Workshop HCV
Ferrara 26-29 maggio 2017

Sergio Boccia, Laura Sighinolfi,
Loredana Simone, Anastasio Grilli,
Silvia Carradori

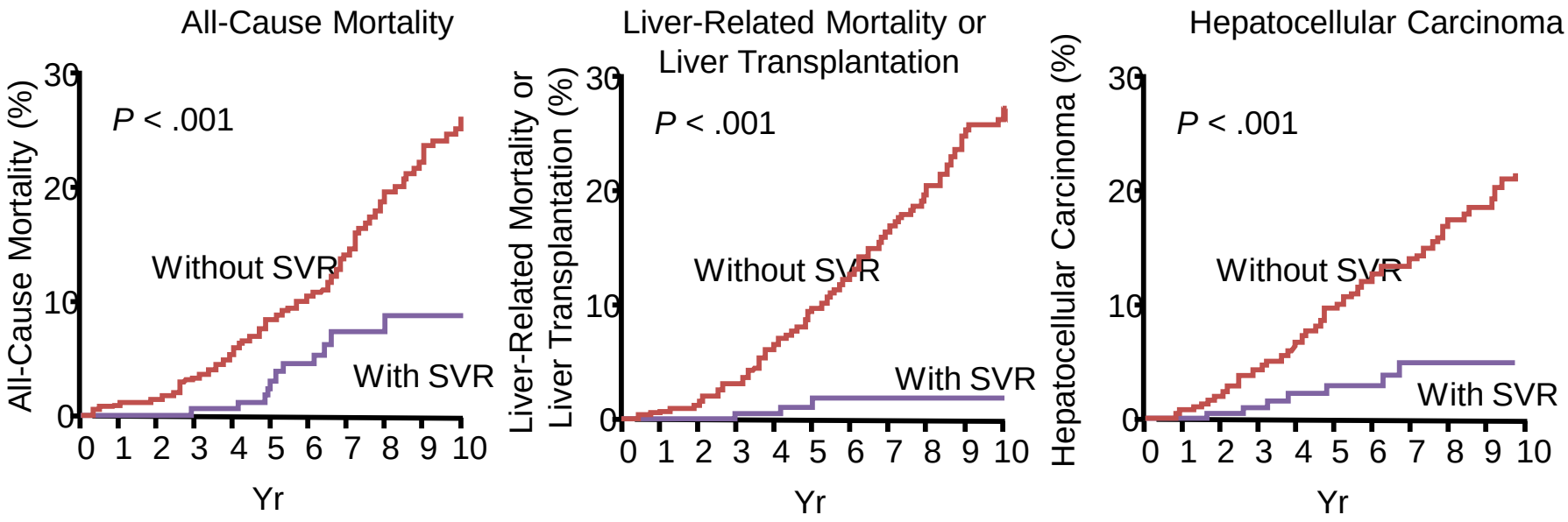
Razionale

- Il paziente con epatite HCV correlata presenta un quadro clinico complesso : numerosi dati epidemiologici correlano infatti l'infezione da HCV a problematiche extraepatiche quali glomerulonefrite, artropatie , crioglobulinemie, malattie cardiovascolari e neurologiche
- A causa della complessità di questi pazienti diventa essenziale definire un approccio multidisciplinare, coinvolgendo in questo percorso anche altri specialisti
- Per tale motivo abbiamo deciso di effettuare due workshop di confronto fra gastroenterologi ed infettivologi e medici di due branche specialistiche, nefrologia e reumatologia
- Scopo di questi incontri è fornire agli specialisti non epatologi nozioni sulle nuove terapie antivirali dirette, efficaci e sicure, ma anche sensibilizzare a ricercare l'HCV nei loro pazienti ed eventualmente trattare quelle situazioni cliniche di loro competenza, che potrebbero essere correlate ,anche indirettamente, alla infezione HCV e che potrebbero giovarsi di una terapia antivirale.
- Si cercherà di costruire un percorso condiviso per proporre la terapia anche a questi pazienti , afferenti ad altri specialisti non epatologi .

Obiettivi della Guarigione dall'Epatite C

- Eliminazione di HCV = Cura
- Ridurre la necrosi ed infiammazione nel fegato
- Arrestare la progressione della fibrosi
- Prevenire la cirrosi e le sue complicanze
- Prevenire il carcinoma del fegato
- Ridurre il bisogno di un trapianto nella cirrosi scompensata
- Aumentare la sopravvivenza
- Prevenire la diffusione dell'Infezione (profilassi)

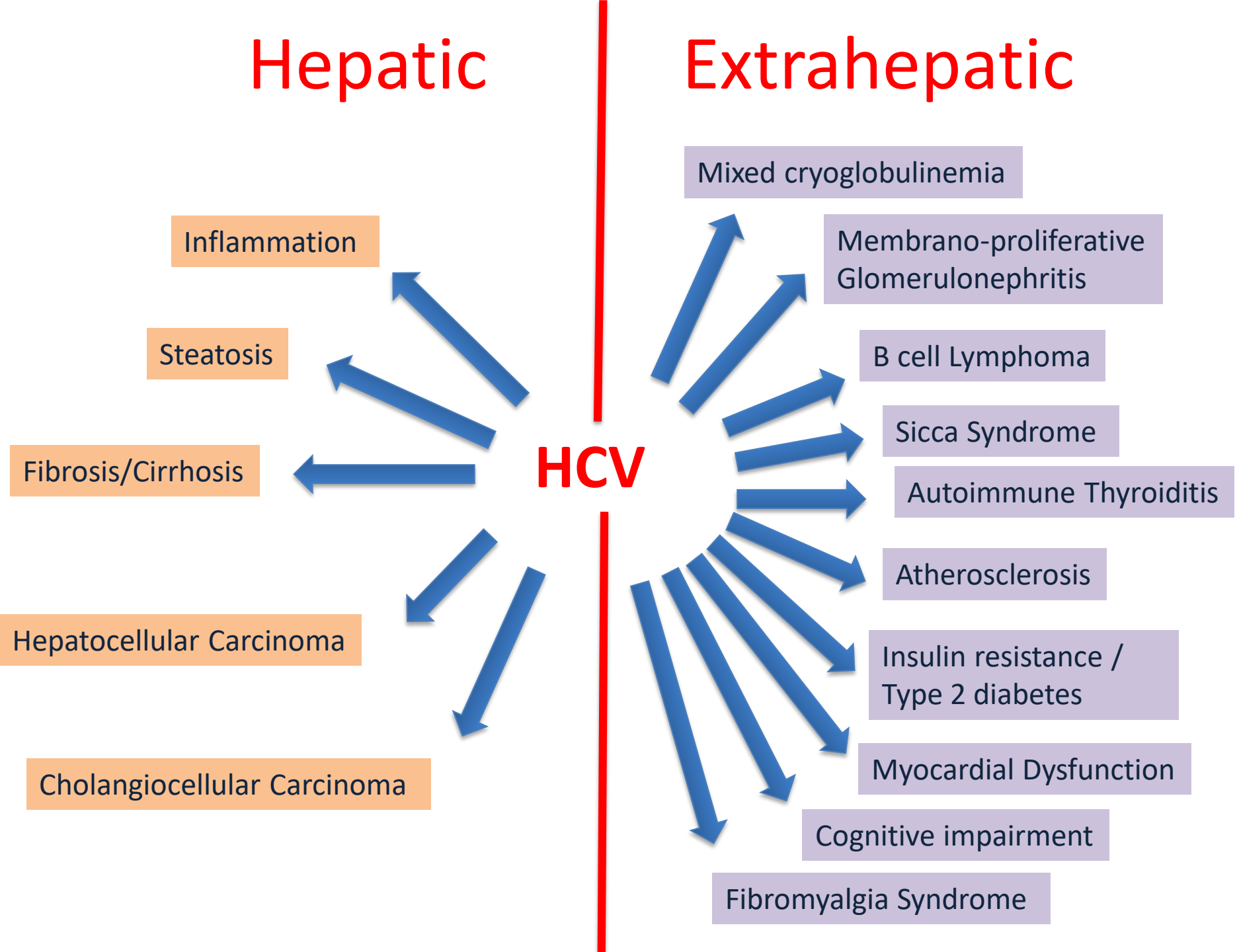
Hepatitis C Virologic Cure Associated With Improved Outcomes



HR: 0.26 (95% CI: 0.14-0.49; *P* < .001)

- Virologic cure does not protect against reinfection

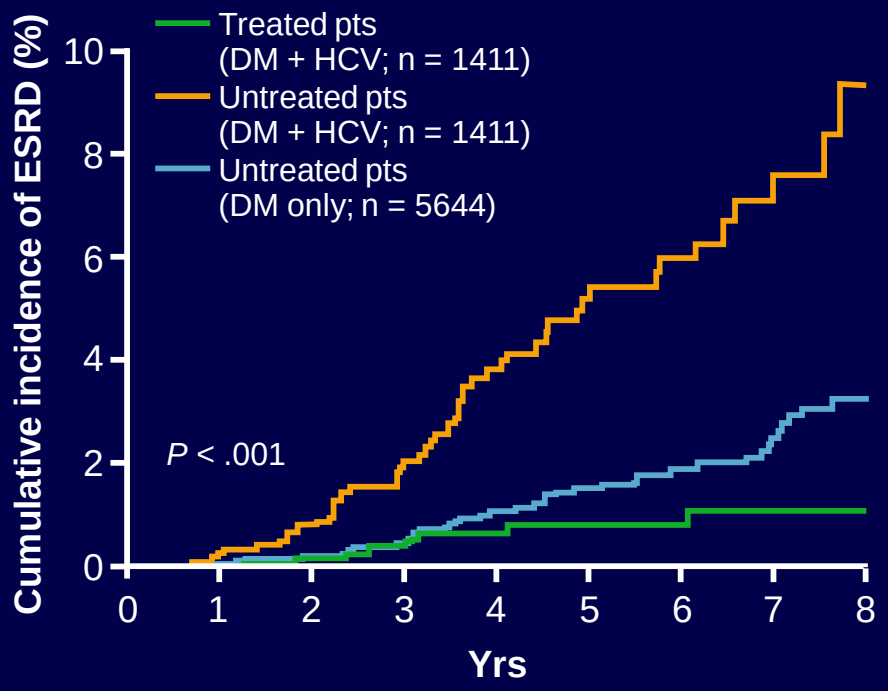
van der Meer AJ, et al. JAMA. 2012;308:2584-2593.


Hepatic
Extrahepatic
HCV
Inflammation
Steatosis
Fibrosis/Cirrhosis
Hepatocellular Carcinoma
Cholangiocellular Carcinoma
Mixed cryoglobulinemia
Membrano-proliferative Glomerulonephritis
B cell Lymphoma
Sicca Syndrome
Autoimmune Thyroiditis
Atherosclerosis
Insulin resistance / Type 2 diabetes
Myocardial Dysfunction
Cognitive impairment
Fibromyalgia Syndrome

Benefits of HCV Therapy Extend Beyond the Liver: Diabetes

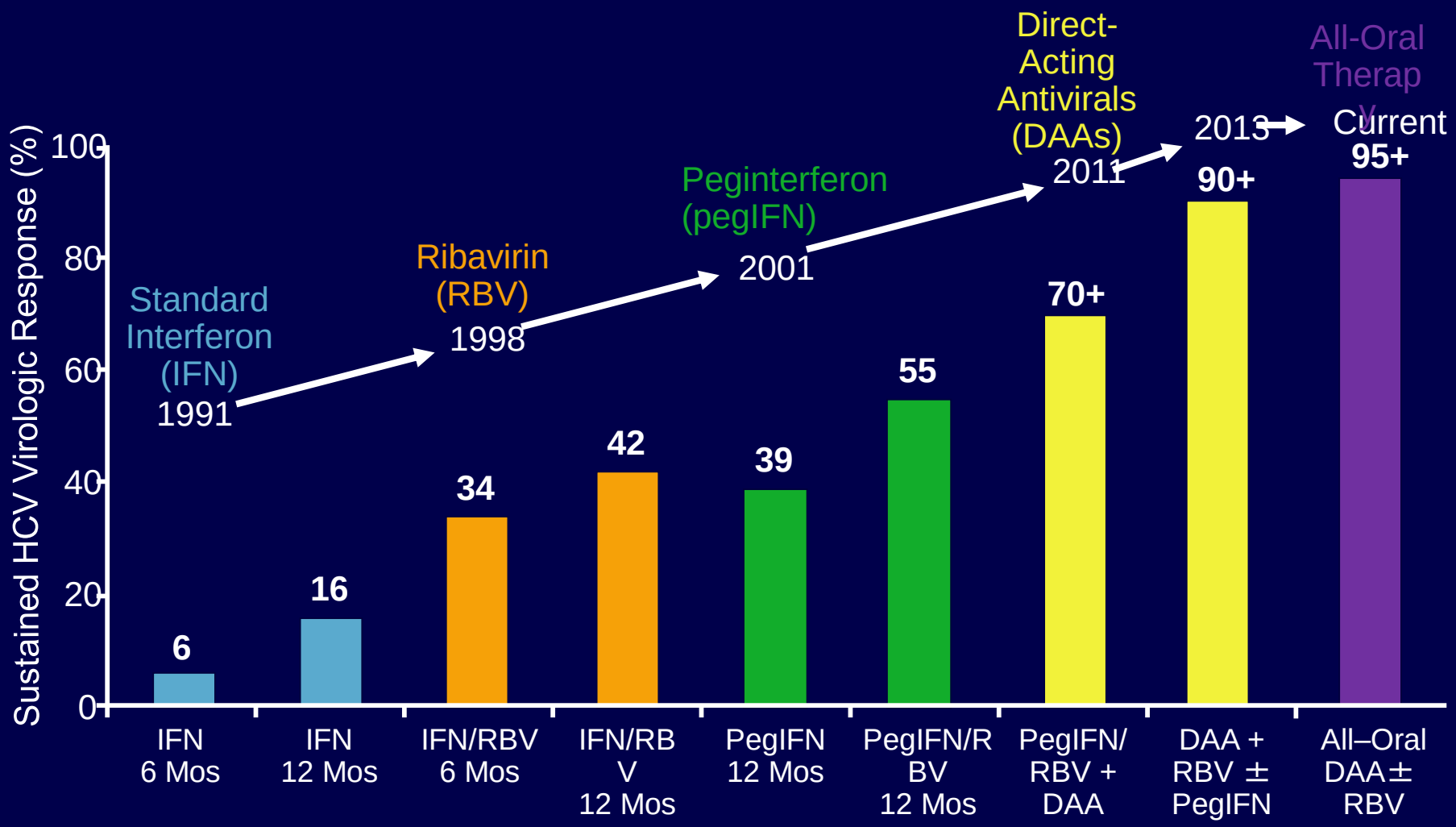
- HCV cure significantly reduces incidence of type 2 DM[1]
  - HCV pts have 2-3 x greater odds of DM[2]
- SVR may prevent and improve IR[3]
  - IR and DM increase risk and rate of fibrosis[2]
- PegIFN + RBV associated with improved renal/cardiovascular outcomes in pts with DM + HCV[4]

ESRD in DM Pts Treated or Untreated With PegIFN + RBV[4]



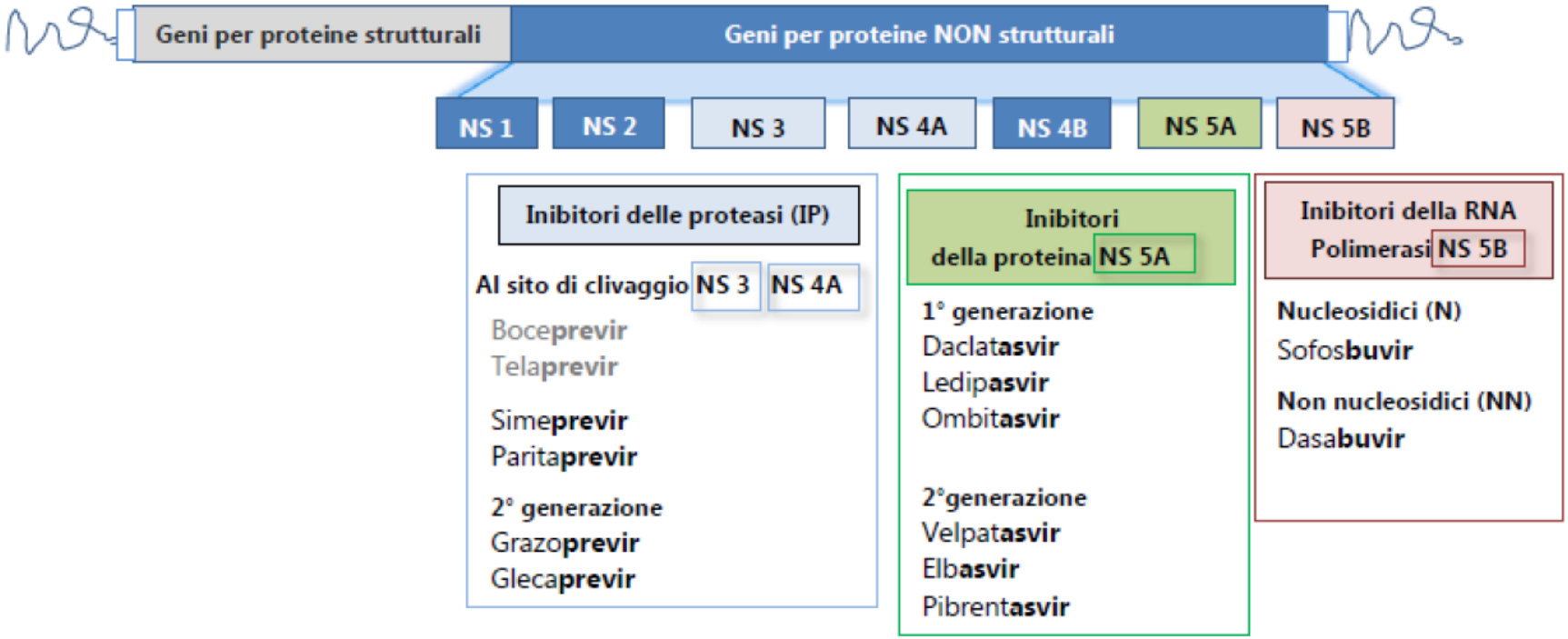
1. Arase Y, et al. Hepatology. 2009;49:739-744.
2. Brandman D, et al. Diabetes Care. 2012;35:1090-1094.
3. Aghemo A, et al. Hepatology. 2012;56:1691-1687.
4. Hsu YC, et al. Hepatology. 2014;59:1293-1302.

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



References in slidenotes

Figura 1 La figura rappresenta il genoma del virus dell'epatite C e i bersagli della poliproteina virale non strutturale in base ai quali sono classificati i DAA [modificato da Myers RP 2015]. La parte terminale del nome del farmaco identifica il meccanismo d'azione e quindi la classe di appartenenza: per convenzione gli inibitori della proteasi al sito di clivaggio NS 3/NS 4A terminano in "**previr**", gli inibitori della proteina NS 5A terminano in "**asvir**", gli inibitori dell'RNA polimerasi NS 5B terminano in "**buvir**".

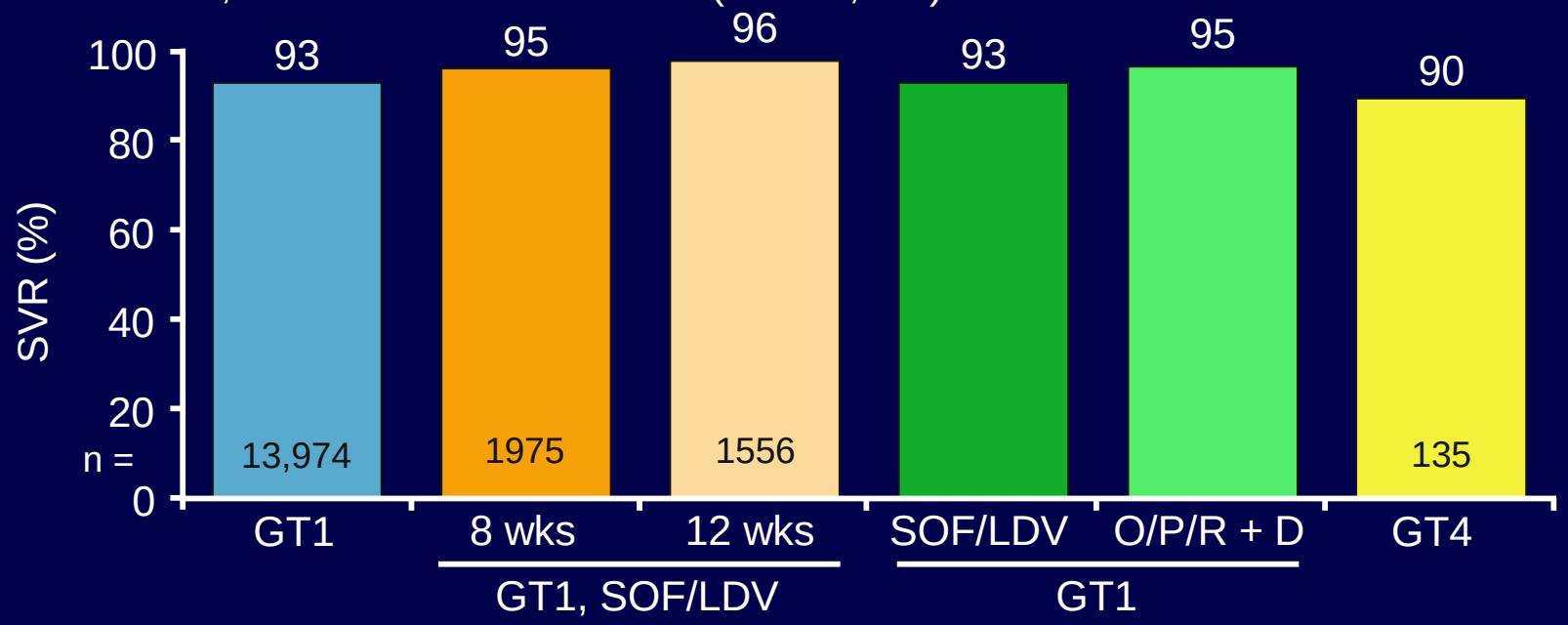


HCV Treatment in 2017

- Many highly effective, highly tolerable options
- All-oral therapy for all
- Most pts receive:
  - 12 wks of treatment
  - 1 pill, once per day
  - Ribavirin-free therapy
- Pts with previous pegIFN/RBV treatment easy to cure

Real-World HCV Treatment in the US VA Healthcare System

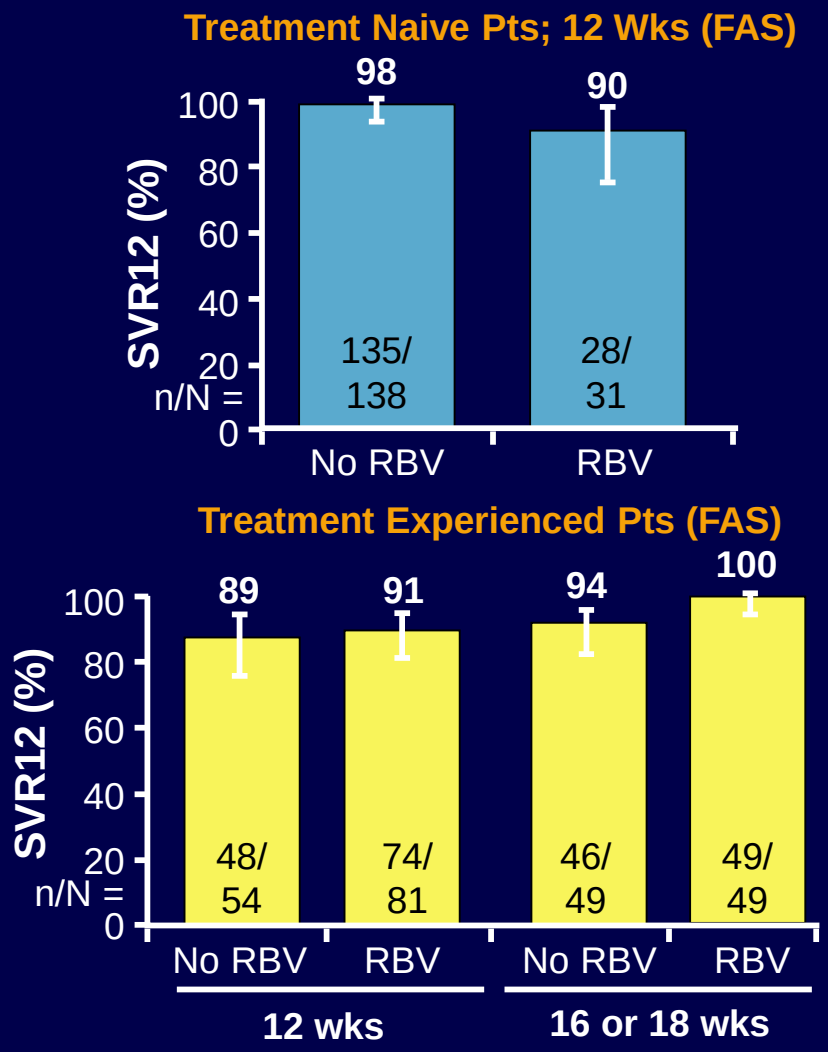
- Analysis of real-world SVR for pts with GT1-4 HCV treated with SOF + RBV ± pegIFN, SOF/LDV, or OBV/PTV/RTV + DSV (N = 17,487)[1]



- Analysis of HCV treatment in VA healthcare system (N = 107,079)[2]
  - Dramatic increases in HCV treatment in 2014-2015 vs 1999-2013 (1999-2011, 1989 to 7196 treatments/yr; 2014, 9180 treatments; 2015, 31,028 treatments)
  - Related to improved antiviral efficacy and availability of funding

1. Ioannou GN, et al. AASLD 2016. Abstract 21. Reproduced with permission.
2. Moon AM, et al. AASLD 2016. Abstract 227.

Elbasvir/Grazoprevir in Compensated Cirrhosis: SVR12

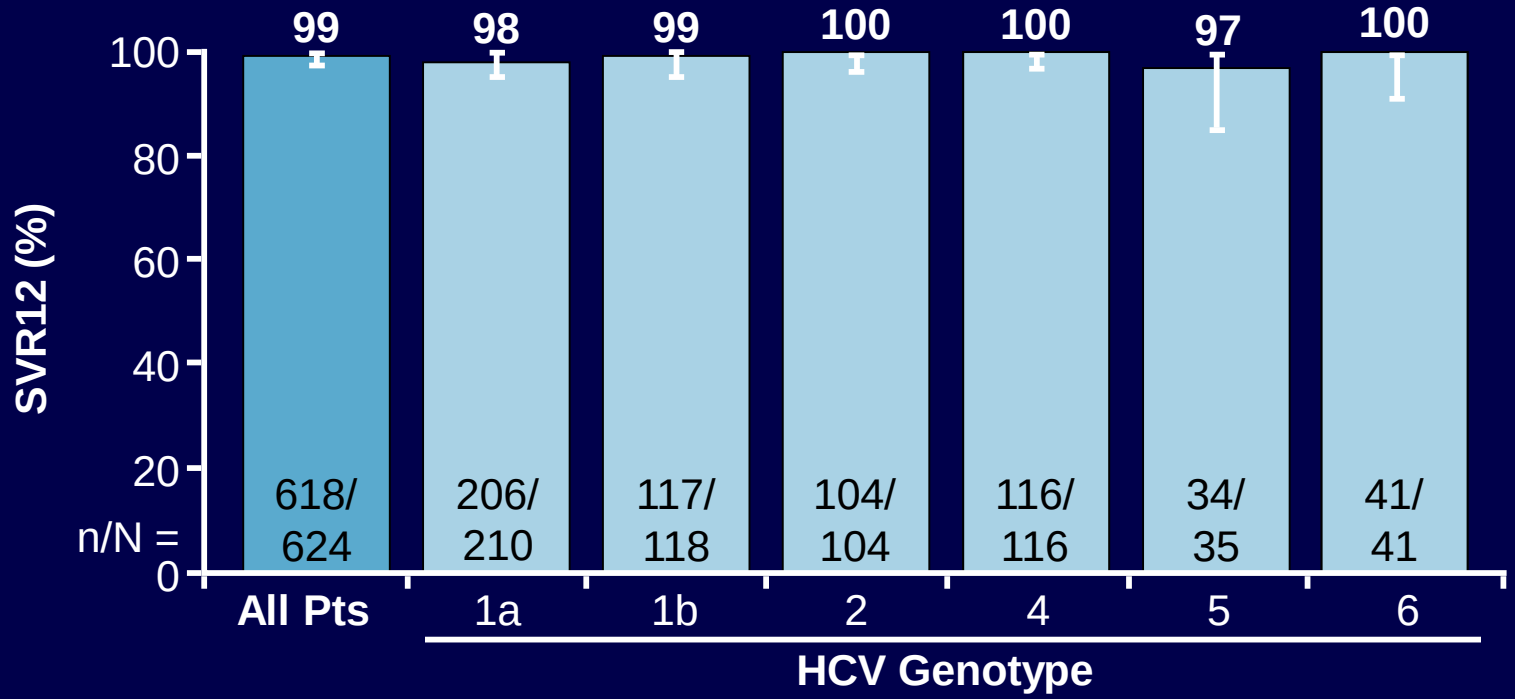


- **Treatment-naive pts**: SVR12 rates similar regardless of RBV use, HCV subtype in FAS and regardless of platelets, cirrhosis determination method, *FibroScan* score in mFAS
  - SVR12 rate range across subgroups treated without RBV: 96% to 100%
- **Previous relapsers (mFAS)**: SVR12 rates not affected by treatment duration or RBV use
- **Previous nonresponders (mFAS)**: SVR12 rates lower with 12-wk, no RBV vs 16/18-wk, + RBV treatment
  - GT1: 92% vs 100%
  - GT4: 67% vs 100%

Jacobson IM, et al. AASLD 2015. Abstract 42. Reproduced with permission. Slide credit: clinicaloptions.com

ASTRAL-1: SVR12 With Sofosbuvir/ Velpatasvir in GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial
  - All pts with GT5 HCV allocated to active Tx because few pts in this group (n = 35)
  - Key baseline characteristics: cirrhosis 19%; Tx exp'd 32%; BL NS5A RAVs 42%
- No impact of cirrhosis, Tx experience, BL NS5A RAVs on SVR rates



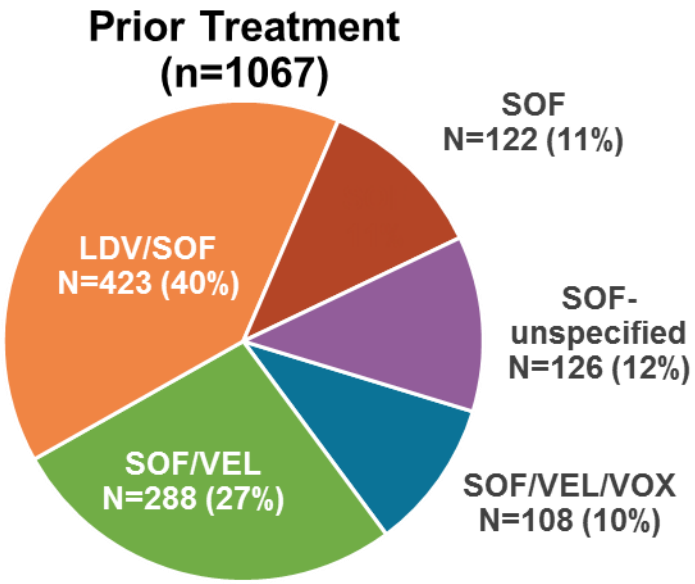
Feld JJ, et al. AASLD 2015. Abstract LB-2. Feld JJ, et al. N Engl J Med. 2015;[Epub ahead of print]. Reproduced with permission.

‡

Long-term Follow-up of >1,000 HCV Patients With Compensated or Decompensated Cirrhosis Who Achieved SVR Following Treatment With Sofosbuvir-Based Regimens

Assessments

- Every 6 mo: HCV RNA; labs, CPT, MELD; any occurrence within preceding 6 mo of HCC, death, liver transplant, and hepatic events, and results of endoscopy or biopsy (if performed); health-related QoL questionnaires
- Baseline and yearly thereafter: transient elastography
- Baseline and Week 240: endoscopy
- End of study: liver biopsy (optional)



Muir A, AASLD, 2016, #880

Demographics and Disease Characteristics

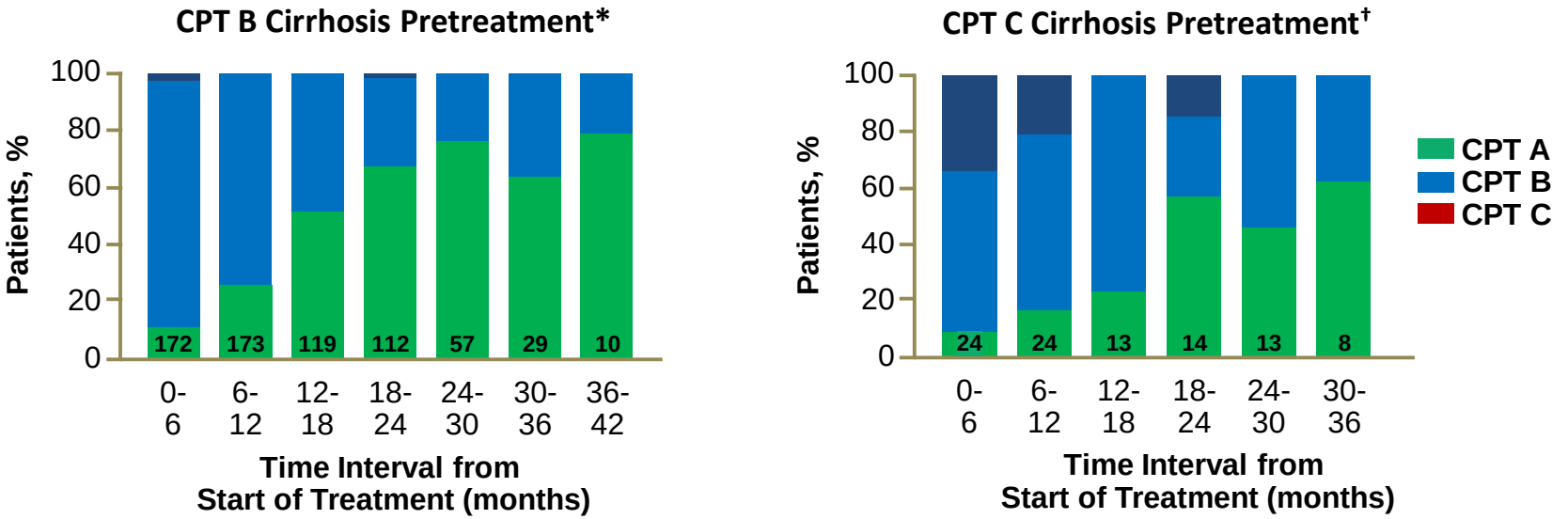
			N=1067
Demographics	Mean age, y (range)		59 (33–83)
	Male, n (%)		712 (67)
	Race, n (%)	White	915 (86)
		Black	92 (9)
	Hispanic/Latino		145 (14)
	Region, n (%)	North America	840 (78)
		Europe	149 (14)
		Australia/New Zealand	71 (7)
	Patient source, n (%)	Clinical study	834 (78)
		Clinical practice	233 (22)
	Mean BMI, kg/m^2 (Q1, Q3)		30 (26, 33)
Disease characteristics	Mean time since HCV diagnosis, y (range)		14 (1–51)
	Cirrhosis, n (%)*		1064 (>99)
	Decompensated		201 (19)
	HCV GT, n (%)	1	592 (55)
		2	49 (5)
		3	148 (14)
		4–6	43 (4)
		Missing	235 (22)
	Median platelets, x10^3/µL (range)		133 (20–626)

*Cirrhosis status determined prior to treatment with SOF-based regimen resulting in SVR. BMI, body mass index;GT, genotype; IL28B, interleukin-28B; Q, quartile.

‡

Long-term Follow-up of >1,000 HCV Patients With Compensated or Decompensated Cirrhosis Who Achieved SVR Following Treatment With Sofosbuvir-Based Regimens

Shift in CPT Classification



- The majority of patients maintained or improved their CPT category relative to pretreatment through up to 36 (CPT C) or 42 (CPT B) months relative to treatment start
- Overall improvements in key laboratory components such as mean bilirubin and mean albumin were observed

*Only 1 patient with CPT B cirrhosis prior to treatment has reached >42 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.
†Only 1 patient with CPT C cirrhosis prior to treatment has reached >36 mo since start of treatment; this patient had CPT A cirrhosis at last assessment.

Muir A, AASLD, 2016, #880

EASL Guidelines 2016 Highlights Summary

EASL
European Association for the Study of the Liver

All patients must be considered for treatment of Hepatitis C

First all oral IFN-free HCV treatment recommendations SOF based regimens recommended across genotypes, disease stages and patient populations

Acute treatment recommendation 8 wks SOF+NS5A (LDV/SOF, SOF/VEL and SOF+DCV), 12 wks SOF+NS5A in co-infected and/or patients with VL above 1M

Sofosbuvir as retreatment backbone due to high barrier to resistance

Guidance on treatment of patients with advanced disease MELD classification cut off 18-20

Screening strategies for HCV infection should be defined according to the local epidemiology of HCV infection, ideally within the framework of national plans

HCV core antigen is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable

Elimination: To achieve HCV elimination will require national plans together with unrestricted access to treatment

Indications for treatment of chronic hepatitis C in 2016: Who should be treated and when?

- **ALL** patients must be considered for treatment of Hepatitis C
- To achieve HCV elimination will require national plans together with forecasted budgeting to expedite unrestricted access to treatment

Treatment must be considered without delay

F0-F1 → F2 → F3 → CTP A → CTP B → CTP C → Post-Transplant

Additional population that should be prioritised:

- HIV Coinfection
- HBV Coinfection
- Clinically significant extra-hepatic manifestations
- High transmitters:
  - Active injection drug users
  - MSMs
  - Prisioners
  - Women of child-bearing age
  - Haemodialysis patients
  - Incarcerated individuals

EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

CTP = Child-Turcotte-Pugh
MSM = Men who have sex with men

Approved HCV drugs in the Europe 2016
First all-oral, IFN-free treatment recommendations

Product	Presentation	Posology
Sofosbuvir	Tablet containing 400 mg of sofosbuvir	One tablet once daily (morning)
Ledipasvir/sofosbuvir	Tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Sofosbuvir/velpatasvir	Tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet twice daily (morning and evening)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg Or Three capsules in the morning and 3 in the evening if body weight ≥75 kg

PEGASYS (PegIFN-α2a) Roche Products Limited, SmPC, November 2014; VIRAFERON-PEG (PegIFN-α2b), Merck Sharp & Dohme Limited. SmPC June 2014; COPEGUS (ribavirin) Roche Products Limited. SmPC, February 2015; REBETOL (ribavirin) Merck Sharp & Dohme Limited. SmPC May 2014; OLYSIO▼(simeprevir), Janssen Products LP. SmPC, March 2015; Limited. DAKLINZA▼ (daclatasvir), Bristol-Myers Squibb Pharmaceutical. SmPC October 2014) HARVONI▼ (ledipasvir/sofosbuvir), Gilead Sciences Europe Ltd. SmPC, November 2014 VIEKIRAX▼ (ombitasvir/paritaprevir/ritonavir), AbbVie Ltd. SmPC, January 2015 EXVIERA▼ (dasabuvir), AbbVie Ltd. SmPC, January 2015); SOVALDI▼ (sofosbuvir), Gilead Sciences Europe Ltd. SmPC, March 2015; HARVONII▼ (ledipasvir/sofosbuvir), Gilead Sciences Europe Ltd. SmPC, November 2015; EASL Recommendations on Treatment of Hepatitis C 2015; Journal of Hepatology 2015 vol. 63, 199–236

Drug-Drug Interactions

www.hep-druginteractions.org

UNIVERSITY OF LIVERPOOL

DRUG INTERACTION CHARTS

Access our comprehensive, user-friendly, free, drug interaction charts

CLICK HERE

Providing clinically useful, reliable, up-to-date, evidence-based information

Drug-Drug interactions: Lipid lowering drugs

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Atorvastatin	◆	■	■	●	■	■	■
Bezafibrate	◆	◆	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	◆	■	◆	◆	◆
Fenofibrate	◆	■	■	◆	■	◆	◆
Fluvastatin	◆	■	■	■	■	■	◆
Gemfibrozil	◆	◆	◆	●	■	◆	◆
Lovastatin	◆	■	■	●	■	■	■
Pitavastatin	◆	■	■	■	◆	■	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	■	■
Simvastatin	◆	■	■	●	■	■	■

SOF: sofosbuvir; LDV: ledipasvir; VEL: velpatasvirl OBV: ombitasvir; PTV: paritepravir; DSV: dasabuvir; GZR: grazoprevir; EBR: elbasvirl DCV: daclatasvir; SMV: simeprevir

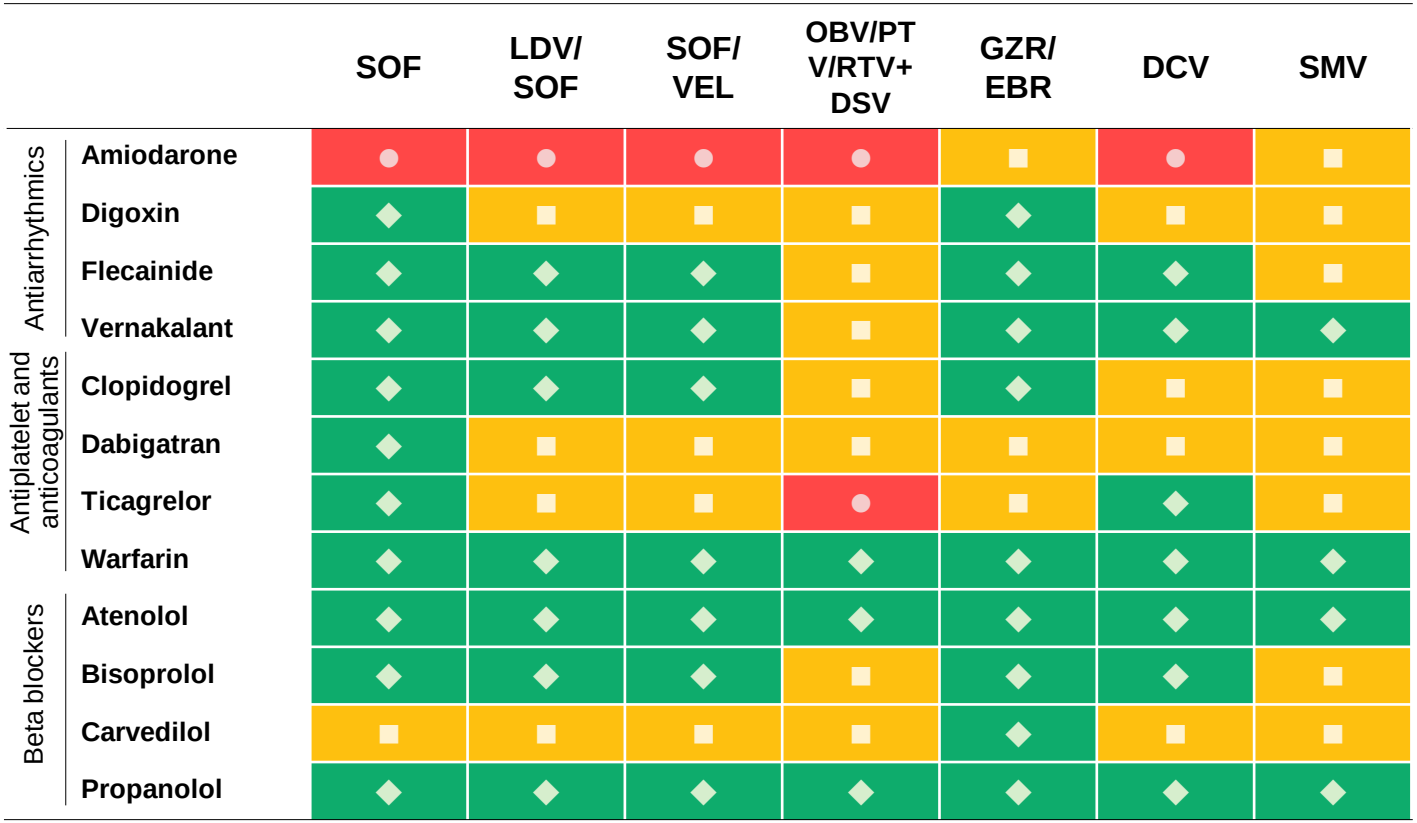
◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be co-administered.

EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Drug-Drug interactions: HCV DAAs and cardiovascular drugs



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Drug-Drug interactions: HCV DAAs and cardiovascular drugs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Calcium channel blockers	Amlodipine	◆	■	■	■	■	■	■
	Diltiazem	◆	■	■	■	◆	■	■
	Nifedipine	◆	◆	◆	■	◆	■	■
Hypertension and heart failure agents	Aliskiren	◆	■	■	●	◆	■	■
	Candersartan	◆	◆	◆	■	■	◆	◆
	Doxazosin	◆	◆	◆	■	◆	◆	■
	Enalapril	◆	◆	◆	■	◆	◆	◆

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Drug-Drug interactions: HCV DAAs and central nervous system

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Anti-depressants	Amitriptyline	◆	◆	◆	■	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆	◆	◆
	Paroxetine	◆	◆	◆	◆	◆	◆	◆
	Setraline	◆	◆	◆	■	◆	◆	◆
	Trazodone	◆	◆	◆	■	◆	◆	■
	Trimipramine	◆	◆	◆	◆	◆	◆	◆
	Venlafaxine	◆	◆	◆	■	◆	◆	◆

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Drug-Drug interactions: HCV DAAs and central nervous system

		SOF	LDV/ SOF	SOF/ VEL	OBV/PTV/RTV+ DSV	GZR/ EBR	DCV	SMV
Anti-psychotics	Amisulpiride	◆	◆	◆	■	◆	◆	◆
	Aripiprazole	◆	◆	◆	■	◆	◆	■
	Chlorpromazine	◆	◆	◆	■	◆	◆	◆
	Clozapine	◆	◆	◆	■	◆	◆	■
	Flupentixol	◆	◆	◆	■	◆	◆	◆
	Haloperidol	◆	◆	◆	■	◆	◆	■
	Olanzapine	◆	◆	◆	■	◆	◆	◆
	Paliperidone	◆	■	◆	■	◆	■	■
	Quetiapine	◆	◆	◆	●	■	◆	■
	Risperidone	◆	◆	◆	■	◆	◆	■
	Zuclopentixol	◆	◆	◆	■	◆	◆	◆

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Drug-Drug interactions: HCV DAAs immunosuppressants

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	◆	●
Etanercept	◆	◆	◆	◆	■	◆	◆
Everolimus	◆	■	■	●	■	■	■
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■
Tacrolimus	◆	◆	◆	■	■	◆	■

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▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2015 vol. xxx, xxx-xxx http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Drug-Drug interactions: HIV ARVs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PTV/RTV+ DSV	GZR/ EBR	DCV	SMV
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆

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◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be co-administered.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Drug-Drug interactions: HIV ARVs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PTV/RTV+ DSV	GZR/ EBR	DCV	SMV
Protease inhibitors	**Atazanavir; atazanavir/r; atazanavir/cobicistat**	◆	◆	◆	■	●	■	●
	Darunavir/rl darunavir/cobicistat	◆	◆	◆	■	●	◆	●
	Lopinavir/r	◆	◆	◆	●	●	◆	●
Entry/Integrase inhibitors	**Dolutegravir**	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobi/emtricitabine/TDF	◆	■	■	●	●	■	●
	Elvitegravir/cobi/emtricitabine/TAF	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Reltegravir	◆	◆	◆	◆	◆	◆	◆

SOF: sofosbuvir; LDV: ledipasvir; VEL: velpatasvirl OBV: ombitasvir; PTV: paritepravir; DSV: dasabuvir; GZR: grazoprevir; EBR: elbasvirl DCV: daclatasvir; SMV: simeprevir: TDF: tenofovir disoproxil fumarate: TAF: tenofovir alafenamide

◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be co-administered.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Drug-Drug interactions: HCV DAAs and illicit recreational drugs

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Amphetamine	◆	◆	◆	■	◆	◆	◆
Cannabis	◆	◆	◆	■	◆	◆	■
Cocaine	◆	◆	◆	■	◆	◆	■
Diamorphine	◆	◆	◆	■	◆	◆	◆
Diazepam	◆	◆	◆	■	◆	◆	■
Gamma-hydroxybutyrate	◆	◆	◆	■	◆	◆	■
Ketamine	◆	◆	◆	■	◆	◆	■
MDMA (ecstasy)	◆	◆	◆	■	◆	◆	◆
Methamphetamine	◆	◆	◆	■	◆	◆	◆
Phencyclidine (PCP)	◆	◆	◆	■	◆	◆	■
Temazepan	◆	◆	◆	◆	◆	◆	◆

SOF: sofosbuvir; LDV: ledipasvir; VEL: velpatasvirl OBV: ombitasvir; PTV: paritepravir; DSV: dasabuvir; GZR: grazoprevir; EBR: elbasvirl DCV: daclatasvir; SMV: simeprevir

◆ No clinically significant interaction expected

■ Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring

● These drugs should not be co-administered.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

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

Combination regimen	SOF + RBV	LDV/SOF ± RBV	SOF/VEL ± RBV	OBV/PTV/ RTV+ DSV ± RBV	OBV/PTV/ RTV ± RBV	GZR/ EBR	SOF + DCV ± RBV	SOF + SMV ± RBV
GT1	✗	✓	✓	✓	✗	✓	✓	Suboptimal
GT2	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT3	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT4	✗	✓	✓	✗	✓	✓	✓	✗
GT5	✗	✓	✓	✗	✗	✗	✓	✓
GT6	✗	✓	✓	✗	✗	✗	✓	✗

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment initiation and monitoring

- Anti-HCV antibodies are the first line diagnostic test for HCV infection.
- **HCV core antigen** is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication).

- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels monitoring can be simplified:

Baseline	Week 2	Week 4	EOT	SVR
✓	optional	optional	✓	✓

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation

- GT1
- GT2/3
- GT4
- GT5/6
- Patients with decompensated cirrhosis, MELD Guidance
- Patients with post-liver transplant recurrence
- Patients with post-liver transplant recurrence
- Patients with renal impairment
- Patients with non-hepatic solid organ transplant recipients
- Patients who failed to achieve SVR on prior antiviral therapy
- Patients with acute hepatitis C
- Treatment recommendations for HBV/HCV co-infection
- Patients who are active drug addicts and/or on stable maintenance substitution

Click on BOXES to go to section

EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation for GT1 patients without and with compensated cirrhosis

	Treatment recommendations for GT1 patients without cirrhosis					
GT	**TN/TE**	**LDV/SOF**	**SOF/VEL**	**OBV/PTV/ RTV+ DSV**	**GZR/EBR**	**SOF + DCV**
GT1a	**TN**	8-12 weeks	12 weeks	12 weeks + RBV	12 weeks, if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 weeks + RBV if HCV RNA>800,000 (5.9 log) IU/ml[b]	12 weeks
	TE	12 weeks + RBV[a] 24 weeks				12 weeks + RBV 24 weeks
GT1b	**TN**	8-12 weeks	12 weeks	8-12 weeks	12 weeks	12 weeks
	TE	12 weeks		12 weeks		

	Treatment recommendations for GT1 patients with compensated cirrhosis					
GT	**TN/TE**	**LDV/SOF**	**SOF/VEL**	**OBV/PTV/ RTV+ DSV**	**GZR/EBR**	**SOF + DCV**
GT1a	**TN**	12 weeks	12 weeks	24 weeks + RBV	12 weeks, if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 weeks + RBV if HCV RNA>800,000 (5.9 log) IU/ml[b]	12 weeks
	TE	12 weeks + RBV[a] 24 weeks				12 weeks + RBV 24 weeks
GT1b	**TN**	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks
	TE					

a. Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.
b. Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.

- For GT1a and GT1b non cirrhotic patients, LDV/SOF should be used for 12 weeks without RBV. LDV/SOF + RBV for 12 weeks or LDV/SOF (without ribavirin) for 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options
- 8 weeks OBV/PTV/RTV+ DSV is not an EMA recommended regimen for GT1b

EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation for GT2 and GT3 patients without and with compensated cirrhosis

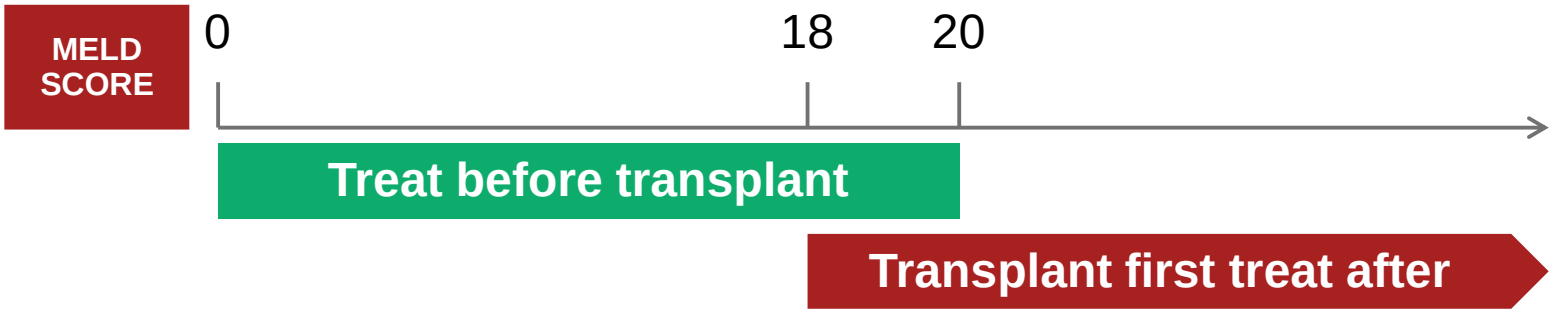
	Treatment recommendations for GT2 and GT3 patients without cirrhosis		
GT	**TN/TE**	**SOF/VEL**	**SOF + DCV**
GT2	**TN/TE**	12 weeks	12 weeks
GT3	**TN**	12 week	12 weeks
	TE	12 week + RBV[a] 24 week	12 week + RBV[a] 24 week

Treatment recommendations for GT2 and GT3 patients with compensated cirrhosis			
GT	**TN/TE**	**SOF/VEL**	**SOF + DCV**
GT2	**TN/TE**	12 weeks	12 weeks
GT3	**TN**	12 week	24 weeks + RBV
	TE	12 week + RBV[a] 24 week	

a. Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation for Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation MELD Score Guidance



- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 can be treated before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation.
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score ≥18-20 should be transplanted first, without antiviral treatment. HCV infection should be treated after liver transplantation.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation for Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation

	Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation MELD score <18-20 treat before liver transplantation		
GT	**LDV/SOF + RBV**	**SOF/VEL + RBV**	**SOF + DCV + RBV**
GT1	12 weeks	12 weeks	12 weeks
GT2	-	12 weeks	12 weeks
GT3	-	24 weeks	24 weeks
GT4	12 weeks	12 weeks	12 weeks
GT5	12 weeks	12 weeks	12 weeks
GT6	12 weeks	12 weeks	12 weeks

Daily ribavirin recommended weight-based dose is 1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively. Ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance.

Patients with decompensated cirrhosis with contraindications to the use of RBV or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of LDV/SOF (GT1, 4, 5 or 6), the fixed-dose combination of SOF/VEL (all genotypes), or the combination of SOF + DCV (all genotypes) for 24 weeks without RBV.

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendation for Patients with renal impairment

	Patients with severe renal impairment (eGFR <30ml/min/1.73m^2) or ESRD on haemodyalisis without an indication for kidney transplantation				
GT	**OBV/PTV/ RTV+ DSV**	**GZR/EBR**	**OBV/PTV/ RTV**	**SOF/VEL**	**SOF + DCV**
GT1a	12 weeks + RBV	12 weeks + RBV	-	-	-
GT1b	12 weeks	12 weeks	-	-	-
GT2	-	-	-	12 weeks	12 weeks
GT3	-	-	-	12 weeks + RBV[a] 24 weeks[a]	12 weeks + RBV[a] 24 weeks[a]
GT4	-	12 weeks	12 weeks	-	-

a. Only if treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m2) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected

- Patients with mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m2) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored.
- SOFr should be used with caution in patients with an eGFR <30 ml/min/1.73 m2 or with end-stage renal disease because no dose recommendation can currently be given for these patients

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

The safety of SOF-based regimens has not been assessed in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) or end stage renal disease (ESRD) requiring haemodialysis

Treatment recommendation for non-hepatic solid organ transplant recipients

	Patients with non-hepatic solid organ transplant recipients		
GT	**LDV/SOF**	**SOF/VEL**	**SOF + DCV**
GT1	✓	✓	✓
GT2	✗	✓	✓
GT3	✗	✓	✓
GT4	✓	✓	✓
GT5	✓	✓	✓
GT6	✓	✓	✓

No need for immunosuppressant drug dose adjustments (with the probable exception of everolimus)

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs

	Patients who failed to achieve SVR with a PegIFN-α and telaprevir, or boceprevir, or simeprevir						
	LDV/SOF	**SOF/VEL**	**OBV/PTV/ RTV + DSV**	**OBV/PTV/ RTV**	**GZR/EBR**	**SOF + DCV**	**SOF + SMV**
GT1	12 weeks + RBV	12 weeks + RBV	-	-	-	12 weeks + RBV	-

	Patients who failed to achieve SVR with a SOF + SMV						
	LDV/SOF	**SOF/VEL**	**OBV/PTV/ RTV + DSV**	**OBV/PTV/ RTV**	**GZR/EBR**	**SOF + DCV**	**SOF + SMV**
GT1 or GT4	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-	-	-	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs

	Patients who failed to achieve SVR with a NS5A-based regimen (LDV, VEL, OMV, EBR, DCV)				
	SOF/VEL + RBV	**SOF + OMV/PTV/RTV + DSV**	**SOF + OMV/PTV/RTV +RBV**	**SOF + GRZ/EBV + RBV**	**SOF + DCV + SMV + RBV**
GT1a		24 weeks	-	24 weeks	24 weeks
GT1b		F0–F2 12 weeks F3–F4 24 weeks	-	F0–F2 12 weeks F3–F4 24 weeks	
GT 3	24 weeks	-	-	-	-
GT 4			F0–F2 12 weeks F3–F4 24 weeks		
GT 5/6	24 weeks	-	-	-	-

- EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

The regimens shown are not EMA approved regimens for retreatment of patients who failed to achieved SVR. The only regimen approved is SOF/VEL+RBV for 24 weeks in GT3 only.

Treatment recommendations for acute hepatitis C

	Patients with acute monoinfection hepatitis C		
	LDV/SOF	**SOF/VEL**	**SOF + DCV**
GT1, 4, 5 and 6	8 weeks	8 weeks	8 weeks
All genotypes	-	8 weeks	8 weeks

	Patients with acute hepatitis C and HIV coinfection and/or baseline HCV RNA level> 1 million IU/ml (6.0 log IU/ml)		
	LDV/SOF	**SOF/VEL**	**SOF + DCV**
GT1, 4, 5 and 6	12 weeks	12 weeks	12 weeks
All genotypes	-	12 weeks	12 weeks

▪EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

The regimens shown are not EMA approved regimens for the treatment of acute hepatitis C

Treatment recommendations for HBV/HCV coinfection

- Patients commencing DAA-based treatment for HCV should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies.
- If HBs antigen is present or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients (“occult” hepatitis B), concurrent HBV nucleoside/nucleotide analogue therapy is indicated.
- Assiduous monitoring of serum aminotransferase levels is indicated in anti-HBs and anti-HBc antibody-positive patients.
- Patients with HBV coinfection should be treated with the same regimens, following the same rules as HCV monoinfected patients

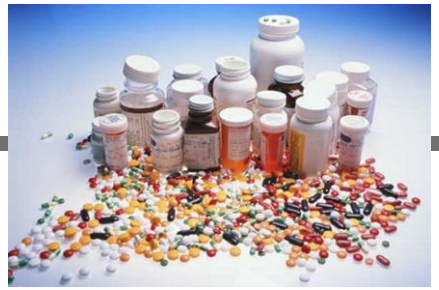
EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016
http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Treatment recommendations of active drug addicts and patients on stable maintenance substitution

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and if negative, annually.
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons.
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting.
- **The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs.** They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken.

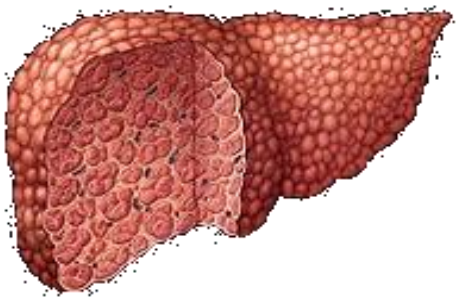
EASL Recommendations on Treatment of Hepatitis C 2016; Journal of Hepatology 2016 http://dx.doi.org/10.1016/j.jhep.2016.09.001 (Accessed September 2016)

Ribavirina



Interazioni

Scelta del Trattamento



Cirrosi

Durata del trattamento

Costi

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 e nei quali la malattia epatica sia determinante per la prognosi;

2. Pazienti con recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR ≥2 (o corrispondente Ishak) o fibrosante colestatica;

3. Pazienti con epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B);

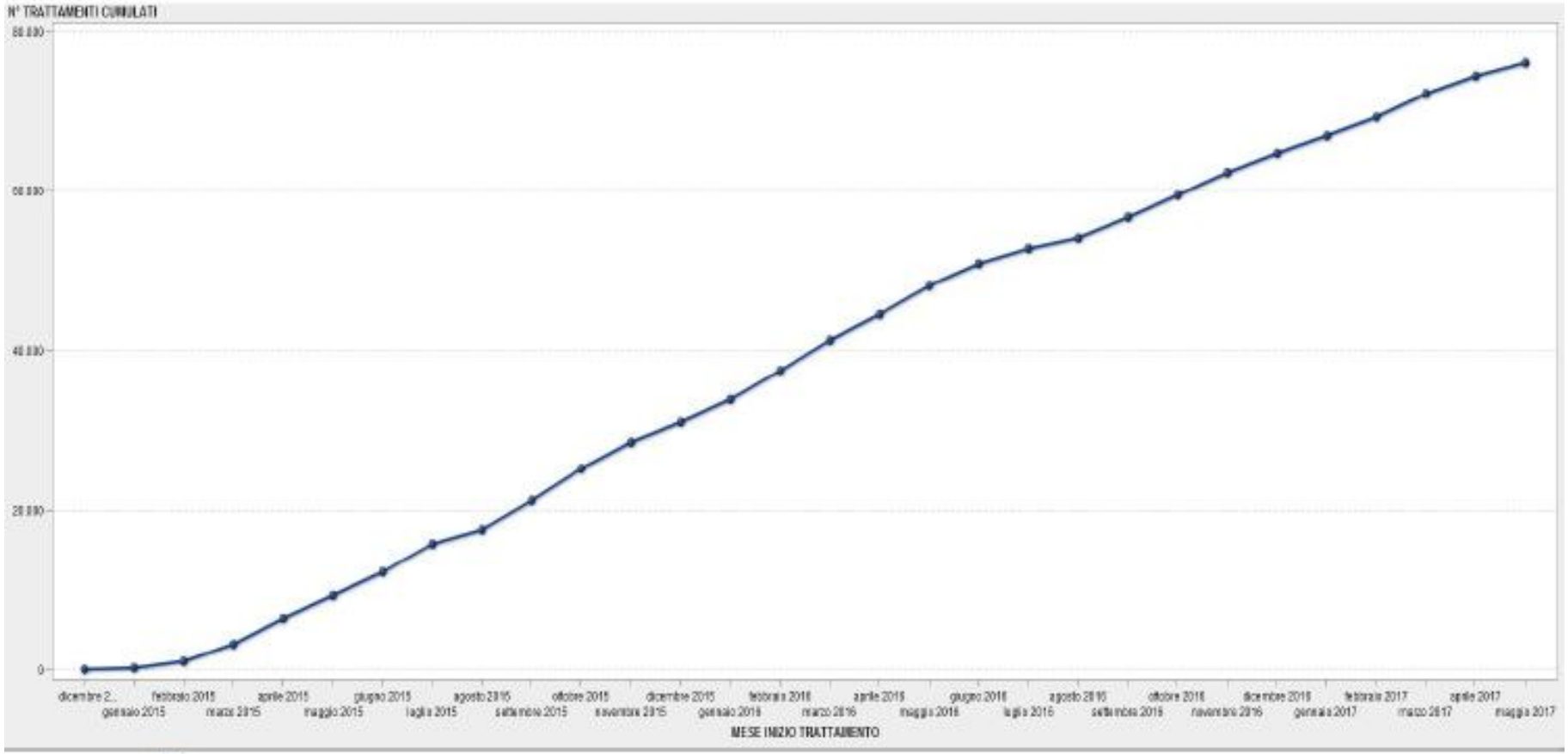
4. Pazienti con epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak);

5. Pazienti in lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di un'attesa in lista di almeno 2 mesi;

6. Pazienti con epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥2 (o corrispondente Ishak).

7. Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)

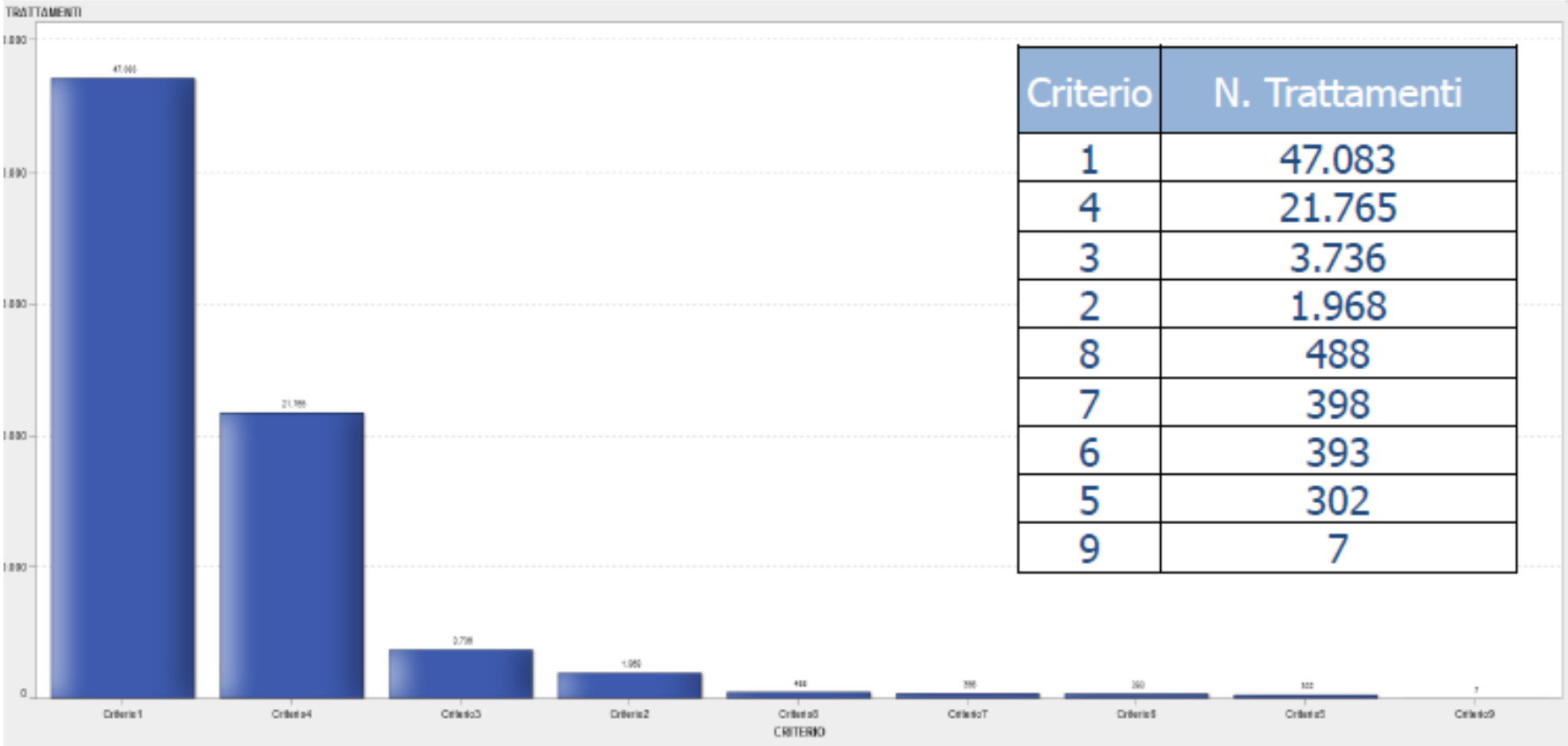
Trend cumulativo dei trattamenti avviati



Agenzia Italiana del Farmaco
AIFA

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

Trattamenti avviati per criterio



Criterio	N. Trattamenti
1	47.083
4	21.765
3	3.736
2	1.968
8	488
7	398
6	393
5	302
9	7

Agenzia Italiana del Farmaco
AIFA

NB: I trattamenti avviati con il precedente criterio 7 sono stati distribuiti, sulla base della stadiazione METAVIR, nei nuovi criteri 7 e 8

NUOVI CRITERI AIFA MARZO 2017

Criterio 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.

Criterio 2: Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.

Criterio 3: Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale).

Criterio 4: Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak).

Criterio 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.

Criterio 6: Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.

Criterio 7: Epatite cronica con fibrosi **METAVIR F2**.

Criterio 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].

Criterio 9: Operatori sanitari infetti.

Criterio 10: Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.

Criterio 11: Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo

Decisioni cliniche e organizzative 2/5/17

DOCUMENTO DI INDIRIZZO
per la definizione delle strategie terapeutiche
da applicare sul breve termine per:

Antivirali diretti
nella terapia dell'epatite C cronica

- Il GdL, in seguito al recente allargamento dei criteri di rimborsabilità, alla disponibilità di nuovi trattamenti e ai nuovi accordi negoziali per i farmaci disponibili, sulla base delle caratteristiche e della numerosità della casistica da trattare ha stabilito di:

  definire criteri omogenei di arruolamento dei pazienti, con l'obiettivo di:

- - garantire, sia per i pazienti già in carico ai singoli Centri che per i pazienti incidenti, l'accesso alla terapia nel più breve tempo possibile a tutti coloro che ne hanno maggiore necessità clinica;
- - programmare, in occasione del controllo ambulatoriale periodico, per tutti i pazienti afferenti al singolo Centro la tempistica del trattamento.
- A tal fine, applicando i principi di priorità clinica sopra descritti, e a partire dai criteri di eleggibilità dei registri AIFA dei DAA, si è deciso di trattare i pazienti che presentano le seguenti caratteristiche: Criteri 1-2-3-4-5-6-7-8(con co-patologie)-9-10-11
- Una volta esauriti i criteri sopra elencati, si inizierà a trattare i pazienti con Fibrosi META-VIR F0-F1 che non presentano comorbilità

CRITERIO 8 MODIFICATO RER

- **Criterio 8:** epatite cronica con fibrosi META-VIR F0-F1 (o corrispondente Ishak) e comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (BMI ≥30 kg/m2), emoglobinopatie e coagulopatie congenite], o in pazienti oncologici che necessitano di chemioterapia o in donne in età fertile.

Sinfonia

LA GESTIONE DELLE COMORBIDITÀ NEL PAZIENTE
HCV POSITIVO: UN APPROCCIO MULTIDISCIPLINARE

2. HCV E REUMATOLOGIA E IMMUNOLOGIA CLINICA

- La prevalenza delle patologie immunitarie sistemiche nella popolazione generale e nei pazienti HCV
- La prevalenza di HCV nei pazienti con patologie immunitarie sistemiche
- L'impatto dello screening HCV sulla diagnosi e sul trattamento dell'A.R.
- I farmaci anti virali disponibili per i pazienti con HCV e malattie immunitarie sistemiche
- La gestione ottimale del paziente HCV con patologie immunitarie sistemiche
- Il contributo che può dare il reumatologo in corso di terapia con DAA
- L'impatto dell'eradicazione dell'HCV nella gestione delle manifestazioni cliniche dell'A.R.
- La gestione delle DDI nelle terapie per le patologie reumatiche
- Un'esperienza pratica di interazione tra reumatologia ed epatologia nella pratica clinica quotidiana
- Quale paziente reumatologico oggi dovrebbe avere la priorità al trattamento HCV