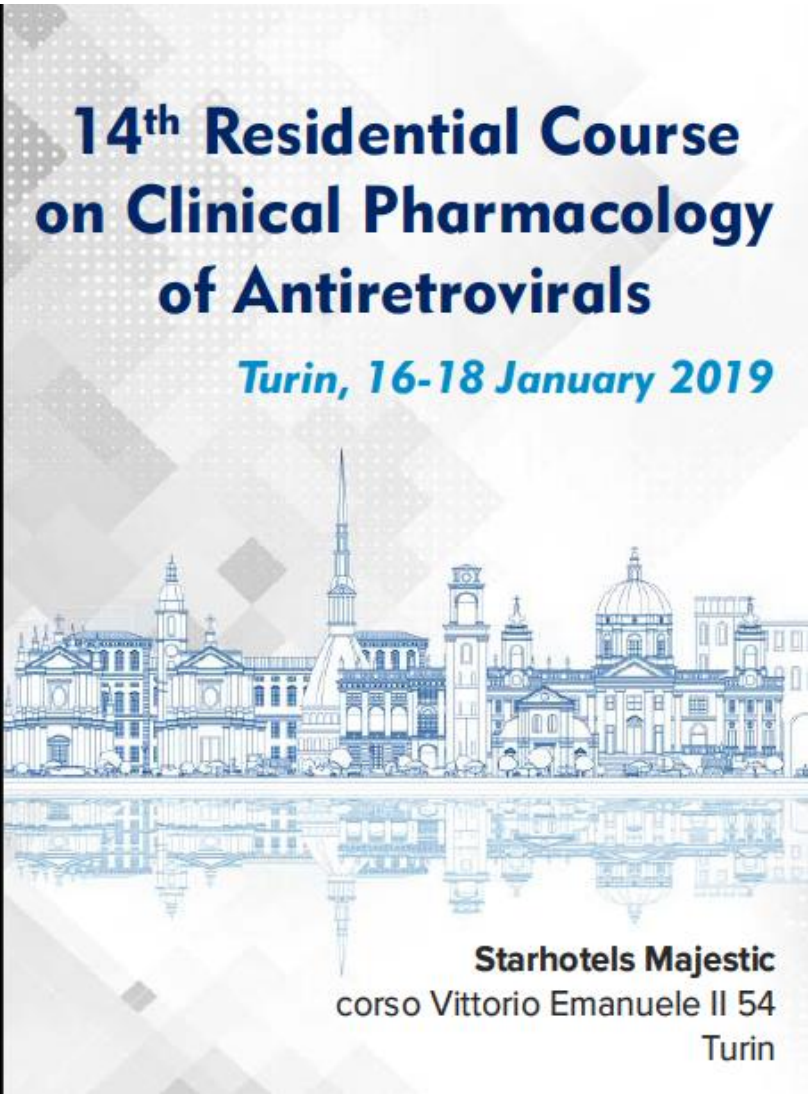
Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Massimo Puoti
Infectious Diseases Dept
ASST GRANDE OSPEDALE
METROPOLITANO NIGUARDA
MILANO



HCV from cure to eradication

“Disclosures”

- Honoraria for consulting or speaking (past 5 years):
- AbbVie, Beckman, BMS, Janssen, Gilead Sciences, MSD, Roche, and ViiV
- Research grants:
- Gilead Sciences, ViiV, Roche, Pfizer Astellas and Novartis
- The presentation will include data on not approved drugs and on approved drugs not used according to SPC

HCV from cure to eradication

- The cure: how we got there
- The cure: the most effective anti infective cure ever seen
- Unmet needs?
- From cure to eradication: new strategies new tools

HCV from cure to eradication

- The cure: how we got there
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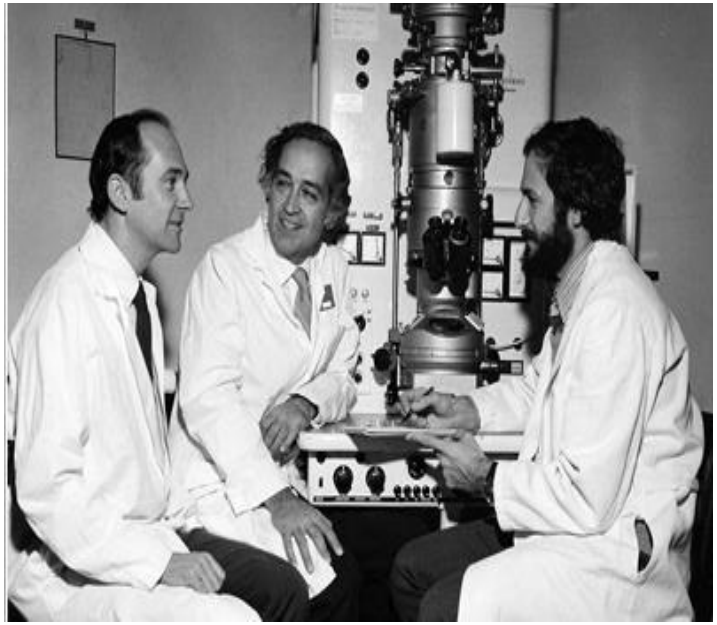
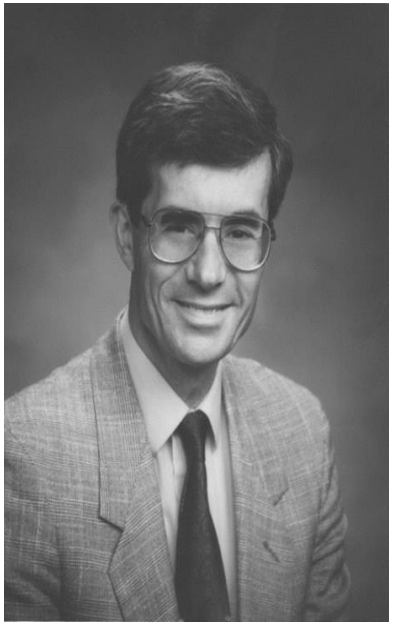
The First Description of Non A non B Hepatitis in Blood Transfusion Recipients

April 10, 1975 THE NEW ENGLAND JOURNAL OF MEDICINE

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

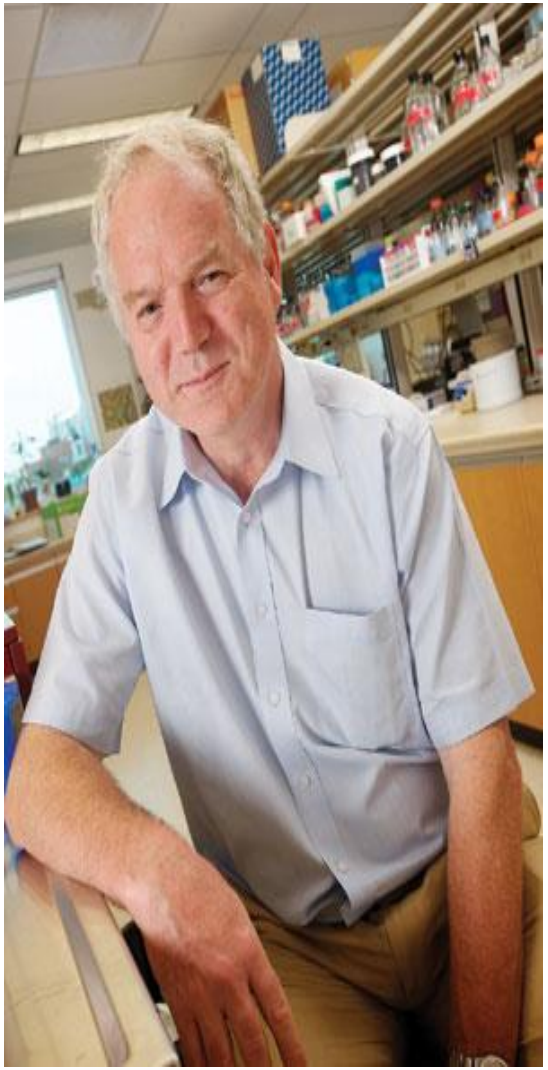
STEPHEN M. FEINSTONE, M.D., ALBERT Z. KAPIKIAN, M-D., ROBERT H. PURCELL, M.D., HARVEY J. ALTER, M.D., AND PAUL V. HOLLAND, M.D.





Feinstone SM et al, N Engl J Med 1975;292:767–770

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

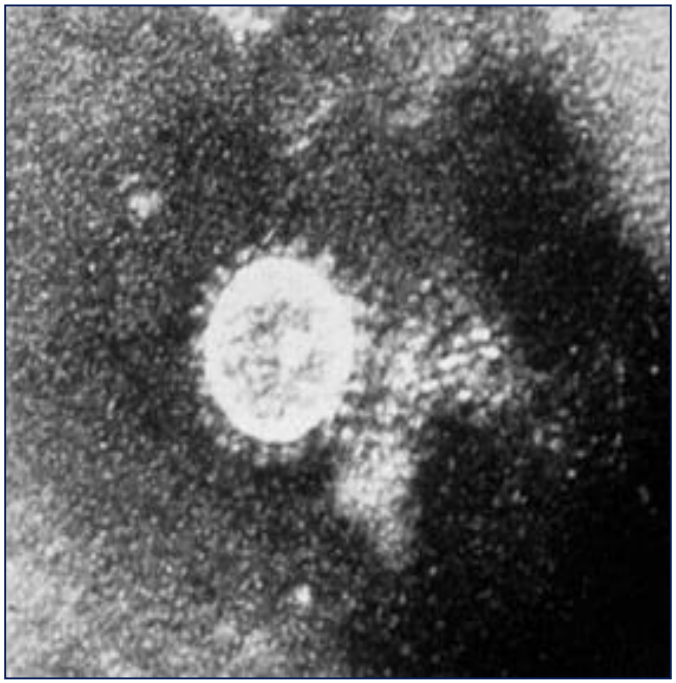
21 APRIL 1989 SCIENCE, VOL. 244

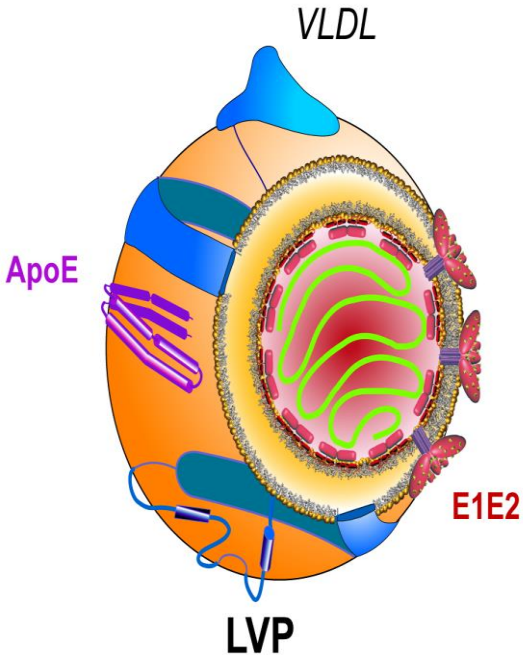
An Assay for Circulating Antibodies to a Major Etiologic Virus of Human Non-A, Non-B Hepatitis

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

The Hepatitis C Virus

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

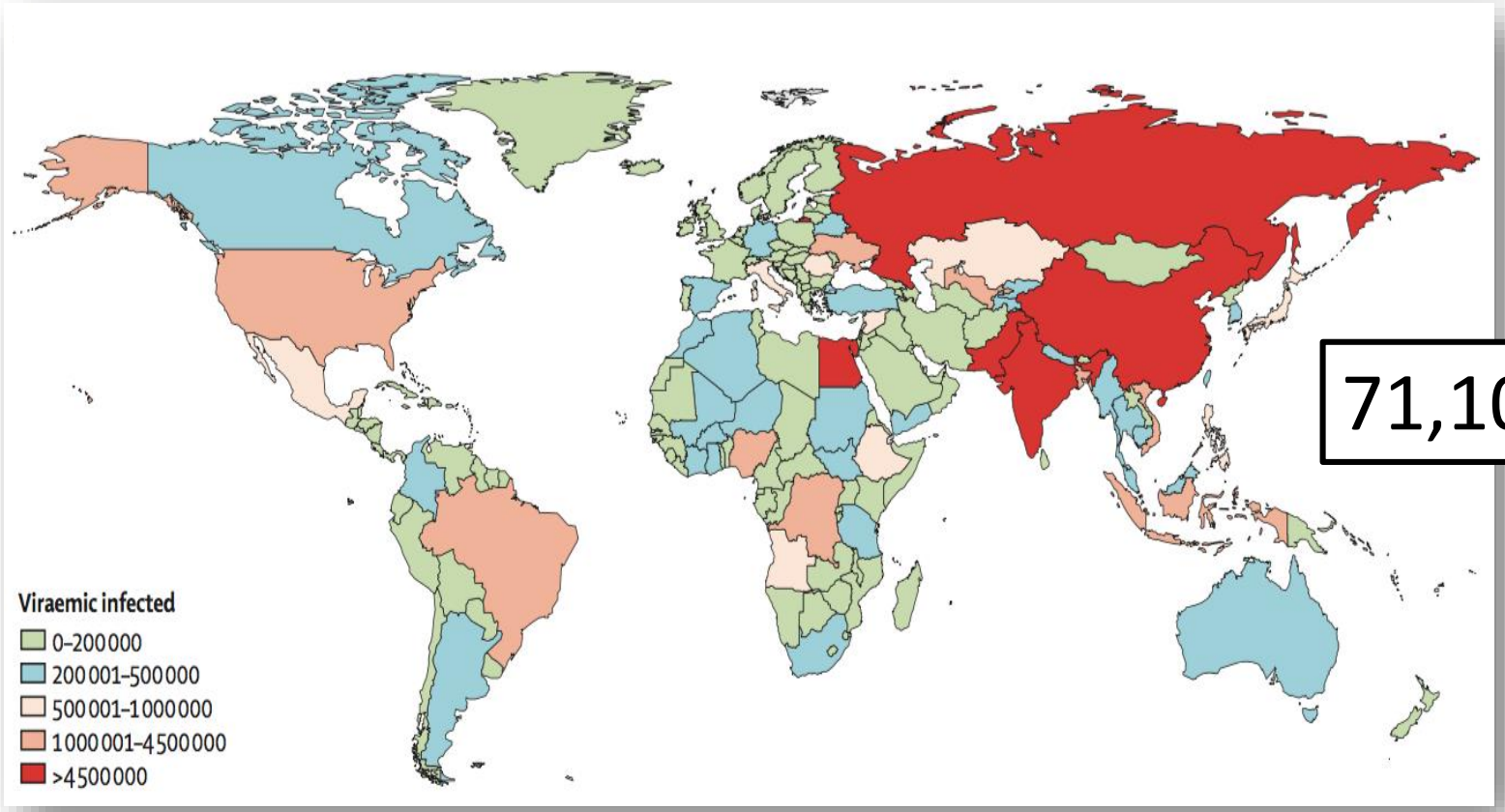




- 7 genotypes, 67 subtypes
- Originated in West Africa or South-East Asia
- Epidemic spread: started in 1900, expanded globally after WW II

Smith et al, Hepatology 2014;59:318-327

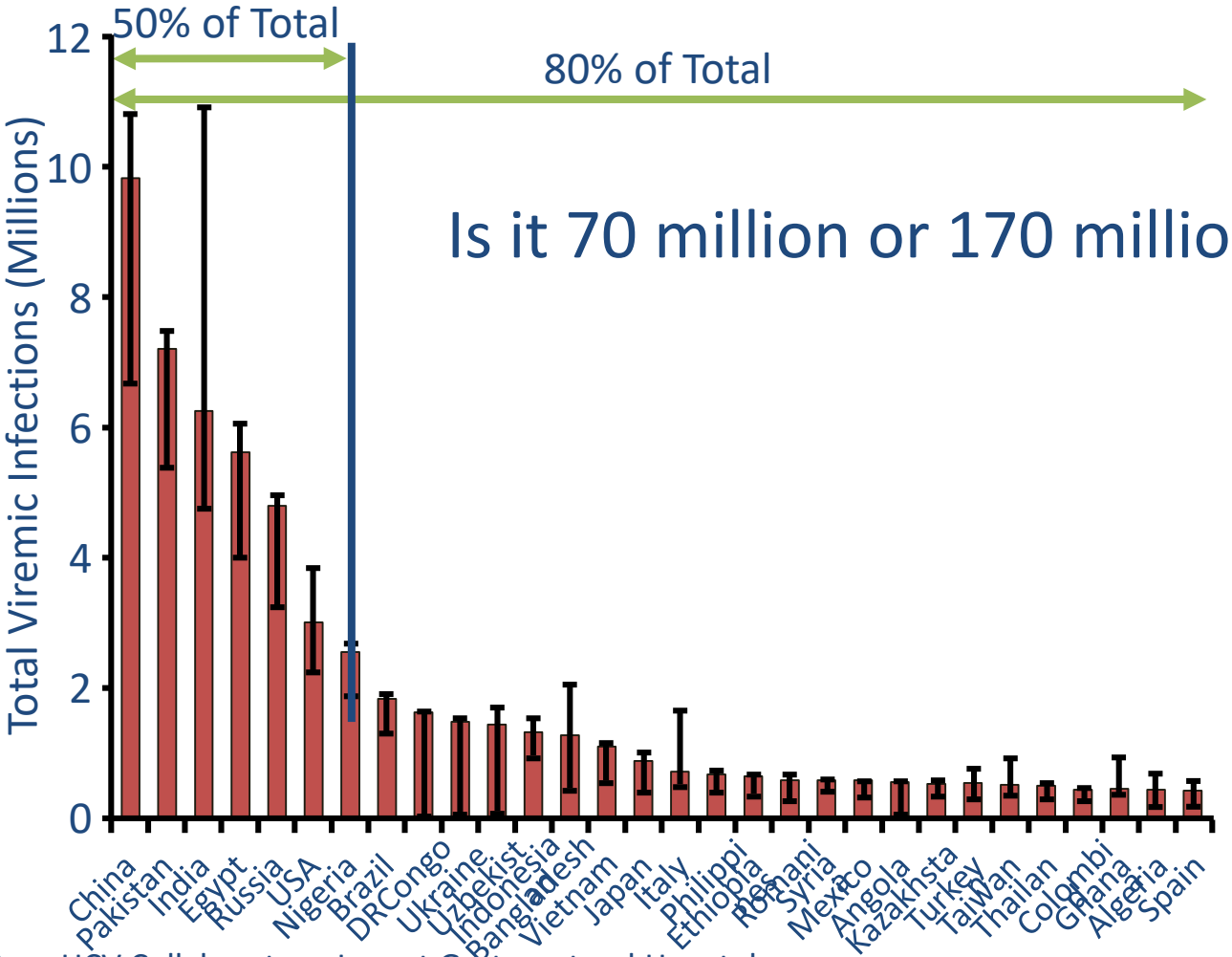
HCV infection worldwide



71,100,000

The Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol 2017;2:161-76

30 Countries Account for 80% of HCV Infections



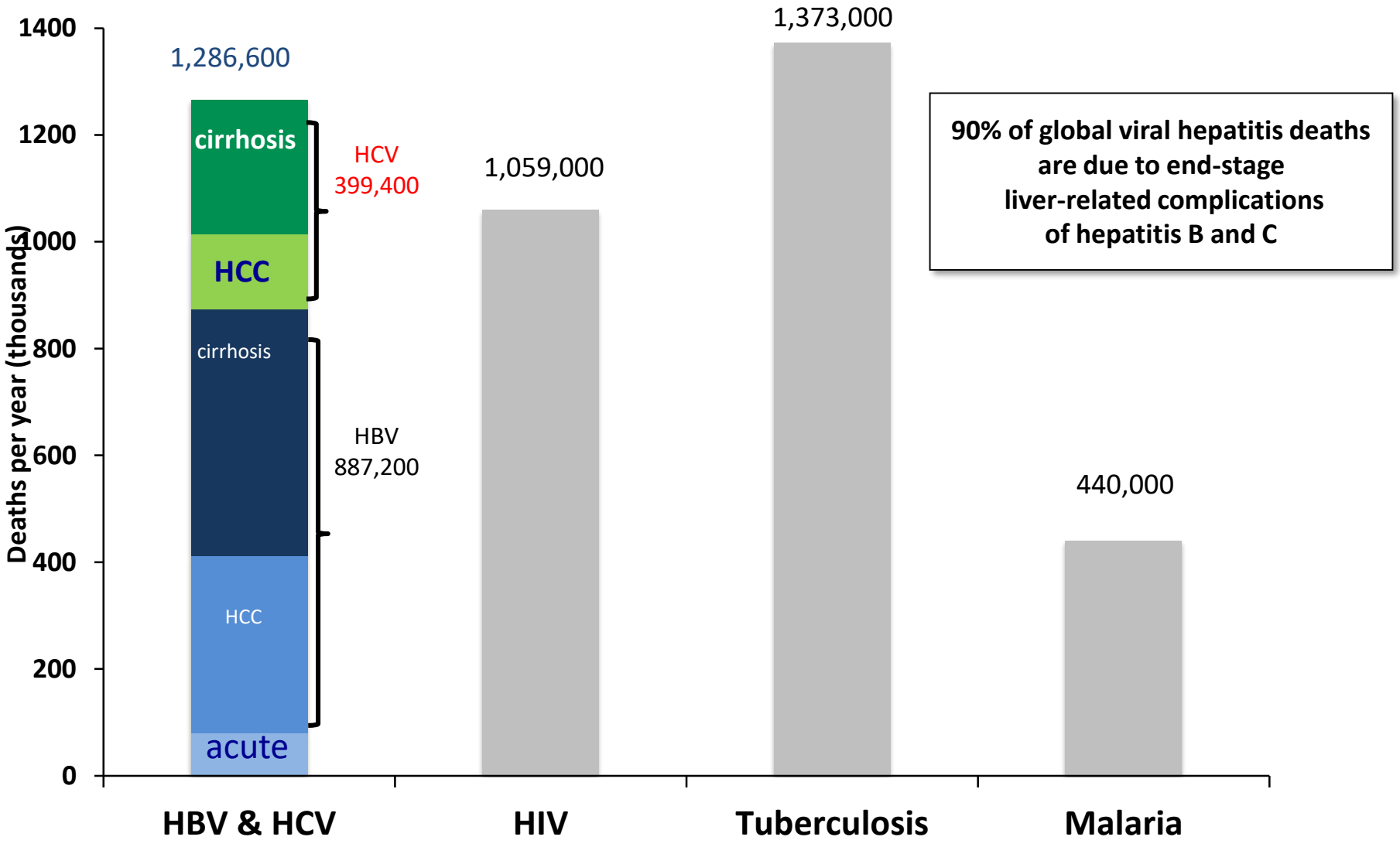
Is it 70 million or 170 million (WHO)?

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2:161-176.

Blach S, et al. AASLD 2016. Abstract 753.

The burden of viral liver disease

In Italy 2010 16.000 deaths due to HCV



WHO 2017 Global Hepatitis Report

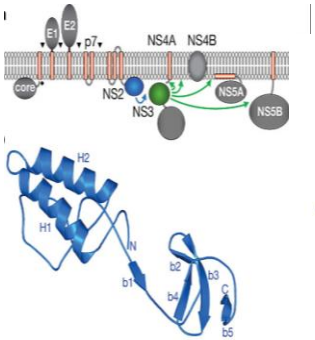
Hepatitis C Virus Life Cycle: 25 Years Ago

Roadblocks to HCV research:

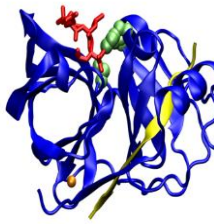
- No virus replication in cell culture
- No small animal models (chimpanzees)

Adapted from CM Rice

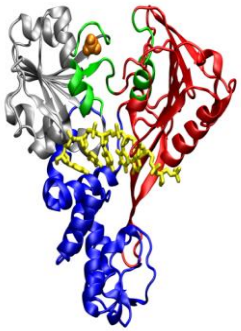
Milestones in hepatitis C therapy



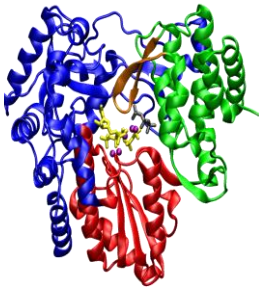
NS2 protease[1]



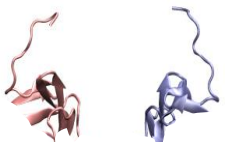
NS3 protease[2]



NS3 helicase[3]



NS5B polymerase[4]



NS5A domain 1[5]

1986 1989 1991 **1996** **1998** **1999** 2001 2003 **20052006** 2011 2013

Replication of Subgenomic Hepatitis C Virus RNAs in a Hepatoma Cell Line

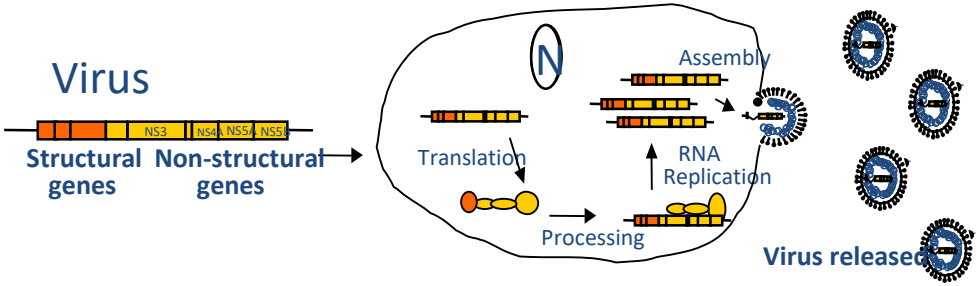
V. Lohmann,[1] F. Körner,[1] J.-O. Koch,[1] U. Herian,[1] L. Theilmann,[2] R. Bartenschlager[1]*

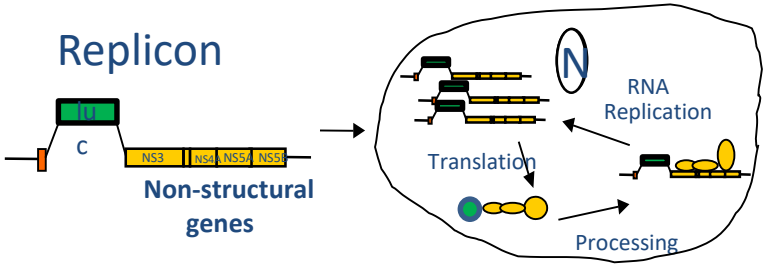
Science, July 1999;285:110-113

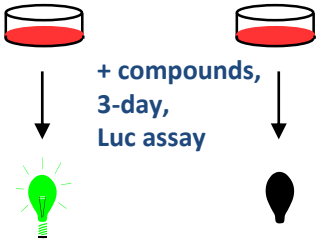
Lorenz IC, *et al. Nature* 2006; **442**:831–835;
2. Kim JL, *et al. Cell* 1996; **87**:343–355;
3. Kim JL, *et al. Structure* 1998; **6**:89–100;
4. Bressanelli S, *et al. Proc Natl Acad Sci* 1999; **96**:13034–13039;
5. Tellinghuisen TL, *et al. Nature* 2005; **435**:374–379.

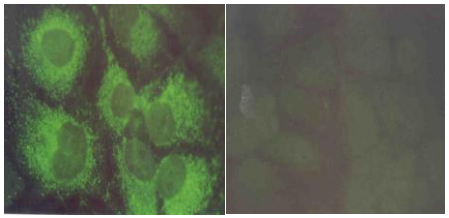
The HCV Replicon Assay

In vitro Assays for HCV







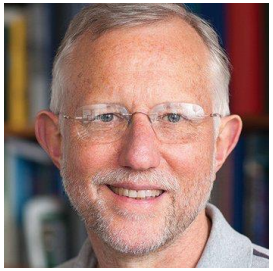


HCV Replicon Naïve cells

- Viral Replication
- NS viral targets
- Non Infectious
- Luc Assay

Evolution of HCV cell culture models
2005: complete cell culture system (HCVcc)

Patient isolate
(JFH1: Japanese Fulminant Hepatitis, gt2a)



Charles T Rice

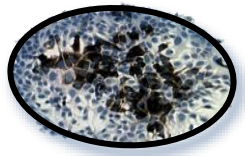
electroporation

Chimpanzee

Huh7.5

HCV virions

Infect naïve cells

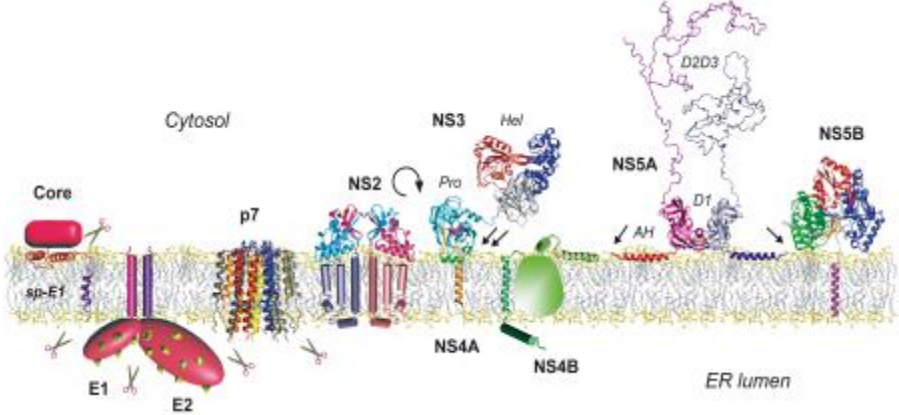


Zhong PNAS 2005
Wakita Nat Med 2005
Pietschmann PNAS 2006
Lindenbach Science 2005
Lindenbach, Meuleman PNAS 2006

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

Fusion and
decapsidation

(+) RNA

2 Traslation

3 Translation and processing
of polyprotein

4 RNA replication

5 Virion assembly

6 Transport and release

miRNA
ISIS 14803 (antisense)
AVI- 4066 (antisense)
Heptazyme (ribozyme)
VGX-410C (small molecules IRES inhibitor) TT 033 (sIRNA)
eIF2α phosphorilation inhibitors:
Nitazoxanide

Inhibitors of viral assembly and release :
Celgosivir

NS5A Inhibitors

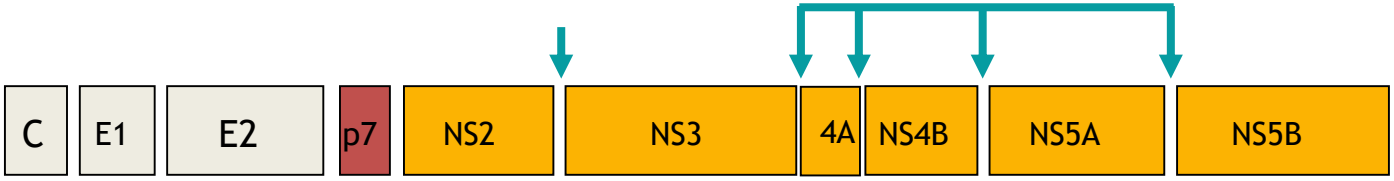
Protease inhibitors

Replication inhibitors:
•NS5B/polymerase
•NNI,
• NI
•NS5A Inhibitors

Cyclophillin Inhibitors

NS2-NS3 protease

NS3 protease



Lindenbach BD & Rice CM. Nature 2005;436:933–938; Moradpour D & Penin F. Curr Top Microbiol Immunol 2013;369:113–142.

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

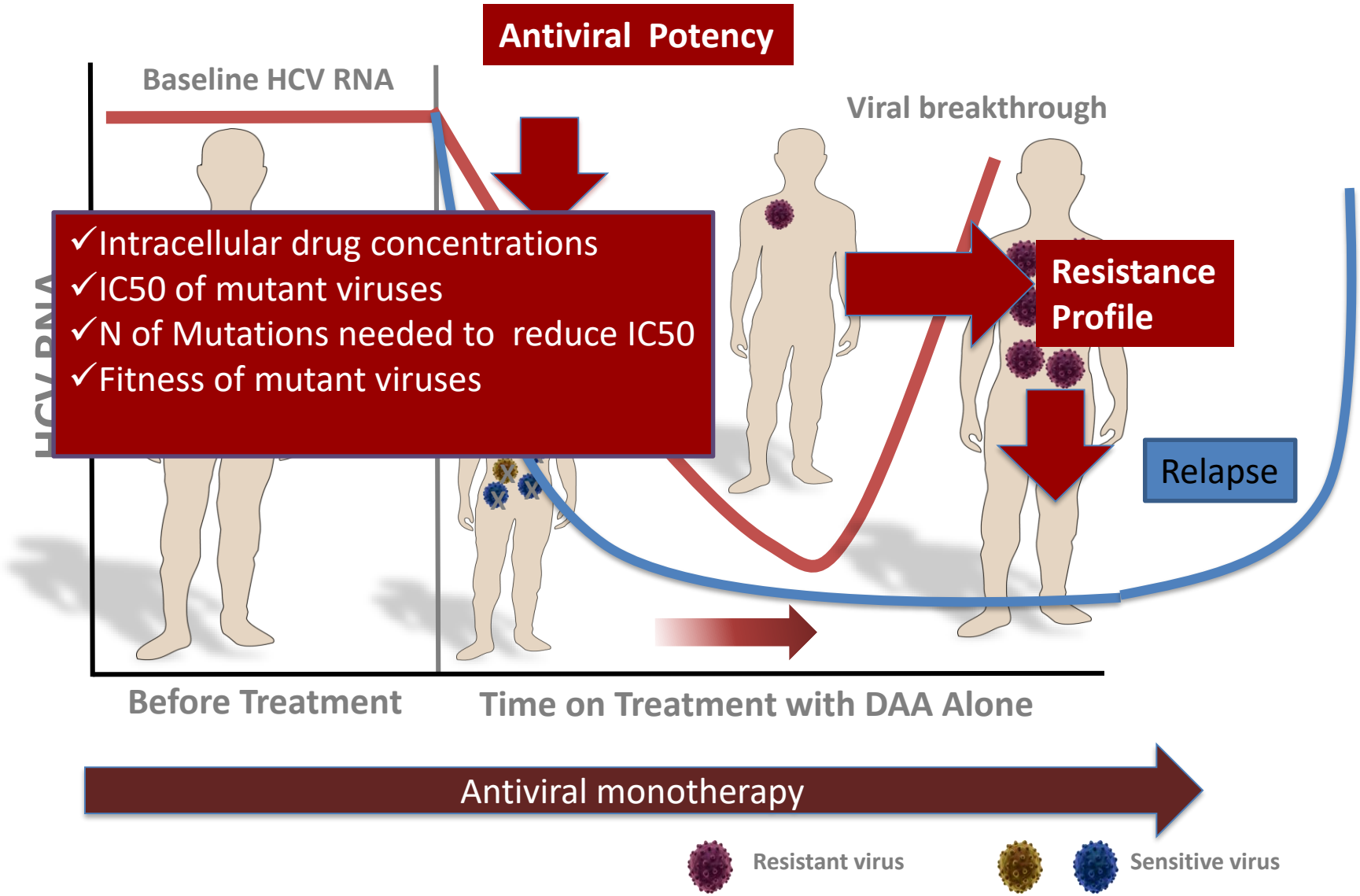
Number of nucleotide change	Probability of generation after one round of replication	Number of virions with nucleotide change(s) produced per day	Number of all possible nucleotide mutants	Fraction of all possible mutants created per day
0	91%	9.1×10^{11}		
1	8.7%	8.7×10^{10}	2.9×10^{4}	1
2	0.4%	4.2×10^{9}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

Not all variants survive

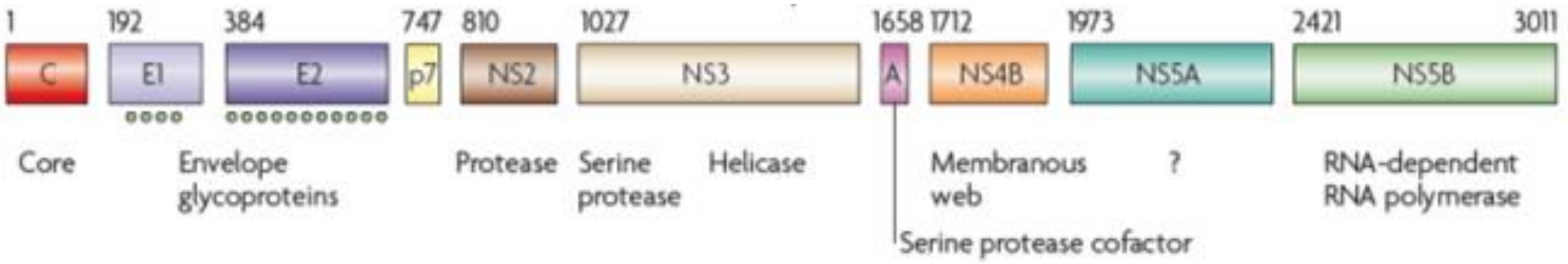
- Dead mutations (variants that can not replicate)
- Immune sensitive mutations (variants eliminated by the immune system)

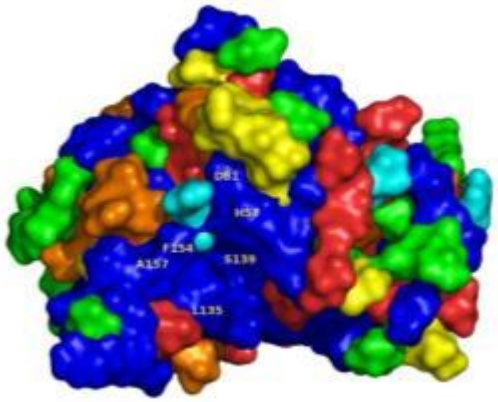
Rong L, et al. Sci Transl Med 2010;2:30ra32; Neumann AU, et al. Science 1998;282:103–107
Domingo E, et al.. Viral Hepatitis Rev 1996;2:247–261; Cuevas JM, et al. J Virol 2009;83:5760–5764

Emergence of Pre-existing Resistant Variants During Treatment with DAA

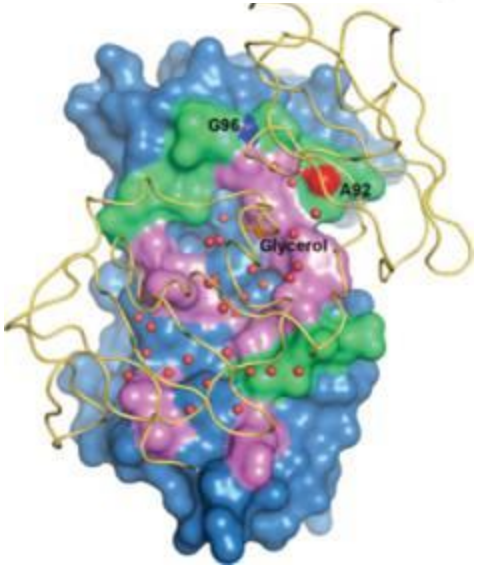


HCV protein variability

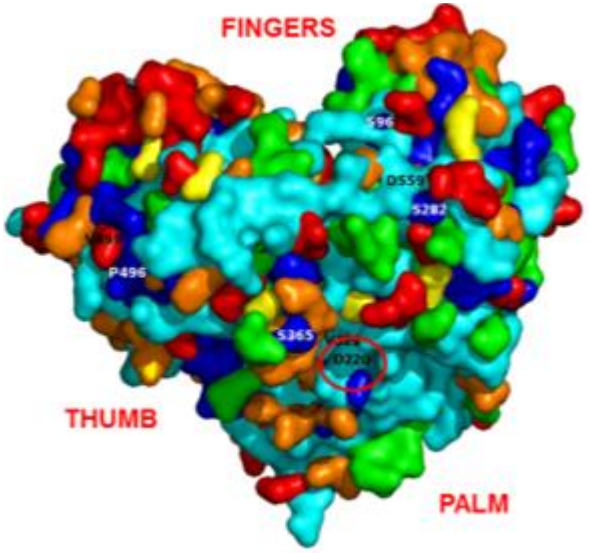




47% amino acid of HCV PROTEASE NS3 are conserved among All HCV-genotypes



46.1% amino acid of HCV NS5A are conserved among All HCV-genotypes



54.8% amino acid of HCV POLYMERASE NS5B are conserved among All HCV-genotypes

Amino acid variability:

0% ≤1% 1-5% 5-10% 10-25% >25%

Cento V, et al. PLoS ONE 2012;7(7):e39652

Love RA, et al. J Vir 2009;83(9):4395–4403

Amino acid variability:

0% ≤1% 1-5% 5-10% 10-25% >25%

Di Maio VC, et al. Antimicrob Agents Chemother 2014;58(5):2781–97

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**  Michael J Sofia
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

Failure & Susceptibility to antiviral therapy.

Different levels of suppression of HCV RNA are required for final eradication of the virus by the immune system (Innate immunity?)

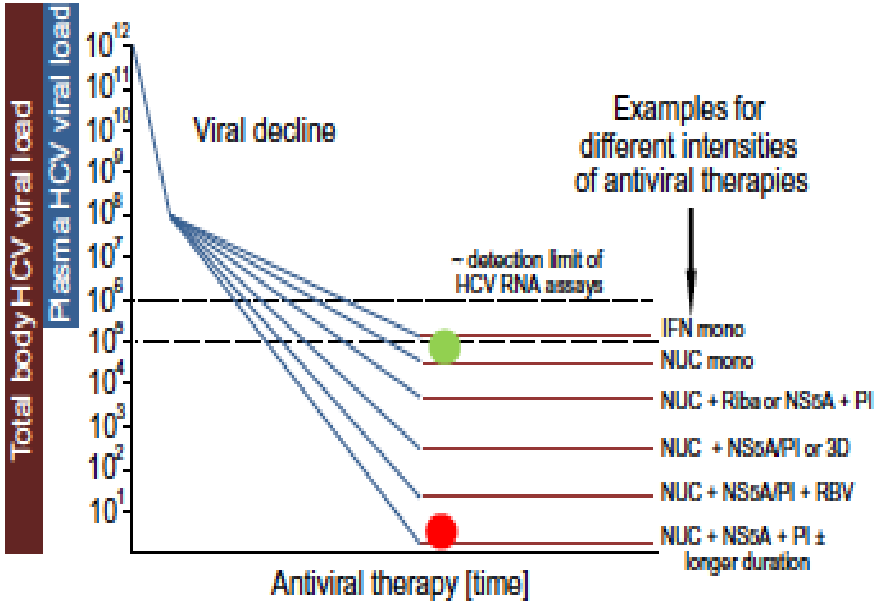
Depending on:

- viral- related factors:
  - **HCV Genotypes**
  - **RASs**
  - **Viremia**
- host-related factors:
  - **Innate immunity (IL28b, IP-10, ISG Previous IFN failure)**
  - **Fibrosis → Disease stage**

.

Failure:
- **Breakthrough**
- **Relapse**

Treatment Modulation by treatment schedule:
- ✓**Ribavirin use**
- ✓**Length of treatment**
- ✓**N of class of drugs**



Difficult to treat patients: IL28b TT or previous treatment failure, HCV G1a/3, HCVRNA > 6 log, Cirrhosis

Easy to treat patients: IL28b CC or no previous treatment , HCV G1b, HCVRNA<6 log, F0-F2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ledipasvir and Sofosbuvir for Untreated HCV Genotype 1 Infection

Nezam Afdhal, M.D., Stefan Zeuzem, M.D., Paul Kwo, M.D., Mario Chojkier, M.D., Norman Gitlin, M.D., Massimo Puoti, M.D., Manuel Romero-Gomez, M.D., Ph.D., Jean-Pierre Zarski, M.D., Ph.D., Kosh Agarwal, M.D., Peter Buggisch, M.D., Graham R. Foster, Ph.D., Norbert Bräu, M.D., M.B.A., Maria Buti, M.D., Ph.D., Ira M. Jacobson, M.D., G. Mani Subramanian, M.D., Ph.D., Xiao Ding, Ph.D., Hongmei Mo, M.D., Jenny C. Yang, Pharm.D., Phillip S. Pang, M.D., Ph.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Andrew J. Muir, M.D., M.H.S., Alessandra Mangia, M.D., and Patrick Marcellin, M.D., Ph.D., for the ION-1 Investigators*

Rapid clearance of HCV-related splenic marginal zone lymphoma under an interferon-free, NS3/NS4A inhibitor-based treatment. A case report

Roberto Rossotti[1]*, Giovanna Travi[1], Annamaria Pazzi[1], Chiara Baiguera[1], Enrica Morra[2], Massimo Puoti[1]

[1]Infectious Diseases Department, "Niguarda Cà Granda" Hospital, Milan, Italy; [2]Oncology/Hematology Department, Niguarda Cancer Center, "Niguarda Cà Granda" Hospital, Milan, Italy

Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study

Jean-Michel Molina, Chloe Orkin, David M Iser, Francisco-Xavier Zamora, Mark Nelson, Christoph Stephan, Benedetta Massetto, Anuj Gaggar, Liyun Ni, Evguenia Svarovskaia, Diana Brainard, G Mani Subramanian, John G McHutchison, Massimo Puoti, Jürgen K Rockstroh, for the PHOTON-2 study team*

The NEW ENGLAND JOURNAL of MEDICINE

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Embargo: March 21, 2017—23:30 GMT

[A: We have edited your paper to avoid repetition, enhance readability, reduce length, and achieve consistency with Lancet style]

Articles
CL
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Ombitasvir, paritaprevir, and ritonavir, with or without dasabuvir, plus ribavirin for patients with hepatitis C virus genotype 1 or 4 infection with cirrhosis (ABACUS) [A: study name added, correct?]: a prospective observational study [A: title OK as edited?]

Salvatore Petta, Marco Marzioni, Pierluigi Russo, Alessio Aghemo, Alfredo Alberti, Antonio Ascione, Andrea Antinori, Raffaele Bruno, Savino Bruno, Antonio Chirianni, Giovanni Battista Gaeta, Edoardo G Giannini, Manuela Merli, Vincenzo Messina, Simona Montilla, Carlo Federico Perno, Massimo Puoti, Giovanni Raimondo, Maria Rendina, Francesca Ceccherini Silberstein, Erica Villa, Anna Linda Zignego, Luca Pani, Antonio Craxì, on behalf of the ABACUS study group* and of the AIFA team*

ORIGINAL ARTICLE

Glecaprevir–Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection

S. Zeuzem, G.R. Foster, S. Wang, A. Asatryan, E. Gane, J.J. Feld, T. Asselah, M. Bourlière, P.J. Ruane, H. Wedemeyer, S. Pol, R. Flisiak, F. Poordad, W.-L. Chuang, C.A. Stedman, S. Flamm, P. Kwo, G.J. Dore, G. Sepulveda-Arzola, S.K. Roberts, R. Soto-Malave, K. Kaita, M. Puoti, J. Vierling, E. Tam, H.E. Vargas, R. Bruck, F. Fuster, S.-W. Paik, F. Felizarta, J. Kort, B. Fu, R. Liu, T.I. Ng, T. Pilot-Matias, C.-W. Lin, R. Trinh, and F.J. Mensa

ABSTRACT

HCV from cure to eradication

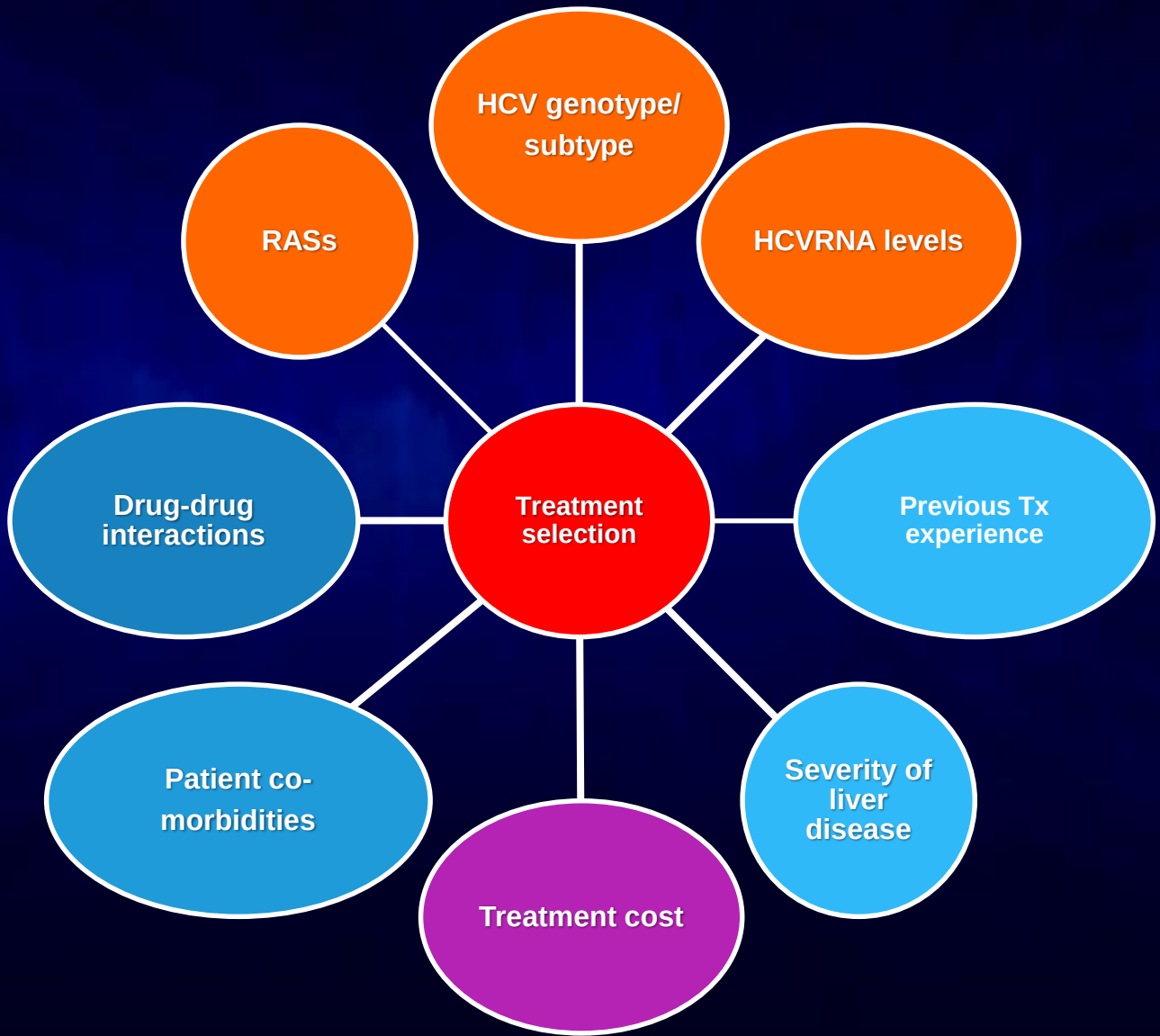
- The cure: how we got there
- The cure: the most effective anti infective cure ever seen
- Unmet needs?
- From cure to eradication: new strategies new tools

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

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%

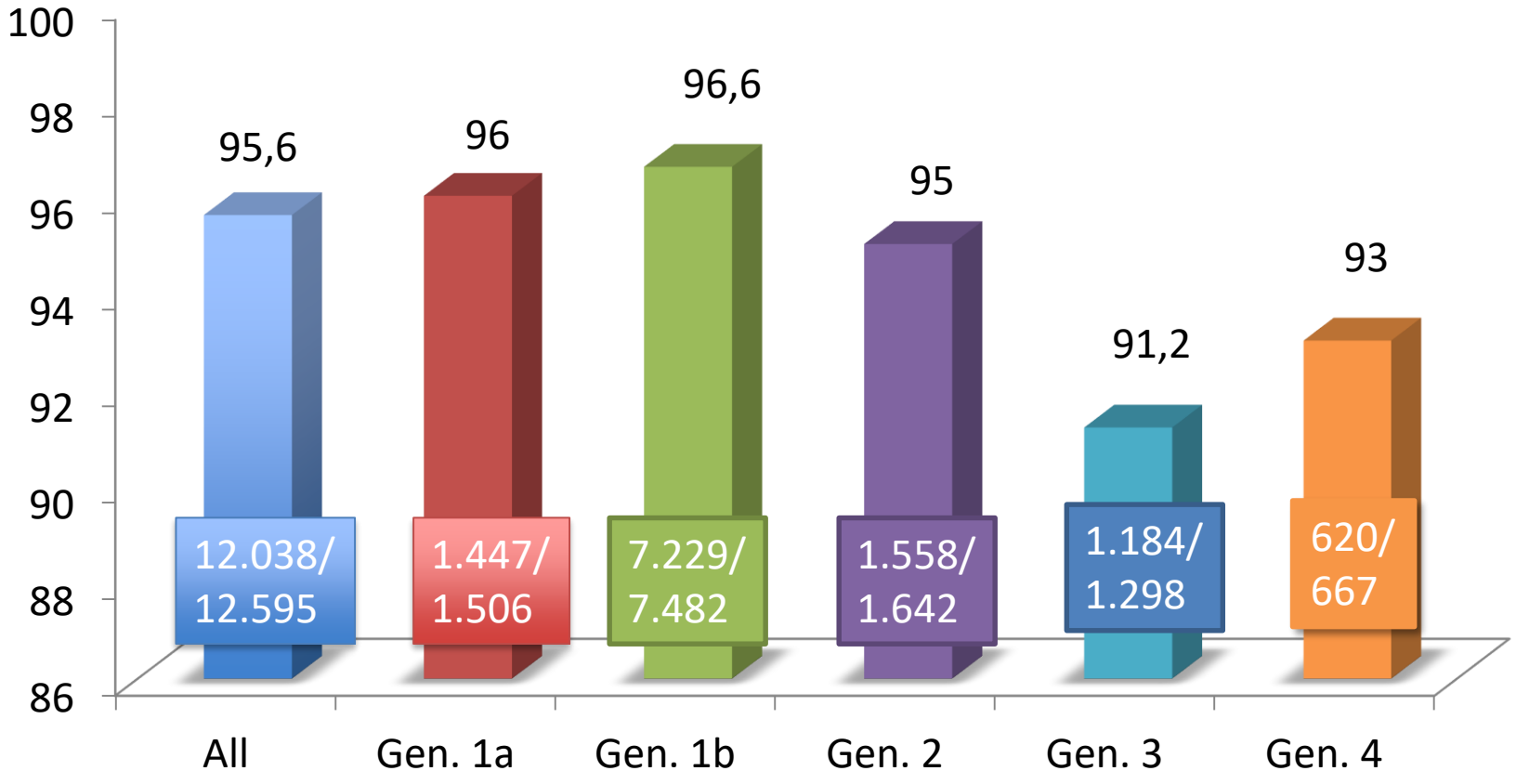
NUCPol i; NNPol I 1st gen NS3/NS4 i; 2nd gen NS3/NS4i 1st gen NS5Ai; 1st gen oangenotypic NS5Ai 2nd gen pangenotypic NS5Ai

Characteristics that Inform Treatment Option Selection



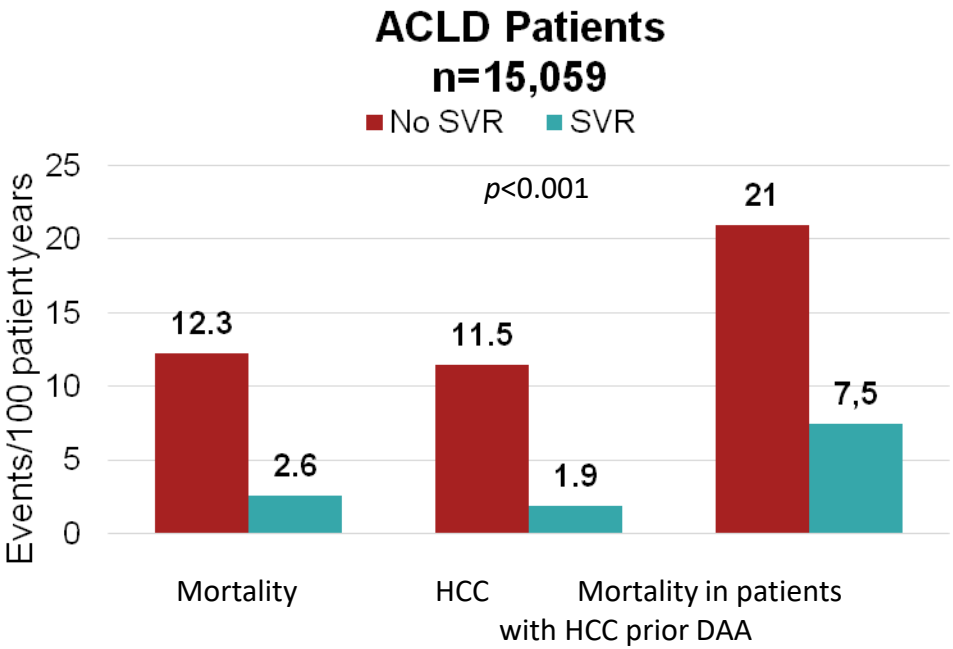
SVR12 in 12.595 HCV infected patients in 4 Italian Regional Registries

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

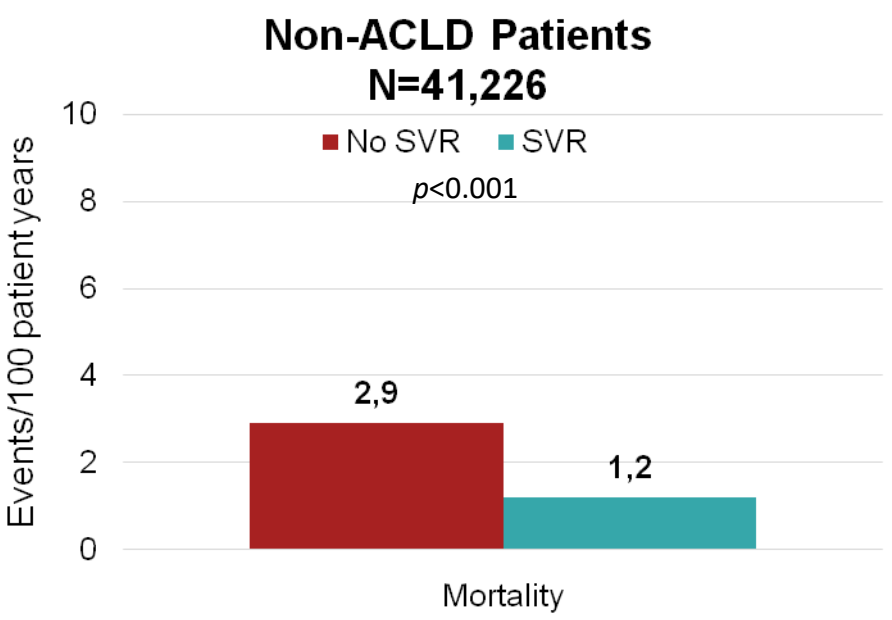


Impact of SVR with DAAs on mortality and HCC

All-cause mortality rates and incident HCC rates in Veterans ± advanced chronic liver disease (ACLD*) in the HCV registry treated with DAAs by 9/30/2016



SVR was associated with 80% reduction in mortality and 84% reduced incidence in HCC



SVR was associated with 60% reduction in mortality

*FIB-4>3.25 at DAA start

Backus, AASLD 2017, Oral 78

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**	Dasabuvir	**Sofosbuvir**
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

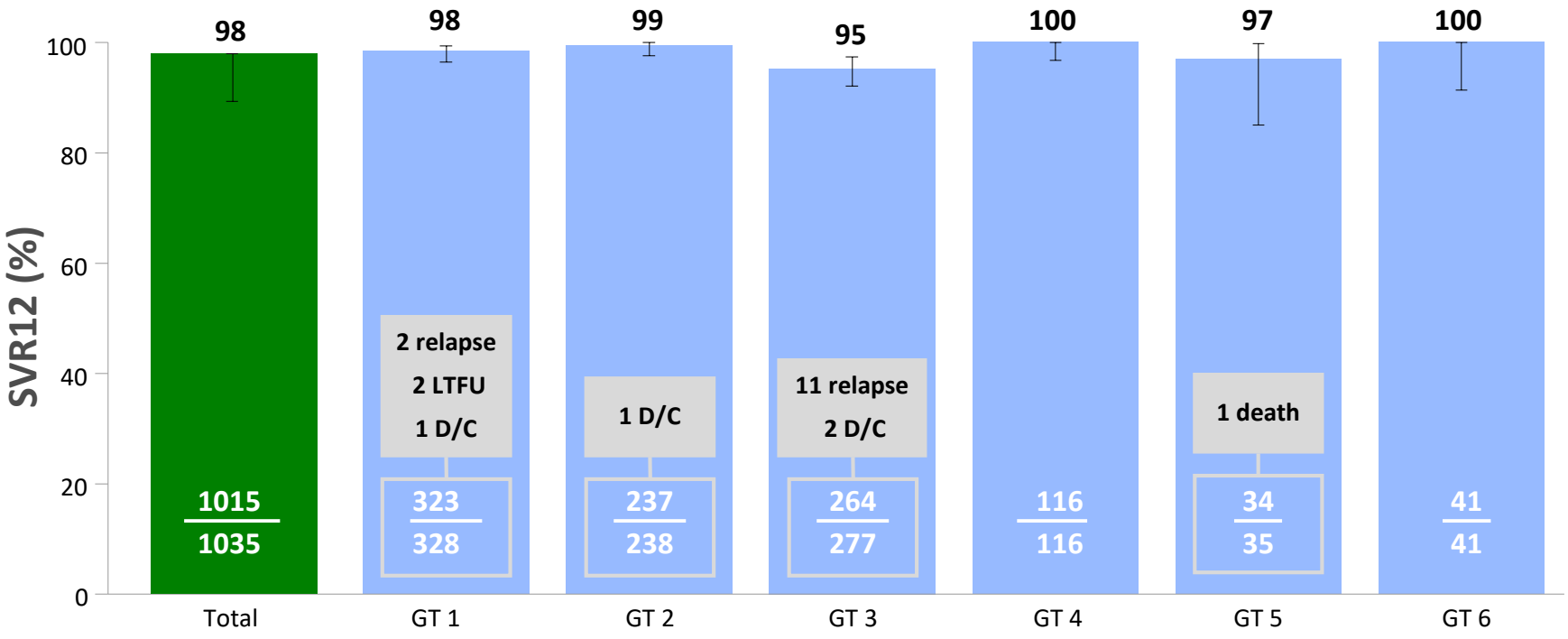
PK and potential for Drug Drug Interactions of Anti HCV oral antivirals

	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
PrOD	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

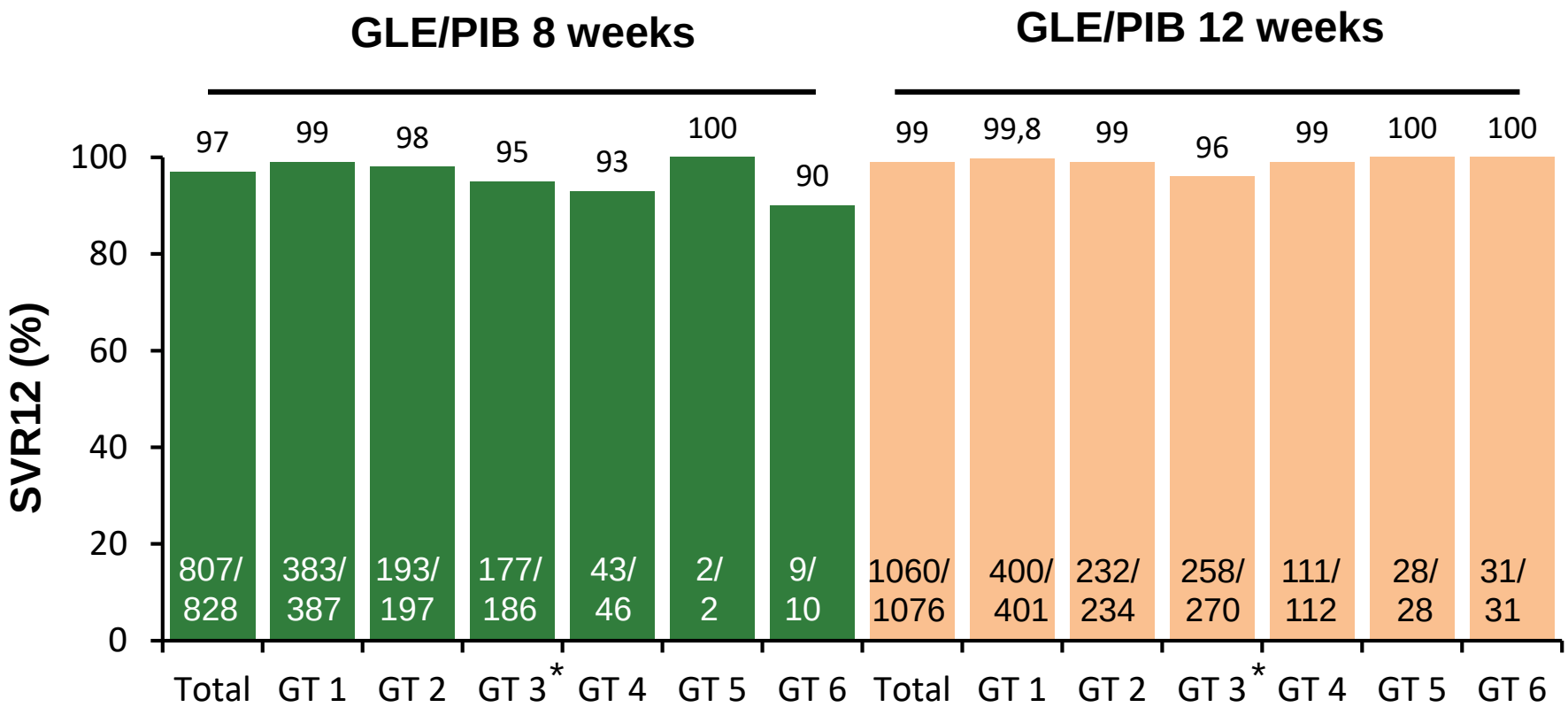
ASTRAL-1, -2, -3

Sofosbuvir + Velpatasvir
Integrated Efficacy: SVR12



Agarwal, EASL 2016, Poster SAT-195

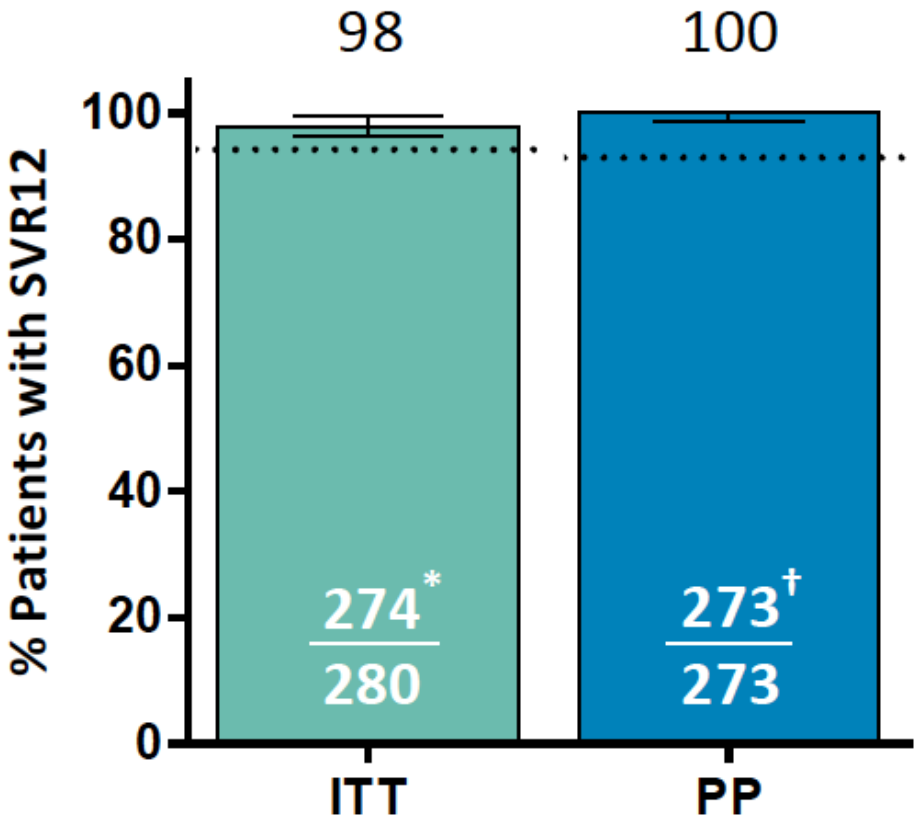
Integrated efficacy and tolerability of GLE/PIB for 8 or 12 weeks in GT 1–6 patients without cirrhosis (APRI < 1?)



*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

PRELIMINARY EFFICACY AND SAFETY OF 8-WEEK GLECAPREVIR/PIBRENTASVIR IN PATIENTS WITH HCV GENOTYPE 1–6 INFECTION AND COMPENSATED CIRRHOSIS: THE EXPEDITION-8 STUDY



- No virologic failures
- Lower 95% confidence interval bounds for the SVR12 rates exceeded the pre-defined efficacy thresholds (dotted lines) for both the ITT and PP populations

*5 patients had missing SVR12 data (all undetectable at last visit) & 1 patient prematurely discontinued treatment

†1 patient dosed for <8 weeks who achieved SVR12, plus 6 non-responders from the ITT population

RS Brown et al AASLD 2018

HCV from cure to eradication

- The cure: how we got there
- The cure: the most effective anti infective cure ever seen
- Unmet needs?
- From cure to eradication: new strategies new tools

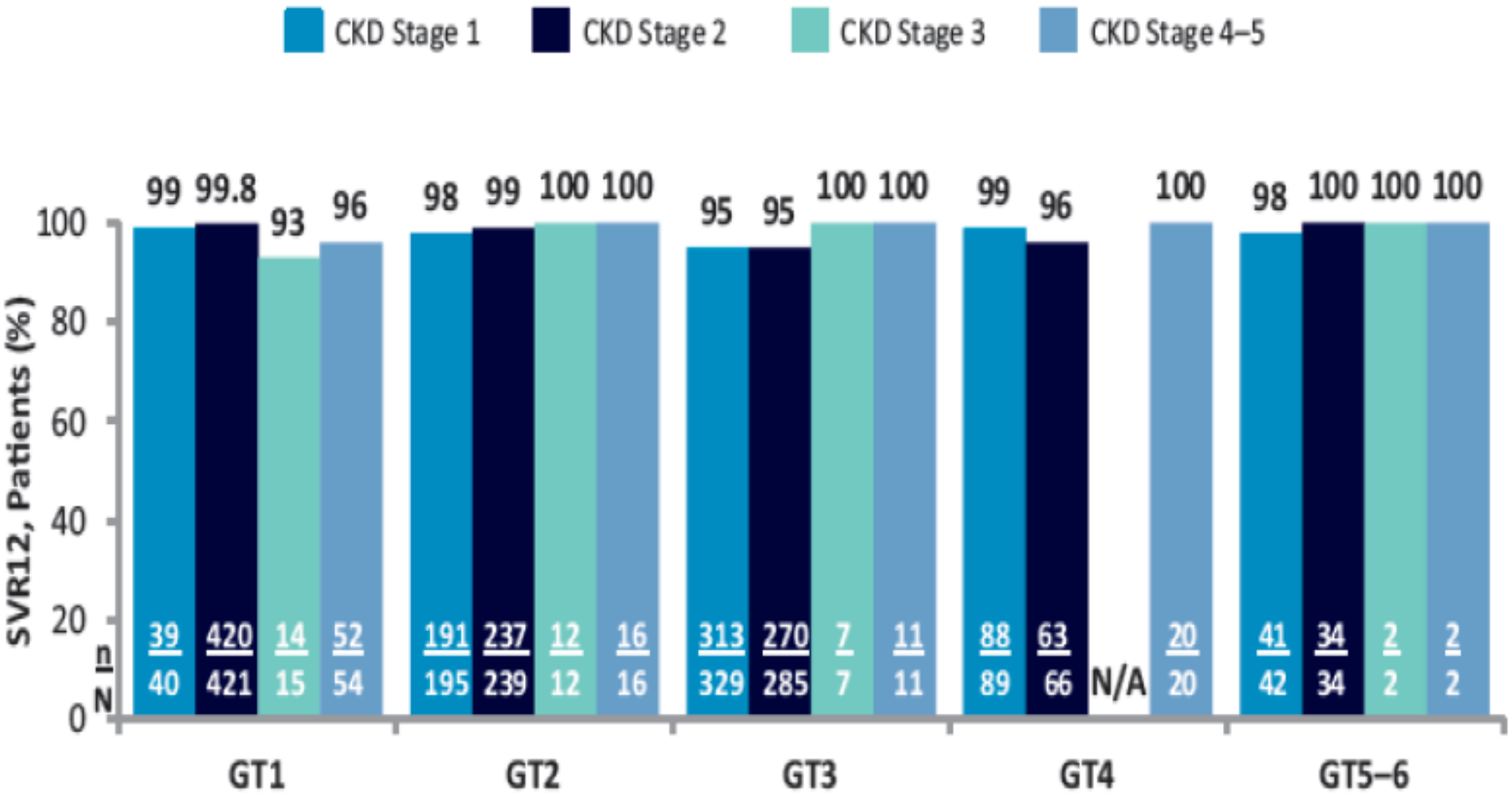
Impact of renal impairment on DAA pharmacokinetics

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**).

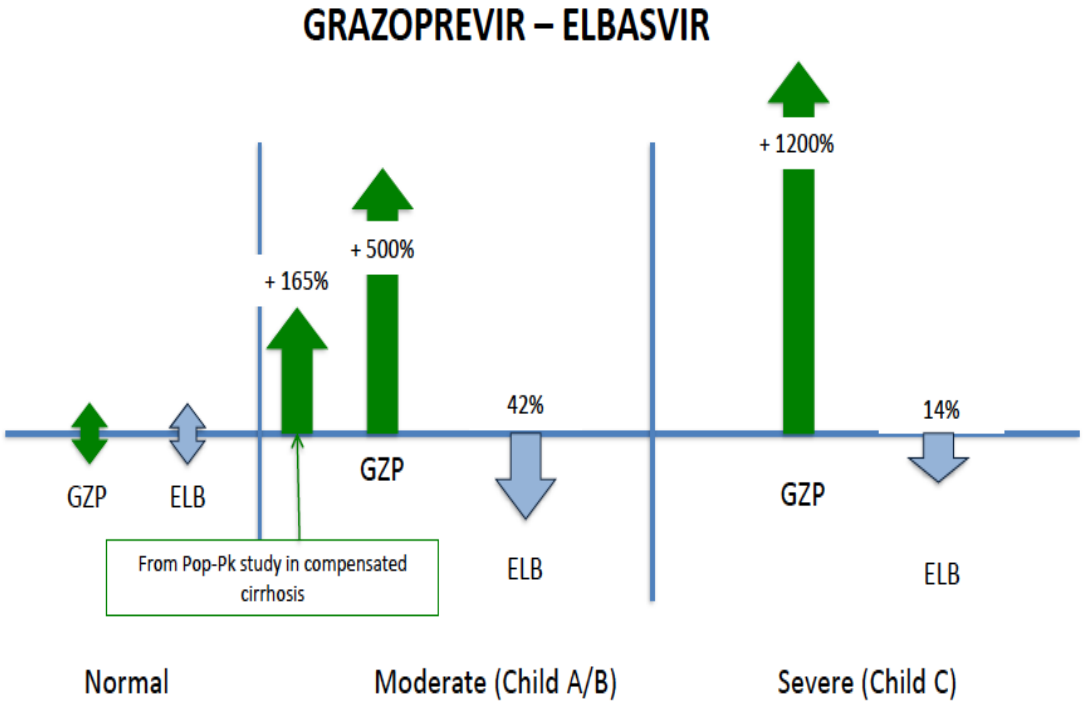
Khatri A, et al. Hepatology 2014; 60 (Suppl):320A;
Harvoni, (July 2016), Maviret (July 2017) Epclusa (July 2017) Summaries of Product Characteristics
Yeh WW, et al. Hepatology 2014; 60 (Suppl 4):1940 (poster presentation).

Glecaprevir/Pibrentasvir in Patients with CKD

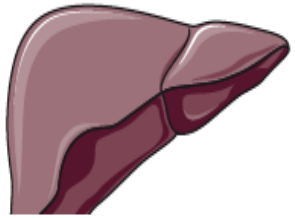


Pol S. et al, Integrated analyses G/P phase2/3 studies EASL 2017

Protease inhibitors are Contraindicated in case of Decompensated Cirhosis



GLECAPREVIR / PIBRENTASVIR



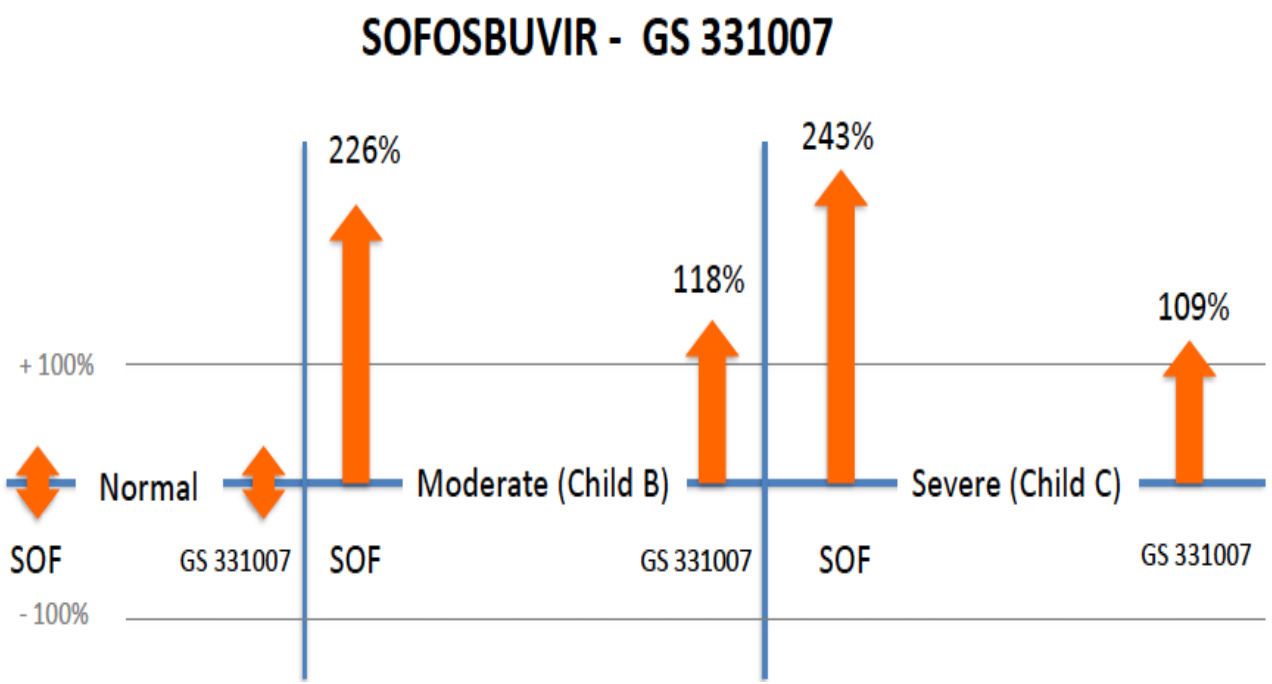
Patients with Impaired LIVER Function

Maviret is not recommended in patients with moderate hepatic impairment (Child-Pugh B) and is contraindicated in patients with severe hepatic impairment (Child-Pugh C).

	Child A	Child B	Child C
GLECAPREVIR	+ 33 %	+ 100 %	+ 1200 %
PIBRENTASVIR	-	+ 26 %	+ 114 %

MAVIRET HIGHLIGHTS OF PRESCRIBING INFORMATION, revised 10/2017

Sofosbuvir and Velpatasvir can be used in case of Decompensated Cirhosis



STEADY-STATE PHARMACOKINETICS OF SOFOSBUVIR AND VELPATASVIR IN HCV-INFECTED SUBJECTS WITHOUT CIRRHOSIS, WITH COMPENSATED CIRRHOSIS, OR WITH DECOMPENSATED CIRRHOSIS IN THE PHASE 3 ASTRAL STUDIES

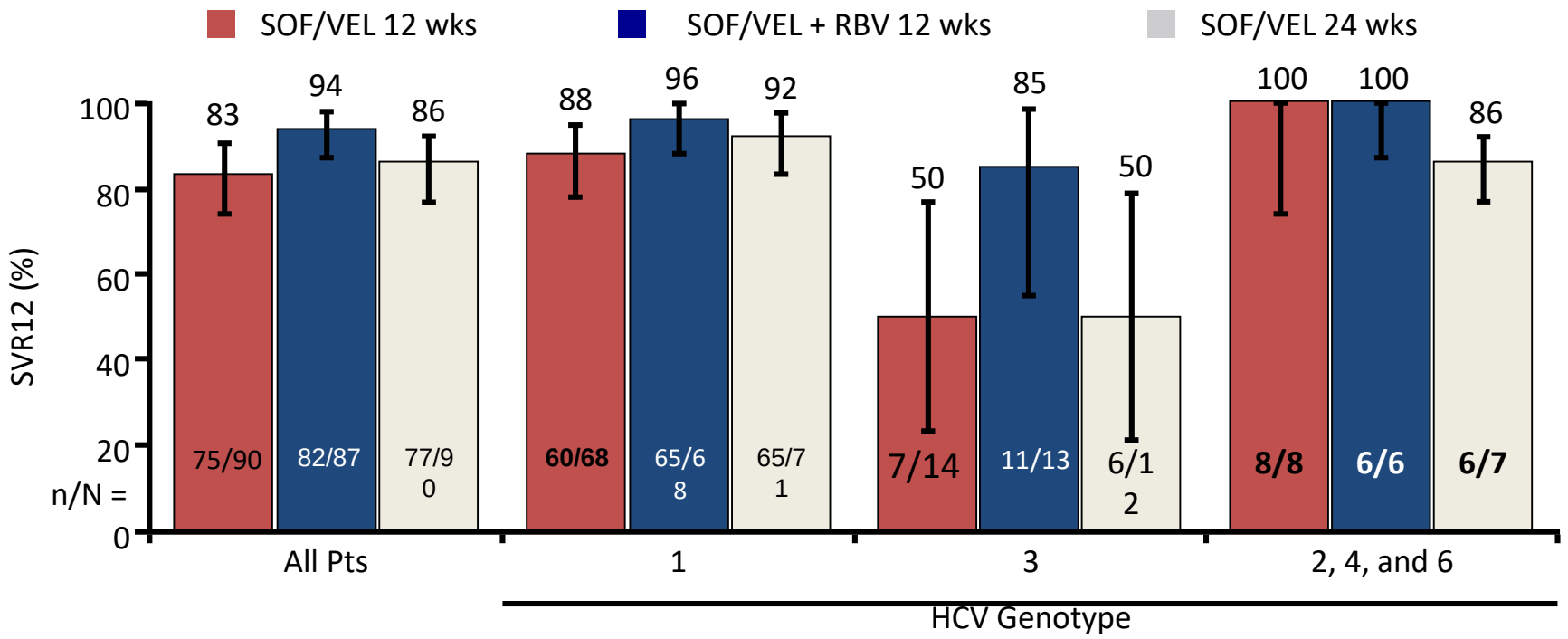
Erik Mogalian , Di An , Yanni Zhu , Yvonne Maruca , Cara Casey , John McNally , John Ling , Anita Mathias

EASL LiverTree™. Mogalian E. Apr 15, 2016; 125563

	NO cirrhosis	COMP. cirrhosis	DECOMP. cirrhosis
AUC	controls	- 7%	- 14 %
Cmax	controls	- 27%	- 41%
C_{24h}	controls	+ 41%	+ 54%

ASTRAL-4: Sofosbuvir/Velpatasvir in Decompensated Cirrhosis

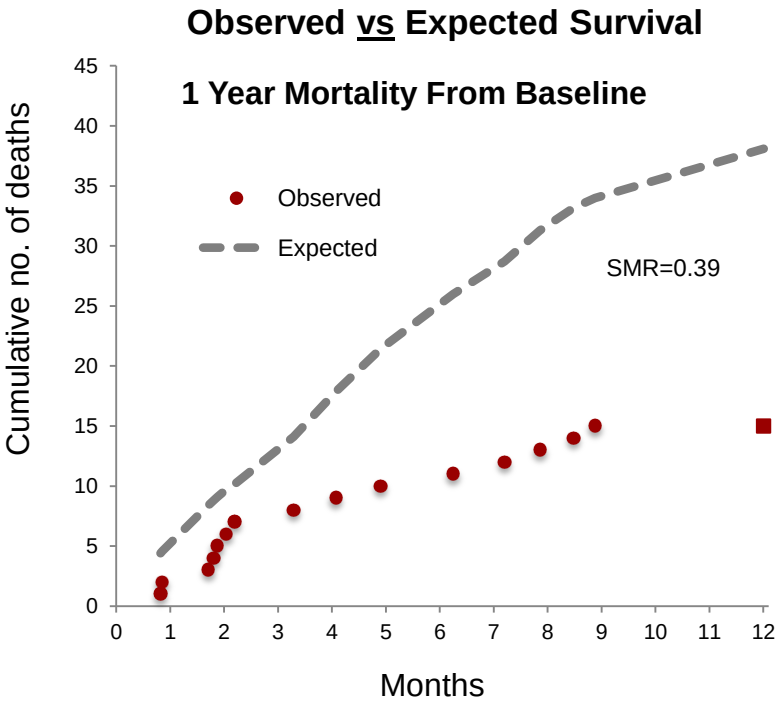
- Open-label trial; HCC and liver transplantation excluded
- In pts with BL MELD > 15, SVR12, score improved in 84%, worsened in 8%; in pts with BL MELD < 15, SVR12, score improved in 52%, worsened in 27%
- AEs consistent with advanced liver disease and RBV toxicity



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

Survival benefit of DAAs in patients with decompensated cirrhosis

Survival model to predict mortality without DAA therapy from liver transplant candidates with hepatic decompensation utilizing the Organ Procurement and Transplantation Network Data



In patients with decompensated liver disease treated with DAAs (LED/SOF+Rbv) in SOLAR trials, a 61% reduction in 1-year mortality was seen when compared with predicted survival in a cohort of patients not treated with DAAs

Kim, AASLD 2017, Poster LB-27

Sofosbuvir in ESRD

The Netherlands Journal of Medicine

LETTER TO THE EDITOR

Full-dose sofosbuvir and daclatasvir for chronic hepatitis C infection in haemodialysis patients

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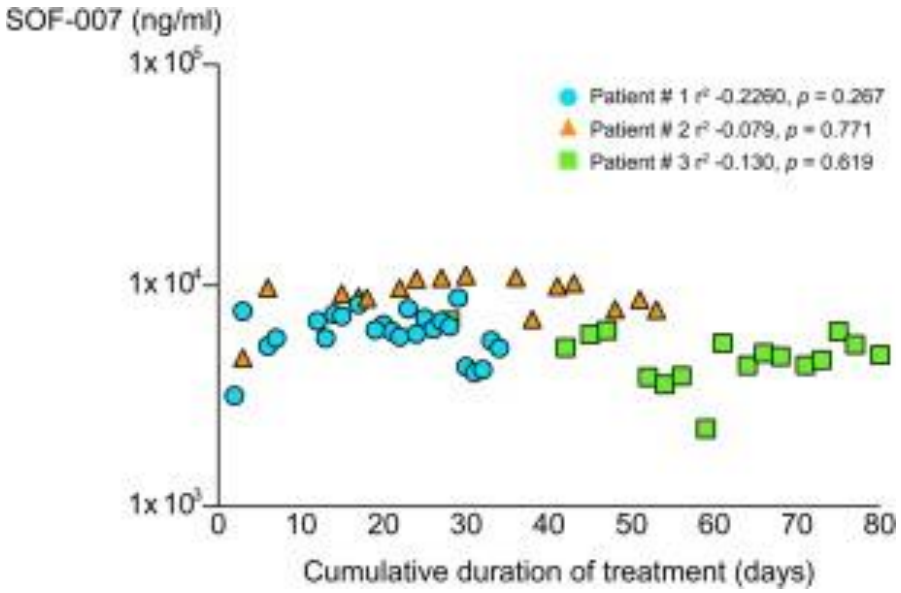
Digestive Diseases and Sciences (2018) 63:1334–1340
https://doi.org/10.1007/s10620-018-4979-6

ORIGINAL ARTICLE

Low-Dose Sofosbuvir Is Safe and Effective in Treating Chronic Hepatitis C in Patients with Severe Renal Impairment or End-Stage Renal Disease

Sunil Taneja[1] · Ajay Duseja[1] · Arka De[1] · Manu Mehta[1] · Raja Ramachandran[2] · Vivek Kumar[2] · Harbir Singh Kohli[2] · Krishan Lal Gupta[2] · Radha Krishan Dhiman[1] · Yogesh Chawla[1]

Received: 12 December 2017 / Accepted: 12 February 2018 / Published online: 26 February 2018



400 mg daily optimal dose
Desnoyer A J Hepatol 201665:40-7

CONS
Biopsy proven interstitial allergic nephritis reporte d in a SOF treated patient with ESRD (Wanchoo R Am J Gastro 2016 111: 148-9)
14% Lactic acidosis in Cirrhotics treated with SOF ESRD risk factor
(Welker MW J Hepatol 2016 64:790-99

The last unmet need: patients with ESLD/ESRD

- Transplantation not contraindicated: treat after liver or Liver/Kidney transplant
- Toxicity of GS 33107 overexposure in ESRD -→ unknown → off label use of SOF/VEL in ESLD/ESRD
- TDM PI in CTP class B

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 oangenotypic NS5Ai ■2nd gen pangenotypic NS5Ai

Test and treat hypothesis:

One or three pills for all HCVRNA + NS5A naives with compensated disease

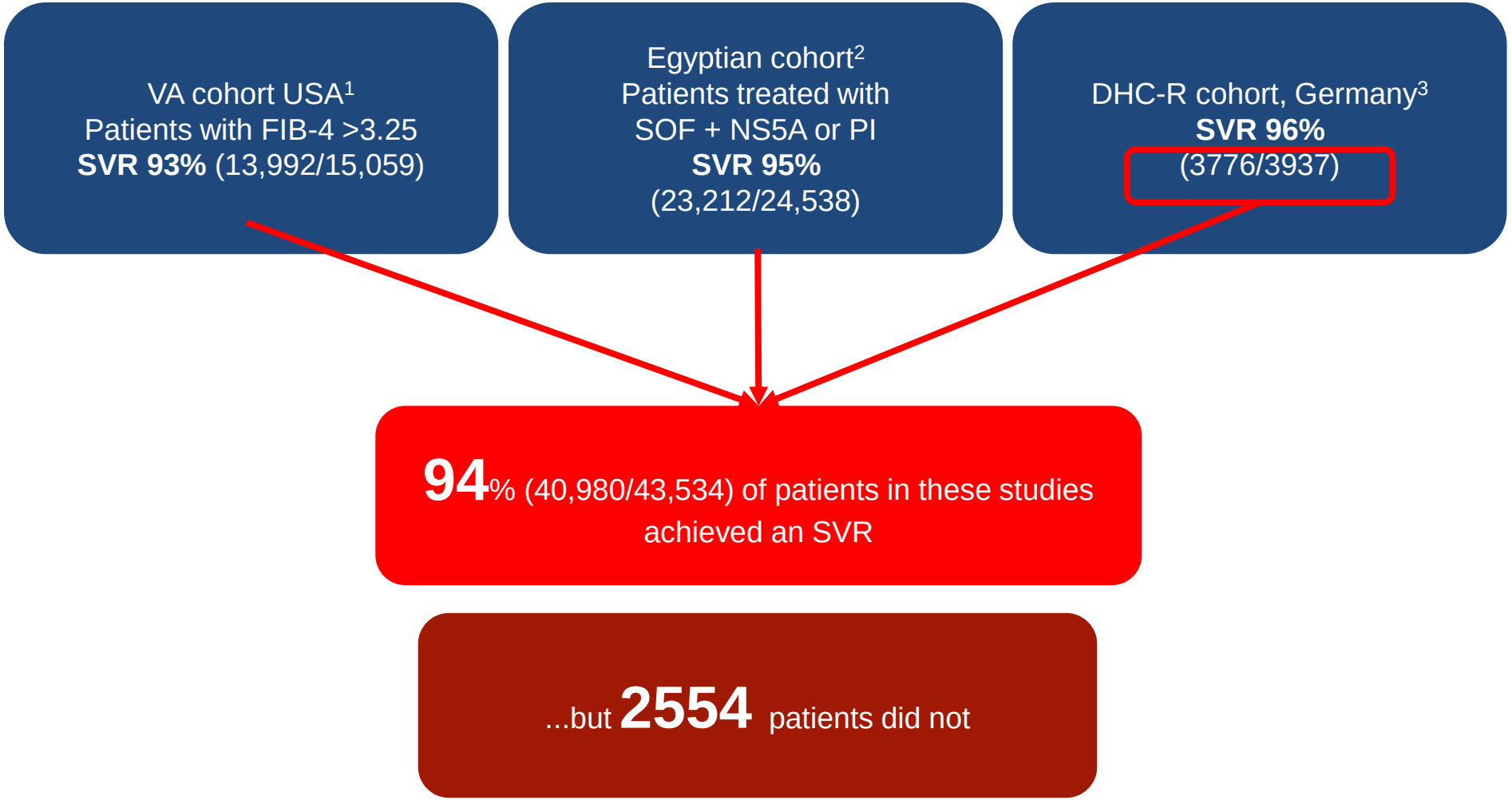
Regimen	Disease stage	GT 1	GT 2	GT 3	GT 4	GT 5	GT 6
SOF/VEL	Without cirrhosis	12 weeks*					
	With compensated cirrhosis						
GLE/PIB	Without cirrhosis	12 weeks§ [8 weeks if APRI (AST/PLATELET RATIO) < 1]					
	With compensated cirrhosis						

*Undertreatment in HCV G3 cirrhotics ;

§ Overtreatment in pts with F0-F3 and undertreatment in HCVG3 experienced

Gilead Sciences Europe Ltd. EPCLUSA▼ (sofosbuvir/velpatasvir) SmPC, October 2017;
AbbVie. MAVIRET▼ (glecaprevir/pibrentasvir) SmPC, August 2017

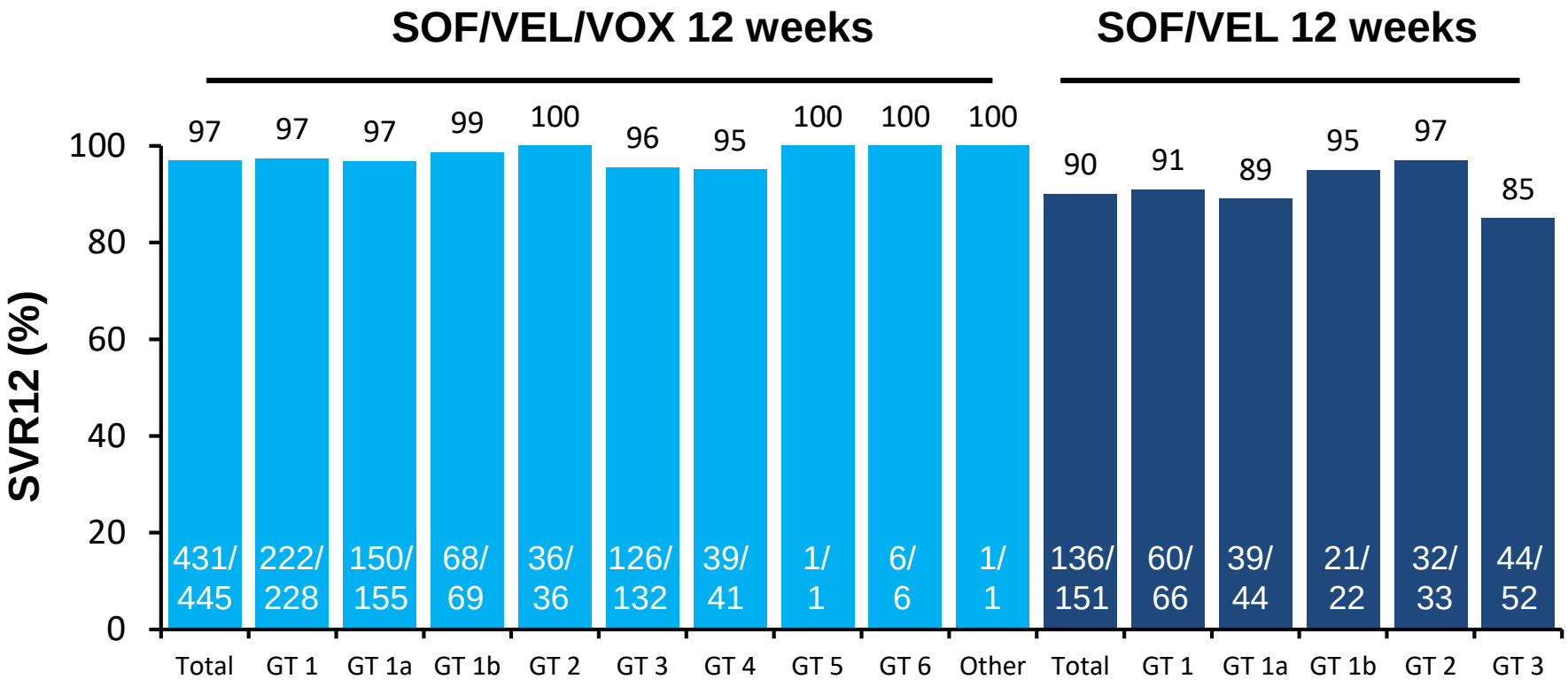
Patients who have experienced DAA treatment failure are a small but important HCV patient population



1. Backus LI, et al. Hepatology 2017;doi: 10.1002/hep.29408;
2. Gomaa A, et al. Hepat Med 2017;9:17–25;
3. Welzel TM, et al. ILC 2016; Poster #SAT-274

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

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

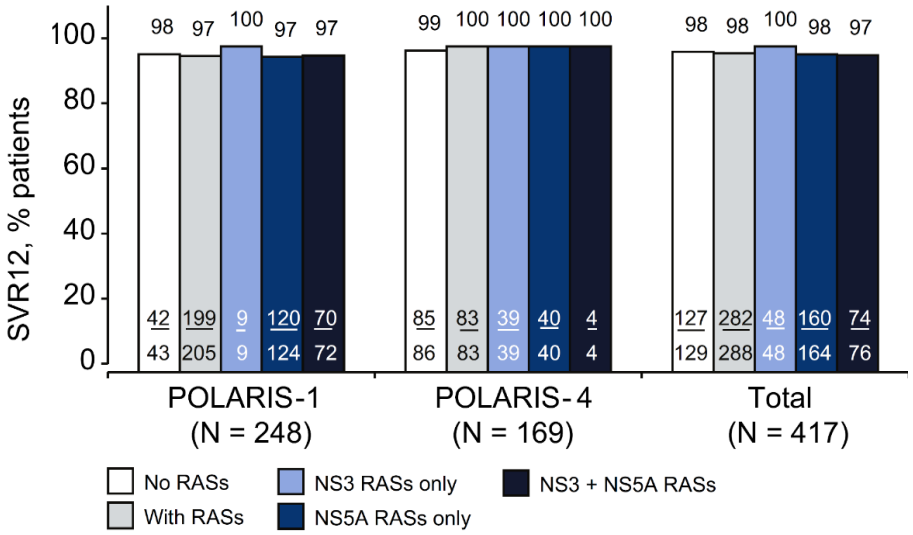


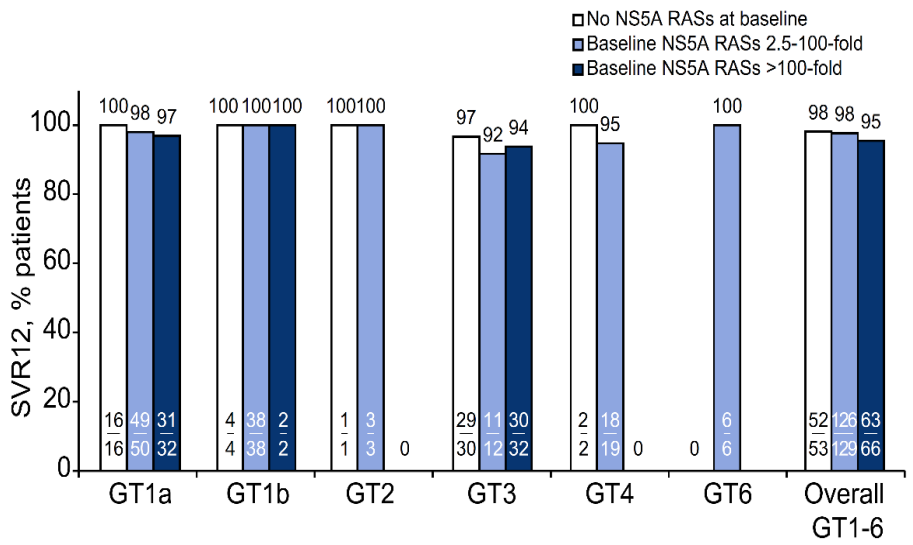
Tolerability of SOF/VEL/VOX for 12 weeks

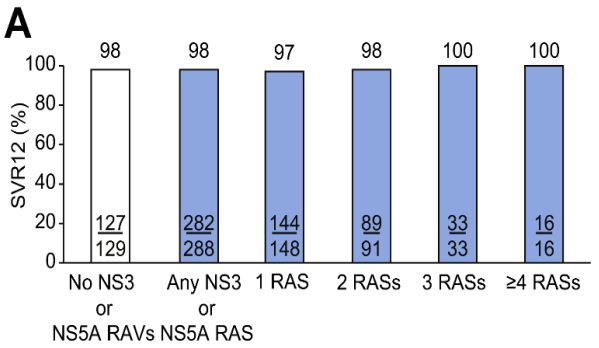
- SAEs were reported in 9 (2%) patients receiving SOF/VEL/VOX for 12 weeks, none were considered treatment-related
- 1 patient died 2 days after completing treatment from an illicit drug overdose

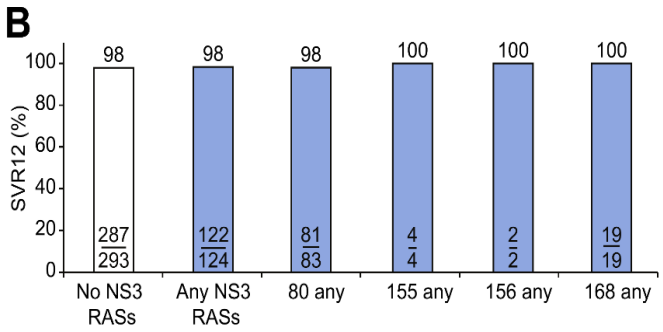
Bourliere M, et al. N Engl J Med 2017;376:2134–46

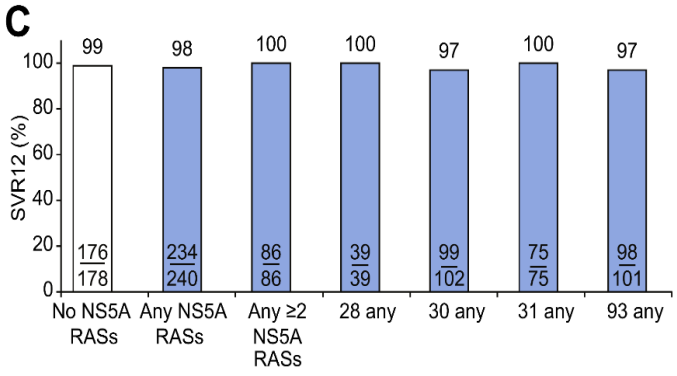
No Impact of RAS on Efficacy of SOF/VEL/VOX for 12 weeks in DAA-experienced Patients











Sarrazin C. et al, J Hepatol 2018;69:1221–1230

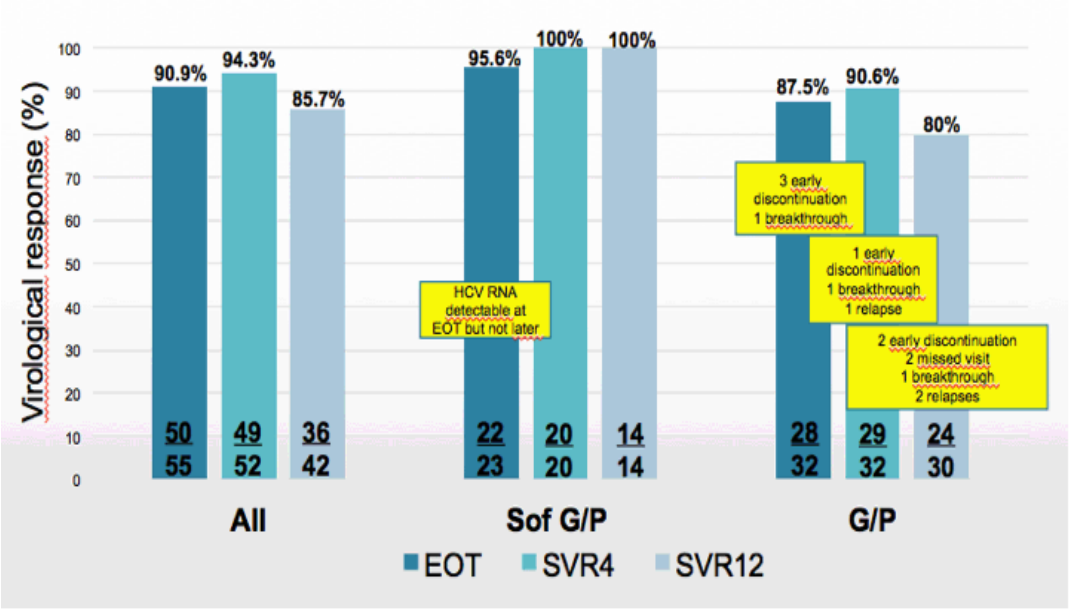
SOF + G/P in Difficult to Treat HCV Patients: Results from French Compassionate Use Program

	All N= 60	SOF G/P N=26	G/P N=34
Age, y, mean (SD)	60.1 (8.3)	58.8 (6.7)	61.0 (9.3)
Gender, Male (%)	47 (78.3)	19 (73.1)	28 (82.4)
BMI, kg/m², mean (SD)	26.9 (4.5)	26.1 (4.2)	27.5 (4.7)
DAA failure (%)	45 (75.0)	26 (100)	19 (55.9)
Mean duration between failure and retreatment (months)	15.6 (8.2)	14.4 (8.7)	17.2 (7.4)
Fibrosis status n (%):			
• FibroScan ≤ 10 kPa	39 (65)	15 (57.7)	24 (70.6)
• FibroScan [10-20] kPa	11 (18.3)	7 (26.9)	4 (11.8)
• FibroScan > 20 kPa	10 (16.7)	4 (15.4)	6 (17.6)
HCV Genotypes			
• 1a	13	5	8
• 1b	9	7	2
• 1g1e1l	4	1	3
• 2	9	1	8
• 3	15	7	8
• 4 & 5	10	5	5
RAS (performed in 52 patients)			
• NS5A alone	31 (59.6%)	17	14
• NS3 alone	1 (1.9%)	0	1
• NS5B alone	2 (3.8%)	1	1
• NS3 + NS5A	3 (5.8%)	2	1
• NS5A + NS5B	1 (1.9%)	1	0
• No amplification or none	14 (26.9%)	4	10
Previous HCV treatment			
• Sofosbuvir + Ledipasvir	18	13	5
• Sofosbuvir + Daclatasvir	16	7	9
• Sofosbuvir/Velpatasvir	2	0	2
• Paritaprevir/r+Ombitasvir±Dasabuvir	4	3	1
• Sofosbuvir+Daclatasvir+Simeprevir	2	0	2
• Grazoprevir/Elbasvir	2	2	0
• Glecaprevir/Pibrentasvir	1	1	0

Open-label study; 60 patients enrolled

SOF + G/P combination *vs.* G/P alone

12-week course without Rbv in 99%



De Ledinghen V. et al, J Hepatol 2018;68:S250

HCV treatment

Sofosbuvir-based treatment and re-treatment regimens provide an SVR of 99.9% at a population level

SVR 96%

1000 people treated with SOF-based regimens

SVR 97%

Treat 40 who require re-treatment with SOF/VEL/VOX

Overall SVR

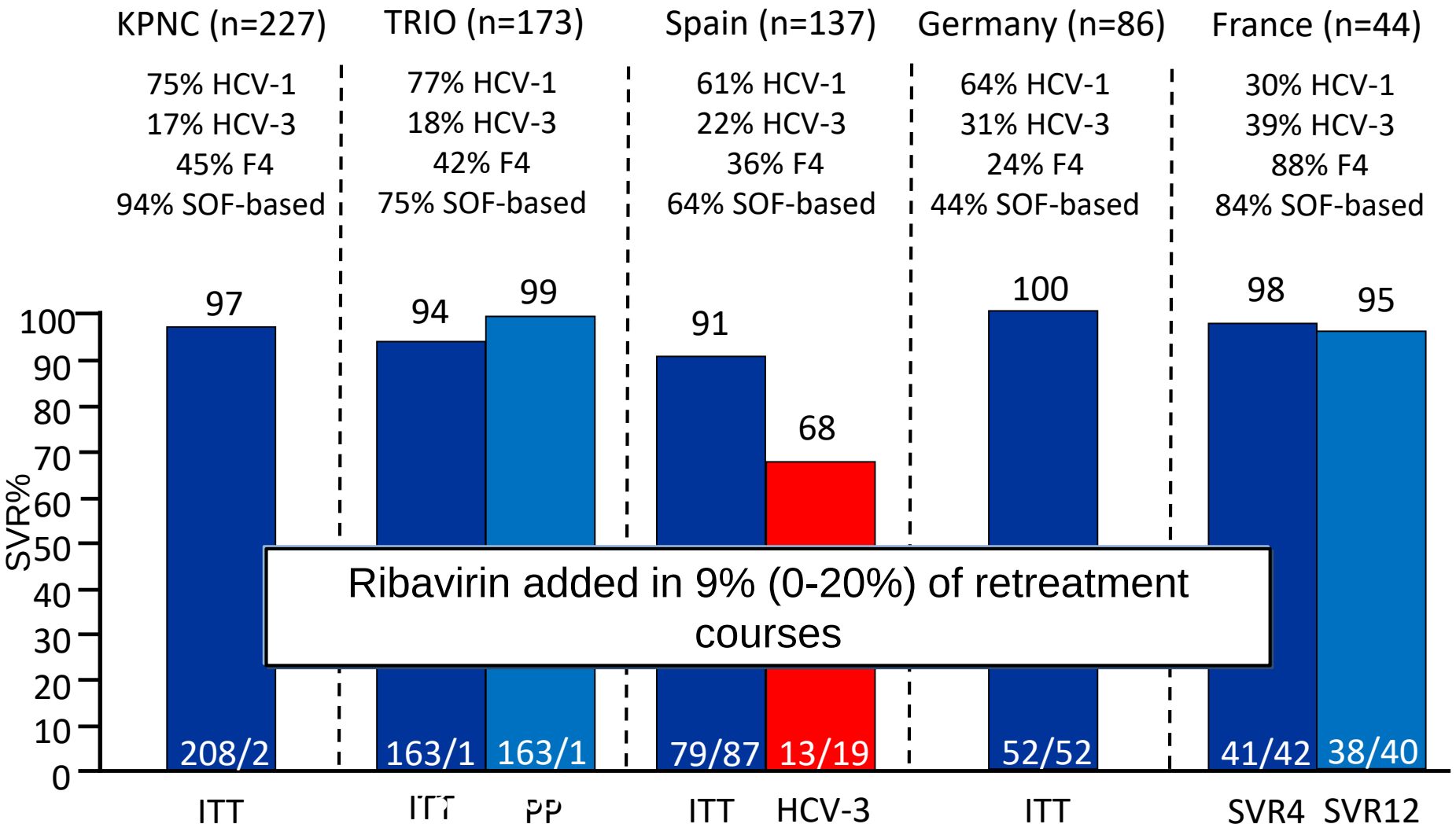
99.9%

With 99.9% SVR, elimination of HCV is a reality!

Flamm S, et al. ILC 2017; Poster #SAT-279; Curry M, et al. ILC 2017; Oral #102; Terrault N, et al. Gastroenterology 2016;151:1131–40; Khalili M, et al. ILC 2017; Poster# SAT-222; Vermehren J, et al. ILC 2017; Poster #FRI-247; Welzel TM, et al. ILC 2016; Poster #SAT-274; Roberts S, et al. ILC 2017; Poster #SAT-280

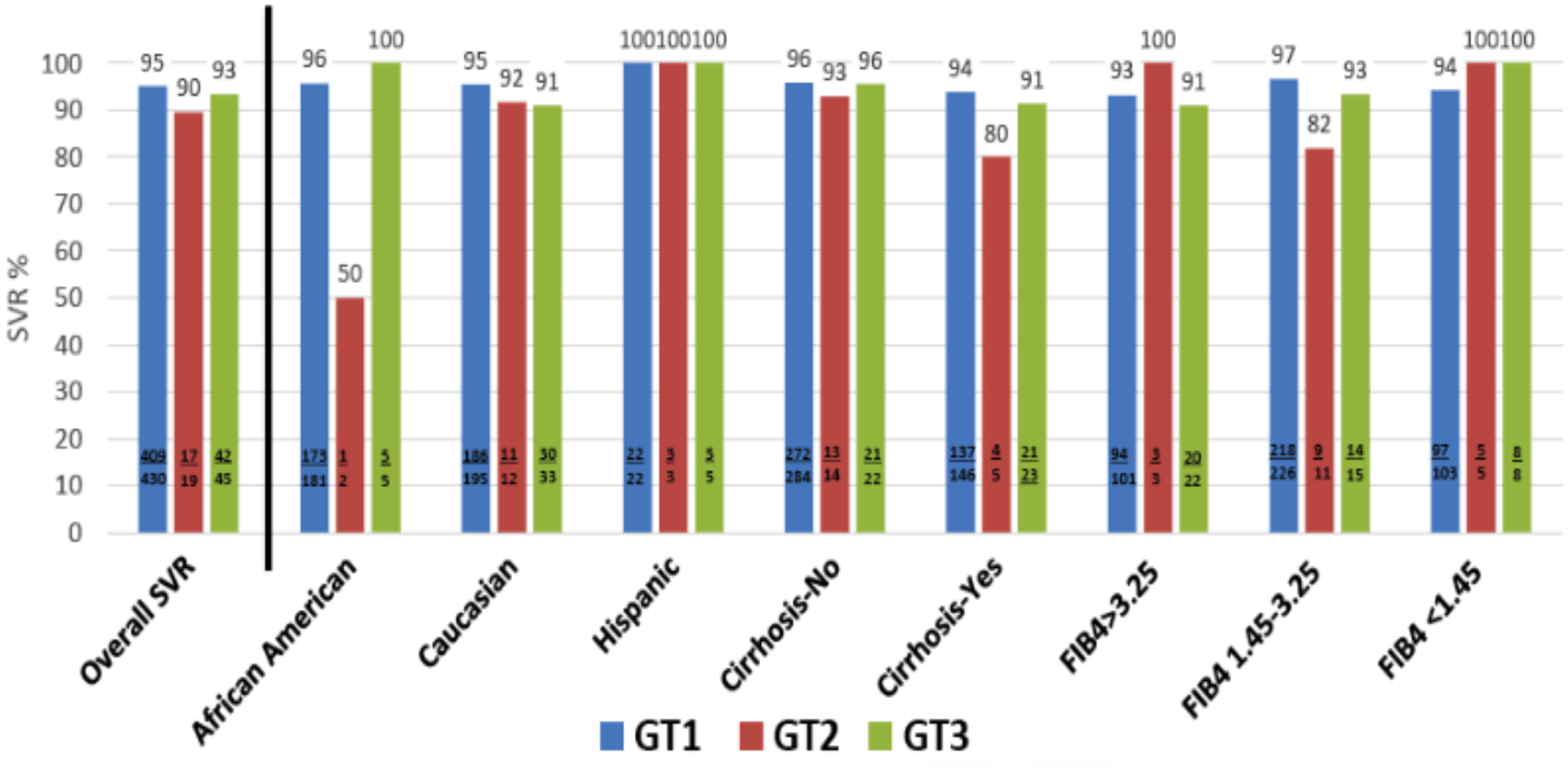
This is a concept slide based on a real-world SVR of 96% calculated from 9391 patients treated with LDV/SOF ± RBV and SOF/VEL ± RBV in the TRIO, HCV-TARGET and DHC-R cohorts. Re-treatment SVR of 97% with SOF/VEL/VOX is reported in the POLARIS-1–4 integrated analysis.
DHC-R: German Hepatitis C – Registry; LDV: ledipasvir; RBV: ribavirin; SOF: sofosbuvir; SVR: sustained virological response; VEL: velpatasvir; VOX: voxilaprevir

SOF/VEL/VOX for Retreatment of HCV Patients: Data from AASLD 2018



AASLD 2018: Saxena, Abs#70; Bacon, Abs#706; Llaneras, Abs#683; Vermehren, Abs#676; Hezode, Abs#620

Effectiveness Analysis: SOF/VEL/VOX in 506 Patients Completing 12-Week Course



Belperio et al, AASLD 2018, Abs #227

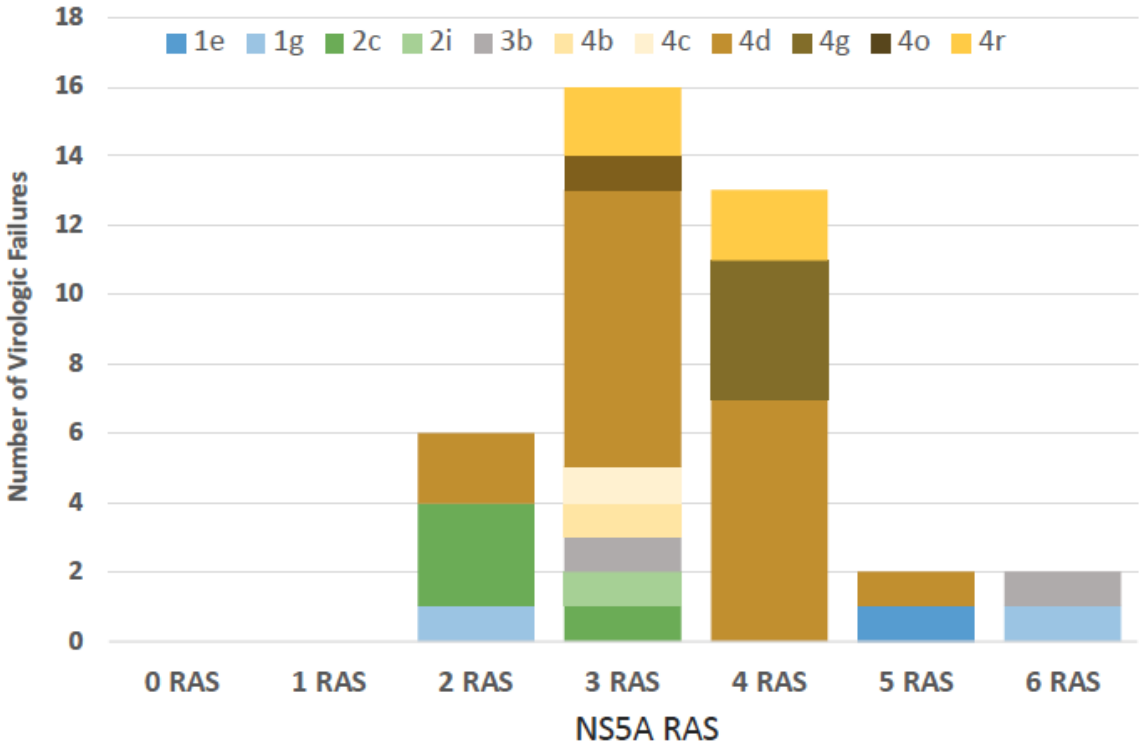
RARE GENOTYPES TEND TO SELECT MULTIPLE NS5A RAS AFTER DAA FAILURE

SHARED HEP C HOPE

Genotype/Subtype	No. of Patients*
1e	1
1g	2
2c	4
2i	1
3b	1
4b	1
4c	1
4d	18
4g	1
4o	1
4r	4

Genotype subtypes were derived from HCV sequence by BLAST and phylogenetic analysis with reference sequences obtained from GenBank

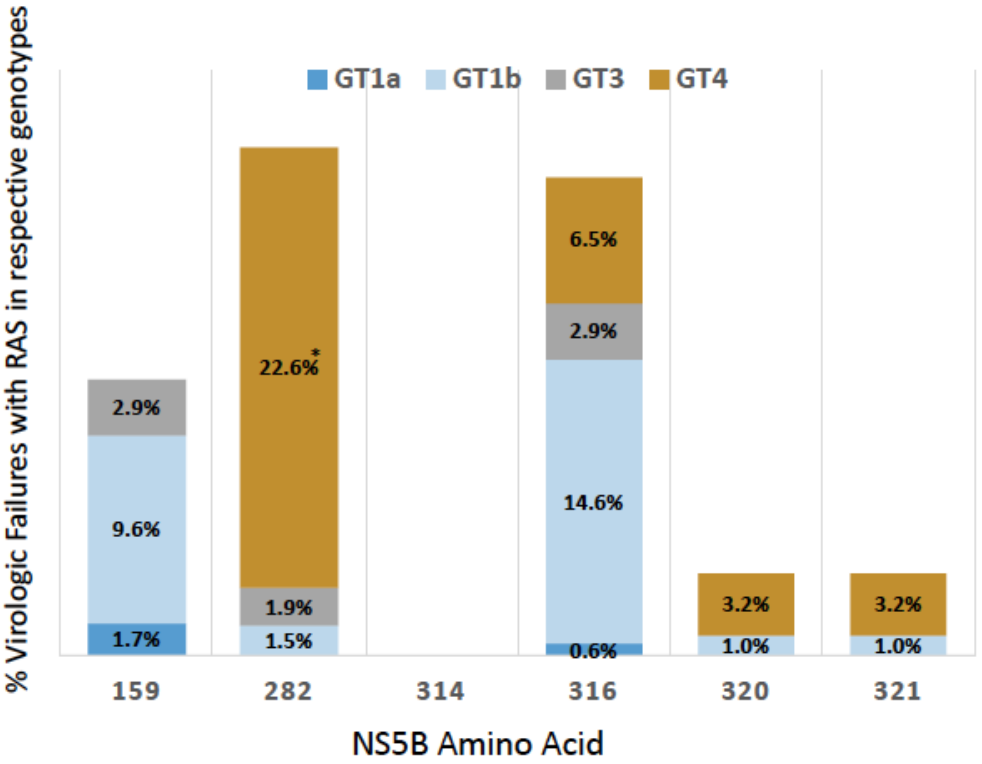
*Patients were treated with OMB-, LDV-, EBR-, or DCV-containing regimens



Note: Some WT GT4 subtypes have diverse amino acids. The impact of resistance remains to be determined.

HIGH FREQUENCY OF S282T MUTATION IN GT4 FAILURES

526 patients received sofosbuvir-based regimens: 179 GT1a/1d, 198 GT1b, 12 GT2, 104 GT3, 31 GT4, 2 GT6



- NS5B S282T rarely detected during clinical development.
- S282T confers 2- to 18- fold reduced drug susceptibility to sofosbuvir in HCV replicons.
- 23% of all GT4 patients selected S282T mutation after failing sofosbuvir-containing regimens.

*3 patients had WST in the Sanger consensus sequence

EASL Recommendations: Retreatment of DAA-Failures

- HCV resistance testing prior to retreatment is useful to guide retreatment, in the context of a multidisciplinary team (clinicians + virologists).

- Patients without cirrhosis or with compensated (CPT A) cirrhosis:
  1) SOF/VEL/VOX for 12 weeks (A1)
  2) SOF + G/P for 12 weeks (B1)
     if predictors of lower response (advanced liver disease, multiple courses of DAA-based treatment, complex NS5A RAS profile)
  3) SOF/VEL/VOX + Rbv or SOF + G/P + Rbv for 12 weeks (C2)
     in very difficult-to-cure patients (patients with NS5A RASs who failed twice a protease and/or an NS5A inhibitor containing regimen)
     and/or treatment duration can be prolonged to 16 to 24 weeks

- Patients with decompensated (CPT B or C) cirrhosis:
  1) SOF/VEL + Rbv 24 weeks (B2)

SOF: Sofosbuvir; G/P: Glecaprevir/Pibrentasvir; Rbv: Ribavirin; VEL: Velpatasvir; VOX: Voxilaprev

EASL 2018 HCV Recommendations, J Hepatol 2018;69:182-236

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 t mortality, is possible with th 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 s strat de

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.

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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]

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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 partel 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.
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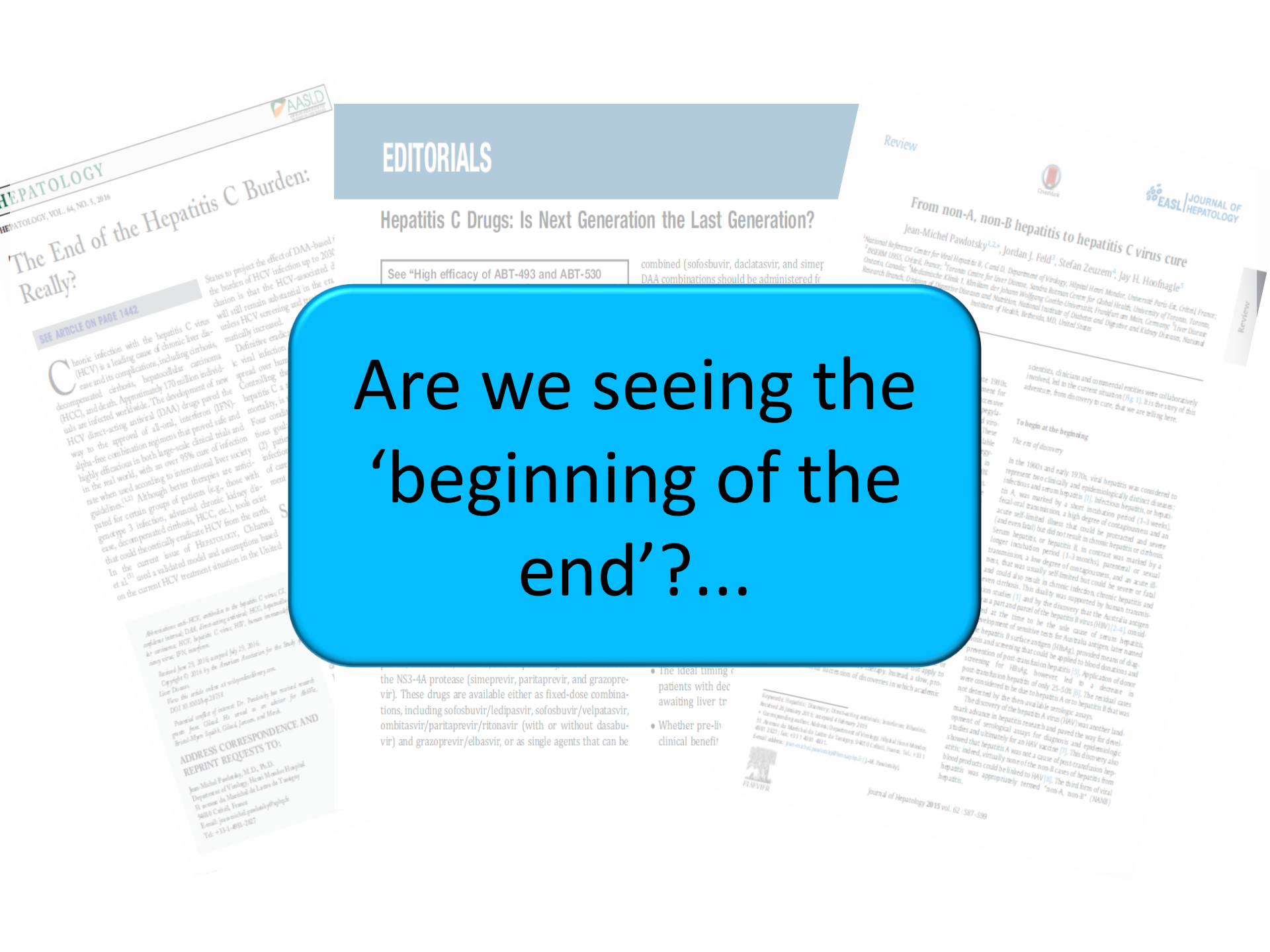
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EASL JOURNAL OF HEPATOLOGY
Are we seeing the 'beginning of the end'?...

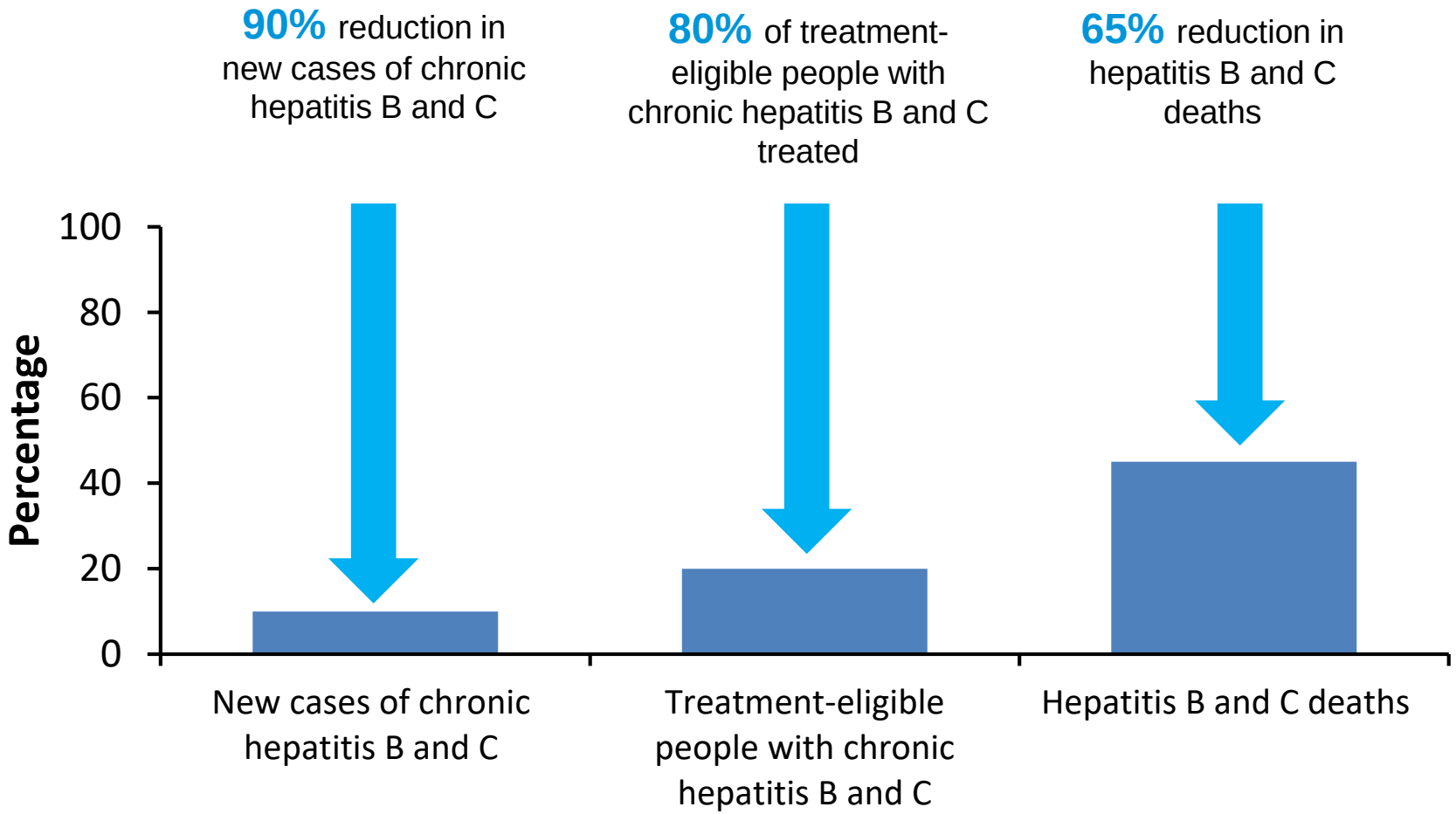
T.S. Eliot “ The Little gidding”

…..to make an end is to make a beginning. The end is where we start from….

HCV from cure to eradication

- The cure: how we got there
- The cure: the most effective anti infective cure ever seen
- Unmet needs?
- From cure to eradication: new strategies new tools

The global targets set by WHO to control viral hepatitis by 2030 are ambitious

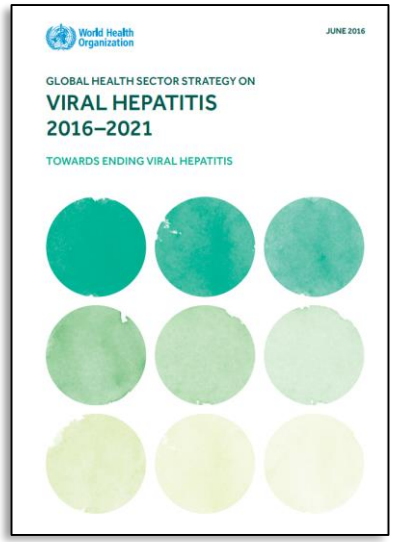


WHO global health sector strategy on viral hepatitis. Available at: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1 (accessed December 2017)

WHO: World Health Organization

Global HCV elimination: the state of play

We have a global strategy to eliminate HCV



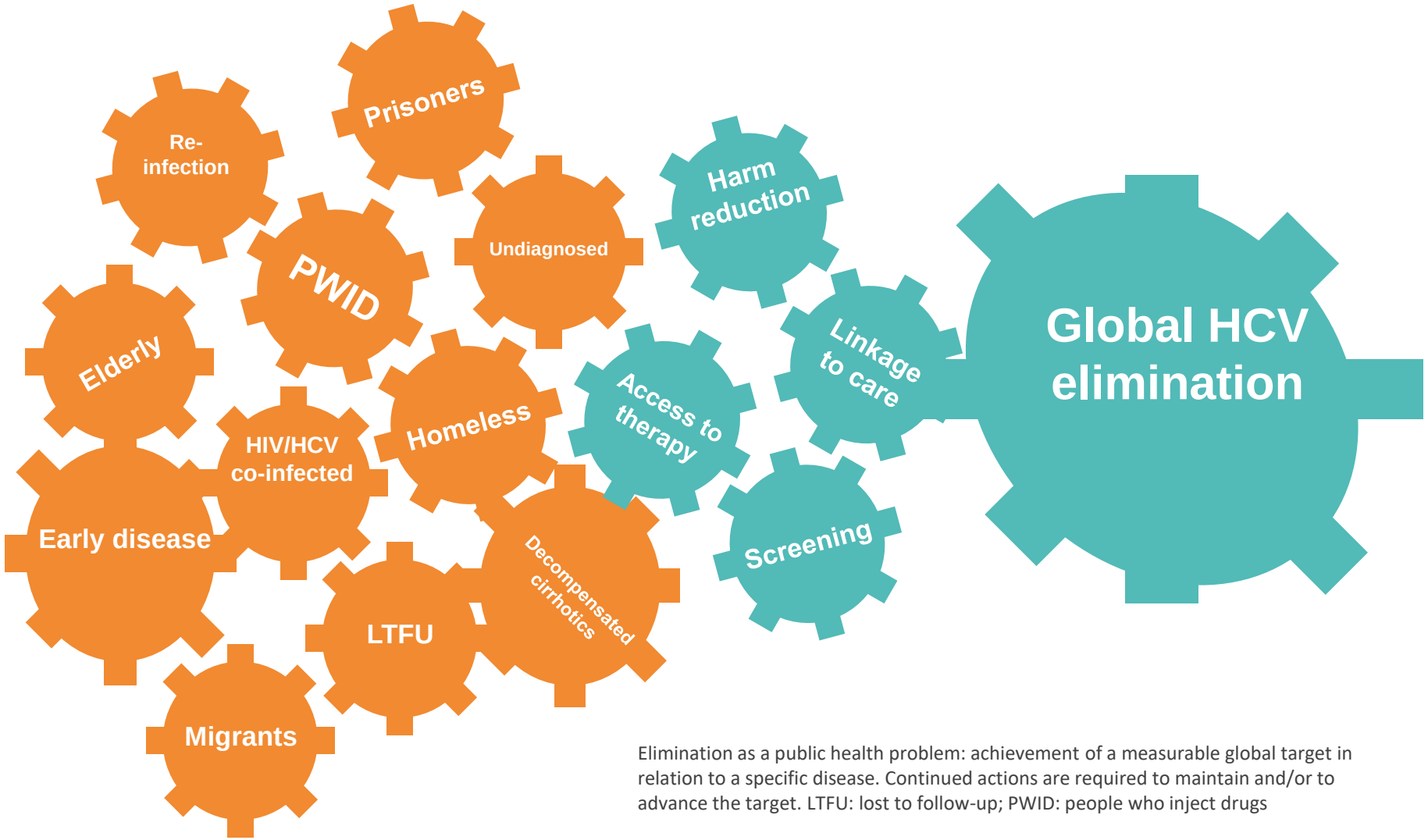
We have therapeutic tools

We have strong interest among many stakeholders in carrying it out

How do we go about implementing the strategy?

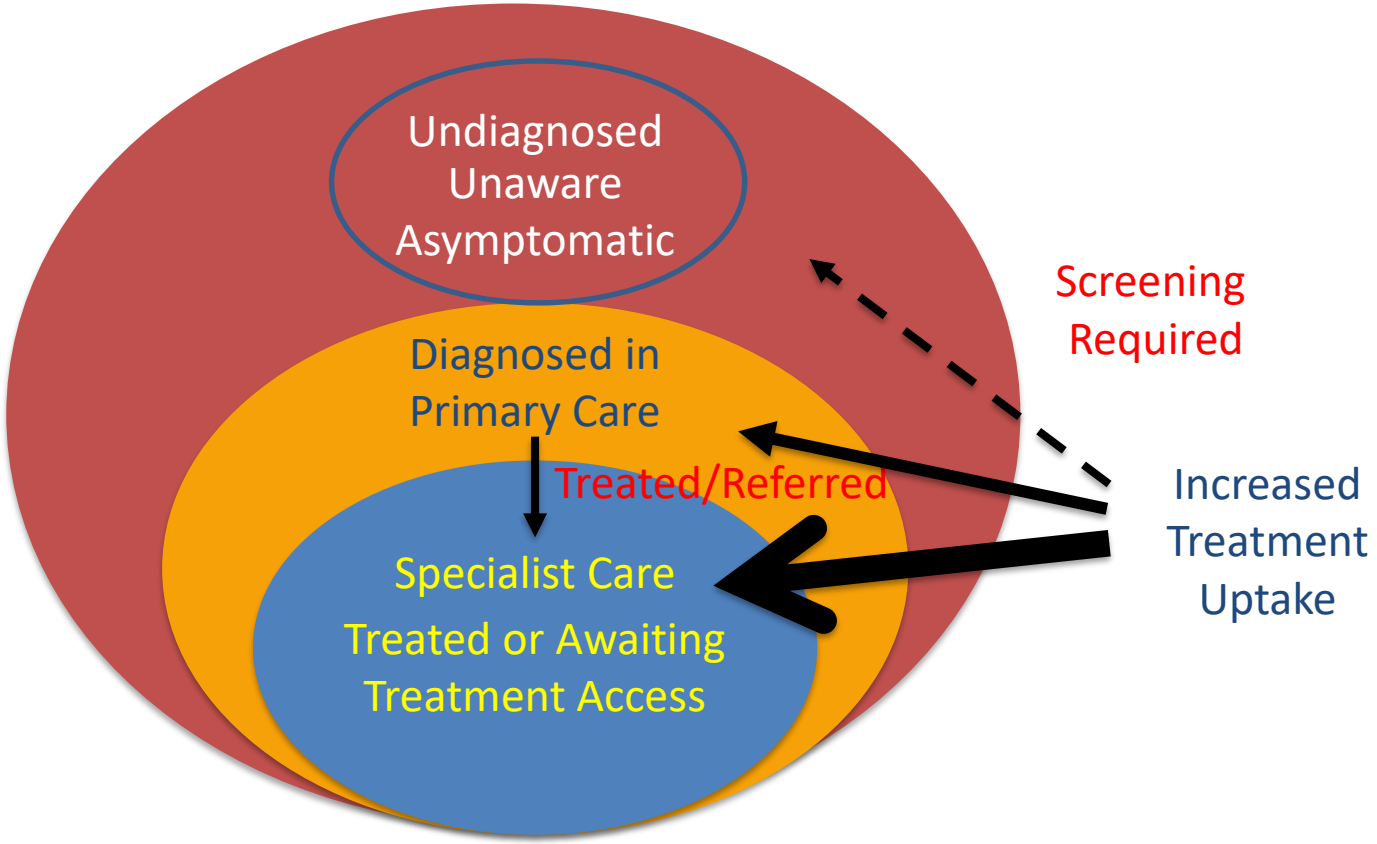
Lazarus J, et al. J Hepatol 2017;67:665–6

Global HCV elimination as a therapeutic goal can seem daunting… but 100 flowers may rise



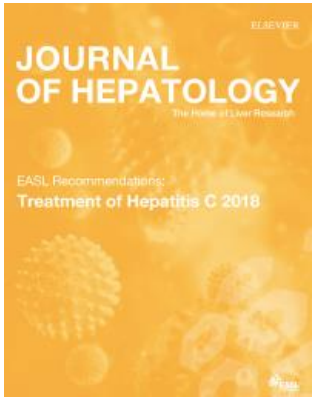
Elimination as a public health problem: achievement of a measurable global target in relation to a specific disease. Continued actions are required to maintain and/or to advance the target. LTFU: lost to follow-up; PWID: people who inject drugs

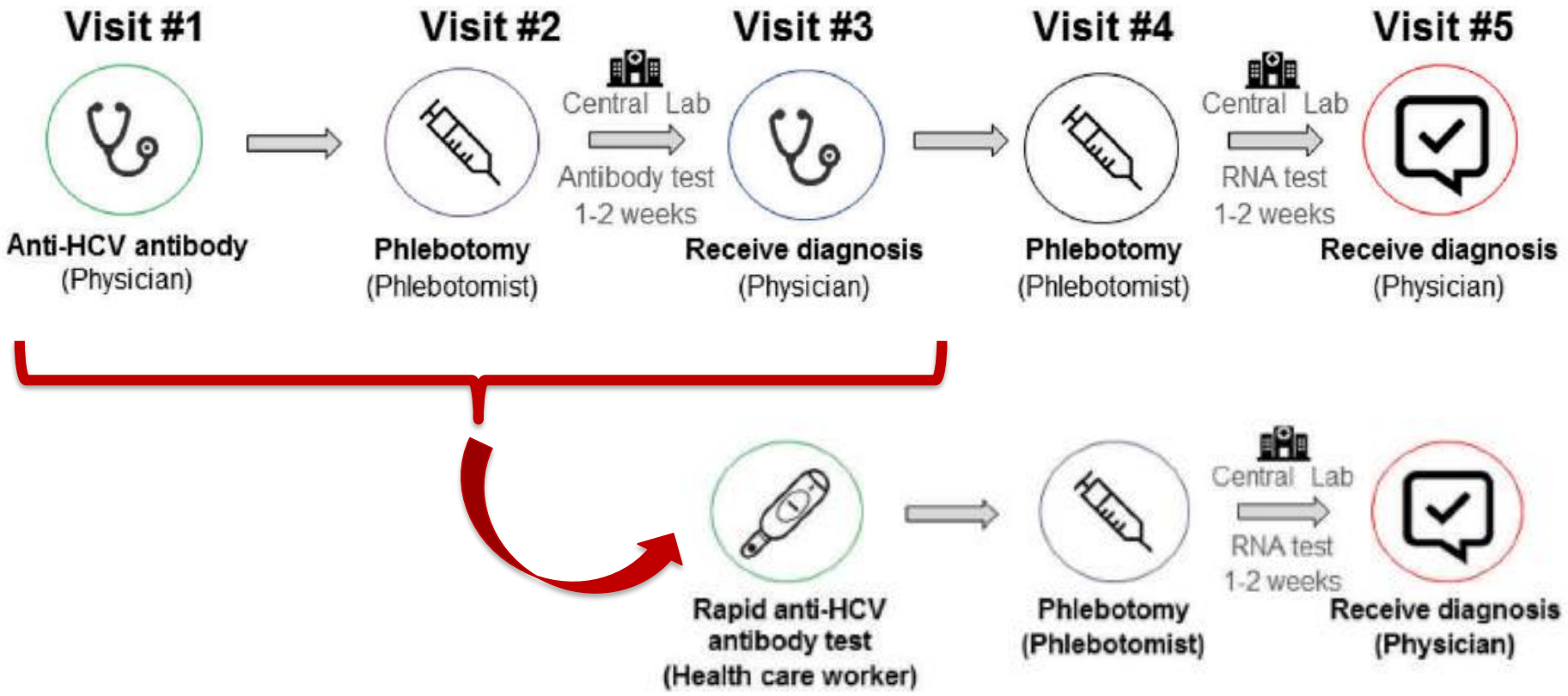
HCV Population



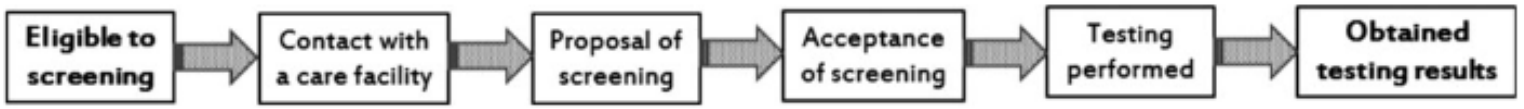
«Rapid diagnostic tests can be used to screen for anti-HCV antibodies»

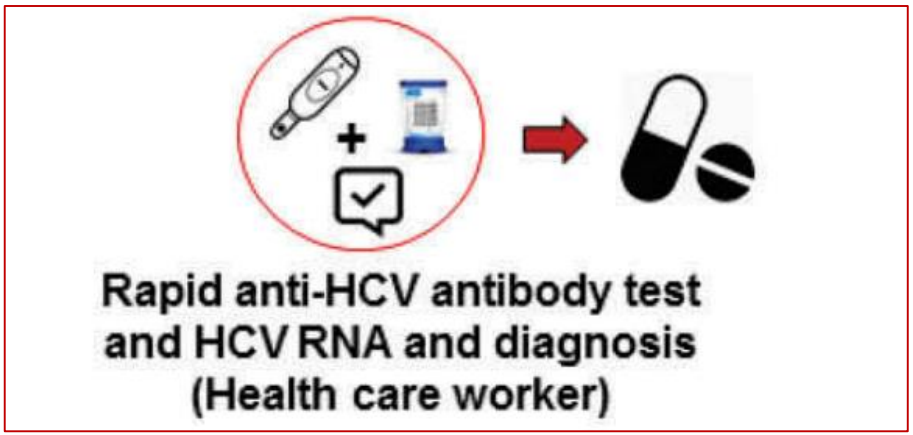
EASL Recommendations on Treatment of Hepatitis C 2018





Towards a 1-visit HCV diagnosis: The cascade of screening





Point-of-care assays are now available that facilitate HCV RNA confirmation and diagnosis in a single visit.

HCV from cure to eradication

- Globally, viral hepatitis is on the rise, and the number deaths per year as the result of virus-induced cirrhosis and liver cancer is now on par with the number of deaths associated with HIV and tuberculosis.
- In 2016, the WHO released its first global health sector strategy on viral hepatitis, with the goal of eliminating viral hepatitis as a public health threat by 2030, particularly those cases caused by HBV and HCV. New strategies new therapeutic and diagnostic tools made this plan feasible
- This ambitious plan would not be possible without the work of three scientists Ralf Bartenschlager, Charles Rice, and Michael Sofia who have truly demonstrated how basic scientific discoveries can pave the way for developing cure for disease and giving life and hope to millions of people in the world
- When we talk about elites and globalization we should take into account that this is the bright face of the moon