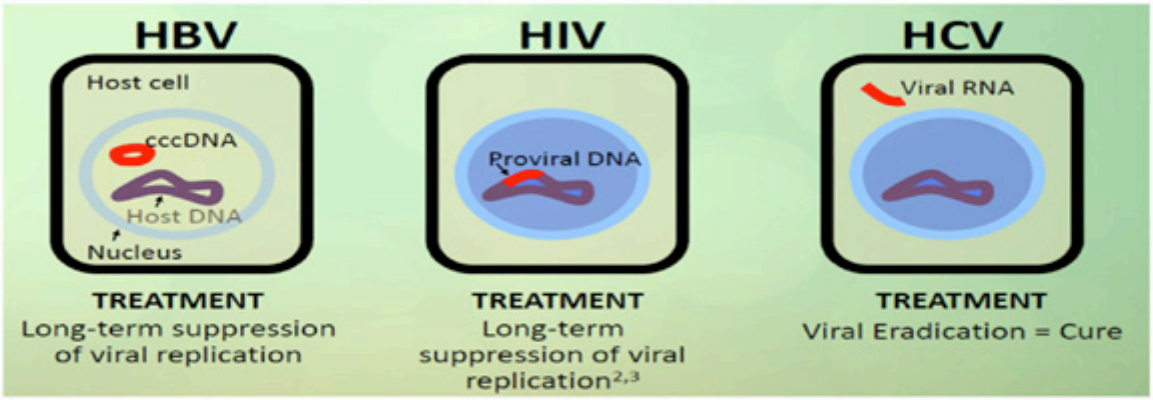
17:45	**Nuove terapie per l'epatite C** *Giuseppe Foti (Reggio Calabria)*

Giuseppe Foti
Unità Operativa Complessa di Malattie Infettive
Azienda Ospedaliera "Bianchi – Melacrino – Morelli"
Reggio Calabria

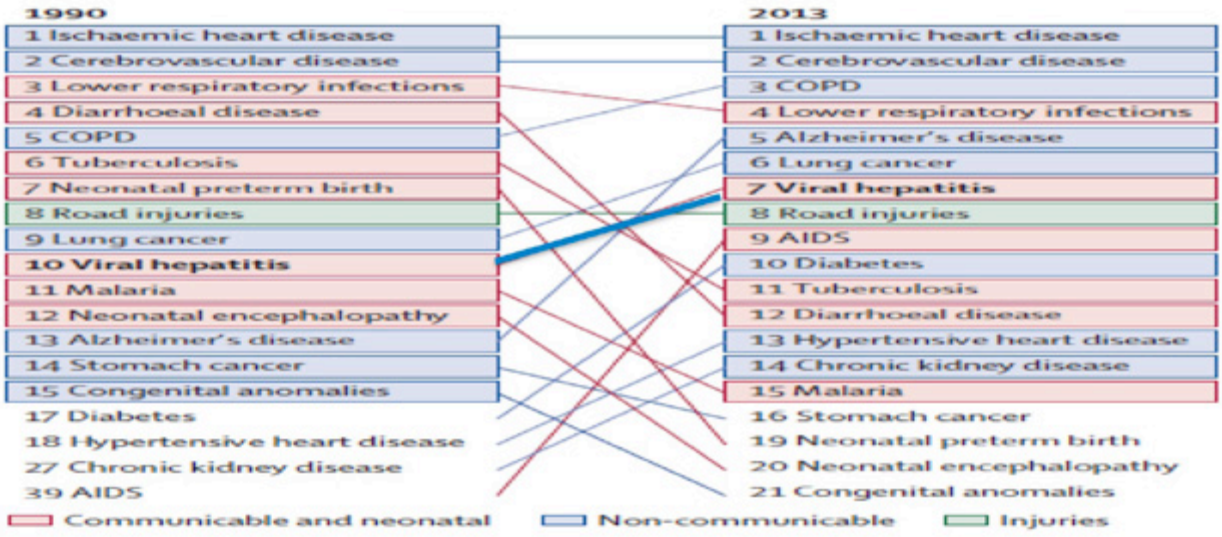
fotigiuseppe@tin.it

Hepatitis C Differs from HIV and HBV No Long-term or Latent Reservoir



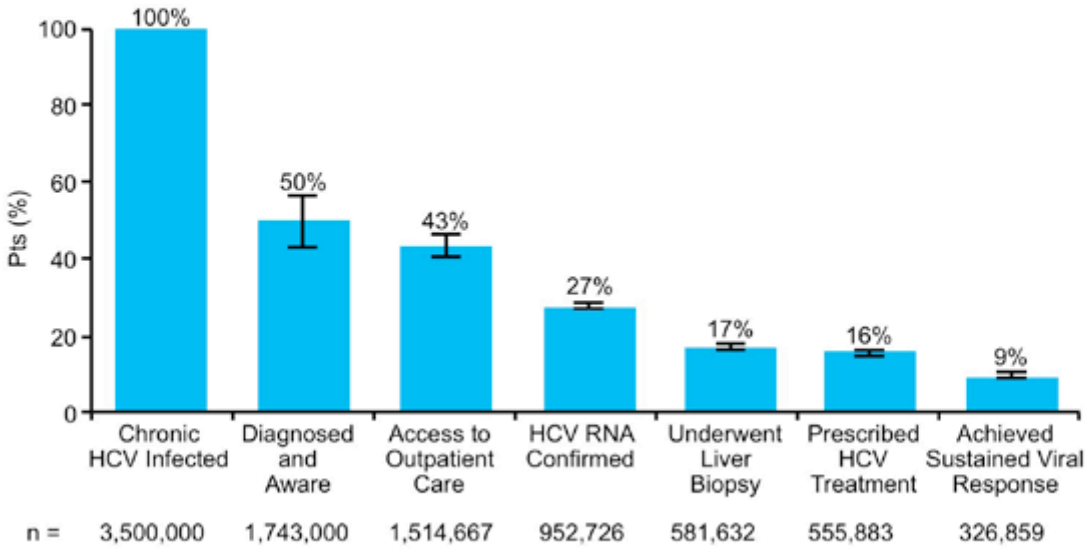
1. Pawlotsky JM. J Hepatol 2006;44:S10-S13; 2. Siliciano JD, Siliciano RF. J Antimicrob Chemother 2004;54:6-9; 3. Lucas GM. J Antimicrob Chemother 2005;55:413-416

The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013



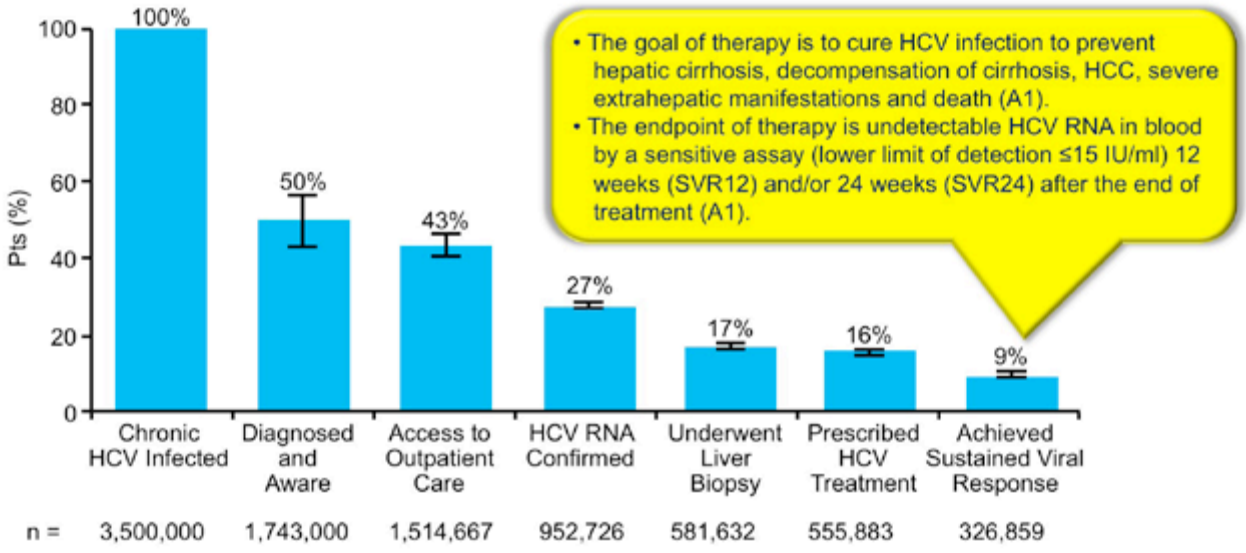
Stanaway et al. The Lancet, Vol 388, N. 10049, p1081–1088, 10 September 2016

Hepatitis C Virus (HCV) in the US: Gaps in Current Practice



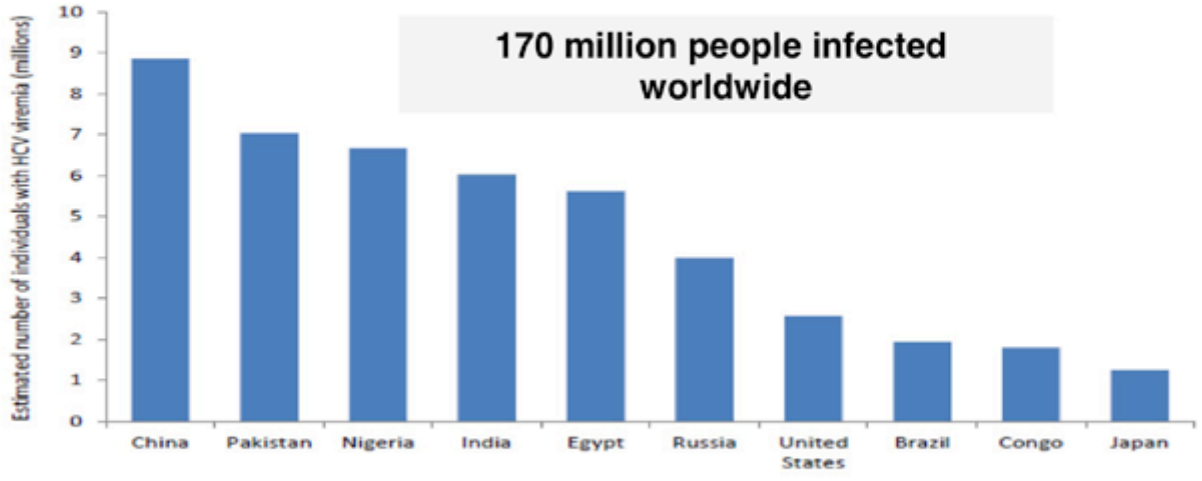
Yehia BR, et al. PLoS One. 2014;9:e101554.

Hepatitis C Virus (HCV) in the US: Gaps in Current Practice



Yehia BR, et al. PLoS One. 2014;9:e101554.

Number of HCV Infected Individuals in the Countries With the Highest Burden of HCV



Thrift et al,Nat Rev Gastroenterol Hepatol 2017 Feb;14(2):122-132.

Piano nazionale per la prevenzione delle epatiti virali da virus B e C (PNEV) - 27 ottobre 2015

Epatite C

Nel nostro Paese, si stima che i pazienti portatori cronici del virus HCV siano oltre un milione, di cui 330.000 con cirrosi.

L'Italia ha il triste primato in Europa per numero di soggetti HCV positivi e mortalità per tumore primitivo del fegato. [12]

Oltre 20.000 persone muoiono ogni anno per malattie croniche del fegato (due persone ogni ora) e, nel 65% dei casi, l'Epatite C risulta causa unica o concausa dei danni epatici.

Le regioni del Sud sono le più colpite: in Campania, Puglia e Calabria, per esempio, nella popolazione ultra settantenne la prevalenza dell'HCV supera il 20%.[12]

[12] Libro Bianco AISF 2011 – Proposta per un piano nazionale per il controllo delle malattie epatiche. Definizione ambiti e possibili interventi. 2011.

http://www.salute.gov.it/imgs/C_17_pubblicazioni_2437_allegato.pdf

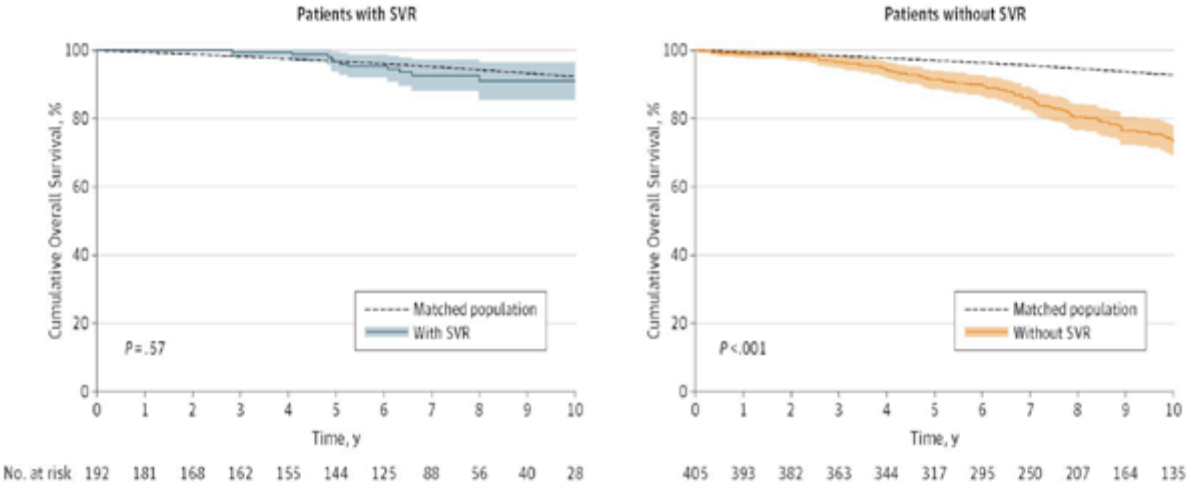
HCV - Therapy

- The goal of therapy is to cure HCV infection to prevent hepatic cirrhosis, decompensation of cirrhosis, HCC, severe extrahepatic manifestations and death (A1).
- The endpoint of therapy is undetectable HCV RNA in blood by a sensitive assay (lower limit of detection ≤15 IU/ml) 12 weeks (SVR12) and/or 24 weeks (SVR24) after the end of treatment (A1).

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

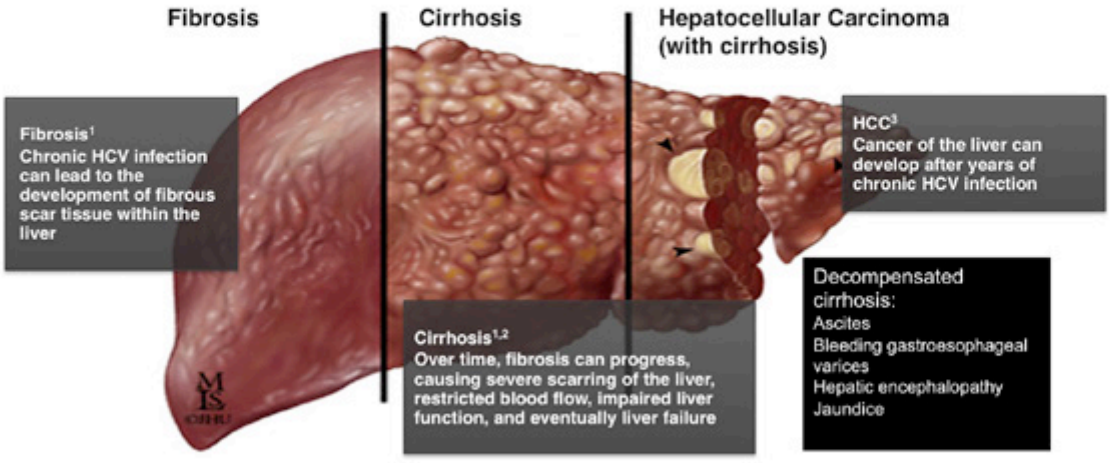
The JAMA Network

Life Expectancy in Patients With Chronic HCV Infection and Cirrhosis Compared With a General Population

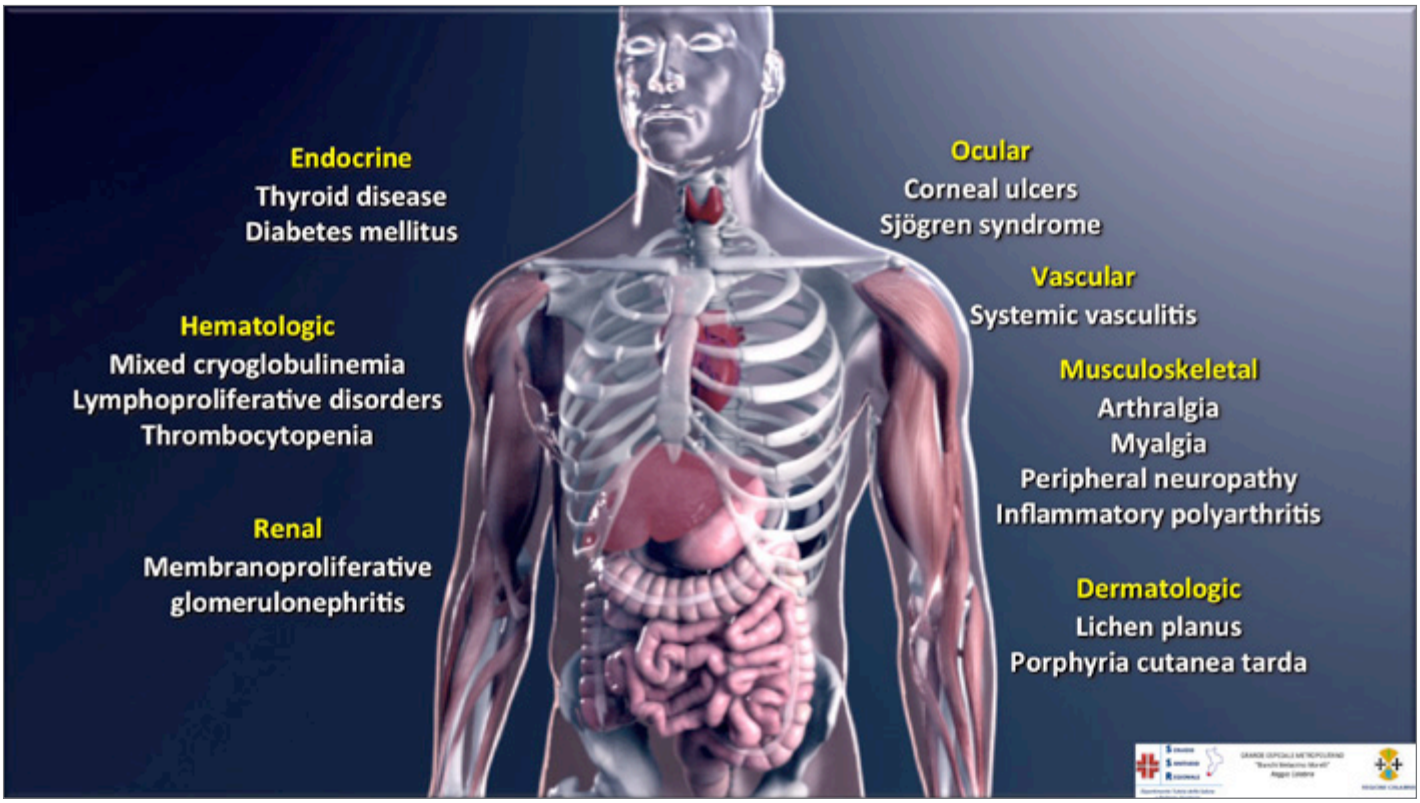


van der Meer AJ et al. JAMA. 2014;312(18):1927-1928. doi:10.1001/jama.2014.12627

Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer

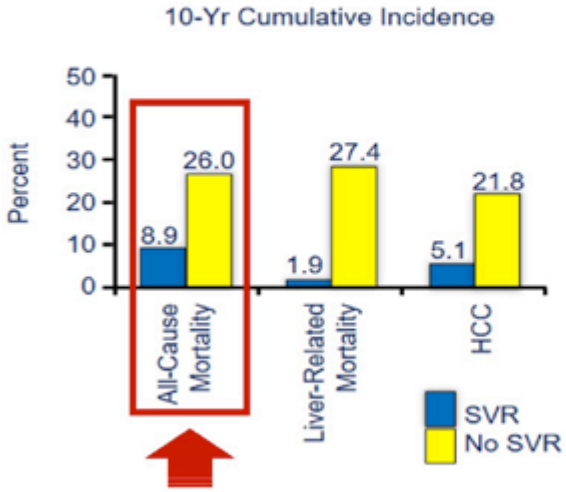


Chronic liver disease includes fibrosis, cirrhosis, and hepatic decompensation; HCC=hepatocellular carcinoma.
1. Highleyman L. Hepatitis C Support Project. http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Fibrosis.pdf. Accessed August 18, 2011;
2. Bataller R et al. *J Clin Invest*. 2005;115:209-218;
3. Medline Plus. http://www.nlm.nih.gov/medlineplus/ency/article/000280.htm. Accessed August 28, 2012;
4. Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed May 8, 2012.



HCV Cure Reduces All-Cause Mortality

- Long-term follow-up study of 530 pts with chronic HCV infection and advanced fibrosis or cirrhosis
  - HCV treatment 1990-2003
  - Follow-up median 8.4 yrs (IQR: 6.4-11.4)
- Main outcome: all-cause mortality
  - Secondary outcomes: liver failure, HCC, liver-related mortality, transplantation
- 10-year cumulative incidence of all outcome measures decreased with SVR



van der Meer AJ, et al. JAMA. 2012;308:2584-2593.

Peg-IFN/RBV – SVR responses

Virus profile	SVR
HCV-2	80-95%
HCV-3 low viremia	75-80%
HCV-3 high viremia	60-70%
HCV-4	50-60%
HCV-1 low viremia	50%
HCV-1 high viremia	30-35%

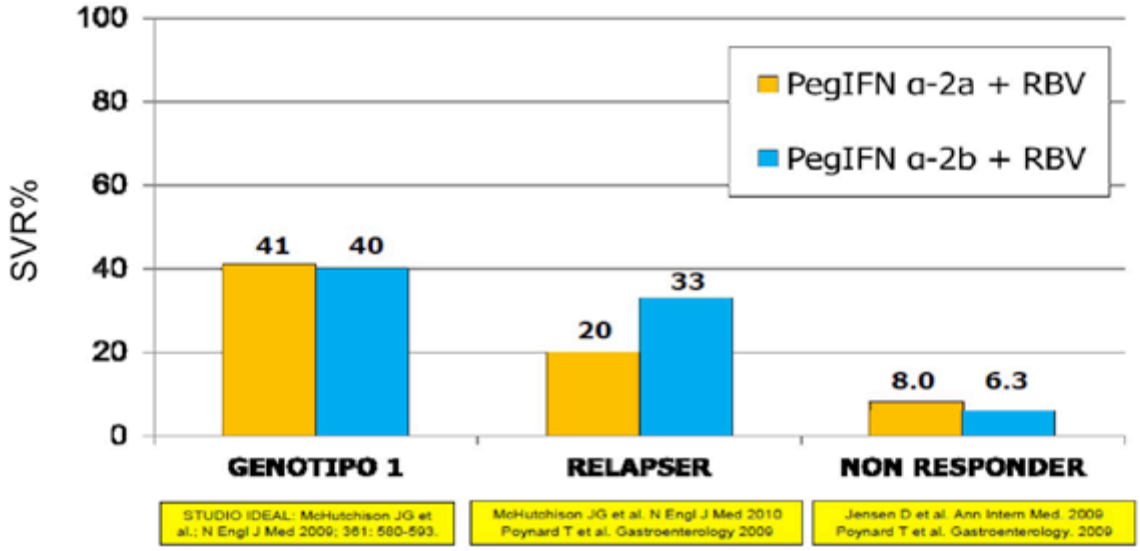
SVR according to baseline Viral Load, fibrosis staging, IL28b genotype

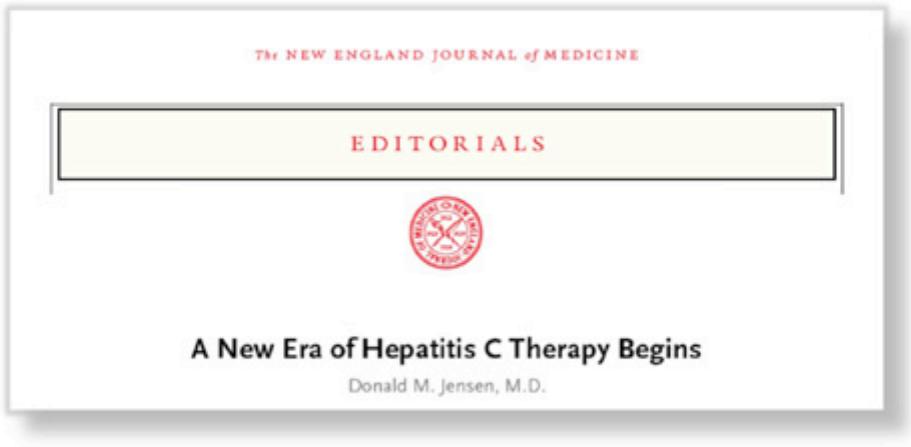
IDEAL Study – SVR rates	IL28b		
	CC	CT	TT
OVERALL	69%	33%	27%
HCV RNA ≤ 600,000 / METAVIR F0-F2	**86%**	63%	52%
HCV RNA ≤ 600,000 / METAVIR F3-F4	63%	25%	0%
HCV RNA > 600,000 / METAVIR F0-F2	70%	29%	23%
HCV RNA > 600,000 / METAVIR F3-F4	37%	21%	**12%**

Testing for IL28b performed in 1604/3070 pts (52%)

McHutchinson JG et al. N Engl J Med 2009 361: 580-593

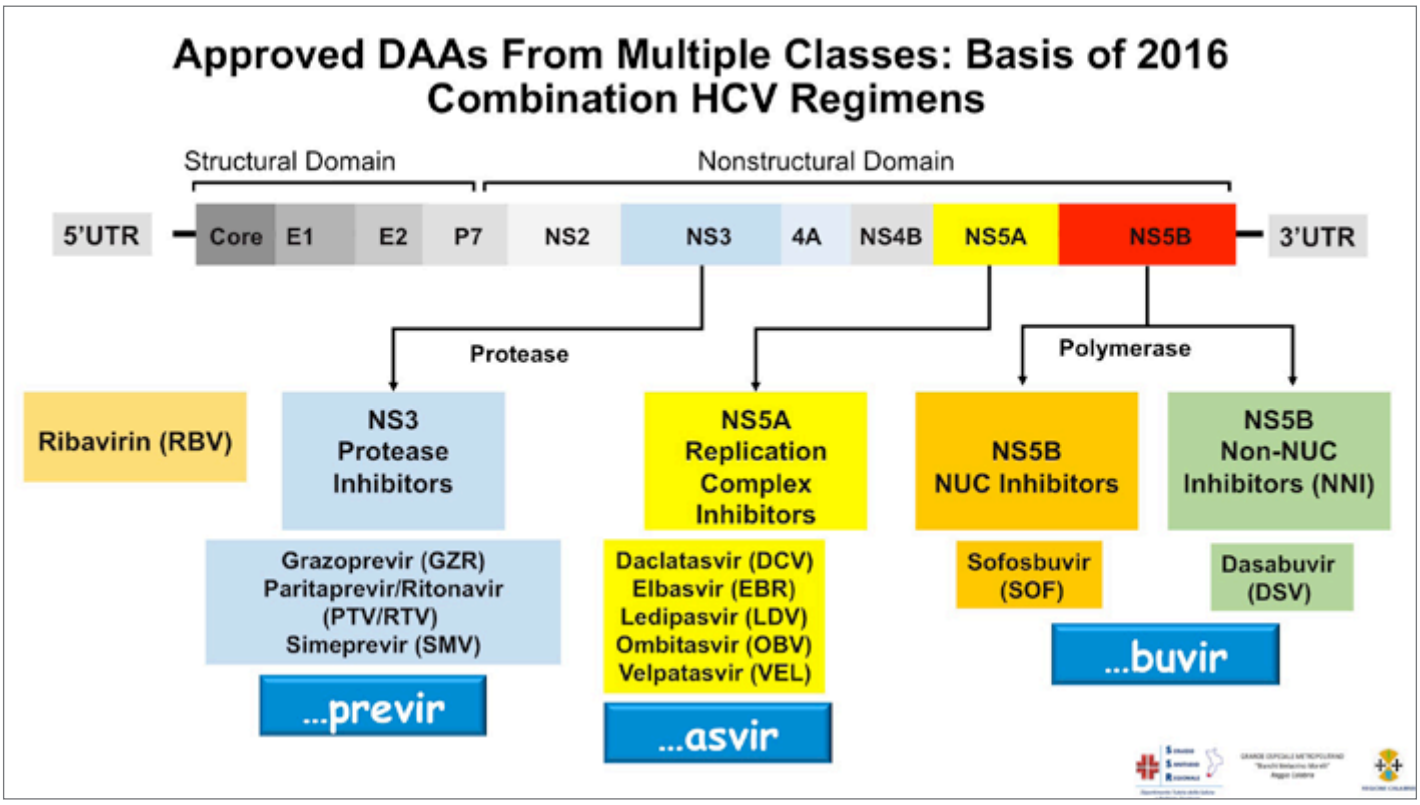
HCV Terapia – Principali problemi irrisolti

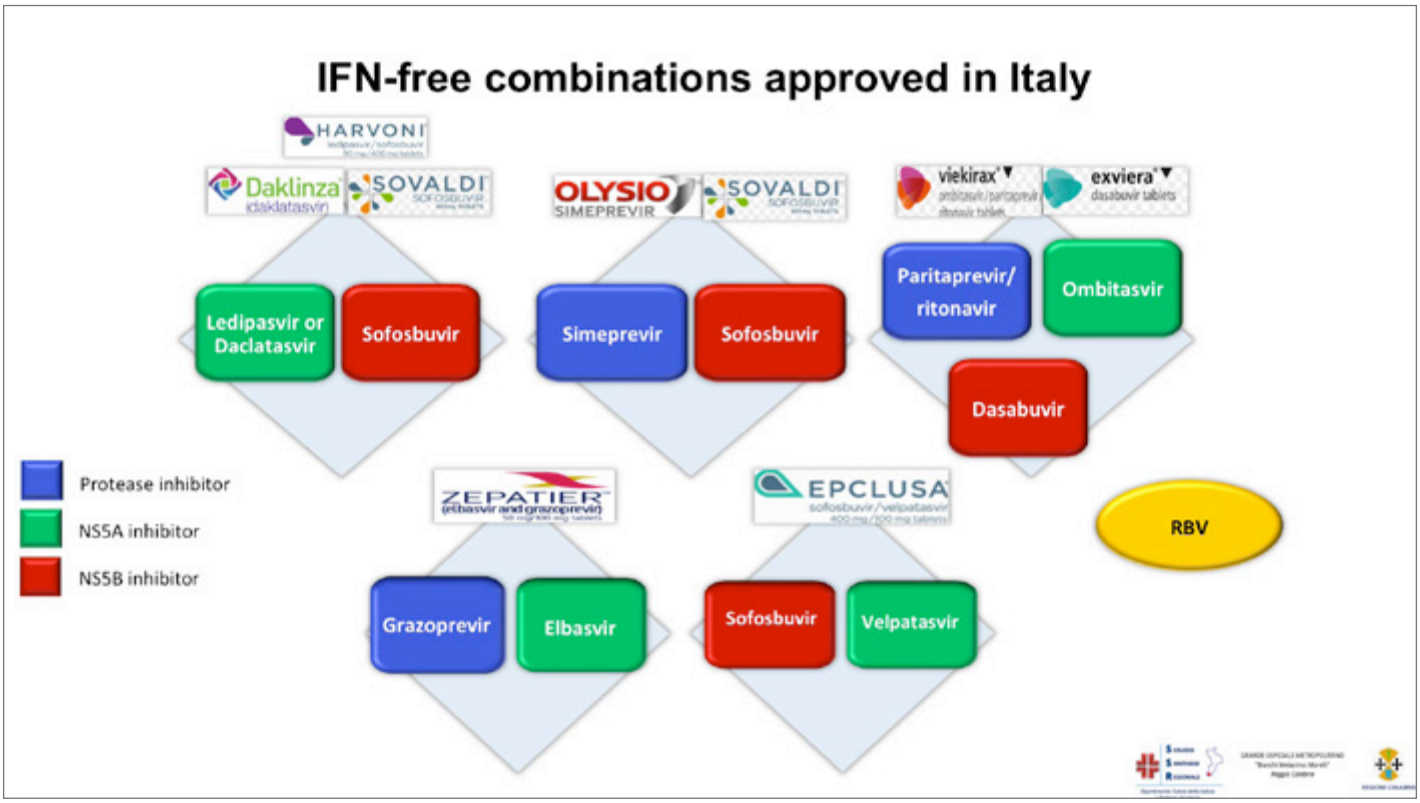


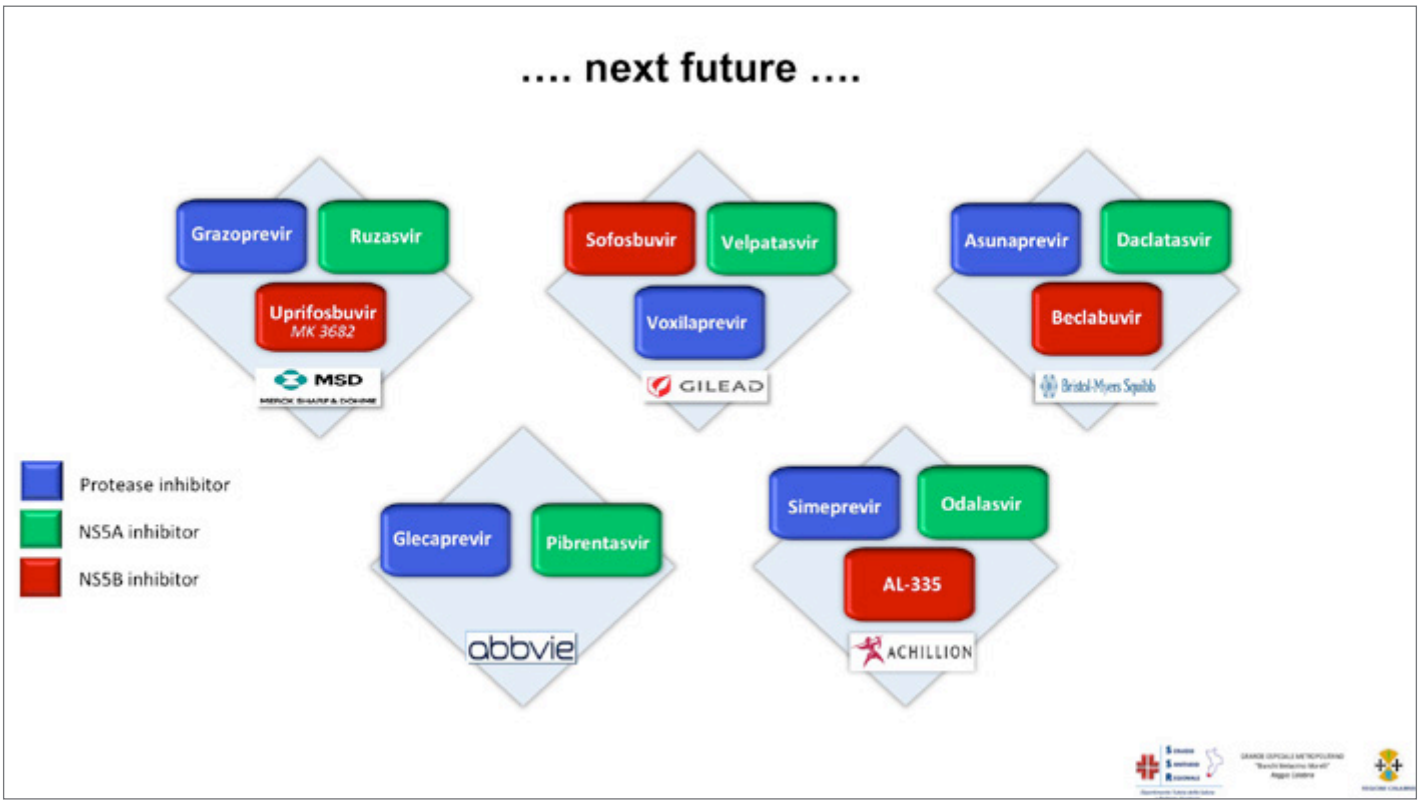


N Engl J Med. 2011 Mar 31;364(13):1272-4.


NAIVE
SPRINT-2
Boceprevir in G 1 Treatment-Naive Patients
28%
NAIVE
ADVANCE Study
Telaprevir for Chronic Untreated HCV Infection
31%
EXP
RESPOND-2
Boceprevir in GT1 Treatment-Experienced Patients
45%
EXP
REALIZE Study
Telaprevir for Previously Treated Chronic HCV Infection
49%


Approved DAAs From Multiple Classes: Basis of 2016 Combination HCV Regimens
Structural Domain
Nonstructural Domain
5'UTR
Core
E1
E2
P7
NS2
NS3
4A
NS4B
NS5A
NS5B
3'UTR
Protease
Polymerase
Ribavirin (RBV)
NS3 Protease Inhibitors
NS5A Replication Complex Inhibitors
NS5B NUC Inhibitors
NS5B Non-NUC Inhibitors (NNI)
Grazoprevir (GZR)
Paritaprevir/Ritonavir (PTV/RTV)
Simeprevir (SMV)
Daclatasvir (DCV)
Elbasvir (EBR)
Ledipasvir (LDV)
Ombitasvir (OBV)
Velpatasvir (VEL)
Sofosbuvir (SOF)
Dasabuvir (DSV)
...previr
...asvir
...buvir

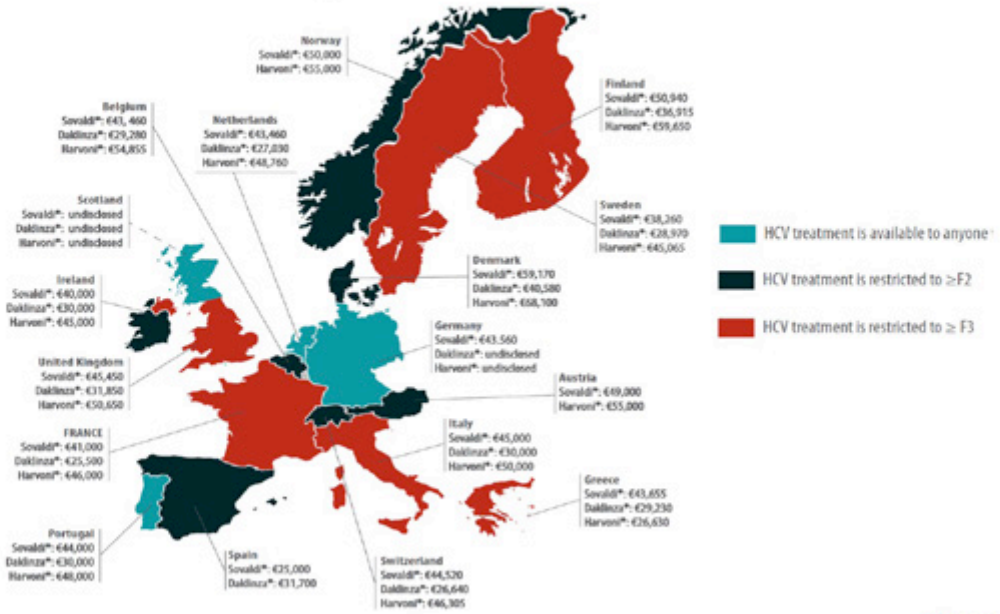

IFN-free combinations approved in Italy
HARVONI
Daklinza
SOVALDI
OLYSIO
SIMEPREVIR
SOVALDI
viekirax
exviera
dasabuvir tablets
Ledipasvir or Daclatasvir
Sofosbuvir
Simeprevir
Sofosbuvir
Paritaprevir/ ritonavir
Ombitasvir
Dasabuvir
Protease inhibitor
NS5A inhibitor
NS5B inhibitor
ZEPATIER
(elbasvir and grazoprevir)
EPCLUSA
sofosbuvir/velpatasvir
RBV
Grazoprevir
Elbasvir
Sofosbuvir
Velpatasvir


.... next future ....
Grazoprevir
Ruzasvir
Uprifosbuvir
MK 3682
MSD
Sofosbuvir
Velpatasvir
Voxilaprevir
GILEAD
Asunaprevir
Daclatasvir
Beclabuvir
Bristol-Myers Squibb
Protease inhibitor
NS5A inhibitor
NS5B inhibitor
Glecaprevir
Pibrentasvir
abbvie
Simeprevir
Odalasvir
AL-335
ACHILLION

Approved IFN-free Regimens for HCV Treatment in Italy

	GT
Sofosbuvir + Daclatasvir (± RBV)	All
Sofosbuvir + Velpatasvir (± RBV)	All
Sofosbuvir/Ledipasvir (± RBV)	1, 4, 5, 6
Grazoprevir + Elbasvir (± RBV)	1, 4
Sofosbuvir + Simeprevir (± RBV)	1, 4
Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir (± RBV)	1
Ombitasvir/Paritaprevir/Ritonavir (± RBV)	4
Sofosbuvir + RBV	2, 3

HCV Treatment Prices and Access Restrictions in Western Europe



hepcoalition.org

F0 → F1 → F2 | F3 → F4

Stiffness <10 kpa | Stiffness >10 kpa

Articolo 32

La Repubblica tutela la salute come fondamentale diritto dell'individuo e interesse della collettività, e garantisce cure gratuite agli indigenti.

HCV patients

AIFA Agenzia Italiana del Farmaco

GU Serie Generale n.75 del 30-3-2017

GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA

1	Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi.	7	Epatite cronica con fibrosi METAVIR F2 (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m²) emoglobinopatie e coagulopatie congenite].
2	Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione	8	Epatite cronica con fibrosi METAVIR F0-F1 (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m²), emoglobinopatie e coagulopatie congenite].
3	Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale)	9	Operatori sanitari infetti.
4	Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak)	10	Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.
5	In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi.	11	Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo
6	Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.		

21 dicembre 2015: n. 30.162 trattamenti

Crit.	N. Trattamenti	%
1	21.576	71,5
4	**5.639**	**18,6**
3	1.177	3,9
2	1.169	3,8
7	279	0,92
5	210	0,69
6	112	0,37

10 aprile 2017 n. 72.589 trattamenti

Crit.	N. Trattamenti	%
1	45.576	62,7
4	**20.275**	**27,9**
3	3.517	4,8
2	1.940	2,6
7	628	0,86
6	365	0,50
5	298	0,41

29 dicembre 2015 n. 183 trattamenti

Crit.	N. Trattamenti	%
1	131	71,5
4	**34**	**18,5**
3	8	4,3
2	1	0,54
7	6	3,2
6	3	1,6
5	0	0,0

7 aprile 2017 n. 461 trattamenti

Crit.	N. Trattamenti	%
1	283	61,4
4	**148**	**32,1**
3	12	2,6
2	5	1,1
7	9	2,0
6	4	0,9
5	0	0,0

IFN-free combination treatment regimens available as valuable options for each HCV genotype.

Combination regimen	Genotype 1	Genotype 2	Genotype 3	Genotype 4	Genotypes 5 and 6
Sofosbuvir + ribavirin	No	Suboptimal	Suboptimal	No	No
Sofosbuvir/ledipasvir ± ribavirin	Yes	No	No	Yes	Yes
Sofosbuvir/velpatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin	Yes	No	No	No	No
Ombitasvir/paritaprevir/ritonavir ± ribavirin	No	No	No	Yes	No
Grazoprevir/elbasvir ± ribavirin	Yes	No	No	Yes	No
Sofosbuvir + daclatasvir ± ribavirin	Yes	Yes	Yes	Yes	Yes
Sofosbuvir + simeprevir ± ribavirin	Suboptimal	No	No	Yes	No

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

Patients with chronic hepatitis C without cirrhosis

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naive	8–12 wk, no ribavirin	12 wk, no ribavirin	12 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naive	8–12 wk, no ribavirin	12 wk, no ribavirin	8–12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced	12 wk, no ribavirin		12 wk, no ribavirin				
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naive	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
	Treatment-experienced		12 wk with ribavirin[c] or 24 wk, no ribavirin				12 wk with ribavirin[c] or 24 wk, no ribavirin	
Genotype 4	Treatment-naive	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

Patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis

Patients	Treatment-naïve or -experienced	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir
Genotype 1a	Treatment-naive	12 wk, no ribavirin	12 wk, no ribavirin	24 wk with ribavirin	No	12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml[b]	12 wk, no ribavirin	No
	Treatment-experienced	12 wk with ribavirin[a] or 24 wk, no ribavirin					12 wk with ribavirin[a] or 24 wk, no ribavirin	
Genotype 1b	Treatment-naive	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk, no ribavirin	12 wk, no ribavirin	No
	Treatment-experienced							
Genotype 2	Both	No	12 wk, no ribavirin	No	No	No	12 wk, no ribavirin	No
Genotype 3	Treatment-naive	No	12 wk with ribavirin[c] or 24 wk, no ribavirin	No	No	No	24 wk with ribavirin	No
	Treatment-experienced							
Genotype 4	Treatment-naive	12 wk, no ribavirin	12 wk, no ribavirin	No	12 wk with ribavirin	12 wk, no ribavirin	12 wk, no ribavirin	12 wk, no ribavirin
	Treatment-experienced	12 wk with ribavirin or 24 wk, no ribavirin				12 wk, no ribavirin if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 wk with ribavirin if HCV RNA >800,000 (5.9 log) IU/ml	12 wk with ribavirin or 24 wk, no ribavirin	12 wk with ribavirin or 24 wk, no ribavirin

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

new challenge

short therapy

Summary of LDV/SOF 8 and 12 Weeks Treatment Data

Populations included in graph: ION-3: TN, NC, GT1 with baseline HCV RNA < 6M IU/mL (noted as < 6M IU/mL hereafter; HCV-TARGET: primarily TN, NC, GT1; TRIO cohort: TN, NC, GT 1, primarily < 6M IU/mL; GECCO: primarily TN, NC, GT1; IFI: primarily TN, NC, GT1, < 6M IU/mL; VA: TN, GT 1, primarily NC, < 6M IU/mL; Cleveland VA: TN, GT1, NC, <6M IU/ML; Queen's Medical Center (Honolulu): GT 1, NC, primarily TN, <6M IU/mL; Kaiser Permanente: GT 1, primarily TN, ~40% non-cirrhotic; St. Joseph's Medical Center (Phoenix): GT 1, primarily TN and non-cirrhotic, < 6M IU/mL

HARVONI® SmPC Gilead Sciences, December 2015; Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888; Terrault, AASLD, 2015, 94; Curry, AASLD, 2015, 1046; Christensen, AASLD, 2015, 1081; Buggisch, AASLD, 2015, 1205; Backus, AASLD, 2015, 93; Marshall, AASLD, 2015, 1154 Roytman, AASLD, 2015, 1121; Lai, AASLD, 2015, 1053; Gill, AASLD, 2015, 1111

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016

Genotype 1, Option 1: Sofosbuvir/ledipasvir

Treatment can be shortened to 8 weeks in treatment-naive patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/ml. This should be done with caution in patients with F3 fibrosis (B1)

In **ION-3** in treatment-naïve patients without cirrhosis (F3 fibrosis was present in only 13% of patients who underwent liver biopsy), the SVR12 rates were 94% (202/215) without ribavirin for 8 weeks, 93% (201/216) with ribavirin for 8 weeks and 95% (205/216) without ribavirin for 12 weeks.

Post-hoc analysis indicated that 8 weeks of treatment yielded an SVR12 rate of 97% (119/123) in patients with an HCV RNA level <6 million (6.8 Log) IU/ml at baseline [42,44].

These results were confirmed by real-world studies from Europe and the United States in the same subgroup of patients, showing comparably high SVR12 rates: 95% (251/263) in the **TRIO** cohort, 97% (150/154) in the HCV **TARGET** cohort, 97% (155/159) in the **GECCO** cohort, 99% (127/128) in the **IFI** cohort, and 98% (47/48) in the **VA-Ohio** cohort [44]

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

EASL JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2016

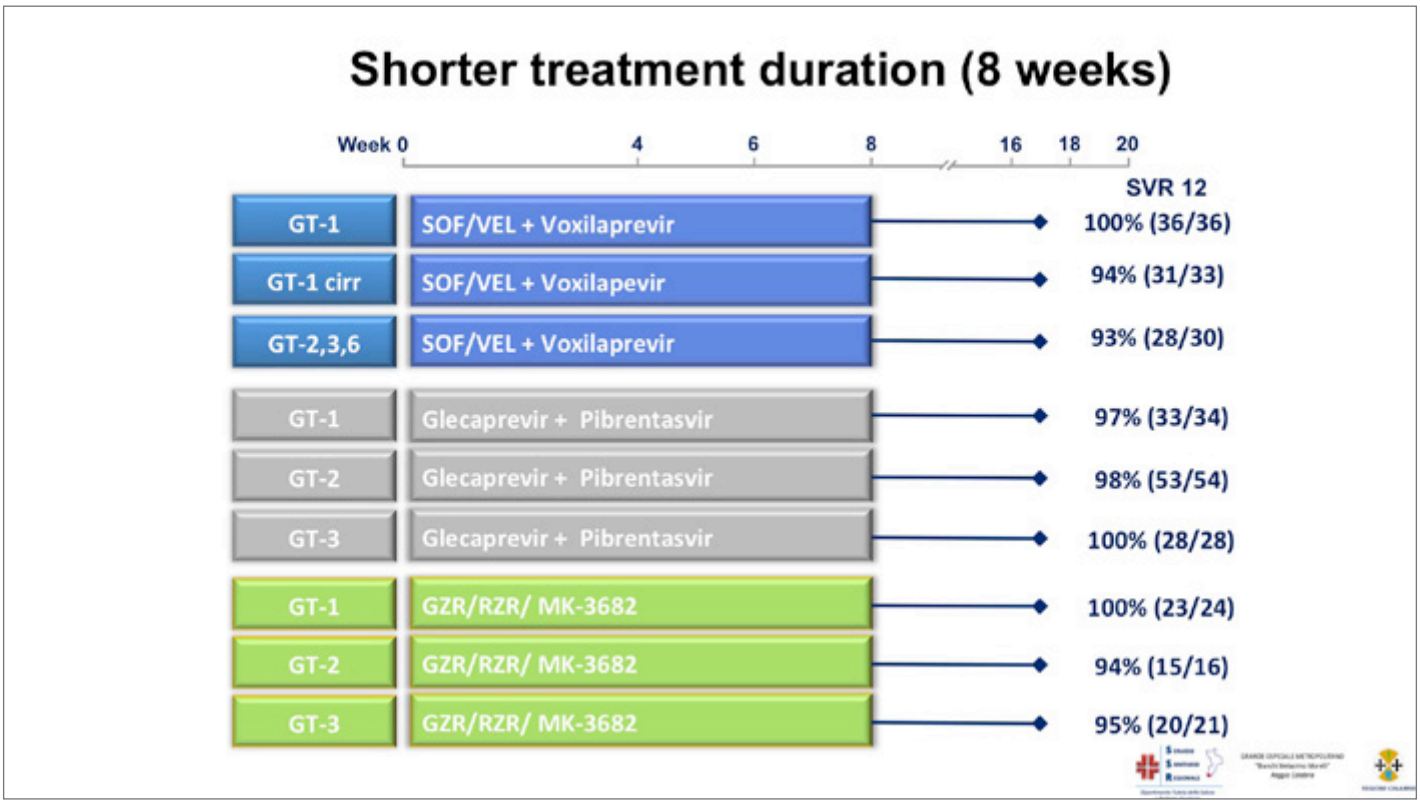
Genotype 1, Option 3: Ritonavir-boosted paritaprevir, ombitasvir and dasabuvir

Treatment-naive patients infected with subtype 1b without cirrhosis can receive the combination of ombitasvir, paritaprevir and ritonavir plus dasabuvir for 8 weeks without ribavirin, with caution in patients with F3 fibrosis (B1)

In the **GARNET** study, the SVR12 rate was 97% (161/166) in patients with genotype 1b infection and no cirrhosis (METAVIR score F0 to F3) after 8 weeks of treatment with ombitasvir, paritaprevir and ritonavir plus dasabuvir without ribavirin.
Among the 15 patients with F3 fibrosis included in this study, 13 achieved SVR12 (data provided to the panel by Abbvie, on request).

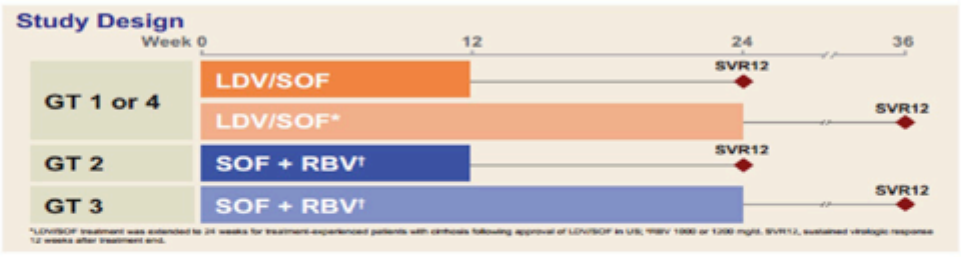
EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194


Sofosbuvir
Voxiplaprevir
Velpatasvir
Glecaprevir
Pibrentasvir
Uprifosbuvir
Grazoprevir
Ruzasvir


Shorter treatment duration (8 weeks)
Week 0
4
6
8
16
18
20
SVR 12
GT-1
SOF/VEL + Voxilaprevir
100% (36/36)
GT-1 cirr
SOF/VEL + Voxilapevir
94% (31/33)
GT-2,3,6
SOF/VEL + Voxilaprevir
93% (28/30)
GT-1
Glecaprevir + Pibrentasvir
97% (33/34)
GT-2
Glecaprevir + Pibrentasvir
98% (53/54)
GT-3
Glecaprevir + Pibrentasvir
100% (28/28)
GT-1
GZR/RZR/ MK-3682
100% (23/24)
GT-2
GZR/RZR/ MK-3682
94% (15/16)
GT-3
GZR/RZR/ MK-3682
95% (20/21)

DAAs Regimens in Patients with Hereditary Bleeding Disorders

Sofosbuvir Regimens in Patients with Hereditary Beeding Disorders



- Phase 2b, multicenter, open-label US study (NCT02120300)
- Primary endpoint: proportion of patients with SVR12
  - HCV RNA < lower limit of quantification (LLOQ) at posttreatment Week 12
  - COBAS® AmpliPrep/COBAS® TaqMan® HCV Test v2.0 (Roche Molecular Diagnostics, Pleasanton, CA; LLOQ 15 IU/mL)
- Key eligibility criteria
  - Hemophilia A, B, or C, or Von Willebrand's disease
  - HCV GT 1, 2, 3, or 4
  - HCV RNA ≥1000 IU/mL at screening
  - HIV-1/HCV coinfected patients (at screening)
    - Suppressed HIV-1 RNA for ≥6 months
    - Stable antiretroviral regimen for >8 weeks
    - CD4 T-cell count >200 cells/mm³
  - Hemoglobin ≥11 g/dL for female and ≥12 g/dL for male patients

120 patients

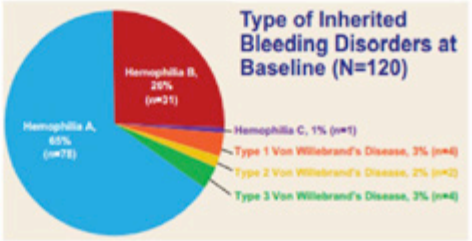
Walsh C et al. Presented at AASLD: The Liver Meeting®, November 13–17, 2015, San Francisco, CA

Sofosbuvir Regimens in Patients with Hereditary Bleeding Disorders

Baseline Characteristics

		LDV/SOF		SOF+RBV		
		12 wk n=99	24 wk n=5	12 wk n=10	24 wk n=6	Total N=120
Demographics	Mean age, y (range)	44 (22–69)	49 (32–63)	48 (30–74)	47 (38–57)	45 (22–74)
	Male, n (%)	93 (94)	5 (100)	9 (90)	6 (100)	113 (94)
	White, n (%)	75 (76)	4 (80)	8 (80)	5 (83)	92 (77)
	Mean BMI, kg/m² (range)	26.9 (18.3–41.5)	31.4 (23.3–45.6)	26.2 (22.8–32.9)	25.2 (20.7–29.7)	26.9 (18.3–45.6)
HCV	HCV GT, n (%)					
	1a	66 (67)	5 (100)	0	0	71 (59)
	1b	31 (31)	0	0	0	31 (26)
	2	0	0	10 (100)	0	10 (8)
	3	0	0	0	6 (100)	6 (5)
	IL28B non-CC, n (%)	76 (77)	3 (60)	3 (30)	1 (17)	83 (69)
	Mean baseline HCV RNA, log_{10} IU/mL (range)	6.2 (3.8–7.5)	6.0 (4.9–7.1)	6.2 (4.3–7.1)	6.6 (5.2–7.5)	6.2 (3.8–7.5)
	Cirrhosis, n (%)	28 (28)	5 (100)	2 (20)	2 (33)	37 (31)
	Prior HCV treatment, n (%)	39 (39)	5 (100)	3 (30)	1 (17)	48 (40)
HIV	HIV infected, n (%)	19 (19)	0	4 (40)	3 (50)	26 (22)
	With cirrhosis	12 (63)	0	1 (25)	2 (67)	15 (58)
Bleeding Disorder Severity*	Mild, n (%)	26 (26)	1 (20)	1 (10)	2 (33)	30 (25)
	Moderate, n (%)	20 (20)	2 (40)	1 (10)	1 (17)	24 (20)
	Severe, n (%)	53 (54)	2 (40)	8 (80)	3 (50)	66 (55)

*Assessed by investigator. BMI, body mass index; IL28B, interleukin-28B; SD, standard deviation.



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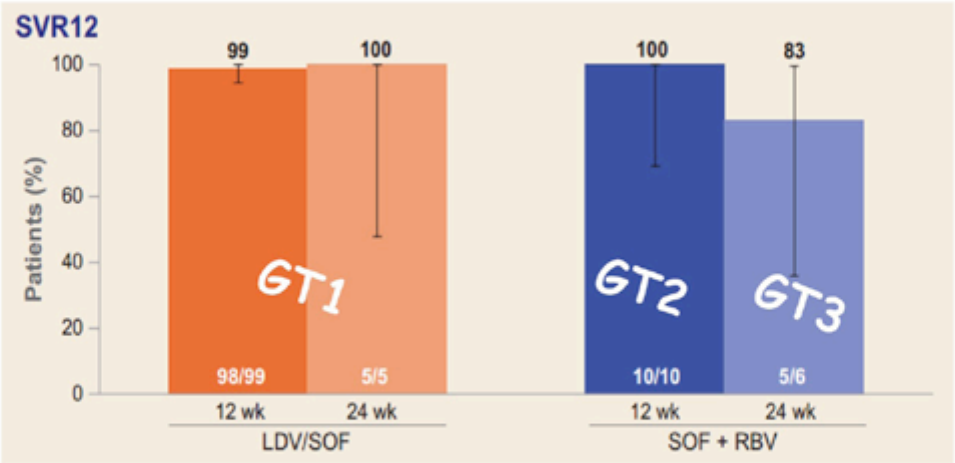
Sofosbuvir Regimens in Patients with Hereditary Bleeding Disorders



- 1 patient with HCV GT 1 was lost to follow-up following Week 4 visit
- 1/6 (17%) with GT 3 relapsed (patient had cirrhosis)

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Sofosbuvir Regimens in Patients with Hereditary Bleeding Disorders

Overall Safety Summary

		LDV/SOF		SOF+RBV	
		12 wk n=99	24 wk n=5	12 wk n=10	24 wk n=6
Overall Safety	Any AE, n (%)	61 (62)	3 (60)	8 (80)	4 (67)
	Grade 3/4 AE, n (%)	5 (5)	0	0	1 (17)
	Serious AE, n (%)	5 (5)	0	0	1 (17)
Laboratory Abnormalities	Grade 3/4, n (%)*	9 (9)	0	1 (10)	1 (17)
	Hemoglobin, n				
	<10 g/dL	0	0	0	0
	<8.5 g/dL	0	0	0	0

*There was one Grade 4 laboratory abnormality: patient had elevated creatine kinase associated with vigorous exercise regimen.

AEs in ≥5% Patients in LDV/SOF 12 Week Treatment Arm*

	LDV/SOF		SOF+RBV	
	12 wk, n=99	24 wk, n=5	12 wk, n=10	24 wk, n=6
Fatigue	29 (29)	1 (20)	3 (30)	2 (33)
Headache	14 (14)	0	3 (30)	0
Diarrhea	7 (7)	0	1 (10)	3 (50)
Hemarthrosis	10 (10)	0	1 (10)	0
Insomnia	6 (6)	0	1 (10)	3 (50)
Nausea	8 (8)	0	1 (10)	1 (17)
Disturbance in attention	6 (6)	0	1 (10)	0
Anxiety	5 (5)	0	1 (10)	0
Muscle hemorrhage	5 (5)	0	0	0

*Data presented as n (%).

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Conclusions

- For patients with HCV and hereditary bleeding disorders, LDV/SOF (GT 1) and SOF + RBV (GT 2 or 3) were highly efficacious
  - No patient with GT 1 experienced virologic failure following 12 or 24 weeks of LDV/SOF
  - 1 patient with GT 3 and cirrhosis treated with SOF + RBV for 24 weeks relapsed
- Treatment was equally effective and safe in patients regardless of bleeding disorder history, cirrhosis status, and HIV status
- Treatment of this population can be safely initiated without special consideration due to their hereditary bleeding disorder

ORIGINAL ARTICLE

Once daily ledipasvir/sofosbuvir fixed-dose combination with ribavirin in patients with inherited bleeding disorders and hepatitis C genotype 1 infection

C. A. M. STEDMAN,* R. H. HYLAND,† X. DING,† P. S. PANG,† J. G. MCHUTCHISON† and E. J. GANE‡
*Gastroenterology Department Christchurch Hospital and University of Otago, Christchurch, New Zealand; †Gilead Sciences Inc., Foster City, CA, United States; and ‡New Zealand Liver Transplant Unit Auckland City Hospital, Auckland, New Zealand

Table 1. Baseline characteristics.

Characteristic	LDV-SOF + RBV $N = 14$
Mean age, year	54
Male, *n* (%)	12 (86)
White, *n* (%)	12 (86)
Mean body mass index, kg m^{-2} (range)	27 (20–34)
HCV genotype, *n* (%)	
1a	10 (71)
1b	4 (29)
Cirrhosis, *n* (%)	1 (7)
IL28B CC, *n* (%)	4 (29)
Mean baseline HCV RNA, $\log_{10}$ IU mL^{-1} (range)	6.5 (5.6–7.5)
Bleeding disorder	
Haemophilia A	8 (57)
Haemophilia B	3 (21)
von Willebrand disease	2 (14)
Factor XIII deficiency	1 (7)

SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin.

Stedman CA et al. Hemophilia. 2016 Mar; 22 (2), 214-217

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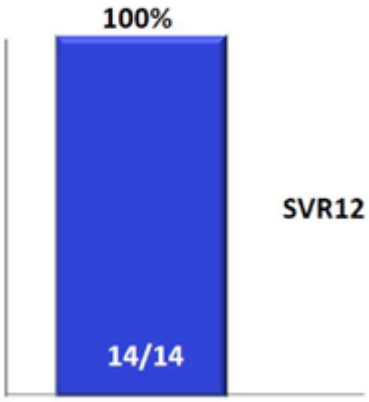

Virologic response

All patients experienced rapid viral suppression after initiating treatment and all 14 (100%, 95% CI: 77– 100%) achieved both SVR4 and SVR12. No patient in this cohort experienced virologic failure during treatment and no patient had experienced virologic relapse by posttreatment week 24.

Table 2. Adverse events in ≥10% of patients.

Preferred term, *n* (%)	LDV/SOF + RBV $N = 14$
Fatigue	7 (50)
Headache	5 (36)
Nausea	4 (29)
Insomnia	3 (21)
Anemia	2 (14)
Exertional dyspnoea	2 (14)
Irritability	2 (14)
Upper respiratory tract infection	2 (14)

SOF, sofosbuvir; LDV, ledipasvir; RBV, ribavirin.

Stedman CA et al. Hemophilia. 2016 Mar; 22 (2), 214-217

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APRIL 13-17, BARCELONA, SPAIN

C-EDGE IBLD: EFFICACY AND SAFETY OF ELBASVIR/GRAZOPREVIR (EBR/GZR) IN SUBJECTS WITH CHRONIC HEPATITIS C VIRUS INFECTION AND INHERITED BLOOD DISORDERS

Christophe Hezode, Massimo Colombo, Ulrich Spengler, Ziv Ben-Ari, Simone Strasser, William M. Lee, Leslie Morgan, Jingjun Qiu, Peggy Hwang, Michael Robertson, Bach-Yen Nguyen, Eliav Barr, Janice Wahl, Barbara Haber, Rohit Talwani, Vito Di Marco

Abstract SAT-128

Study 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)
- 159 patients randomized to immediate treatment with EBR/GZR or deferred treatment where patients received placebo for 12 weeks and then open-label EBR/GZR starting at FUW4

Hezode C, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. SAT-128

Demographics	GZR + EBR (Immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Gender, n (%)		
Male	80 (74.8)	39 (75.0)
Female	27 (25.2)	13 (25.0)
Race, n (%)		
White	81 (75.7)	40 (76.9)
African-American	19 (17.8)	9 (17.3)
Asian	6 (5.6)	3 (5.8)
Other	1 (0.9)	0 (0)
HCV genotype, n (%)		
G1a	47 (43.9)	18 (34.6)
G1b	46 (43.0)	27 (51.9)
G1 other	2 (1.9)	0 (0)
G4	12 (11.2)	6 (11.5)
G6	0 (0)	1 (1.9)
Prior treatment history, n (%)		
Naive	53 (49.5)	27 (51.9)
Experienced	54 (50.5)	25 (48.1)
Cirrhosis, n (%)	26 (24.3)	12 (23.1)
HIV coinfected, n (%)	6 (5.6)	4 (7.7)
IL28B CC, n (%)	27 (25.2)	9 (17.3)
Blood disorder, n (%)		
Sickle Cell Anemia	19 (17.8)	10 (19.2)
β Thalassemia	41 (38.3)	20 (38.5)
von Willebrand / Hemophilia A/B	47 (43.9)	22 (42.3)

DTG = deferred treatment group; ITG = immediate treatment group

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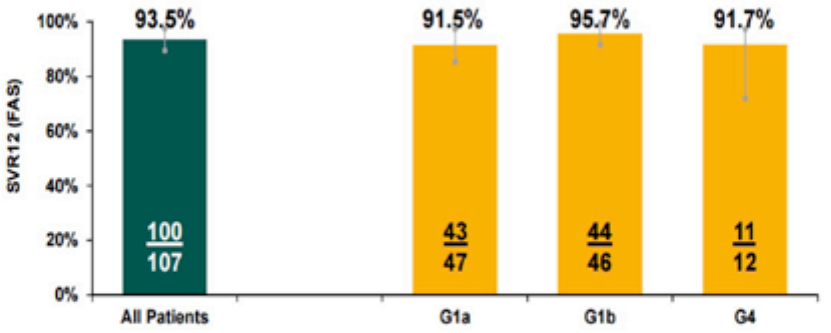
SVR12: Primary Efficacy Analysis Immediate Treatment Group, Full Analysis Set



	All Patients	G1a	G1b	G4
Breakthrough	0	0	0	0
Relapse	6	4	1	1
LTFU/Early DC	1	0	1	0
SVR12 (mFAS)	100/106 (94.3%)	43/47 (91.5%)	44/45 (97.8%)	11/12 (91.7%)

LTFU= Lost to follow up / Early discontinuation due to reasons other than virologic failure
mFAS = Modified Full Analysis Set

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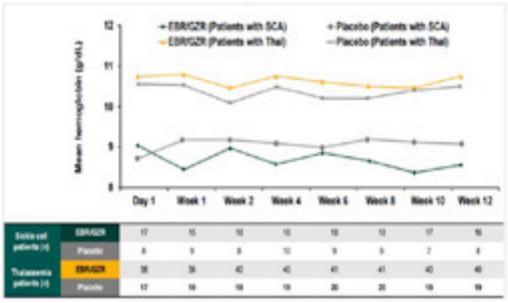
Adverse Events – Liver Enzymes – On-Treatment Hemoglobin Levels

	GZR + EBR (immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Any adverse event, n (%)	77 (72.0)	33 (63.5)
Headache	23 (21.5)	6 (11.5)
Fatigue	18 (16.8)	4 (7.7)
Nausea	9 (8.4)	8 (15.4)
Asthenia	8 (7.5)	2 (3.8)
Abdominal pain	7 (6.5)	2 (3.8)
Arthralgia	7 (6.5)	3 (5.8)
Pyrexia	6 (5.6)	0 (0)
Nasopharyngitis	6 (5.6)	2 (3.8)
Drug-related AE, n (%)	36 (33.6)	16 (30.8)
Serious AE†, n (%)	3 (2.8)	6 (11.5)
Discontinued due to an AE, n (%)	0 (0)	1‡ (1.9)
Death, n (%)	0 (0)	0 (0)

	GZR + EBR (immediate) 12 weeks (n = 107)	Placebo (Deferred) 12 weeks (n = 52)
Alanine aminotransferase, n (%)		6 (11.5)
Grade 3: 5.1 – 10.0 x ULN	0 (0)	1 (1.9)
Grade 4: >10.0 x ULN	1 (0.9)	
Aspartate aminotransferase, n (%)		
Grade 3: 5.1 – 10.0 x ULN	1 (0.9)	2 (3.8)
Grade 4: >10.0 x ULN	0 (0)	1 (1.9)
ALT/AST >500 IU/L, n (%)	0 (0)	1 (1.9)
ALT/AST >3 x baseline and >100 IU/L, n (%)	1 (0.9)	1 (1.9)
Bilirubin, n (%)		
Grade 3: 2.6 – 5.0 x ULN	12 (11.2)	9 (17.3)
Grade 4: >5 x ULN	8 (7.5)	3 (5.8)
>2.5-5 x baseline	2 (1.9)	0 (0)
>5x baseline	0 (0)	0 (0)
Alkaline phosphatase >3x ULN, n (%)	0 (0)	0 (0)



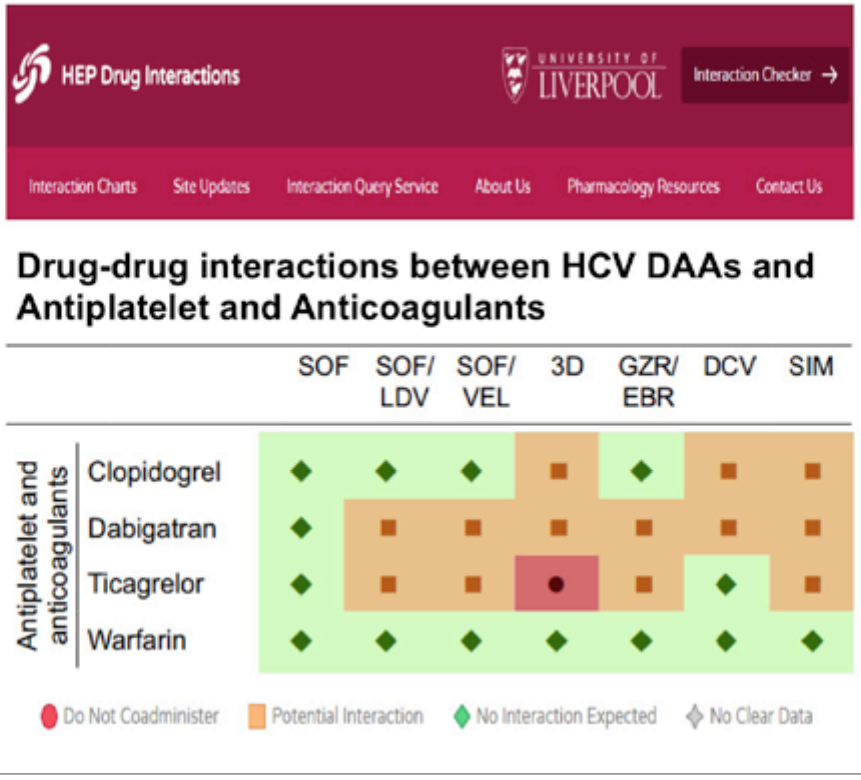
Hezode C, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. SAT-128

Conclusions

- A 12 week regimen of EBR/GZR was highly efficacious among patients with inherited blood disorders and HCV G1/4 infection
- High efficacy was maintained across many important patient subgroups including those with cirrhosis and HIV coinfection, and across all inherited blood disorders
  - A lower response was seen among GT1a patients with baseline NS5A RAVS
- EBR/GZR is generally well tolerated when administered to patients with inherited blood disorders and HCV infection
- EBR/GZR had no impact on measures of hematology and clotting, and no impact on the treatment of the underlying blood disorder

Hezode C, et al. 51st EASL; Barcelona, Spain; April 13-17, 2016. Abst. SAT-128


HARVONI
SOVALDI
Daklinza
daklatasvir
OLYSIO
SIMEPREVIR
viekirax
exviera
dasabuvir tablets
ZEPATIER
EPCLUSA
Pradaxa
REVOLADE
BRILIQUE
TICAGRELOR
Plavix
Coumadin 5
warfarin sodico
Fragmin
ELIQUIS
Xarelto
rivaroxaban
Tiklid 250 mg
Efient
CLEXANE
Sintrom 4 mg
Acenocumarol
Xagrid
anagrelide
AriXtra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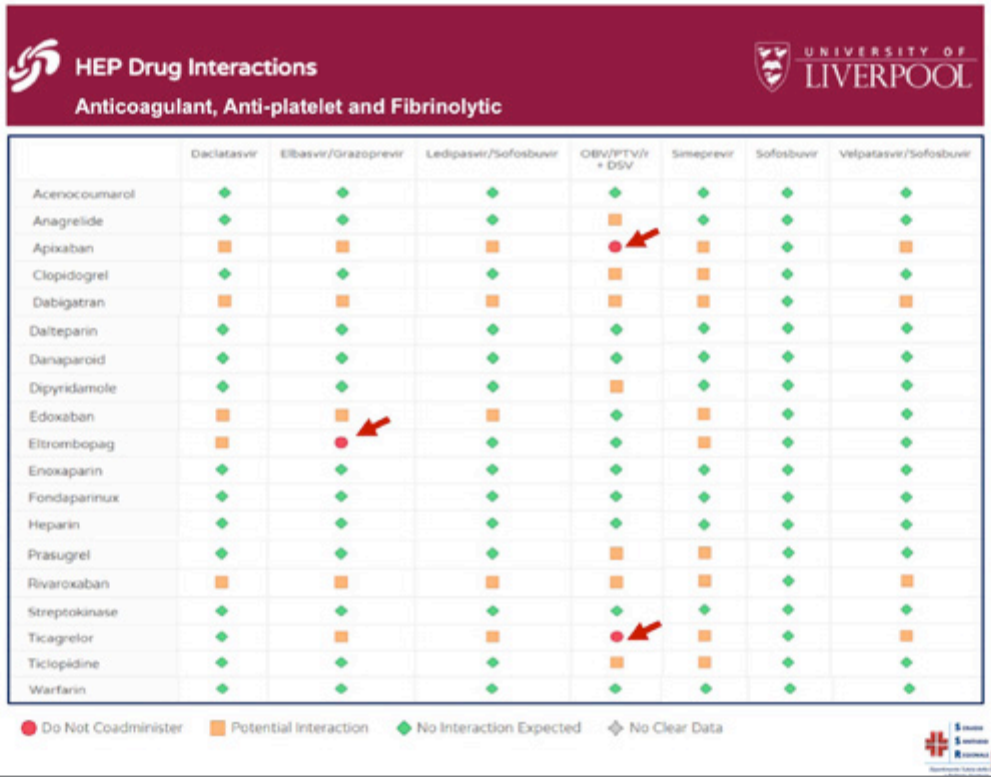
Drug-drug interactions between HCV DAAs and Antiplatelet and Anticoagulants
SOF
SOF/ LDV
SOF/ VEL
3D
GZR/ EBR
DCV
SIM
Antiplatelet and anticoagulants
Clopidogrel
Dabigatran
Ticagrelor
Warfarin
Do Not Coadminister
Potential Interaction
No Interaction Expected
No Clear Data



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Patients with Bleeding Disorders

- The management of chronic hepatitis C in haemophilia is similar to the non-haemophilic population and HCV DAAs are applicable to patients with haemophilia.
- In a study with the fixed-dose combination of grazoprevir and elbasvir administered for 12 weeks without ribavirin, SVR12 was achieved in 91% (42/ 46) of patients with von Willebrand disease or haemophilia A or B [144].

[144] Hezode C, Colombo M, Spengler U, Ben-Ari Z, Strasser S, Lee WM, et al. CEDGE IBLD: efficacy and safety of elbasvir/grazoprevir (EBR/GZR) in subjects with chronic hepatitis C virus infection and inherited blood disorders. J Hepatol 2016;64:S753

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

Patients with Bleeding Disorders

- Over 100 liver transplants have been carried out in haemophilic patients worldwide.
- Factor VIII/IX concentrate is administered immediately before the surgery, either by bolus injection or continuous infusion, and for the immediate post-operative period for 12–48 h, after which no further concentrate is required.
- Coinfection with HIV/HCV is not a contraindication to liver transplantation in haemophilia.
- The indications for liver transplantation in humans with haemophilia are the same as non-haemophilic individuals, but the procedure has the major advantage of producing a phenotypic cure of the haemophilia as a result of factor VIII production by the transplanted liver

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

Patients with Bleeding Disorders

Recommendations

- The indications for HCV therapy are the same in patients with and without bleeding disorders (A1).
- Potential drug-drug interactions in HCV-HIV coinfected patients receiving antiretroviral agents requires careful selection of agents (A1).

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017 Jan;66(1):153-194

Goal Is Elimination of Hepatitis C Infection

2030 WHO Targets

90%	Diagnosed
80%	Treated
65%	Reduced Mortality

World Health Organization

WHO. Towards the elimination of hepatitis B and C by 2030.
Mitruka K, et al. MMWR Morb Mortal Wkly Rep. 2015;64:753-757.