Corso residenziale di aggiornamento
a cura della regione Sicilia

I° CONVEGNO REGIONALE SIFO "MEETING DI PRIMAVERA"

IL RUOLO DEL FARMACISTA NEI NUOVI MODELLI DI CURA

TAORMINA 11/12/13 MAGGIO 2017

"Epatite C Nuove opportunità terapeutiche"

MARIARITA CANNAVO'

U.O.D. EPATOLOGIA
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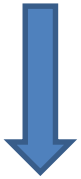
CATANIA

ARNAS GARIBALDI CATANIA
AZIENDA OSPEDALIERA DI RILIEVO NAZIONALE DI ALTA SPECIALIZZAZIONE

The Primary Goal of HCV Therapy

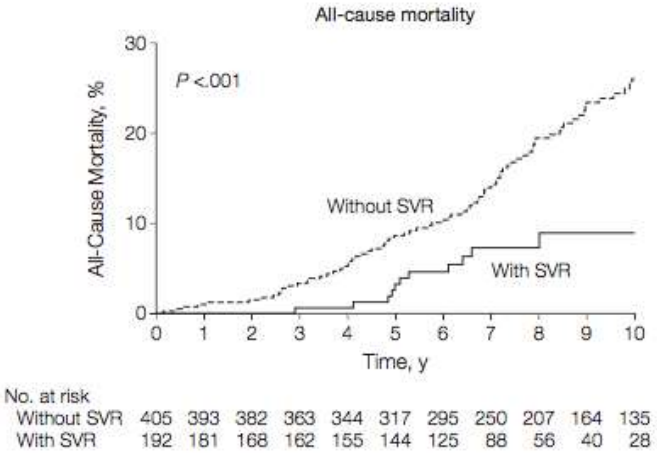


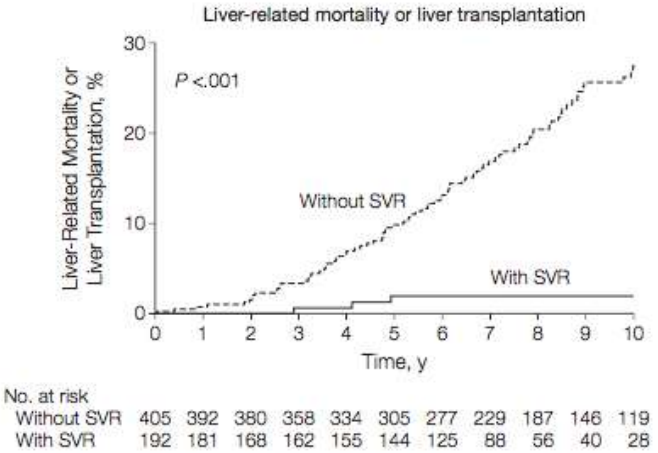
To Cure the Infection

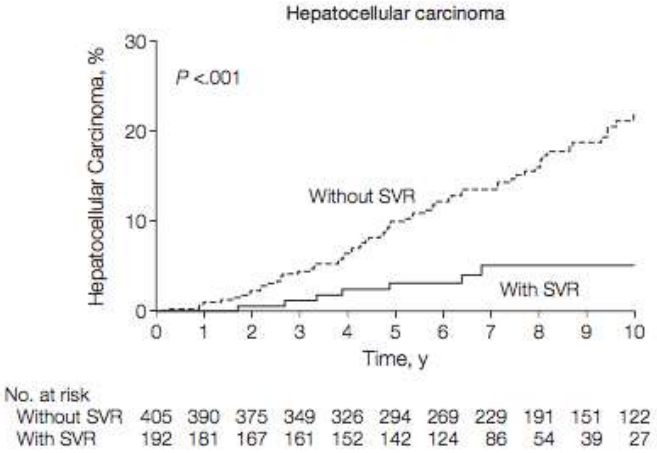
HCV RNA undetectable
12/24 weeks after the end of treatment

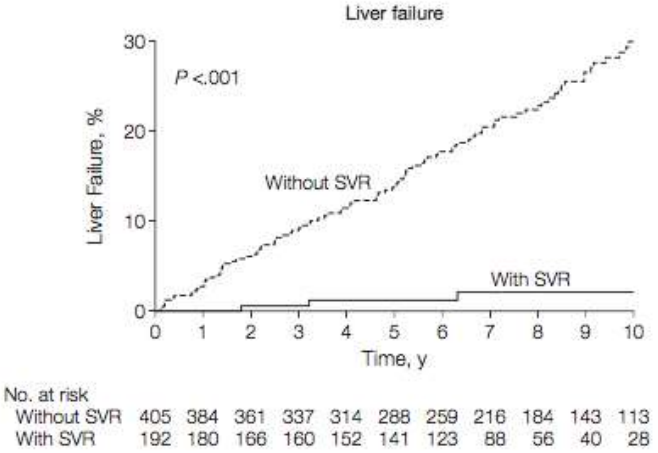
EASL CPG, J Hepatol in press

SVR and all-cause of mortality (Europe and Canada)



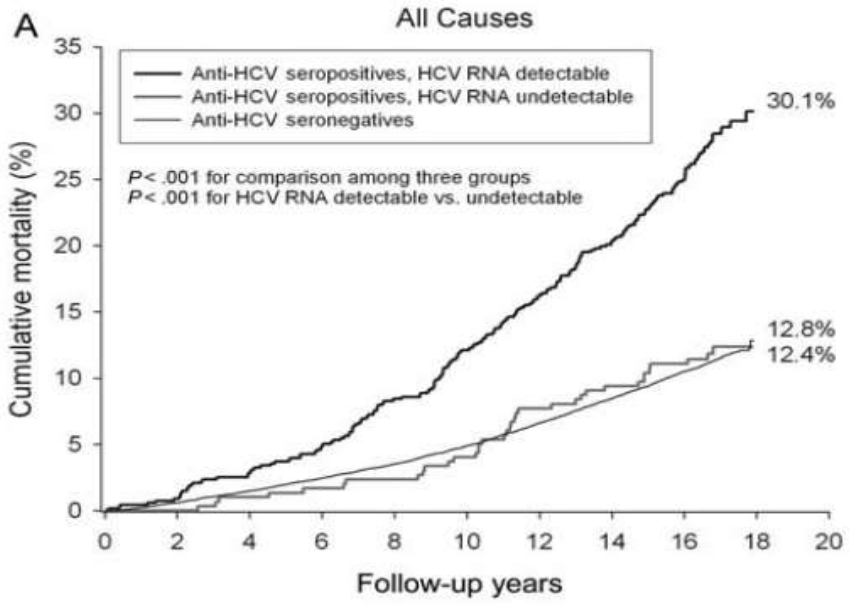






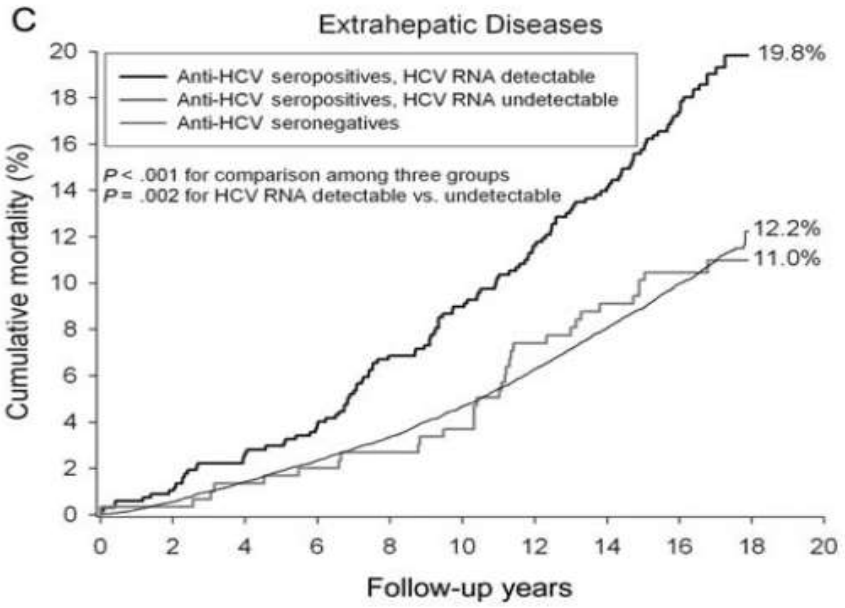
Van der Meer AJ, JAMA 2012

Risk of HCV infection on Hepatic and Extrahepatic Deaths: the R.E.V.E.A.L. – HCV Study Group



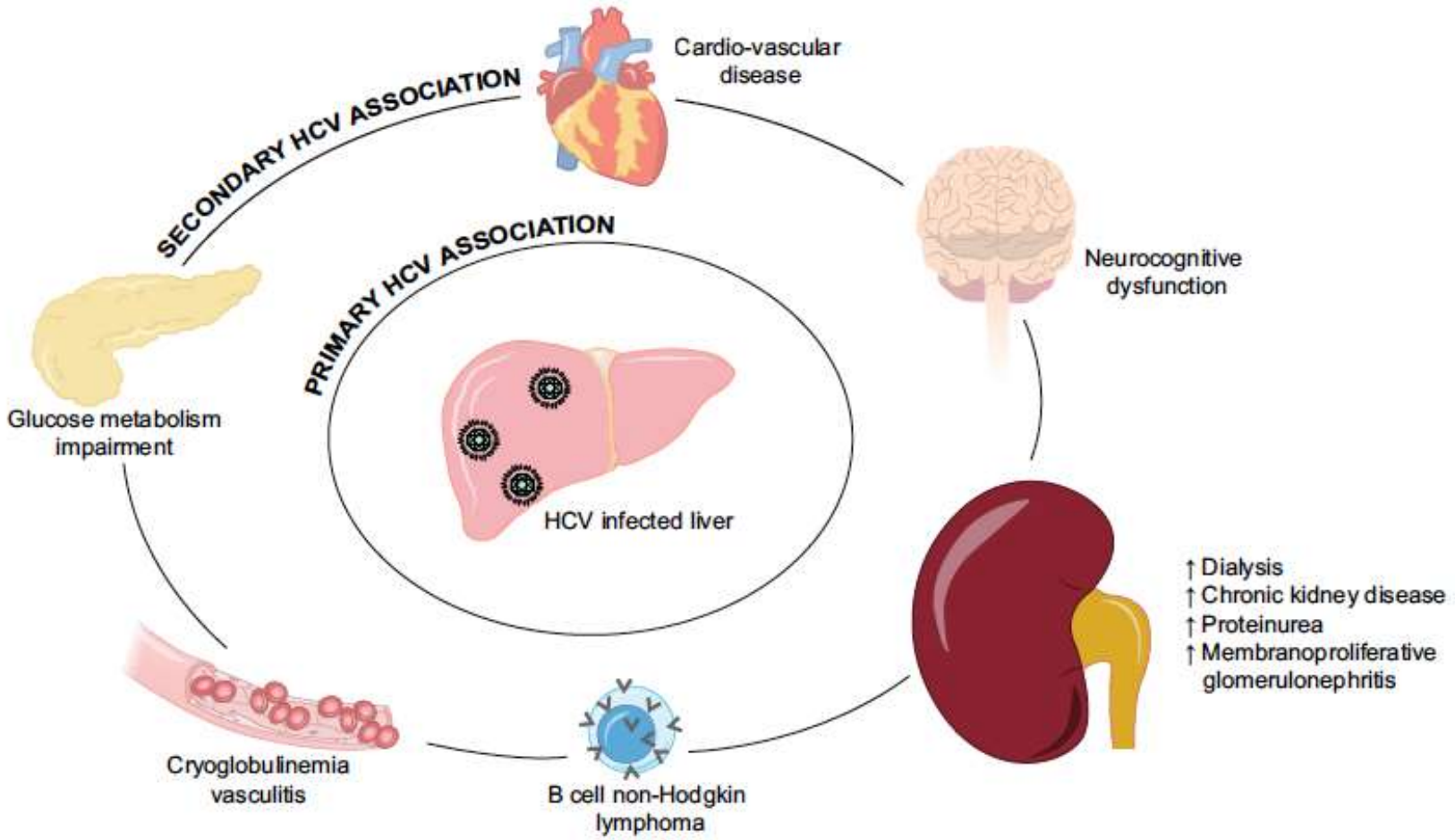
A prospective community-based cohort study in Taiwan
23,820 adults, 30-65 yrs, mean f-u 16.2 yrs

- **Circulatory diseases**
- **Kidney diseases**
- Esophageal cancer
- Prostate cancer
- Thyroid cancer



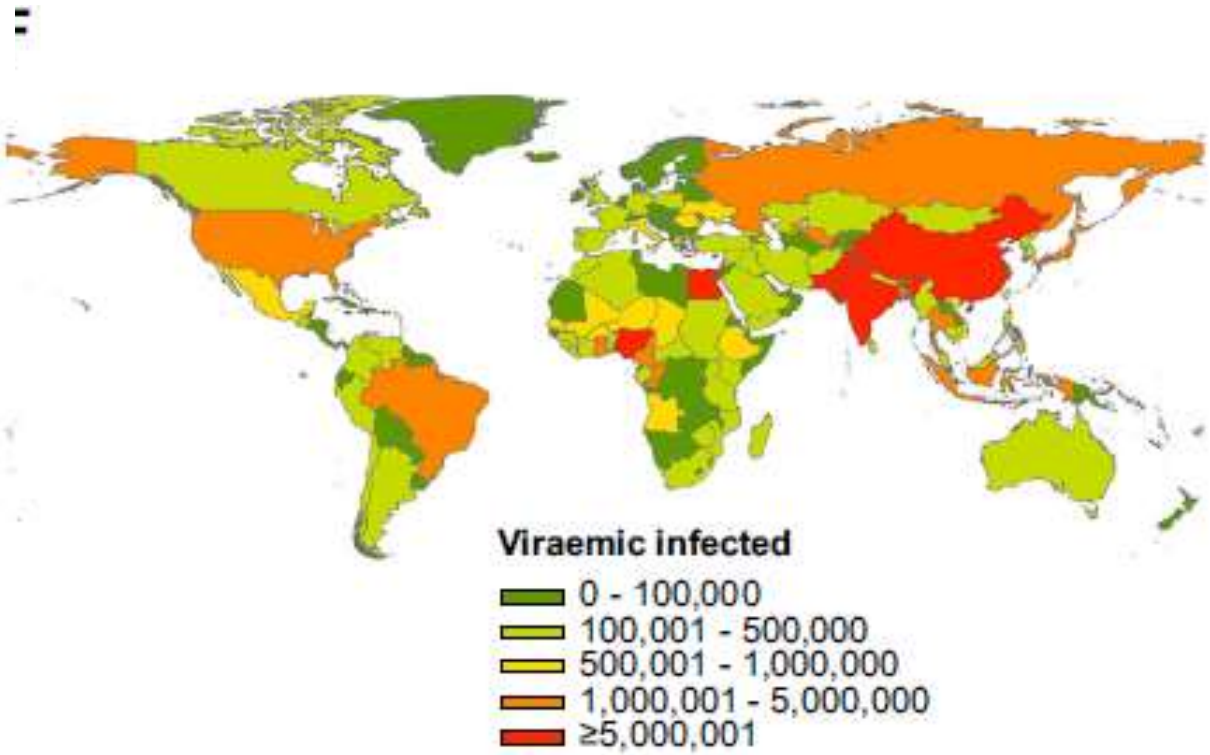
Lee MH, J Infect Dis 2012

Hepatitis C Infection: a systemic disease



Cacoub P, J Hepatol 2016

HCV global distribution



- 115–150 million people globally have chronic hepatitis C infection.
- **Many of them are unaware they are infected and do not receive care and treatment**
- Most viraemic infections (75 million people) are among adults
- Approximately 500 000 people die each year from hepatitis C-related liver diseases.

World Health Organization (WHO). Hepatitis C Fact Sheet N°164. http://www.who.int/mediacentre/factsheets/fs164/en/#. Updated July 2015 Accessed September 14, 2015; Gower E et al J Hepatol 2014.

Prevalenza HCV in Italia

- Stima individui affetti da epatite C in Italia

≈ 500.000

20.000 morti/anno per cirrosi e HCC in Italia
(60% correlate al virus C)

Mortalità in Sicilia nel 2015	
per cirrosi	850
HCC	180

WHO Global Hepatitis Strategy Targets

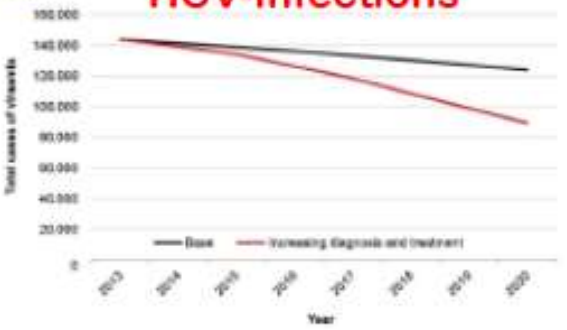
	2020	2030
Expand & enhance services	Compared to baseline 2015	
HBV-Vaccination	>90% coverage infants 50% coverage health care workers	90% coverage health care workers
HBV-birth dose vaccination	80% coverage	
Blood safety		0 new infections through blood products
Safe medical practices	75% reduction in new infections	
Harm reduction services	reach 50% of IVDA's	
HBV & HCV diagnosis		90% of chronic viral hepatitis diagnosed
HBV & HCV treatment		90% of eligible patients treated 90% of treated suppressed (HBV) / cured (HCV)
Reduce new Infections		
New HBV-Infections	20% reduction	90% reduction
New HCV-Infections	50% reduction	70% reduction
Mother-to-Child Transmission		95% reduction
Reduce Deaths		
HBV-related deaths		60% reduction
HCV-related deaths		60% reduction

Impact of Screening: Modelling

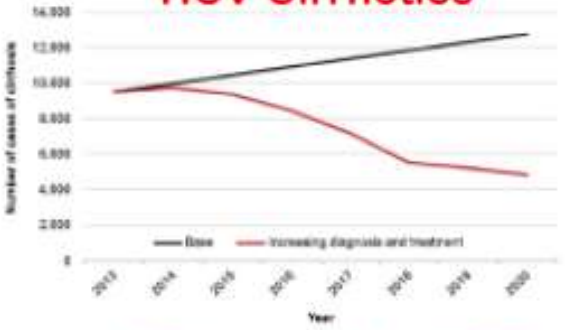
Cramp *et al.*, BMC GE 2014; 14: 137

- **Main messages**
  - If treatment continues as it is, liver-related mortality would ↑ by 90% in 2030
  - Treatment increase with DAA's by 115% until 2018 → 50% reduction in liver-related mortality by 2020
  - Would require an increase in diagnosis of 140% by 2018

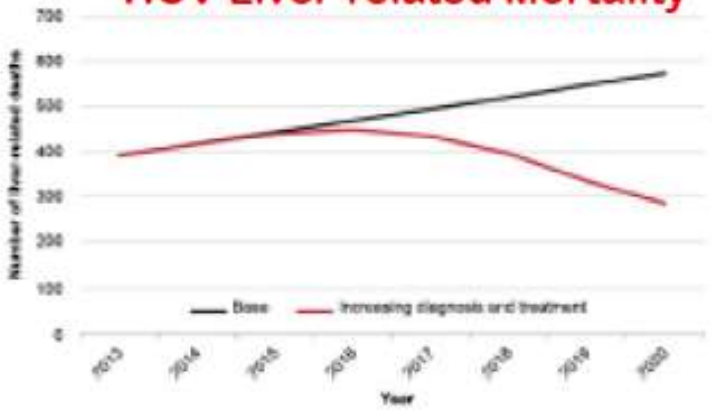
HCV-Infections



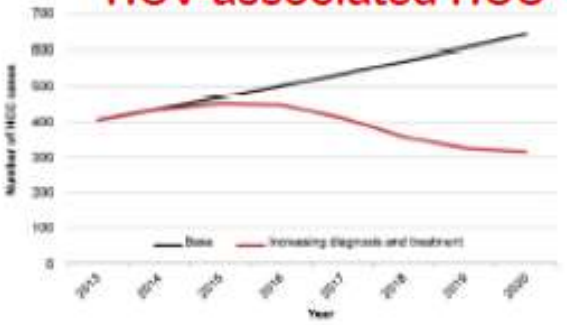
C HCV-Cirrhotics



HCV Liver-related Mortality



E HCV-associated HCC



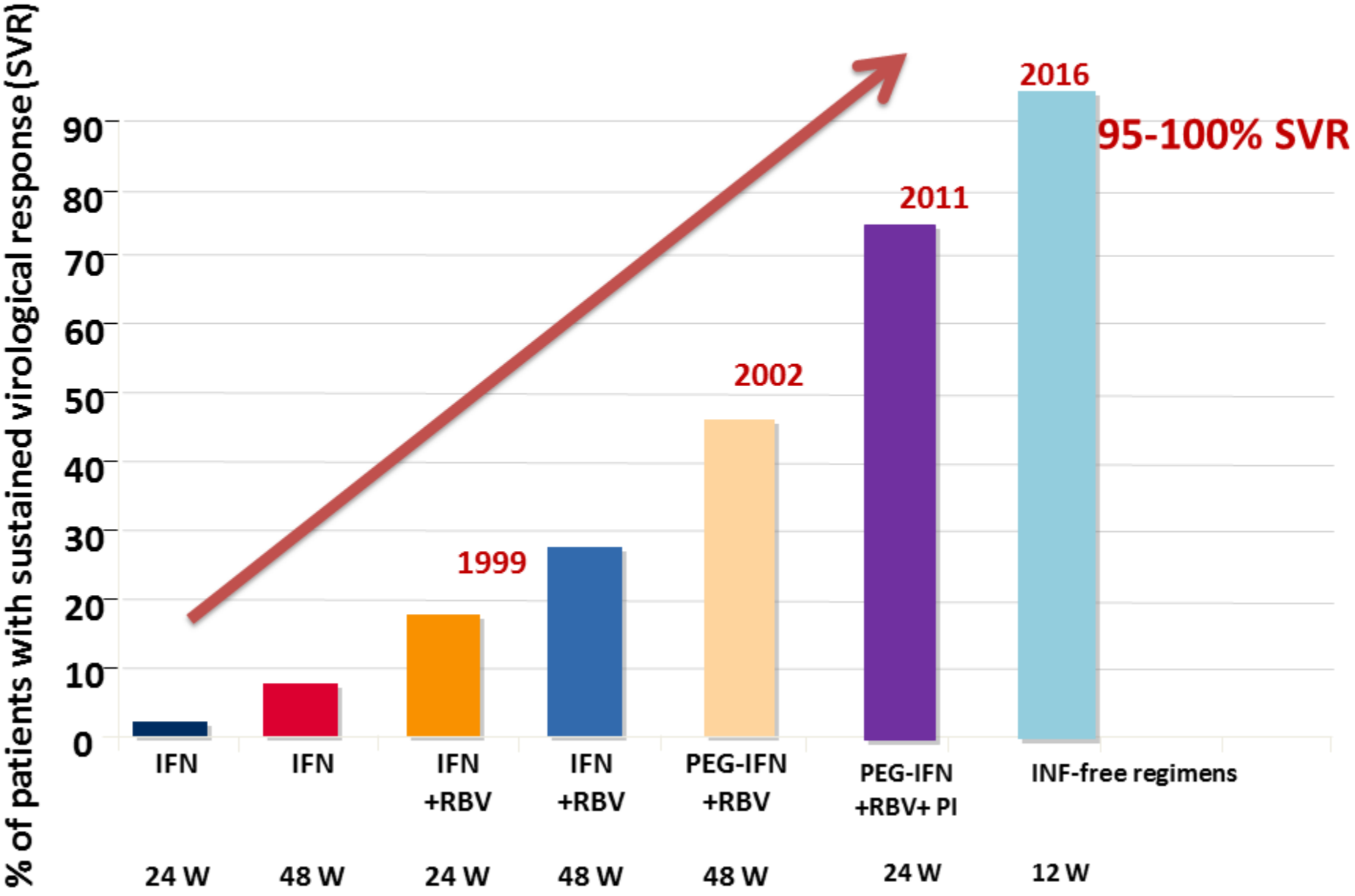
Quali soggetti sono a rischio di aver contratto un'infezione da virus dell'epatite C (HCV) e devono essere sottoposti a ricerca dei marcatori virali?

Categorie a rischio di infezione da HCV:
- Tossicodipendenti (attivi o che lo siano stati in passato)
- Consumatori di droghe per via inalatoria

Categorie a rischio di esposizione a HCV:
- Emodializzati
- Persone sottoposte a procedure invasive mediche, odontoiatriche o estetiche (tatuaggi) in ambienti a basso standard di sterilizzazione dello strumentario
- Personale sanitario
- Persone emotrasfuse o sottoposte a trapianto d'organo prima degli anni '90
- Emofilici che abbiano ricevuto emoderivati prima degli anni '90
- Familiari e partner sessuali di soggetti con infezione da HBV/HCV
- Bambini nati da madri con infezione da HBV o HCV
- Carcerati
- Soggetti con infezione da HIV
- Soggetti con attivita sessuale promiscua o con precedenti malattie sessualmente trasmesse
- Immigrati provenienti da aree ad alta endemia di infezione da HBV/HCV*

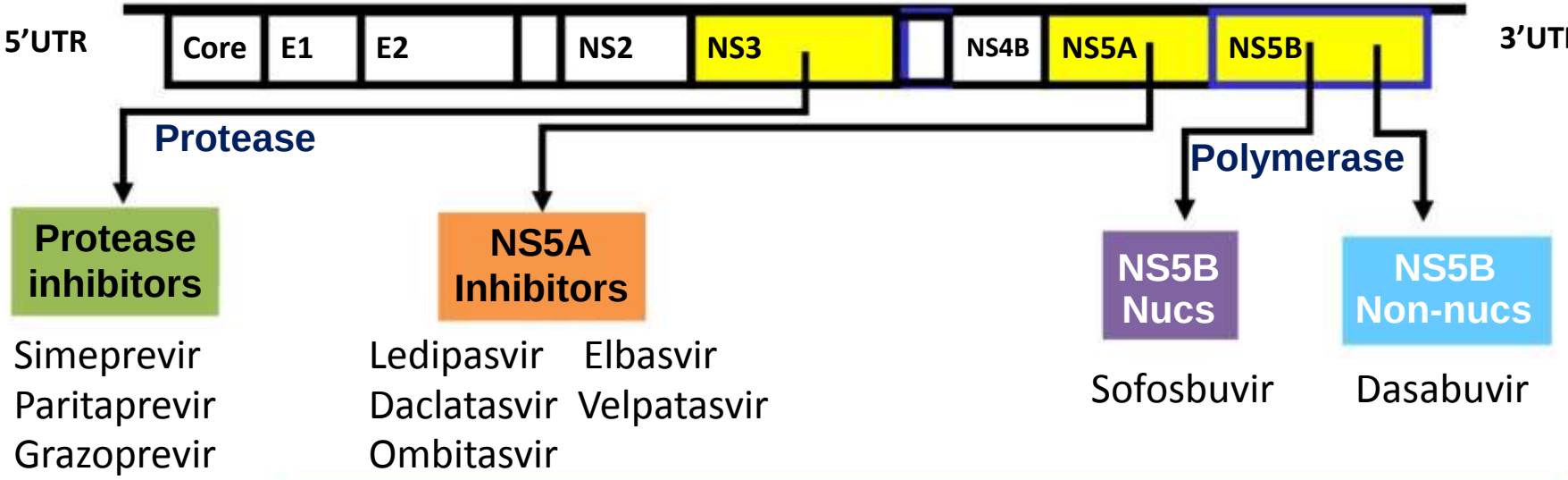
La ricerca dei virus dell'epatite C deve essere effettuata nei soggetti con:
- Transaminasi alterate in almeno 2 occasioni
- Malattia epatica da *altra causa (alcol, sindrome metabolica, malattie autoimmuni)*
- Donne in gravidanza
- Prima di intraprendere trattamenti con farmaci immunosoppressivi

La rivoluzione della terapia per HCV



2- Scheda Eleggibilità e Dati Clinici (EDC)			
Di seguito sono riportate le tipologie (vedi i criteri) dei pazienti candidabili al trattamento con medicinali ad azione antivirale diretta di seconda generazione (DAAs) nell'ordine progressivo di priorità in base all'urgenza clinica definito dalla Commissione Tecnico Scientifica dell'AIFA secondo le indicazioni del Tavolo tecnico AIFA sull'Epatite C.			*testo fisso*
E	Tipologia di paziente:	Paziente 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 1*
		Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione	*Criterio 2* *La sicurezza e l'efficacia di ZEPATIER non sono state stabilite nei soggetti sottoposti a trapianto di fegato (blocca)*
		Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale)	*Criterio 3*
		Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak)	*Criterio 4*
		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 5*
		Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione	*Criterio 6* *Vedi la nota RCP per il criterio 2 (blocco)*
		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/m^2), emoglobinopatie e coagulopatie congenite]	*Criterio 7*
		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/m^2), emoglobinopatie e coagulopatie congenite]	*Criterio 8*
		Operatori sanitari infetti	*Criterio 9*
		Epatite cronica o cirrosi epatica in pazienti con insufficienza renale cronica in trattamento emodialitico	*Criterio 10*
		Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo	*Criterio 11*

Multiple Validated Drug Targets in 2017



	DAA Regimens in Use	Direct Acting Antiviral Class
Current	Sofosbuvir + RBV	NUC
	Sofosbuvir + Simeprevir	NUC + PI
	Sofosbuvir + Ledipasvir	NUC + NS5A
	Paritaprevir + Ombitasvir + Dasabuvir +/- RBV	PI + NS5B + NNI
	Sofosbuvir + Daclatasvir	NUC + NS5A
FDA/EMA/AIFA approved	Grazoprevir + Elbasvir	PI + NS5A
	Sofosbuvir + Velpatasvir	NUC + NS5A

IFN-free Treatment Regimens: 2016

SVR>90% (+/- cirrhosis)

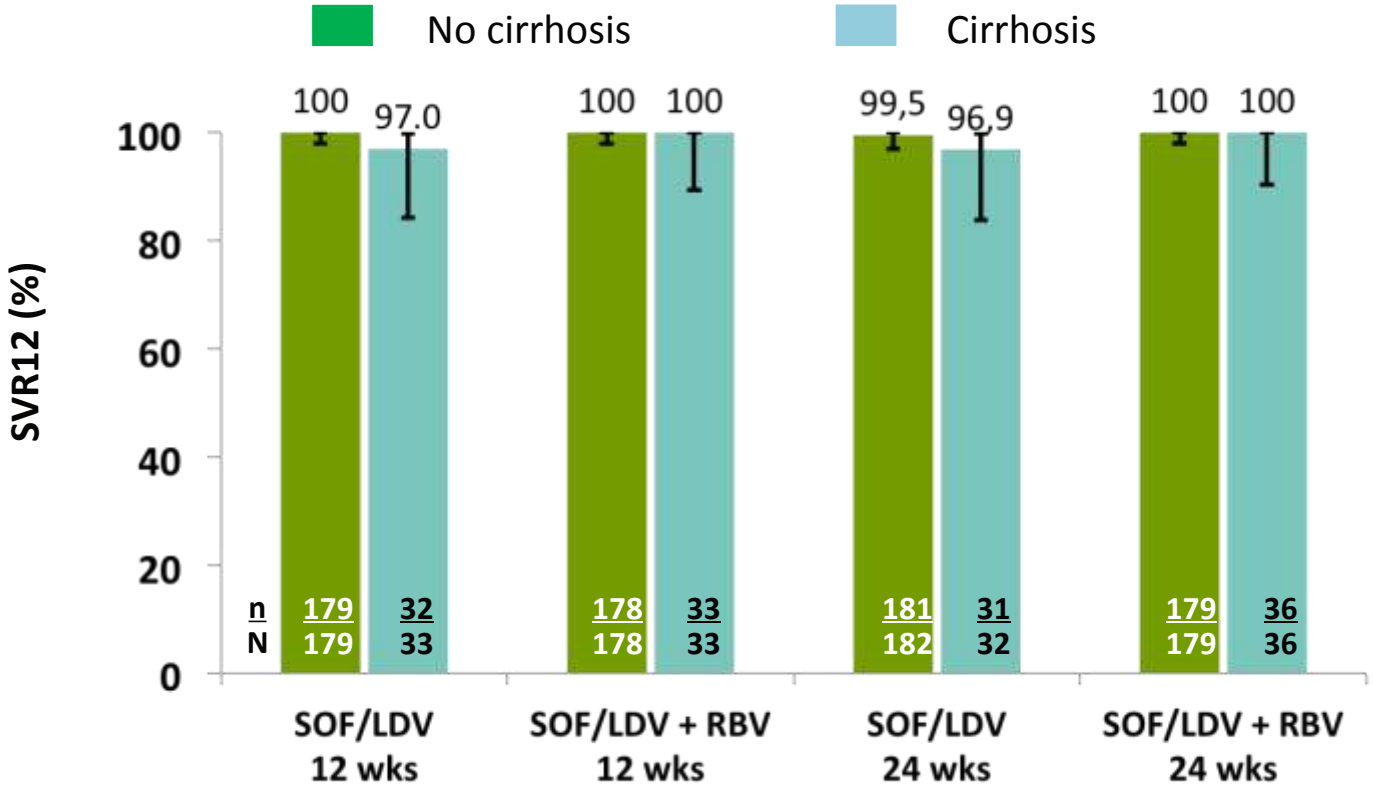
12 (8-24) weeks

SVR confirmed in *real life*

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 CPG, J Hepatol 2016

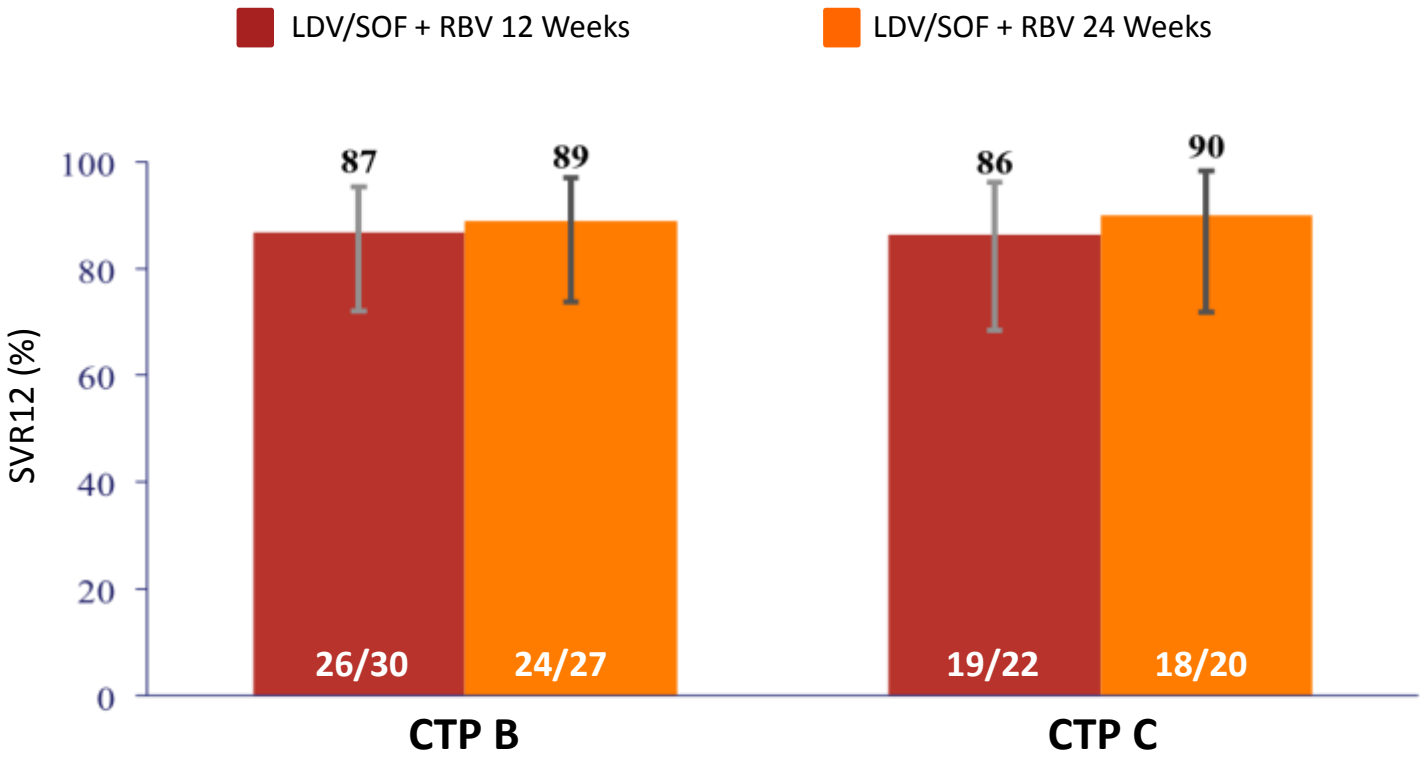
ION-1: SVR rates in GT1, treatment-naive, cirrhotic patients (subgroup analysis)



•* Subgroup results do not include patients
•who withdrew consent or were lost to follow-up.

Afdhal N, et al. New Engl J Med 2014.

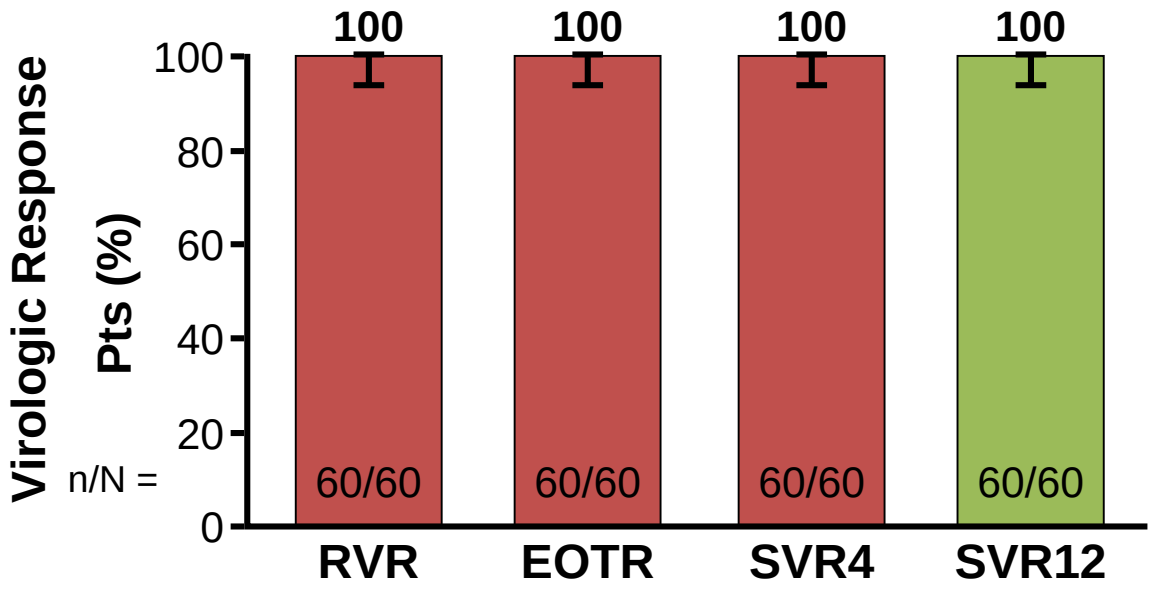
Solar-1 Trial: LDV/SOF + RBV in decompensated cirrhosis



SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Michael Charlton, Gastroenterology 2015

TURQUOISE III: 12 Wks of OBV/PTV/RTV + DSV Without RBV in Cirrhotic GT1b

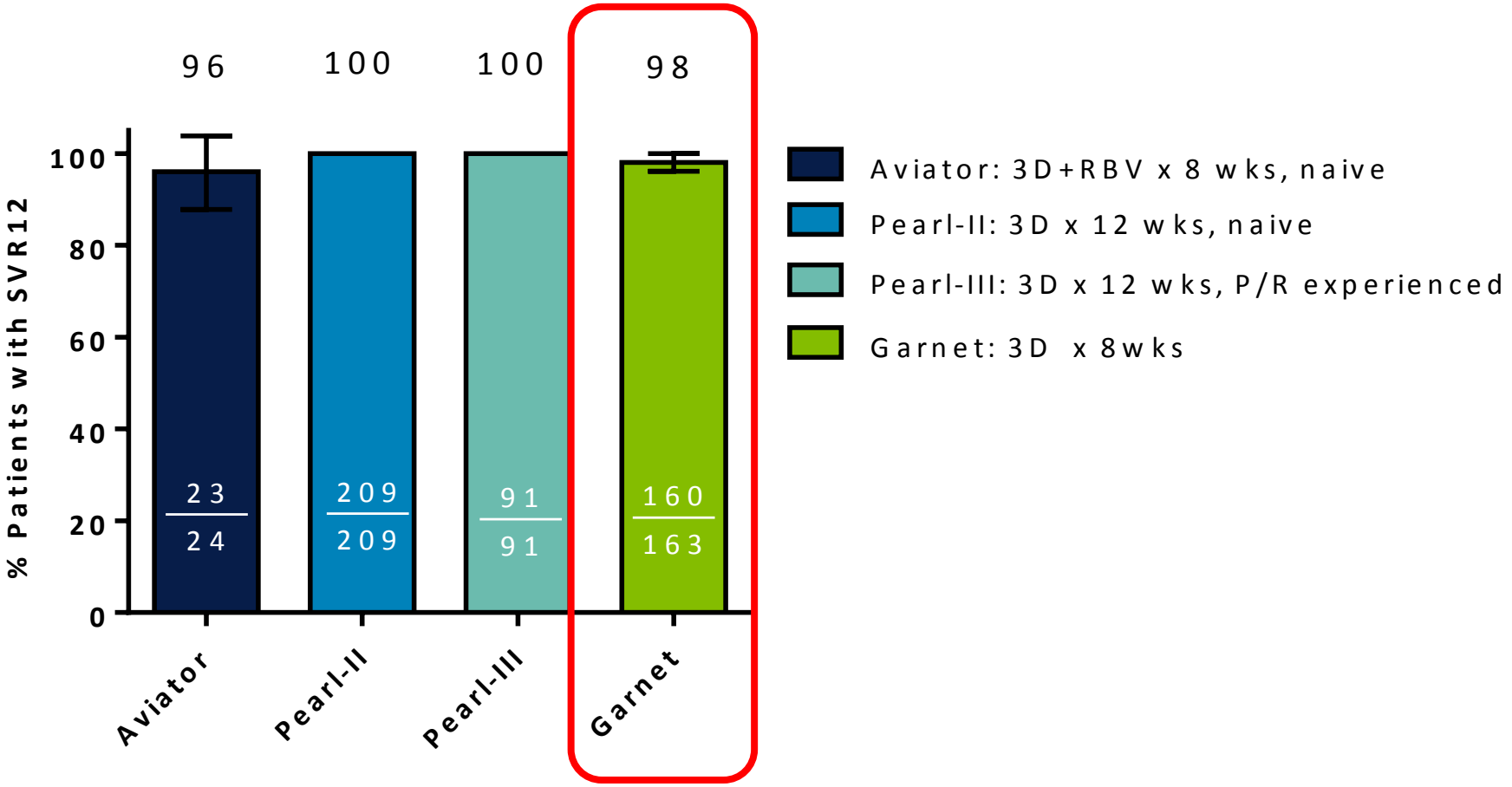


AASLD guidance now recommends OBV/PTV/RTV + DSV **12 wks without RBV** for GT1b cirrhotics

Still need 24 wks + RBV for GT1a cirrhotics, naive or experienced

Poordad F, et al. AASLD 2015. Abstract 1051.
AASLD/IDSA. HCV Guidance. April 2016.

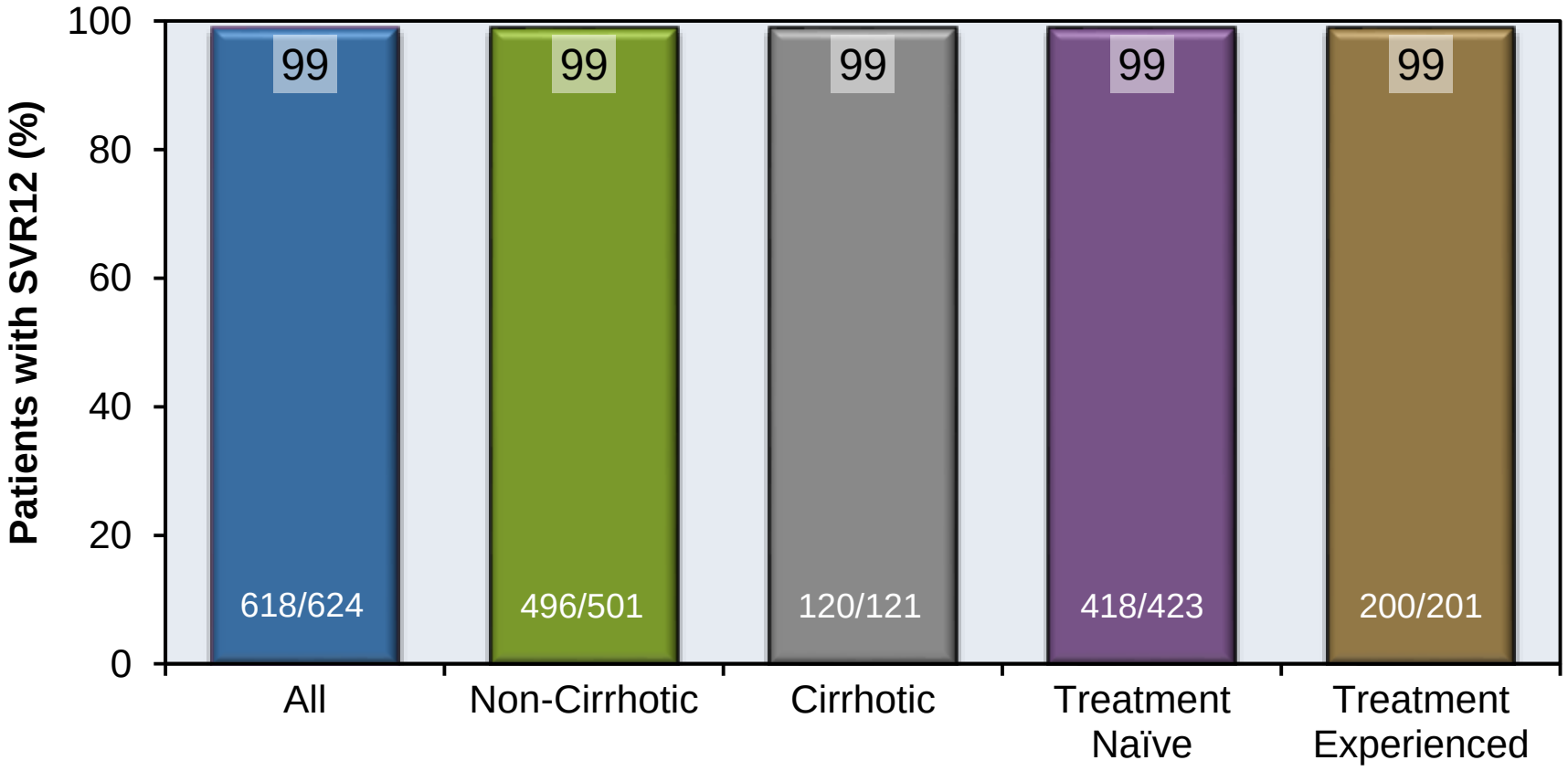
GARNET: 8 Wks of OBV/PTV/RTV + DSV Without RBV in naïve GT1b without cirrhosis patients



Welzel TM, AASLD/EASL Special Conference, 23 Sept 2016

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Results

ASTRAL-1: SVR12 Results by Cirrhosis & Treatment Experience



Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

TARGET and TRIO: Real-World Efficacy of VEL/SOF

- SVR12 rates comparable between analyses of real-world pts with GT1-6 HCV treated with VEL/SOF ± RBV

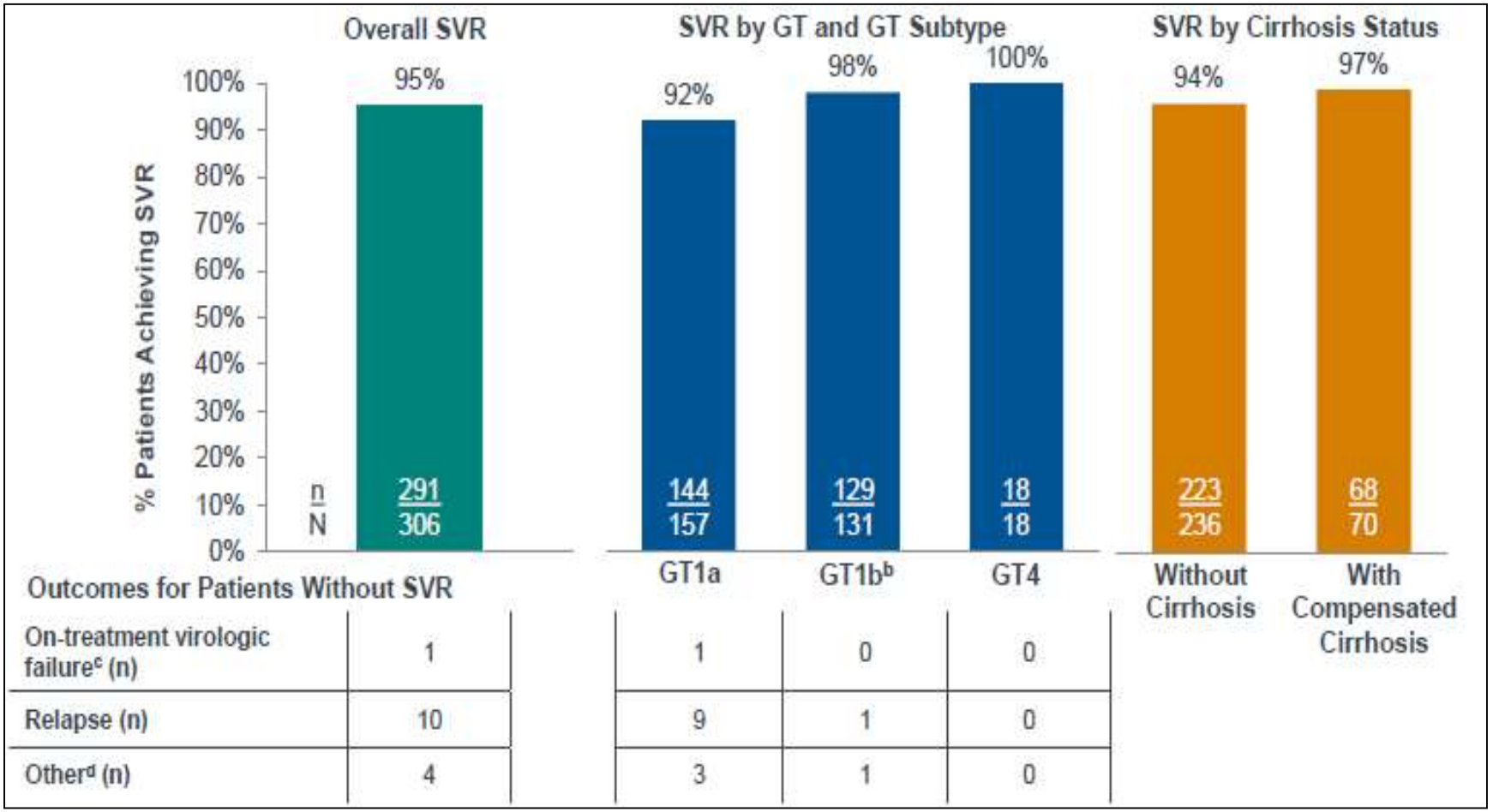
Source	HCV Genotype, %				SVR12, n/N (%)	
	1	2	3	4-6	Per Protocol	Evaluable
TRIO Network[1] (n = 89)	100	--	--	--	29/30 (97)	--
TRIO Network[2] (n = 676)*	--	58	36	6	167/173 (97)	--
HCV-TARGET Study[3] (N = 495)†	19	34	42	6	119/126 (94)‡	121/128 (95)‡

*Included 59 pts (8.7%) treated with VEL/SOF + RBV. †Included 108 pts (22%) treated with VEL/SOF + RBV. ‡For pts missing SVR12 outcome, data replaced with HCV RNA test results obtained during posttreatment Wks 4-12.

- Safety evaluated in HCV-TARGET study[3]
- AEs: VEL/SOF, 55%; VEL/SOF + RBV, 80% (serious AEs: 2% vs 9%, respectively)Most common AEs in VEL/SOF-treated pts: fatigue (12%), headache (14%), nausea (8%), anemia (1%), dizziness (3%), influenzalike illness (5%), arthralgia (4%), diarrhea (4%), vomiting (3%), abdominal pain (2%)

1. Tsai N, et al. EASL 2017. Abstract SAT-244. 2. Curry M, et al. EASL 2017. Abstract PS-102.
3. Khalili M, et al. EASL 2017. Abstract SAT-222

ZEPATIER (elbasvir/grazoprevir): Efficacia per 12 w in pazienti HCV TN GT1 o G4 — C-EDGE TN [a,1]



Outcomes for Patients Without SVR

On-treatment virologic failure[c] (n)	1	1	0	0	
Relapse (n)	10	9	1	0	
Other[d] (n)	4	3	1	0	

TN = treatment-naïve; GT = genotype; SVR = sustained virologicresponse.
aImmediatetreatment arm results are presented
bIncludesgenotype 1 subtypes other than 1a or 1b
c Includespatients with virologicbreakthrough
dOtherincludes patients who discontinued due to adverse event, lost to follow-up, or patient withdrawal
1. Zeuzem S et al. Ann Intern Med. 2015;163:1-13.

TRIO, HCV-TARGET, VA: Real-World Efficacy of EBR/GZR

- Analyses of SVR12 rates in HCV-infected pts using specialty pharmacies and providers in US TRIO Network,[1] US and international clinical practices,[2] and US Veterans Affairs Healthcare System[3]

Source, n/N (%)	Pts With GT1 HCV	SVR12, %	
		Per Protocol	Evaluable
TRIO Network[1] (N = 462)	410/462 (89)	245/253 (97)	--
HCV-TARGET Study[2] (N = 319)*	319/319 (100)	135/139 (97)†	147/159 (92)†
VA Healthcare System*[3] (N = 2436)	2324/2436 (95)	2190/2257 (97)‡	2328/2436 (96)‡

*Included 22 pts treated with EBR/GZR + RBV. †For pts missing SVR12 outcome, data replaced with SVR4 outcome. ‡For pts missing SVR12 outcome, data replaced with HCV RNA test results obtained during posttreatment Wks 4-12.

Safety evaluated in HCV-TARGET study[2]

AEs: EBR/GZR, 34%; EBR/GZR + RBV, 50% (serious AEs: 5% vs 0%, respectively).Most common AEs in EBR/GZR-treated pts: fatigue (9%), headache (8%), nausea (5%), diarrhea (3%), influenzalike illness (3%), decreased appetite (3%), dizziness (2%), vomiting (3%), abdominal discomfort (2%), abdominal pain upper (2%)

Drug-drug interactions with novel all oral interferon free antiviral agents

DAA Regimen	% of Patients with AMBER DDIs	% of Patients with RED DDIs
SOF/RBV	9.6	0
SOF/DAC	33.4	0.4
SOF/LDV	40.2	0
OBV/PTV/r + DSV (3D)	57.0	8.4

- PPI
- HIV antiretrovirals
- Illicit drugs
- Immunosuppressants
- Cardiovascular drugs
- Lipid lowering drugs
- Central nervous system drugs

Pharmacokinetic data of DAAs in HCV patients

Drug *HCV targets*	Metabolism	Elimination	Regular oral daily dosage	Adjustment if GFR <60 ml/min/1.73 m²	Adjustment if GFR <30 ml/min/1.73 m² or HD	Ciclo/Tacro interactions	Pharmacokinetic data
Sofosbuvir *NS5B*	Mainly renal, the active metabolite GS-461203 via phosphorylation is dephosphorylated into inactive metabolite GS-331007	Urine (80%) Feces (14%)	400 mg	No	Insufficient data	No	After one single dose of 400 mg, increased AUC by 171% and 451% for sofosbuvir and GS-331007, respectively
Simeprevir *NS3/4A protease*	Hepatic	Biliary (91%) Urine (<1%)	150 mg	No	Insufficient data	Yes, need IS blood level Not recommended with Ciclo	Increased Cmax and AUC by 34% and 62%, respectively
Daclatasvir *NS5A replication complex*	Hepatic	Feces (88%) Urine (7%)	60 mg	No	No	No	26% increased AUC in HD patients
Ledipasvir *NS5A (co-formulation with sofosbuvir)*	Hepatic, minimal, not CYP450 mediated	Feces (>80%) Urine (<1%)	90 mg	No	Insufficient data	Yes, need IS blood level	No AUC increased if normal renal function Increased AUC if GFR <30 ml/min/1.73 m²
Paritaprevir/ritonavir/ ombitasvir/ dasabuvir *NS3/4A protease/ HIV protease/NS5A polymerase*	Hepatic	Feces (>86%) Urine (2-11%)	75 mg/ 50 mg/ 25 mg/ 500 mg	No	No, if GFR 15-30 ml/min/1.73 m² Caution for ESRD or HD	Yes, need to decrease IS dose	Increased AUC by 45% and 144% for paritaprevir and ritonavir, respectively
Grazoprevir/elbasvir *NS3/4A protease/ NS5A*	Hepatic (CYP3A)	Urine <1% for both drugs	100 mg/ 50 mg	No	No	Yes, Not recommended with Ciclo. Increased Tacro AUC	Increased AUC by 46% and 40% for GZR and EBR, respectively. In HD patients, increased AUC by 25% and 10% for GZR and EBR, respectively.

Cacoub P, J Hepatol 2016

Pazienti difficili da trattare

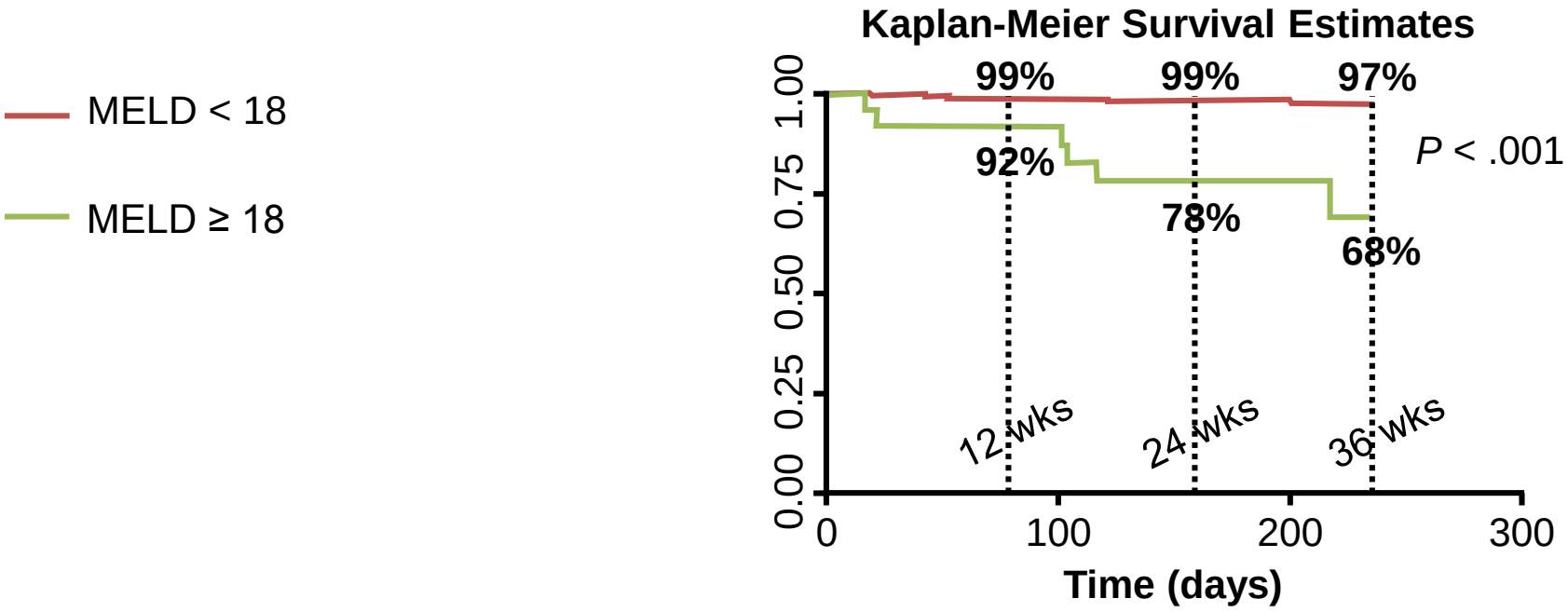
- Cirrosi scompensata (C-P B/C)
- Cirrosi Genotipo 3 (C-P A: 85% C-P B/C: 70% 24 wk+RBV)
- Insufficienza renale (GFR < 30, CKD stadio 4/5)
- Fallimenti ai DAAs di prima e seconda generazione (resistenze virali)
    - Utilizzare combinazione di almeno 2 farmaci senza resistenza
    - Utilizzare Sofosbuvir
    - Aggiungere ribavirina
    - Prolungare il trattamento a 24 settimane
    - Attendere nuovi farmaci (pazienti che non hanno urgenza)

Pazienti difficili da trattare

- **Cirrosi scompensata (C-P B/C)**
- Cirrosi Genotipo 3 (C-P A: 85% C-P B/C: 70% 24 wk+RBV)
- Insufficienza renale (GFR < 30, CKD stadio 4/5)
- Fallimenti ai DAAs di prima e seconda generazione (resistenze virali)

Hepa-C Registry: SVR, Safety, and Deaths With HCV Tx in Advanced Liver Disease

- SVR12 rate lower for CP B/C vs CP A (78% vs 94%; *P* < .001)
  - SAE incidence higher for CP B/C vs CP A (50% vs 11.7%; *P* < .001)
  - Death rate higher for CP B/C vs CP A (6.4 % vs 0.9%; *P* < .001)



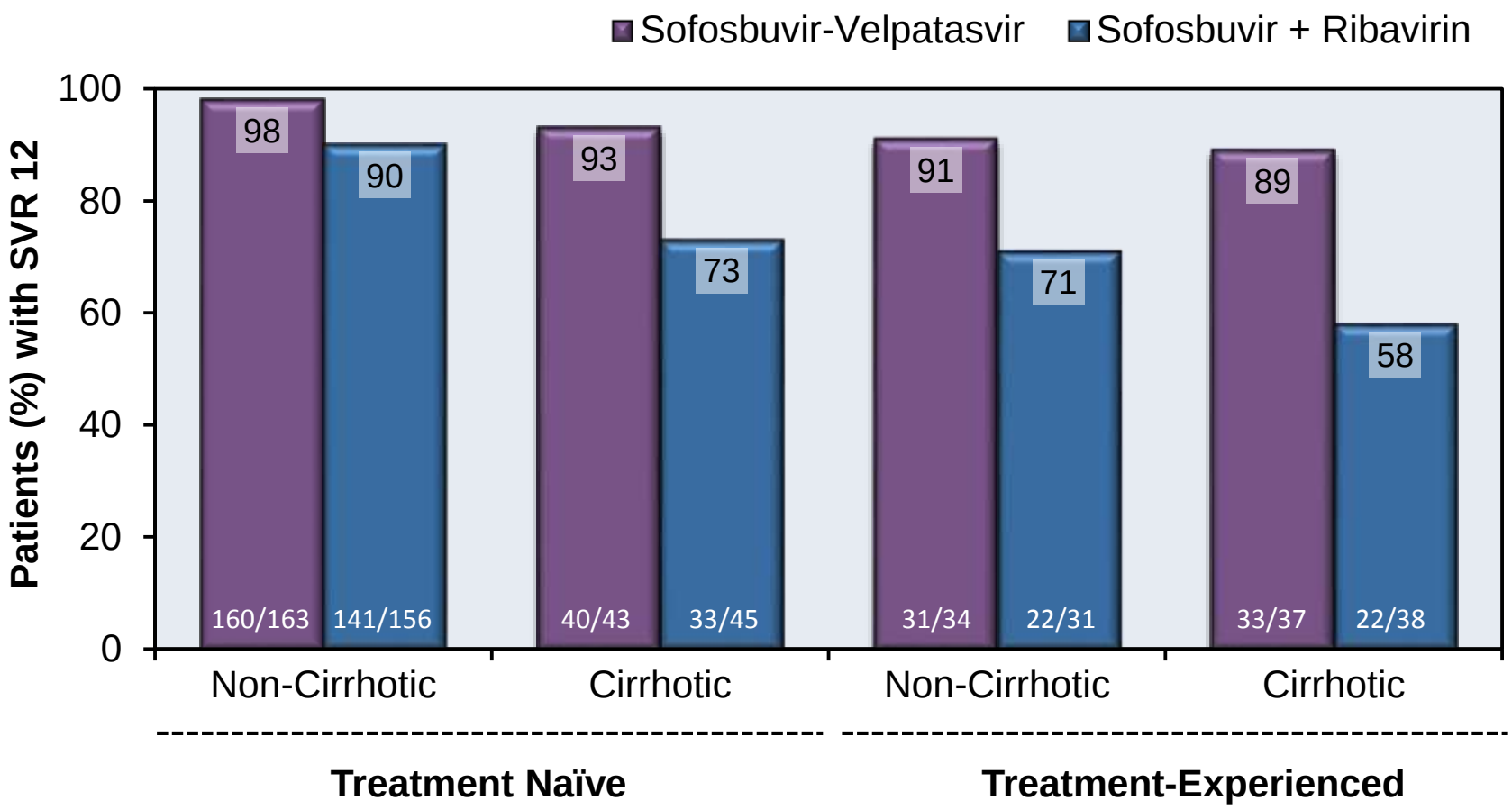
Fernández-Carrillo C, et al. EASL 2016. Abstract GS01.

Pazienti difficili da trattare

- Cirrosi scompensata (C-P B/C)
- **Cirrosi Genotipo 3 (C-P A: 85% C-P B/C: 70% 24 wk+RBV)**
- Insufficienza renale (GFR < 30, CKD stadio 4/5)
- Fallimenti ai DAAs di prima e seconda generazione (resistenze virali)

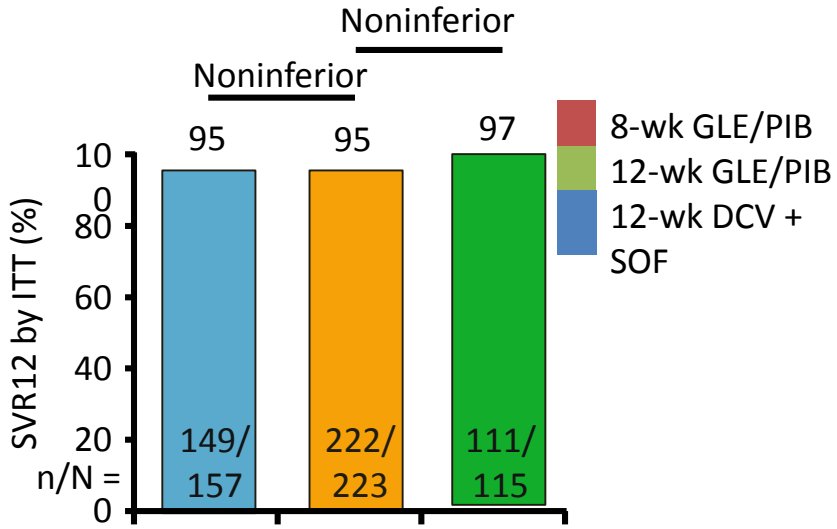
Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Results

ASTRAL-3: SVR12 Results by Cirrhosis & Treatment Experience



Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

ENDURANCE-3: GLE/PIB in GT3 HCV Without Cirrhosis



Failure, n (%)			
Breakthrough	1 (1)	1(<1)	0
Relapse	5 (3)	3 (1)	1 (1)
AE-related d/c	0	1(<1)	1 (1)
LTFU	2 (1)	4(2)*	2 (2)

*2 other failures due to consent withdrawal and noncompliance.

Most pts had history of IDU (63% to 66%)

AE, n (%)	G/P 8 Wks (n = 157)	G/P 12 Wks (n = 233)	SOF + DCV (n = 115)
Any AE	98 (62)	177 (76)	80 (70)
▪Possibly DAA related	63 (40)	112 (48)	50 (43)
Serious AE	3 (2)	5 (2)	2 (2)
AEs in ≥ 10% of pts			
▪Headache	31 (20)	60 (26)	23 (20)
▪Fatigue	20 (13)	44 (19)	16 (14)
▪Nausea	19 (12)	32 (14)	15 (13)

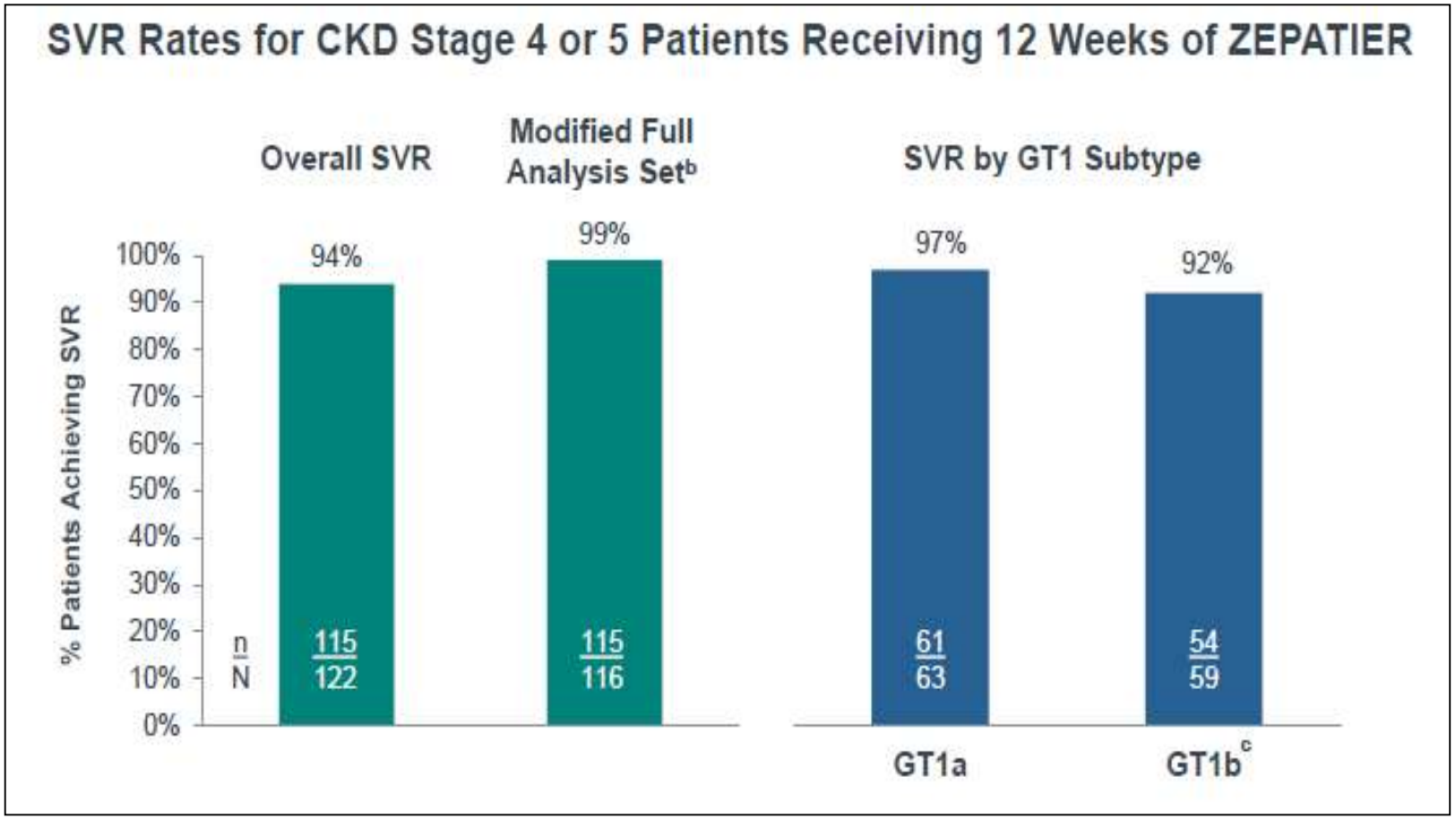
- Grade ≥ 3 laboratory abnormalities: no clinically relevant ALT increases, 1 isolated bilirubin increase (G/P 8 wks), 1 isolated neutrophil count decrease (G/P 12 wks)

Foster GR, et al. EASL 2017. Abstract GS-007. Reproduced with permission

Pazienti difficili da trattare

- Cirrosi scompensata (C-P B/C)
- Cirrosi Genotipo 3 (C-P A: 85% C-P B/C: 70% 24 wk+RBV)
- **Insufficienza renale (GFR < 30, CKD stadio 4/5)**
- Fallimenti ai DAAs di prima e seconda generazione (resistenze virali)

ZEPATIER (elbasvir/grazoprevir): Efficacia in pazienti HCV G1 con CKD Stadio 4 o 5 — C-SURFER [1]



a Immediatetreatment and pharmacokinetic arm results are presented.
b Pre-specified primary analysis population, which excluded patients not receiving at least one dose of study treatment and those with missing data due to death or early study discontinuation for reasons unrelated to treatment response.
c Includes genotype 1 subtypes other than 1a or 1b.
1. Roth D et al. Lancet. 2015;386:1537–1545.

Pazienti difficili da trattare

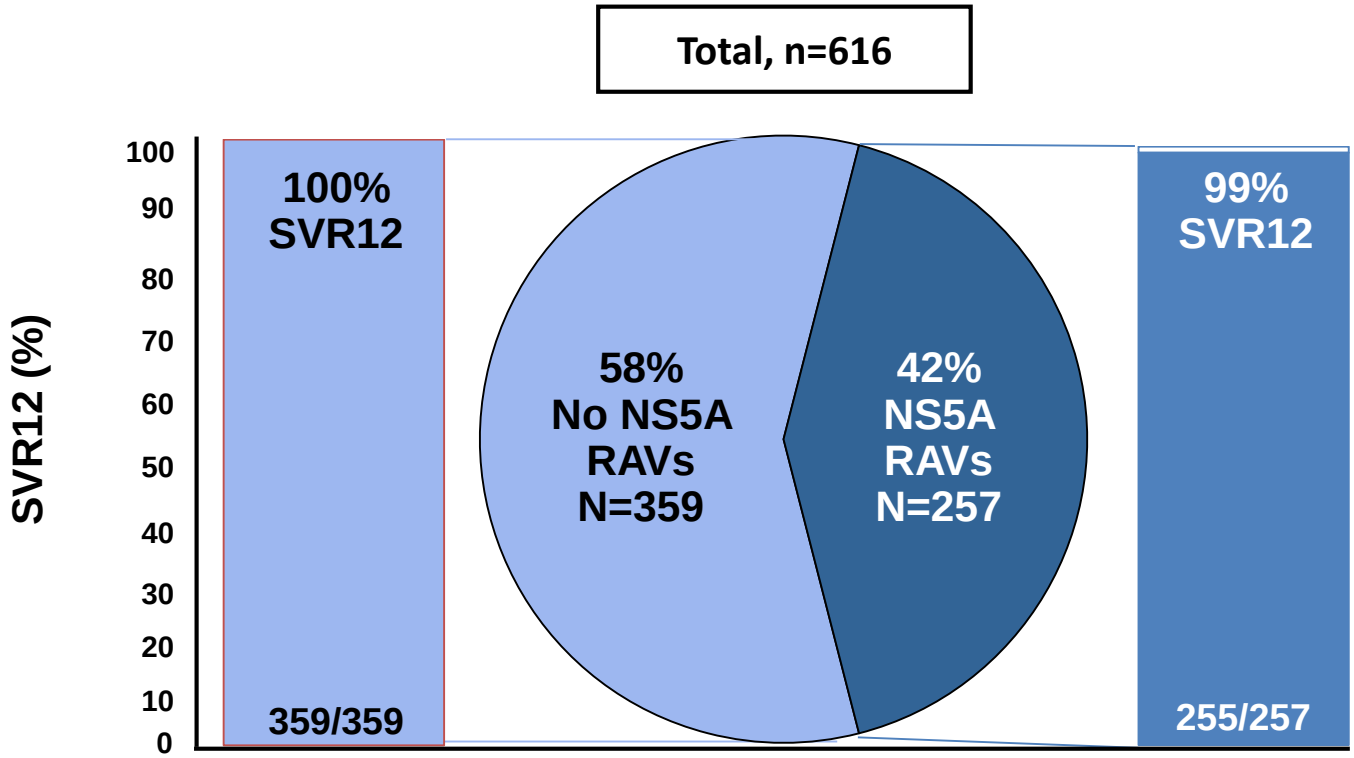
- Cirrosi scompensata (C-P B/C)
- Cirrosi Genotipo 3 (C-P A: 85% C-P B/C: 70% 24 wk+RBV)
- Insufficienza renale (GFR < 30, CKD stadio 4/5)
- **Fallimenti ai DAAs di prima e seconda generazione (resistenze virali)**

Failed treatment	Geno-type	Sofosbuvir/ ledipasvir	Sofosbuvir/ velpatasvir	Ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Ombitasvir/ paritaprevir/ ritonavir	Grazoprevir/ Elbasvir	Sofosbuvir and daclatasvir	Sofosbuvir and simeprevir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir and dasabuvir	Sofosbuvir plus ombitasvir/ paritaprevir/ ritonavir	Sofosbuvir plus grazoprevir/ elbasvir	Sofosbuvir plus daclatasvir plus simeprevir
Sofosbuvir alone, or sofosbuvir plus ribavirin, or sofosbuvir plus PegIFN-α and ribavirin	5 or 6	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
Sofosbuvir and simeprevir	1	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
	4	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	No	No	No	No
NS5A inhibitor-containing regimen (ledipasvir, velpatasvir, ombitasvir, elbasvir, daclatasvir)	1a	No	No	No	No	No	No	No	24 wk with ribavirin	No	24 wk with ribavirin	24 wk with ribavirin
	1b	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	2	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	3	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No
	4	No	No	No	No	No	No	No	No	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)	12 wk with ribavirin (F0-F2) or 24 wk with ribavirin (F3-F4)
	5 or 6	No	24 wk with ribavirin	No	No	No	No	No	No	No	No	No

RACCOMANDAZIONI EASL 2016

Sofosbuvir-Velpatasvir in HCV Genotype 1, 2, 4, 5, or 6
ASTRAL-1: Resistance

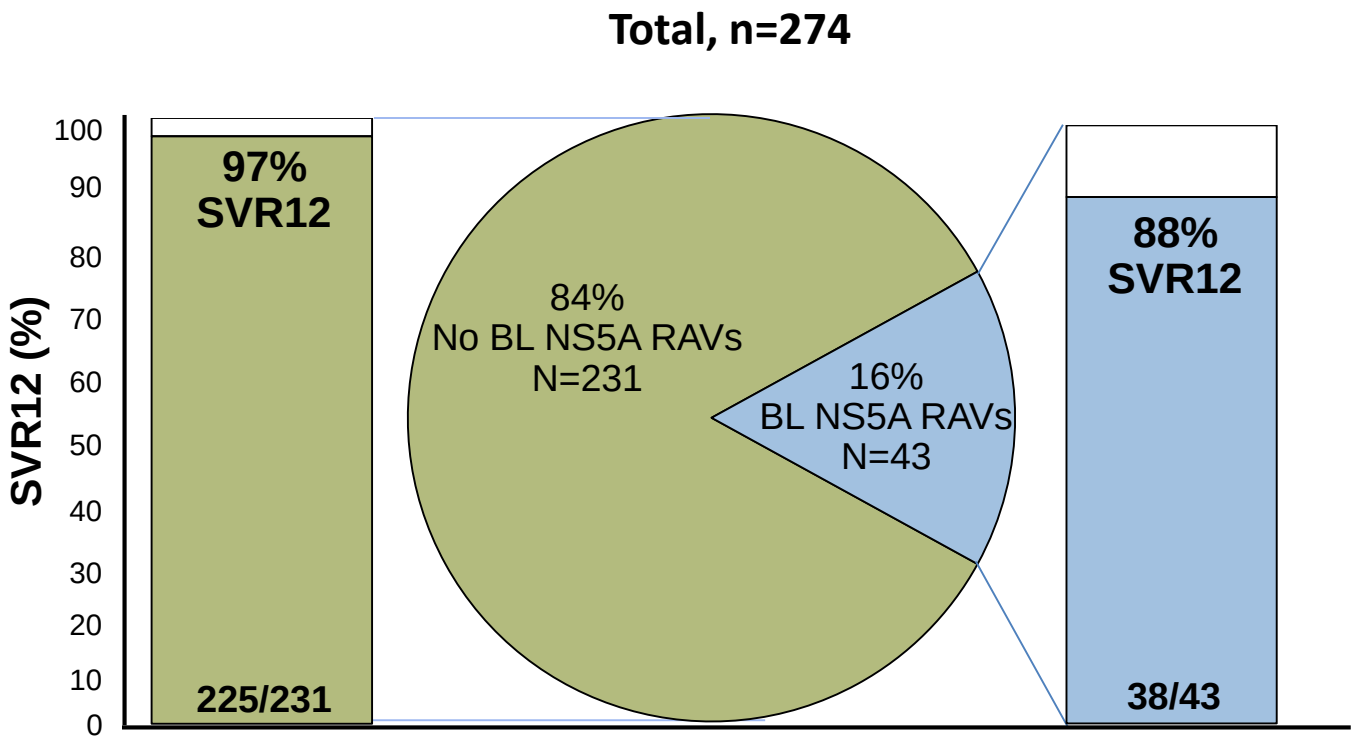
Baseline NS5A Resistance-Associated Variants and SVR12



Source: Feld JJ, et al. N Engl J Med. 2015;373:2599-607.

Sofosbuvir-Velpatasvir in HCV Genotype 3
ASTRAL-3: Resistance

Baseline NS5A Resistance-Associated Variants and SVR12

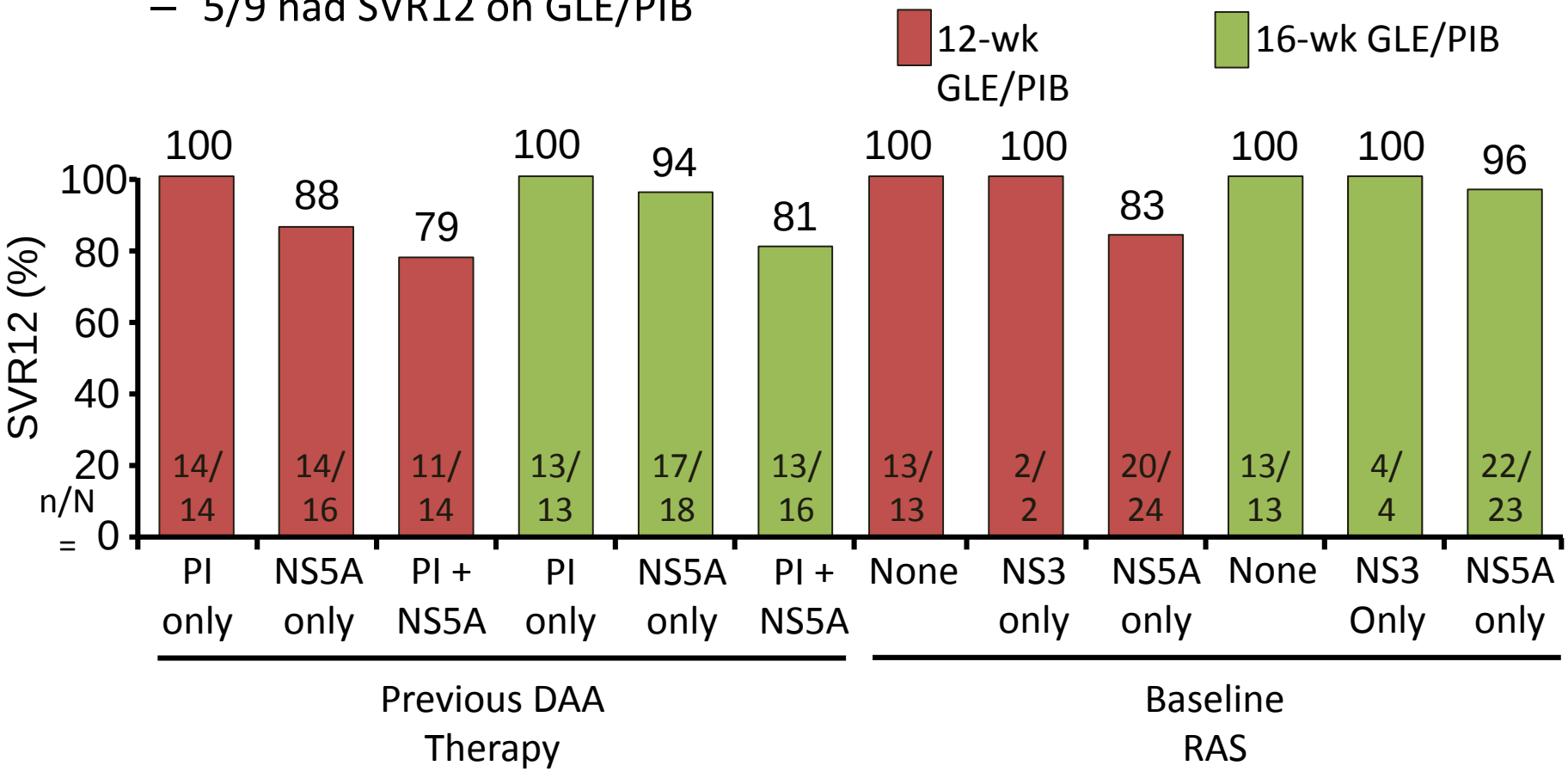


- SVR12 was 84% (21/25) in patients with Y93H

Source: Foster GR, et al. N Engl J Med. 2015;373:2608-17.

MAGELLAN-1: GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with both NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB



Poordad F, et al. EASL 2017. Abstract PS-156.

Multiple Validated Drug Targets in 2017-2018

DRUG	ABBREVIATION	CLASS
Glecaprevir	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir	PIB	NS5A inhibitor
Ruzasvir	RZR	NS5A inhibitor
Uprifosbuvir (formerly MK-3682)	UPR	NS5B polymerase nucleotide inhibitor

Epatologia Garibaldi-Nesima
(maggio 2015 – aprile 2017)

pazienti trattati:	473	
NR/breaktrough:	0	
relapser:	16	13 CE; 3 F3

CARATTERISTICHE CLINICHE	
N	473
F3 (>9.9 Kpa)	189
C-P A	242
C-P B	42
HCC	24

GENOTIPO	
1a	79
1b	282
2	58
3	34
4	17
5	3

Epatologia Garibaldi-Nesima
(maggio 2015 – aprile 2017)

SEVERI EVENTI AVVERSI: 9 (1,9%)

- Neurite ottica ischemica (2)
- Ittero (2) *
- Urosepsi (1)*
- Eritema cutaneo pruriginoso (1)*
- Spondilodiscite (1)*
- Deterioramento funzione renale (1)
- Bradicardia e impianto di PM (1)*

DECEDUTI: 3

- Sepsi
- IMA
- Insufficienza epatica

* *Discontinued therapy*

Epatologia Garibaldi-Nesima
(maggio 2015 – aprile2017)

TIPOLOGIA DI TRATTAMENTO	n.	NR
SOFOSBUVIR+RIBAVIRINA	36	7
PEG-IFN+SIMEPREVIR+RIBAVIRINA	7	0
SOFOSBUVIR+SIMEPREVIR +/-ribavirina	40	2
SOFOSBUVIR/LEDIPASVIR +/-ribavirina	**163**	**3**
SOFOSBUVIR+DACLATASVIR +/-ribavirina	**69**	**2**
PARITAPREVIR+OMBITASVIR+DASABUVIR +/-ribavirina	**145**	**0**
PARITAPREVIR+OMBITASVIR +/-ribavirina	**4**	**0**
GRAZOPREVIR + ELBASVIR	**6**	**0**

“Con le nuove terapie abbiamo sconfitto l’Epatite C?”
“si, ma…

- L’introduzione dei DAAs ha rivoluzionato la terapia dell’epatite C
- L’eradicazione virale può essere raggiunta con i nuovi DAAs nella quasi totalità dei pazienti, tuttavia molti individui non sono a conoscenza del loro stato di portatore del virus
- Il trattamento dei pazienti con malattia lieve/moderata è in grado di prevenire l’insorgenza di Cirrosi, HCC e manifestazioni extraepatiche correlate al virus C
- Nei pazienti con cirrosi (compensata e scompensata) l’eradicazione non equivale alla “cura” (persiste rischio di HCC, scompenso e morte)
- ***Una strategia basata non solo sul criterio della gravità consente di ottenere maggiori vantaggi sanitari, economici e sociali***

Grazie per l'attenzione !

UOD DI EPATOLOGIA

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A.Bellia **C.Cocuzza**

C.Trovato