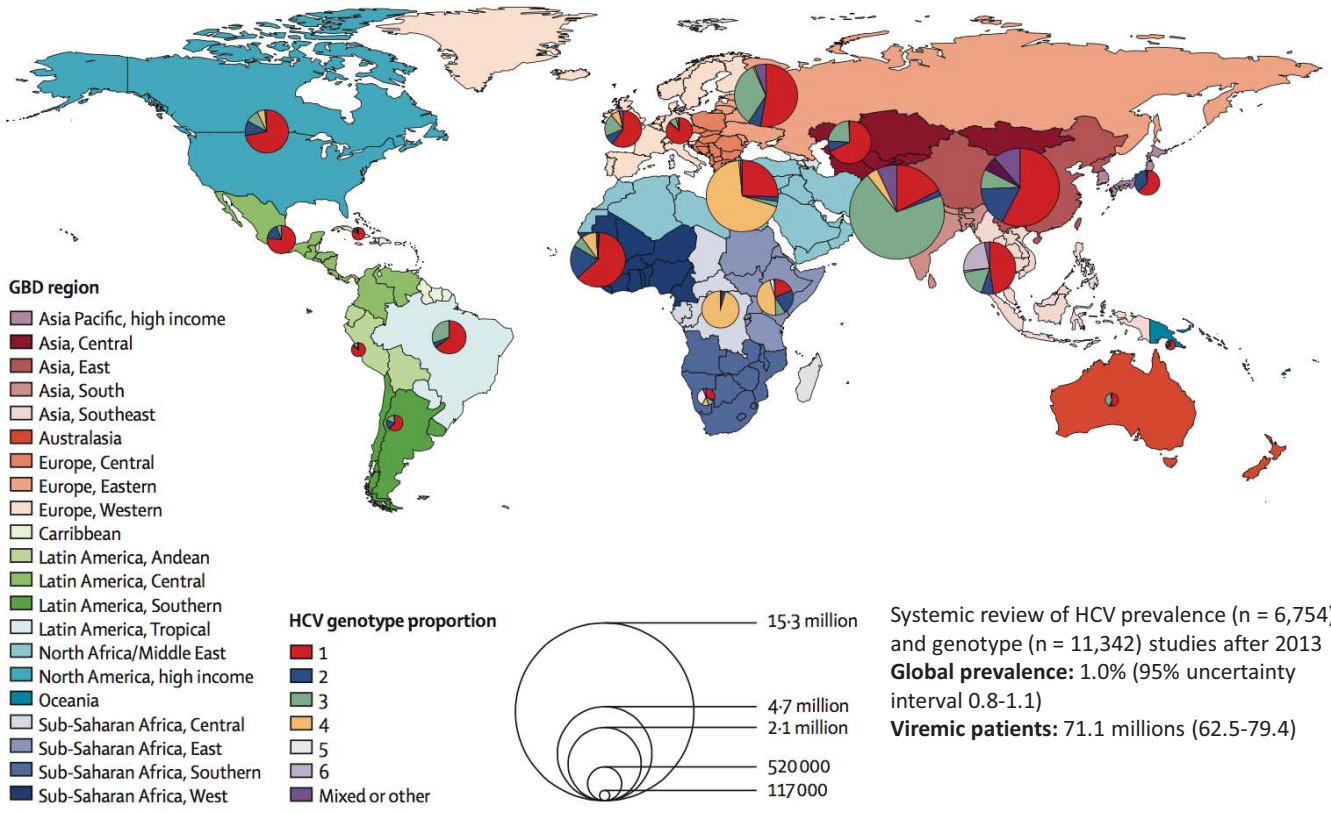
Global Prevalence and Genotype Distribution of HCV in 2015

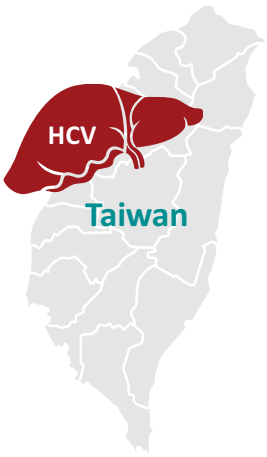


Systemic review of HCV prevalence (n = 6,754) and genotype (n = 11,342) studies after 2013
Global prevalence: 1.0% (95% uncertainty interval 0.8-1.1)
Viremic patients: 71.1 millions (62.5-79.4)

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

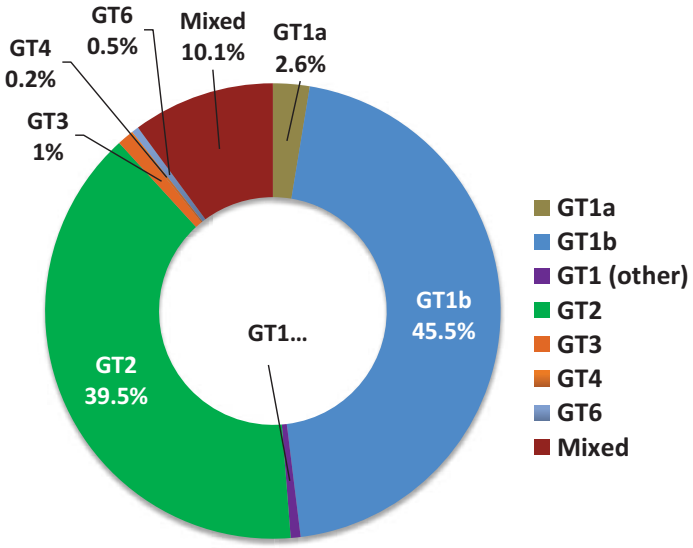
HCV Prevalence and Genotypes Distribution in Taiwan: Global Survey Polaris 2015

HCV infection is one of the leading causes of chronic hepatitis, liver cirrhosis, and HCC worldwide



HCV viremic population
489,000 [310,000-877,000]

HCV viremic prevalence
2.1% [1.3%-3.7%]

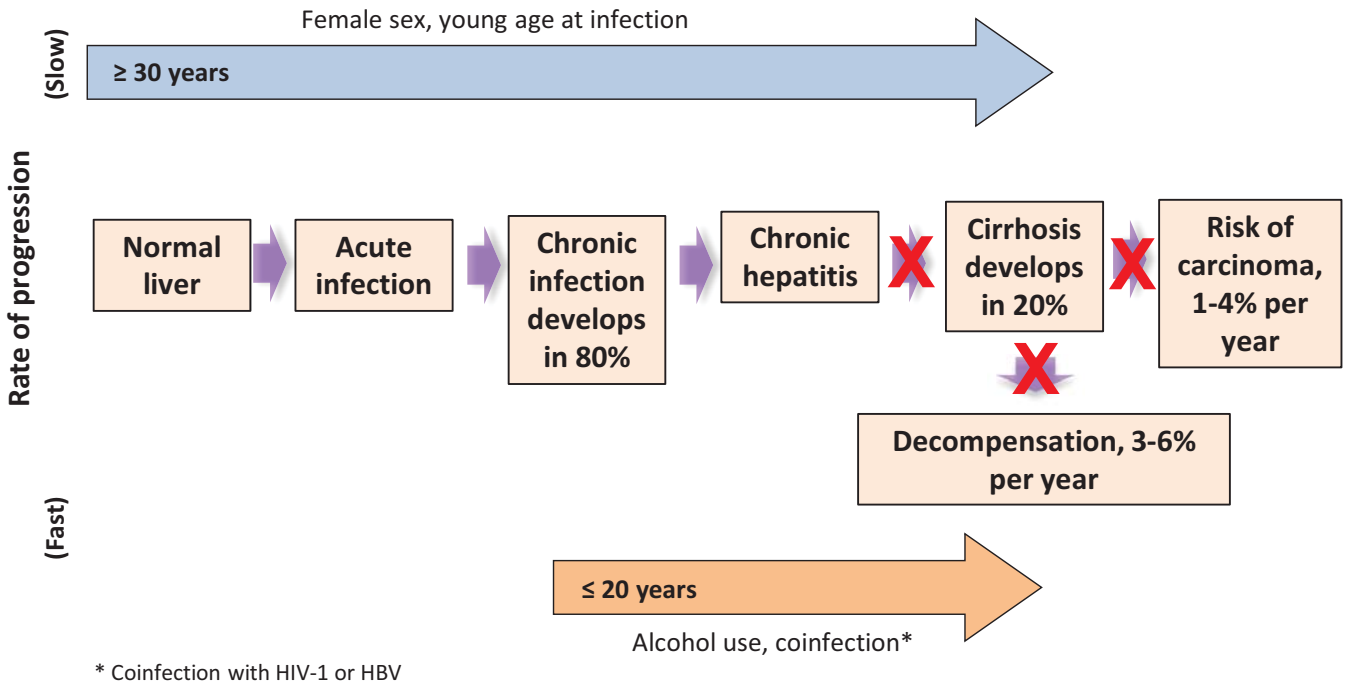


Dominant GT in Taiwan: GT1b & GT2

- 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

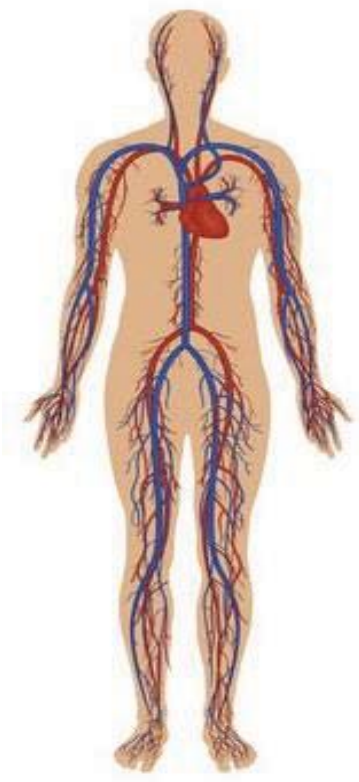
Lauer GM, et al. N Engl J Med 2001;345:41-52

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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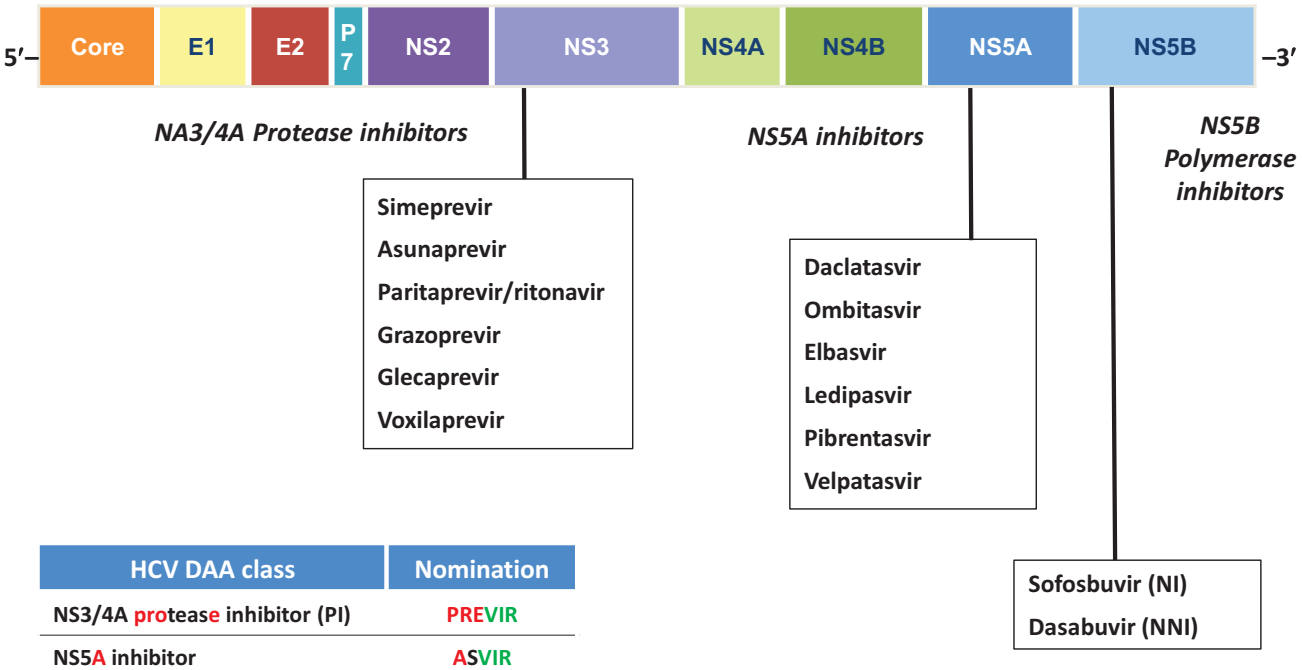
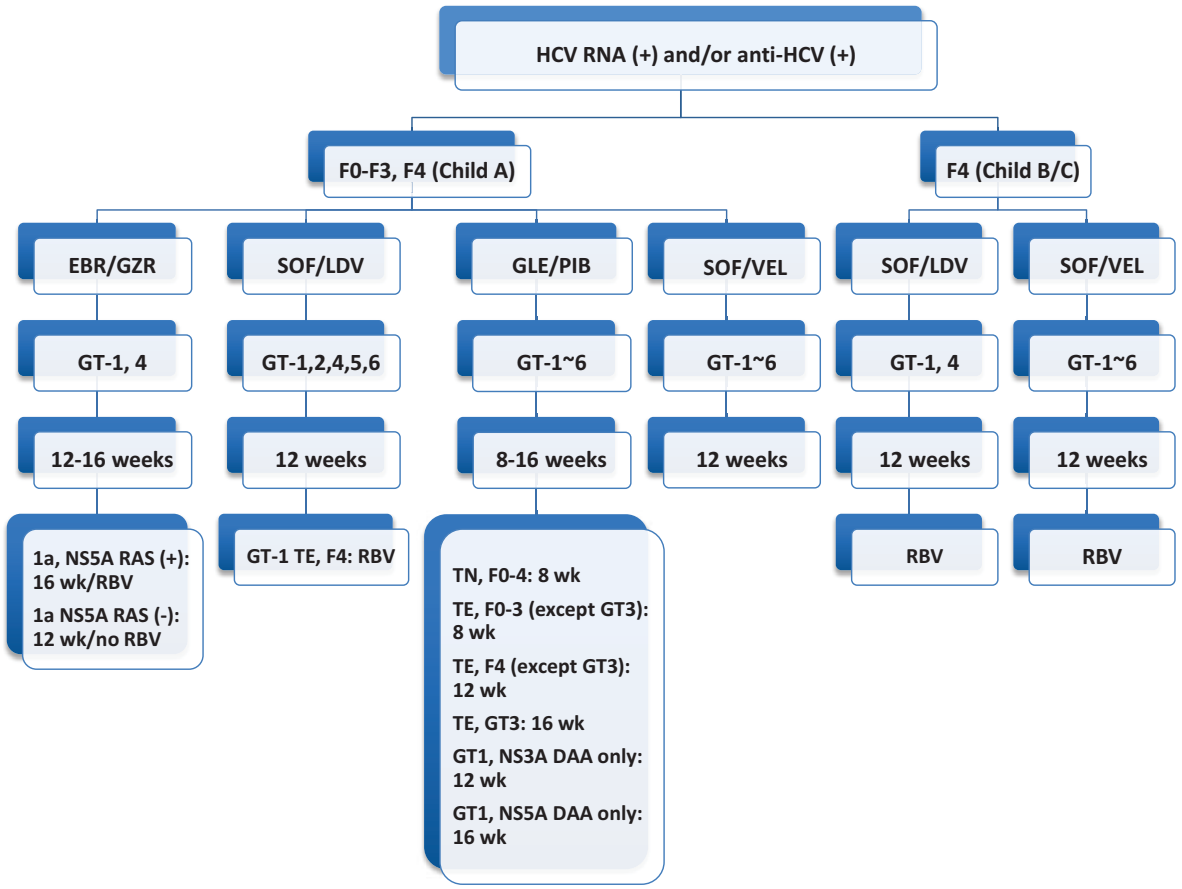
Therapeutic Targets of Licensed DAAs for HCV (Licensed)



HCV DAA class	Nomination
NS3/4A protease inhibitor (PI)	PREVIR
NS5A inhibitor	ASVIR
NS5B polymerase inhibitor	BUVIR

Cocktail combination therapy is required and mandatory !

C肝患者符合健保給付條件 (2020) [Practical Use]



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

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
Sofosbuvir Velpatasvir	1a	1b	2	3	4	5	6
Glecaprevir Pibrentasvir	1a	1b	2	3	4	5	6
Sofosbuvir Velpatasvir Voxilaprevir	1a	1b	2	3	4	5	6

IFN-free DAAs for HCV-Infected Patients: EASL Guideline

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	8 wk	No	8-12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	8 wk	No	8-12 wk	8 wk (F0-F2) 12 wk (F3)	8 wk (F0-F2) 12 wk (F3)
	Treatment-experienced	12 wk	8 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 3	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 4	Treatment-naïve	12 wk	8 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No

- SOF/VEL/VOX for 8 weeks in HCV-1a: 92% SVR_{12}
- SOF/VEL for 12 weeks in HCV-1a: 99% SVR_{12}

EASL. J Hepatol 2018;69:461-511

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Main Considerations of HCV DAAs in HCV Patients

Efficacy and safety

DDI consideration

Concomitant drugs

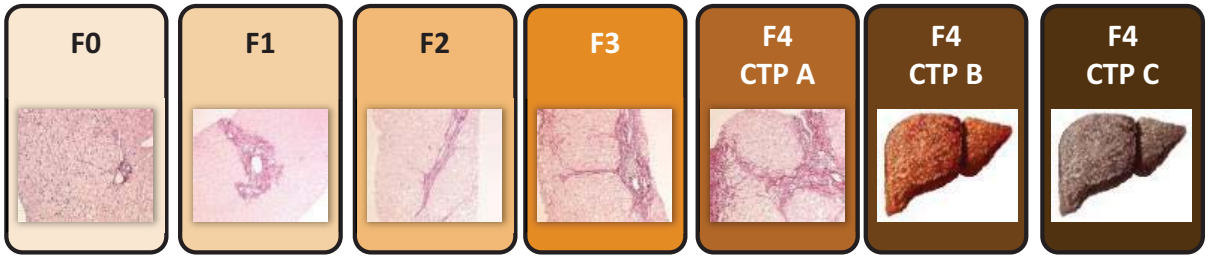
Adherence consideration

Pill burden

Treatment duration

Treatment style

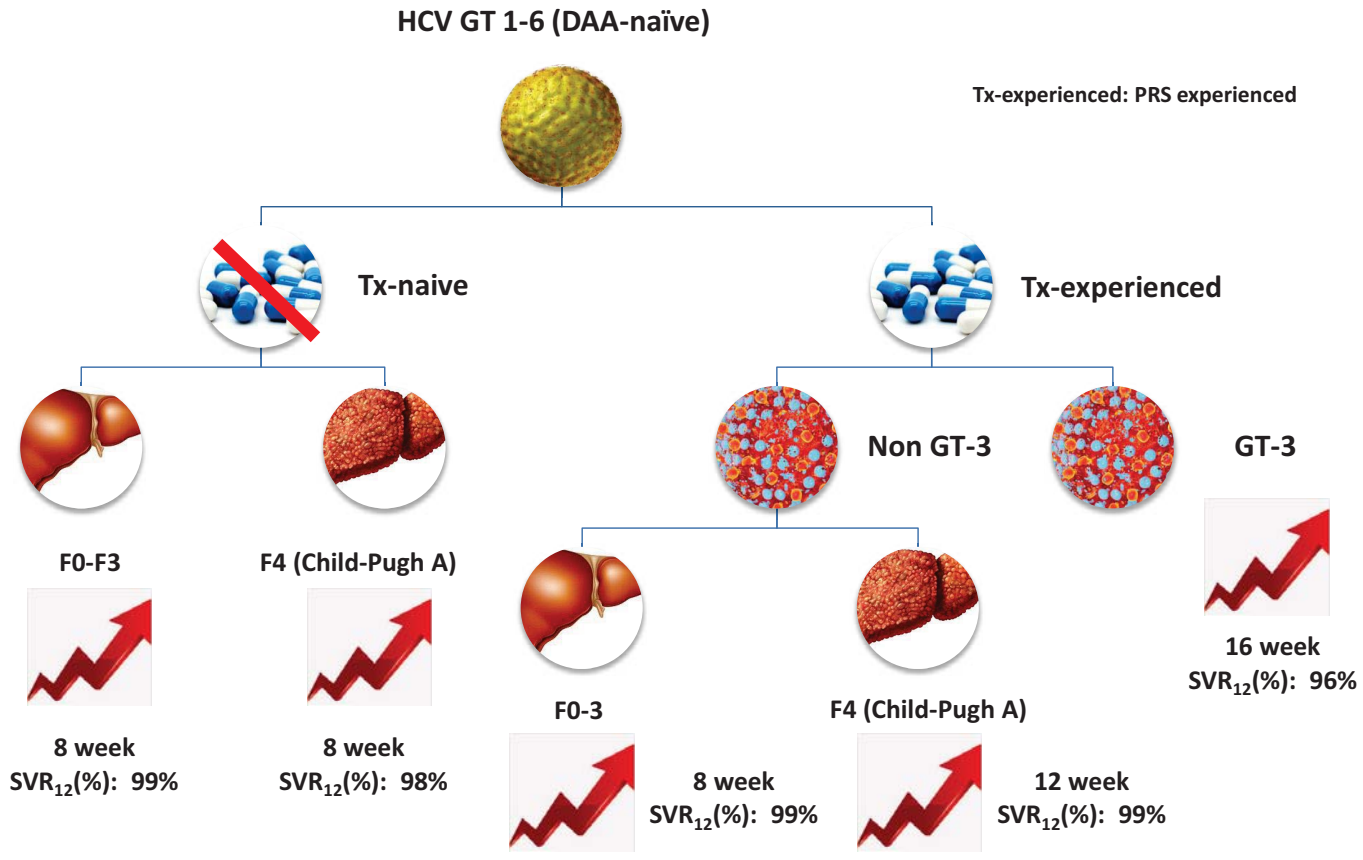
Glecaprevir/Pibrentasvir vs. Sofosbuvir/Velpatasvir: Spectrum for Stage of Liver Disease



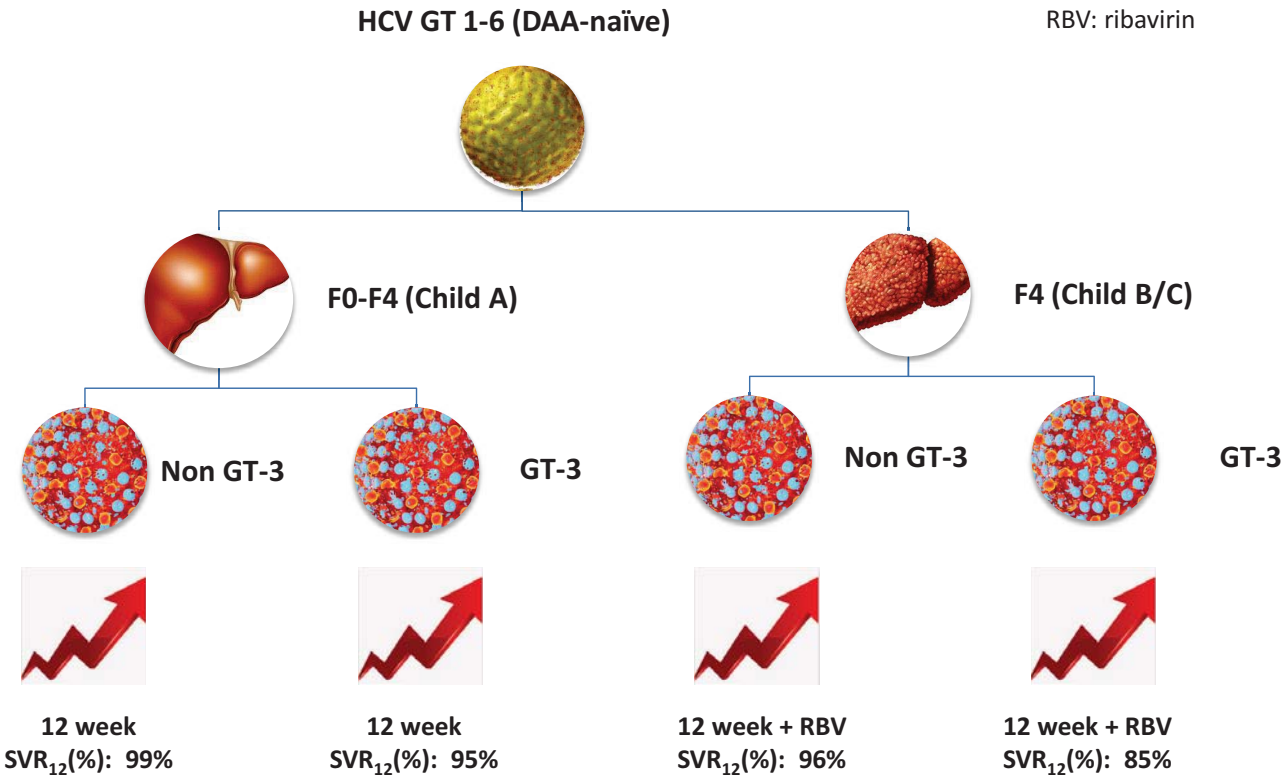
	F0	F1	F2	F3	F4 CTP A	F4 CTP B	F4 CTP C
GLE/PIB	O	O	O	O	O	X	X
SOF/VEL	O	O	O	O	O	O	O

- HCV NS3/4A protease inhibitors (PIs) are contraindicated for patients with current or past history of decompensated cirrhosis. Use of PI-based DAAs has potential risk of liver damage which may result in more severe hepatic decompensation or deaths.

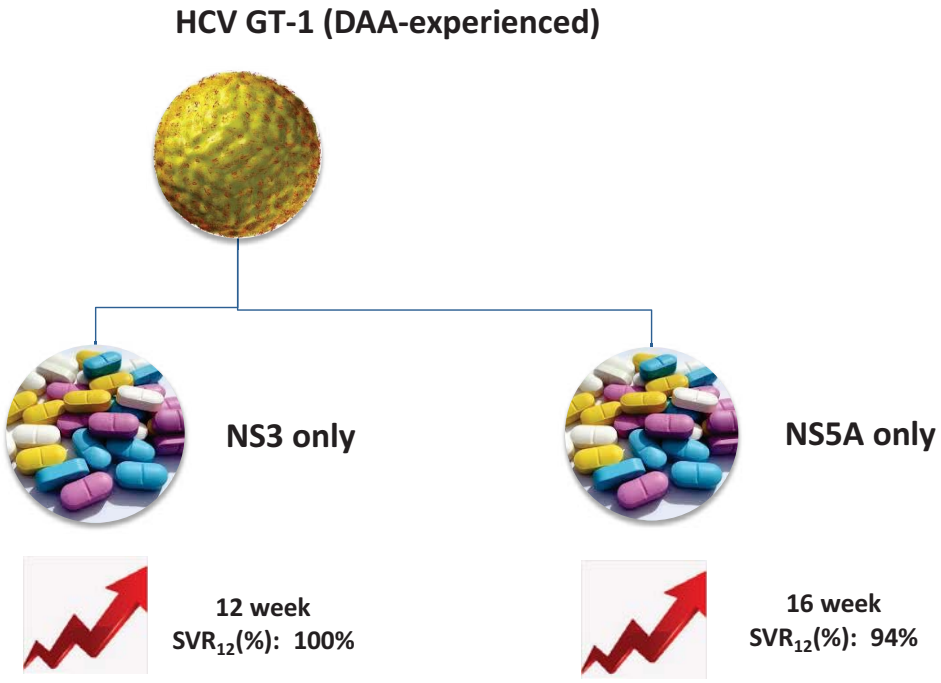
Glecaprevir/Pibrentasvir: Evidence and Flow of Usage (DAA-Naïve)



Sofosbuvir/Velpatasvir: Evidence and Flow of Usage (DAA-Naïve)



Glecaprevir/Pibrentasvir: Evidence and Flow of Usage (DAA-experienced)



Safety of Glecaprevir/Pibrentasvir for HCV Genotype 1-6 Patients: Integrated Analysis

- **Design (N = 2265):** integrated analysis of ENDURANCE-I, II, III, and IV, EXPEDITION-I, MAGELLAN-I, SURVEYOR-I and II

Event, n (%)	Non-cirrhotic patients (n = 1977)	Compensated cirrhotic patients (n = 288)	Total (N = 2265)
Any AE	1316 (67)	213 (74)	1529 (68)
AE occurring in ≥ 10% patients			
Headache	363 (18)	47 (16)	410 (18)
Fatigue	272 (14)	58 (20)	330 (15)
Any SAE	31 (2)	17 (6)	48 (2.1)
DAA-related SAE	1 (< 0.1)	0 (0)	1 (< 0.1)
Any AE leading to DC	8 (0.4)	0 (0)	8 (0.4)
Any DAA-related AE with ≥ grade 3	4 (0.2)	0 (0)	4 (0.2)
Any fatal AE	2 (0.1)	0 (0)	2 (< 0.1)
Death	5 (0.3)	1 (0.3)	6 (0.3)
Laboratory abnormalities	**Non-cirrhotic patients, n/N (%)**	**Compensated cirrhotic patients, n/N (%)**	**Total, n/N (%)**
ALT ≥ grade 3 (> 5X ULN)	2/1975 (0.1)	0 (0)	2/2263 (< 0.1)
Total Bil ≥ grade 3 (> 3X ULN)	6/1975 (0.3)	2/288 (0.7)	8/2263 (0.4)

Dufour JF, et al. EASL 52nd Annual Meeting, Amsterdam, Netherland, 2017

Integrated Safety Analysis of Sofosbuvir/Velpatasvir in HCV Patients: ASTRAL 1-3

Patients, n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF+RBV 12 Week N=132	SOF+RBV 24 Week N=275
AE	821 (79)	89 (77)	101 (77)	260 (95)
Grade 3 or 4 AE	33 (3)	1 (<1)	3 (2)	24 (9)
SAE	23 (2)*	0	2 (2)	15 (5)
AE leading to treatment D/C	2 (<1)^	2 (2)	0	9 (3)
Death	3 (<1)*	0	0	3 (1)**

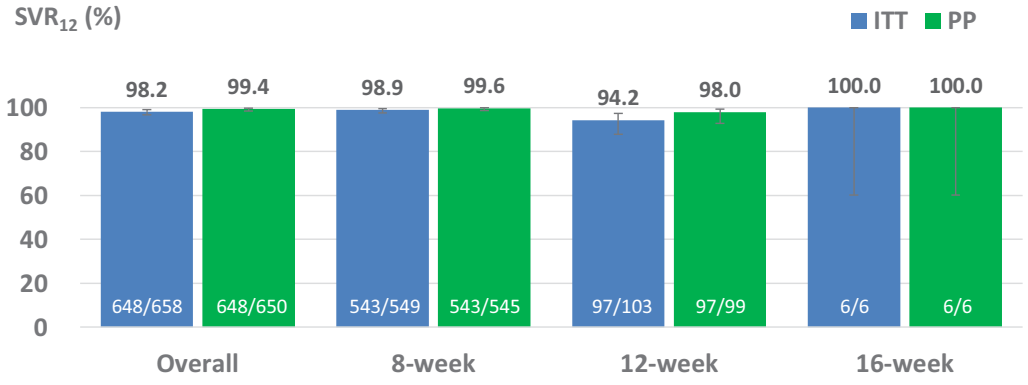
*No SAE was assessed as related to SOF/VEL (Severe AEs were rare in SOF/VEL-treated patients, with headache, anxiety, and acute myocardial infarction occurring >1 patient (both cases of acute myocardial infarction were assessed as not related to SOF/VEL treatment by the investigators) **None were assessed as related to study treatment ^Two subjects D/C SOF/VEL for AEs; (1 D/C day 1 due to difficulty concentrating, headache, and anxiety and 1 D/C day 13 of due to anxiety)

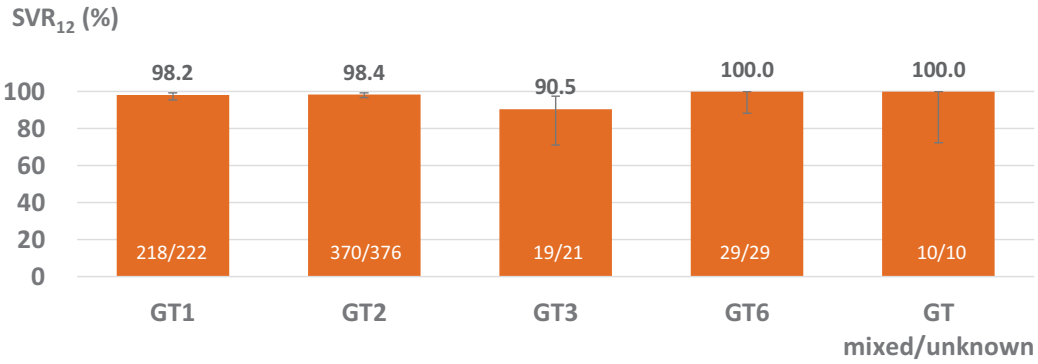
Patients, n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF+RBV 12 Week N=132	SOF+RBV 24 Week N=275
Headache	296 (29)	33 (28)	29 (22)	89 (32)
Fatigue	217 (21)	23 (20)	47 (36)	105 (38)
Nausea	135 (13)	13 (11)	19 (14)	58 (21)
Insomnia	87 (8)	11 (9)	18 (14)	74 (27)
Nasopharyngitis	121 (12)	12 (10)	2 (2)	33 (12)
Cough	57 (6)	4 (3)	6 (5)	35 (13)
Irritability	49 (5)	4 (3)	9 (7)	40 (15)
Pruritus	33 (3)	5 (4)	7 (5)	35 (13)
Dyspepsia	33 (2)	4 (3)	5 (4)	30 (11)

Treatment with SOF/VEL for 12 weeks was well tolerated and had a safety profile similar to that of placebo treatment

Jacobson IM, et al. EASL 51th Annual Meeting, Barcelona, Spain, 2016

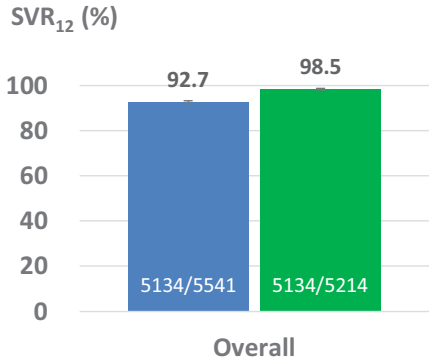
Glecaprevir/Pibrentasvir for HCV: Real-World Study in Taiwan





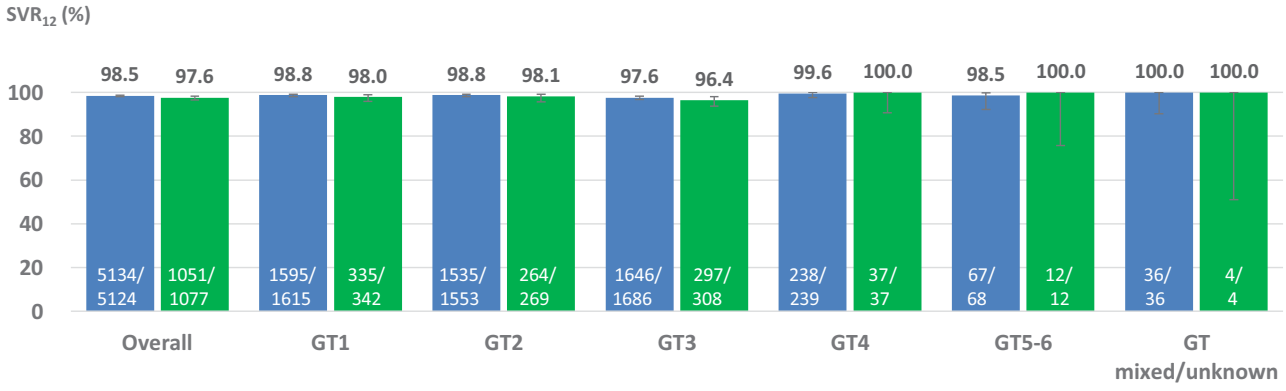
Liu CH, et al. Liver Int 2019 [Epub ahead of print]

Sofosbuvir/Velpatasvir: Global Integrated Efficacy Analysis of 12 Practice Cohorts



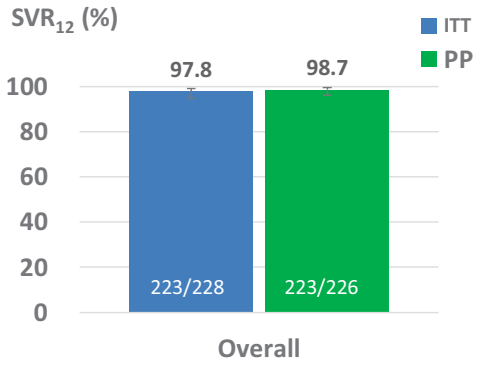
407 patients did not achieve SVR12/24 (7.3%)

- Overall **non-virological** failure rate **5.9%** (327/5541)
  - LTFU 4% (219/5541)
- Overall **virological** failure rate **1.4%** (80/5541)

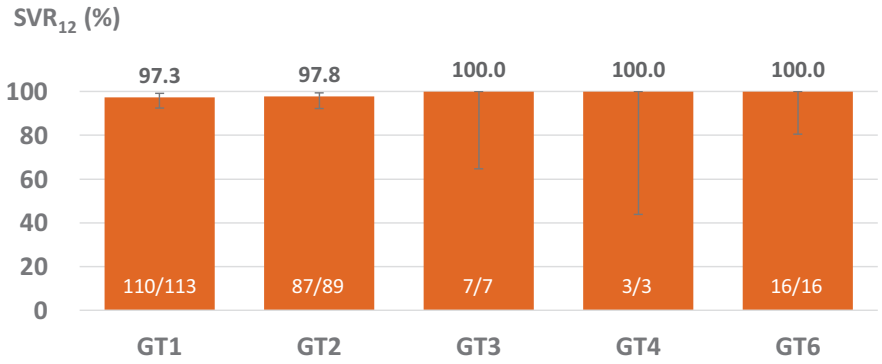


Mangia A, et al. EASL 54th Annual Meeting, Vienna, Austria, 2019

Sofosbuvir/Velpatasvir: Efficacy of Generic Version in Taiwan



- Overall **non-virological** failure rate **0.9%** (2/228)
- Overall **virological** failure rate **1.3%** (3/226)



Liu CH, et al. Aliment Pharmacol Ther 2018;47:1690-8

SVR_{12} According to Different DAA Regimens (NHI in Taiwan) (2019/09/27)

用藥療程 DAA Regimen	治療人數 Total Treated [1]	達追蹤人數 # of complete Follow-up [2]	偵測不到病毒人數 Undetectable [3]	偵測到病毒人數 Detectable [4]	太早驗人數 (偵測不到病毒人數) Incorrect testing time (# of undetectable [5] ([6])	提早停藥人數 (%) Withdrawal from treatment [7]	完成治療但未回診檢測 (%) No return for RNA testing at 12w [8]	SVR-12W[1] [3]/[2]	SVR-12W[2] ([3]+[6])/([2]-[8])	SUR-12W[3] [3]/([3]-[4])
Total	42,042	10,158	8,559	133	0 (0)	318 (3.1%)	1,148 (11.3%)	84.3%	95.0%	98.5%
DCV+ASV/1b/24w	48	1	0	0	0 (0)	1 (100%)	0 (0%)	0.0%	0.0%	--
PrOD/1b/12w	25	12	9	1	0 (0)	0 (0%)	2 (16.7%)	75.0%	90.0%	90.0%
EBR/GZR±r/1a/12w	82	15	13	0	0 (0)	1 (6.7%)	1 (6.7%)	86.7%	92.9%	100.0%
EBR/GZR±r/1a/16w	2	0	--	--	--	--	--	--	--	--
EBR/GZR±r/1b/12w	5,814	1,327	1,118	14	0 (0)	36 (2.7%)	159 (12%)	84.3%	95.7%	98.8%
SOF/LDV±r/1a1b2456/12w	19,458	4,328	3,600	53	0 (0)	180 (4.2%)	495 (11.4%)	83.2%	93.9%	98.5%
SOF+r/2/12w	73	28	24	0	0 (0)	2 (7.1%)	2 (7.1%)	85.7%	92.3%	100.0%
GLE/PIB/1a1b23456/8w	13,542	4,124	3,534	62	0 (0)	73 (1.8%)	455 (11%)	85.7%	96.3%	98.3%
GLE/PIB/1a1b23456/12w	1,328	318	257	3	0 (0)	24 (7.5%)	34 (10.7%)	80.8%	90.5%	98.8%
GLE/PIB/1a1b3/16w	96	5	4	0	0 (0)	1 (20%)	0 (0%)	80.0%	80.0%	100.0%

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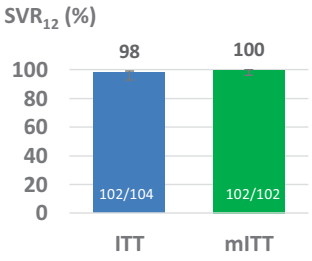
Glecaprevir/Pibrentasvir (G/P) for HCV GT 1-6 Patients with Renal Impairment: EXPEDITION-4

- **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 (%)	26 (25)
Age, median years (range)	57 (28 – 83)
BMI, median kg/m^2 (range)	26 (18 – 45)
IL28B non-CC, n (%)	80 (77)
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	13 (12)
Stage 5	91 (88)
Hemodialysis	85 (82)



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. New Engl J Med 2017;377:1448-55

Glecaprevir/Pibrentasvir in Renally-Impaired Patients with Chronic HCV Genotype 1–6 Infection: EXPEDITION-5

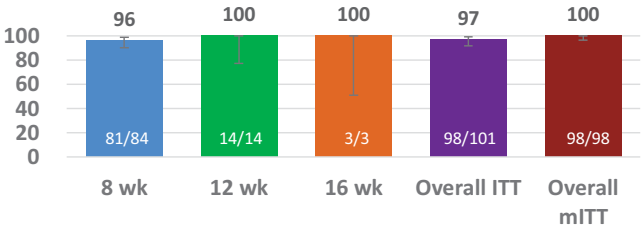
- **EXPEDITION-5:** Treatment-naive or PRS-experienced HCV GT1–6-infected patients with CKD stage 3b, 4, or 5 were treated with a US and/or EU label-approved G/P regimen (8–16 weeks)

Baseline Demographics	8 wk (n = 84)	12 wk n = 13)	16 wk (n = 4)
Male, n (%)	51 (61)	7 (54)	2 (50)
White, n (%)	62 (74)	8 (62)	4 (100)
Age, year, median (range)	59 (32, 84)	58 (49, 87)	62 (54, 70)
BMI, kg/m^2, median (range)	24.9 (16.8, 53.5)	28.7 (17.1, 41.1)	24.3 (17.7, 26.8)
HCV genotype, n (%)			
1	46 (55)	9 (69)	0 (0)
2	26 (31)	1 (8)	0 (0)
3	9 (11)	2 (15)	4 (100)
4	3 (4)	1 (8)	0 (0)
HCV RNA, $\log_{10}$ IU/mL, median (range)	5.9 (3.2, 7.2)	5.6 (4.8, 7.2)	6.6 (5.4, 6.9)
Fibrosis stage, n (%)			
F0-1	61 (73)	0 (0)	4 (100)
F2	5 (6)	0 (0)	0 (0)
F3	16 (19)	0 (0)	0 (0)
F4	1 (1)*	13 (100)	0 (0)
Missing	1 (1)	0 (0)	0 (0)
Prior treatment, n (%)			
Naive	69 (82)	12 (92)	0 (0)
Experienced	15 (18)	1 (8)	4 (100)

Baseline Demographics	8 wk (n = 84)	12 wk n = 13)	16 wk (n = 4)
CKD stage, n (%)			
stage 3b	4 (5)	3 (23)	0 (0)
stage 4	14 (17)	2 (15)	1 (25)
stage 5	66 (79)	8 (62)	3 (75)
On dialysis	66 (79)	8 (62)	3 (75)
Hemodialysis	63 (96)	7 (88)	3 (100)
Peritoneal dialysis	3 (4)	1 (12)	0 (0)

* Despite the staging by FibroTest, other evidence confirmed the subject was non-cirrhotic

SVR$_{12}$ (%)



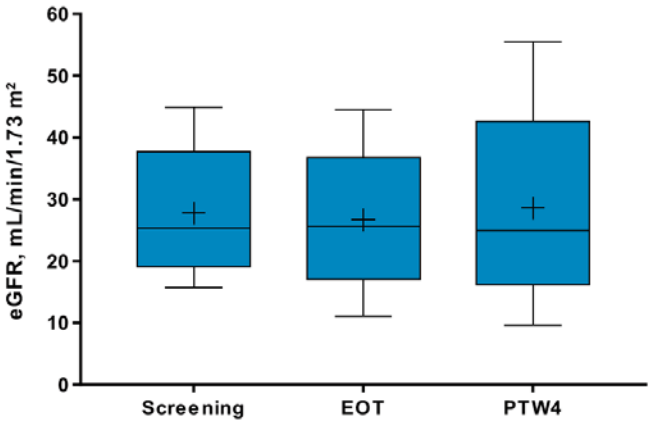
- **Non-SVR$_{12}$ in arm 8 wk:** discontinue (2) and missing SVR$_{12}$ (1)

Lawitz E. et al. Liver Int 2019 [Epub ahead of print]

Glecaprevir/Pibrentasvir in Renally-Impaired Patients with Chronic HCV Genotype 1–6 Infection: EXPEDITION-5

Adverse event, n (%)	Total N = 101
Any AE	57 (56)
AEs leading to study drug DC*	2 (2)
Serious AE	12 (12)
Grade ≥ 3 AE	13 (13)
Drug-related serious AE	0 (0)
Death	0 (0)
AEs occurring in ≥ 5% total patients	
Pruritus	16 (16)
Hypertension	6 (6)
Generalized pruritus	6 (6)
Bronchitis	5 (5)
Laboratory abnormalities (grade ≥ 3)	
AST > 5X ULN	0 (0)
ALT > 5X ULN	0 (0)
Total bilirubin > 3X ULN	0 (0)

* AEs of ileus and pruritus; the latter was considered DAA-related and started on Day 5 leading to study drug discontinuation and resolved by Day 18.



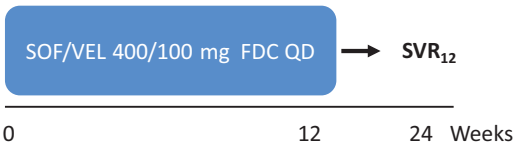
Of the 24 patients with CKD 3b/4 and available data, mean eGFR remained unchanged from screening to EOT to PTW4

No patient experienced an AE of worsening renal function or started dialysis during or post treatment

Lawitz E. et al. Liver Int 2019 [Epub ahead of print]

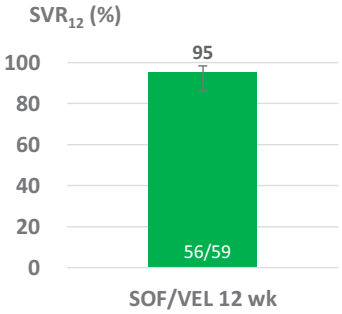
Sofosbuvir/Velpatasvir for 12 Weeks in Patients on Dialysis

- **Design (N = 59):** one arm SOF/VEL for 12 weeks
- **Criteria:** any HCV GT, compensated or decompensated liver disease, HD/PD included



Characteristics	SOF/VEL (N = 59)
Age, y, mean (range)	60 (33-91)
Male, n (%)	35 (59)
White, n (%)	31 (53)
BMI, kg/m², mean (range)	26 (17-39)
HCV genotype, n (%)	
1	25 (42)
1a	15 (25)
1b	11 (19)
Other	1 (2)
2	7 (12)
3	19 (32)
4	4 (7)
6	2 (3)

Characteristics	SOF/VEL (N = 59)
Compensated cirrhosis, n (%)	17 (29)
IL28B CC, n (%)	23 (30)
HCV RNA, log_{10} IU/mL, mean (range)	5.8 (3.1-7.7)
Prior Tx experience, n (%)	13 (22)
Types of dialysis, n (%)	
Hemodialysis	54 (92)
Peritoneal dialysis	5 (9)
Duration of dialysis, y, mean (range)	7 (0-40)
Prior renal transplant, n (%)	19 (32)

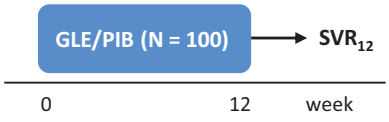


Patient, n (%)	SOF/VEL (N = 59)
Virologic failure	2 (3)
Relapse	2 (3)
Others	1 (2)

Borgia SM, et al. J Hepatol 2019 [Epub ahead of print]

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)

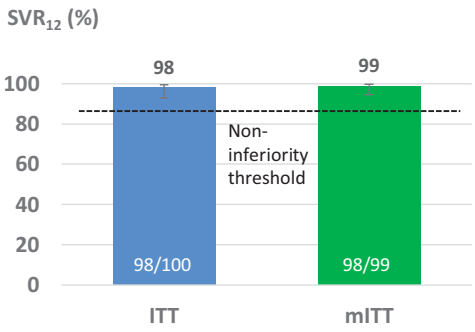
Characteristics	G/P 12 wk (N = 100)
Time since transplant, m, median (range)	55.6 (4.2, 545.3)
eGFR, mL/min/1.73m², median (range)	62.3 (28.7, 132.2)

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

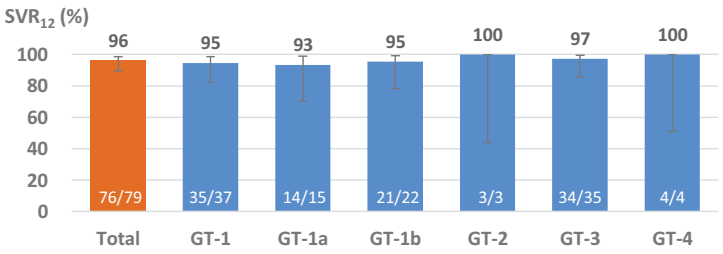
Sofosbuvir/Velpatasvir for HCV Genotype 1-4 Liver Transplant Recipients

- **Design:** single-arm, open label study in liver transplant recipients (F0 to F4 Child A) with recurrent chronic HCV GT 1-6 (viremia ≥ 3 months) post transplantation in Spain, UK and Switzerland

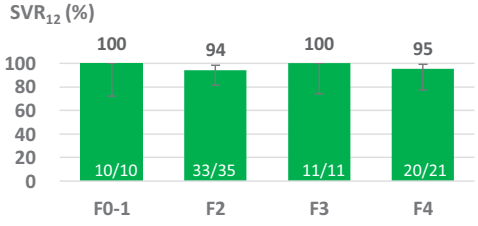
Characteristic	Patient (N = 79)
Age, y, mean (range)	62 (45, 81)
Male, n (%)	64 (81)
White, n (%)	65 (82)
BMI, kg/m², mean (range)	28 (18, 39)
HCV GT, n (%)	
1a/1b	15/22 (19/28)
2/3/4	3/35/4 (4/44/5)
Fibrosis stage (FibroTest), n (%)	
F0-1/F2/F3/F4	10/35 (13/44)
F3/F4/missing	11/21/2 (14/27/3)
TE, n (%)	47 (60)
Cirrhosis/no cirrhosis)	5/42 (6/53)
PR (DAA/no DAA)	43/4 (54/5)
Time since transplant, y, mean (range)	8.7 (0.3-23.9)
Immunosuppression use, n (%)	
Tacrolimus	56 (71)
Cyclosporine	11 (14)
Sirolimus/everolimus	8/5 (10/6)
Mycophenolate	19 (24)
Azathioprine/prednisolone	9/1 (11/1)

Disposition	Patient (N = 79)
Complete drug	78 (99)
Discontinue*	1 (1)

* DC on day 7 due to hyperglycemia



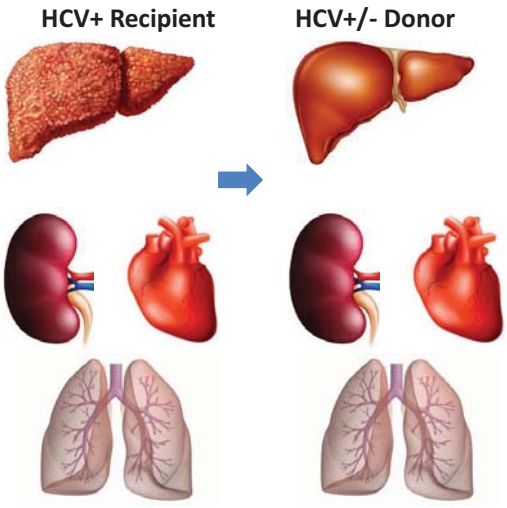
Relapse: 1a and 3 in 1; **Non-VF:** 1b in 1



Agarwal K, et al. J Hepatol 2018;69:603-7

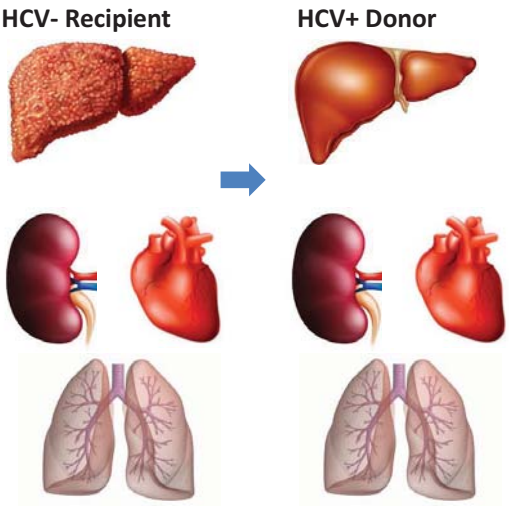
Potential Role of DAAs in Solid Organ Transplantation

Recurrent HCV Infection
HCV Superinfection



Recurrent infection (acute): prophylaxis (?), preemptive (?) DAAs (level III)
Recurrent infection (chronic): DAA (level I)
HCV superinfection: DAAs (level I)

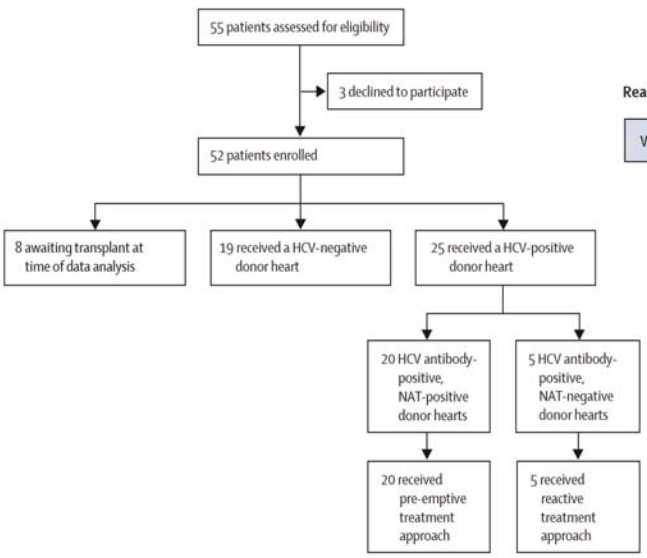
***De novo* HCV Infection**

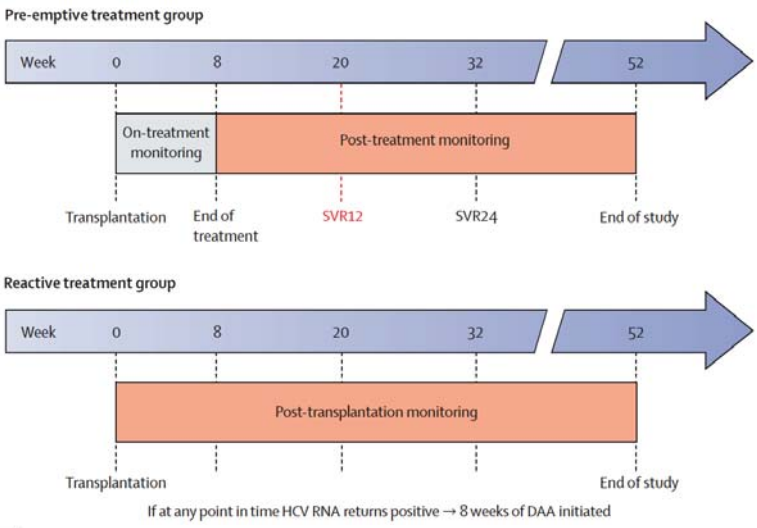


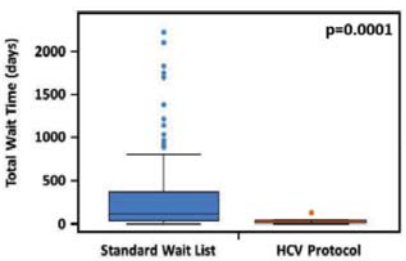
De novo infection (acute): prophylaxis (?), preemptive (?) DAAs (level III)
De novo infection (chronic): DAA (level I)

Preemptive DAA Therapy in Donor HCV-Positive to HCV-Negative Cardiac Transplantation

- **Design:** open-label, single arm, proof of concept study; G/P treatment before being transported to operation room, total DAA treatment 8 weeks; NAT (+) donors to HCV-negative recipients







- **HCV protocol: 20 days (IQR: 8-57)**
- **Standard wait list: 113 days (IQR: 40-366)**

Bethea E, et al. Lancet Gastroenterol Hepatol 2019;4:771-80

Preemptive DAA Therapy in Donor HCV-Positive to HCV-Negative Cardiac Transplantation

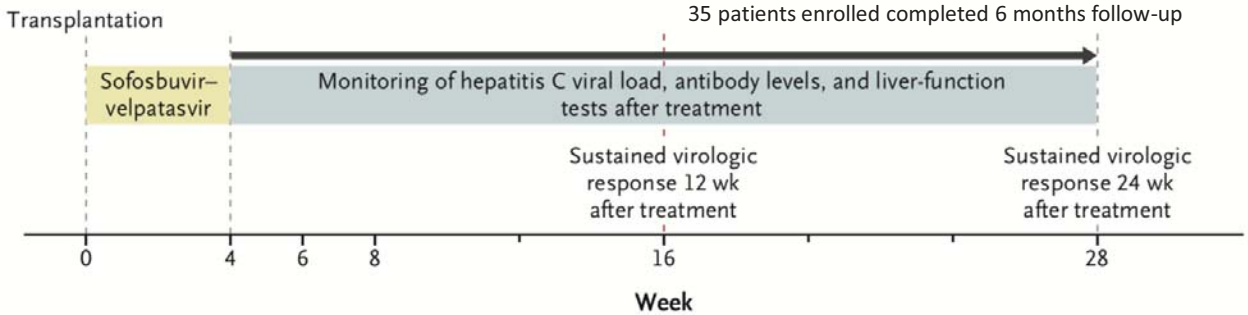
	eGFR (mL/min per 1·73 m²)	Time from HCV-positive consent to transplantation (days)	Donor NAT	Donor genotype	Donor viral load (IU/mL)	Peak recipient viral load (IU/mL)	Time to unquantifiable or undetectable viral load (days)	SVR12*
1	50	20	+	1a	36 000	0	0	Yes
2	>60	10	+	1a	13 000 000	1100	3	Yes
3	45	8	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
4	38	79	+	1a	7 640 000	458	1	Yes
5	45	83	+	3	2 540 000	0	0	Yes
6	47	1	+	1a	6 070 000	498	8	Yes
7	12†	2	+	1a	3 760 000	213	7	Yes
8	>60	9	+	1a	2 450 000	1060	9	Yes
9	>60	37	+	1a	4 620 000	409	7	Yes
10	>60	130	+	1	1 010 000	0	0	Yes
11	35	1	+	Indeterminant	232	0	0	Yes
12	>60	1	+	3	446 000	0	1	Yes
13	28	27	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
14	39	25	+	Indeterminant	9 930 000	7300	14	Yes
15	42	10	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
16	20	17	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
17	30†	41	+	1a	4200000	643	14	Yes
18	28	2	–	NA	Undetectable (NAT–)	Undetectable (NAT–)	Undetectable (NAT–)	NA
19	>60	57	+	Indeterminant	420	0	0	Yes
20	>60	60	+	1b	>100 000 000	5110	14	Yes
21	>60	78	+	Indeterminant	5 610 000	892	4	Yes
22	>33	2	+	1a	1 060 000	123	7	Yes
23	>60	264	+	1a	3 210 000	0	0	Yes
24	40	14	+	1a	1930	0	0	Yes
25	>60	37	+	1a	37 000 000	2190	17	Yes

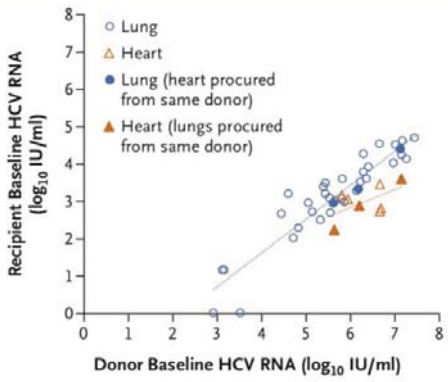
- No treatment-related AE or HCV-attributable AEs or SAEs
- No drug reactions or interactions have necessitated a relapse or cessation of therapy
- Patient and allograft survival: 100% at a median follow-up of 10.7 months [range 6.5-10.8]

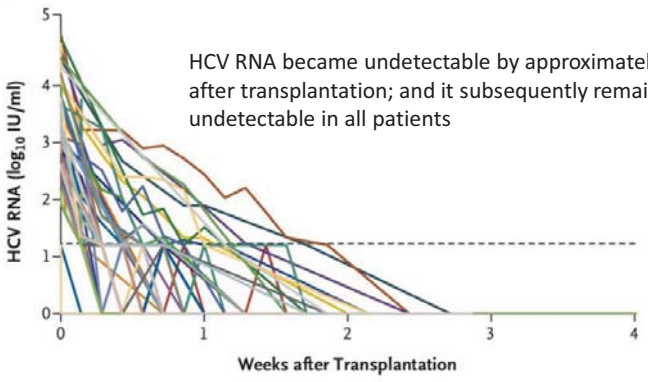
Bethea E, et al. Lancet Gastroenterol Hepatol 2019;4:771-80

Heart and Lung Transplant from HCV Infected Donors to Uninfected Recipients: DONATE HCV Trial

- **Design (N = 44):** pre-emptive sofosbuvir/velpatasvir for 4 weeks, a few hours after heart (n = 8) and lung (n = 36) transplantation



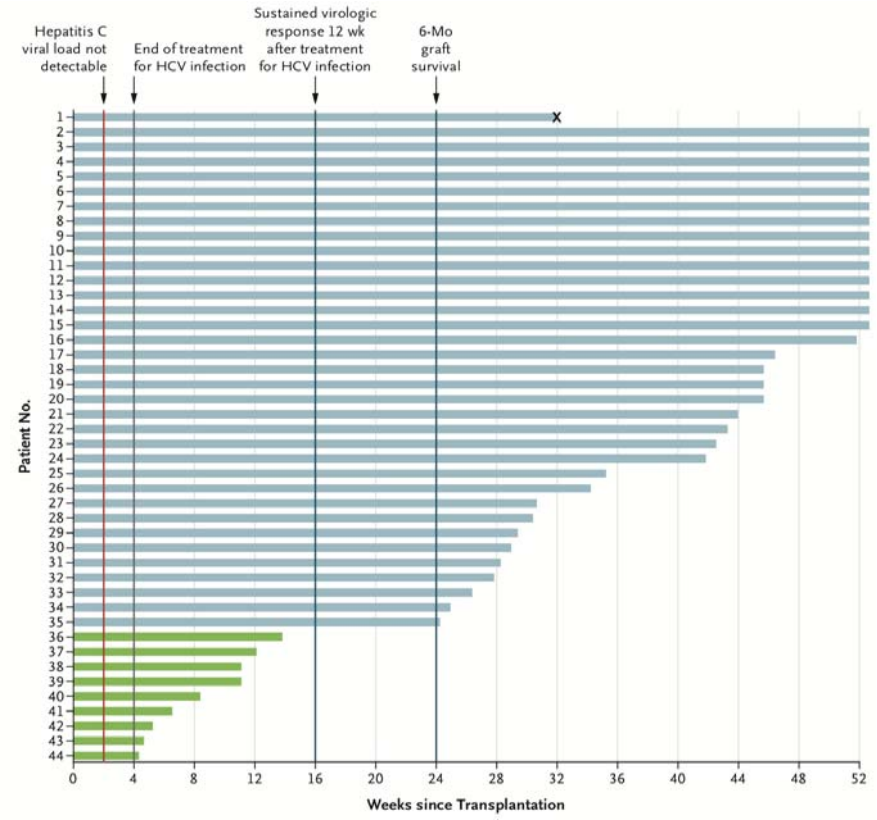




HCV RNA became undetectable by approximately 2 weeks after transplantation; and it subsequently remained undetectable in all patients

Woolley AE, et al. N Engl J Med 2019;380:1606-17

Heart and Lung Transplant from HCV Infected Donors to Uninfected Recipients: DONATE HCV Trial



Results of Patient Follow-up after Transplantation

The black X indicates that Patient 1 died at week 32. The green bars represent patients who had not completed 16 weeks of follow-up by July 31, 2018

SVR_{12}: 35/35 (100%) [95% CI: 90-100]

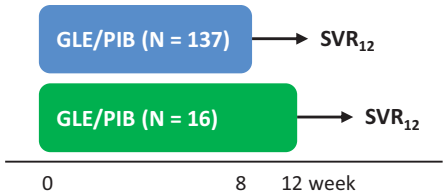
Safety:

1) No treatment-related serious adverse events identified.
2) More cases of acute cellular rejection in lung-transplant recipients receiving SOF/VEL, but the difference was not significant after adjustment for possible confounders.

Woolley AE, et al. N Engl J Med 2019;380:1606-17

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



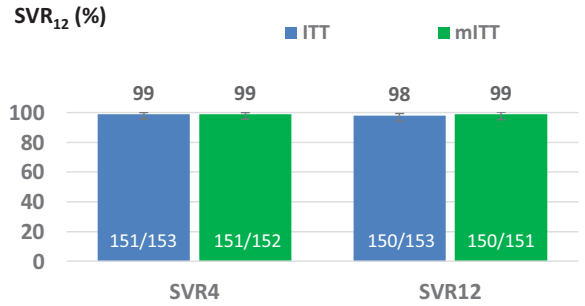
- Non-cirrhosis: 8 wk; cirrhosis: 12 wk
- ART naïve with CD4 count ≥ 500 cells/mm3 or ≥ 29% or on a stable ART regimen for at least 8 weeks prior to screening with CD4 count ≥ 200 cells/mm3 or ≥ 14%, and plasma HIV-1 RNA < LLOQ

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/m², 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/mm³, 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

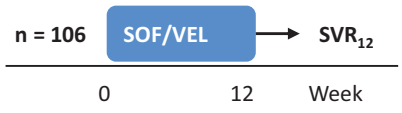
Events, n (%)	G/P 8 wk (N = 137)	G/P 12 wk (N = 16)
Any AE	86 (63)	8 (50)
Grade 1 (mild)	52 (60)	3 (38)
Serious AE	3 (2)*	1 (6)**
DAA-related	0 (0)	0 (0)
AE leading to drug DC	0 (0)	1 (6)**
AEs occurring in ≥ 5% of patients		
Fatigue	18 (13)	0 (0)
Nausea	12 (9)	1 (6)
Headache	12 (9)	0 (0)
Nasopharyngitis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

Sofosbuvir/Velpatasvir in Patients Coinfected with HCV & HIV-1: ASTRAL-5

- **Design:** open-label, single-arm, phase 3 study
- **Broad inclusion criteria:** HCV GT 1-6, TE/TN, 30% with compensated cirrhosis, on stable ART for ≥ 8 weeks, CD4 ≥ 100 cells/mm3, HIV RNA ≤ 50 copies/mL
- **HIV drugs:** inclusion of NNRTI, integrase inhibitor, and PI regimens with TDF/FTC or ABC/3TC



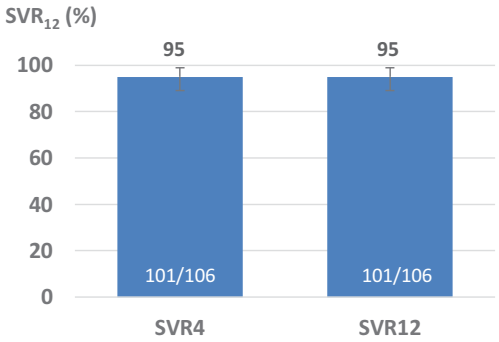
	SOF/VEL 12 wk (n = 106)
Age, y, mean (range)	54 (25-72)
Male, n (%)	91 (86)
Black, n (%)	48 (45)
BMI, kg/m^2, mean (range)	27.2 (18.6-43.4)
IL28B CC, n (%)	24 (23)
Cirrhosis, n (%)	19 (18)
HCV RNA, log10 IU/mL, mean (range)	6.3 (5.0-7.4)
HCV GT, n (%)	
1a/1b	66/12 (62/11)
2/3	11/12 (10/11)
4	5 (5)

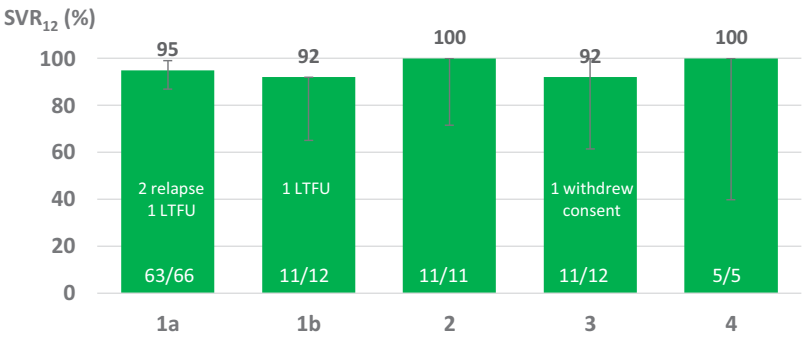
	SOF/VEL 12 wk (n = 106)
CD4 count, cells/µL, mean (range)	598 (183-1513)
NRTI backbone	
TDF-based with boosted agent (RTV or COBI)	56 (53)
TDF-based without boosted agent	36 (33)
ABC/3-TC-based	15 (14)
ART use at baseline	
PI (DRV, LPV or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (> 1 of the above class)	7 (7)

COBI: cobicistat, RAL: raltegravir, EVG: elvitegravir

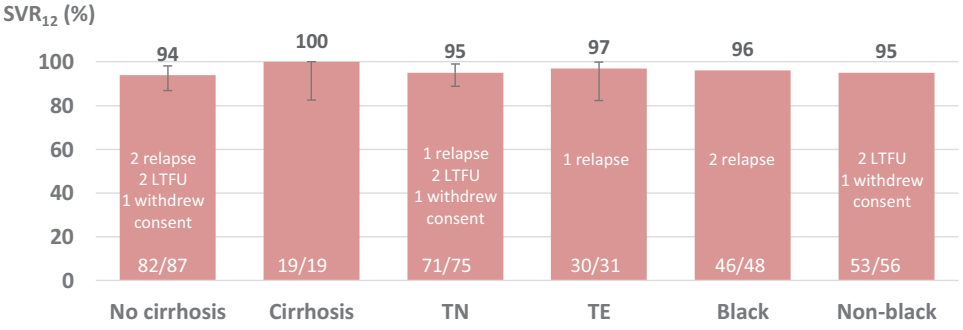
Wyles D, et al. Clin Infect Dis 2017;65:6-12

Sofosbuvir/Velpatasvir in Patients Coinfected with HCV & HIV-1: ASTRAL-5





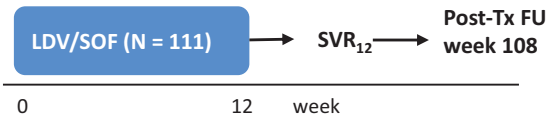
- No SVR_{12}: 2 relapse, 2 LTFU, 1 withdrew consent
- 2 patients pending SVR_{12}, both achieved SVR_4



Wyles D, et al. Clin Infect Dis 2017;65:6-12

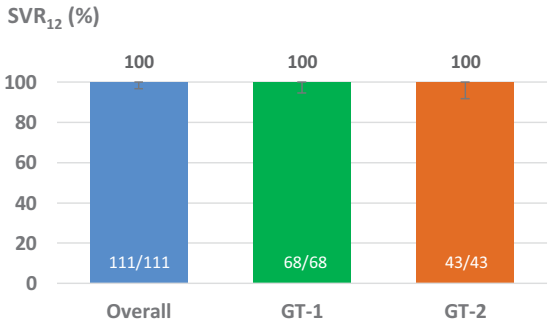
Ledipasvir/Sofosbuvir for 12 Weeks in Patients with Chronic Hepatitis C and B Coinfection: Phase 3 Study in Taiwan

- **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%)



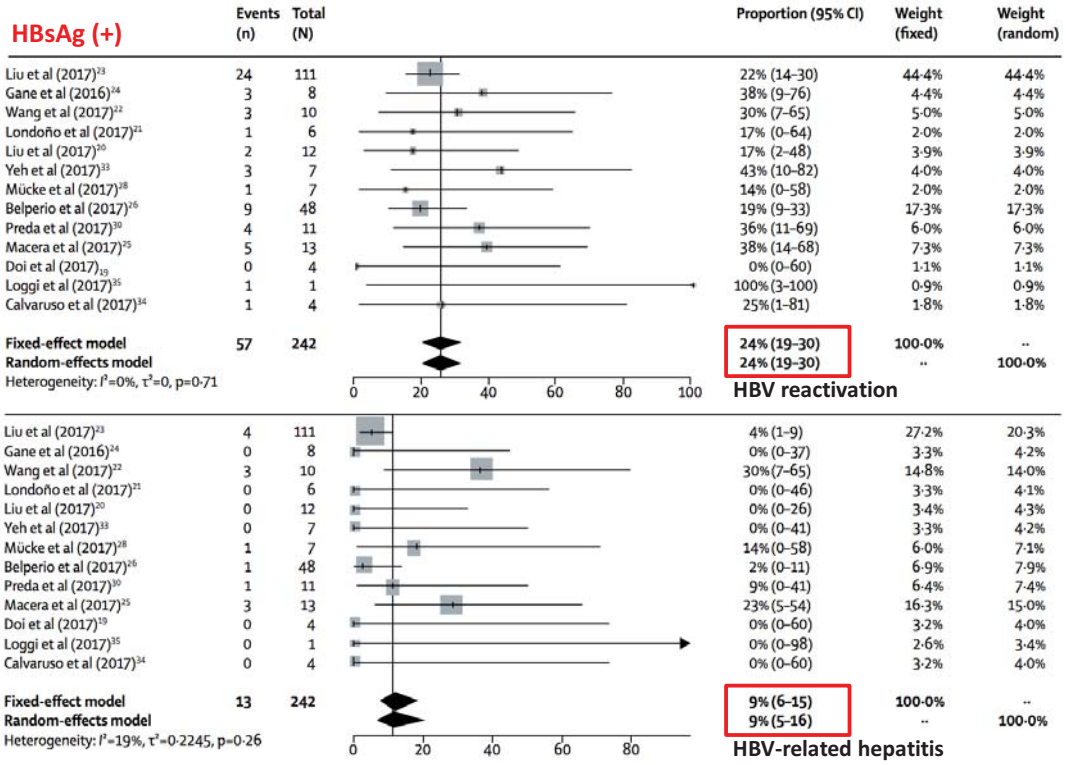
	Patients, n (%)	Patient (N = 111)
Overall safety	Any AE	66 (60)
	Grade 3-4 AE	1 (< 1)
	Serious AE	4 (4)*
	Tx DC due to AE	0 (0)
Laboratory abnormalities	Grade 3-4	1 (< 1)**

* 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 ≥ $2\log_{10}$ 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

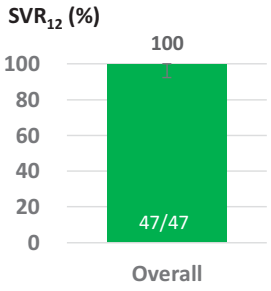
Mücke MM, et al. Lancet Gastroenterol Hepatol 2018;3:172-80

Glecaprevir/Pibrentasvir for Adolescents with Chronic Hepatitis C: DORA Part 1 Study

- **DORA:** phase 2/3, non-randomized, open-label study for patients aged 12-17 years with the same dose of G/P as adults

Characteristic	Total (N = 47)
Age, y, median (range)	14 (12-17)
Male, n (%)	21 (45)
White, n (%)	35 (75)
Weight, kg, median (range)	58 (32-109)
HCV GT, n (%)	
1a/1b	24/13 (51/28)
2	3 (6)
3	4 (9)
4	3 (6)
Cirrhosis, n (%)	0 (0)
Treatment-naïve, n (%)	36 (77)
HCV RNA, $\log_{10}$ IU/mL, median (range)	6.2 (4.6, 7.2)
Fibrosis, n (%)	
F0-1	45 (96)
F2	1 (2)
F3	1 (2)
HIV (+), n (%)	2 (4)
Baseline RAS	
None	33/44 (75)
NS3 only	0 (0)
NS5A only	11/44 (25)
NS3 and NS5A	0 (0)

Adverse event, n (%)	Total (N = 47)
Any AE	41 (87)
Serious AE	0 (0)
AE leading to drug DC	0 (0)
AEs in ≥ 10% of all patients	
Nasopharyngitis	12 (26)
URI	9 (19)
Headache	8 (17)
Fatigue	5 (11)
Oropharyngeal pain	5 (11)
Pyrexia	5 (11)
Lab abnormalities	0 (0)
ALT ≥ grade 3 (> 5X ULN)	0 (0)
AST ≥ grade 3 (> 5X ULN)	0 (0)
T-Bil ≥ grade 3 (> 3X ULN)	0 (0)

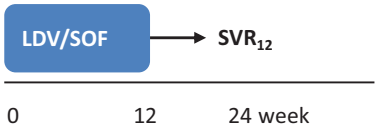


Population	G/P (300/120 mg) formula in adults	
	GLP AUC_{24} (ng.hour/mL)	PIB AUC_{24} (ng.hour/mL)
HCV-infected adolescents (12 to < 18 years, n = 47)	4.380 (157) [2,688-70,300]	1,440 (47) [428-3,380]
HCV-infected adults without cirrhosis	4800 (122) [123-297,000]	1,430 (57) [148-14,200]

Jonas MM, et al. Hepatology 2019 [Epub ahead of print]

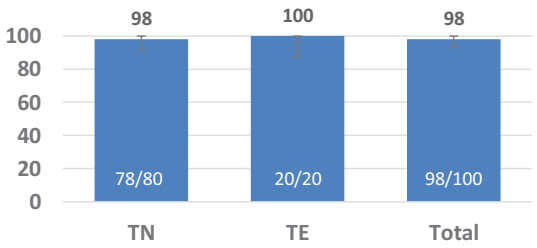
Ledipasvir/Sofosbuvir for HCV GT1 Adolescents 12-17 Years Old

- **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/1.73m², 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



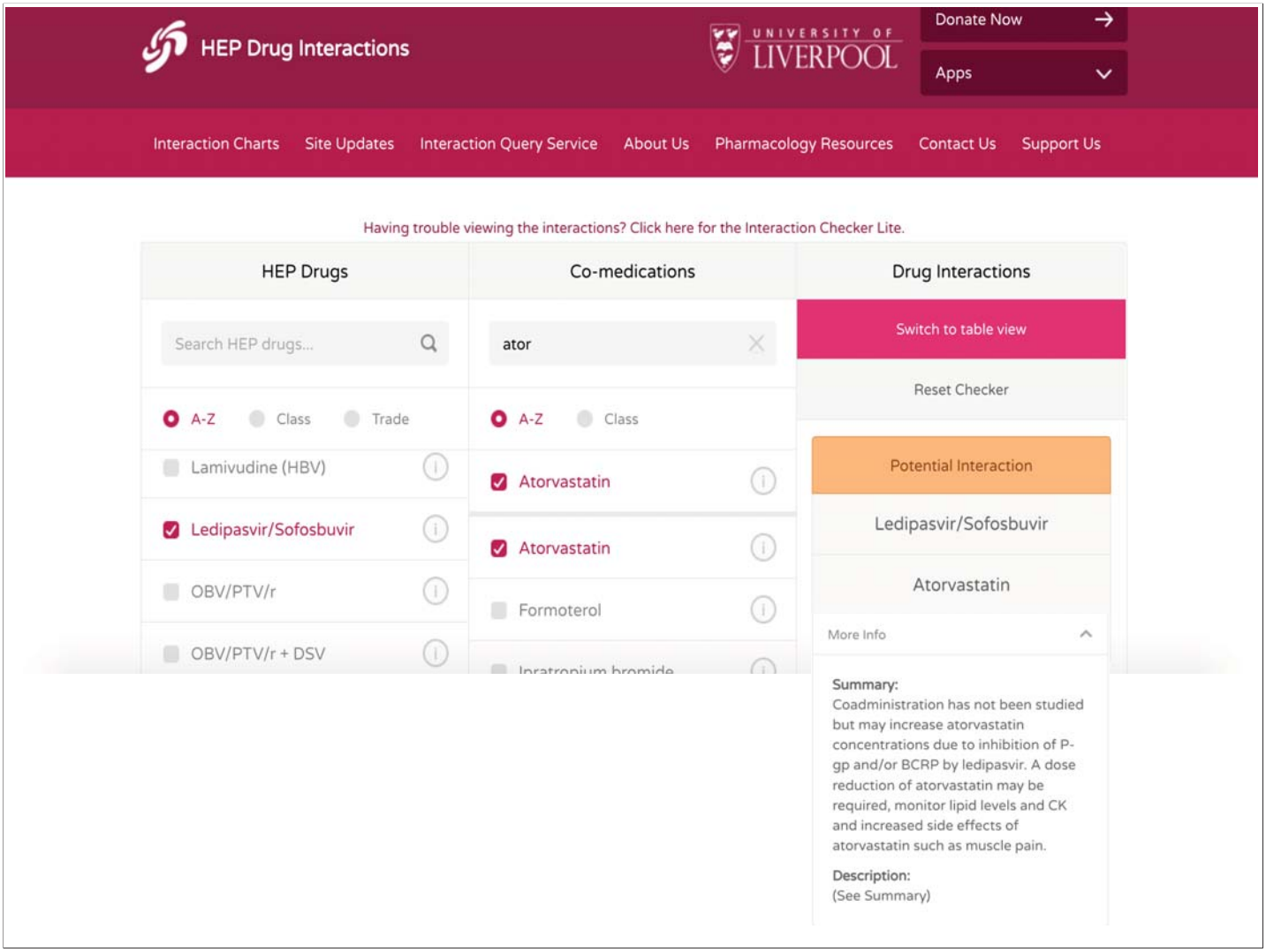
	Adolescents vs. Adults % GMR (90% CI)
SOF	
AUC_{tau} (ng.h/mL)	160 (138, 185)
C_{max} (ng/mL)	156 (127,190)
GS-331007	
AUC_{tau} (ng.h/mL)	105 (91, 122)
C_{max} (ng/mL)	139 (120, 161)
LDV	
AUC_{tau} (ng.h/mL)	127 (95, 170)
C_{max} (ng/mL)	162 (125, 209)
C_{tau} (ng/mL)	128 (95, 172)

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

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

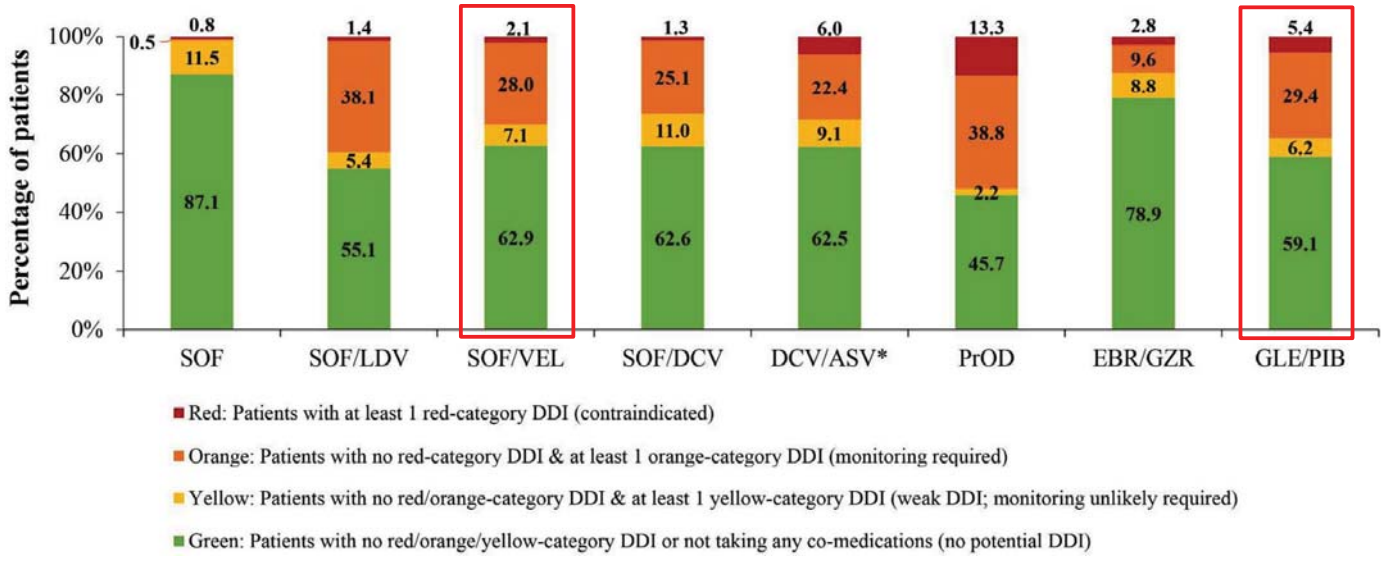
HCV (Epidemiology, Natural History, Treatment, Public Health Issue)

1. HCV epidemiology and natural history: Global & Taiwan's view
2. Introduction: direct acting antivirals (DAAs)
3. DAA in usual population: pangenotypic regimens
   - Glecaprevir/pibrentasvir
   - Sofosbuvir/velpatasvir
4. Special Population
   - Severe renal impairment (RI)
   - Organ transplantation: chronic and de novo
   - HIV coinfection
   - HBV coinfection
   - Adolescents and Children
5. Drug drug interaction (DDI), pill characters
6. Public health perspectives



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

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

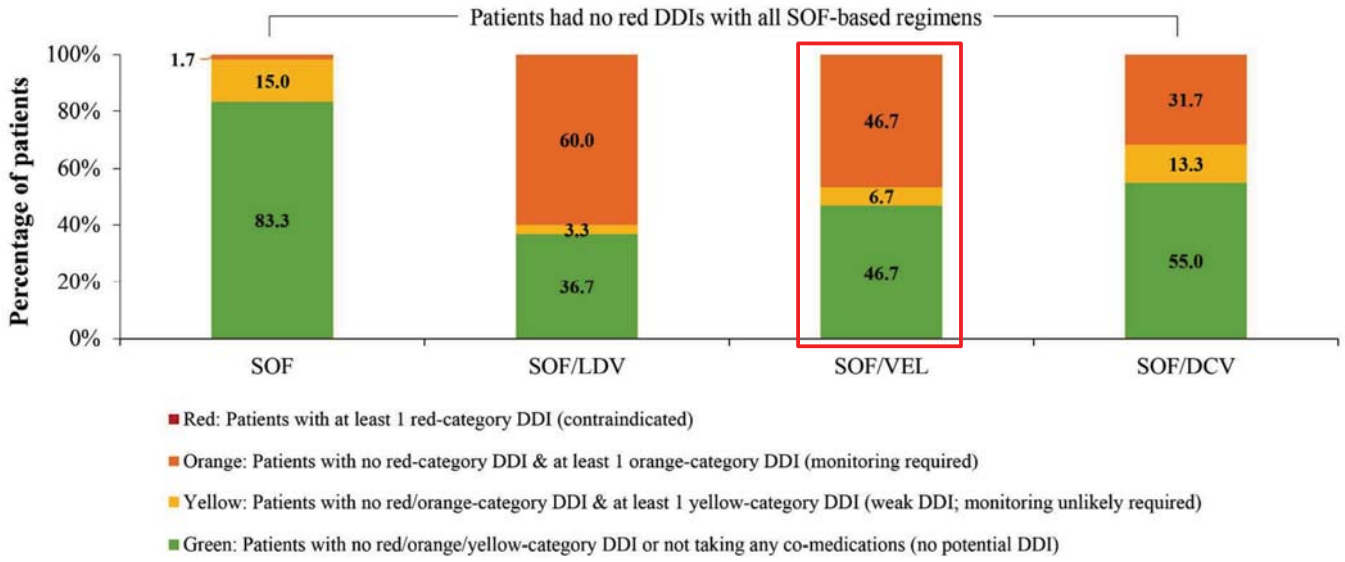


- Red: Patients with at least 1 red-category DDI (contraindicated)
- Orange: Patients with no red-category DDI & at least 1 orange-category DDI (monitoring required)
- Yellow: Patients with no red/orange-category DDI & at least 1 yellow-category DDI (weak DDI; monitoring unlikely required)
- Green: Patients 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

Glecaprevir/Pibrentasvir and Sofosbuvir/Velpatasvir: Red-Flag DDI

Class	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
Anti-arrhythmia	-	amiodarone, dronedarone
Anticoagulant, antiplatelet	dabigatran, eltrombopag	-
Heart failure, pulmonary hypertension	aliskiren, bosentan	bosentan
Lipid lowering agent	atorvastatin, lovastatin, simvastatin	-
Anticonvulsant	carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone	carbamazepine, eslicabazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide
Antipsychotics	pimozide	-
Anxiolytics	amobarbital	amobarbital
Anti-TB	rifampin, rifabutin, rifapentine	rifampin, rifabutin, rifapentine
HIV-NNRTI	efavirenz, nevirapine, etravirine	efavirenz, nevirapine, etravirine
HIV-PI	all	tipranavir
Herbals	St. John's wart	St. John's wart
Contraceptives	ethinylestradiol	-
Anti-cancer	vinblastine, vincristine	-

Characterization of Pills (GLE/PIB vs. SOF/VEL)

Direct Acting Antivirals	Length (mm)	Width (mm)	Daily pills	Frequency	Food Effect	Grinding
Maviret (GLE/PIB)	18.8	10.0	3	QD	with meals	No
Epclusa (SOF/VEL)	20.0	10.0	1	QD	with/without meals	No

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4. Special Population
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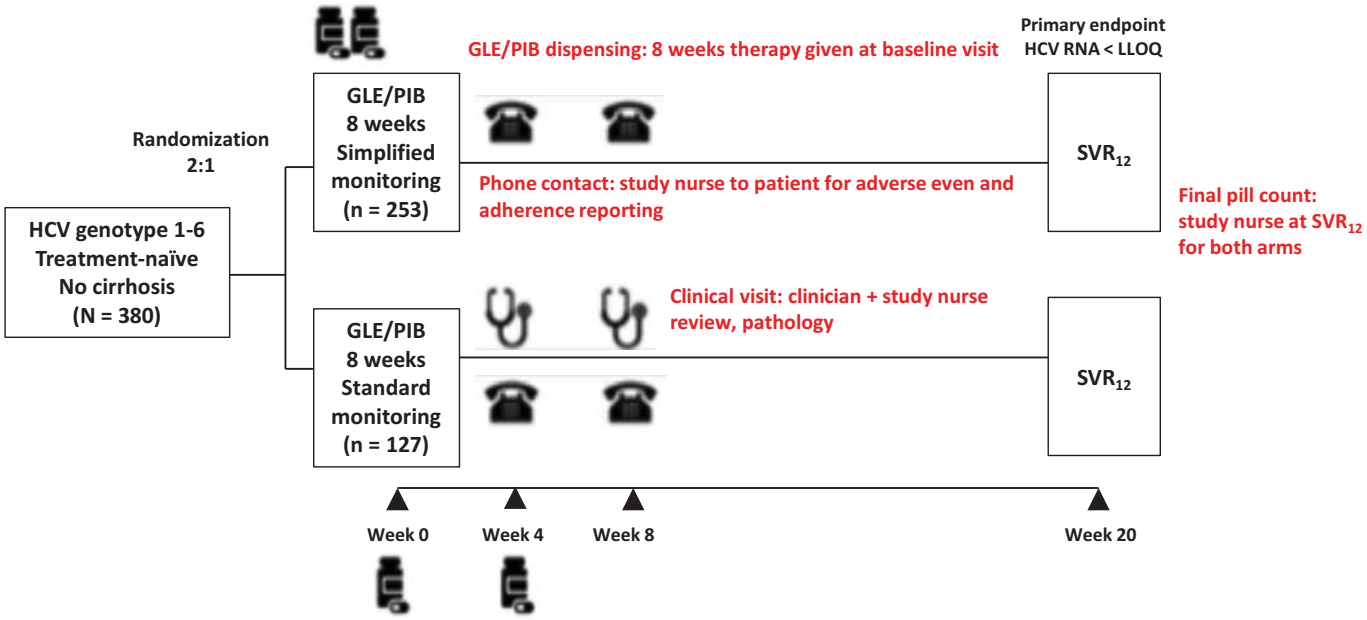
   - Adolescents and Children
5. Drug drug interaction (DDI), pill characters
6. Public health perspectives

Standard vs. Simplified Monitoring of Initial Treatment of GLE/PIB: SMART-C

- **Design:** investigator-initiated, open-label phase 3b, randomized controlled trial



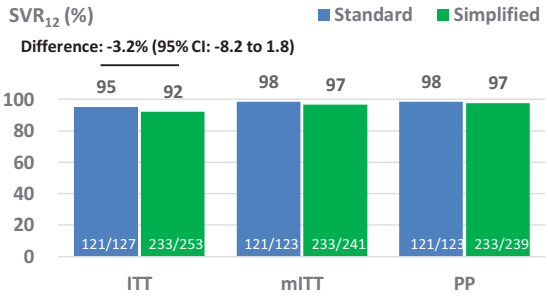
Primary endpoint: SVR_{12} in ITT population (6% non-inferiority margin)

Secondary endpoints: SVR_{12} in modified ITT and PP populations, adherence, treatment discontinuation and completion, safety

Dore GJ, et al. J Hepatol 2019 [Epub ahead of print]

Standard vs. Simplified Monitoring of Initial Treatment of GLE/PIB: SMART-C

Characteristic	All Patients (N = 380)	Standard Monitoring (n = 127)	Simplified Monitoring (n = 253)
Age, yrs, median (range)	51 (22-79)	50 (24-79)	52 (22-73)
Male, n (%)	229 (60)	72 (57)	157 (62)
White/Asian/Black/other, n (%)	291/34/20/35 (77/9/5/9)	97/12/7/11 (76/9/6/9)	194/22/13/24 (77/9/5/9)
HCV genotype, n (%)			
1	179 (47)	61 (48)	118 (47)
1a/1b/1 not specified, n	124/51/4	47/14/0	77/37/4
2	52 (14)	17 (13)	35 (14)
3	121 (32)	41 (32)	80 (32)
4	18 (5)	4 (3)	14 (6)
5	1 (<1)	1 (1)	0 (0)
6	8 (2)	3 (2)	5 (2)
GT indeterminate	1 (<1)	0 (0)	1 (<1)
HCV RNA, log_{10} IU/mL, median (range)	6.28 (2.49, 7.74)	6.29 (2.85, 7.71)	6.27 (2.49, 7.74)
Fibrosis stage 0-1/2/3, n (%)	283/78/19 (74/21/5)	93/29/5 (73/23/4)	190/49/14 (75/19/6)
HIV coinfection, n (%)	27 (7)	13 (10)	14 (6)
OST, n (%)	38 (10)	17 (13)	21 (8)



mITT: excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
PP: excludes death (n = 1), LTFU (n = 14), missing HCV RNA (n = 1), or treatment discontinuation (n = 2).

Outcome	Standard (n = 127)	Simplified (n = 253)	Δ % (95% CI)
Virologic failure, n (%)	2 (2)	6 (2)	0.8 (-2.1, 3.7)
▪ On treatment, n	0	NA	
▪ Post treatment, n	2	NA	
Failure for other reasons, n (%)	4 (3)	14 (6)	-2.2 (-6.3, 2.0)
▪ Death	0	1 (<1)	
▪ Discontinuation	0	2 (1)	
▪ LTFU or missing HCV RNA	4 (3)	11 (4)	

Dore GJ, et al. J Hepatol 2019 [Epub ahead of print]

Standard vs. Simplified Monitoring of Initial Treatment of GLE/PIB: SMART-C

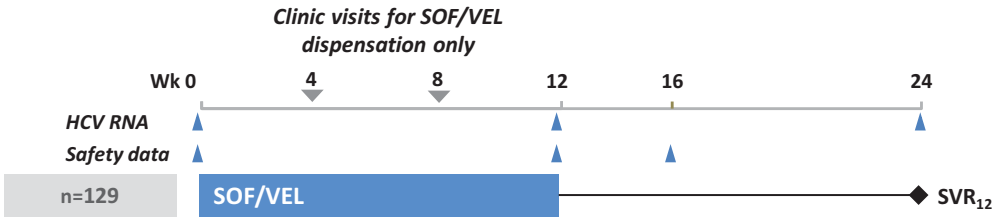
- **Median adherence (assessed by pill count at week 20):** 100% in both arms

  Adherence > 95%: 98% standard vs 96% simplified

Treatment Emergent AEs, n (%)	Standard Monitoring (n = 127)	Simplified Monitoring (n = 253)
AEs	70 (55)	133 (53)
▪ Grade 1/2	69 (54)	131 (52)
▪ Grade 3	1 (0.8)	2 (0.8)
▪ Grade 4	0	0
Common AEs (> 5%)		
▪ Fatigue	30 (14)	52 (15)
▪ Headache	26 (12)	43 (13)
▪ Nausea	25 (12)	17 (5)
Serious AEs	0	3 (1.2)
Unscheduled visits		
▪ On treatment	3 (2)	11 (4)
▪ Total	8 (6)	20 (8)

Dore GJ, et al. J Hepatol 2019 [Epub ahead of print]

Sofosbuvir/Velpatasvir in a Setting with Minimal Monitoring in India



Baseline Demographics		SOF/VEL 12 Weeks (n=129)
Male, n (%)		76 (59)
Mean age, y (range)		42 (19-75)
Mean BMI, kg/m² (range)		24 (15-40)
Mean HCV RNA , log_{10}IU/mL (SD)		5.9 (0.96)
HCV GTs, n (%)	GT 1	28 (22)
	1a	6 (5)
	1b	22 (17)
	GT 3	90 (70)
	3a	61 (47)
	3b	11 (9)
	3g/3i/3k	12 (10)
	GT 4	7 (5)
	GT 6	1 (<1)
	Indeterminate	3 (2)
Treatment experienced, n (%)		11 (9)
Cirrhotic, n (%)		42 (33)

Characteristics	SVR_{12}, n/N (%)
Overall	120/129 (93)
GT	
1	26/28 (93)
1a	5/6 (83)
1b	21/26 (96)
3	84/90 (93)
4	7/7 (100)
6	0/1 (0)
Indeterminate	3/3 (100)
Cirrhosis	
No	79/87 (91)
Yes	41/42 (98)
Treatment experience	
Naive	110/118 (93)
Experienced	10/11 (91)
Adherence	
< 80%	7/8 (88)
≥ 80%	113/121 (93)

- **Virologic failure:** 1 (on-treatment), 2 (relapse)
- No discontinuation due to AEs and no deaths during the study period
- 12 patients (9%) had Grade 3-4 laboratory abnormalities and none were considered as drug-related

Sood A, et al. Hepatol Int 2019;13:173-9

WHO Targets: Eliminating HCV by 2030

2016

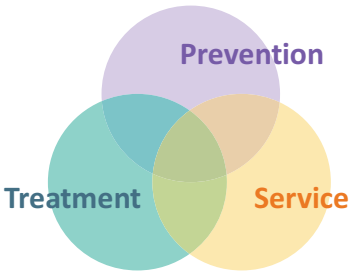
World Health Organization

Combating HBV and HCV to reach elimination by 2030

Background

HBV and HCV: A heavy burden of mortality that is increasing

In 2013, viral hepatitis was **a leading cause of death** worldwide (1.46 million deaths, a toll higher than that from HIV, tuberculosis or malaria, and on the increase since 1990)



Combining prevention and treatment to combat hepatitis makes elimination feasible

- ✓ Prevention needs
- ✓ New medicines
- ✓ Reaching five service coverage

World Health Organization. Combating hepatitis B and C to reach elimination by 2030. Advocacy brief. Available at: https://www.who.int/hepatitis/publications/hep-elimination-by-2030brief/en/ (Accessed on 2019/09/05)

Main Focus of WHO HCV Guideline

3T =

Treat All		Treat Simple		Test Simple
Offering treatment to all individuals diagnosed with HCV infection who are 12 years of age or older, irrespective of disease stage	+	Simplifying the HCV treatment by applying pan-genotypic regimens	+	Obviating the need for genotyping before treatment, and testing only for viremic infection and SVR before and after treatment

3P =

Pan-genotypic		Pan-fibrotic		PI-free for DCC
Obviate the need for genotyping before treatment initiation	+	Applicable regimens, irrespective of disease stage with excellent safety and efficacy	+	Low risk of hepatotoxicity and potential drug-drug interactions (DDIs)
SOF/VEL		F0 / F1 / F2 / F3		SOF/VEL 12 weeks ✓
SOF+DCV		F4 CTP A / F4 CTP B / F4 CTP C		SOF+DCV 12/24 weeks ✓
GLE/PIB				GLE/PIB 8/12/16 weeks ✗

WHO HCV guideline 2018

Targets for Eliminating Chronic Viral Hepatitis C