MEDIZINISCHE KLINIK 1
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Frankfurt am Main

UNIVERSITÄTS KLINIKUM FRANKFURT

HCV Therapies: The Last challenges

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Stefan Zeuzem, MD

University Hospital, Frankfurt, Germany

Disclosures

Advisory boards: AbbVie, Gilead Sciences, Intercept, and Janssen
Speaker: AbbVie, Gilead Sciences, and
Merck Sharp & Dohme

Challenge No. 1

Omit Discrepencies between (Inter)national Guidelines

Treatment-Naive Genotype 3 Patients with compensated cirrhosis

AASLD & IDSA

- Glecaprevir/Pibrentasvir x 12 weeks
- Sofosbuvir/Velpatasvir
  x 12 weeks

EASL

- Glecaprevir/Pibrentasvir x 12 weeks
- The combination of Sofosbuvir/Velpatasvir is not recommended in treatment-naive ... patients … with compensated (Child-Pugh A) cirrhosis

AASLD/IDSA: HCV Guidance. www.HCVGuidance.org on January 03,2019

EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol (2018), https://doi.org/10.1016/j. jhep.2018.03.026

Challenge No. 2

Shorten (Inter)national Guidelines

Size of International Guidelines

- AASLD/IDSA: 265 pages; EASL 51 pages
- Short guidelines for practioners needed:
  - 2 pangenotypic regimen (dose, duration)
  - Protease inhibitor contraindicated in patients with decompensated cirrhosis, sofosbuvir not licensed in CDK-4/5
  - App available to check for potential DDI
  - For special populations contact/refer to specialist (children, decompensated cirrhosis/transplant evaluation, HCC)

Challenge No. 3

Drug-Drug interactions

Important drug-drug interactions* (DDI) of dual antiviral combinations

	DDI
Sofosbuvir + Ledipasvir	Amiodaron, anticonvulsants, antacids, PPI (high dose), rifampicin, St John‘s Worth, statins
Sofosbuvir + Velpatasvir	Amiodaron, anticonvulsants, antacids, PPI (high dose), rifampicin, efavirenz, St John‘s Worth, statins
Grazoprevir + Elbasvir	Dabigatran, anticonvulsants, antimycotics, bosentan, St John‘s Worth, atazanavir, darunavir, lopinavir, u.a., efavirenz, statins, ciclosporin, modafinil
Glecaprevir + Pibrentasvir	Dabigatran, anticonvulsants, rifampicin, ethinylestradiol, St John‘s Worth, atazanavir, darunavir, efavirenz, statins, ciclosporin, omeprazol

*HEP Drug Interactions, University of Liverpool: http://www.hep-druginteractions.org
*HEP Mobile Apps (Apple, Android)

But some challenges remain with e.g. anticonvulsants, herbal preparations, etc.

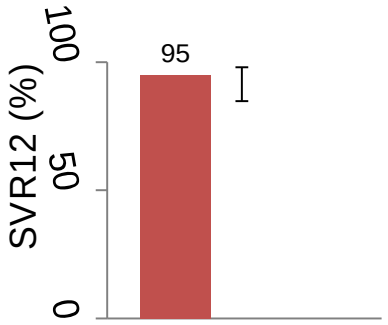
Challenge No. 4

TreaTment of Patients with CKD stage-4/5 and decompensated Cirrhosis

SOF/VEL for 12 weeks is safe and effective in patients undergoing dialysis

Baseline demographics

n (%) or mean (range)	SOF/VEL N=59
Age (years)	60 (33–91)
Male	35 (59)
White	31 (53)
BMI (kg/m2)	26 (17–39)
HCV genotype 1 1a/1b/other 2 3 4/6/indeterminate	 25 (42) 13 (22)/11 (19)/1 (2) 7 (12) 16 (27) 4 (7)/2 (3)/5 (9)
Compensated cirrhosis	17 (29)
IL28B CC genotype	23 (39)
HCV RNA (log10 IU/mL)	5.8 (3.1–7.7)
Prior treatment experience	13 (22)
Type of dialysis Hemodialysis Peritoneal dialysis	 54 (92) 5 (8)
Duration of dialysis (years)	7.3 (0–40)
Prior renal transplant	19 (32)



Patients, n (%)	SOF/VEL N=59
Virologic failure Relapse	2 (3) 2 (3)
Other	1 (2)

Safety, n (%)	SOF/VEL N=59
AE Grade 3 AE Serious AE	47 (80) 7 (12) 11 (19)
Treatment discontinuation due to AE	0
Death	2 (3)
Grade 3/4 laboratory abnormality	25 (42)
AEs in ≥10% patients Headache Fatigue Nausea Vomiting Insomnia	 10 (17) 8 (14) 8 (14) 8 (14) 6 (10)

No Grade 3 or serious AEs were treatment related

Challenge No. 5

TreaTment of Patients with decompensated cirrhosis with Transplant option

Consensus Statement for Treatment of Patients with Decompensated Cirrhosis

Recommendation 2.1

We suggest that HCV-infected patients with decompensated cirrhosis with CTP Class B and/or MELD less than 20 on the waiting list for liver transplantation, who are without refractory portal hypertensive symptoms or other conditions requiring more immediate transplantation, should be treated with antiviral therapy.

Recommendation 2.2

We suggest that HCV-infected patients with advanced decompensated cirrhosis (MELD 30) or those who are expected to undergo liver transplantation within 3 months should not undergo antiviral therapy.

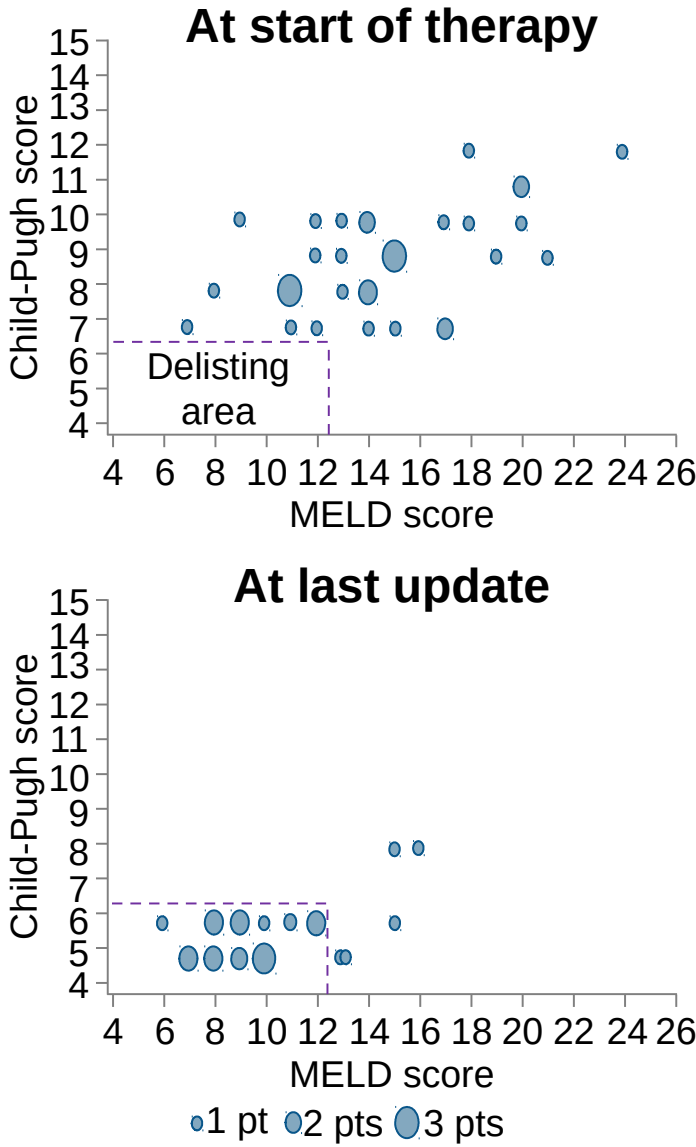
Recommendation 2.3

We suggest that HCV-infected patients with decompensated cirrhosis with intermediate MELD scores and/or low MELD scores but refractory portal hypertensive complications who are on the waiting list be offered treatment with antiviral therapy selectively.

Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

Delisting of liver transplant candidates with chronic HCV infection after viral eradication: Outcome after delisting

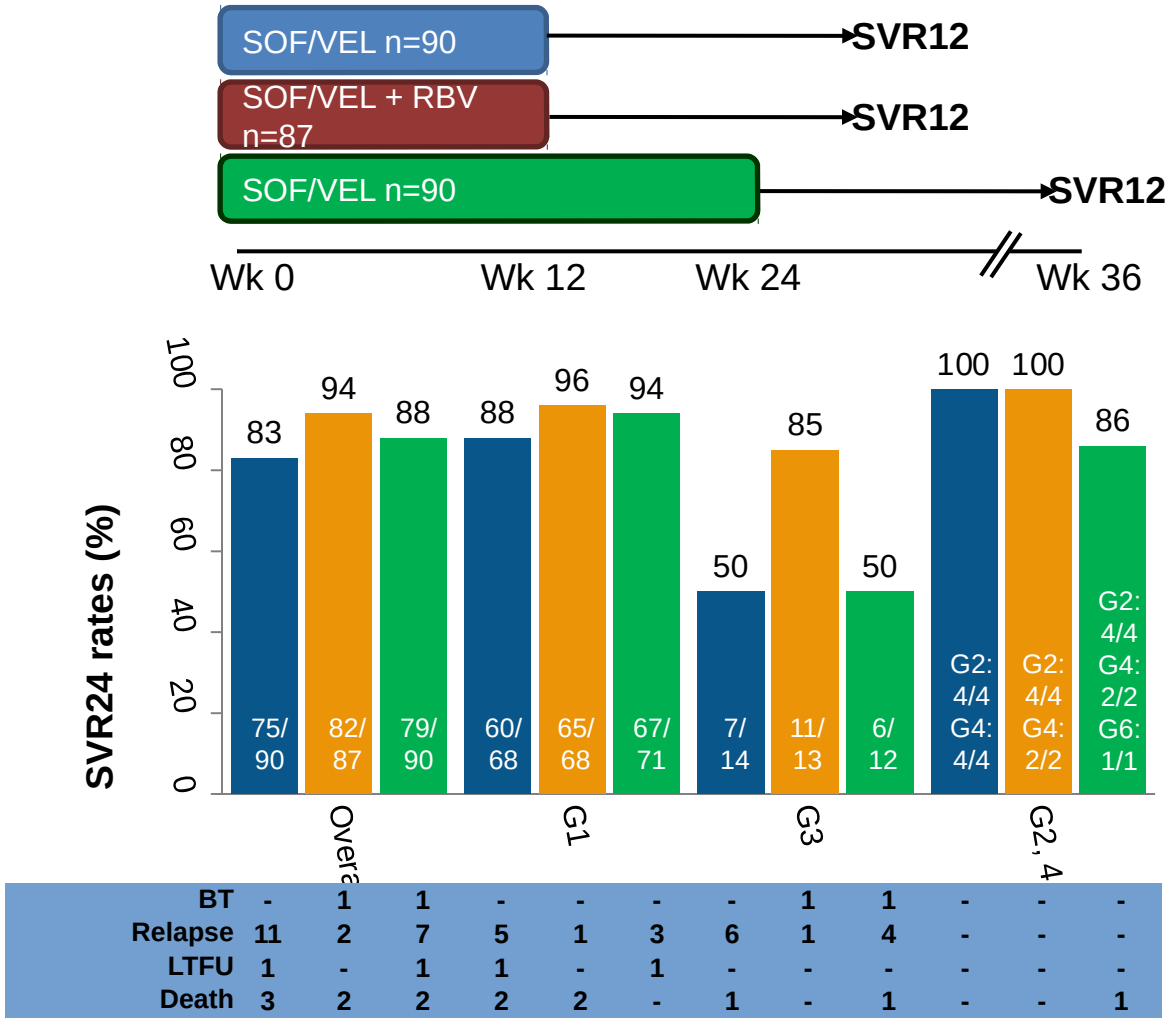
Variable	HR	95% CI	p-value
Δ MELD at 12 wks	1.315	1.181–1.464	<0.0001
BL MELD <16 16–20 >20	 Ref 0.176 0.094	 0.075–0.41 0.029–0.305	 <0.0001 <0.0001



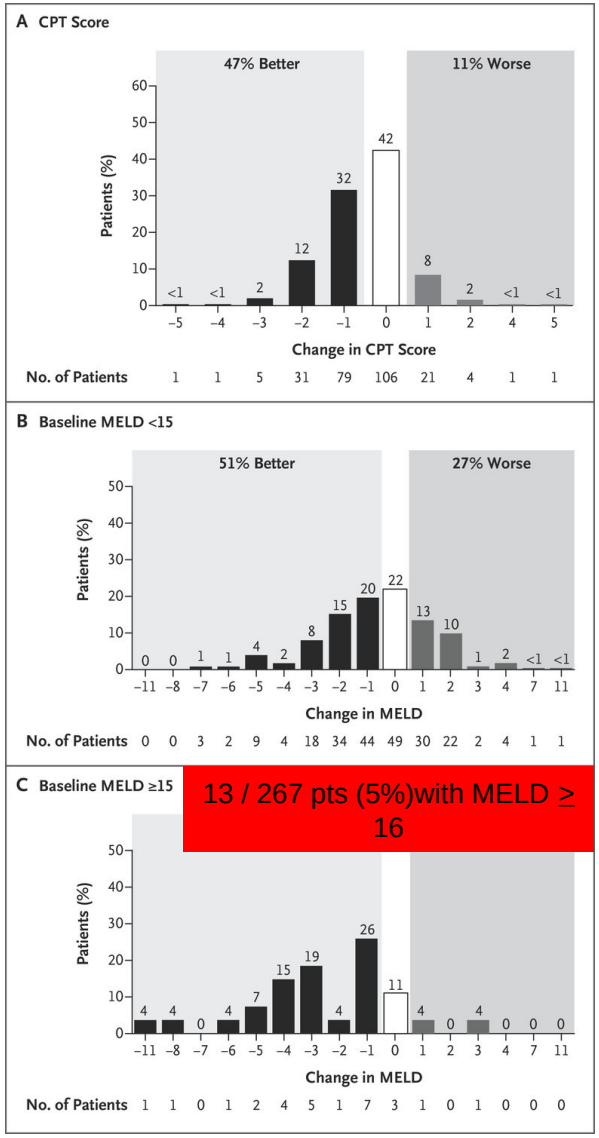
Challenge No. 6

TreaTment of Patients with decompensated cirrhosis without Transplant option

ASTRAL-4: SOF/VEL for HCV in Patients with Decompensated Cirrhosis



Clinical Benefits of SVR with SOF/VEL in Decompensated Cirrhotic Patients



13 / 267 pts (5%)with MELD ≥ 16

Table 3. Adverse Events and Hematologic Abnormalities.

Event	Sofosbuvir–Velpatasvir for 12 Wk (N=90)	Sofosbuvir–Velpatasvir plus Ribavirin for 12 Wk (N=87)	Sofosbuvir–Velpatasvir for 24 Wk (N=90)
		number (percent)	
Discontinuation of treatment because of adverse event	1 (1)	4 (5)	4 (4)
Death during treatment or follow-up	3 (3)	3 (3)	3 (3)
Serious adverse event during treatment	17 (19)	14 (16)	16 (18)
Any adverse event during treatment	73 (81)	79 (91)	73 (81)
Common adverse events*			
Fatigue	23 (26)	34 (39)	21 (23)
Nausea	22 (24)	22 (25)	18 (20)
Headache	23 (26)	18 (21)	17 (19)
Anemia	4 (4)	27 (31)	3 (3)
Diarrhea	6 (7)	18 (21)	7 (8)
Insomnia	9 (10)	12 (14)	9 (10)
Pruritus	10 (11)	4 (5)	4 (4)
Muscle spasm	3 (3)	10 (11)	4 (4)
Dyspnea	4 (4)	9 (10)	2 (2)
Cough	2 (2)	9 (10)	0
Hematologic event			
Reduced hemoglobin level			
<10 g/dl	7 (8)	20 (23)	8 (9)
<8.5 g/dl	1 (1)	6 (7)	1 (1)
Reduced lymphocyte count			
350 to <500 per mm^3	10 (11)	12 (14)	8 (9)
<350 per mm^3	3 (3)	12 (14)	6 (7)
Reduced neutrophil count			
500 to <750 per mm^3	2 (2)	1 (1)	2 (2)
<500 per mm^3	0	1 (1)	1 (1)
Reduced platelet count			
25,000 to <50,000 per mm^3	15 (17)	10 (11)	18 (20)
<25,000 per mm^3	1 (1)	0	0
Reduced white-cell count			
1000 to <1500 per mm^3	1 (1)	1 (1)	4 (4)
<1000 per mm^3	1 (1)	1 (1)	0

* Common adverse events occurred in at least 10% of patients in any group.

Curry MP et al., *N Engl J Med* 2015;373:2618-2628

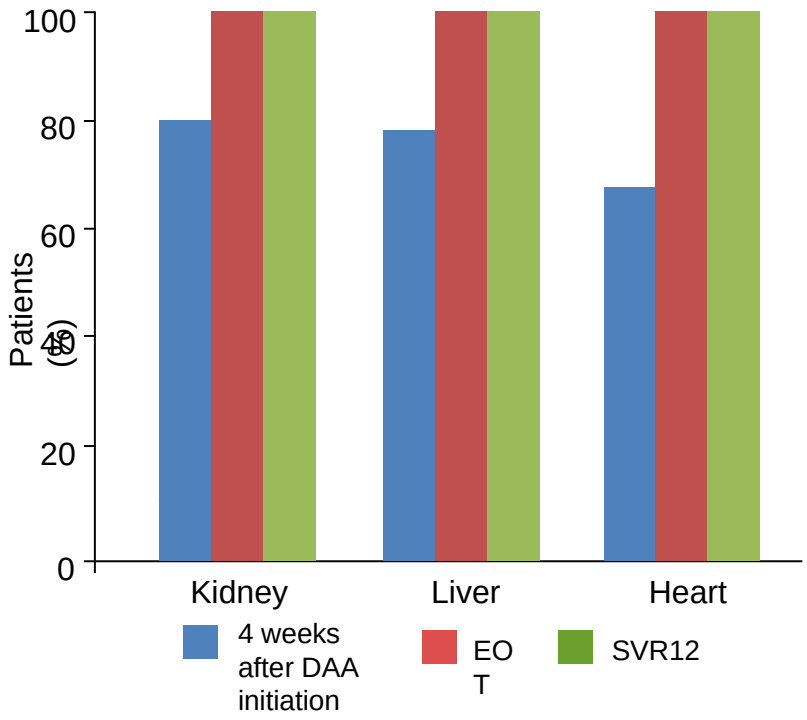
Challenge No. 7

Transplantation of HCV positive Organs

Transplantation of hepatitis C-positive solid organ allografts into hepatitis C-negative recipients

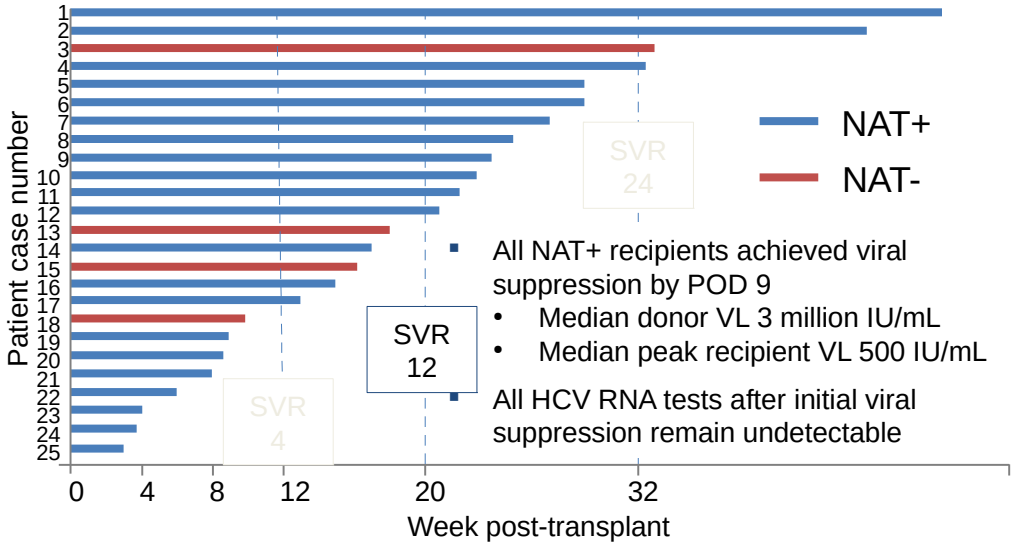
	Kidney	Liver	Heart
Patients transplanted, n	54	11	10
Patients started on DAA therapy, n	36	11	7
Age, years	67.5	62.5	60.6
Male, n	40	6	6
Time on waitlist, days	275.0	191.2	370.3
Time on waitlist after consenting to receive HCV organs, days	33.1	48.6	33
Treatment regimen, daily x 12 weeks LDV 90 mg and SOF 400 mg GLE 100 mg and PIB 40 mg VEL 100 mg and SOF 400 mg	 16 19 1	 0 10 1	 3 4 0
Time from transplant to initiation of DAA	43.7	27.2	44.7

Virologic response after initiation of DAA therapy



Preemptive, pan-genotypic DAA therapy in cardiac transplantation from HCV-positive donor to HCV-negative recipient

preemptive



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NAT, nucleotide acid testing; POD, post-operative day

Preemptive administration of GLE/PIB results in prevention of chronic HCV infection in HCV-negative cardiac transplant recipients receiving HCV-infected donor hearts

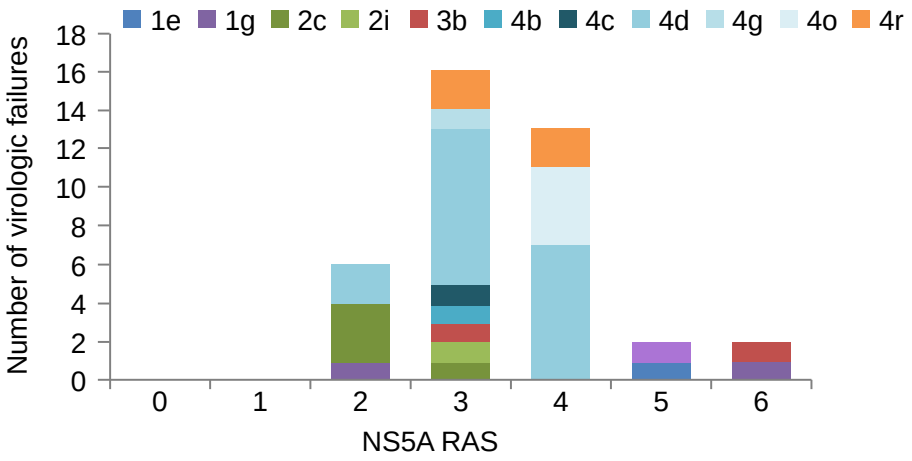
This strategy has the potential to decrease heart transplant wait times and improve post-transplant outcomes

Challenge No. 8

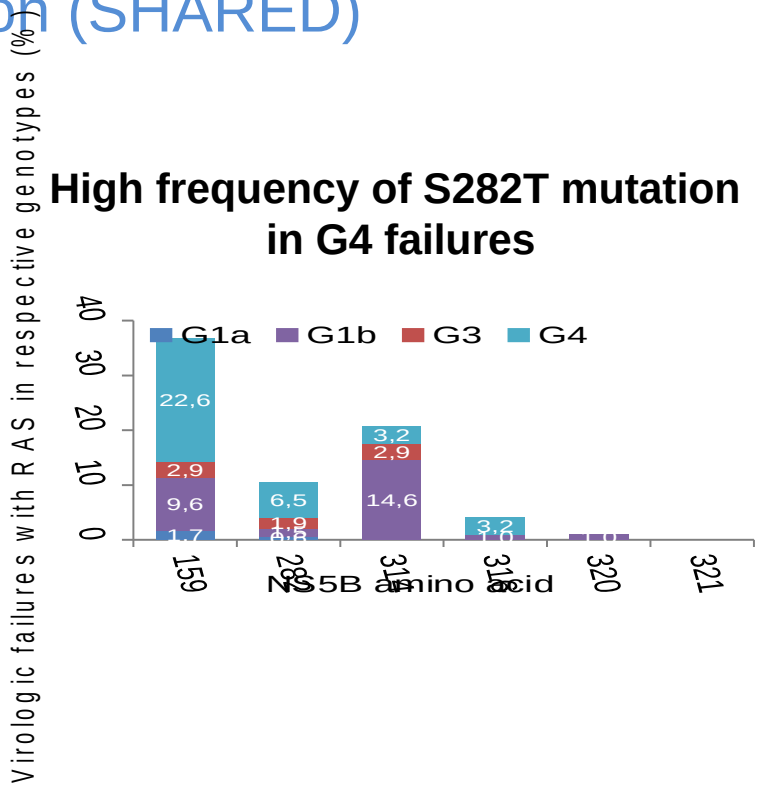
NON-responders to SOF/VEL/VOX

A real world resistance profile of virologic failures collected from an international collaboration (SHARED)

Rare genotypes tend to select multiple NS5A RAS after DAA failure



High frequency of S282T mutation in G4 failures



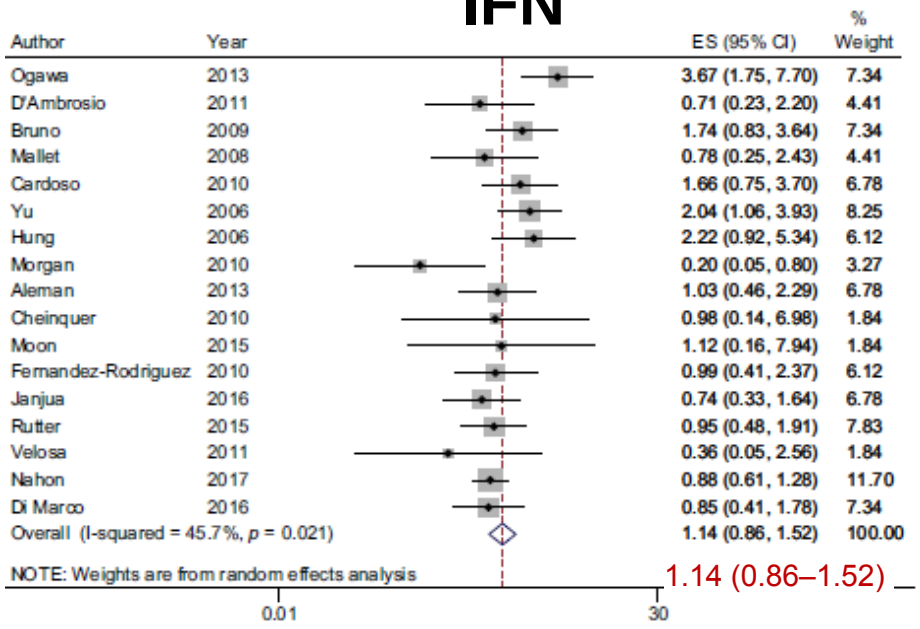
- RAS patterns are unique among genotypes
- New RAS were observed in real-world clinics
- “Rare genotypes” tend to select multiple RAS
- 20% of the G4 patients selected NS5B S282T after failing SOF-regimens

Challenge No. 9

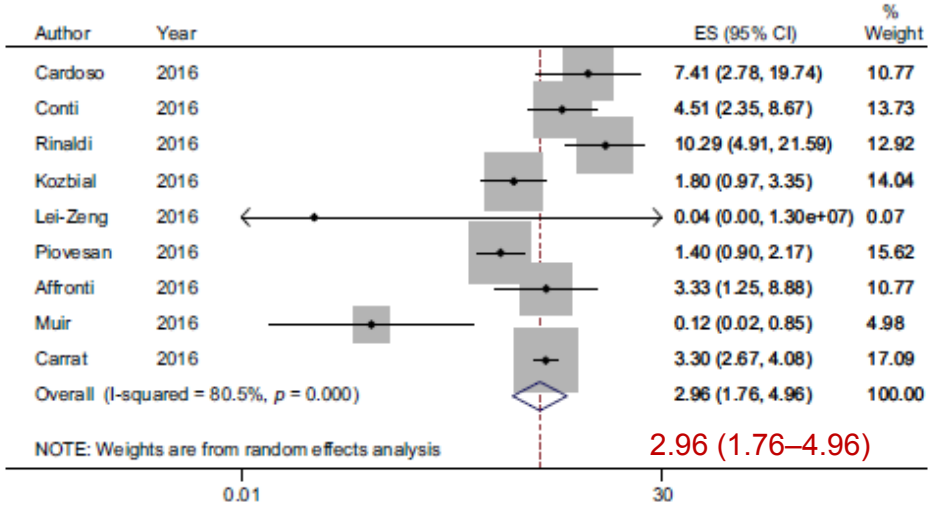
HCV Treatment in patients with HCC, BCLC stage B / C

A meta-analysis of the risk of HCC occurrence following SVR to IFN or DAAs

IFN



DAA



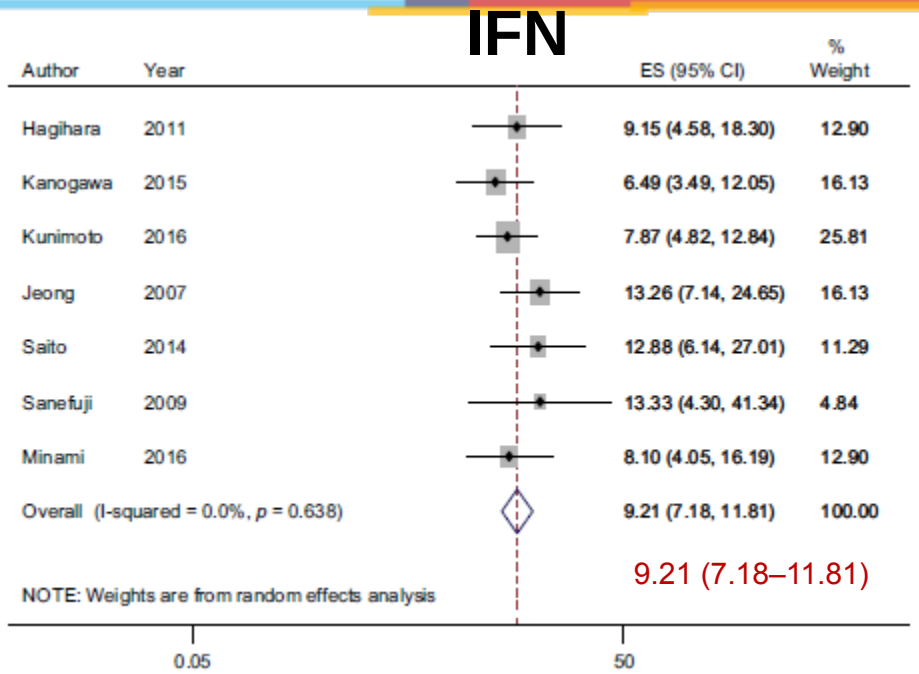
Meta regression of HCC occurrence

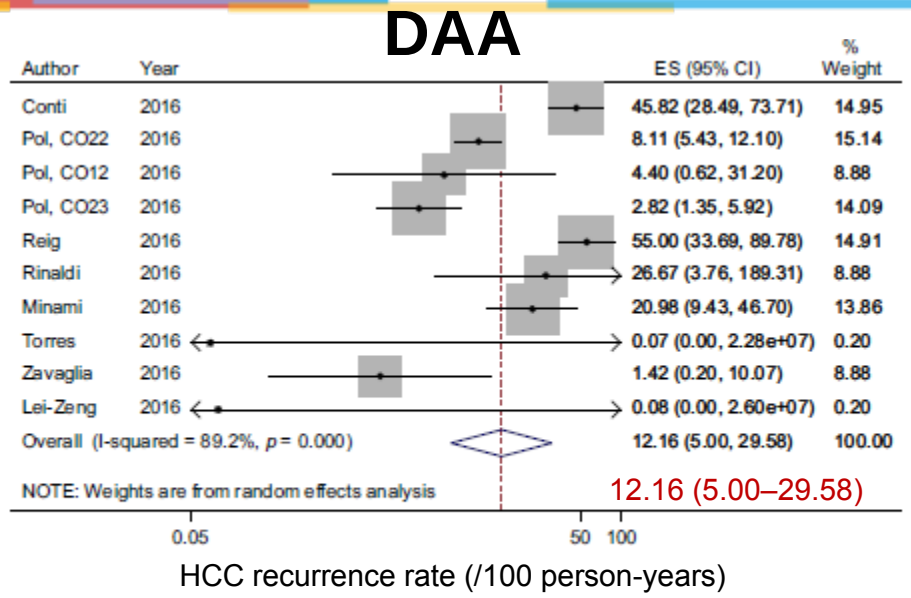
	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.88	0.75	0.56–0.99	0.04
Average age	1.11	1.06	0.99–1.14	0.12
DAA treatment	2.77	0.68	0.18–2.55	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12

RR: risk ratio

A meta-analysis of the risk of HCC recurrence following SVR to IFN or DAAs





Meta regression of HCC reccurrence

	Unadjusted RR	Adjusted RR	95% CI	P-value
Average follow-up	0.86	0.79	0.55–1.15	0.19
Average age	1.11	1.11	0.96–1.27	0.14
DAA treatment	1.36	0.62	0.11–3.45	0.56

Waziry R, et al. J Hepatol 2017;67:1204–12

Consensus Statement for Management of Patients with Decompensated Cirrhosis and HCC

- *Recommendation 3.1*
  We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are not expected to undergo liver transplantation within a short time (3-6 months), should be treated with antiviral therapy.
- *Recommendation 3.2*
  We suggest that HCV-infected patients with decompensated cirrhosis and HCC, who are expected to undergo liver transplantation within a short time (3-6 months), should not be treated with antiviral therapy.

Paucity of data, therefore pragmatic approach

Primary benefit is prevention of waitlist drop off due to worsening decompensation,

Potentially lower SVR rates

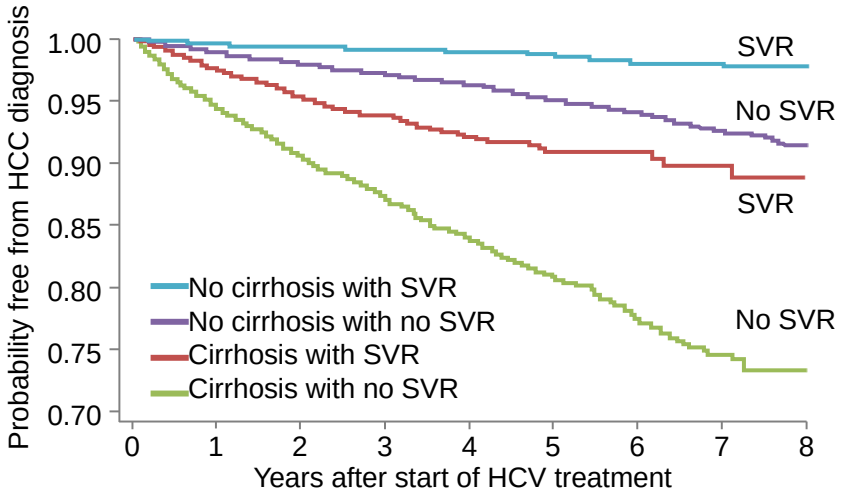
Potentially more aggressive tumor growth

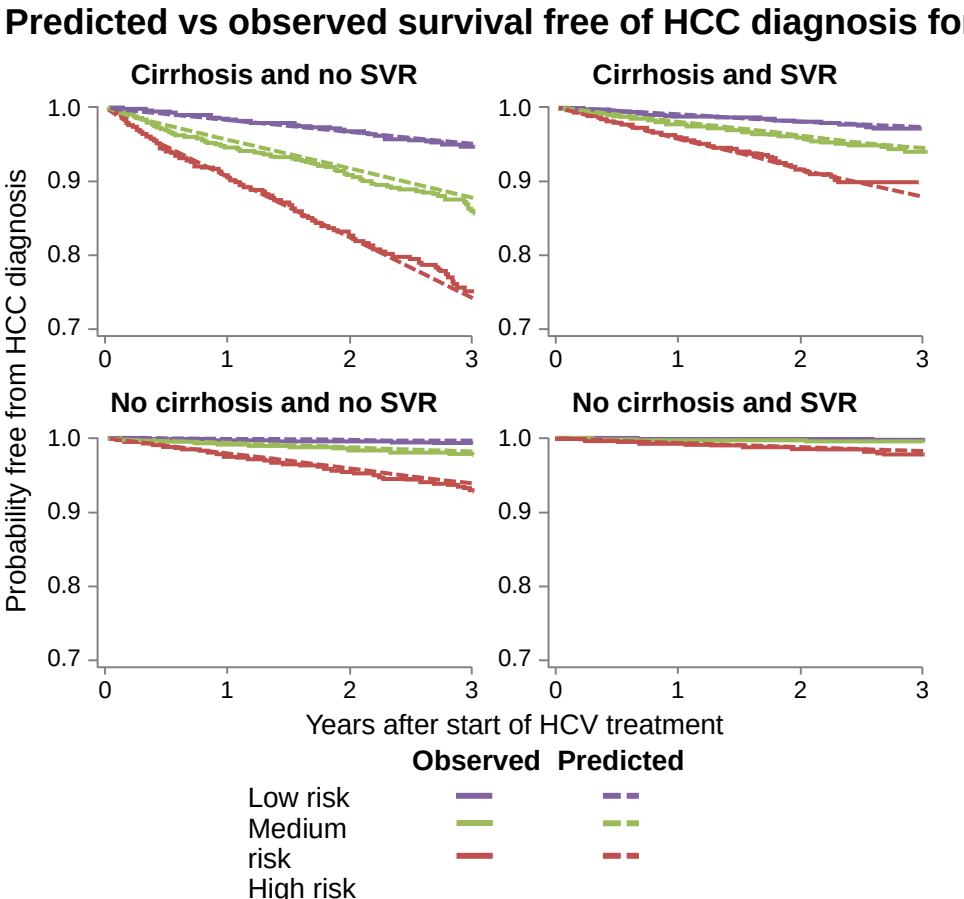
Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

Challenge No. 10

HCC surveillance in patients with SVR

Risk-based HCC surveillance strategies based on risk prediction models in patients who received antiviral treatment for HCV





Risk-based HCC surveillance strategies based on risk prediction models in patients who received antiviral treatment for HCV

www.hccrisk.com

	1	2	3	4	5	6
Cirrhosis	**Yes**	**Yes**	**Yes**	**No**	**No**	**No**
SVR	No	Yes	Yes	No	No	Yes
Age	65	55	66	65	55	65
Albumin	3.3	4.1	3.6	3.8	4.1	4.1
AST	40	25	45	35	35	35
ALT	30	35	30	30	45	45
Platelet	110	145	110	145	201	250
3-yr HCC risk	25.9 %	1.6 %	11.1 %	7.0 %	0.6 %	0.3 %
	Screening recommended			Screening not recommended		

- Screening/not screening with overlapping HCC risk
- Theoretically not screen low risk regardless of cirrhosis status

Challenge No. 11

Diagnosis rates, linkage to care, access to daas

HCV treatment: linkage to care

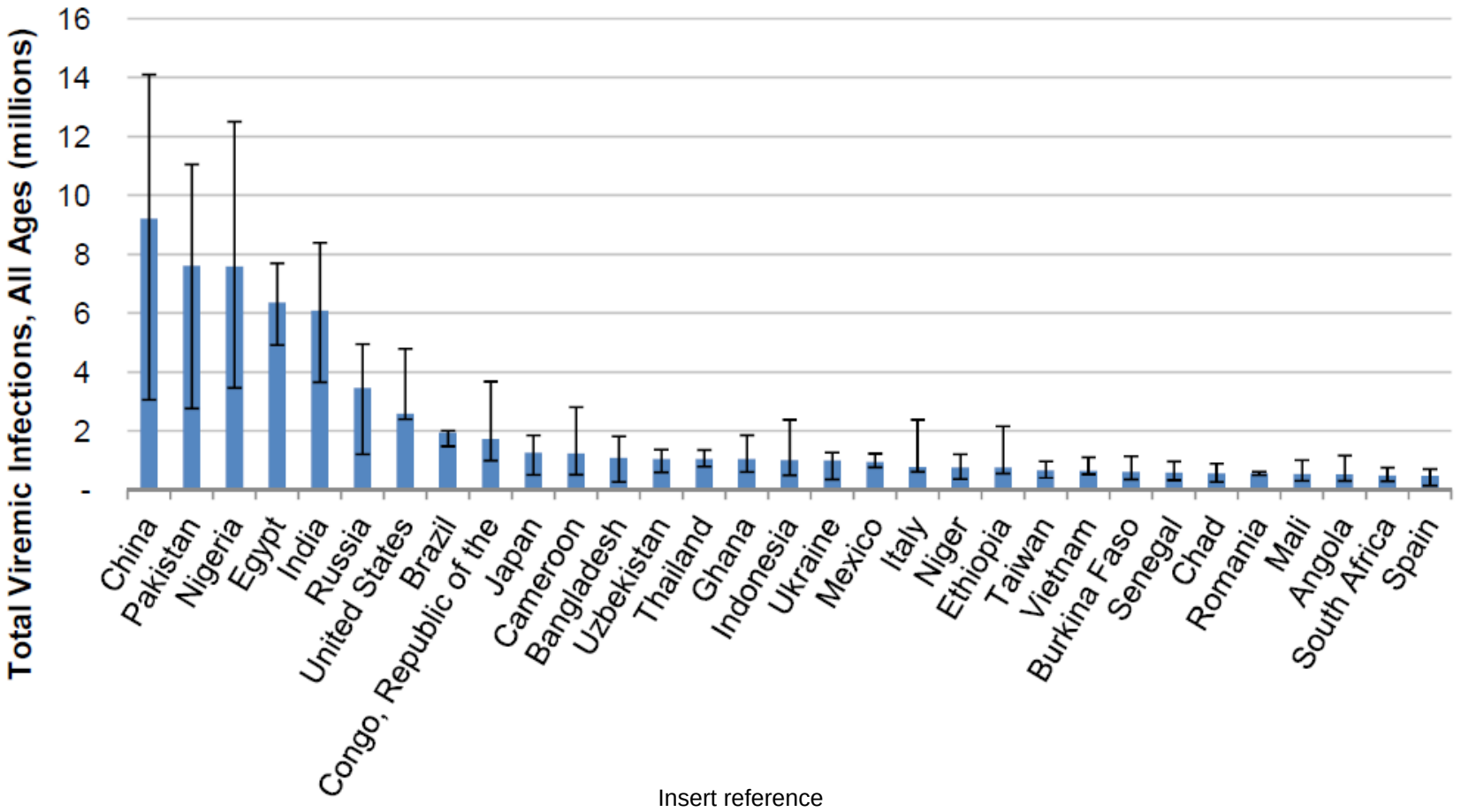
- Enhanced HCV screening and diagnosis
- Expanded models of HCV treatment and care
- Specific strategies for highly marginalised patients
- National HCV strategies and political leadership
- Removal of restrictions on access to DAA therapy
- Increased and broadened HCV prescribers

Challenge No. 12

Vaccine Development

Total Viremic HCV Infections

Countries Responsible for 80% of Global Infections



Insert reference

Gower, E., Estes C., Hindman, S., Razavi-Shearer, K., Razavi, H.,
Global epidemiology and genotype distribution of the hepatitis C virus.
Journal of Hepatology (2014)

WHO global health sector HCV strategy

Prevention targets

- **90%** of infants have HBV birth dose vaccination
- **100%** of blood donations screened
- **90%** have access to safe injections
- **15 x** Increase in the number of sterile needles and syringes provided per injecting drug user per year

Testing targets

- **90%** of people aware of infection

Treatment targets

- **80%** of patients treated
- **90%** of HCV patients cured

World Hepatitis Alliance. Available at: https://www.youtube.com/watch?v=cVttqfgExL0;
WHO. Draft global health sector strategy on viral hepatitis, 2016–2021. Available at: www.who.int/hepatitis/news-events/strategy2016-2021/Draft_global_health_sector_strategy_viral_hepatitis_13nov.pdf?ua=1
(Both accessed February 2017)

WHO: World Health Organization

Conclusions

- Several challenges remain in small populations. Most likely that these populations disappear faster than the challenges are solved
  - e.g. patients with decompensated cirrhosis
- Some challenges remain in large populations
  - e.g. HCC surveillance after SVR
- Some challenges are key to reduce the burden of disease in geographic regions and populations
  - Diagnosis rates, linkage to care, and access to DAAs
- One challenge to indeed eliminate HCV globally
  - Vaccine development