Terapia con DAA's
nel trattamento dell'epatopatia cronica HCV

Barbara Menzaghi

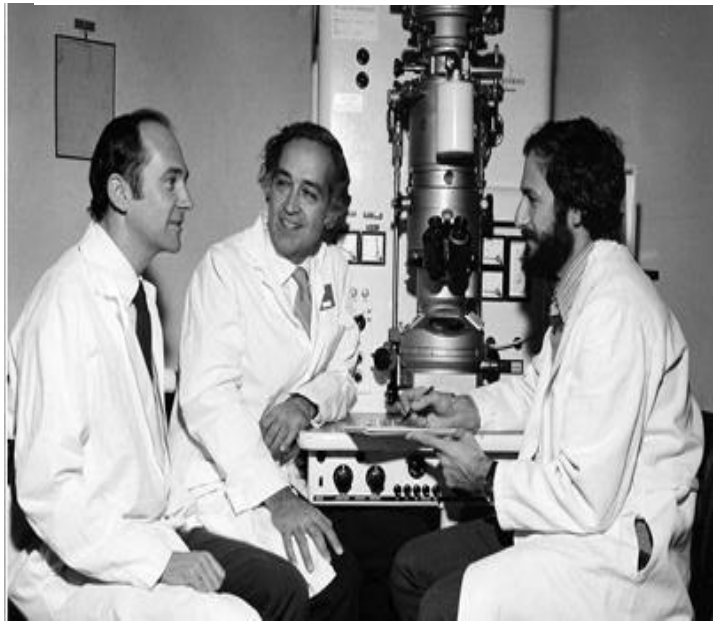
The First Description of Non A non B Hepatitis in Blood Transfusion Recipients

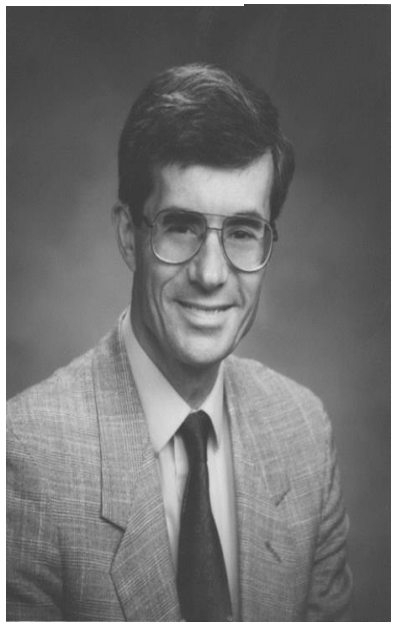
Vol. 292 No. 15 TRANSFUSION-ASSOCIATED HEPATITIS — FEINSTONE ET AL. 767

TRANSFUSION-ASSOCIATED HEPATITIS NOT DUE TO VIRAL HEPATITIS TYPE A OR B

STEPHEN M. FEINSTONE, M.D., ALBERT Z. KAPIKIAN, M.D., ROBERT H. PURCELL, M.D., HARVEY J. ALTER, M.D., AND PAUL V. HOLLAND, M.D.

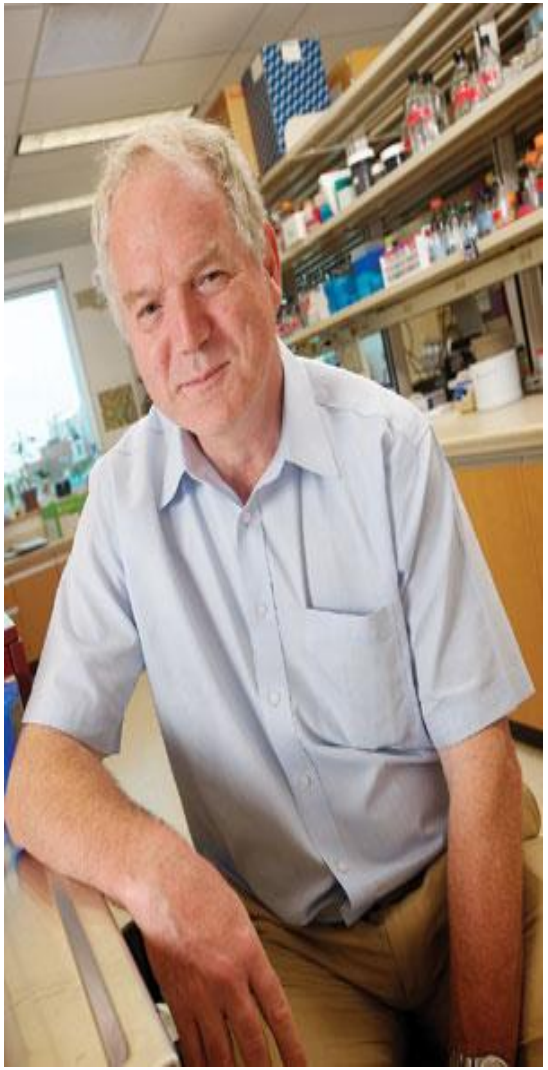
Abstract Twenty-two patients who had an episode of transfusion-associated hepatitis not positive for hepatitis B antigen were examined for development of antibody to hepatitis A and B antigens, cytomegalovirus and Epstein–Barr virus. Antibody response to the 27-nm virus-like hepatitis A antigen was measured by immune electron microscopy. In none of the 22 patients studied did serologic evidence of infection with hepatitis A virus develop during the study period. Nine of the 22 patients had antibody responses to cytomegalovirus, but it was difficult to relate these seroconversions to their hepatitis. In addition, all 22 patients had pre-existing antibody to the Epstein–Barr virus. It seems likely that at least a proportion of such antigen-negative transfusion-associated hepatitis is caused by other infectious agents, not yet identified. (N Engl J Med 292:767-770, 1975)





Feinstone, N Engl J Med 1975.

The Discovery of the Hepatitis C Virus and Development of a Serological Assay



SCIENCE, VOL. 244 21 APRIL 1989

Isolation of a cDNA Clone Derived from a Blood-Borne Non-A, Non-B Viral Hepatitis Genome

QUI-LIM CHOO, GEORGE KUO, AMY J. WEINER, LACY R. OVERBY, DANIEL W. BRADLEY, MICHAEL HOUGHTON

21 APRIL 1989 SCIENCE, VOL. 244

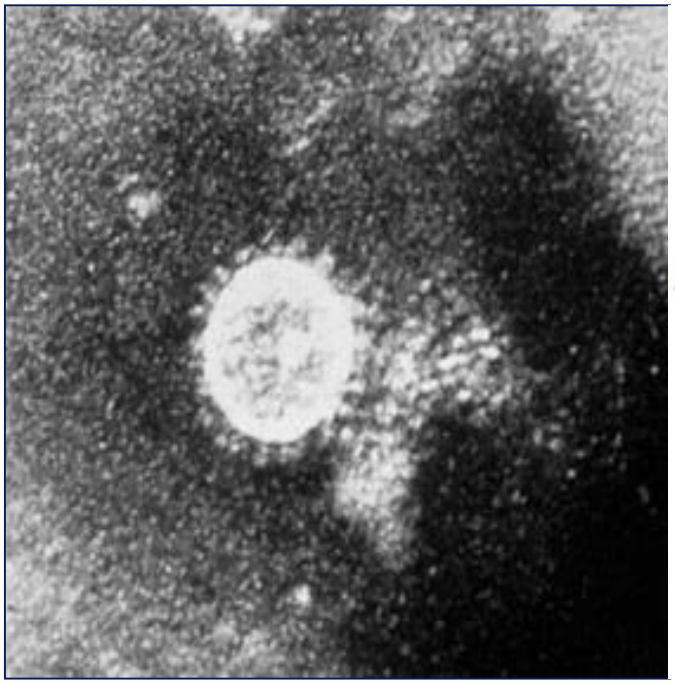
An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis

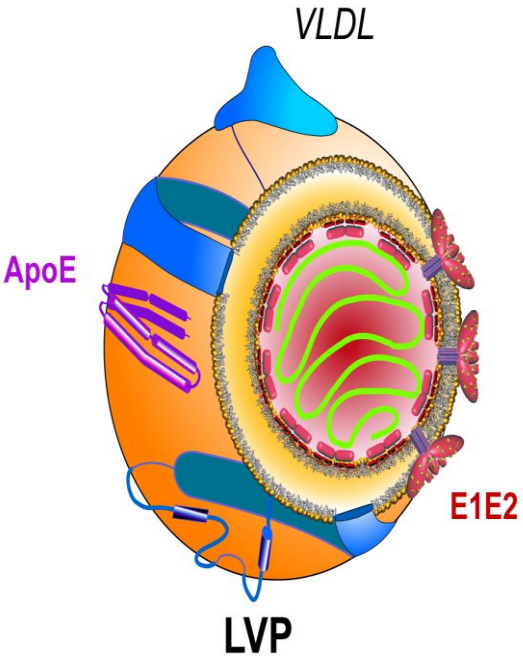
G. KUO, Q.-L. CHOO, H. J. ALTER, G. L. GITNICK, A. G. REDEKER, R. H. PURCELL, T. MIYAMURA, J. L. DIENSTAG, M. J. ALTER, C. E. STEVENS, G. E. TEGTMEIER, F. BONINO, M. COLOMBO, W.-S. LEE, C. KUO, K. BERGER, J. R. SHUSTER, L. R. OVERBY, D. W. BRADLEY, M. HOUGHTON

Choo , Science 1989; Kuo, Science 1989.

The Hepatitis C Virus

- +SS RNA 9.6 Kb
- Flaviviridae family
- Hepacivirus genus

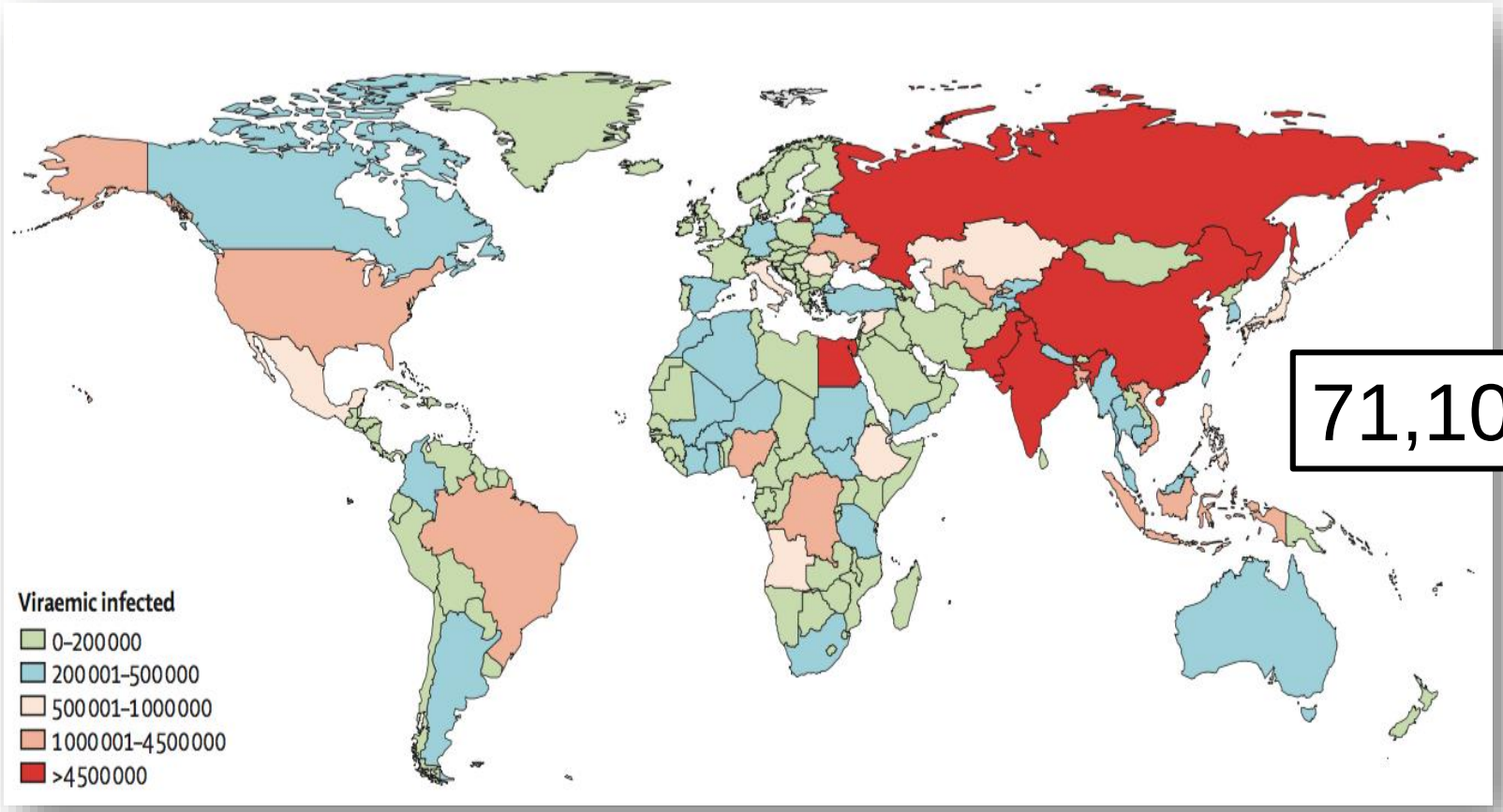




- 7 genotypes, 67 subtypes
- Originated in West Africa or South-East Asia
- Epidemic spread: started in 1900, expanded globally after WW II

Smith, Hepatology 2014.

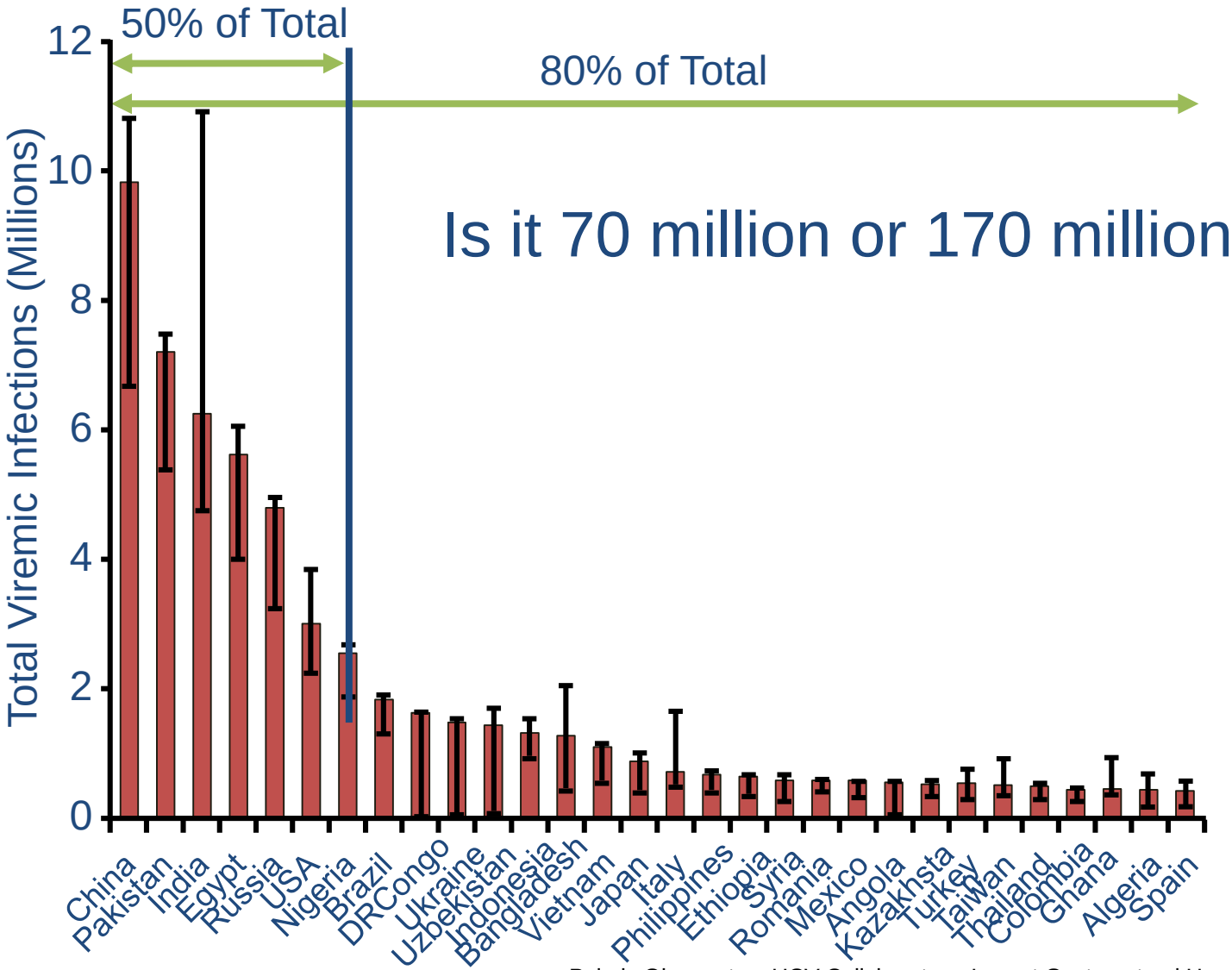
HCV infection worldwide



71,100,000

The Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017

30 Countries Account for 80% of HCV Infections

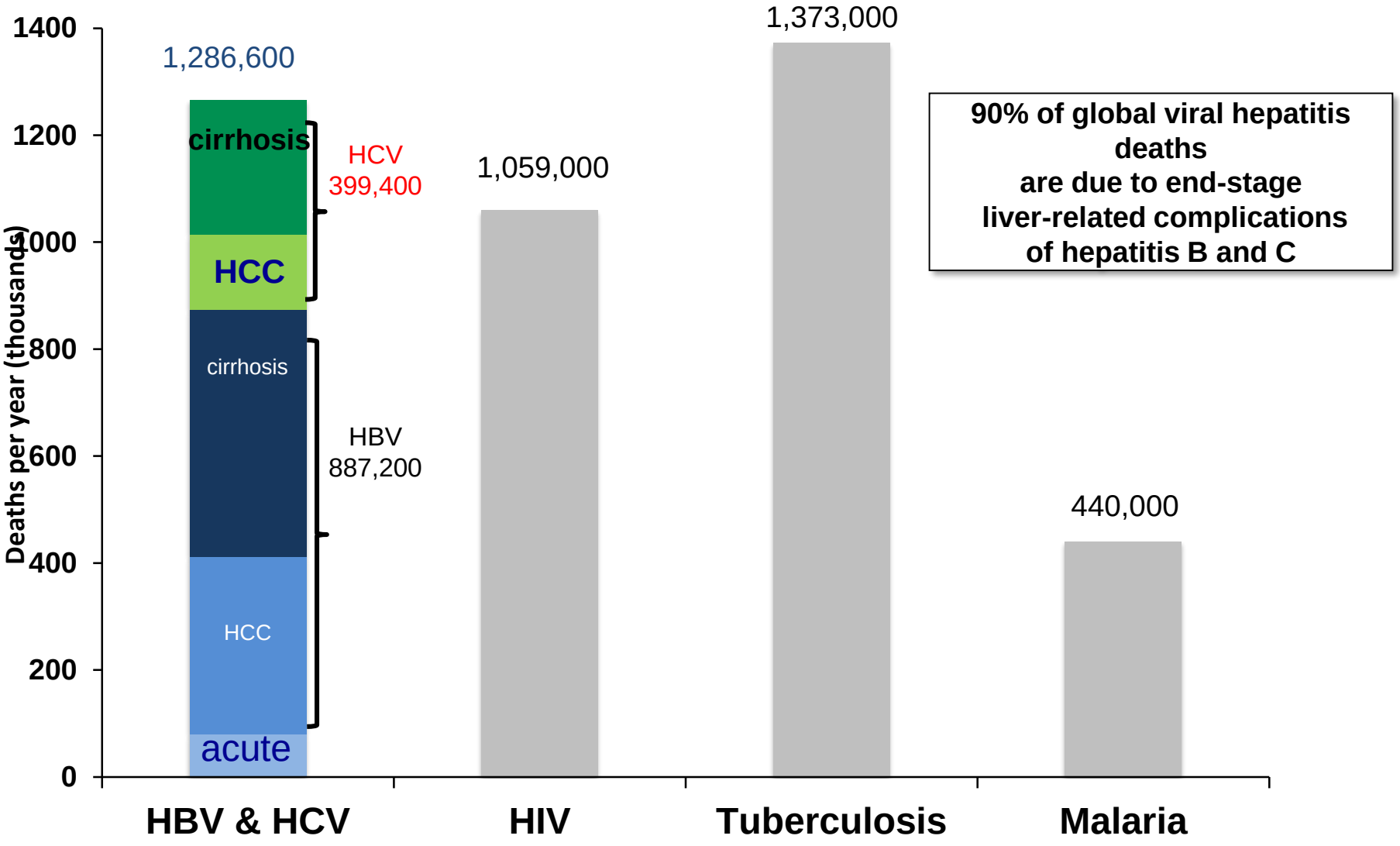


Is it 70 million or 170 million (WHO)?

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017; Blach, AASLD 2016.

The burden of viral liver disease

In Italy 2010 16.000 deaths due to HCV



WHO 2017 Global Hepatitis Report

Hepatitis C Virus Life Cycle: 25 Years Ago

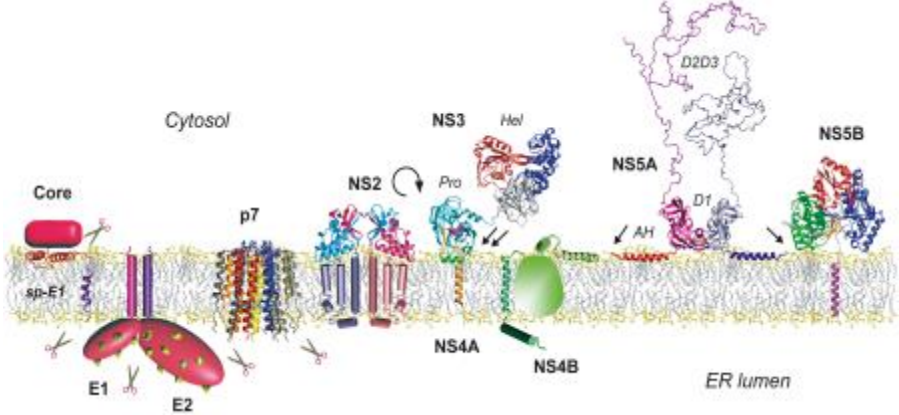
Roadblocks to HCV research:

- No virus replication in cell culture
- No small animal models (chimpanzees)

Adapted from CM Rice

HCV targets for therapy

Drugs active on viral enzymes
Drugs active on host cell enzymes



"entry inhibitors"
mAbs anti-E2/CD81,
PRO 206 Ezetimibe

1 Receptors binding
And endocytosis

miRNA
ISIS 14803 (antisense)
AVI- 4066 (antisense)
Heptazyme (ribozyme)
VGX-410C (small molecules IRES inhibitor) TT 033 (sIRNA)
eIF2a phosphorilation inhibitors:
Nitazoxanide

2 Traslation

Fusion and decapsidation

(+) RNA

6 Transport and release

Inhibitors of viral assembly and release : Celgosivir

5 Virion assembly

3 Translation and processing of polyprotein

4 RNA replication

NS5A Inhibitors

Protease inhibitors

Replication inhibitors:
•NS5B/polymerase
•NNI,
• NI

Cyclophillin inhibitors

NS2–NS3 protease

NS3 protease

C	E1	E2	p7	NS2	NS3	4A	NS4B	NS5A	NS5B

Membrane

Serine protease domain

RNA-dipendent RNA polymerase

Lindenbach, Nature 2005; Moradpour, Curr Top Microbiol Immunol 2013

HCV: probability of the presence of viral variants

Hepatitis C virus: ~9600 nucleotides
Error rate during replication: ~10^{-4} – 10^{-5} per copied nucleotide
Viral turnover: ~10^{12} virions produced every day

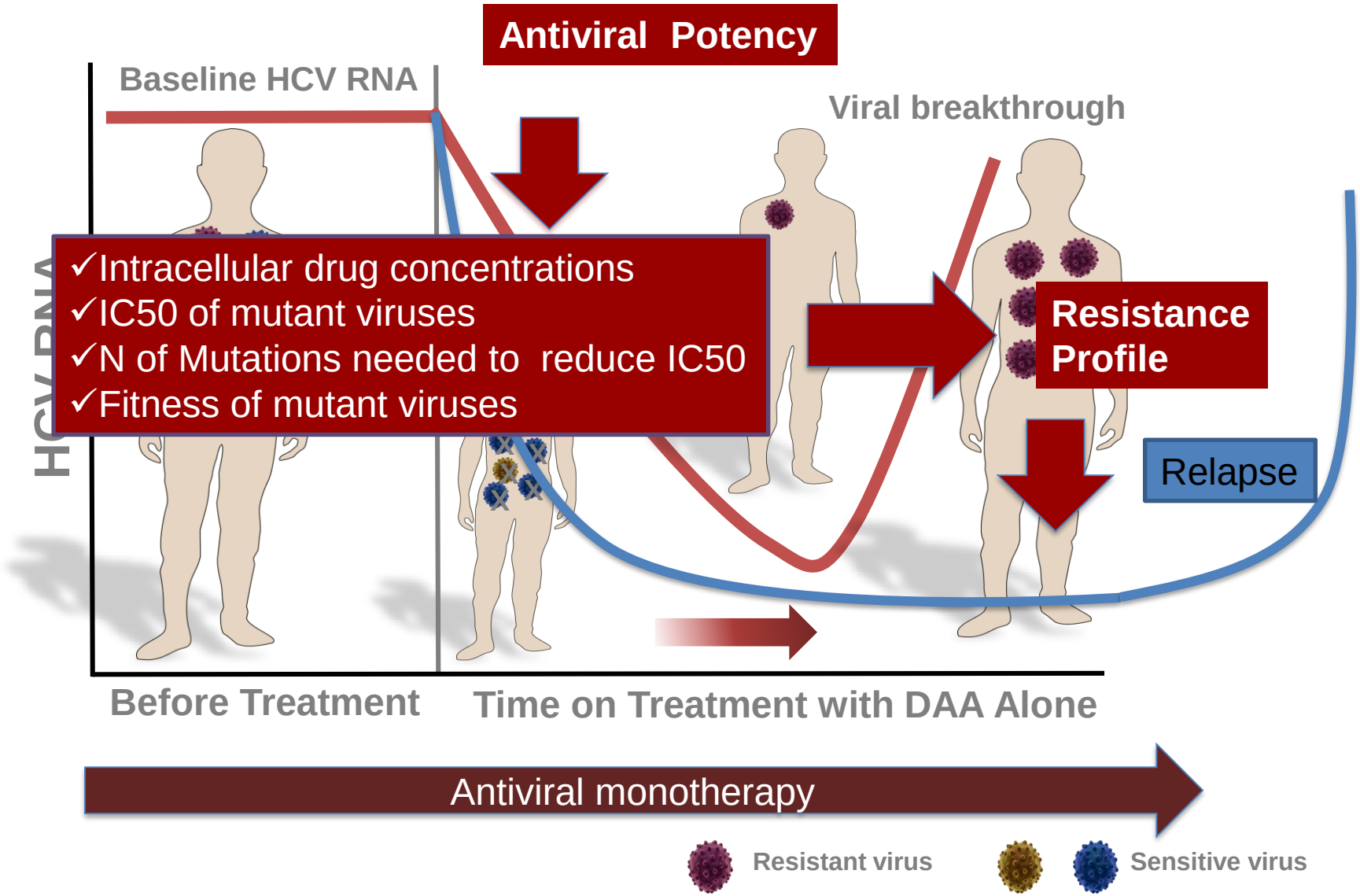
Number of nucleotide change	Probability of generation after one round of replication	Number of virions with nucleotide change(s) produced per day	Number of all possible nucleotide mutants	Fraction of all possible mutants created per day
0	**91%**	**9.1×10^{11}**		
1	**8.7%**	**8.7×10^{10}**	**2.9×10^{4}**	**1**
2	**0.4%**	**4.2×10^{9}**	**4.1×10^{8}**	**1**
3	**0.001%**	**1.3×10^{8}**	**4.0×10^{12}**	**3.4×10^{-5}**

Not all variants survive

- Dead mutations (variants that can not replicate)
- Immune sensitive mutations (variants eliminated by the immune system)

Rong, Sci Transl Med 2010; Neumann, Science 1998; Domingo, Viral Hepatitis Rev 1996; Cuevas, J Virol 2009

Emergence of Pre-existing Resistant Variants During Treatment with DAA



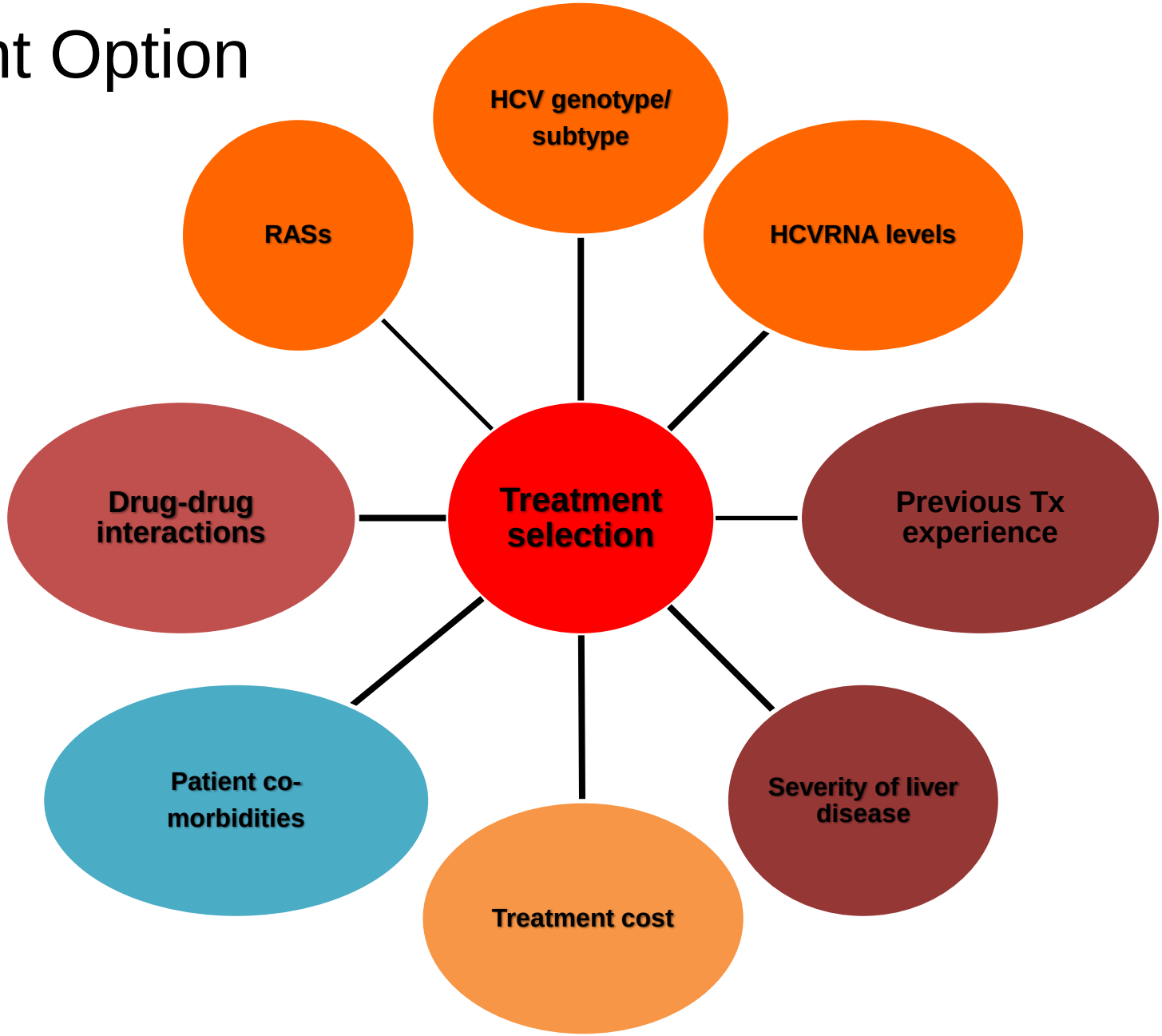
Characteristics of 1st gen DAA

Drug class	NS3/NS4 Inhibitors (--- "previrs")	NS5A inhibitors (…"asvirs")	NS5B inhibitors (…"buvirs")	
	1st gen 2nd wave	1st gen	NN	NUC
Drugs	Paritaprevir/r Simeprevir	Ledipasvir, Ombitasvir Elbasvir **Daclatasvir**	Dasabuvir	**Sofosbuvir**
Antiviral Potency	▯	▯	▯	▯
Resistance profile	▯	▯	▯	▯
Pangenotypic efficacy	▯	▯ / ▯	▯	▯

STRATEGY Combinations of DAA genotype specific to achieve potent antiviral effect, high barrier to resistance and broad genotypic spectrum

Modified from Shinazi Liv Int 2014

Characteristics that Inform Treatment Option Selection



Efficacy of DAA combination regimens according to HCV genotype in RCT (most single arm studies) with 1st gen DAAs

Combination regimens for 8 – 24 weeks	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	<75%	85%	85%	<75%	< 85%
SOF + SIM ± RBV	<90%	---	---	90-93%	---
SOF/LDV ± RBV	90-96%	---	< 90%	90-96%	90-96%
OBV/PTV/r + DSV (3D) ± RBV	95-97%	---	---	---	--
OBV/PTV/r (2D) ± RBV	---	---	---	95-97%	---
EBR/GZR ± RBV	92-97%	---	---	92-95%	---
SOF + DCV ± RBV	94%	90-95%	87-92%	90%	87%

NUCPol i; NNPol I; 1st gen NS3/NS4 i; 2nd gen NS3/NS4i; 1st gen NS5Ai; 1st gen pangenotypic NS5Ai; 2nd gen pangenotypic NS5Ai

Aggiornamento epatite C

- Con l'obiettivo finale di favorire l'accesso alle nuove terapie per tutti i pazienti affetti da epatite C cronica e garantire al tempo stesso la sostenibilità del SSN, si è reso inizialmente necessario individuare una strategia di accesso modulata sulla base dell'urgenza clinica al trattamento.
- Di conseguenza, l'AIFA, tramite la Commissione Tecnico Scientifica (CTS), ha individuato i criteri di rimborsabilità prioritaria al trattamento con i nuovi DAAs sulla base dei risultati emersi dai lavori del Tavolo tecnico epatite C istituito presso l'Agenzia.

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
2. Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione
3. Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B)
4. Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishack)
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
6. Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione (decisione CTS del 05/04/2016); in precedenza "Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR≥2 (o corrispondente Ishack)"
7. Epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishack) (solo per simeprevir)

Aggiornamento dati Registri AIFA DAAs

Epatite C cronica

3 Aprile 2017

Ufficio Registri di monitoraggio

AIFA
Agenzia Italiana del Farmaco

Agenzia Italiana del Farmaco
AIFA

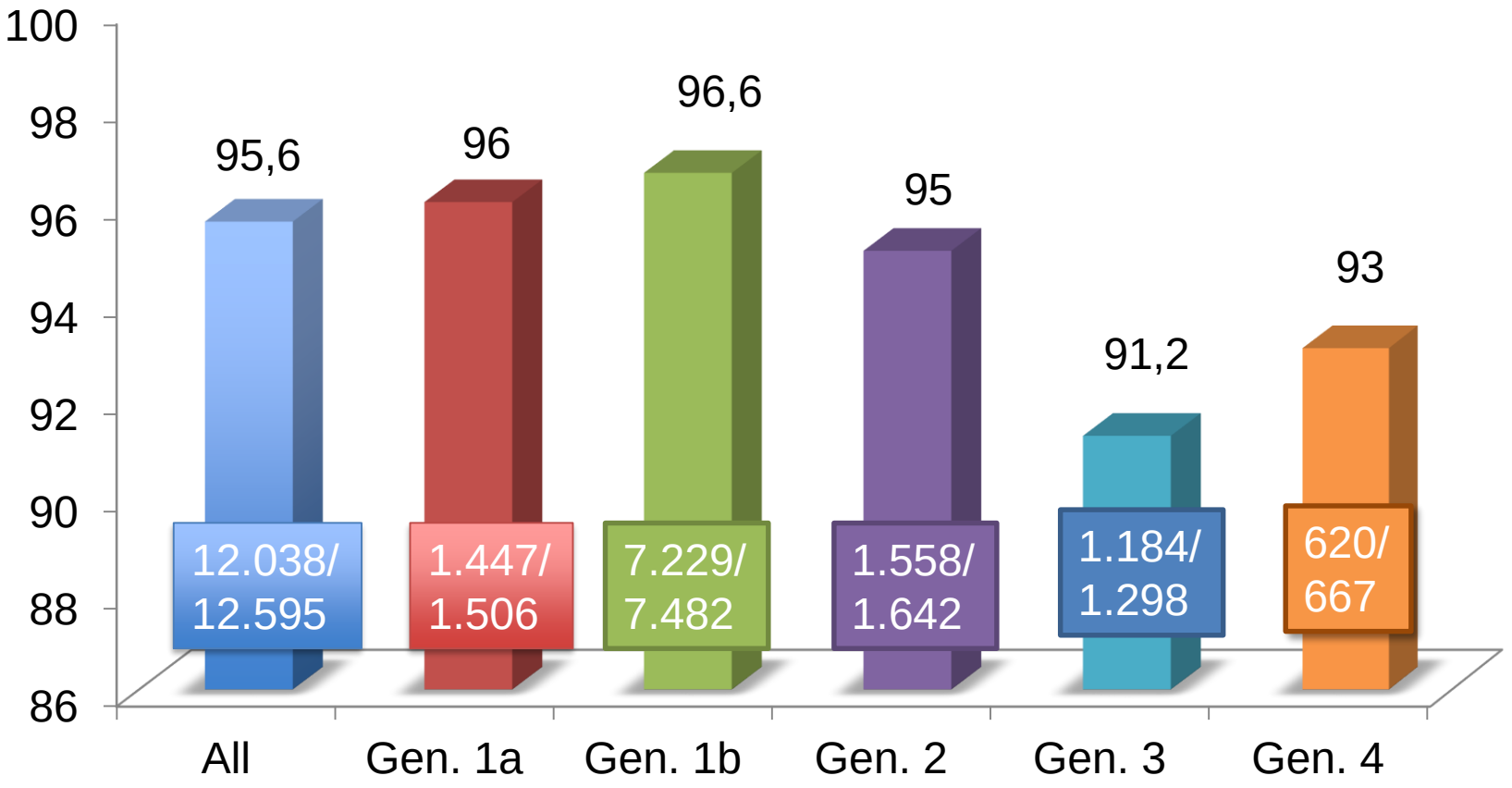
Trattamenti avviati per criterio

71.970 pazienti

Criterio	N. Trattamenti
1	Cirrosi 45.269
4	F3 20.030
3	Extraep. 3.465
2	OLT 1.932
7	F2 628
6	T Non LT 349
5	Lista OLT 297

SVR12 in 12.595 HCV infected patients in 4 Italian Regional Registries

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



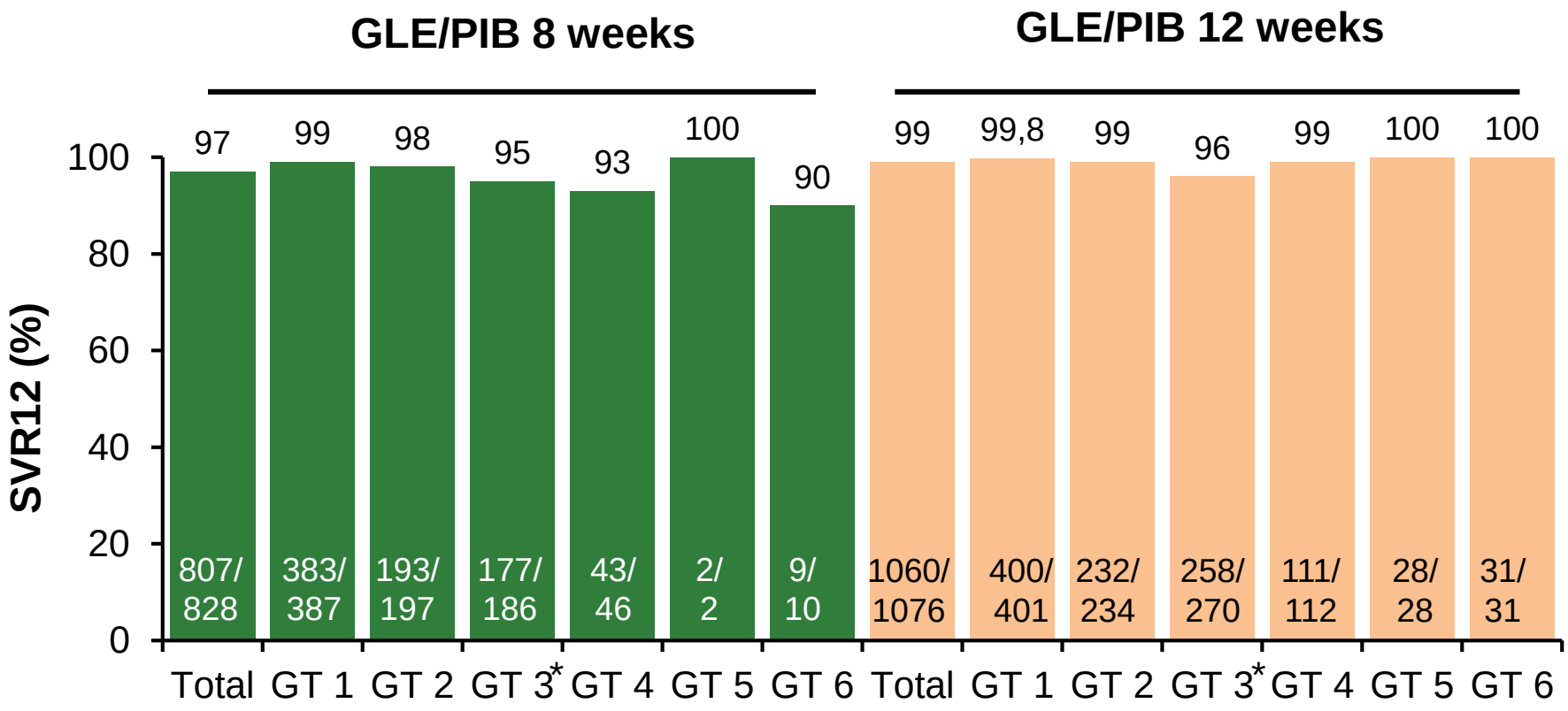
Characteristics of 2nd gen DAA registered and not registered in Europe

Drug class	NS3/NS4 Inhibitors (--- "previrs")		NS5A inhibitors (…"asvirs")		NS5B inhibitors (…"buvirs")	
	1st gen 2nd wave	2nd gen	1st gen	2nd gen	NN	NUC
Drugs	Paritaprevir/r Simeprevir	**Grazoprevir Glecaprevir Voxilaprevir**	Ledipasvir, Ombitasvir Elbasvir **Daclatasvir**	**Velpatasvir Pibrentasvir** **Ruzasvir Odalasvir**	Dasabuvir	**Sofosbuvir** **Uprifosbuvir AL-335**
Antiviral Potency	▯	▯	▯	▯	▯	▯
Resistance profile	▯	▯	▯	▯	▯	▯
Pangeno-typic efficacy	▯	▯	▯/▯	▯	▯	▯

STRATEGY Combinations of DAA to achieve potent antiviral effect, high barrier to resistance and broad genotypic spectrum → Development of FDC

Modified from Shinazi Liv Int 2014

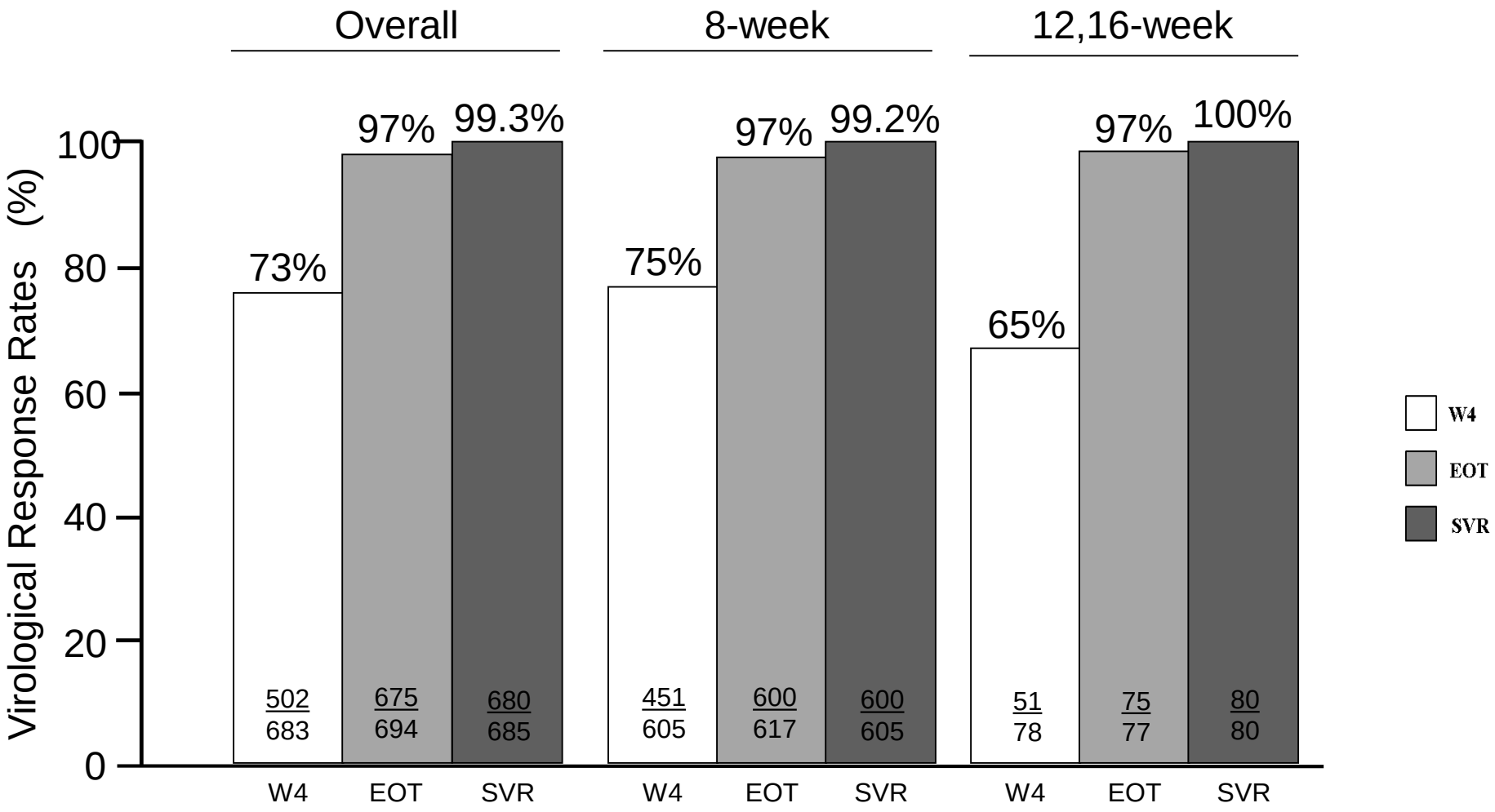
Integrated efficacy and tolerability of GLE/PIB for 8 or 12 weeks in GT 1–6 patients without cirrhosis



*GT 3 patients included in the analysis were TN only. GLE/PIB for 8 weeks or 16 weeks (not 12 weeks) is approved in the EU for the treatment of patients without cirrhosis depending on their genotype and prior treatment experience. Studies included: ENDURANCE-1, -2, -3, -4, EXPEDITION-4, SURVEYOR-1, -2. TE=IFN or SOF-based regimens (n=16); patients experienced with a DAA other than SOF were excluded. TE: treatment-experienced; TN: treatment-naïve

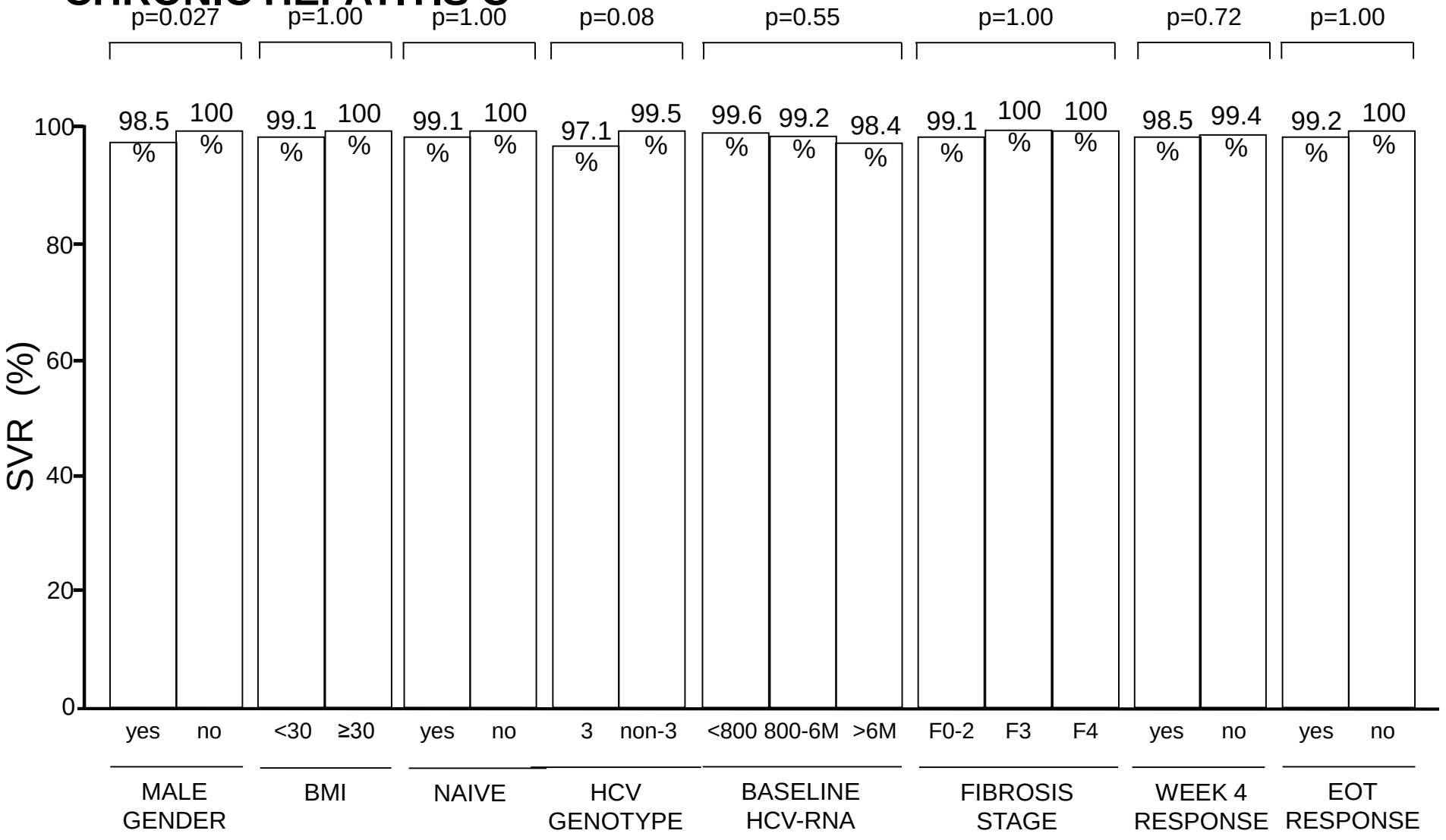
Puoti M, et al. ILC 2017; Poster #SAT-233

REAL-LIFE EFFECTIVENESS AND SAFETY OF GLECAPREVIR/PIBRENTASVIR AMONG 723 PATIENTS WITH CHRONIC HEPATITIS C



D'Ambrosio, J Hepatology in press

REAL-LIFE EFFECTIVENESS AND SAFETY OF GLECAPREVIR/PIBRENTASVIR AMONG 723 PATIENTS WITH CHRONIC HEPATITIS C



D'Ambrosio, J Hepatology in press

Efficacy of DAA combination regimens according to HCV genotype in RCT (most single arm studies)

Combination regimen	GT1	GT2	GT3	GT4	GT5-6
SOF + RBV	<75%	85%	85%	<75%	< 85%
SOF + SIM ± RBV	<90%	---	---	90-93%	---
SOF/LDV ± RBV	90-96%	---	< 90%	90-96%	90-96%
OBV/PTV/r + DSV (3D) ± RBV	95-97%	---	---	---	--
OBV/PTV/r (2D) ± RBV	---	---	---	95-97%	---
EBR/GZR ± RBV	92-97%	---	---	92-95%	---
SOF + DCV ± RBV	94%	90-95%	87-92%	90%	87%
SOF/VEL ± RBV	97%	97%	94%	94%	93%
GLE/PIB	99%	99%	95%	99%	--
SOF/VEL/VOX	99%	99%	99%	99%	100%

■NUCPol I; ■NNPol I; ■1st gen NS3/NS4 i; ■2nd gen NS3/NS4i; ■1st gen NS5Ai; ■ 1st gen pangenotypic NS5Ai; ■2nd gen pangenotypic NS5Ai

Treatment duration of HCV treatment regimens for patients without cirrhosis: EASL 2018

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

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

(EASL HCV Recommendations, J Hepatol 2018)

Treatment duration of HCV treatment regimens for patients with cirrhosis: EASL 2018

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	12 wk
	Treatment-experienced	12 wk	12 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk	12 wk
	Treatment-experienced	12 wk	12 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	12 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 3	Treatment-naïve	No	12 wk	12 wk	No	No	No
	Treatment-experienced	No	16 wk	12 wk	No	No	No
Genotype 4	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	12 wk
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

(EASL HCV Recommendations, J Hepatol 2018)

HEPATOLOGY

HEPATOLOGY, VOL. 66, NO. 6, 2017

Modeling Cost-Effectiveness and Health Gains of a "Universal" Versus "Prioritized" Hepatitis C Virus Treatment Policy in a Real-Life Cohort

Loreta A. Kondili,[1] Federica Romano,[2] Francesca Romana Rolli,[2] Matteo Ruggeri,[2] Stefano Rosato,[1] Maurizia Rossana Brunetto,[3] Anna Linda Zignego,[4] Alessia Ciancio,[5] Alfredo Di Leo,[6] Giovanni Raimondo,[7] Carlo Ferrari,[8] Gloria Taliani,[9] Guglielmo Borgia,[10] Teresa Antonia Santantonio,[11] Pierluigi Blanc,[12] Giovanni Battista Gaeta,[13] Antonio Gasbarrini,[2] Luchino Chessa,[14] Elke Maria Erne,[15] Erica Villa,[16] Donatella Ieluzzi,[17] Francesco Paolo Russo,[15] Pietro Andreone,[18] Maria Vinci,[19] Carmine Coppola,[20] Liliana Chemello,[15] Salvatore Madonia,[21] Gabriella Verucchi,[18] Marcello Persico,[22] Massimo Zuin,[23] Massimo Puoti,[19] Alfredo Alberti,[15] Gerardo Nardone,[13] Marco Massari,[24] Giuseppe Montalto,[25] Giuseppe Foti,[26] Maria Grazia Rumi,[23] Maria Giovanna Quaranta,[1] Americo Cicchetti,[2] Antonio Craxì,[25] and Stefano Vella,[1] on behalf of the PITER Collaborating Group*

DETERMINA 24 marzo 2017: Ridefinizione dei criteri di trattamento per la terapia dell'Epatite C cronica. (Determina n. 500/2017). (17A02374) (GU Serie Generale n.75 del 30-3-2017)

- Sono approvati i seguenti criteri di trattamento per la terapia dell'epatite C cronica:
- criterio 7: **epatite cronica con fibrosi METAVIR F2** (o corrispondente Ishak) **e/**o comorbilità a rischio di progressione del danno epatico [co-infezione HBV, co-infezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥30 kg/m2), emoglobinopatie e coagulopatie congenite];
- criterio 8: **epatite cronica con fibrosi METAVIR F0-F1** (o corrispondente Ishak) e/ o comorbilità a rischio di progressione del danno epatico [co-infezione HBV, co-infezione 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.**

HEPATOLOGY

HEPATOLOGY, VOL. 64, NO. 5, 2016

The End of the Hepatitis C Burden: Really?

SEE ARTICLE ON PAGE 1442

Chronic infection with the hepatitis C virus (HCV) is a leading cause of chronic liver disease and its complications, including cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and death. Approximately 170 million individuals are infected worldwide. The development of new HCV direct-acting antiviral (DAA) drugs paved the way to the approval of all-oral, interferon (IFN)-alpha-free combination regimens that proved safe and highly efficacious in both large-scale clinical trials and in the real world, with an over 95% cure of infection rate when used according to international liver society guidelines.[1,2] Although better therapies are anticipated for certain groups of patients (e.g., those with genotype 3 infection, advanced chronic kidney disease, decompensated cirrhosis, HCC, etc.), tools exist that could theoretically eradicate HCV from the earth. In the current issue of HEPATOLOGY, Chhatwal et al.[3] used a validated model and assumptions based on the current HCV treatment situation in the United States to project the effect of DAA-based t the burden of HCV infection up to 2030 clusion is that the HCV-associated d will still remain substantial in the era unless HCV screening and treatment matically increased.

Definitive eradication of a high ic viral infection that took cent spread over human populations Controlling the infection, th hepatitis C a rare disease with th mortality, is possible with t Four conditions must be t tious goal: (1) Infected p (2) patients with a cu infection must have ac of care; (3) treatment ment must be afford

Screening

The vast maj their infection. Finding ther political wil acceptance for individ large-sca framewo and strat

Abbreviations: anti-HCV, antibodies to the hepatitis C virus; CI, confidence interval; DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon.

Received June 29, 2016; accepted July 29, 2016.

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Potential conflict of interest: Dr. Pawlotsky has received research grants from Gilead. He served as an advisor for AbbVie, Bristol-Myers Squibb, Gilead, Janssen, and Merck.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:
Jean-Michel Pawlotsky, M.D., Ph.D.
Department of Virology, Henri Mondor Hospital
51 avenue du Maréchal de Lattre de Tassigny
94010 Créteil, France
E-mail: jean-michel.pawlotsky@inserm.fr
Tel: +33-1-4981-2827

EDITORIALS

Hepatitis C Drugs: Is Next Generation the Last Generation?

See "High efficacy of ABT-493 and ABT-530 treatment in patients with HCV genotype 1 or 3 infection and compensated cirrhosis," by Gane E, Poordad F, Wang S, et al, on page 651.

Much has been written about the "hepatitis C virus (HCV) drug revolution." For an individual who started to work on the newly discovered HCV in 1990, at the time happy to describe rates of sustained virologic response (SVR) on the order of 6% with standard interferon (IFN)-α administered 3 times per week for 6 months,[1] the current HCV treatment landscape could look miraculous. It is simply the result of an enormous intellectual, scientific, and financial effort of the publicly funded academic and the industrial sectors to solve a major public health problem, building on the experience accumulated in the fight against the human immunodeficiency virus.

This unprecedented effort led to the approval of IFN-free treatment regimens based on combinations of direct-acting antiviral (DAA) drugs. Four classes of HCV DAAs are available in the United States and Europe, including inhibitors of the HCV RNA-dependent RNA polymerase (the nucleotide analog sofosbuvir and the non-nucleoside inhibitor dasabuvir), nonstructural 5A (NS5A) protein inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir, and velpatasvir), and inhibitors of the NS3-4A protease (simeprevir, paritaprevir, and grazoprevir). These drugs are available either as fixed-dose combinations, including sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, ombitasvir/paritaprevir/ritonavir (with or without dasabuvir) and grazoprevir/elbasvir, or as single agents that can be combined (sofosbuvir, daclatasvir, and simep DAA combinations should be administered fo weeks, with or without weight-based rib to baseline parameters, including the HCV type, the stage of fibrosis, prior HCV comorbidities, and co-administered med tical use is guided by recommendations larly updated by the international liver

In phase II and III clinical trial approved drug combinations, SVR achieved in most patient groups, w effects. Real-world studies involvi tients from various continents con and the excellent safety and toler approved HCV DAA combination issues remained unsolved:

- The ideal treatment durat ment can be shortened t
- Many groups of patien with ribavirin, a medic to achieve high rates
- Treatment of genoty cure genotype, wit lower SVR rates th
- The ideal timing patients with dec awaiting liver tr
- Whether pre-li clinical benefi

Review

CrossMark

EASL | JOURNAL OF HEPATOLOGY

From non-A, non-B hepatitis to hepatitis C virus cure

Jean-Michel Pawlotsky[1,2,*], Jordan J. Feld[3], Stefan Zeuzem[4], Jay H. Hoofnagle[5]

[1]National Reference Center for Viral Hepatitis B, C and D, Department of Virology, Hôpital Henri Mondor, Université Paris-Est, Créteil, France; [2]INSERM U955, Créteil, France; [3]Toronto Centre for Liver Disease, Sandra Rotman Centre for Global Health, University of Toronto, Toronto, Ontario, Canada; [4]Medizinische Klinik 1, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany; [5]Liver Disease Research Branch, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, United States

Review

Summary

The hepatitis C virus (HCV) was discovered in the late 1980s. Interferon (IFN)-α was proposed as an antiviral treatment for chronic hepatitis C at about the same time. Successive improvements in IFN-α-based therapy (dose finding, pegylation, addition of ribavirin) increased the rates of sustained virologic response, i.e., the rates of curing HCV infection. These rates were further improved by adding the first available direct-acting antiviral (DAA) drugs to the combination of pegylated IFN-α and ribavirin. An IFN-free era finally started in 2014, yielding rates of sustained virologic response over 90% in patients treated for 8 to 24 weeks with all-oral regimens. Major challenges however remain in implementation of these new treatment strategies, not only in low- to middle-income countries, but also in high-income countries where the price of these therapies is still prohibitive. Elimination of HCV infection through treatment in certain areas is possible but raises major public health issues.

Introduction

Twenty-five years after the discovery of the hepatitis C virus (HCV), new orally administered antiviral drug combinations yielding infection cure rates over 90% were approved in 2014–2015 in Europe, the US and other regions of the world. Some called it a "revolution". A revolution is defined by "a sudden, complete or marked change in something". This definition does not apply to what happened to the field of HCV therapy. Instead, a slow, progressive, successful succession of discoveries in which academic scientists, clinicians and commercial entities were collaboratively involved, led to the current situation (Fig. 1). It is the story of this adventure, from discovery to cure, that we are telling here.

To begin at the beginning

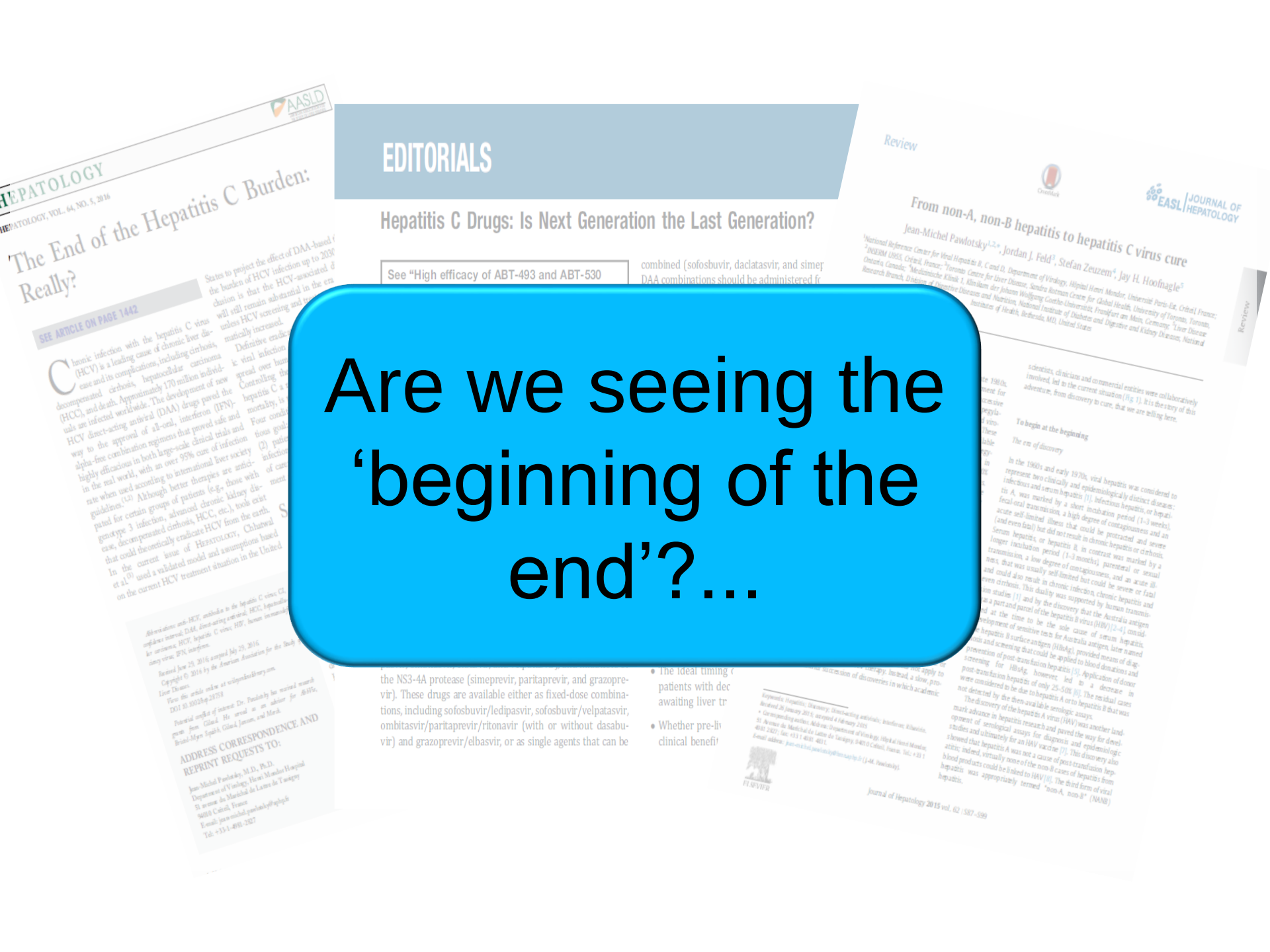
The era of discovery

In the 1960s and early 1970s, viral hepatitis was considered to represent two clinically and epidemiologically distinct diseases: infectious and serum hepatitis [1]. Infectious hepatitis, or hepatitis A, was marked by a short incubation period (1–3 weeks), fecal-oral transmission, a high degree of contagiousness and an acute self-limited illness that could be protracted and severe (and even fatal) but did not result in chronic hepatitis or cirrhosis. Serum hepatitis, or hepatitis B, in contrast was marked by a longer incubation period (1–3 months), parenteral or sexual transmission, a low degree of contagiousness, and an acute illness that was usually self-limited but could be severe or fatal and could also result in chronic infection, chronic hepatitis and even cirrhosis. This duality was supported by human transmission studies [1] and by the discovery that the Australia antigen was a part and parcel of the hepatitis B virus (HBV) [2–4], considered at the time to be the sole cause of serum hepatitis. Development of sensitive tests for Australia antigen, later named the hepatitis B surface antigen (HBsAg), provided means of diagnosis and screening that could be applied to blood donations and prevention of post-transfusion hepatitis [5]. Application of donor screening for HBsAg, however, led to a decrease in post-transfusion hepatitis of only 25–50% [6]. The residual cases were considered to be due to hepatitis A or to hepatitis B that was not detected by the then-available serologic assays.

The discovery of the hepatitis A virus (HAV) was another landmark advance in hepatitis research and paved the way for development of serological assays for diagnosis and epidemiologic studies and ultimately for an HAV vaccine [7]. This discovery also showed that hepatitis A was not a cause of post-transfusion hepatitis; indeed, virtually none of the non-B cases of hepatitis from blood products could be linked to HAV [8]. The third form of viral hepatitis was appropriately termed "non-A, non-B" (NANB)

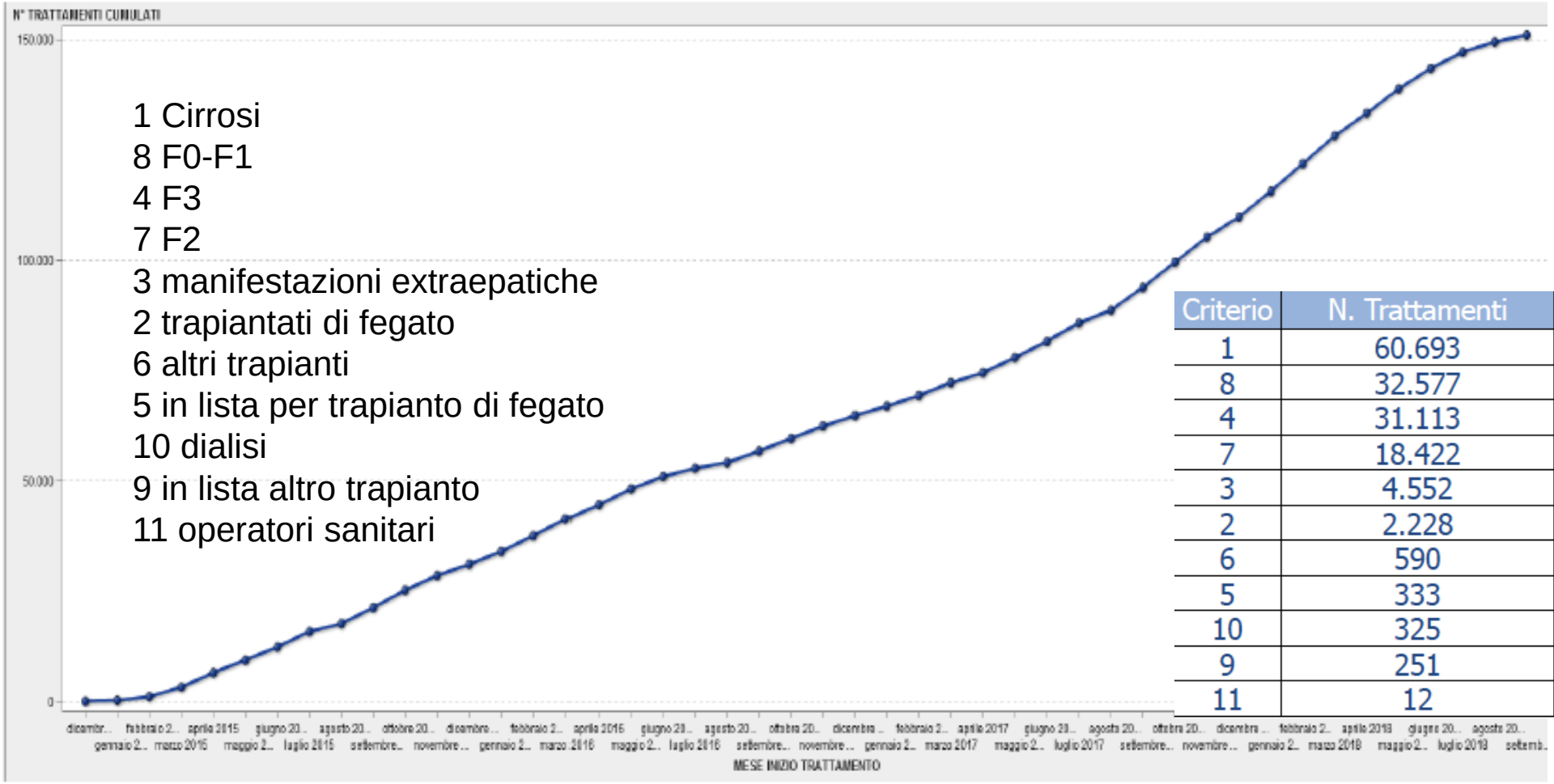
Keywords: Hepatitis; Discovery; Direct-acting antivirals; Interferon; Ribavirin.
Received 26 January 2015; accepted 4 February 2015

* Corresponding author. Address: Department of Virology, Hôpital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France. Tel.: +33 1 4981 2827; fax: +33 1 4981 4813.
E-mail address: jean-michel.pawlotsky@inserm.fr (J.-M. Pawlotsky).


HEPATOLOGY
The End of the Hepatitis C Burden: Really?
EDITORIALS
Hepatitis C Drugs: Is Next Generation the Last Generation?
Review
From non-A, non-B hepatitis to hepatitis C virus cure
Are we seeing the 'beginning of the end'?...

Trattamenti anti HCV in Italia aggiornamento 17 settembre 2018

Trend cumulativo dei trattamenti avviati



1 Cirrosi
8 F0-F1
4 F3
7 F2
3 manifestazioni extraepatiche
2 trapiantati di fegato
6 altri trapianti
5 in lista per trapianto di fegato
10 dialisi
9 in lista altro trapianto
11 operatori sanitari

Criterio	N. Trattamenti
1	60.693
8	32.577
4	31.113
7	18.422
3	4.552
2	2.228
6	590
5	333
10	325
9	251
11	12

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

HCV treatment, key populations and therapeutic issues

- Poly-pharmacy and comorbidities
- People who inject drugs and patients receiving opioid substitution therapy
- Patients with renal impairment, including haemodialysis patients
- Previous DAAs failures
- Adolescents and children
- Neurocognitive and neuropsychiatric dersorders
- HBV co-infection

HCV treatment, key populations and therapeutic issues

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PK and potential for Drug Drug Interactions of Anti HCV oral antivirals

	Excretion	Drug solubility with gastric Ph	Enzymes		Transporters	
			Substrates	Inhibition	Substrates	Inhibition
SOF	Renal Metabolite GS 33107	Minimal effect	CatA CES1 Hint1 Phosph UMP-CMP & NDP kinases	No	PgP BCRP	
VEL	Biliary	Important Decrease	CYP2B6 CYP2C8 CYP3A4	No	PgP BCRP OATP1B1 OATP1B3	PgP BCRP OATP1B1 OATP1B3
VOX	Biliary	Mild decrease	CYP1A2, CYP 2C8, CYP3A4	No	BCRP OATP1B1	BCRP, OATP1B1/3, BSEP
EBR	Biliary	No effect	CYP3A	No	PgP	PgP BCRP
GZR	Biliary	No effect	CYP3A4	CYP3A4	OATP1B1/3 PgP	BCRP
GLE	Biliary	Mild decrease	CYP3A4/5CYP2D6, 2C9, and 2C8.	CYP2C8, CYP2C9 CYP3A4. UGT1 UGT1A4	PgP BCRP	PgP BCRP OATP1B1/3B SEP
PIB	Biliary	No effect	None	None	PgP BCRP OATP1B1 OATP1B3	PgP BCRP OATP1B1 OATP1B3
3D	Biliary	No effect	CYP3A4 CYP2C8	CYP3A4 CYP2C8 UGT1A1 CYP2C19	PgP BCRP OATP1B1/3	OCT1 PgP BCRP OATP1B1/3

mild potential for DDI; moderate potential for DDI; high potential for DDI

HCV treatment, key populations and therapeutic issues

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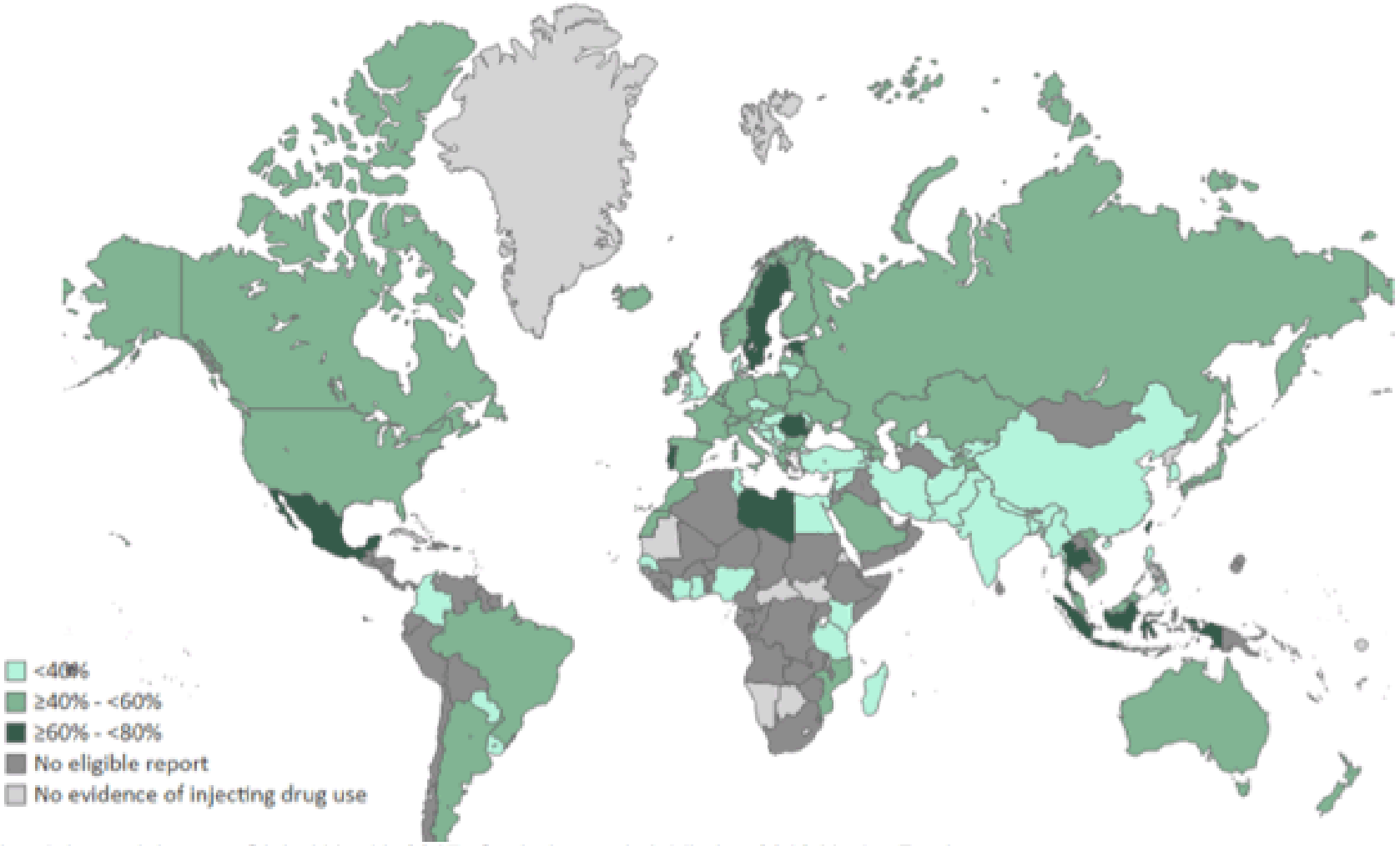
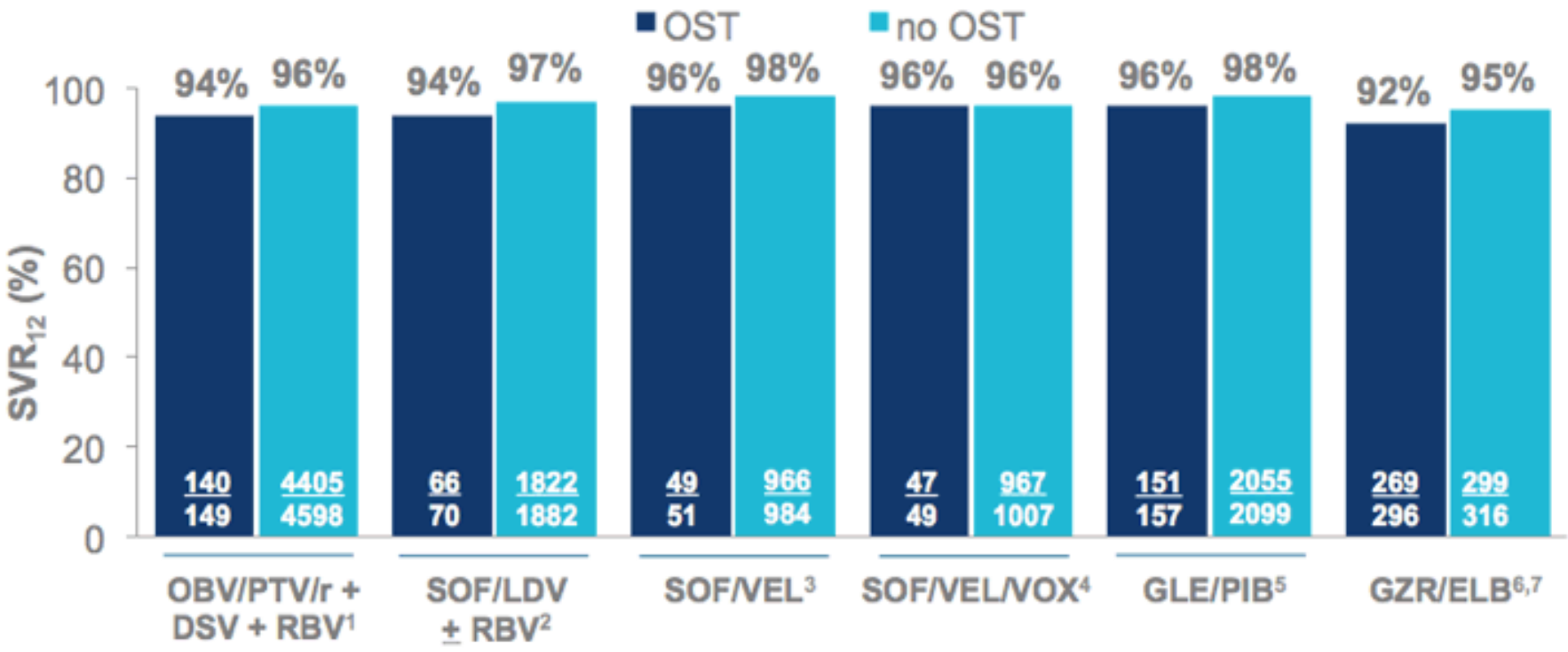
The burden of HCV among PWID is considerable

- 6.1M (3.4-9.2) PWID are living with HCV infection (39%)



Degenhardt L, et al. Lancet Global Health 2017, Grebely, et al. Addiction 2018 Under Review

People receiving OST – phase II/III trials

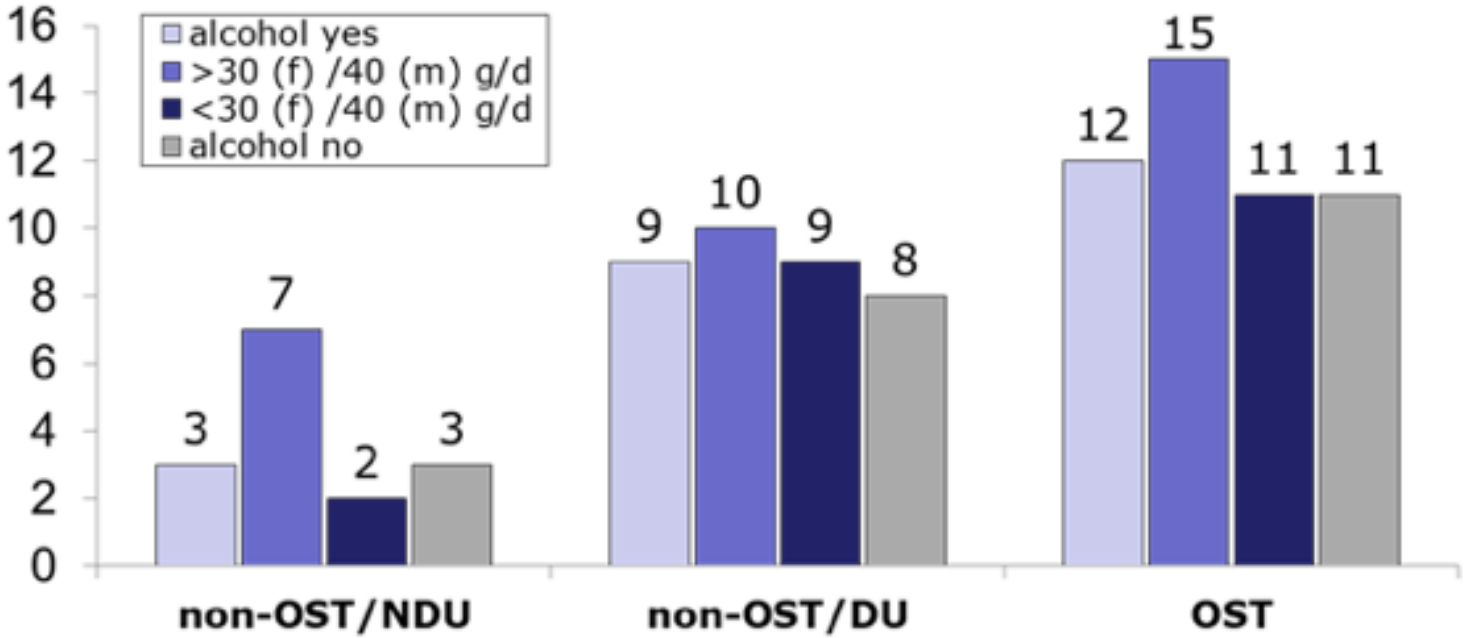


1) Grebely J, et al *ILC 2017* (FRI-236). 2) Grebely *CID* 2016. 3) Grebely *CID* 2016. 4) Grebely J, *ILC 2017* (FRI-235). 5) Grebely J, *INHSU 2017*. 6) Zeuzem, S. *Ann Intern Med* 2015. 7) Dore, GJ *Ann Intern Med* 2016. 8) Grebely J, Hajarizadeh B, and Dore GJ *Nat Rev in Gastroenterology & Hepatology* 2017.

Scaling up HCV-DAA treatment in patients on opioid substitution therapy - does alcohol or cannabis consumption diminish cure rates? Data from the German Hepatitis C Registry (DHC-R)

Christiansen S et al.: EASL 2018 Paris, France - Abstract # PS-036

Lost to follow up (LTFU) according to alcohol consumption



In alcohol and in non-alcohol consuming patients proportion of LTFU did not differ significantly within each group but was significantly higher in OST compared to non-OST/NDU. LTFU occurred mainly after end of therapy (EOT)

Scaling up HCV-DAA treatment in patients on opioid substitution therapy - does alcohol or cannabis consumption diminish cure rates? Data from the German Hepatitis C Registry (DHC-R)

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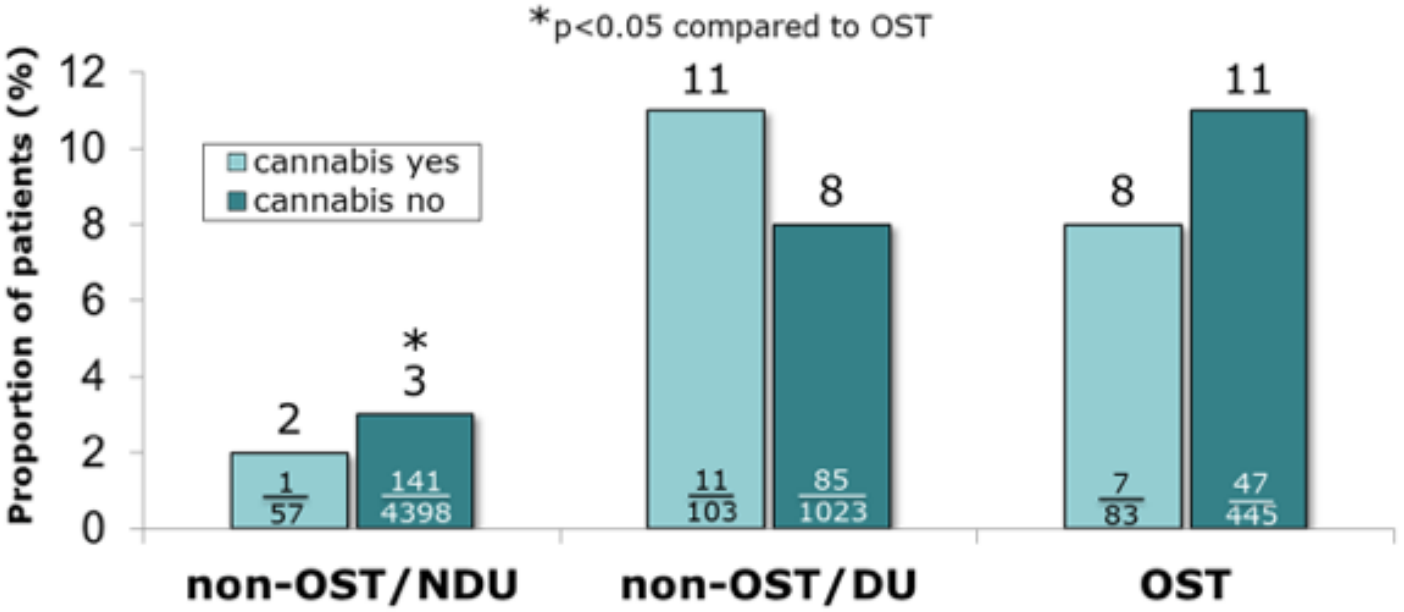
Lost to follow up (LTFU) according to cannabis consumption

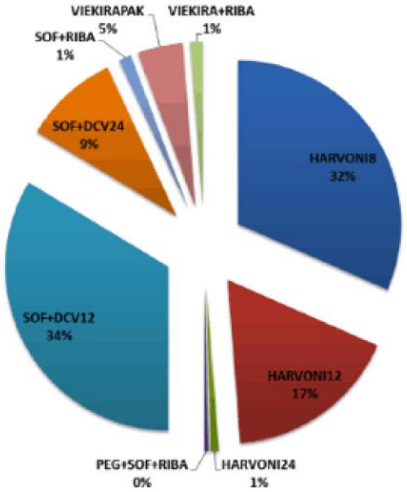


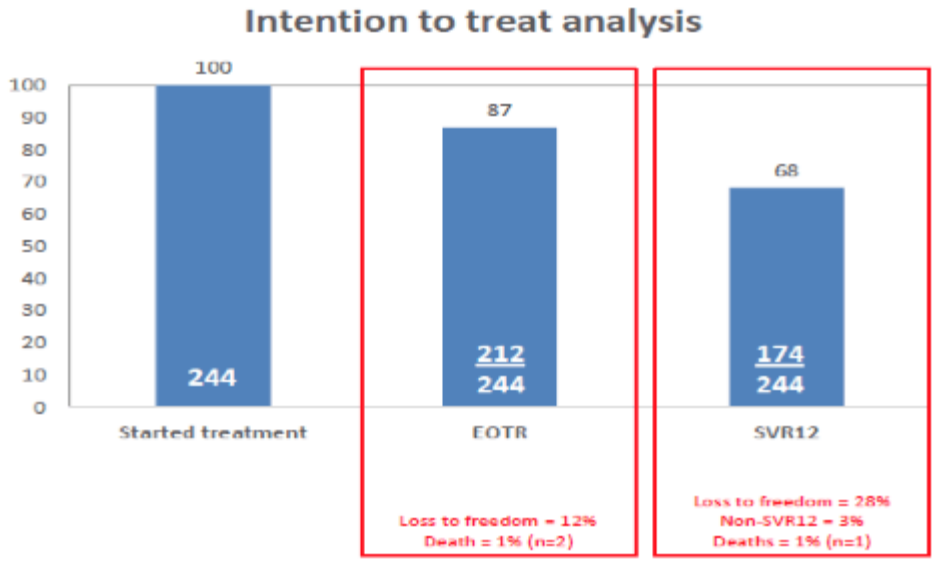
In contrast, consumption of cannabis was not a risk factor for LTFU. Indeed, in cannabis consuming patients the proportion of lost-to-follow-up did not differ significantly between groups

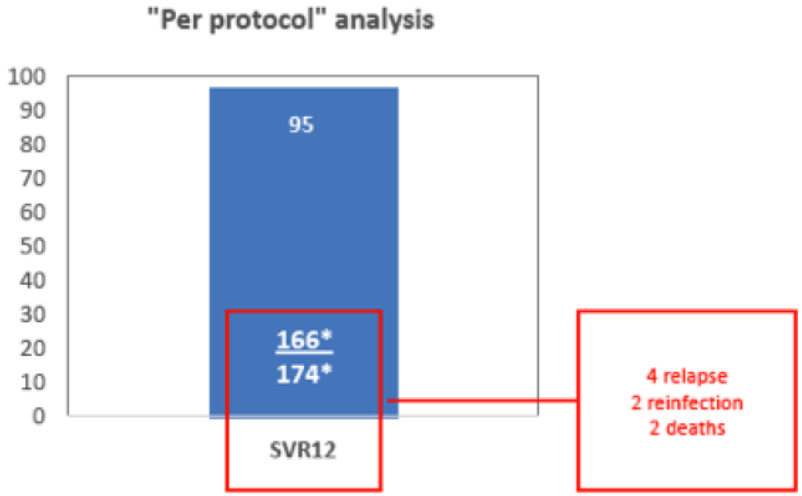
Outcomes of Treatment for Hepatitis C Virus Infection in the Prison Setting

McDonald et al.: EASL 2017 April 19-23 Amsterdam Netherlands

	N = 244
Age (median, IQR)	41
Male gender (n, %)	212 (87%)
Ethnicity - Caucasian (n, %) - Indigenous (n, %) - Other (n, %)	 174 (71%) 30 (12%) 40 (17%)
Body Mass Index kg/m²(mean)	30.3
ALT U/L (median, IQR)	98 [56-154]
HCV RNA level IU/mL (median, IQR)	684,000 [207,000 – 2,613,000]
HCV genotype - 1a - 1b - 2 - 3 - 4 - 6	 112 (46%) 13 (5%) 5 (2%) 113 (46%) 0 (0%) 1 (0.4%)
LSM kPa (median, IQR) < 9.5 (n, %) 9.5 – 12.5 (n, %) > 12.5 (n, %)	 153 (63%) 35 (14%) 56 (23%)
Hepatitis B coinfection - HBsAg + (n, %) - HBsAg - , HBcAb + - HBsAb +	 5/165 (3%) 46/148 (31%) 132/168 (79%)
HIV coinfection (n, %)	5 (2.0%)
Decompensated liver disease (n, %)	10 (4.0%)







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EASL Recommendations on Treatment of Hepatitis C 2018☆

Treatment of special groups

People who inject drugs and patients receiving opioid substitution therapy

Recommendations

- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and HCV RNA. PWIDs who are HCV RNA-negative should be tested for HCV RNA annually and following any high-risk injecting episode (**A1**).
- PWIDs should be provided with appropriate access to OST and clean drug injecting equipment as part of widespread comprehensive harm reduction programs, including in prisons (**A1**).
- All PWIDs who are infected with HCV have an indication for antiviral therapy, as DAA-based therapies are safe and effective in HCV-infected patients receiving OST, those with a history of injecting drug use and those who recently injected drugs (**A1**).
- HCV treatment should be offered to HCV-infected patients in prison (**B1**).
- Pre-therapeutic education should include discussions of HCV transmission, risk factors for fibrosis progression, treatment, reinfection risk, and harm reduction strategies (**B1**).
- In patients on OST, DAA-based anti-HCV therapy does not require methadone or buprenorphine dose adjustment (**A1**).
- Harm reduction, education and counselling should be provided to PWIDs in the context of HCV treatment to prevent HCV reinfection following successful treatment (**B1**).
- Following SVR, monitoring for HCV reinfection ideally through bi-annual, at least annual HCV RNA assessment should be undertaken in PWIDs with an ongoing risk behaviour (**A1**).
- Retreatment should be made available, if reinfection is identified during post-SVR follow-up (**A1**).

HCV treatment, key populations and therapeutic issues

- Poly-pharmacy and comorbidities
- People who inject drugs and patients receiving opioid substitution therapy
- **Patients with renal impairment, including haemodialysis patients**
- Previous DAAs failures
- Adolescents and children
- Neurocognitive and neuropsychiatric dersorders
- HBV co-infection

Impact of renal impairment on DAA pharmacokinetics

Change in exposure compared to healthy subjects with normal renal function	Mild impairment (eGFR = 60-89 mL/min/1.73m^2)	Moderate impairment (eGFR = 30-59 mL/min/1.73m^2)	Severe impairment (eGFR = <30 mL/min/1.73m^2)
Sofosbuvir	↑ 61%*	↑ 107%†	↑ 171%
GS-331007	↑ 55%*	↑ 88%†	↑ 451%

- Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease because no dose recommendation can currently be given for these patients (**B1**).

Khatri, Hepatology 2014;;Harvoni, (July 2016), Maviret (July 2017) Epclusa (July 2017) Summaries of Product Characteristics; Yeh, Hepatology 2014.

AASLD THE LIVER MEETING® 2017 WASHINGTON, DC OCTOBER 20-24

Effectiveness of Elbasvir/Grazoprevir in Patients With Chronic Hepatitis C and Chronic Kidney Disease: Results From the Veterans Affairs System

Kramer JR et al.: AASLD: The Liver Meeting 2017; Washington, DC, USA; October 20-24, 2017.

Table 1. Baseline Clinical Characteristics of HCV/CKD Patients Treated with EBR/GZR by CKD Stages

Characteristic N, (%)	Stage 3 CKD n=781	Stage 4-5 CKD n=747	All CKD Patients (N=1528)
Age, mean (SD)	65.8 (6.0)	63.8 (5.2)	64.9 (5.7)
Black	484 (62.0)	547 (73.2)	1031 (67.5)
Male	749 (95.9)	732 (98.0)	1481 (96.9)
GT1a	351 (44.9)	447 (59.8)	798 (52.2)
GT1b	387 (49.6)	257 (34.4)	644 (42.1)
GT4	11 (1.4)	13 (1.7)	24 (1.6)
GT2, 3, missing GT	12 (1.5)	7 (0.9)	19 (1.2)
Prior interferon	79 (10.1)	90 (12.0)	169 (11.1)
Prior BOC/TEL/SOF/ SIM+SOF	3 (0.4)	2 (0.3)	5 (0.3)
Prior LDV/SOF, PrOD, SOF/VEL	28 (3.6)	18 (2.4)	46 (3.0)
Compensated cirrhosis	135 (17.3)	149 (20.0)	284 (18.6)
Decompensated cirrhosis	103 (13.2)	201 (26.9)	304 (19.9)
Depression	480 (61.5)	414 (55.4)	894 (58.5)
Diabetes	472 (60.4)	585 (78.3)	1057 (69.2)
History of drug abuse	440 (56.3)	396 (53.0)	836 (54.7)
History of alcohol abuse	497 (63.6)	416 (55.7)	913 (59.8)
HIV	31 (4.0)	45 (6.0)	76 (5.0)
History of kidney transplant	10 (1.3)	53 (7.1)	63 (4.1)
History of liver transplant	5 (0.6)	19 (2.5)	24 (1.6)
eGFR – Mean (SD)	50.6 (12.7)	12.7 (7.6)	32.1 (21.7)
% bvl ≥6M IU/ml*	133 (17.0)	93 (12.5)	226 (14.8)

LDV/SOF, ledipasvir/sofosbuvir; PrOD, paritaprevir/ritonavir/ombitasvir and dasabuvir; SOF, sofosbuvir; VEL: velpatasvir; SIM, simeprevir; BOC, boceprevir; TEL, telaprevir; IFN, Interferon; BVL, baseline viral load

Distribution of Patients by CKD Stages

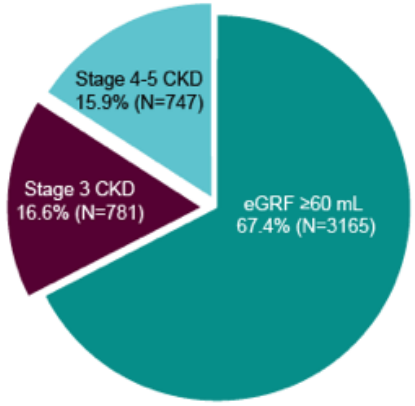


Figure 3. SVR Rate Overall and by CKD Stages

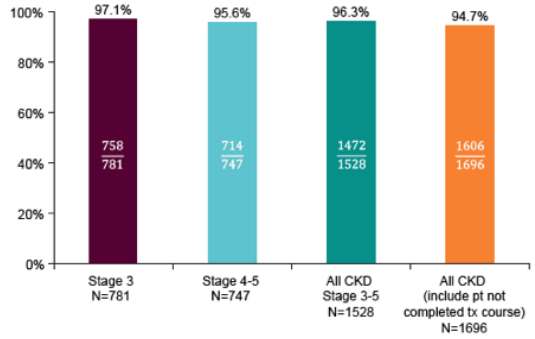
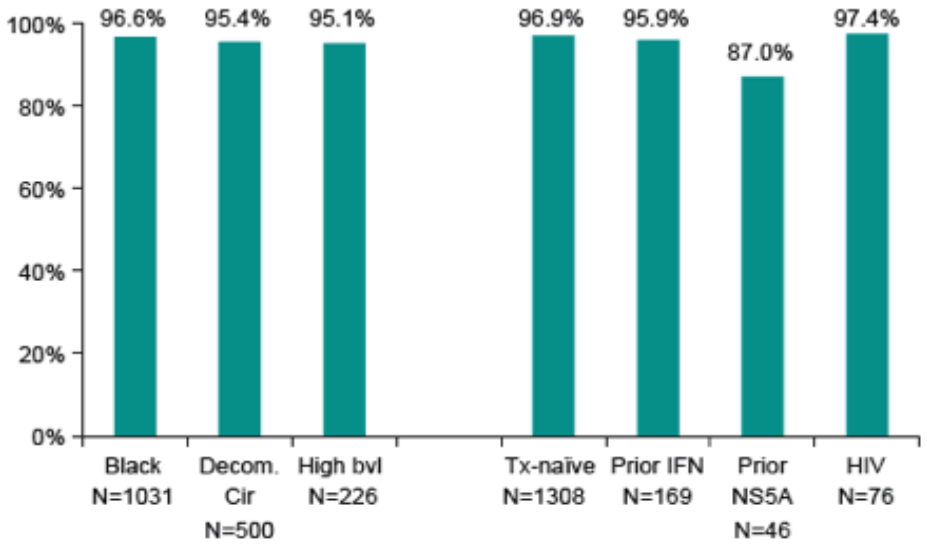


Figure 5. SVR (PP) Rates in EBR/GZR Patients with CKD Stages 3-5



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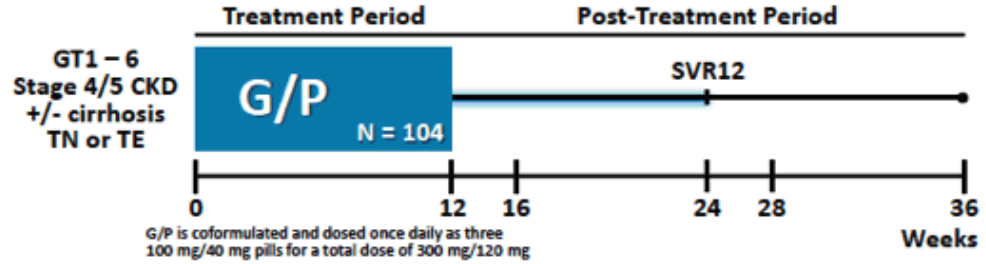
EXPEDITION-4: Objective and Study Design



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)

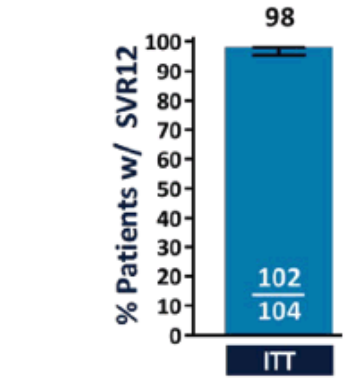
Endpoints

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

Baseline Clinical Characteristics Continued

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)

SVR12 by Intent-to-treat (ITT) Analysis



Breakthrough	0
Relapse	0
Discontinuation	1
LTFU	1

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Patients with renal impairment, including haemodialysis patients

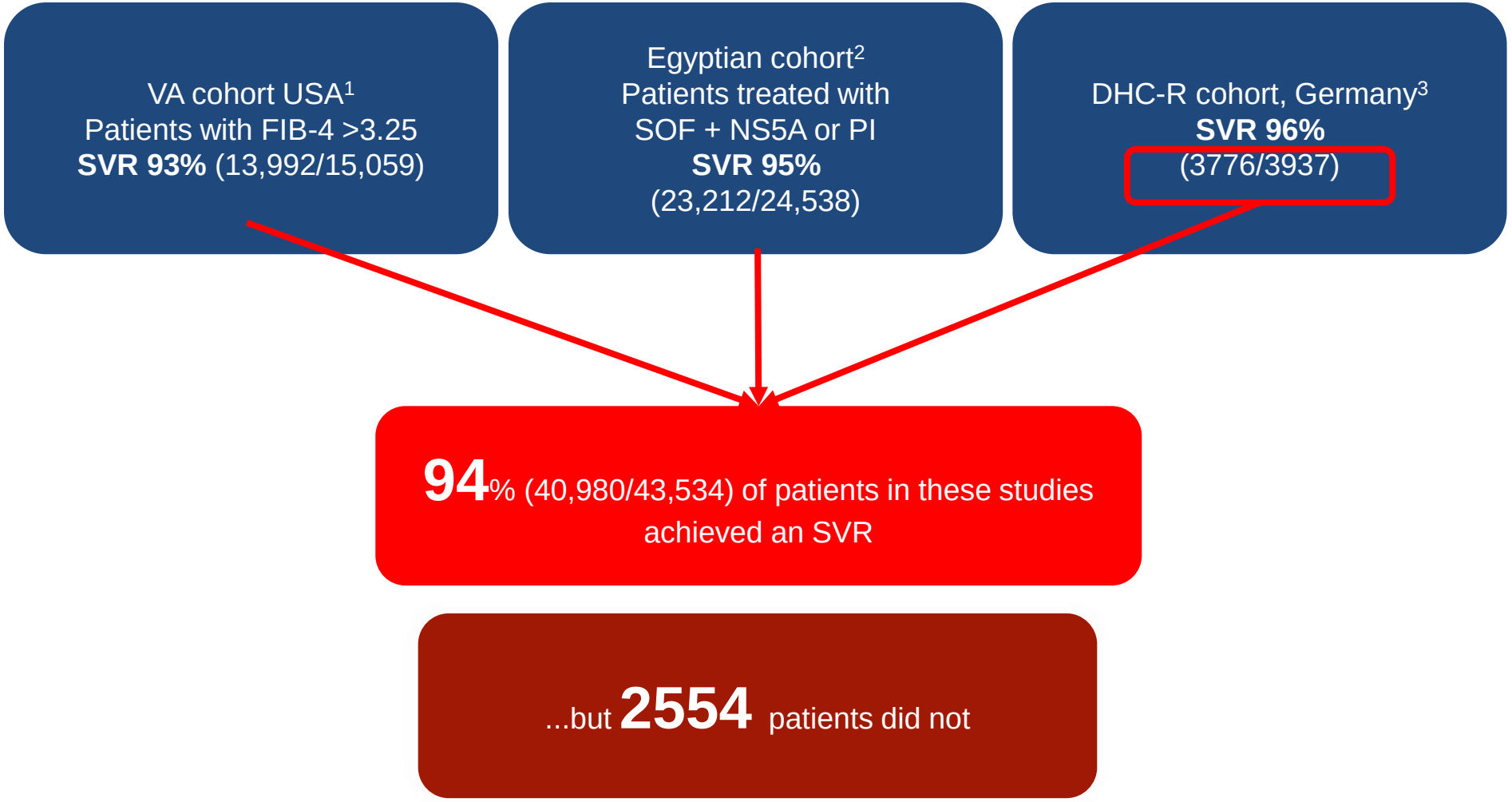
Recommendations

- Patients with HCV infection and mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m^2) should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored (**A1**).
- Patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) and patients with end-stage renal disease on haemodialysis should be treated in expert centres, with close monitoring by a multidisciplinary team (**B1**).
- Sofosbuvir should be used with caution in patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease, only if an alternative treatment is not available, because no dose recommendation can currently be given for these patients (**B1**).
- Patients infected with all genotypes with severe renal impairment (eGFR <30 ml/min/1.73 m^2), or with end-stage renal disease on haemodialysis, without an indication for kidney transplantation, should be treated with the fixed-dose combination of glecaprevir and pibrentasvir for 8 or 12 weeks, according to the general recommendations (**A1**).
- Patients infected with HCV genotype 1a and treatment-naïve patients infected with genotype 4 with severe renal impairment (eGFR <30 ml/min/1.73 m^2), or with end-stage renal disease on haemodialysis, without an indication for kidney transplantation and with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml), can be treated with the combination of grazoprevir and elbasvir for 12 weeks (**A1**).
- Patients infected with HCV genotype 1b with severe renal impairment (eGFR <30 ml/min/1.73 m^2), or with end-stage renal disease on haemodialysis, without an indication for kidney transplantation, can be treated with the combination of grazoprevir and elbasvir for 12 weeks, or with the combination of ritonavir-boosted paritaprevir, ombitasvir and dasabuvir for 12 weeks (**A1**).
- The risks *vs.* benefits of treating patients with end-stage renal disease and an indication for kidney transplantation before or after renal transplantation require individual assessment (**B1**).

HCV treatment, key populations and therapeutic issues

- Poly-pharmacy and comorbidities
- People who inject drugs and patients receiving opioid substitution therapy
- Patients with renal impairment, including haemodialysis patients
- **Previous DAAs failures**
- Adolescents and children
- Neurocognitive and neuropsychiatric dersorders
- HBV co-infection

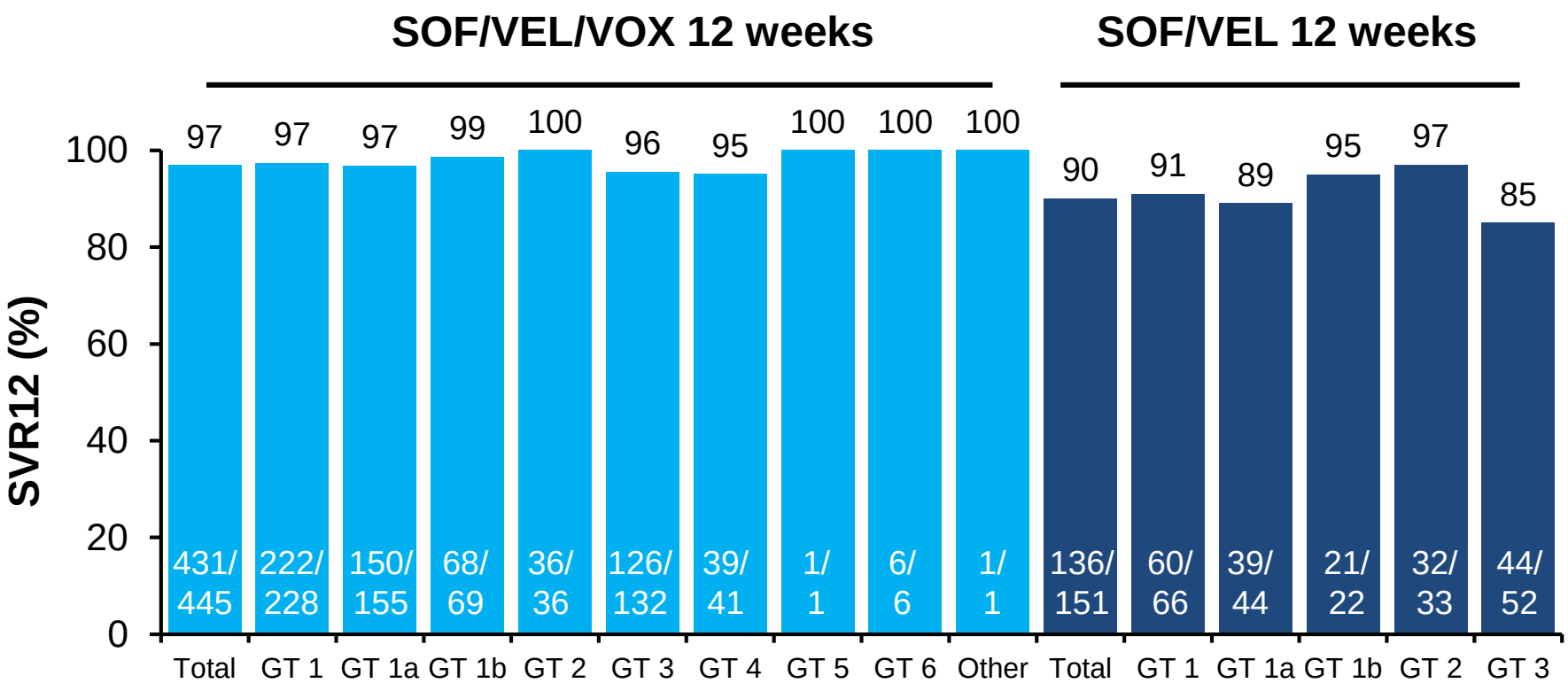
Patients who have experienced DAA treatment failure are a small but important HCV patient population



VA: Veterans Affairs; DHC-R: German Hepatitis C Registry

1. Backus, Hepatology 2017; 2. Gomaa, Hepat Med 2017; 3. Welzel, ILC 2016.

SOF/VEL/VOX for 12 weeks is effective in GT 1–6 DAA-experienced patients



Tolerability of SOF/VEL/VOX for 12 weeks

- SAEs were reported in 9 (2%) patients receiving SOF/VEL/VOX for 12 weeks, none were considered treatment-related
- 1 patient died 2 days after completing treatment from an illicit drug overdose

Bourliere, N Engl J Med 2017.

HCV treatment, key populations and therapeutic issues

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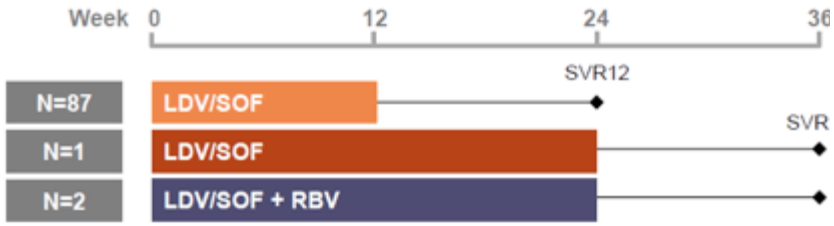
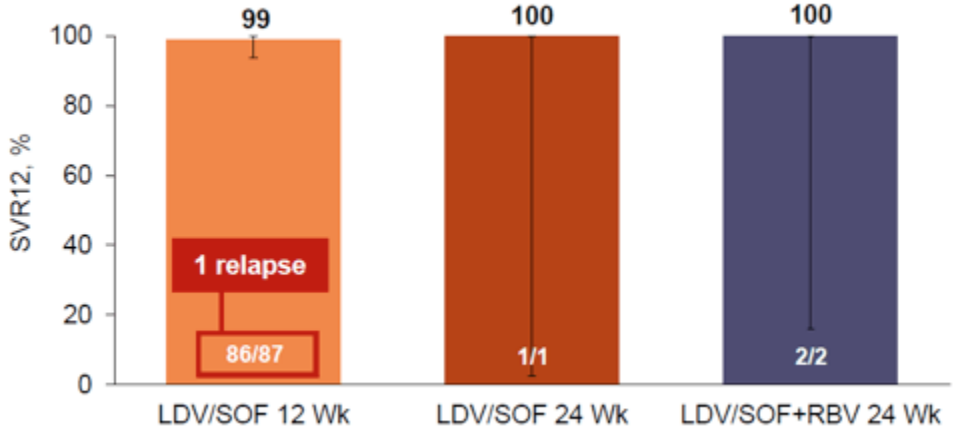
Ledipasvir/Sofosbuvir ± Ribavirin for 12 or 24 Weeks Is Safe and Effective in Children 6-11 years old with Chronic Hepatitis C Infection

Karen FM. Et al.: EASL 2017 April 19-22 Amsterdam Netherland





	LDV/SOF ± RBV n=90
Mean age, y (range)	9 (6–11)
Male, n (%)	53 (59)
White, n (%)	71 (79)
Mean weight, kg (range)	33 (18–76)
Mean BMI, kg/m^2 (range)	18 (13–31)
HCV GT 1, n (%)	86 (96)
HCV GT 3, n (%)	2 (2)
HCV GT4, n (%)	2 (2)
Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	6.0 (4.6–7.3)
HCV RNA ≥800,000 IU/mL, n (%)	54 (60)
Treatment experienced, n (%)	18 (20)
Cirrhosis*, n (%)	2 (2)
IL28B CC, n (%)	23 (26)
Vertical transmission (infected mother), n (%)	87 (97)

* Cirrhosis status unknown in 63 (70%) patients

In summary, in GT1, 3, or 4 infected patients 6 to 11 years old, a single tablet regimen of LDV/SOF 45/200mg ± RBV for 12 or 24 weeks resulted in impressive high SVR12 rates ≥ 99%; within the study LDV/SOF 45/200 mg was very well tolerated

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EASL Recommendations on Treatment of Hepatitis C 2018☆

Treatment of special groups

Adolescents and children

Recommendations

- Adolescents aged 12 years and above infected with genotype 1, 4, 5 or 6 who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, should be treated with the fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg) for 12 weeks (**B1**).
- Adolescents aged 12 years and above infected with genotype 2 or 3 who are treatment-naïve or treatment-experienced, without cirrhosis or with compensated (Child-Pugh A) cirrhosis, can be treated with other regimens approved for adults, with caution pending more safety data in this population (**C2**).
- In children younger than 12 years, treatment should be deferred until DAAs, including pangenotypic regimens, are approved for this age group (**B1**).

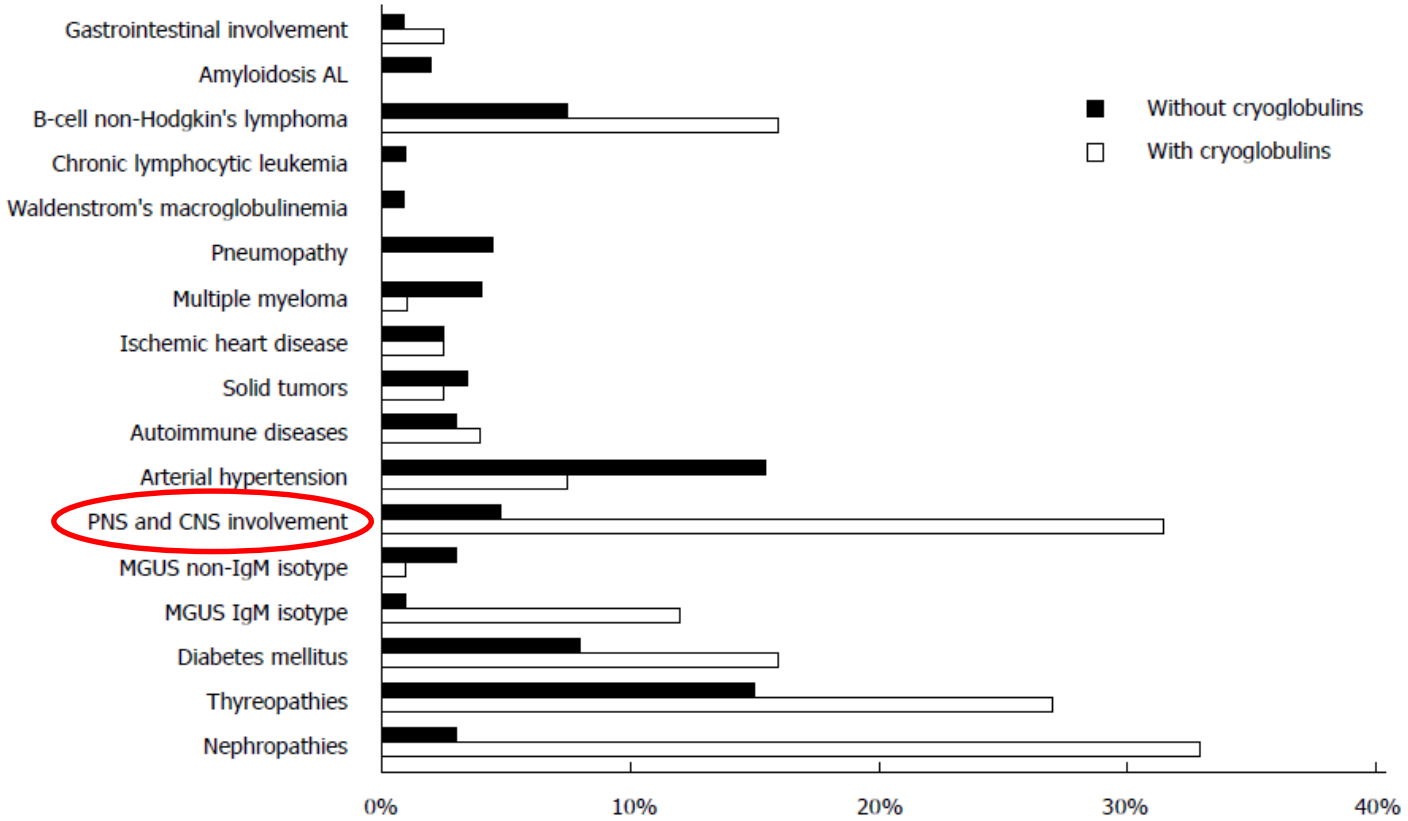
HCV treatment, key populations and therapeutic issues

- Poly-pharmacy and comorbidities
- People who inject drugs and patients receiving opioid substitution therapy
- Patients with renal impairment, including haemodialysis patients
- Previous DAAs failures
- Adolescents and children
- **Neurocognitive and neuropsychiatric desorders**
- HBV co-infection

WJG

Hepatitis C virus-associated neurocognitive and neuropsychiatric disorders: Advances in 2015

Monaco S *et al*. November 14, 2015 | Volume 21 | Issue 42 |



Summary of major extra-hepatic manifestations observed in patients with chronic hepatitis C virus infection. Percentages of patients are represented in graphic form. The presence or absence of cryoglobulinemia is indicated by white and black, respectively. The most convincing associations of chronic hepatitis C virus (HCV) infection are with subsets of B-cell non-Hodgkin lymphoma (B-NHL), membranous or membrano-proliferative glomerulonephritis, IgM monoclonal gammopathy of undetermined significance (MGUS), peripheral neuropathy, and central nervous system (CNS) disorders.

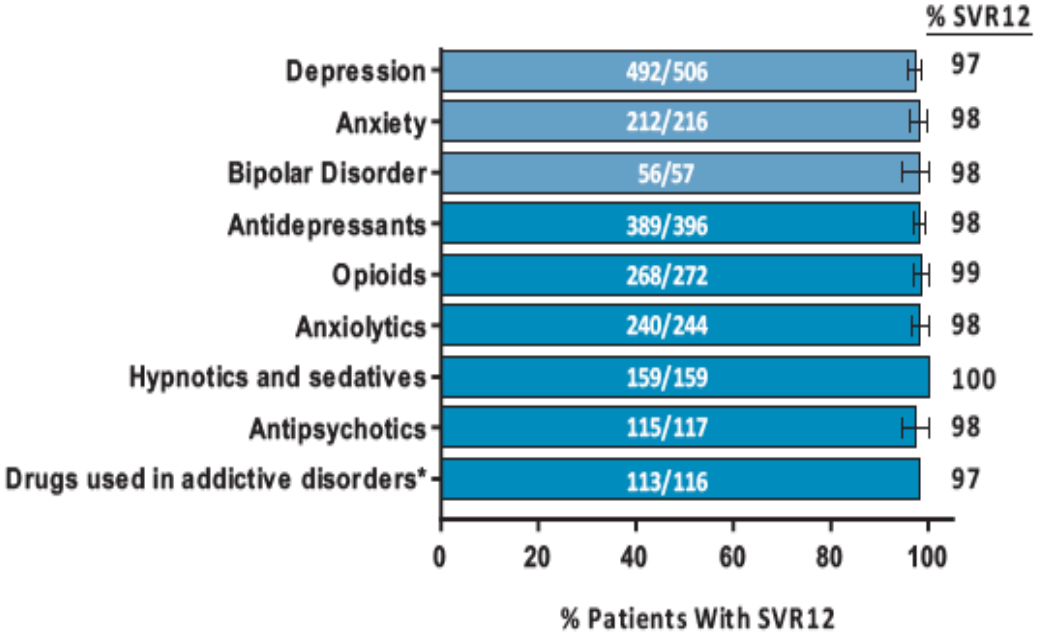
Integrated Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients With Psychiatric Disorders

Back D et al.: 7th International Network on Hepatitis Care in Substance Users
19–21 September 2018, Lisbon, Portugal

METHODS

- Data were pooled for 2522 treatment-naïve and -experienced patients with chronic HCV genotype (GT) 1–6 infections who received G/P once-daily (QD) for 8, 12, or 16 weeks in ten Phase 2 and 3 trials
  - Data were included for all patients who received at least 1 dose of study drug in an intent-to-treat analysis
- Patients were classified as having a psychiatric disorder if they had:
  - Medical history of psychiatric or neurological disorder including anxiety, bipolar disorder, cognitive or psychiatric disorder, depression, Parkinson's disease, seizure disorder/convulsion, OR
  - Concomitant medication use of antidepressants or antipsychotics as defined by Anatomical Therapeutic Chemical (ATC) Classification System[8]
- Concomitant neurological drugs were allowed in G/P clinical trials except for carbamazepine, phenytoin, pentobarbital, phenobarbital, and primidone
  - These 5 neurological drugs are contraindicated for concomitant use with G/P in EU, but not in US

Figure 4. Subgroup Efficacy Analysis by Psychiatric Disorders or CNS Mediations Using an ITT Analysis



ITT, intent-to-treat.

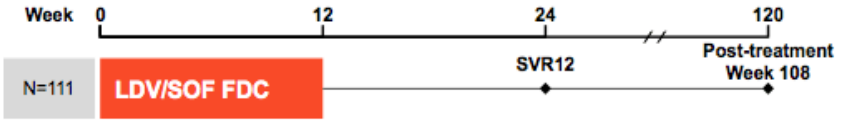
*89/116 (76.7%) had ≥80% treatment compliance; all other subgroups had more than 84% of patients with ≥80% treatment compliance.

HCV treatment, key populations and therapeutic issues

- Poly-pharmacy and comorbidities
- People who inject drugs and patients receiving opioid substitution therapy
- Patients with renal impairment, including haemodialysis patients
- Previous DAAs failures
- Adolescents and children
- Neurocognitive and neuropsychiatric dersorders
- **HBV co-infection**

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

Karen FM. Et al.: EASL 2017 April 19-22 Amsterdam Netherland

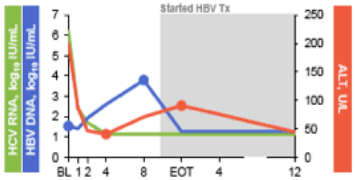


		LDV/SOF 12 weeks N=111
HCV	Mean age, y (range)	55 (32–76)
	Male, n (%)	42 (38)
	Mean BMI, kg/m^2 (range)	25 (17–34)
	IL28B CC, n (%)	85 (77)
	GT 1 / GT 2, n (%)	68 (61) / 43 (39)
	HCV treatment experienced, n (%)	37 (33)
	Mean baseline HCV RNA, $\log_{10}$ IU/mL (range)	5.9 (3.8–7.1)
	Cirrhosis, n (%)	18 (16)
	Mean ALT, U/L (range)	68 (17–281)
HBV	HBsAg positive, n (%)	110* (99)
	HBeAg positive, n (%)	1 (<1)
	GT B/ GT C n (%)	37 (33) / 5 (5)
	GT Missing†	69 (62)
	HBV treatment experienced, n (%)	5 (4)
	Mean baseline HBV DNA, $\log_{10}$ IU/mL (range)	2.1 (1.3–5.8)
	Baseline HBV DNA <LLOQ, n (%)	37 (33)

Results: Two Asymptomatic Patients Started HBV Therapy

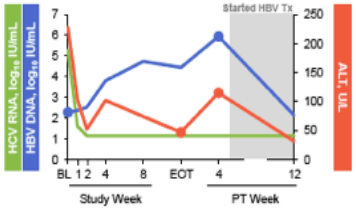
60-year-old female, HCV GT 1b, HBeAg negative, with cirrhosis

- HBV DNA increased from 1.54$\log_{10}$ IU/mL (BL) to 3.8$\log_{10}$ IU/mL at Day 57 (Week 8)
- Associated with ALT increase from nadir value of 41 to 71 IU/mL
- Started HBV treatment on study Day 71



61-year-old male, HCV GT 2, HBeAg negative, without cirrhosis

- HBV DNA increased from 2.28$\log_{10}$ IU/mL (BL) to 5.95$\log_{10}$ IU/mL 30 days post last dose (post-treatment Week 4)
- Associated with ALT increase from nadir value of 47 to 115 IU/mL
- Started HBV treatment during post-treatment follow-up Week 5



n, %	Overall N=111	BL HBV DNA <LLOQ n=37	BL HBV DNA ≥LLOQ n=74
Increase to ≥LLOQ	31 (28)	31 (84)	—
+ ALT >2x ULN	0	0	—
Increase >1 – <2 $\log_{10}$ IU/mL	37 (33)	11 (30)	26 (35)
+ ALT >2x ULN	1 (<1)	0	1 (1)
Increase ≥2 $\log_{10}$ IU/mL (any visit)	24 (22)	11 (30)	13 (18)
+ ALT >2x ULN	4 (4)	0	4 (5)

Results: HBV Clinical Reactivation, Multivariate Analysis

Factors Associated with HBV DNA Increase >1$\log_{10}$ IU/mL and ALT >2x ULN

HBV Reactivation	No n=106	Yes n=5	p-Value
Mean baseline ALT, U/L (range)	64 (17–281)	149 (40–228)	0.0032
Mean baseline HBV DNA, $\log_{10}$ IU/mL (range)	2.05 (1.28–5.83)	2.97 (1.54–5.46)	0.0188

In conclusion, LDV/SOF for 12 weeks achieved 100% SVR12 rate in patients with HBV and HCV GT 1 or 2 infections. Silent HBV viral reactivation was observed in 63% of patients (70/111) with however, no patient experienced clinical signs or symptoms of HBV reactivation. 5 (5%) patients had concomitant increase in ALT; 2 (2%) patients were started on HBV therapy

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 March 2016
EMA/199242/2016

EMA reviews direct-acting antivirals for hepatitis C

Review to investigate possible hepatitis B re-activation

HBV coinfection

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Recommendations on Treatment of Hepatitis C 2018☆

European Association for the Study of the Liver*

Recommendations

- Patients with HBV-HCV coinfection should be treated with the same anti-HCV regimens, following the same rules as HCV monoinfected patients (**B1**).
- Patients coinfected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nucleoside/nucleotide analogue treatment according to the EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection (**A1**).
- Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped (**B1**).
- In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue therapy should be initiated if HBs antigen and/or HBV DNA are present (**B1**).
- HBs antigen-negative, anti-HBc antibody-positive patients undergoing anti-HCV treatment should be monitored monthly for ALT and tested for HBs antigen and HBV DNA in case of ALT elevation (**B1**).


QUANDO PENSI DI AVERE TUTTE LE RISPOSTE, LA VITA TI CAMBIA TUTTE LE DOMANDE..

Grazie