Innovazione nella terapia del virus HCV: stato dell'arte e prospettive future

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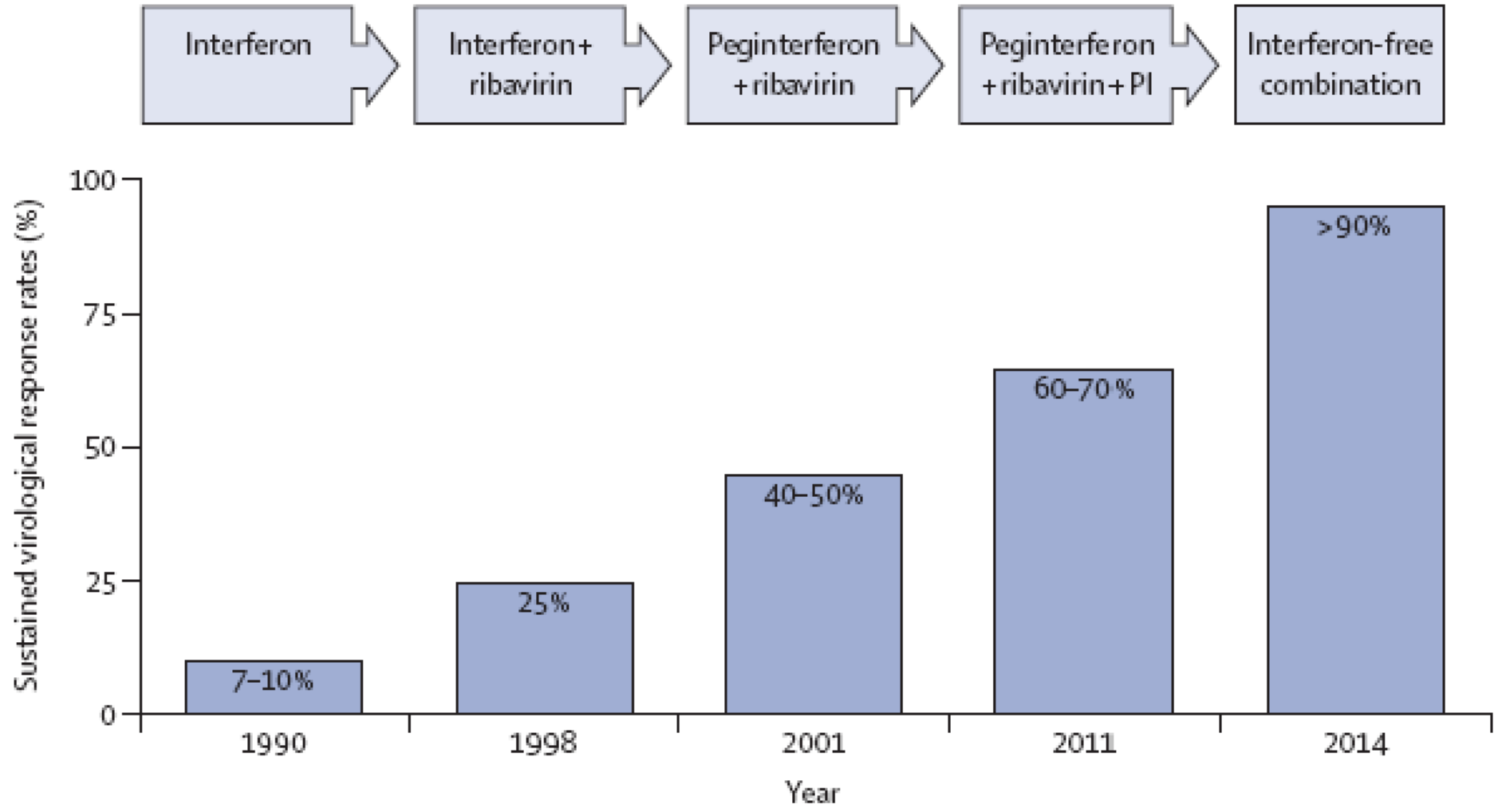
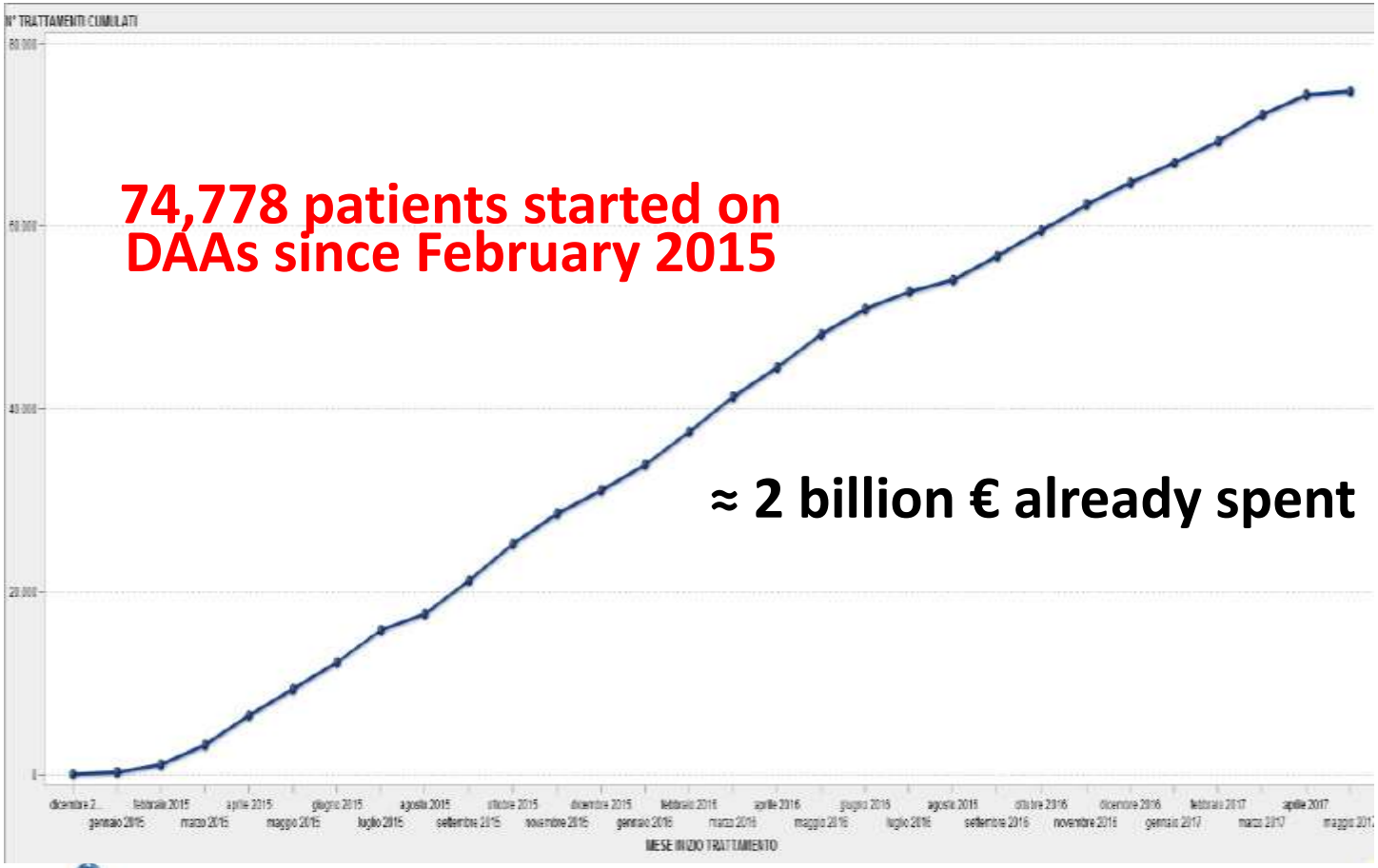
Treatment Evolution in HCV



Prescription of DAAs in Italy
(updated 8 May, 2017)

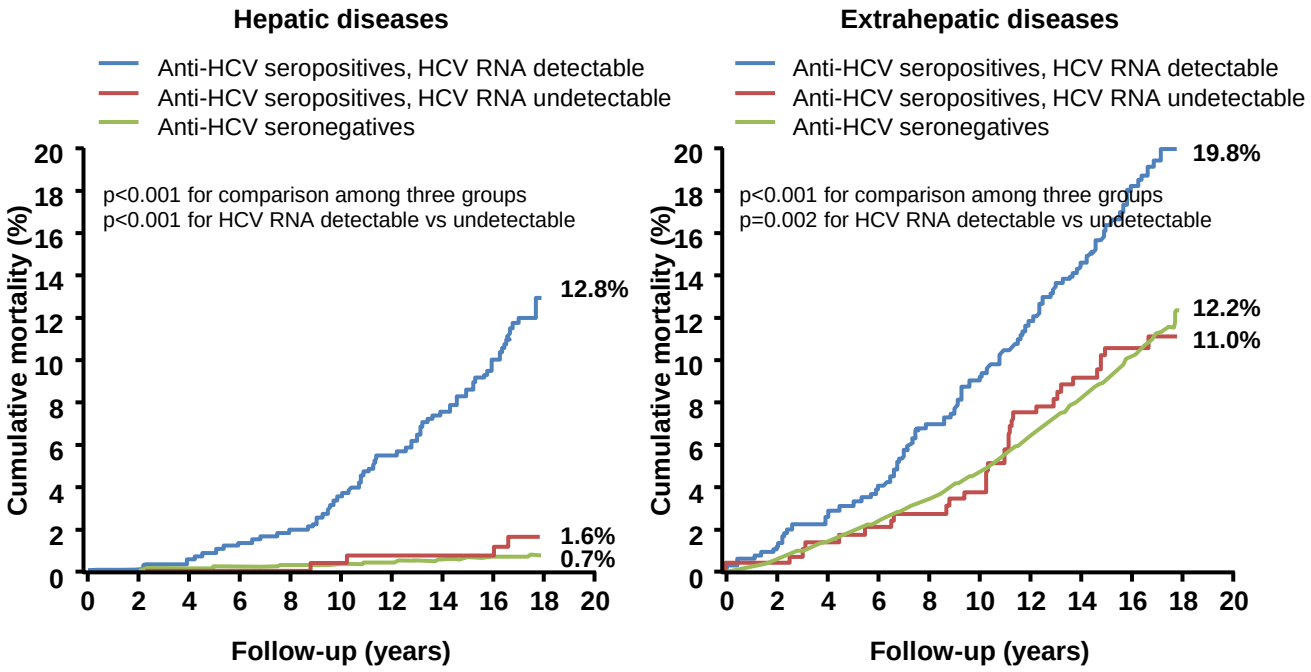


AIFA

Chronic HCV increases mortality from hepatic and non-hepatic diseases

The REVEAL HCV Cohort Study

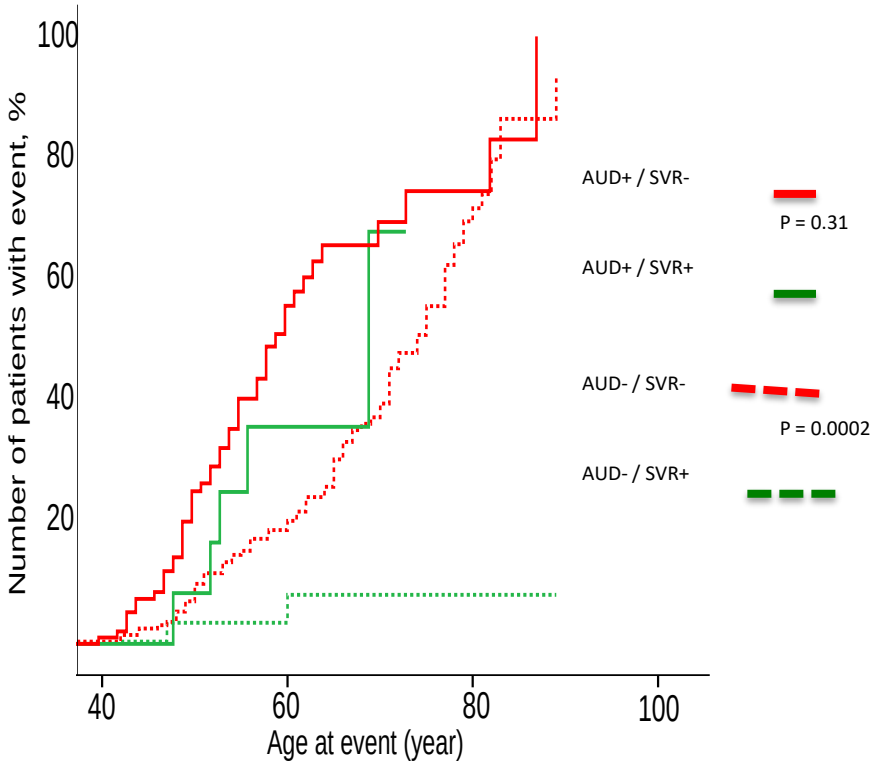
23 820 adults in Taiwan prospectively followed since 1991/2
1095 were anti-HCV positive; 69.4% had detectable HCV RNA



LEE *et al,* J Infect Dis 2012;206:469–477

Clinical outcome in HCV patients treated with DAAs : is there any concern with alcohol use disorders (AUD)?

- Sultanik P et al EASL 2016: THU-370 :
  - 341 cirrhotic patients (2006-2015)
  - SVR : 13% (IFN-based)
  - Evolution to ESLD/HCC
  - SVR slow down ESLD only in those without AUD



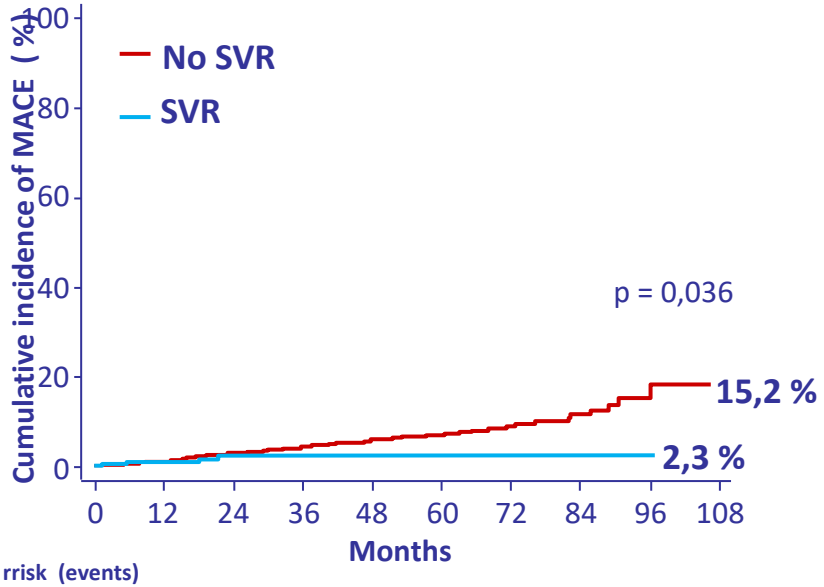
Number of patients at risk

patients SVR-/AUD+	n = 100	97	20	3	0
patients SVR+/AUD+	n = 12	11	60	0	0
patients SVR-/AUD-	n = 196	188	106	13	0
patients SVR+/AUD-	n = 33	31	20	3	0

Cardiovascular events after SVR : CirVir cohort

- CirVir cohort: 878 HCV cirrhotic viremic patients with every 6 mo visit
- Median FU : 51,5 months – 62 patients had 79 cardiovascular events

Major Adverse Cardiovascular Events according to SVR



Number of rrisk (events)										
No SVR	856 (9)	751 (12)	653 (9)	528 (8)	417 (3)	292 (5)	184 (4)	102 (3)	30 (1)	2
SVR	306 (2)	175 (2)	113 (0)	67 (0)	34 (0)	22 (0)	10 (0)	3 (0)	1 (0)	0

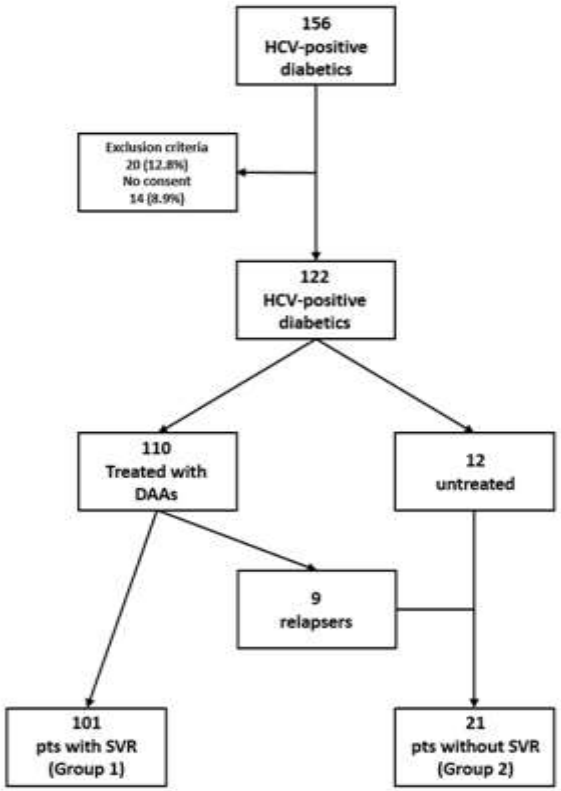
Incidence		1 an	2 ans	3 ans	4 ans	5 ans	6 ans	7 ans	8 ans
No SVR	%	1,1	2,8	4,3	6,0	6,8	8,7	11,4	15,2
	(IC 95%)	(0,6-2,1)	(1,8-4,2)	(3,0-6,1)	(4,4-8,2)	(5,0-9,2)	(6,4-11,8)	(8,2-15,7)	(10,5-21,8)
SVR	%	0,7	2,3	2,3	2,3	2,3	2,3	2,3	2,3
	(IC 95%)	(0,2-2,9)	(0,8-6,4)	(0,8-6,4)	(0,8-6,4)	(0,8-6,4)	(0,8-6,4)	(0,8-6,4)	(0,8-6,4)

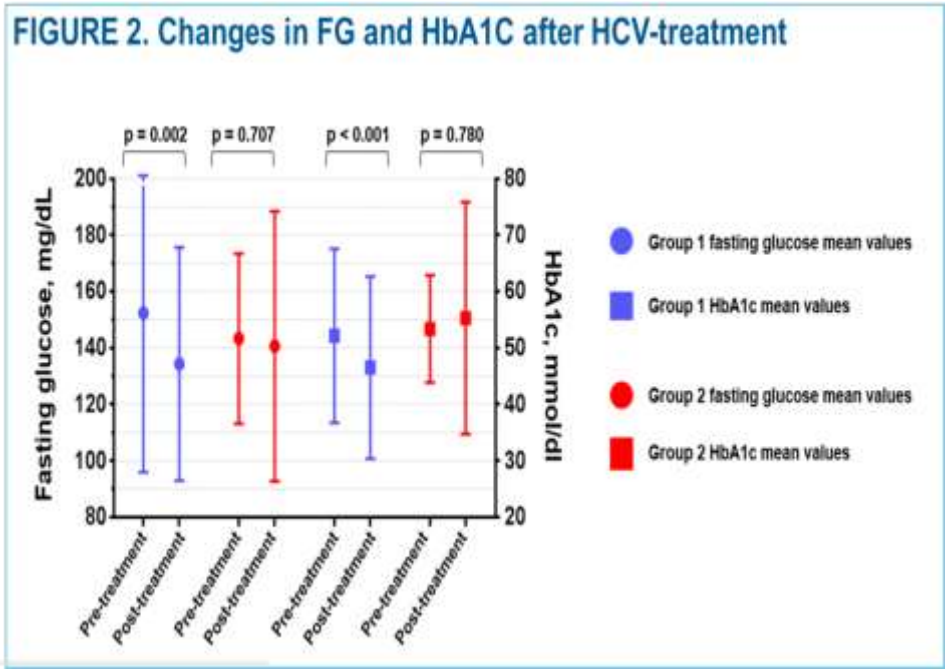
- **Decrease of MACE in patients with SVR**

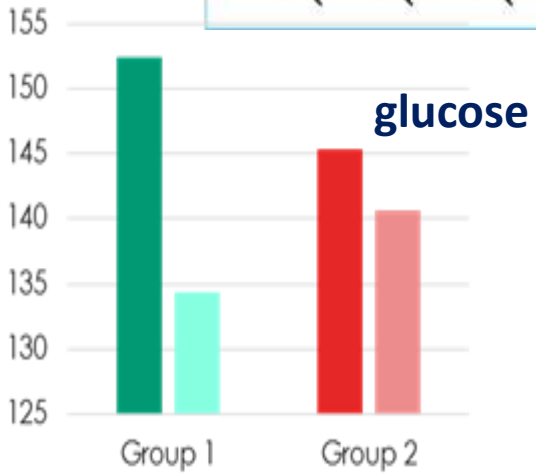
Cacoub P et al. EASL 2017, Abs. PS-032

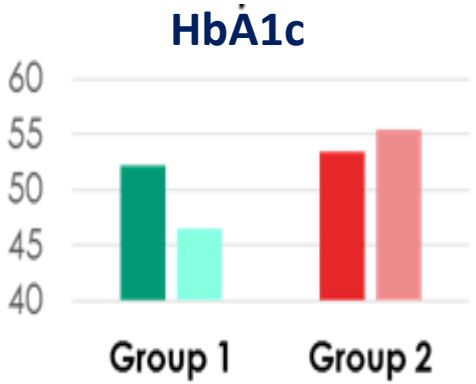
Marked improvement of glycaemic control in diabetic patients with chronic hepatitis C achieving Sustained Virologic Response after direct acting antiviral therapy

A. Ciancio et al.

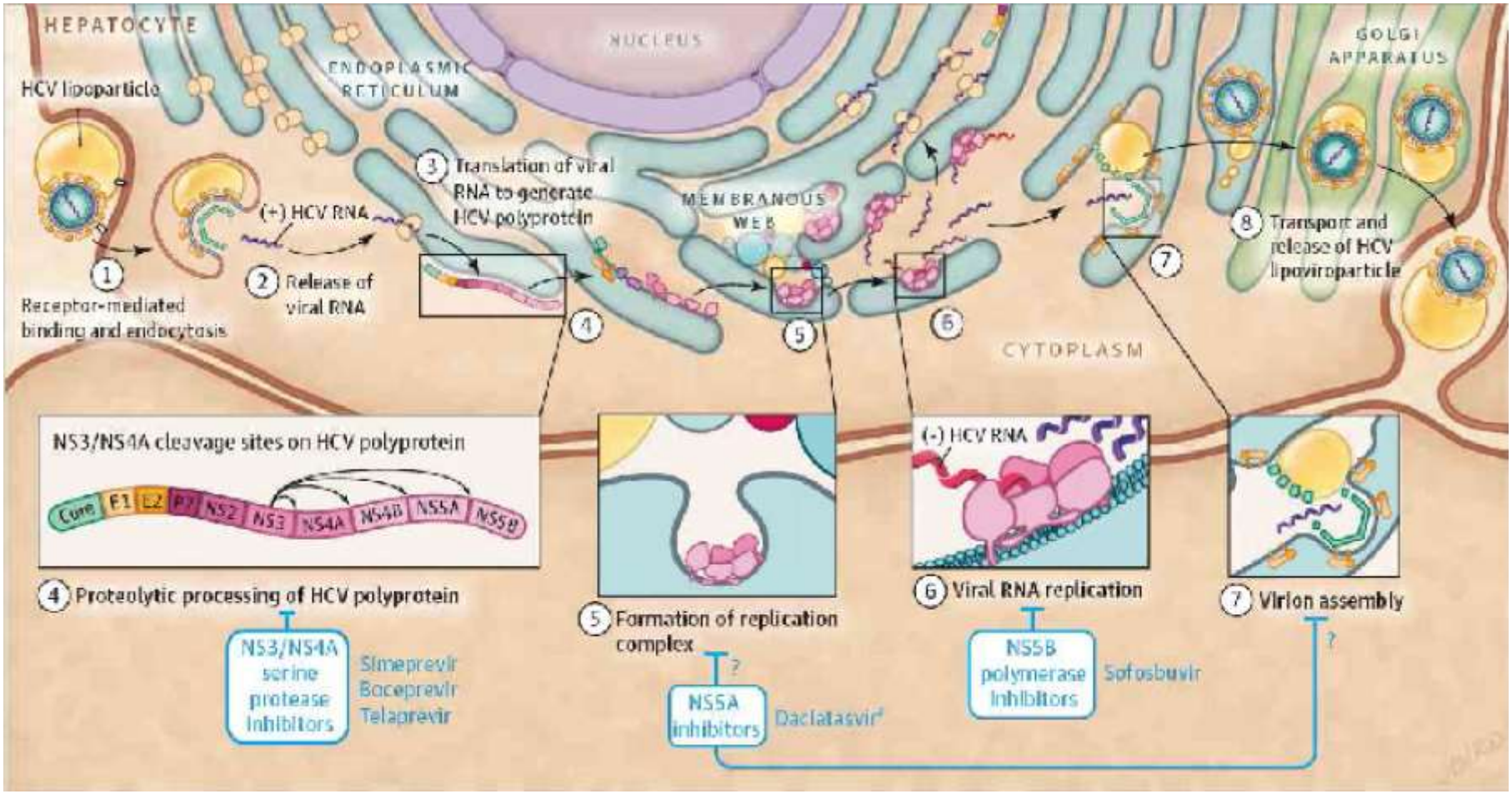








Mechanisms of Action



DAA classes and subclasses

Drug Class	Subclass	Potency	Resistance barrier
Protease inhibitors "- previr"	1st Generation first wave i.e. Telaprevir/Boceprevir	**Medium-Low**	**Low**
	1st Generation 2nd wave i.e. Simeprevir/Asunaprevir Paritaprevir/r	**Medium**	**Low**
	2nd Generation Voxilaprevir GS 9857 Grazoprevir Glecaprevir (ABT 493)	**High**	**High**
NS5a inhibitor " ..asvir"	1st Generation Daclatasvir, Ledipasvir Ombitasvir, Elbasvir	**High**	**Medium- High**
	2nd Generation Velpatasvir Pibrentasvir (ABT530) Ruzasvir (MK3682)	**High**	**High**
Polymerase inhibitors "..buvir" NN	Dasabuvir	**Low-Medium**	**Low**
Nucleos/tides	2nd Generation : Sofosbuvir; MK 3682	**High**	**High**

EASL

Treatment Indications

- **All treatment-naïve and treatment-experienced patients with compensated or decompensated chronic liver disease due to HCV must be considered for therapy**

=> UNIVERSAL ACCESS TO THERAPY

- **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 Ishack).

- **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 (o corrispondente Ishack) 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:** Epatite cronica con fibrosi METAVIR F0-F1 (o corrispondente Ishack) 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 9:** Operatori sanitari infetti.

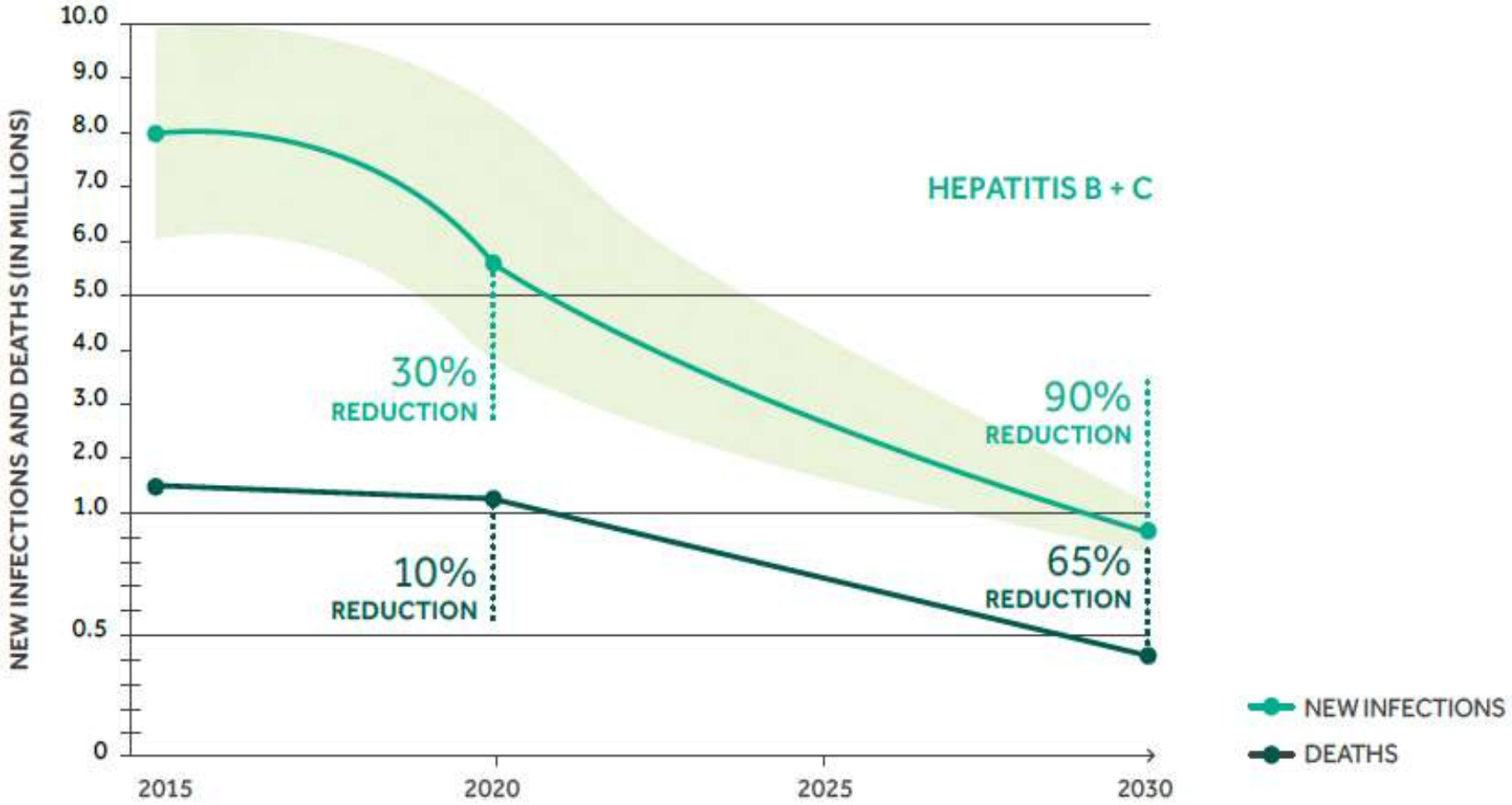
- **Criterio 10:** Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.

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

Patients Who Should beTreated Without Delay

- Significant fibrosis or cirrhosis (METAVIR score F2, F3, F4), including decompensated cirrhosis
- Clinically significant extra-hepatic manifestations
- HCV recurrence after liver transplantation
- Individuals at risk of transmitting HCV
  - Active injection drug users
  - MSM with high-risk sexual practices
  - Women of child-bearing age who wish to get pregnant
  - Hemodialysis patients
  - Incarcerated individuals

WORLD HEALTH ORGANIZATION GLOBAL HEALTH SECTOR STRATEGY



World Health Organization

WHO Global Health Sector HCV Strategy

Global targets for 2030

- **90%** diagnosed
- **90%** of eligible people treated
- **90%** of those treated are cured
- **50%** of PWID covered by harm reduction services by 2020

- **70%** reduction in HCV incidence
  - 50% reduction by 2020
- **Zero** new infections due to unsafe blood transfusions
- **75%** reduction in new infections due to unsafe medical practices by 2020

- **60%** reduction in HCV-related deaths

WHO. Draft global health sector strategy on viral hepatitis, 2016–2021. Available at: www.who.int/hepatitis/news-events/strategy2016-2021/Draft_global_health_sector_strategy_viral_hepatitis_13nov.pdf?ua=1 (accessed January 2016)

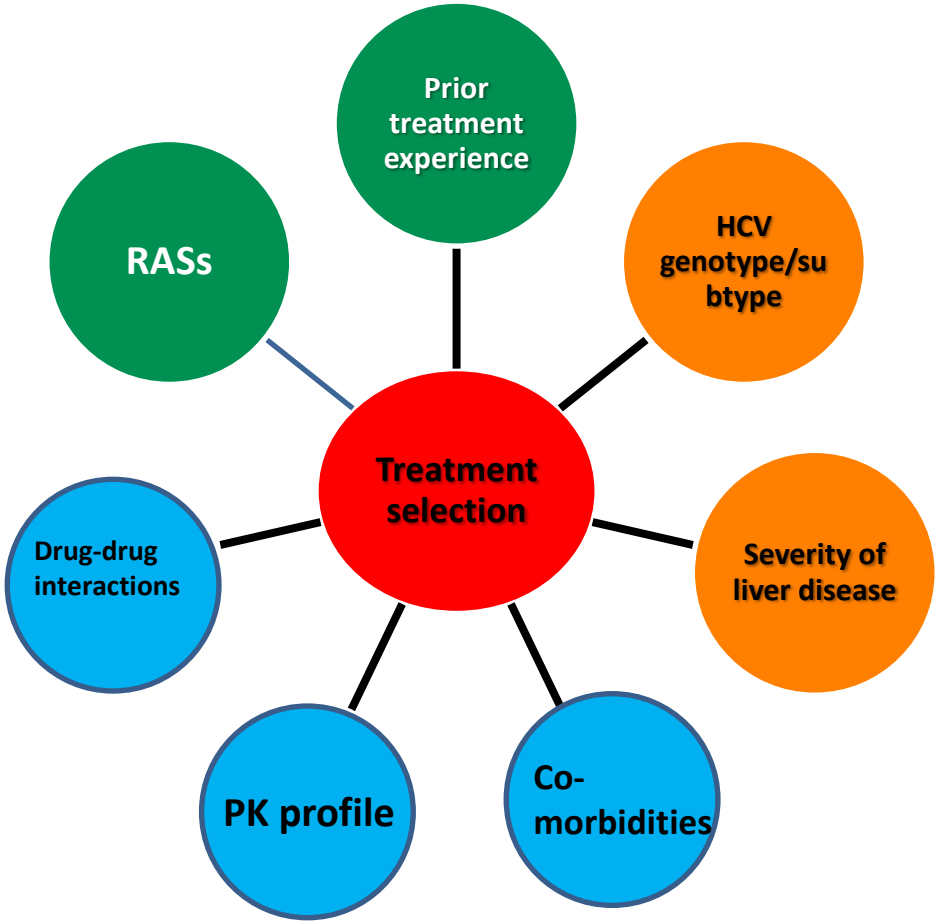
Based on currently licensed drugs.
Updated regularly, following approval of newdrug regimens by the European MedicinesA gency and other national European agencies

EASL 2016: IFN-Free Treatment Options

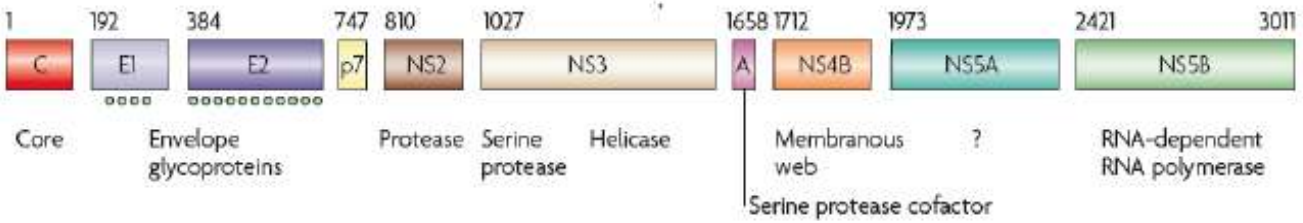
Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	No	Suboptimal	Suboptimal	No	No
SOF/LDV ± RBV	Yes	No	No	Yes	Yes
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV	Yes	Yes	Yes	Yes	Yes
SOF + SIM ± RBV	Suboptimal	No	No	Yes	No

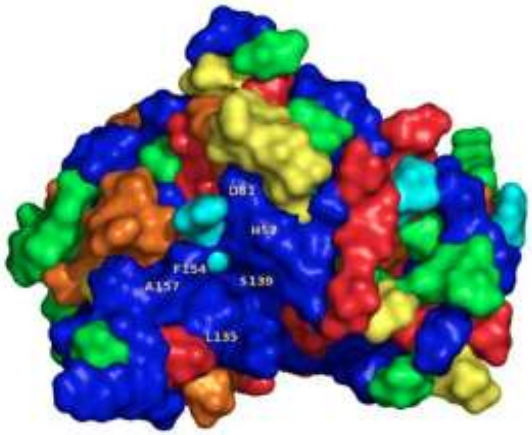
EASL HCV Treatment Recommendations 2016

Tayloring treatment in individual patients

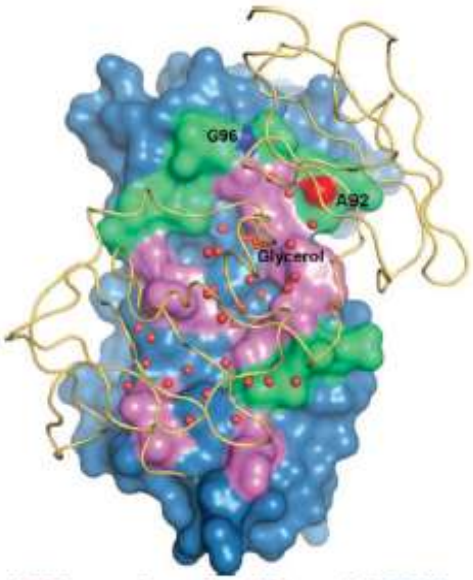


HCV PROTEINS VARIABILITY

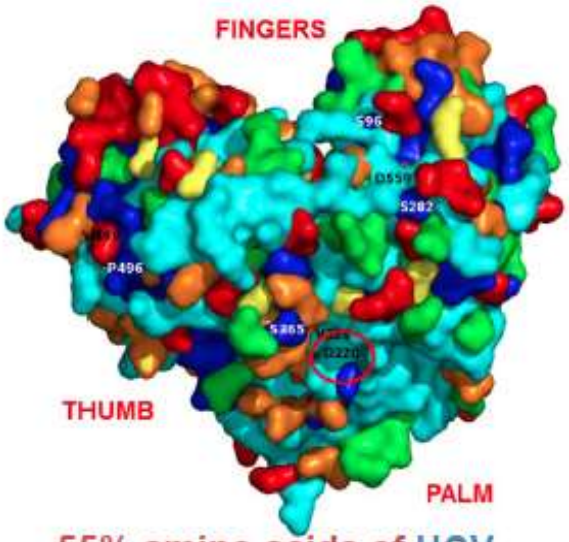




47% amino acids of HCV PROTEASE NS3 are conserved among all HCV-genotypes



46% amino acids of HCV NS5A are conserved among all HCV-genotypes



55% amino acids of HCV POLYMERASE NS5B are conserved among all HCV-genotypes

Amino acid variability:

0% ≤1% 1-5% 5-10% 10-25% >25%

Cento et al., PLoS ONE 2012

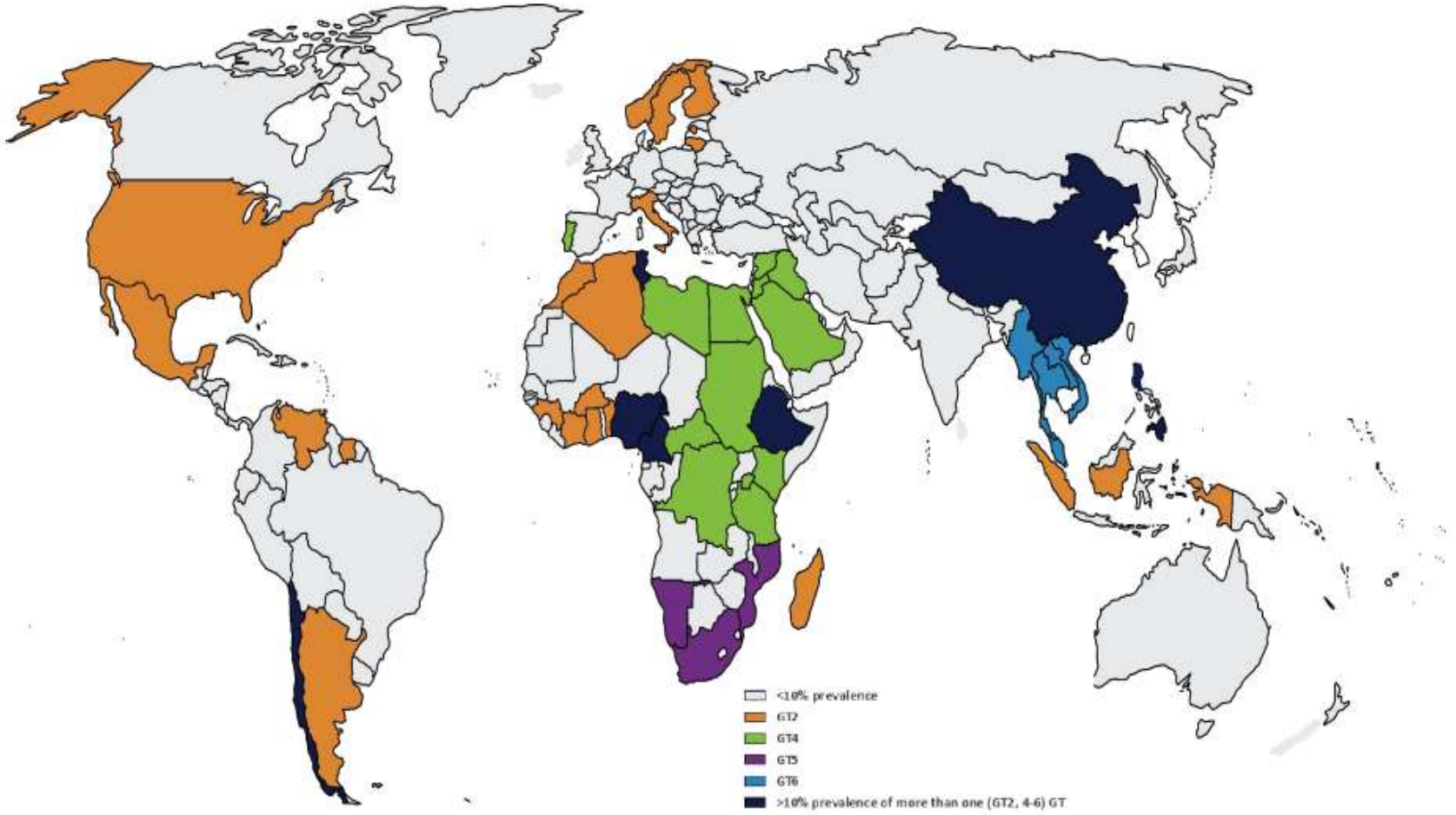
Love et al., J Vir 2009

Amino acid variability:

0% ≤1% 1-5% 5-10% 10-25% >25%

Di Maio et al., AAC 2014

Global Prevalence of GT2 (9%), 4 (8%), 5 (1%) and 6 (5%)



Hassanein T, et al. LB-15, AASLD 2016.

DAA classes and subclasses: antiviral potency and resistance barrier according to HCV genotype

Drug Class	Subclass	1 b	1a	2	3	4
Protease inhibitors	1st Generation first wave i.e. Telaprevir/Boceprevir					
	1st Generation 2nd wave i.e. Simeprevir Paritaprevir/r Asunaprevir					
	2nd Generation Grazoprevir Glecaprevir (ABT 493) Voxilaprevir (GS5897)					
NS5a Inhibitor	1st Generation Ledipasvir Ombitasvir Elbasvir					
	Daclatasvir 2nd Generation Velpatasvir Pibrentasvir (ABT 530) Ruzasvir (MK3682)					
NN Polymerase Inhibitors	Dasabuvir					
Nucleos/tides Polymerase inhibitors	2nd Generation : Sofosbuvir MK 3682					

High Moderate Low Very low

DETERMINA 22 maggio 2017

Riclassificazione del medicinale per uso umano «Sovaldi», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 959/2017)

DETERMINA 22 maggio 2017

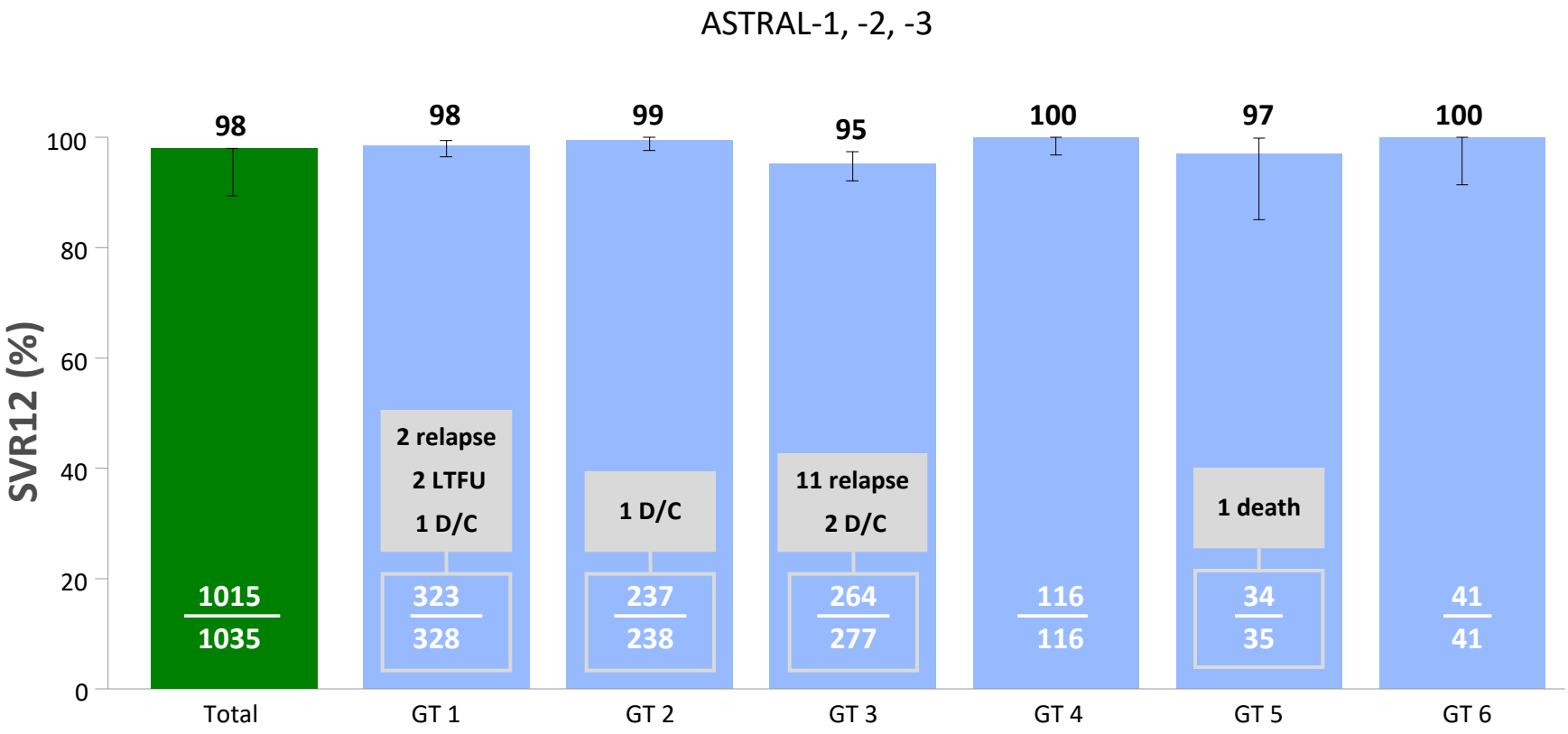
Riclassificazione del medicinale per uso umano «Harvoni», ai sensi dell'articolo 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 960/2017)

The Italian way: IFN-Free Treatment Options

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV					
SOF/LDV ± RBV					
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV					
SOF + SIM ± RBV					

EASL HCV Treatment Recommendations 2016

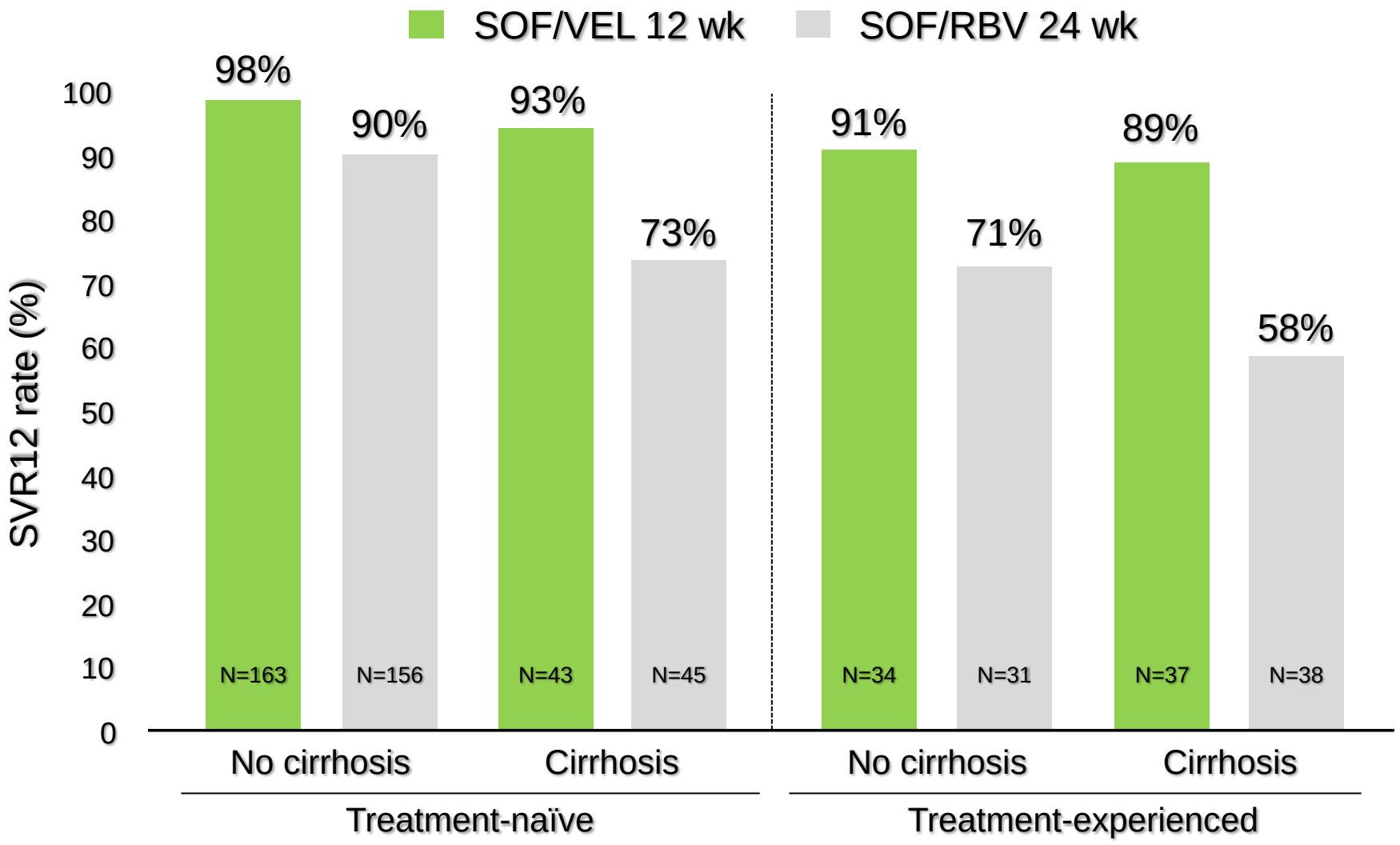
Sofosbuvir + Velaptasvir Integrated Efficacy: SVR12



Agarwal, EASL 2016, Poster SAT-195

Sofosbuvir + Velpatasvir

ASTRAL-3– Phase III, TN and TE (26%), Gt 3, 30% cirrhosis, 12 weeks



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

High SVR12 rates with SOF/VEL for 12 weeks were achieved by patients with multiple factors historically associated with virologic failure

ASTRAL-1, -2, -3

Patients, n/N (%)	GT1 n=328	GT2 n=238	GT3 n=277	GT4 n=116	GT5 n=35	GT6 n=41	
Overall	**323/328 (98)**	**237/238 (99)**	**264/277 (95)**	**116/116 (100)**	34/35 (97)	41/41 (100)	1015/1035 (98)
0 factor	**33/33 (100)**	**13/13 (100)**	**53/53 (100)**	**11/11 (100)**	3/4 (75)	5/5 (100)	118/119 (99)
1 factor	**148/151 (98)**	**80/81 (99)**	**108/111 (97)**	**31/31 (100)**	21/21 (100)	17/17 (100)	405/412 (98)
2 factors							342/347 (99)
3 factors	**44/45 (98)**	**30/30 (100)**	**29/34 (85)**	**25/25 (100)**	4/4 (100)	4/4 (100)	136/142 (96)
4 factors	**2/2 (100)**	**3/3 (100)**	**0/1 (0)**	**9/9 (100)**	0	0	14/15 (93)

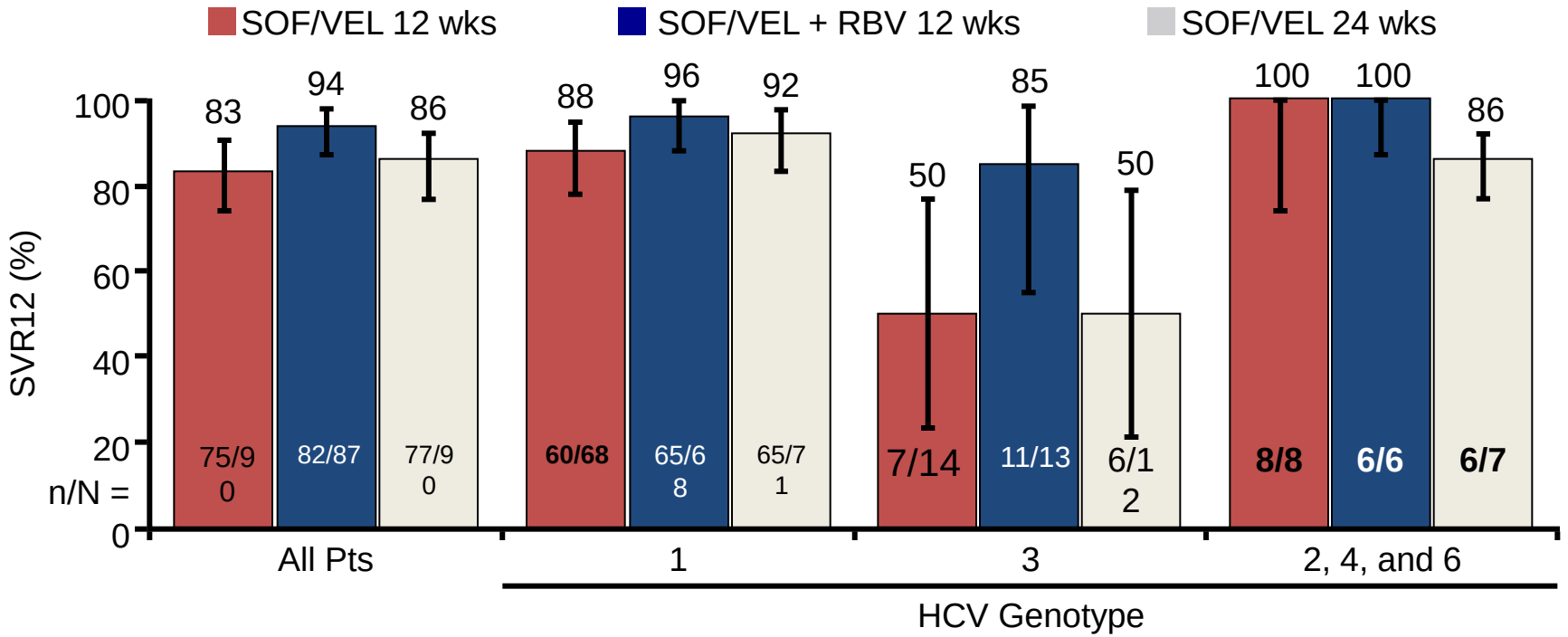
HCV GT 3 > 2 factors vs ≤2 factors p< 0.001

Baseline factors analysed included presence of NS5A RAVs, presence of cirrhosis, baseline HCV RNA ≥800 IU/mL, and prior HCV treatment.

Agarwal, EASL 2016, Poster SAT-195

ASTRAL-4: Sofosbuvir/Velpatasvir in Decompensated Cirrhosis

- Open-label trial; HCC and liver transplantation excluded
- In pts with BL MELD > 15, SVR12, score improved in 84%, worsened in 8%; in pts with BL MELD < 15, SVR12, score improved in 52%, worsened in 27%
- AEs consistent with advanced liver disease and RBV toxicity



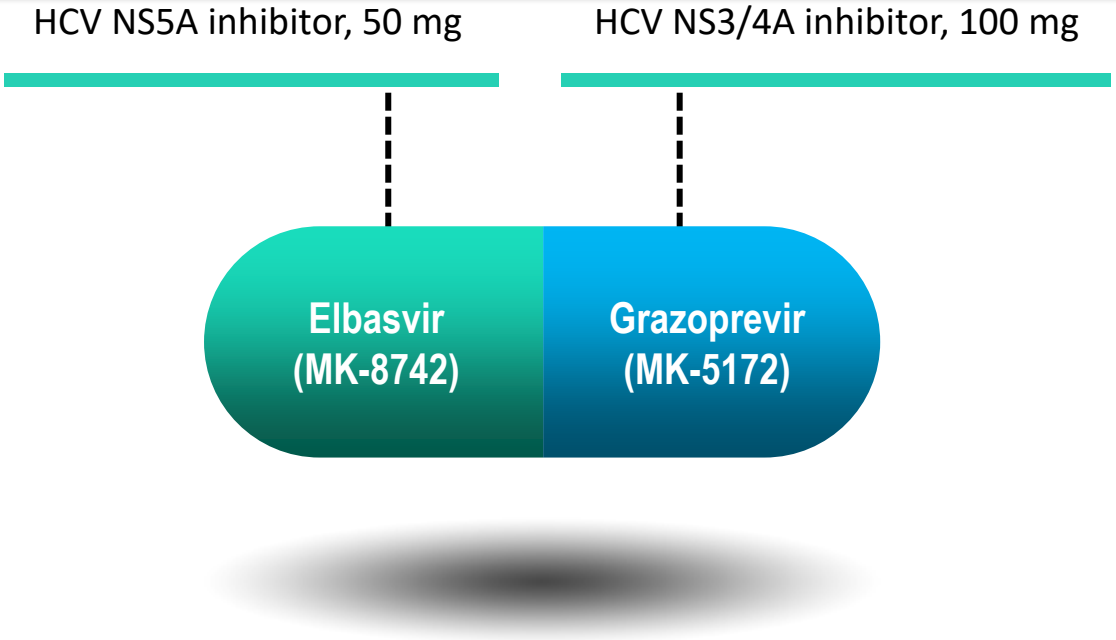
Charlton MR, et al. AASLD 2015. Abstract LB-13.
Curry MP, et al. N Engl J Med. 2015;[Epub ahead of print].

The Italian way: IFN-Free Treatment Options

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV					
SOF/LDV ± RBV					
SOF/VEL ± RBV	Yes	Yes	Yes	Yes	Yes
OBV/PTV/r + DSV (3D) ± RBV	Yes	No	No	No	No
OBV/PTV/r (2D) ± RBV	No	No	No	Yes	No
GZR/EBR ± RBV	Yes	No	No	Yes	No
SOF + DCV ± RBV					
SOF + SIM ± RBV					

EASL HCV Treatment Recommendations 2016

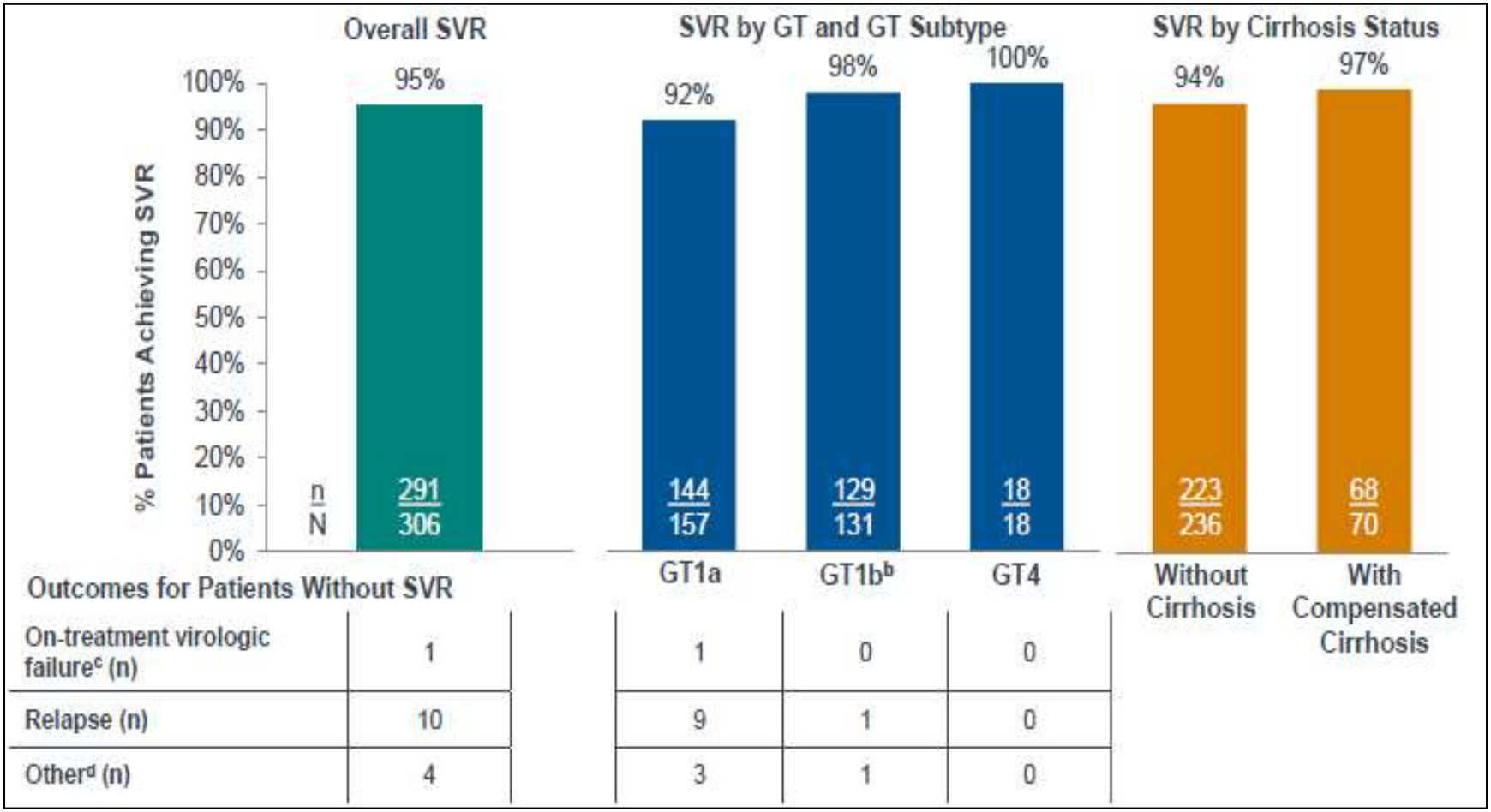
Elbasvir/Grazoprevir



- Combinazione a dose fissa, compressa film rivestita, 1 volta al giorno, con o senza cibo
- Ampia attività contro la maggior parte dei genotipi di HCV *in vitro*[1-3]
- Efficacia dimostrata in pazienti HCV naïve e pre-trattati, cirrotici e non-cirrotici, con co-infezione HIV-HCV e altre comorbidità [4-6]

1. Summa V, et al. Antimicrobial Agent Chemother 2012:56;4161; 2. Coburn CA,, et al. ChemMedChem 2013; 8: 1930; 3. Harper S, et al. ACS Med Chem Lett. 2012 Mar 2;3(4):332; 4. Zeuzem et al., Ann Int Med 2015; 163:1; 5. Lawitz et al., Lancet 2015; 385:1075; 6. Rockstroh et al., Lancet HIV 2015; 2:e319

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.

EASL

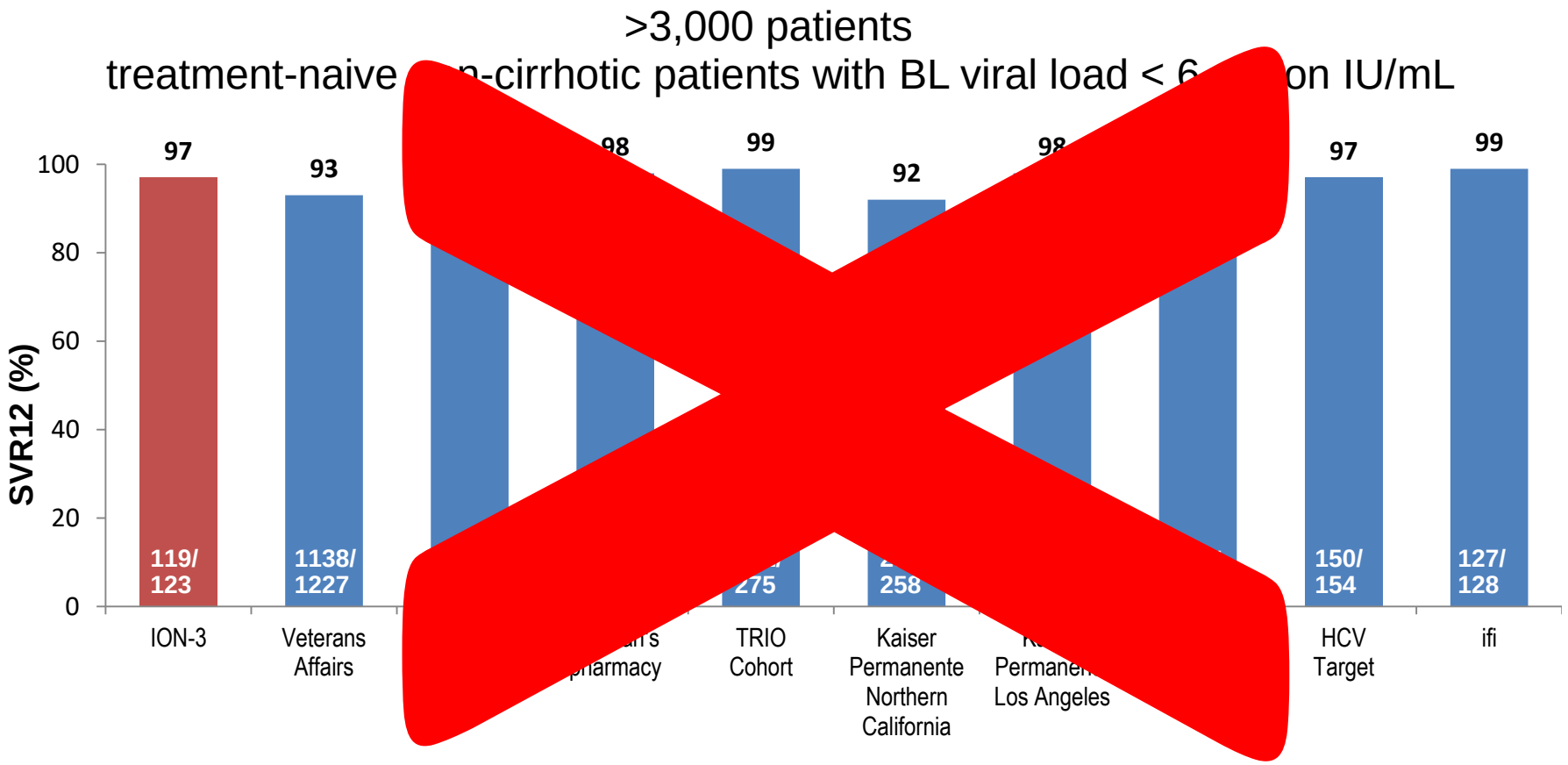
Genotype 1a Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/LDV ± RBV	8-12 wk	12 wk + RBV	12 wk	12 wk + RBV
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D)± RBV	12 wk + RBV	12 wk + RBV	24 wk + RBV	24 wk + RBV
GZR/EBR ± RBV	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	12 wk	12 wk + RBV*¶

*24 wk without RBV if RBV contraindicated or poorly tolerated

¶Only if presence of NS5A RASs at baseline, if resistance testing available

SVR12 in ION-3 Compared to Real-World Cohorts of GT1 patients treated with LDV/SOF 8 weeks



Kowdley. **ION-3**. NEJM *
Backus, **VA**, Hepatology 2016 ***
Afdhal. **TRIO**. LBP-519 ***
Buggisch. **IFI**. SAT-243 ***
Latt. **Kaiser**. SAT-227 **
Qureshi. **Burman's**. SAT-192 **

Terrault. **HCV-TARGET**. AASLD 2015 **
EASL 16 **
Curry. **GECCO**. AASLD 2015 ***
Buggisch. **DHC-R**. SAT-241 ***
Lai. **Kaiser**. SAT-177 ***

*Post hoc analysis ** Per Protocol *** ITT analysis ; patients were primarily treatment-naive non-cirrhotic patients with BL viral load < 6 million IU/mL

Genotype 1a Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D)± RBV	12 wk + RBV	12 wk + RBV	24 wk + RBV	24 wk + RBV
GZR/EBR ± RBV	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000¶

EASL

Genotype 1b Options

Combinationregimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/LDV	[illegible]	12 wk	12 wk	12 wk
SOF/VEL	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D)	[illegible]	12 wk	12 wk	12 wk
GZR/EBR	12 wk	12 wk	12 wk	12 wk
SOF + DCV	12 wk	12 wk	12 wk	12 wk

Genotype 1b Options

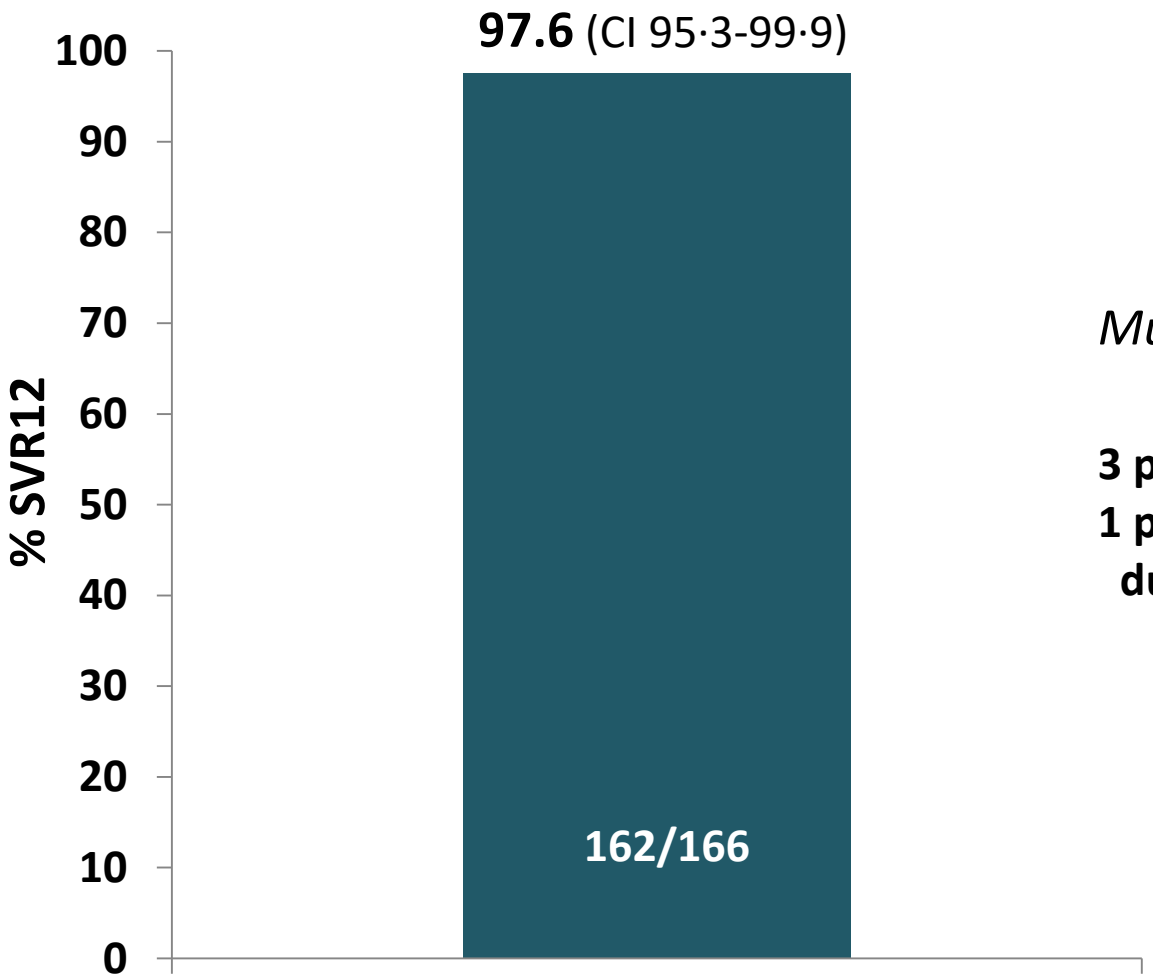
Combinationregimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/LDV ± RBV	12 wk§	12 wk	12 wk	12 wk + RBV 24 wk
SOF/VEL	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D)	12 wk	12 wk	12 wk	12 wk
GZR/EBR	12 wk	12 wk	12 wk	12 wk
SOF + DCV ± RBV	12 wk	12 wk	24 wk + RBV	24 wk + RBV
SOF + SMV ± RBV	12 wk		24 wk + RBV	24 wk + RBV

§ shortening treatment to lessthan 12 weeks is NotRecommended for HIV-infected patients, African American or those withk nown IL28B polymorphism CT or TT for othersi tshould be done at the discretionof the practitioner

Genotype 1b Options

Combinationregimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp[d]	Rx-naïve	Rx-exp[d]
SOF/VEL	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r + DSV (3D)	8-12 wk	12 wk	12 wk	12 wk
GZR/EBR	12 wk	12 wk	12 wk	12 wk

Ombitasvir, paritaprevir, and ritonavir plus dasabuvir for 8 weeks in previously untreated patients with hepatitis C virus genotype 1b infection without cirrhosis



GARNET Study

Multicentre, open label, phase 3b

3 patients had non-1b genotype
1 patient discontinued on day 45 due to an dverse event

Welzel T et al. Lancet GastroenterolHepatol.2017, ePub April 12

Genotype 2 Options

Combination regimen (EASL The Home of Hepatology)	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL	12 wk	12 wk	12 wk	12 wk
SOF + DCV	12 wk	12 wk	12 wk	12 wk

Combination regimen (AASLD American Association for the Study of Liver Diseases)	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL	12 wk	12 wk	12 wk	12 wk
SOF + DCV	12 wk	12 wk	16-24 wk± RBV	16-24 wk± RBV

Genotype 3 Options

Combination regimen (EASL The Home of Hepatology)	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL ± RBV	12 wk	12 wk + RBV*¶	12 wk + RBV*¶	12 wk + RBV*¶
SOF + DCV ± RBV	12 wk	12 wk + RBV*¶	24 wk + RBV	24 wk + RBV

¶ Only if presence of NS5A RAS Y93H at baseline, if resistance testing available
* 24 wk without RBV if RBV contraindicated or poorly tolerated

Combination regimen (AASLD American Association for the Study of Liver Diseases)	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL ± RBV	12 wk	12 wk	12 wk + RBV¶	12 wk + RBV
SOF + DCV ± RBV	12 wk	12 wk	24 wk + RBV¶	24 wk + RBV

¶Only if presence of NS5A RAS Y93H at baseline, if resistance testing available

Genotype 2 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL	12 wk	12 wk	12 wk	12 wk

Genotype 3 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL ± RBV	12 wk	12 wk + RBV*¶	12 wk + RBV*¶	12 wk + RBV*¶

¶ Only if presence of NS5A RAS Y93H at baseline, if resistance testing available

* 24 wk without RBV if RBV contraindicated or poorly tolerated

Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/LDV ± RBV	12 wk	12 wk	12 wk	12 wk + RBV Or 24 wk *
SOF/VEL	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D) + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if RR 16 wk + RBV if NR or BT	12 wk	12 wk if RR 16 wk + RBV if NR or BT

*24 wk without RBV if RBV contraindicated or poorly tolerated

Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/LDV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D)± RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000
SOF + DCV ± RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*
SOF + SIM ±RBV	12 wk	12 wk + RBV*	12 wk	12 wk + RBV*

*24 wk without RBV if RBV contraindicated or poorly tolerated

Genotype 4 Options

Combination regimen	No cirrhosis		Compensated cirrhosis	
	Rx-naïve	Rx-exp	Rx-naïve	Rx-exp
SOF/VEL ± RBV	12 wk	12 wk	12 wk	12 wk
OBV/PTV/r (2D)± RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV	12 wk + RBV
GZR/EBR ± RBV	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000	12 wk	12 wk if HCV RNA ≤800,000 or 16 wk + RBV if HCV RNA >800,000

*24 wk without RBV if RBV contraindicated or poorly tolerated

Demographic and virological characteristics of 23.384 HCV patients included in 4 regional registries according to HCV genotypes

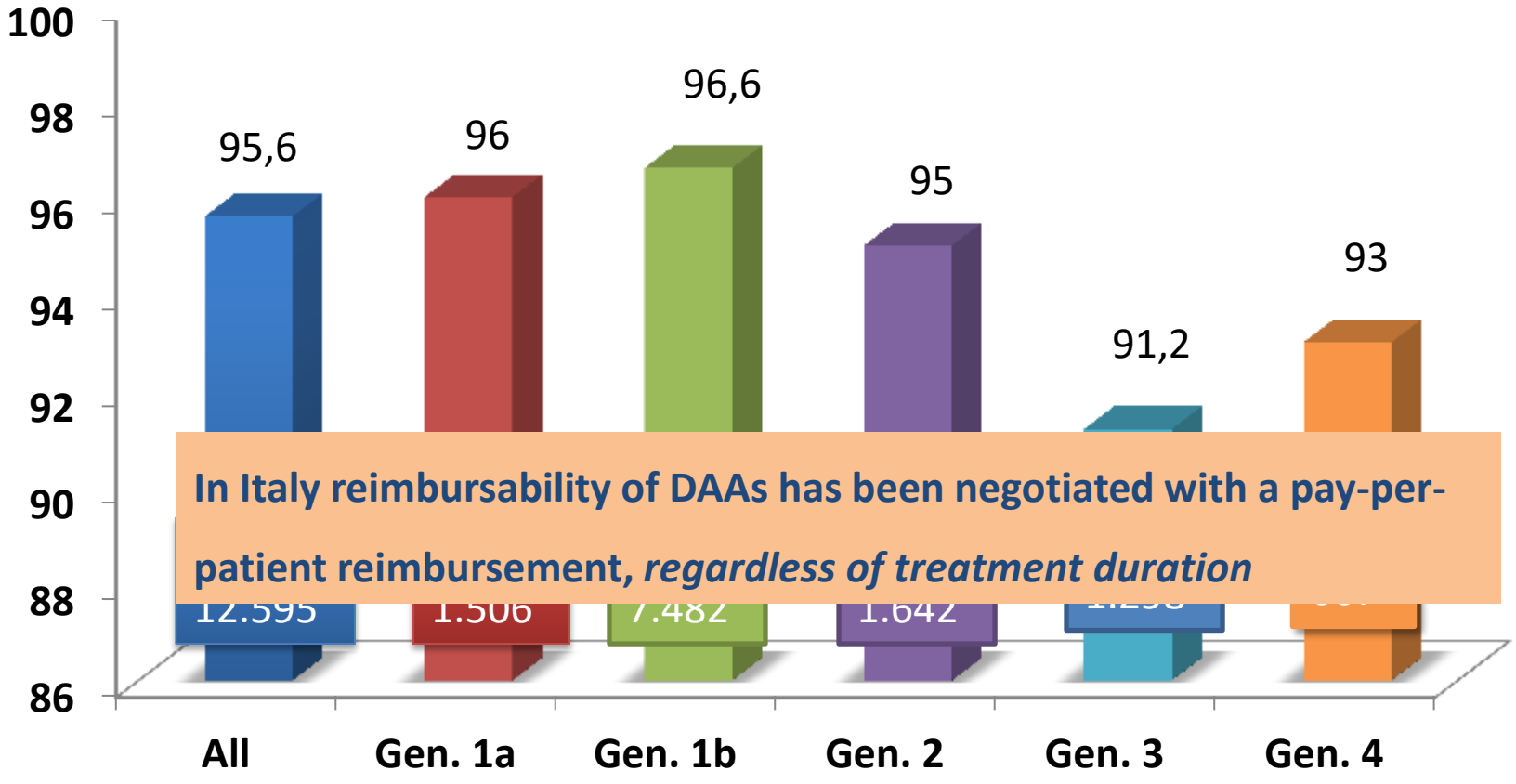
Campania, Lombardia, Sicilia, Veneto

Gen	Age	F4	F3	TE	PLT	Bil	Alb	HIV+	On OLT WL
1a	54.5 (21-84)	63%	26%	18.7 (2.8-75)	141 (12-980)	0.94 (0.2-49)	3.89 (2.2-5.5)	26%	0.7%
1b	65 (18-90)	63%	27%	17.3 (2-75)	144 (14-994)	0.93 (0.1-33)	3.88 (1.7-5.6)	3.2%	0.7%
2	68.7 (29-84)	60%	25%	16.3 (2-70)	148 (11-660)	1.0 (0.2-37)	3.9 (2.3-5.5)	2.3%	0.5%
3	52.3 (25-81)	69%	21%	20.7 (5-75)	131 (15-597)	1.11 (0.1-39)	3.94 (1.9-5.2)	21%	1.3%
4	55.8 (24-80)	68%	21%	18.5 (2-72)	143 (20-449)	0.91 (0.2-7.6)	3.92 (1.9-4.9)	24%	1%

Viganò M et al, DLD 2017; doi: 10.1016/j.dld.2017.03.027

SVR12 in 12.595 HCV infected patients in 4 Italian Regional Registries

(66% F4 and 28% F3 stratified according to HCV Genotypes)



In Italy reimbursability of DAAs has been negotiated with a pay-per-patient reimbursement, *regardless of treatment duration*

Viganò M et al, DLD 2017; doi: 10.1016/j.dld.2017.03.027

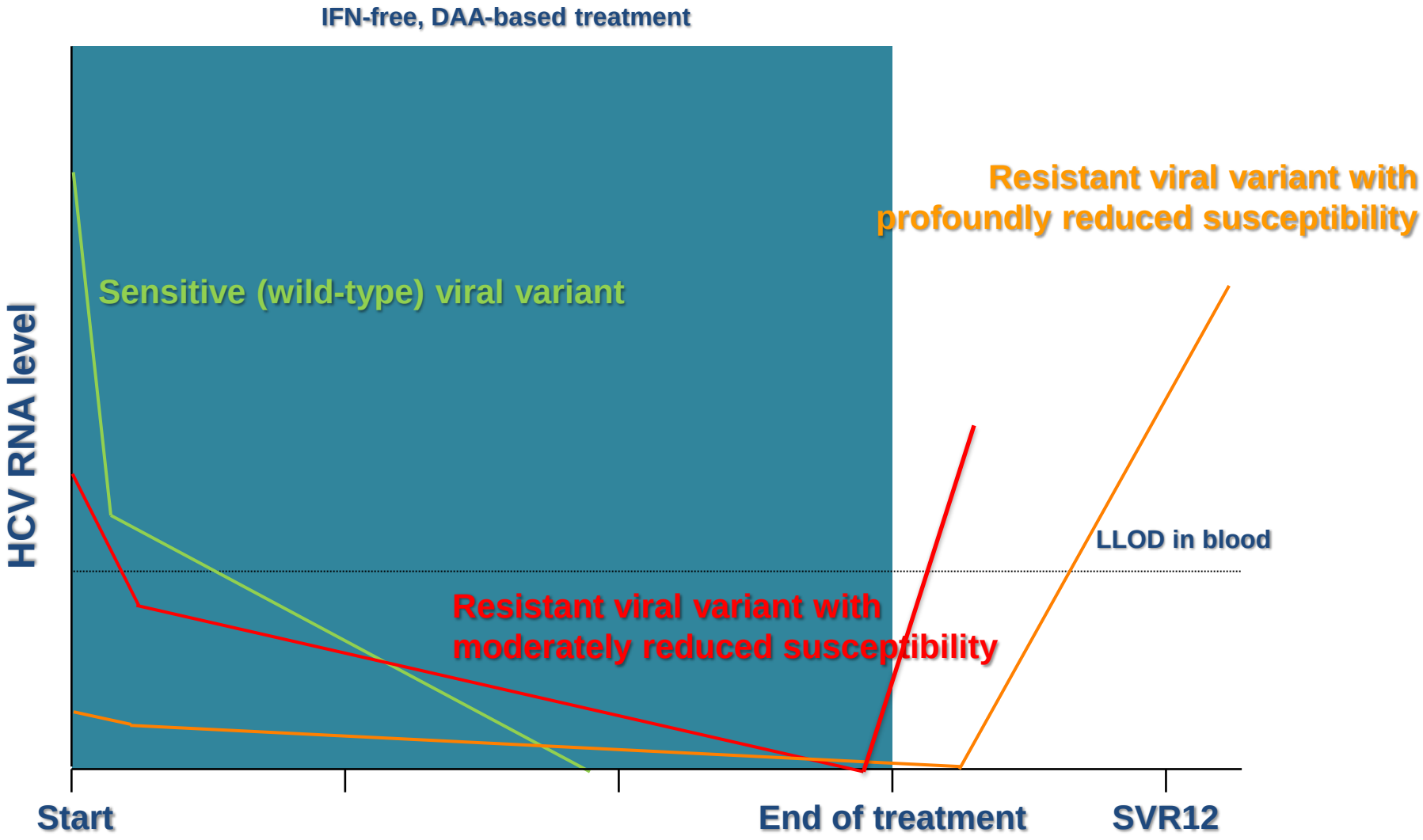
2-5% of patients fail to achieve SVR with current DAAs

IFN-free, DAA-based regimen	Trial(s)	Genotype/subtype	Number of patients with virologic failure analyzed	RASs present at virologic failure		
				NS3 protease RASs	NS5A RASs	NS5B RASs
Sofosbuvir/ledipasvir	Integrated analysis of Phase II and III trials[16]	1a	42	NA	M28A/T, K24R, Q30E/H/K/L/R/Y, L31M/P, S38F, Y93C/H/N	S282T, L320I/V, L159F, V321A
		1b	9	NA	L31I/M/V, Y93H	
	Genotype 4 and 5 trial[31]	4	1	NA	S93C	S282T
		5	1	NA		S282T
Ombitasvir/paritaprevir/ritonavir plus dasabuvir	Integrated analysis of Phase II and III trials[33]	1a	67	R155K, D168A/F/H/I/L/N/T/V/Y	M28A/T/V, Q30E/K/R	C316Y, M414I/T, S556G/R
		1b	7	D168A/F/H/I/L/N/T/V/Y	Y93H	C316Y, M414I/T, S556G/R
Ombitasvir/paritaprevir/ritonavir	PEARL-1[34]	4	3	Y56H, D168V	L28S/V, M31I/M, T58P/S	NA
Sofosbuvir plus daclatasvir	ALLY-2[36]	1a	10	NA	Q30E/Q/R, Y93N	
		1b	1	NA		
		2	1	NA	L31M	
		3	1	NA	A30S	
	ALLY-3[20]	3	16	NA	L31I, Y93H	
	ALLY-3+[37]	3	4	NA	Y93H	
Sofosbuvir plus simeprevir	COSMOS[21]	1a	6	R155K, D168E, I170T	NA	
	OPTIMIST-1[22]	1	31	R155K, D168E, I170T	NA	
	OPTIMIST-2[23]	1	16	R155K, D168E, I170T, N174G	NA	

ACCEPTED MANUSCRIPT

Pawlotsky JM, Gastroenterology 2016

Sensitive and Resistant HCV Variant Kinetics on Treatment



EASL RECOMMENDATIONS 2016
HCV Resistance testing prior to First Line DAA

Knowledge based medicine approach

Resistance testing not available

↓

Optimize therapy
To avoid treatment failure

↓

SOF/LDV, SOF/DCV, SOF/SIM
Add RBV in GT 1a, 4,5,6 TE
SOF VEL: add RBV in G3 TE patients and cirrhotics
GZR/EBR use 16 weeks with RBV in HCV GT1a HCVRNA > 800.000

Precision Medicine approach

Resistance testing Available, reliable, interpretable understandable

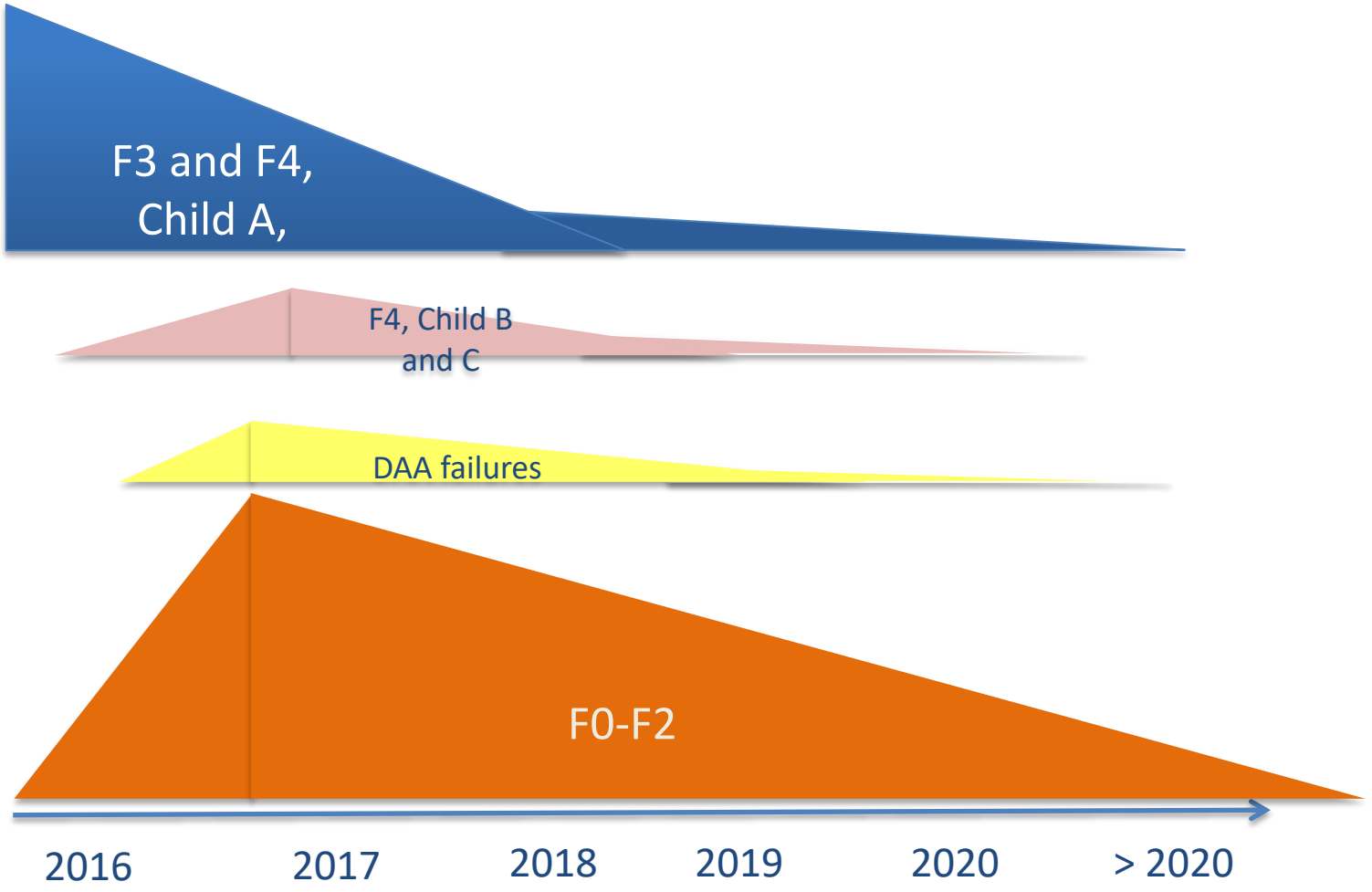
↓

Presence of NSAs RASs (10-15%) Conferring high level resistance (popseq or NGS > 15%)

↓

Add ribavirin and or increase treatment duration in patients with NS5As RASs

HCV patients still to be treated in Italy: the outlook



What is recommended after treatment failure

AASLD/IDSA

- Stress deferral unless urgent treatment needed
- PI/PR → SOF/NS5A as PR
- DAA → RAS testing for all
  - **No RAS**: SOF/NS5A/RBV x 24w
  - **NS3**: SOF/NS5A/RBV x 24w
  - **NS5A**: SOF/SMV/RBV x 24w
  - **NS3 + NS5A**:
    - SOF + ELB/GZV/RBV x 12w
    - SOF + PrOD/RBV x 12w 1b/24w 1a
    - SOF/VEL + RBV x 24w
- **G3**: - **SOF/RBV**: SOF/DCV/RBV x 12w or SOF/VEL/RBV x 12w
  - **SOF/DCV**: SOF/VEL/RBV x 24w

EASL

- Brief mention of treatment deferral as alternative
- PI/PR → SOF/NS5A + RBV
- DAA → consider RAS testing
  - **All**: F0-2 + RBV & F3/4 24w + RBV
  - **SOF/SIM**: SOF/NS5A
  - **SOF/NS5A**:
    - SOF + ELB/GZV + RBV
    - SOF + PrOD + RBV
    - SOF + SMV + DCV + RBV
  - **G2,3,5,6**: SOF/VEL + RBV x 24w

Failure to previous DAA treatment

(what we are missing)

Sequencing for identification of RAS at NS3, NS5A e NS5B genes is recommended

Elbasvir/Grazoprevir + Sofosbuvir + Ribavirina for 12/24 weeks (Gt1 o 4)

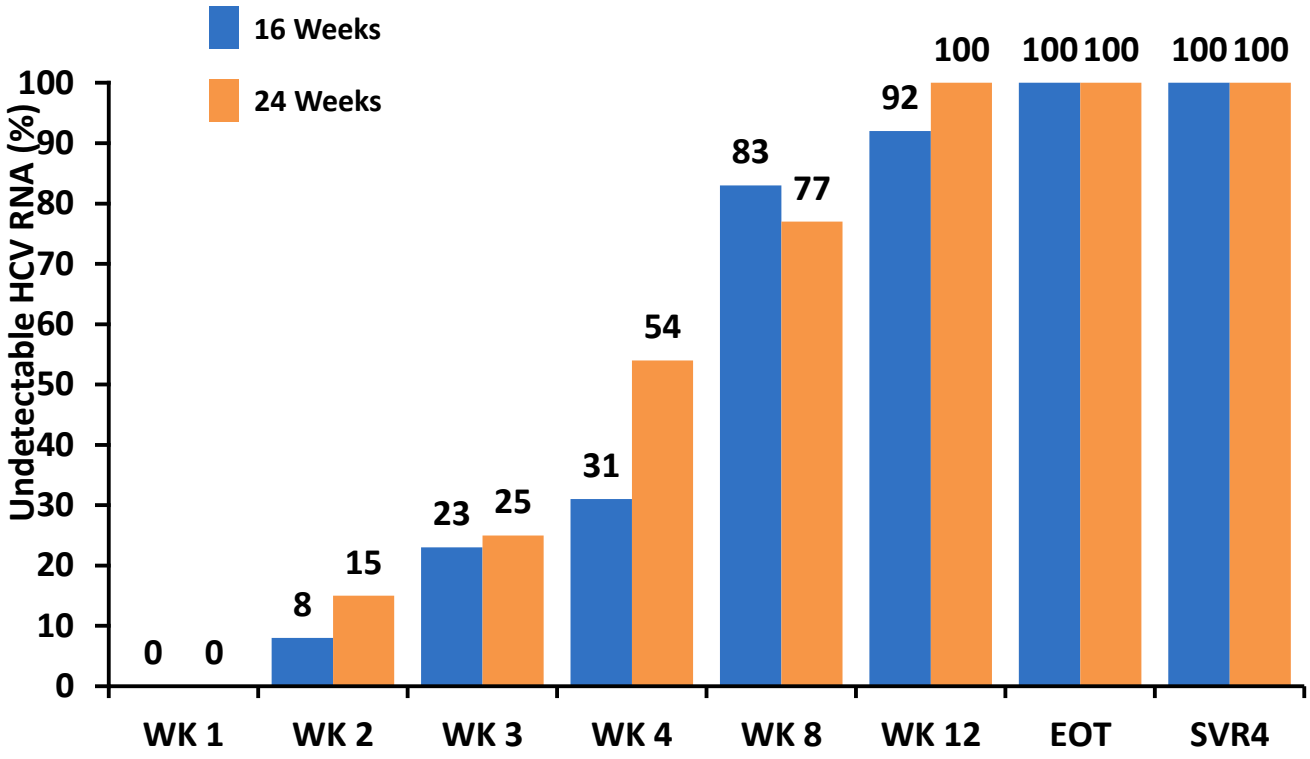
Elbasvir/Grazoprevir + Sofosbuvir + Ribavirina for 12/24 weeks (Gt1 o 4)

Ombitasvir/Paritaprevir/Ritonavir + Sofosbuvir + Ribavirina for 12/24 weeks (GT4)

Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir + Sofosbuvir + Ribavirina for 12/24 weeks (Gt1)

Daclatasvir + Simeprevir + Sofosbuvir + Ribavirina for 12/24 weeks (Gt1)

Retreatment for 16 weeks with SOF + GZV + EBV + Ribavirin of patients with HCV genotype 1 and 4 with non-SVR after SOF + LDV or DCV or SMV:Results



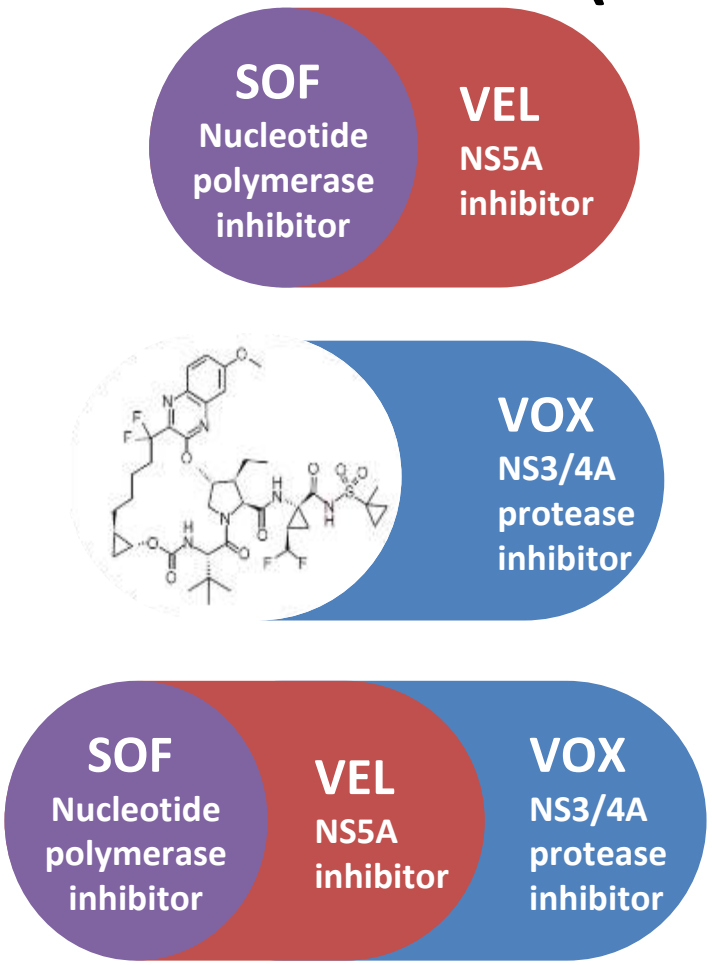
N	13	13	13	13	13	12[1]	13	13	12[1]	13	13	13	13	11[2]	13	10[3]
N undetectable	0	0	1	2	3	3	4	7	10	10	12	13	13	11	13	10

1: one missingg value
2: two missing values (one patient died, one patient ongoing)
3: three missing values (one patient died, two patients ongoing)

de Ledinghehn V, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-18.

Pangenotypic Single Tablet Regimen with Inhibitors of HCV NS5B (Nucleotide) + NS5A + NS3(SOF,VEL,VOX)

PAN



Sofosbuvir (SOF)/Velpatasvir (VEL)

- **SOF:** Nucleoside polymerase inhibitor with activity against HCV GT 1-6
- **VEL:** Potent pangenotypic NS5A inhibitor

Voxilaprevir (VOX)

- HCV NS3/4A PI with potent antiviral activity against GT 1-6, including most RASs

SOF/VEL/VOX

- Once daily, oral, fixed-dose combination (400/100/100 mg) for GT 1-6

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

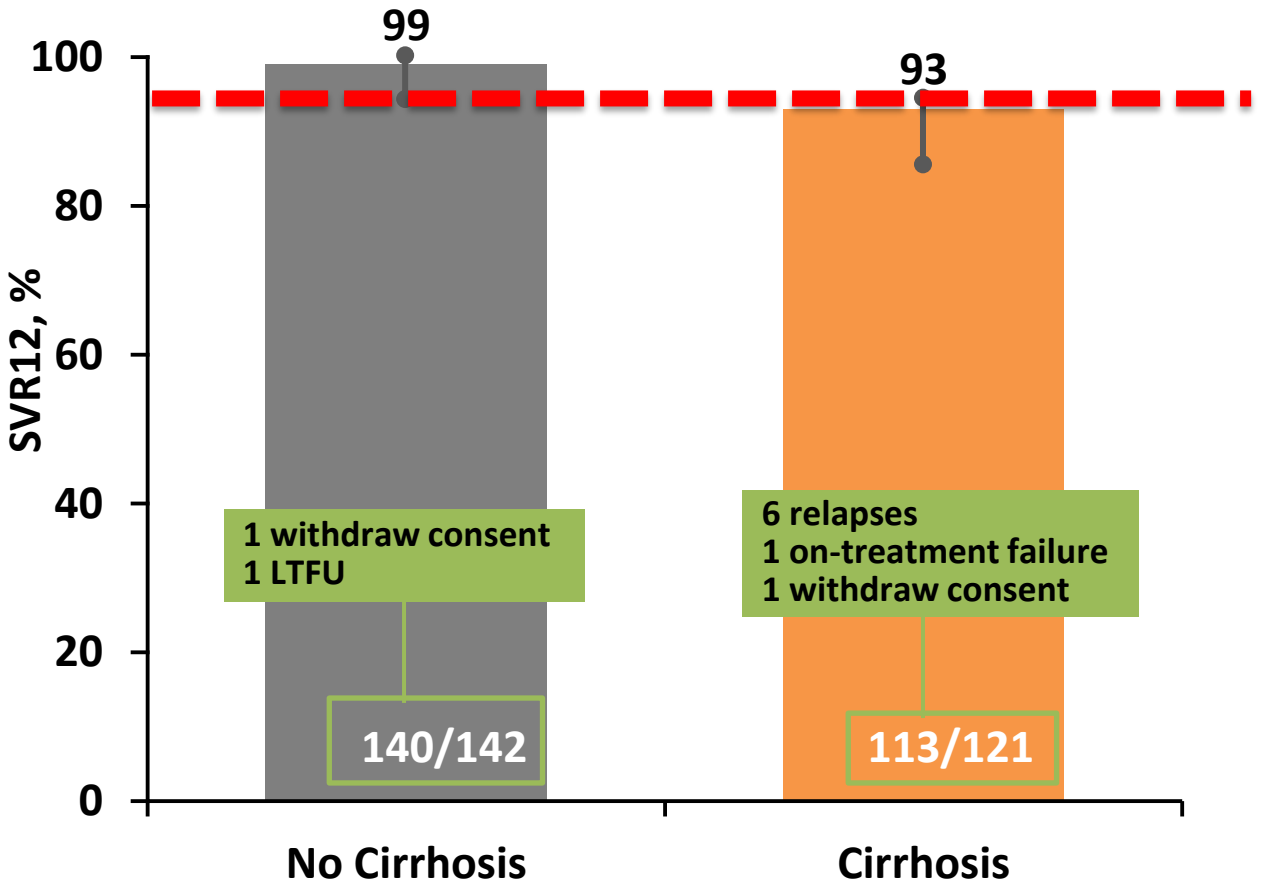
POLARIS-1 Study: Phase 3 Study of SOF/VEL/VOX as a Salvage Regimen in NS5A Experienced Patients with HCV Genotype 1 - 6

- Double-blind, randomized controlled trial
  - SOF/VEL/VOX for 12 weeks (n=263)
  - Placebo for 12 weeks (n=152)
- Male (76%) with mean age 58 years (27 to 84)
- Genotypes: 1a (38%, n=101), 1b (17%), 2 (2%) 3 (30%, n=78), 4 (8%), 5/6 (2%)
- Cirrhosis, 46% (n=121)
- Prior HCV treatment exposure
  - LDV, n= 133
  - DCV, n= 70
  - Ombitasvir (PrOD), n = 30
  - Other, n = 30

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

POLARIS-1 Study:
Results (SVR12) by Cirrhosis Status

SOF/VEL/VOX 12 Weeks (n=263)



Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

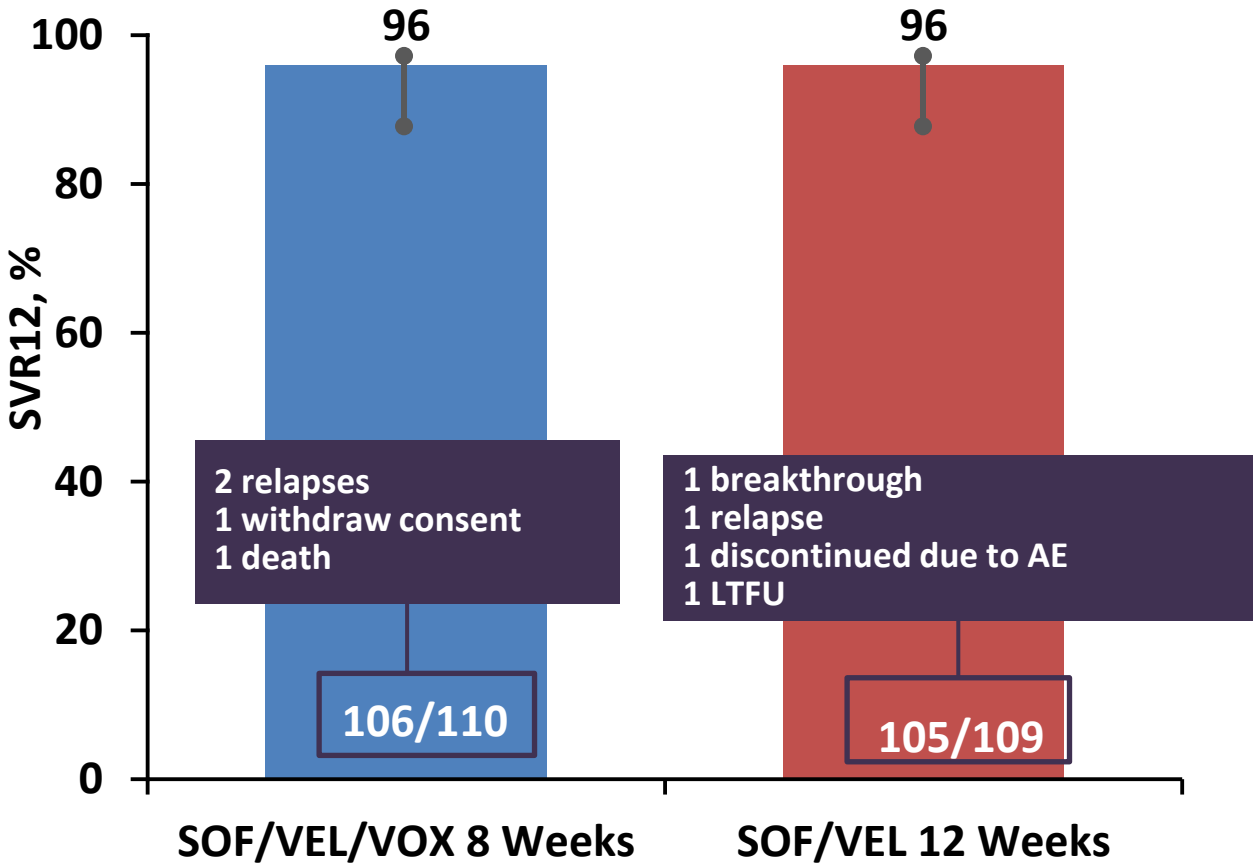
POLARIS-1 Study: Adverse Events

- Only 1 patient with cirrhosis who relapsed (gt 4) developed the NS5A Y93H
- Discontinue due to AE, 1 with SOF/VEL/VOX; 3 placebo

Patients, n (%)	SOF/VEL/VOX 12 Weeks n=263	Placebo 12 weeks n=152
Headache	66 (25)	26 (17)
Fatigue	56 (21)	30 (20)
Diarrhea	47 (18)	19 (13)
Nausea	37 (14)	12 (8)

Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

POLARIS-3: Results (SVR12)

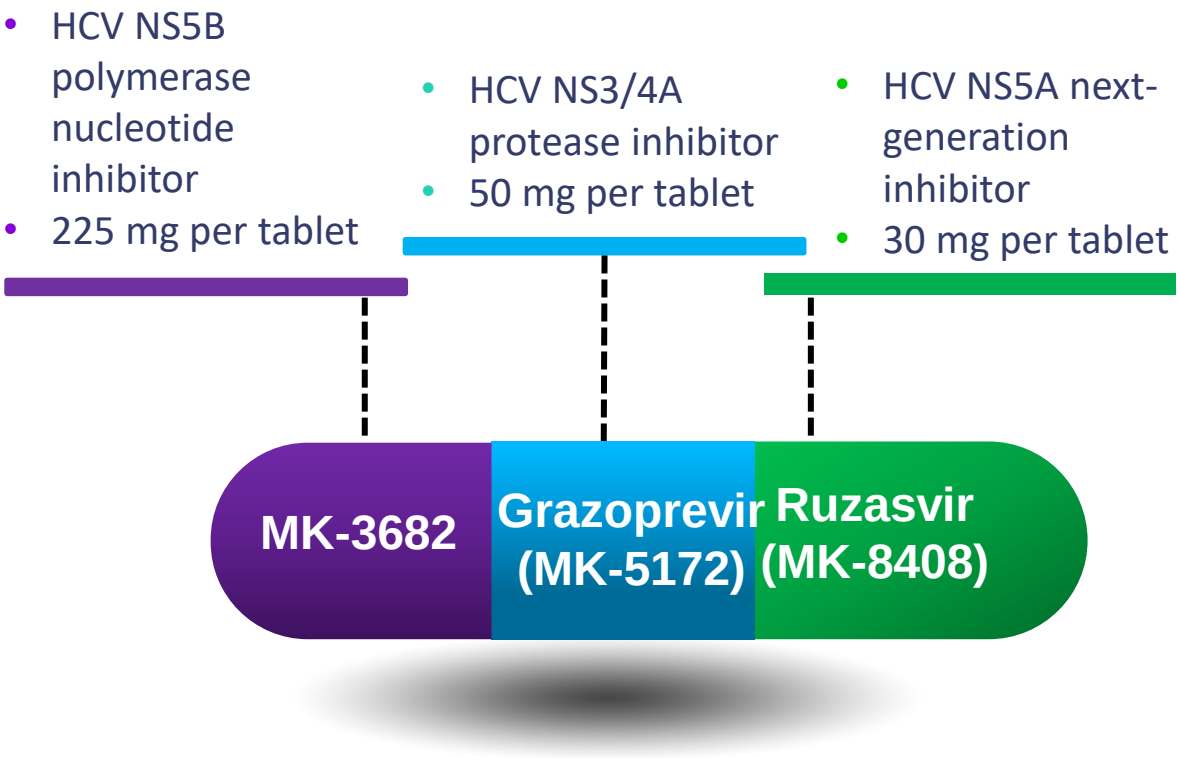


- There were 6 patients with Y93H in the SOF/VEL/VOX group and 4 in the SOF/VEL group; all achieved SVR12
- No treatment emergent RASs in the SOF/VEL/VOX group.
  In the SOF/VEL group, both virologic failures had Y93H

Foster G, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 258.

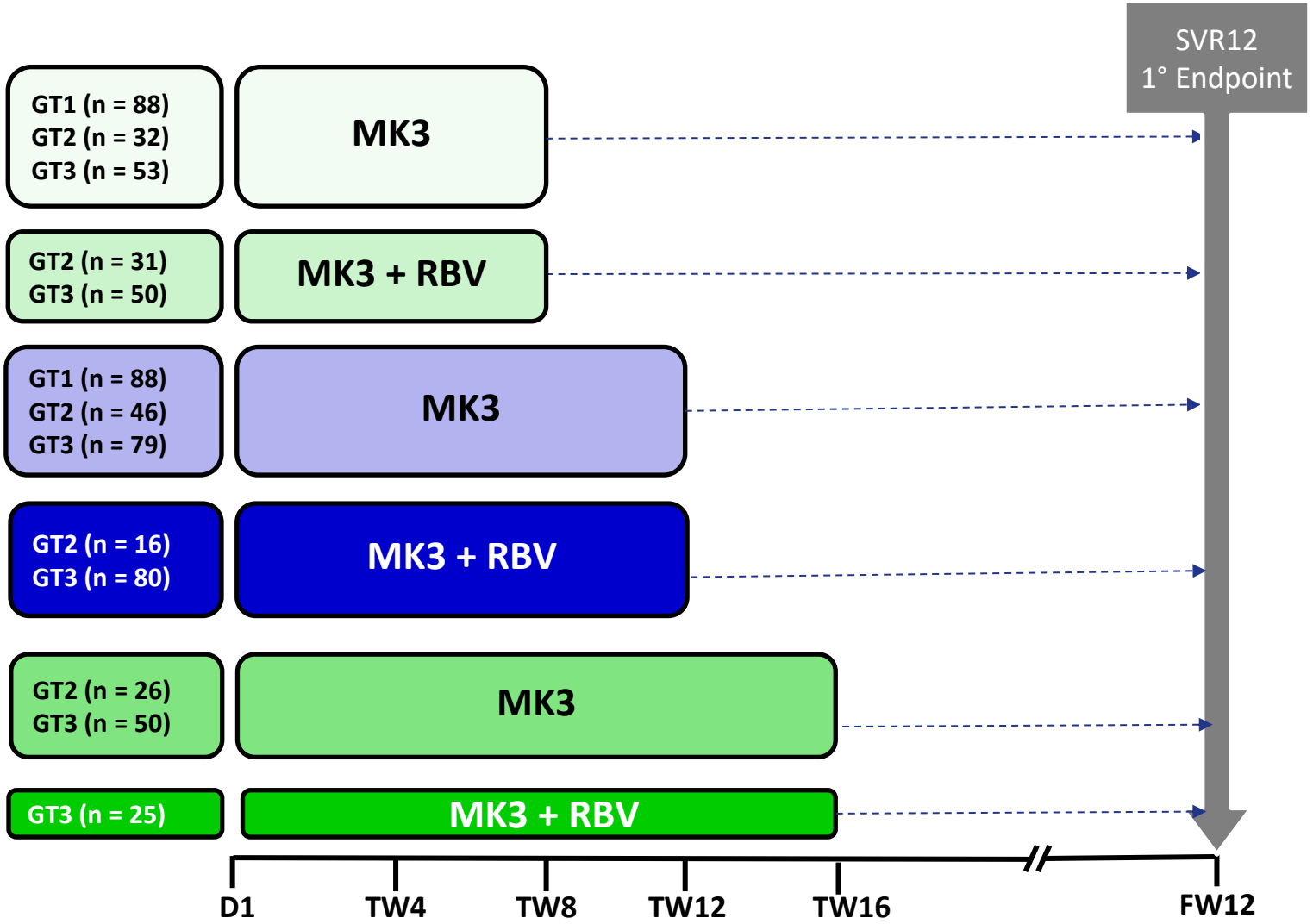
MK3: MK-3682/Grazoprevir/Ruzasvir

- **MK3 is a three-drug regimen formulated into a fixed-dose combination tablet. The regimen is given as two tablets, once-daily, without regard to food.**
- **Triplet also called MK-3682B**



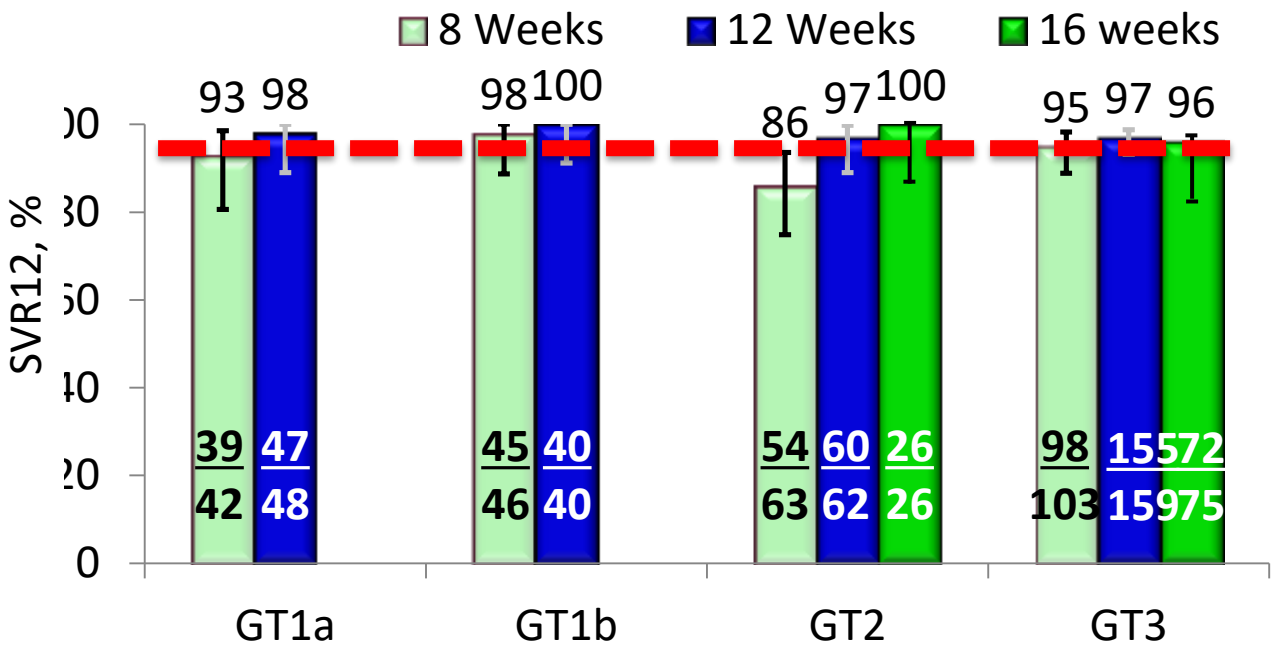
Lawitz E, et al. Abstract #110, AASLD 2016.

C-CREST Part B:
(MK3: MK-3682/Grazoprevir/Ruzasvir; N=664)



Lawitz E, et al. Abstract #110, AASLD 2016.

SVR12 by Genotype (Full Analysis Set): 8, 12 or 16 Weeks

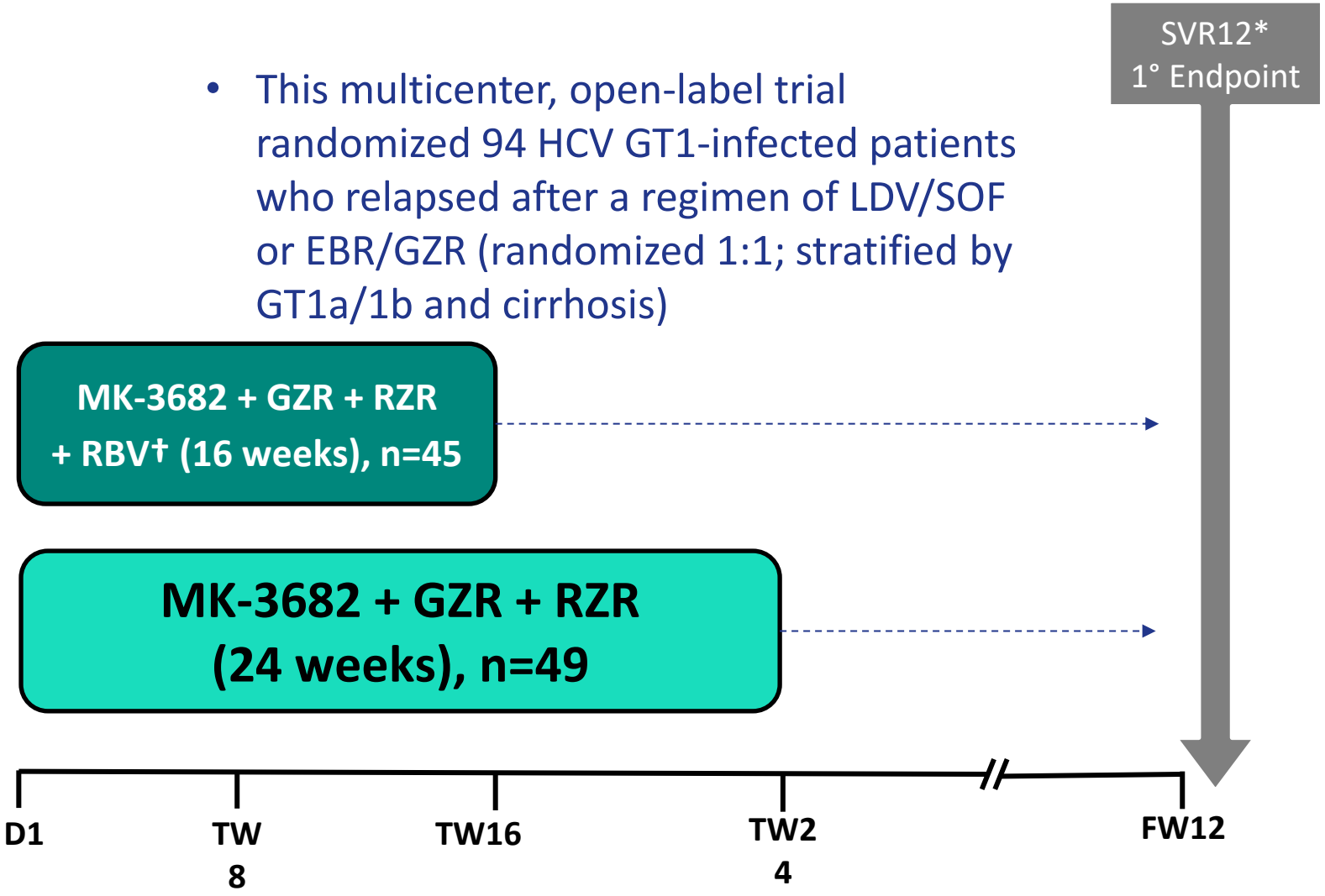


Relapse	**2**	**0**		**1**	**0**		**7**	**0**	**0**	**4**	**3**	**2**
Discontinuation (DR-AE)*	**0**	**0**		**0**	**0**		**1**	**0**	**0**	**0**	**0**	**0**
Reinfection*	**1**	**0**		**0**	**0**		**0**	**0**	**0**	**0**	**0**	**0**
Non-virologic failure*	**0**	**1**		**0**	**0**		**1**	**2**	**0**	**1**	**1**	**1**

Lawitz E, et al. Abstract #110, AASLD 2016.

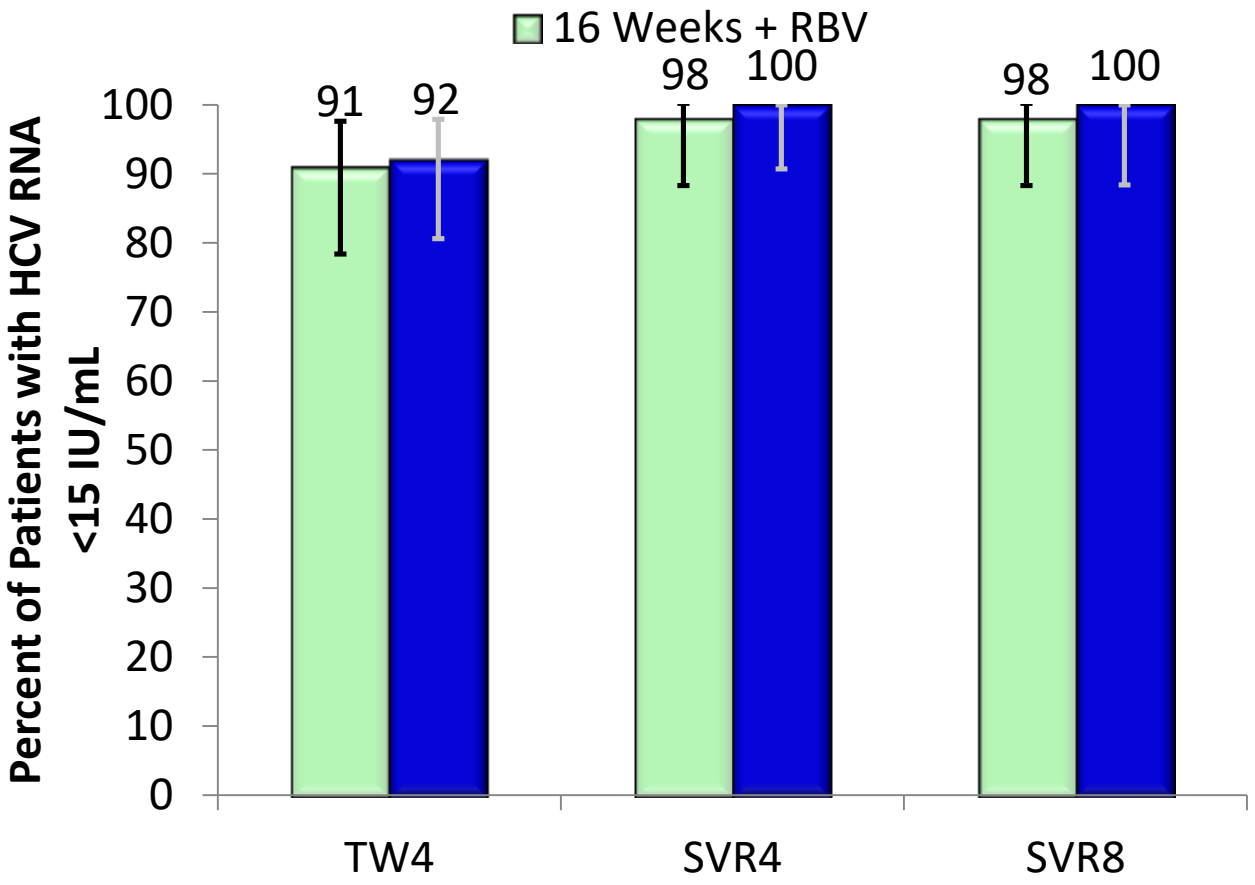
C-SURGE: Study Design

- This multicenter, open-label trial randomized 94 HCV GT1-infected patients who relapsed after a regimen of LDV/SOF or EBR/GZR (randomized 1:1; stratified by GT1a/1b and cirrhosis)



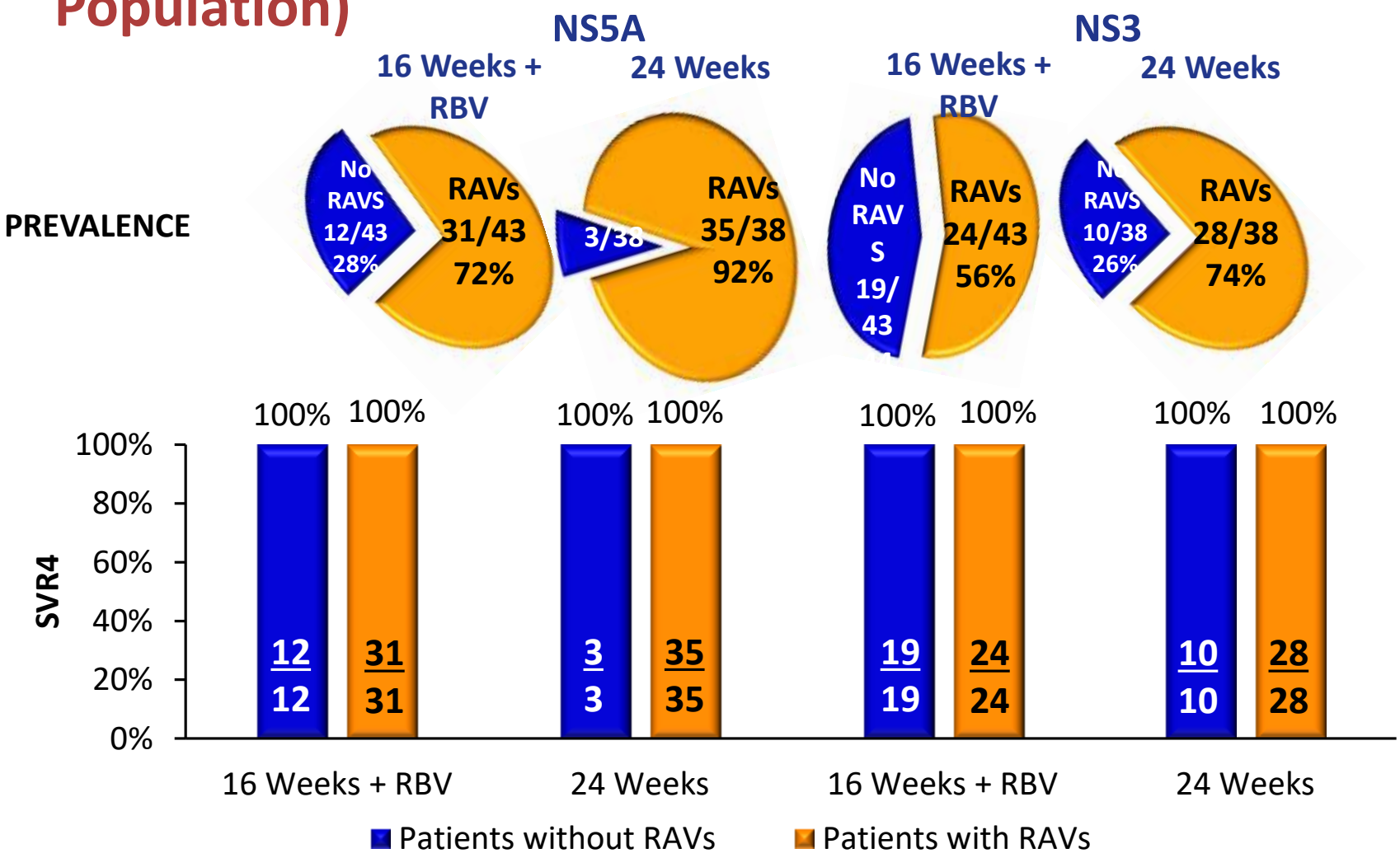
Wyles D, et al. Abstract #193, AASLD 2016.

C-SURGE: Results – Efficacy (Full Analysis Set)



Wyles D, et al. Abstract #193, AASLD 2016.

No Impact of Baseline NS5A or NS3 RAVs on SVR4 (Resistance Analysis Population)



SVR4=proportion of patients with HCV RNA <15 IU/mL at 4 weeks after end of treatment.
*RAVs detected by next-generation sequencing with 15% sensitivity; NS5A RAV: any change from wild-type at 4 positions (28, 30, 31, or 93); NS3 RAVs = any change from wild-type at 14 positions (36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175).
† Excludes 1 patient from the 16-week group who withdrew after receiving 3 doses of study medication; Includes 38 of 49 patients who have reached follow-up week 4.

C-SURGE 1

Glecaprevir (GLE)(ABT-493)/Pibrentasvir (PIB) (ABT-530): Known as G/P

In vitro:[1,2]

- Additive/synergistic antiviral activity
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg., positions 80, 155, and 168) and NS5A polymorphisms (eg., positions 28, 30, 31 and 93)

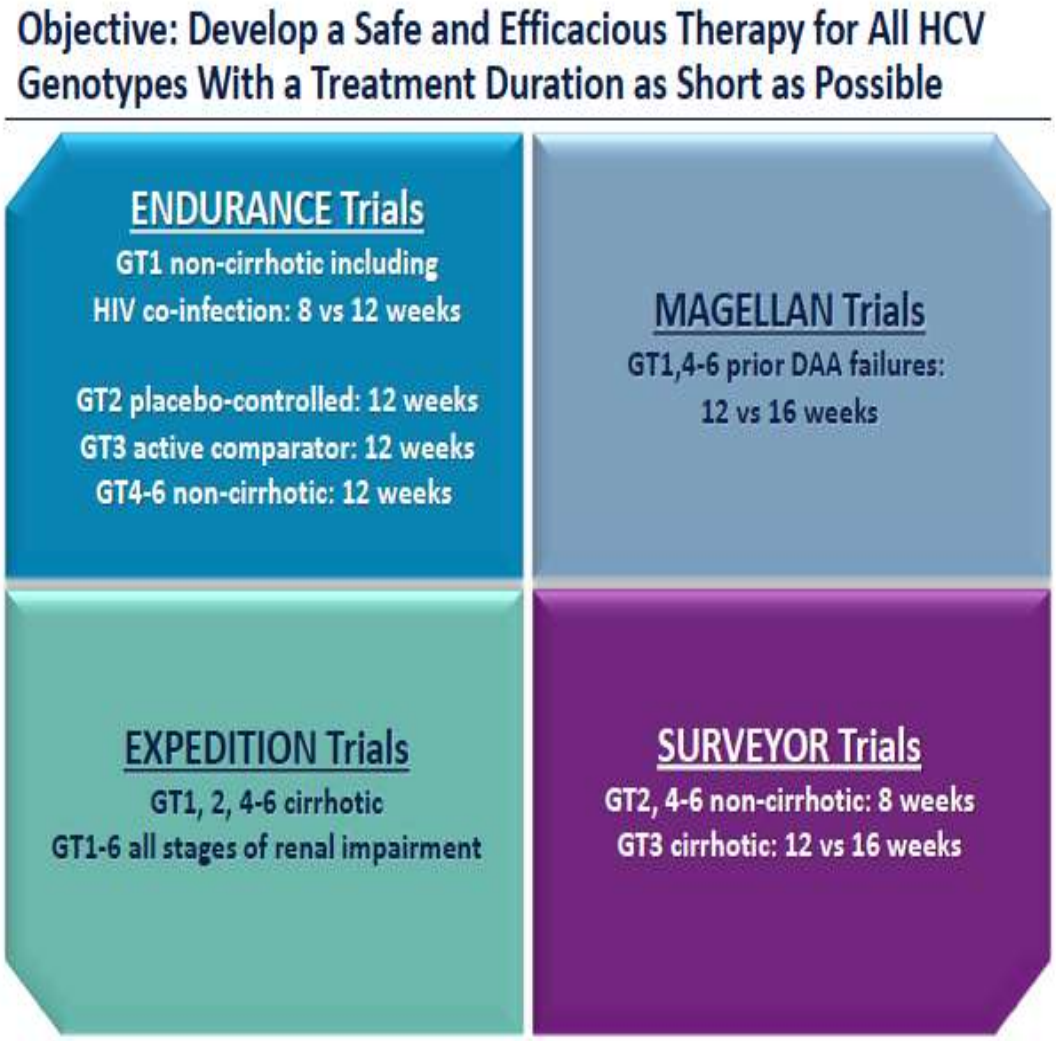
Clinical PK & metabolism:

- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. Abstract 636. CROI, 2014.
2. Ng TI, et al. Abstract 639. CROI, 2014.

Glecaprevir (ABT-493)/Pibrentasvir (ABT-530): Clinical Development Program



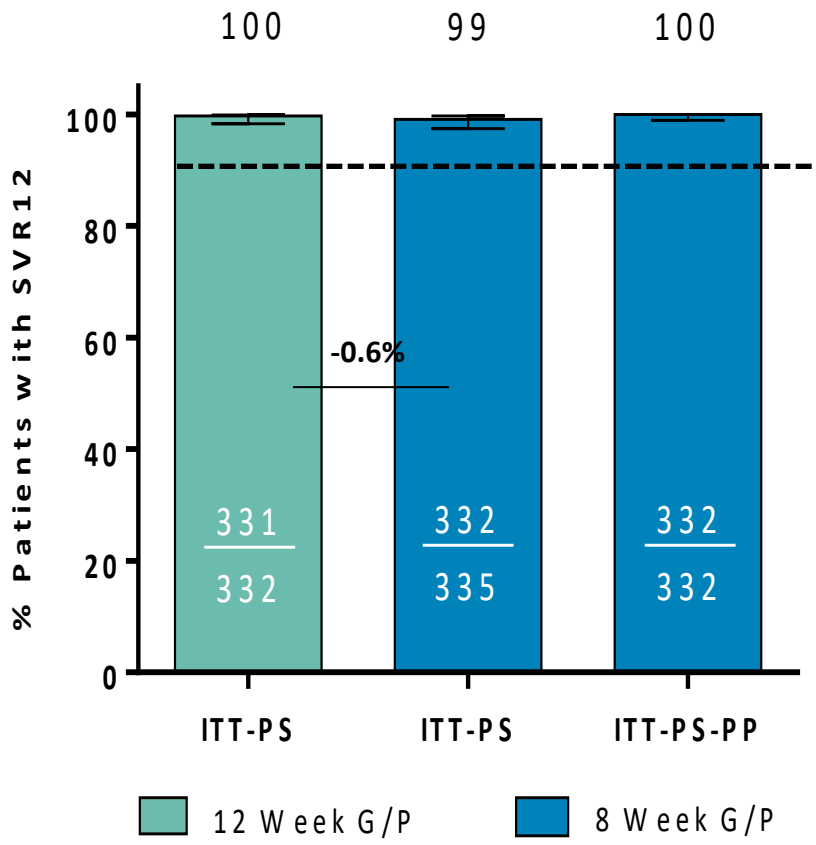
Glecaprevir (ABT-493)/Pibrentasvir (ABT-530)

Study Name	Patient Population	Duration	SVR_{12} Rate
ENDURANCE-1 (#253)	GT1 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN), and patients co-infected with HIV-1	8 Weeks	99% (n=348/351)
ENDURANCE-2 (#73)	GT2 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN)	12 Weeks	99% (n=195/196)
ENDURANCE-3	GT3 without cirrhosis, new to treatment	8 Weeks	95% (n=149/157)
ENDURANCE-4 (#114)	GT4, 5 or 6 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN)	12 Weeks	100% (mITT) GT4 (120/120) GT5 (26/26) GT6 (19/19)

Glecaprevir (ABT-493)/Pibrentasvir (ABT-530)

Study Name	Patient Population	Duration	SVR_{12} Rate
SURVEY OR-2 (Part 3) (#113)	GT3, with or without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN, SOF/RBV or pegIFN/SOF)	12-16 Weeks	TE noncirrhotic 91% (20/22) (12 weeks) 96% (21/22) (16 weeks) TN cirrhotic 98% (39/40) TE cirrhotic 96% (45/47)
SURVEY OR-2 (Part 4) (#LB-15)	GT2, 4, 5, 6 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN, SOF/RBV or pegIFN/SOF)	8 Weeks	97% (n=196/203)
EXPEDITION-IV (#LB-11)	GT1-6; renal impairment, with or without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN, SOF/RBV or pegIFN/SOF)	12 Weeks	SVR4 99% (N-103/104)

GLE/PIB x 8 Weeks or 12 Weeks in GT1 Noncirrhotics



Primary endpoint threshold: 91%

ITT-PS: ITT population, excluding HIV co-infected *and* SOF-experienced patients

ITT-PS-PP: ITT-PS population excluding patients with premature D/C or virologic failure prior to week 8, and missing data in the SVR12 window

Zeuzem S, et al. Abstract #253, AASLD 2016.

Most Difficult-to-Cure: HCV Genotype 3

HCV GT3 has become the most difficult-to-cure genotype

Current AASLD-recommended treatment options for patients with prior HCV treatment experience (TE) and/or cirrhosis include:

Sofosbuvir (SOF) + Daclatasvir

- **Recommend 24 weeks with ribavirin (RBV) for patients with:**
  - » **Cirrhosis**
  - » **Prior TE and cirrhosis**

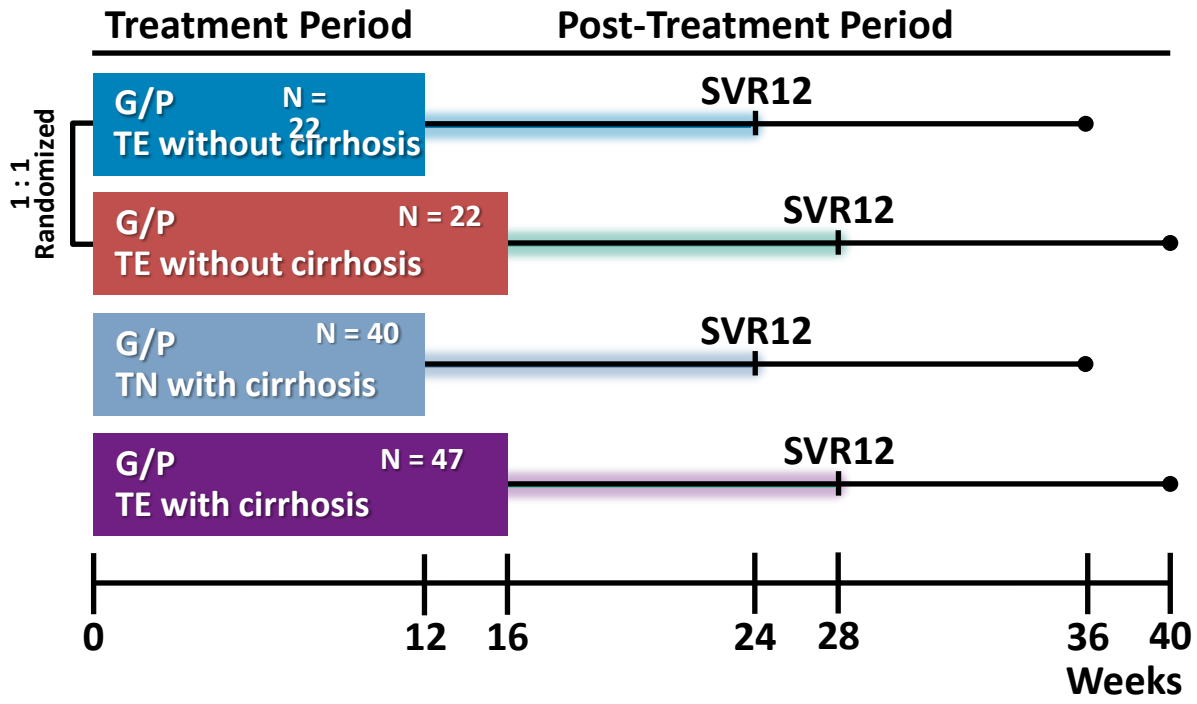
SOF + Velpatasvir

- **Recommend addition of RBV for patients with:**
  - » **Cirrhosis or TE (if testing shows Y93H baseline polymorphisms)**
  - » **Prior TE and cirrhosis**

Improved ribavirin (RBV)-free treatment options for GT3 are needed, particularly for those with prior HCV TE and/or compensated cirrhosis

Wyles D, et al. Abstract #113, AASLD 2016.

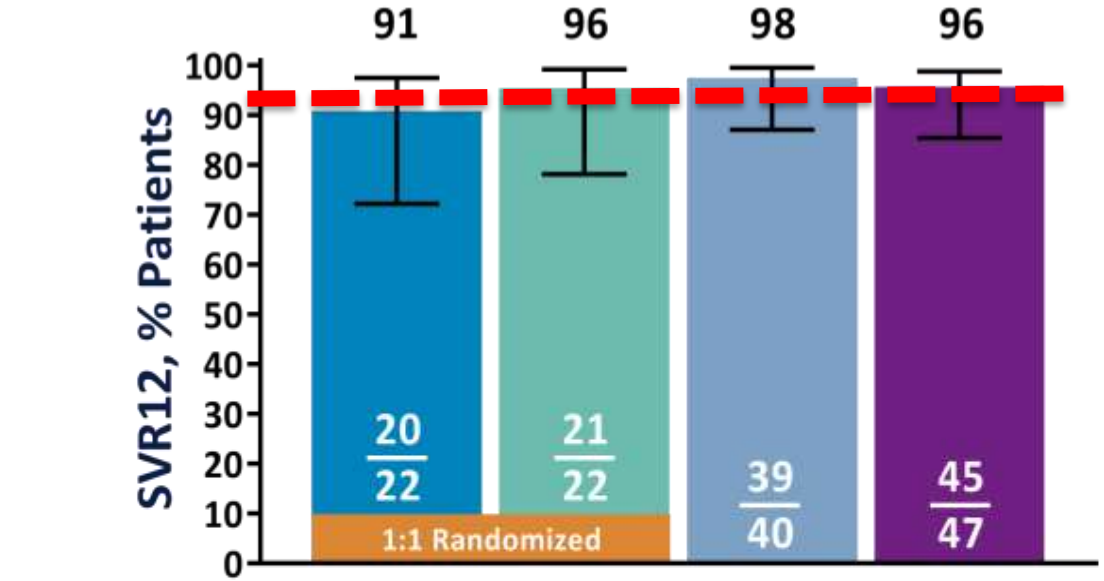
SURVEYOR-II Part 3: Study Design and Patient Population



- Included GT3
- Patients without cirrhosis or with compensated cirrhosis
- Excluded prior treatment with HCV DAA other than SOF
- Excluded HBV or HIV coinfection

Wyles D, et al. Abstract #113, AASLD 2016.

SURVEYOR-II, Part 3: SVR 12 With GLE/PIB x 12 or 16 Weeks



Weeks	12	16	12	16
Cirrhosis	-	-	+	+
T-Experience	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles D, et al. Abstract #113, AASLD 2016.

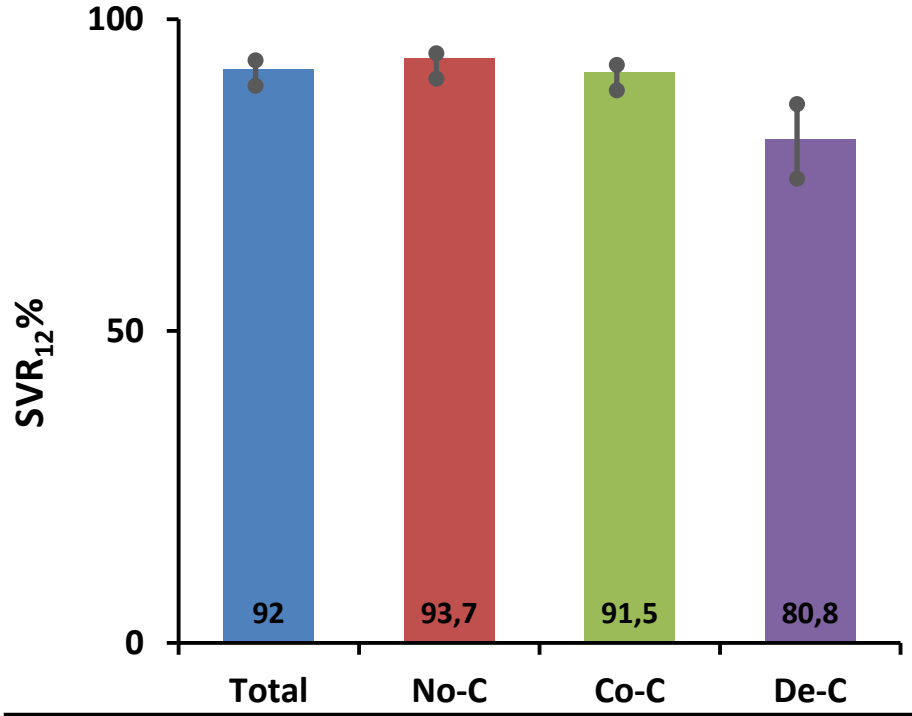
HCV Therapies in Specific Populations

Madrid-CoRe (Madrid Coinfection Registry): Baseline Characteristics

Variable	N = 2030
Age years – median (IQR)	50 (47 – 54)
Male – n (%)	1591 (78.4)
CD4+ T cells/µL – median (IQR)	570 (356 – 785)
cART – n (%)	1930 (95.1)
Liver disease severity	
No cirrhosis – n (%)	1125 (55.4)
Compensated cirrhosis – n (%)	754 (37.1)
Decompensated cirrhosis – n (%)	146 (7.2)
Unknown – n (%)	5 (0.3)
History of hepatocellular carcinoma – n (%)	15 (0.7)
Liver transplantation – n (%)	17 (0.8)
Liver transplantation waiting list – n (%)	7 (0.3)
Severe extrahepatic manifestations – n (%)	143 (7.0)
Anti-HCV – naïve – n (%)	1256 (61.9)
Liver stiffness kPa – median (IQR)	11.4 (8.1 – 20.2)

Berenguer J, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 78.

Treatment Outcomes by Severity of Liver-Disease



No-C = no cirrhosis
Co-C = compensated cirrhosis
De-C = decompensated cirrhosis

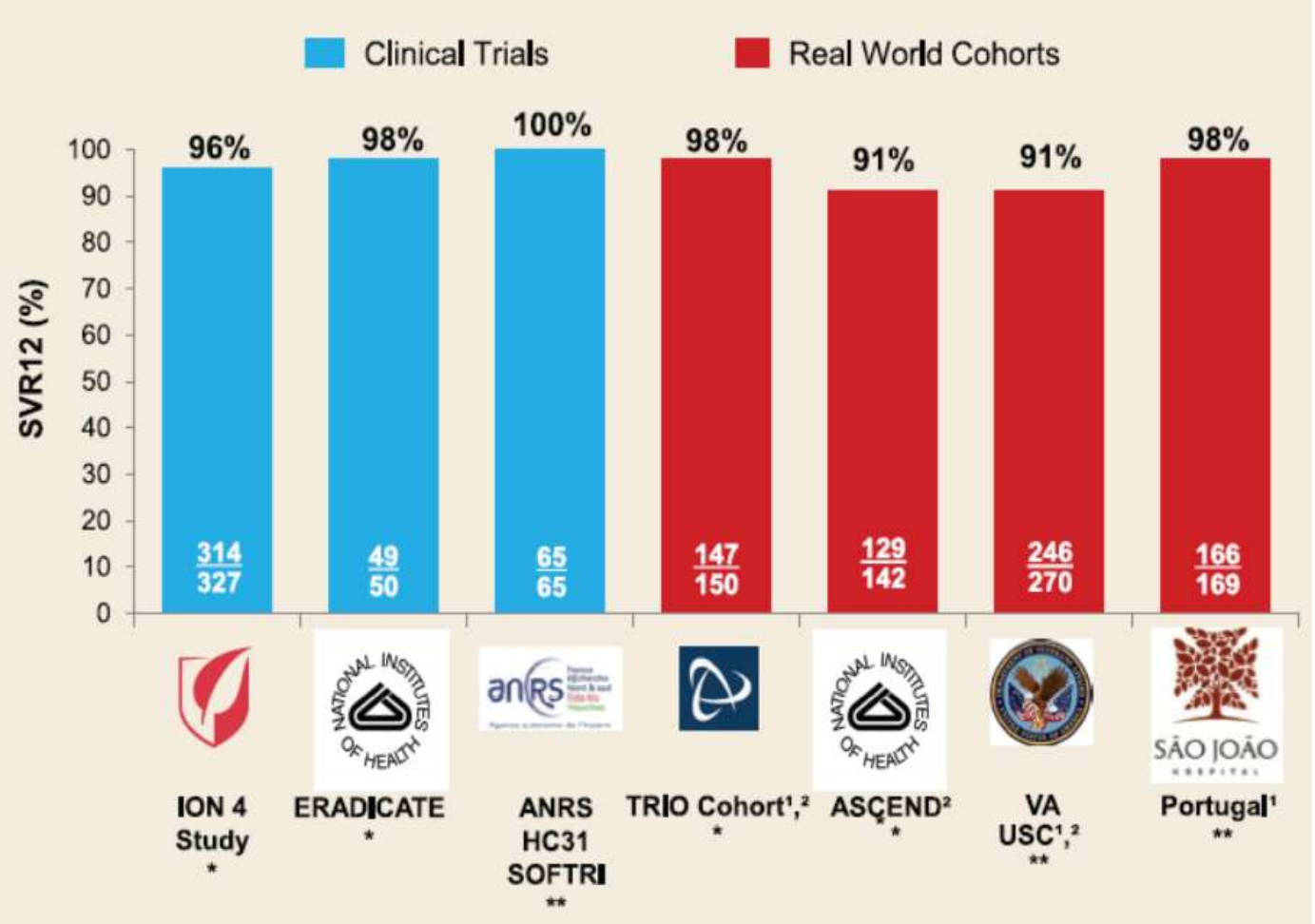
Decompensated cirrhosis, SOF+SMV, SOF+RBV, SMV+DCV were independently associated with treatment failure

No.	2030	1125	754	146
SVRITT	1867 (92.0)	1054 (93.7)	690 (91.5)	118 (80.8)
SVR (95% CI)	(90.7 – 93.1)	(92.1 – 95.0)	(89.3 – 93.4)	(73.5 – 86.9)
Relapse	89 (4.4)	36 (3.2)	36 (4.8)	17 (11.6)
Breakthrough	5 (0.2)	3 (0.3)	1 (0.1)	1 (0.7)
DC Due to AE	14 (0.7)	7 (0.6)	5 (0.7)	2 (1.4)
DC Other	36 (1.8)	23 (2.0)	10 (1.3)	3 (2.0)
Death	19 (0.9)	2 (0.2)	12 (1.6)	5 (3.4)

* Severity of liver disease was not evaluated in 5 patients

Berenguer J, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 78.

SVR12 in GT 1 HIV/HCV Coinfected Patients Treated with LDV/SOF for 12-24 weeks: Clinical Trials Compared to Real-World Cohorts

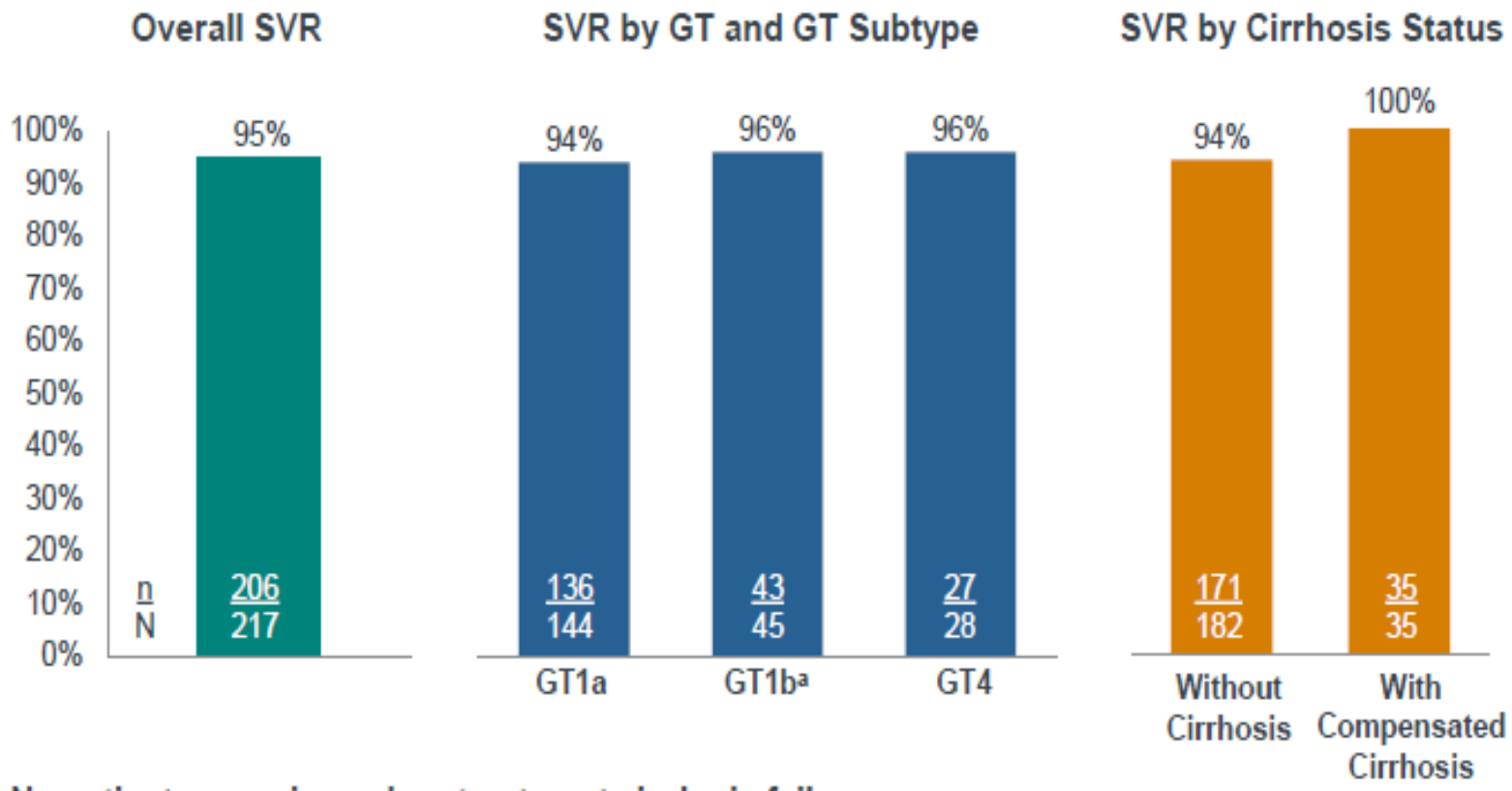


†ITT analysis in GT1 patients; *ITT analysis; ** Per Protocol; [1] ±RBV; [2] small number of patients may have received 8 weeks of LDV/SOF

Naggie S, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 892.

Elbasvir/grazoprevir): efficacia in pazienti TN con coinfezione HCV/HIV-1 G1 o G4 — C-EDGE COINFECTION

SVR Rates for HCV/HIV-1 Coinfected Patients Receiving 12 Weeks of ZEPATIER

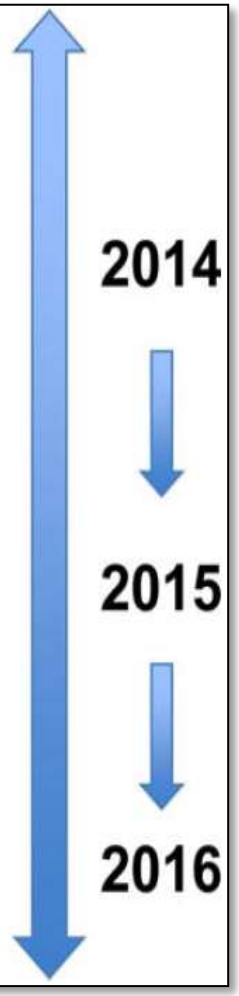


- No patients experienced on-treatment virologic failure
- 3% (7/217) of patients relapsed after treatment

HCV = hepatitis C virus; HIV = human immunodeficiency virus; GT = genotype; SVR = sustained virologic response.
a Includes genotype 1 subtypes other than 1a or 1b.

DAA: dose, creatinina clearance, utilizzo in pazienti con Malattia Cronica Renale (CKD)

Medication	Dose	Clearance	Use in CKD Stage IV and V
Sofosbuvir	400 mg daily	Renal 81% GI 15%	eGFR 15-29 ml/min: Not recommended. eGFR < 15 ml/min: Not recommended. Limited data available.
Simeprivir	150 mg daily	Renal < 1%	eGFR 15-29 ml/min: Dose adjustment not required. eGFR < 15 ml/min: Not recommended. Limited data available.
Daclastavir	60 mg daily. Use with Sofosbuvir	Renal 7% GI 88%	eGFR 15-29 ml/min: Dose adjustment not required. eGFR < 15 ml/min: Dose adjustment not required.
Ledipasvir	90 mg daily	Renal 1% GI 86%	eGFR 15-29 ml/min: Dose adjustment not required. eGFR < 15 ml/min: Not recommended.
Ombitasvir/ Paritaprevir/ ritonavir ---------- Dasabuvir	12.5 mg/ 75 mg/ 50 mg x 2 tabs ---------- 250 mg x 2 tabs	Renal <2% GI 90%	eGFR 15-29 ml/min: Dose adjustment not required. eGFR < 15 ml/min: Dose adjustment not required. Not studied in dialysis patients – limited data.
Grazoprevir/ Elbasvir	100 mg/50 mg daily	Renal <1%	eGFR 15-29 ml/min: Dose adjustment not required. eGFR < 15 ml/min: Dose adjustment not required. Dialysis population studied.

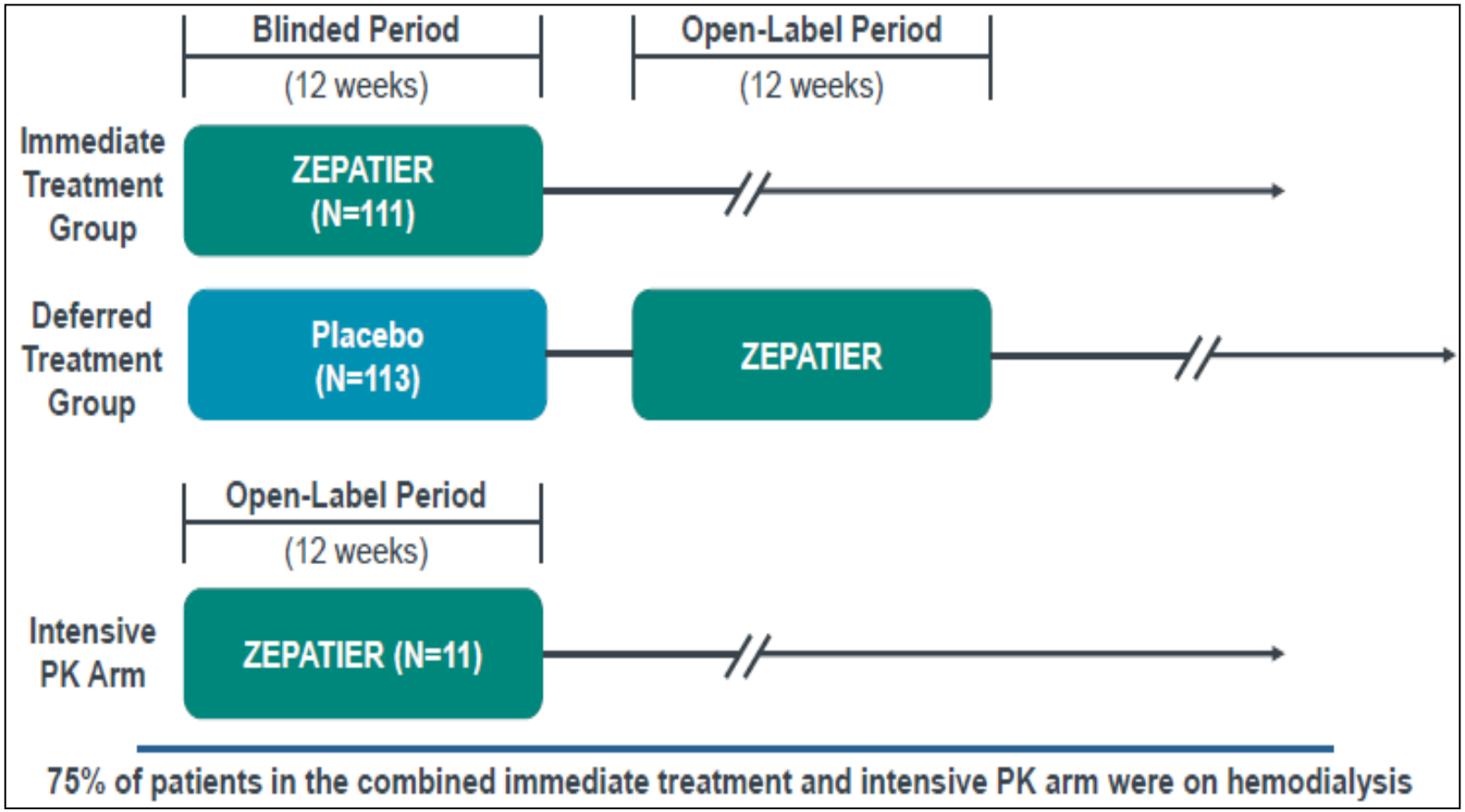


Abbreviations: eGFR, estimated glomerular filtration rate; GI, gastrointestinal.

Pedraza, Ladino, and Roth. CLINICAL LIVER DISEASE, VOL 7, NO 5, MAY 2016

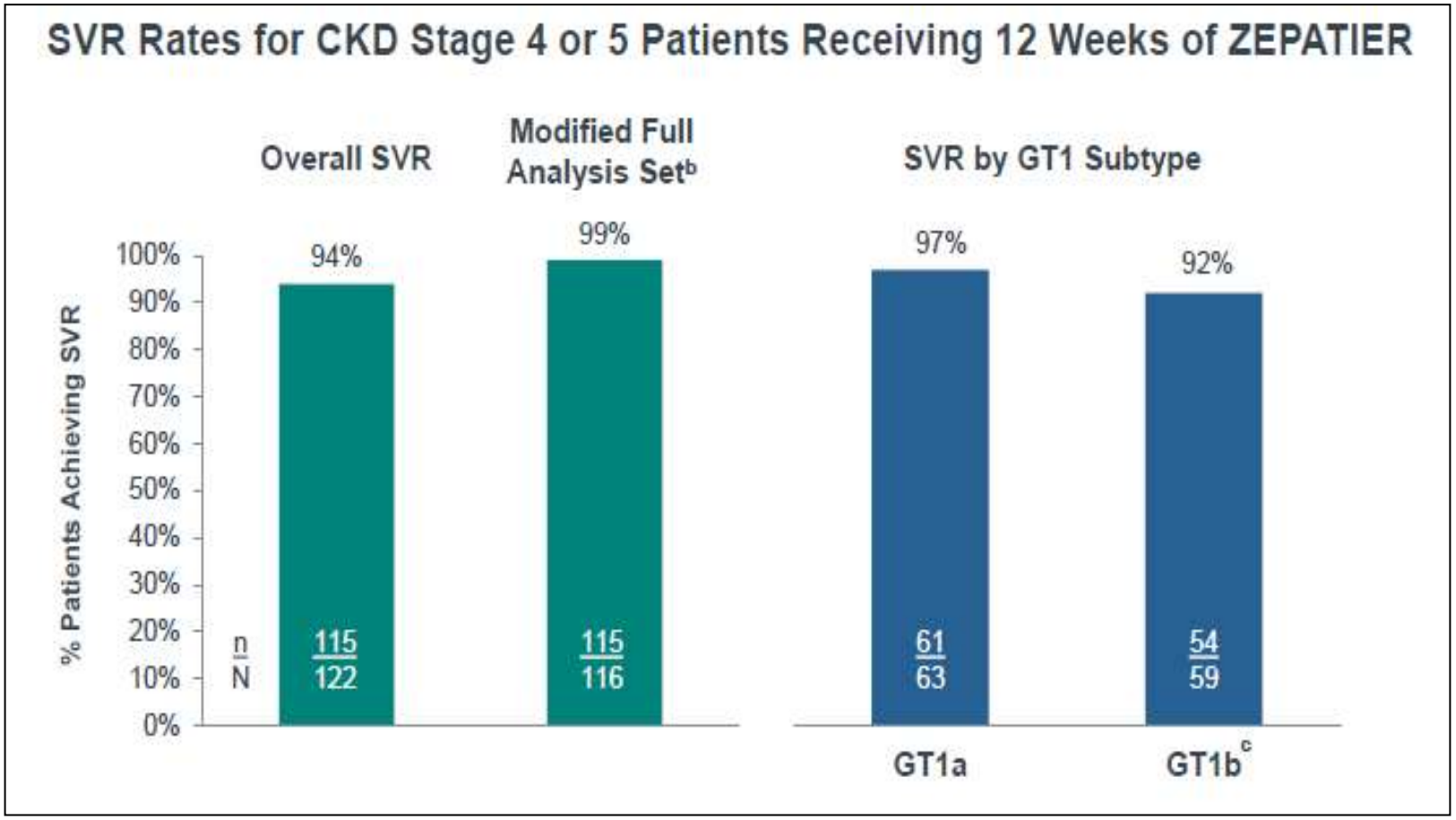
Elbasvir/grazoprevir in pazienti HCV G1 con Malattia Cronica Renale (CKD) avanzata: Disegno dello Studio C-SURFER [1,2]

Treatment-Naive or Treatment-Experienced [a] HCV GT1 Patients With or Without Cirrhosis With Advanced CKD (Stage 4 or 5)[b]



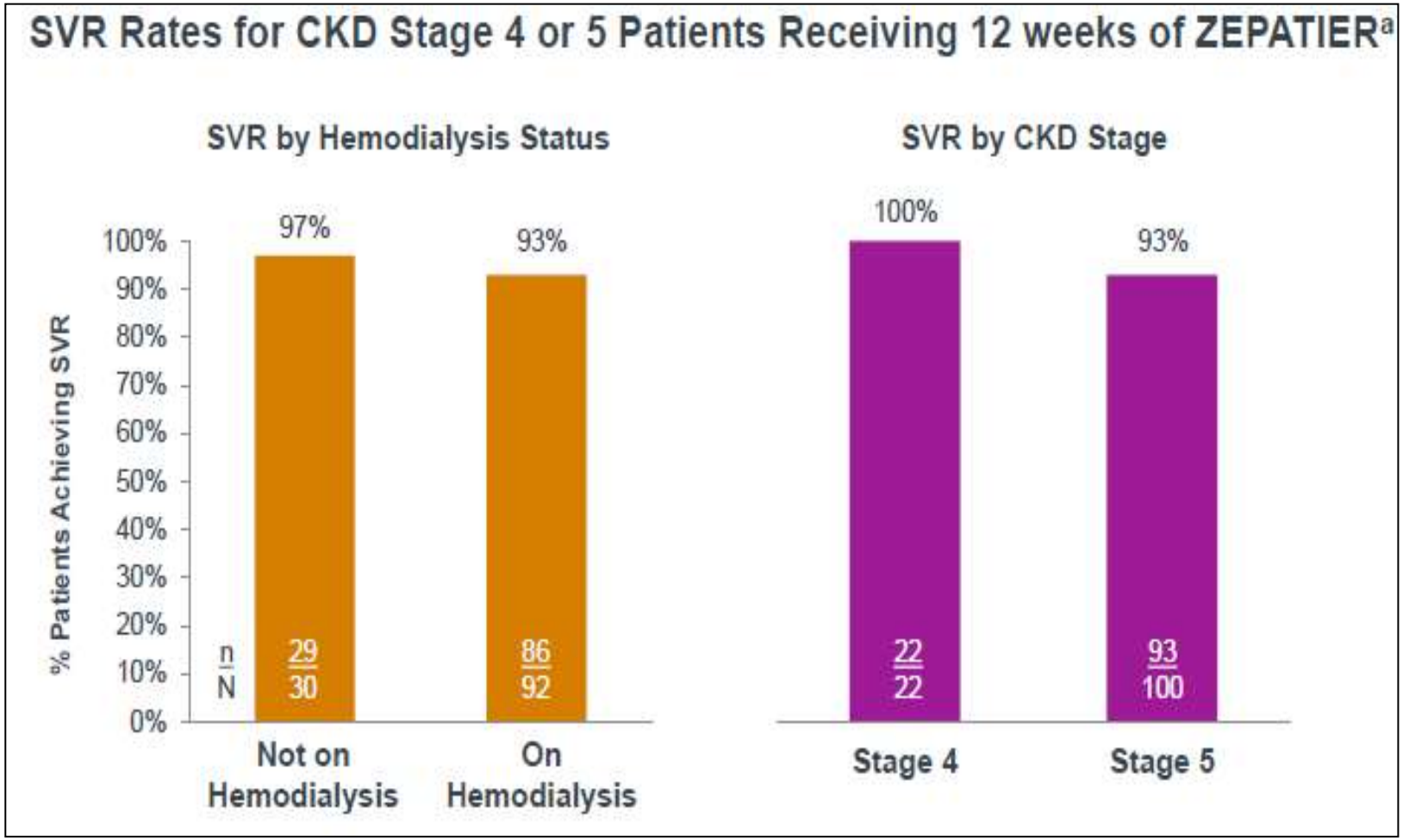
a Patients who failed treatment with IFN or pegIFN+/-RBV
b Stage4 CKD was defined as eGFR15-29 ml/min/1.73 m2. Stage 5 CKD was defined as eGFR<15 ml/min/1.73 m2
1. Roth D et al. Lancet. 2015;386:1537–1545; 1. ZEPATIER RCP.

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.

Elbasvir/grazoprevir: stratificazione dati di Efficacia in pazienti HCV G1 con CKD Stadio 4 o 5 — C-SURFER [1]

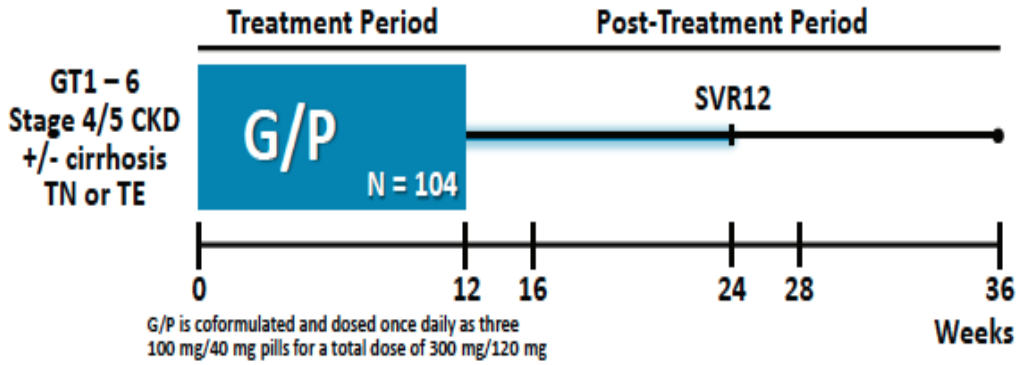


a Immediate treatment and pharmacokinetic arm results are presented.

1. Roth D et al. Lancet. 2015;386:1537–1545.

EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults with Renal Impairment and Chronic Hepatitis C Virus Genotype 1 – 6 Infection

EXPEDITION-4: Objective and Study Design



Objective

- Determine the efficacy and safety of pangenotypic G/P for 12 weeks in patients with HCV GT1-6 and stage 4 or 5 chronic kidney disease (CKD)

Endpoints

- **Efficacy:** SVR12 defined as HCV RNA below the lower limit of quantification (LLOQ; 15 IU/mL)
- **Safety:** adverse events (AEs) and laboratory abnormalities

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

EXPEDITION-IV: Baseline Demographics and Clinical Characteristics

Characteristic	G/P N = 104
Male, n (%)	79 (76)
Black race, n (%)	26 (25)
Age, median years (range)	57 (28 – 83)
BMI, median kg/m^2 (range)	26 (18 – 45)
IL28B non-CC genotype, n (%)	80 (77)
HCV RNA, median $\log_{10}$ IU/mL (range)	5.9 (3.4 – 7.5)
Concomitant PPI use, n (%)	43 (41)

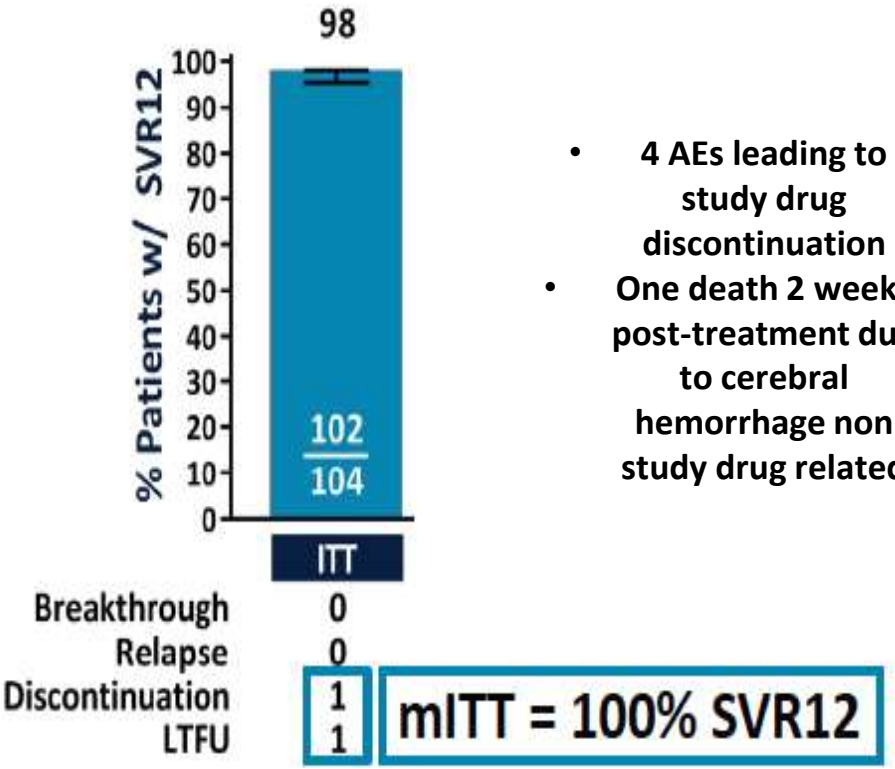
Characteristic, n (%)	G/P N = 104
HCV genotype	
1a / 1b / other	23 (22) / 29 (28) / 2 (2)
2	17 (16)
3	11 (11)
4 / 5 / 6	20 (19) / 1 (1) / 1 (1)
Prior treatment history	
Naïve	60 (58)
IFN/pegIFN ± RBV	42 (40)
SOF + RBV ± pegIFN	2 (2)
Compensated cirrhosis	
Yes	20 (19)
No	84 (81)
CKD stage	
Stage 4	13 (12)
Stage 5	91 (88)
Hemodialysis	85 (82)

Patients were enrolled across 9 countries:

Australia, Belgium, Canada, France, Greece, Italy, New Zealand, the United Kingdom, and United States

Gane E, et al. 67th AASLD;

EXPEDITION-IV: Results – SVR12 by intent-to-treat (ITT) Analysis



- 4 AEs leading to study drug discontinuation
- One death 2 weeks post-treatment due to cerebral hemorrhage non study drug related

Gane E, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-11.

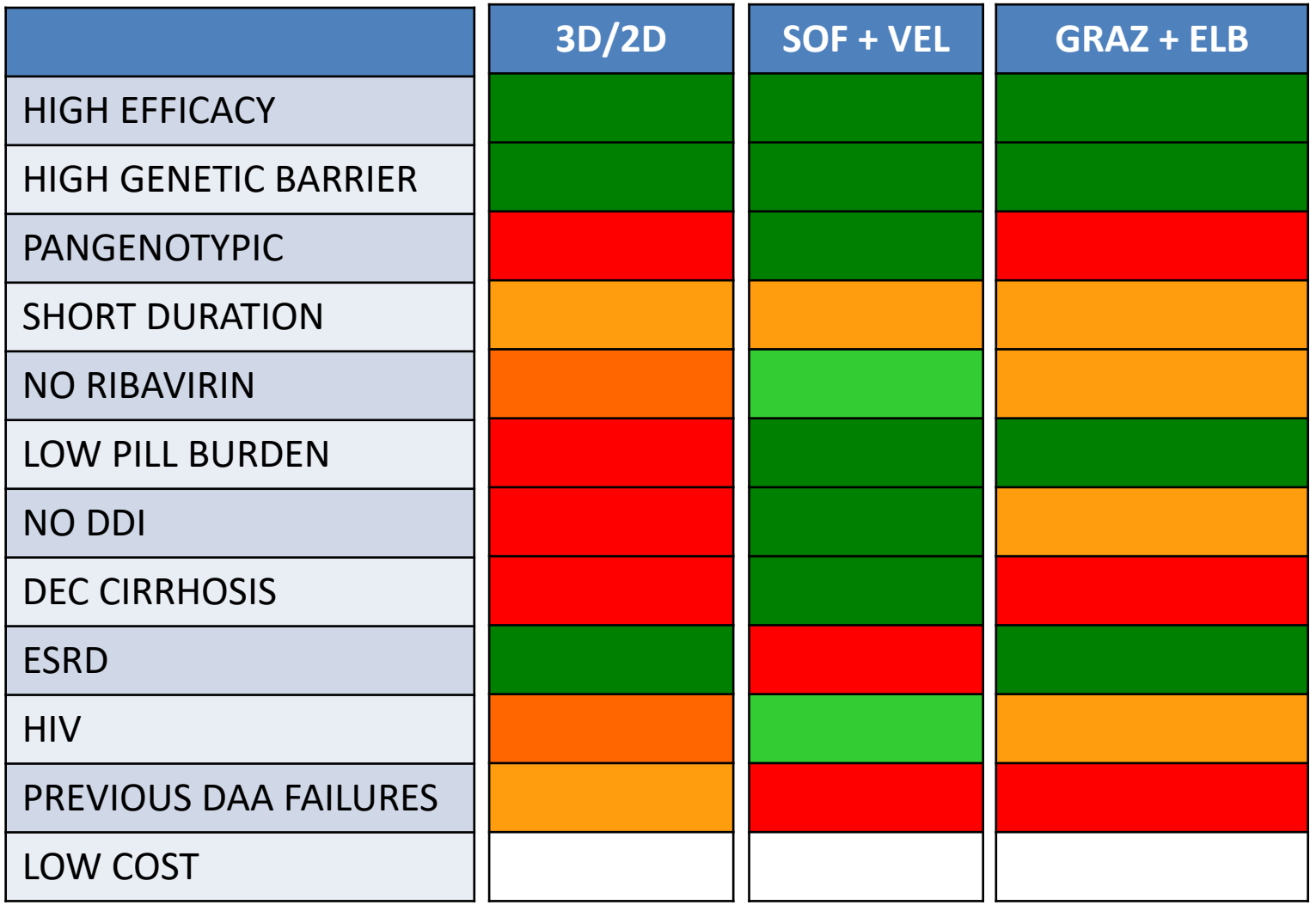
Where we go: the future 10 commandments for the magic drug

1. HIGH **E**FFICACY
2. LOW **R**ESISTANCE (high genetic barrier)
3. FOR **A**LL GENOTYPES
4. SHORT **D**URATION
5. TOLERAB**I**LITY & NO R**i**BAVIRIN
6. PHARMA**C**OKINETIC (low pill burden)
7. ONLY OR**A**L REGIMEN or 1 SHOT INJECTION (IFN free)
8. NO OR FEW DRUG IN**T**ERACTION
9. AVAILABLE: C**I**RRHOSIS, ESRD, HIV-HCV…
10. C**O**ST REDUCTIO**N** (access program)

HCV ERADICATION WORLDWIDE

Courtesy of T Asselah.

DO WE HAVE PERFECTOVIR ?



Upcoming treatment options in HCV

Combo	NS5 A	NS3 /NS 4	NUC	Activity on genotypes	Need for RBV	Treatment duration	ESRD?
Glecaprevir (ABT 493) + Pibrentasvir (ABT 530) G/P				All	No	8 weeks NS5A TN NC pangenoypic) 12 w NS5A TE & C	YES
Sofosbuvir + Velpatasvir + Voxilaprevir (GS5897)				All	No	8 weeks HCV G3 12 weeks NS5A TE	NO
Grazoprevir + Ruzasvir (MK 8408) + MK 3682				All	No	?	?
Odalasvir, Simeprevir, AL 335				?	?	?	?

WILL WE HAVE PERFECTOVIR ?

	GLEC+PIB (G/P)	SOFO+VEL+VOX	GRAZ+Ruzasvir +MK 3682
HIGH EFFICACY			
HIGH BARRIER			
PANGENOTYPIC			
SHORT DURATION			
NO RIBAVIRIN			
LOW PILL BURDEN			
NO DDI			
DEC CIRRHOSIS			
ESRD			
HIV			
DAA FAILURES			
LOW COST			

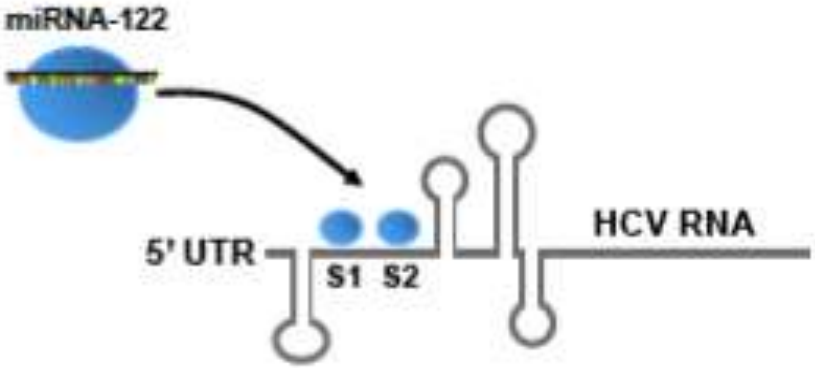
Hepatitis C Virus and miR-122
Introduction

MiR-122

- Highly conserved liver-specific miRNA
- Key regulator of cholesterol and fatty-acid synthesis [1,2]
- Important host factor for hepatitis C virus replication

MiR-122 and HCV RNA

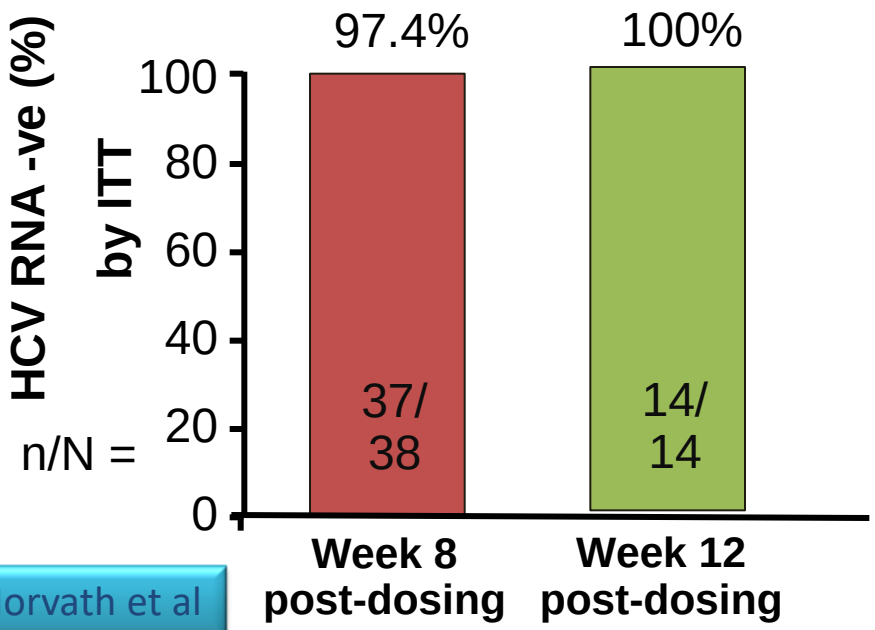
- 5′ UTR contains two highly conserved miR-122 binding sites (S1 and S2) [3,4]
- MiR-122 binding promotes HCV RNA stability and accumulation [3,5], and protects the HCV genome from degradation [6,7,8]



1. Krützfeldt et al, *Nature* 2005
2. Esau et al, *Cell Metab* 2006
3. Jopling et al, *Science* 2005
4. Jopling et al, *Cell Host Microbe* 2008
5. Lanford et al, *Science* 2010
6. Machlin et al, *PNAS* 2011
7. Sedano et al, *Cell Host Microbe* 2014
8. Li et al, *J. Virol* 2015

RG-101 IN COMBINATION WITH 4 WEEKS OF ORAL DIRECT ACTING ANTIVIRAL THERAPY ACHIEVES HIGH VIROLOGIC RESPONSE RATES IN TREATMENT NAÌVE GENOTYPE 1 AND 4 CHRONIC HEPATITIS C PATIENTS: INTERIM RESULTS FROM A RANDOMISED, MULTICENTER, PHASE 2 STUDY

- 79 naïve, non-cirrhotic patients with chronic GT1 or 4 HCV infection enrolled (mean age 45.0 years, 54.4% females, 86.1% F0/F1, 77.2% HCV GT1, mean baseline viral load 5.8 log10 IU/mL)
- Pts. received a 2 mg/kg subcutaneous (SC) injection of RG-101 on Day 1, with 4 weeks of an oral DAA (either ledipasvir/sofosbuvir, simeprevir, or daclatasvir) followed by a second 2 mg/kg SC injection of RG-101 on Day 29



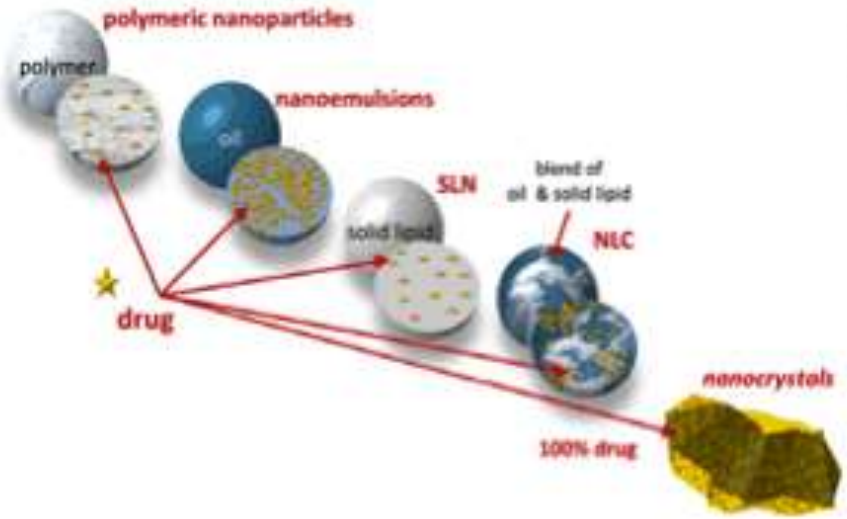
- Most frequent AEs: headache (11.4%) and fatigue (11.4%)
- No severe AEs,

2 injections of RG-101 with a 4 week course of a DAA are well tolerated and obtain high virologic response rates at 8 and 12 weeks posttreatment, suggesting an effective brief curatve regimen

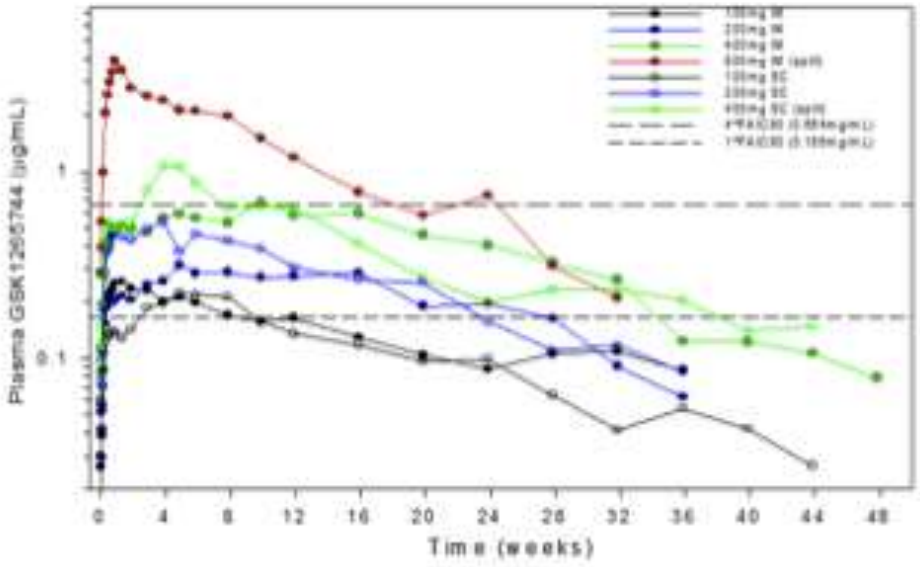
GS08 G. Horvath et al

Long-acting nanoformulations of antiviral drugs for treatment and prevention of infection

- Drug nanocrystal suspended in liquid = nanosuspension
  - Nano-dimensions vastly increase drug dissolution rate
  - Allows high drug loading compared to matrix approaches



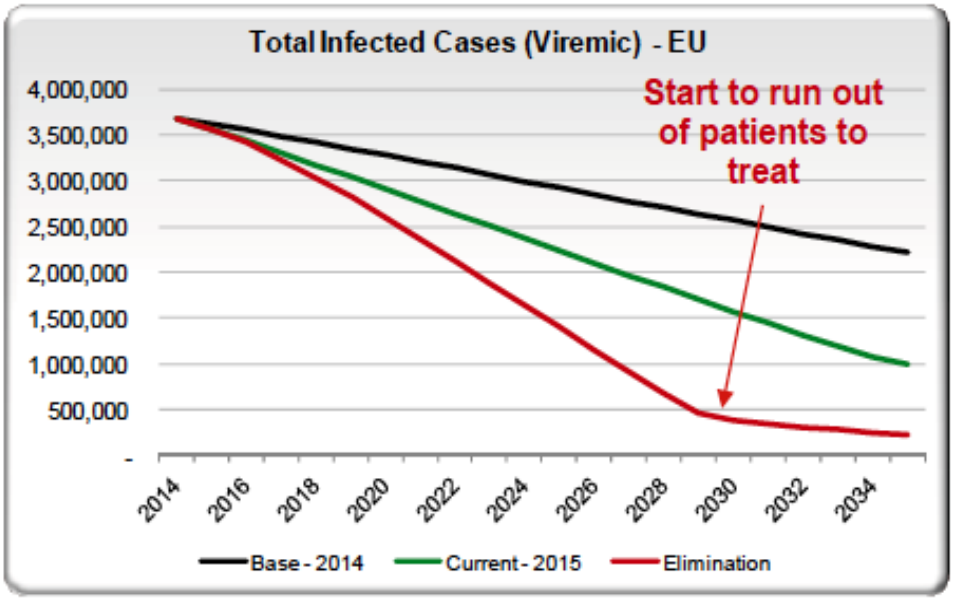
Rilpivirine and Cabotegravir (GSK1265744) are clinical-stage candidates

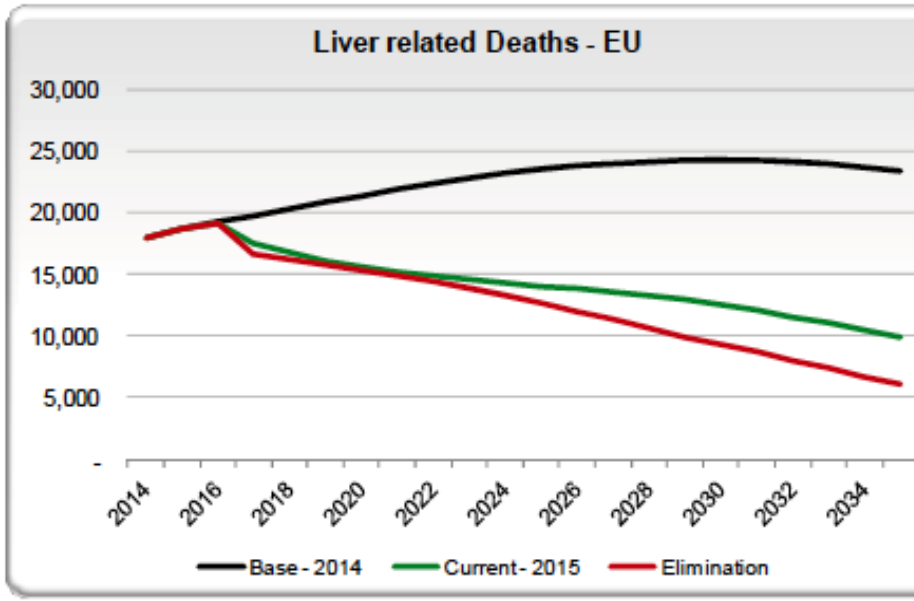


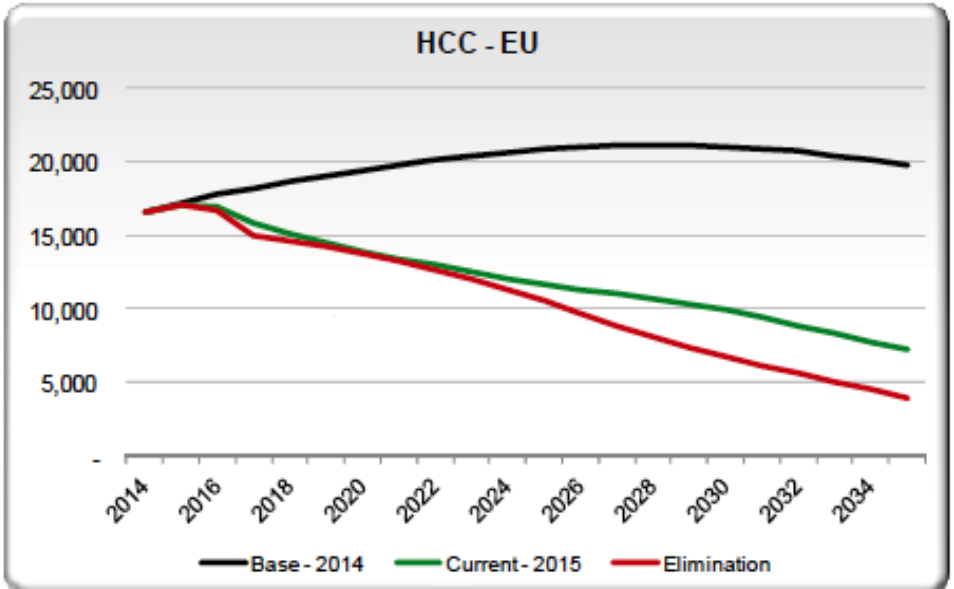
Cabotegravir (analogue to dolutegravir) as a single IM (gluteal) or SC (abdominal) injection provides detectable drug in plasma for 48 Weeks

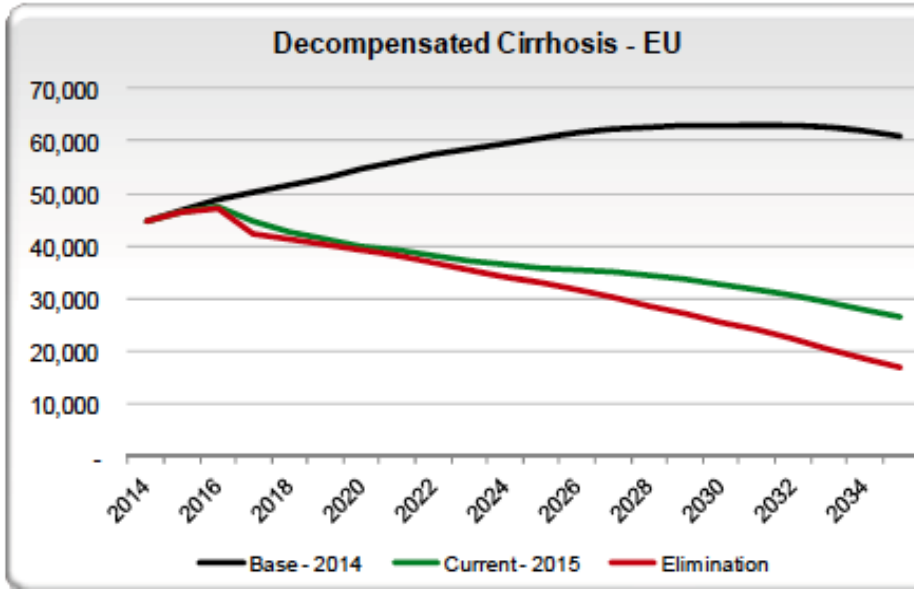
Margolis DA, Brinson CC, Eron JJ, et al. 2014 CROI; Abstract 91LB

HCV infections will decline 90% by 2030 and 95% by 2035, while LRD will decline 55% by 2030 and 70% by 2035







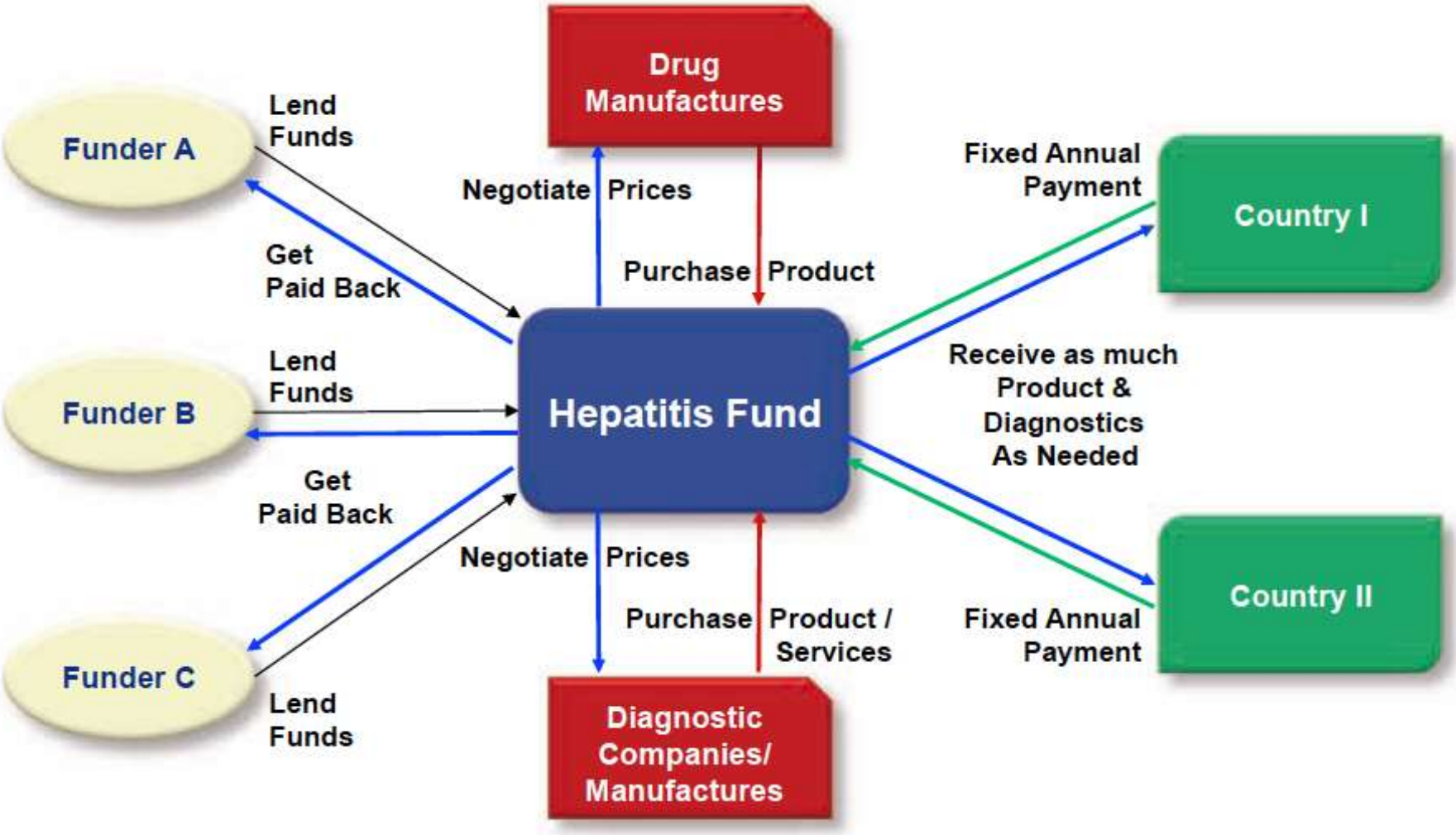


Simple, Effective, but Out of Reach? Public Health Implications of HCV Drugs

John W. Ward, M.D., and Jonathan H. Mermin, M.D., M.P.H.

The availability of simple, safe, and curative regimens creates opportunities for improving the health of the millions of patients living with HCV infection. At a population level, the effect of HCV medications will be determined by affordability and equitable access to HCV testing, care, and treatment. Only through these improvements can our focus be directed to what matters most: reducing the morbidity and mortality associated with HCV infection, stopping HCV transmission, and ultimately eliminating HCV as a public health threat in the United States and worldwide.

Hepatitis Fund: The fund will negotiate & purchase products/services & provide it to countries in return for a fix annual payment



The funders are not donating money. They are loaning funds that will be paid back in the following 10-15 years.

HIGH SUSTAINED VIROLOGICAL RESPONSE RATES USING GENERIC DIRECT ACTING ANTIVIRAL TREATMENT FOR HEPATITIS C, IMPORTED INTO AUSTRALIA

Viral Response REDEMPTION-1 vs Published

Background

- The high prices of these new medications prevent patient access to highly effective HCV treatment
- Generic versions of the DAAs sofosbuvir, ledipasvir, daclatasvir are being mass produced for 1% of the current US retail price[1]
- Under the laws of Australia[2], the UK[3], and many other countries, individuals have the right to import a three month supply of medication, for their personal use

1. Hill A. Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals. Clin Inf Dis. 2014
2. https://www.tga.gov.au/personal-importation-scheme
3. https://www.gov.uk/government/organisations/hm-revenue-customs

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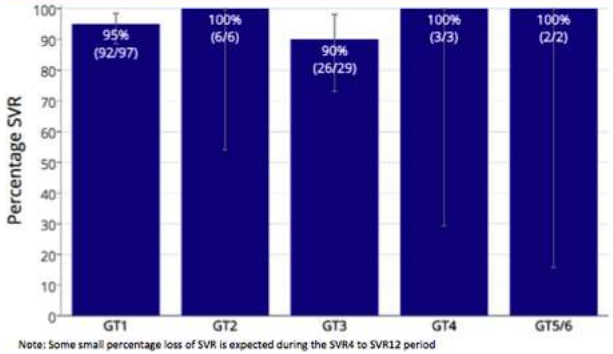
REDEMPTION-1 Overall SVR4 Results For Generics



Note: Some small percentage loss of SVR is expected during the SVR4 to SVR12 period

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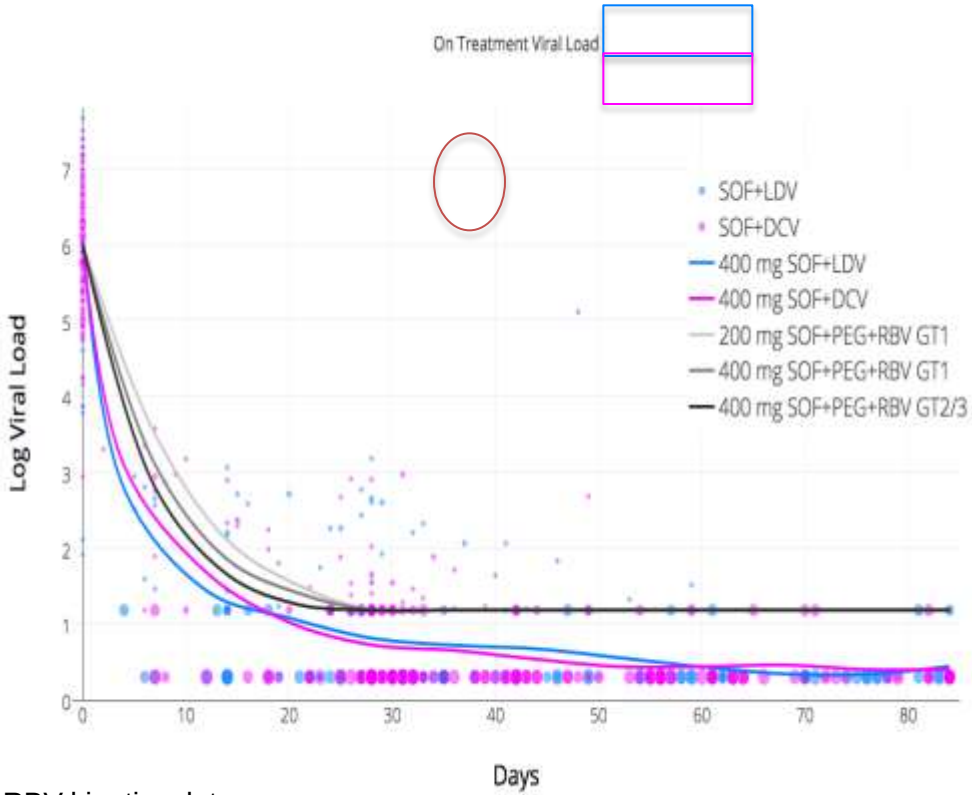

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SOF+PEG+RBV kinetics data source:
http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(13)70033-1/fulltext

On April 12, 1955, Edward R. Murrow asked Jonas Salk who owned the patent to the polio vaccine. “Well, the people, I would say,” Salk responded. “There is no patent. **Could you patent the sun?”**

GRAZIE PER L'ATTENZIONE