MEDIZINISCHE KLINIK 1
des Klinikums
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

UNIVERSITÄTS KLINIKUM FRANKFURT

Hepatitis C: The Elimination

The last difficult to treat patients

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Disclosures

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

Challenge No. 1

HOMELESS PEOPLE / PWID

Iceland: 95% of eligible HCV infected patients were initiated on treatment within three years. Results from the treatment as prevention for hepatitis C (TRAP HepC) program

WHO treatment coverage targets: 90% diagnosis and 80% treatment of eligible patients by 2030

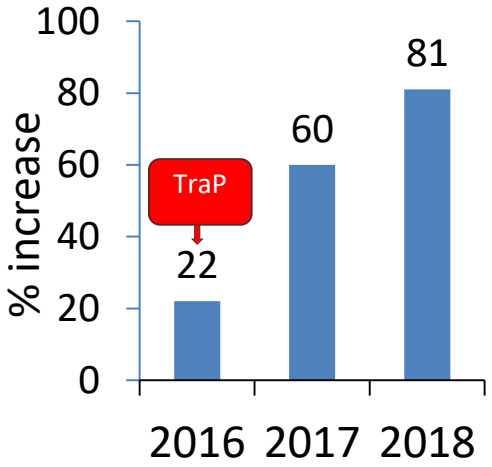
Icelandic TraP HepC program aims to offer HCV treatment to all known cases within a 36-month period (2016–2018), focusing on those most likely to transmit

Demographics

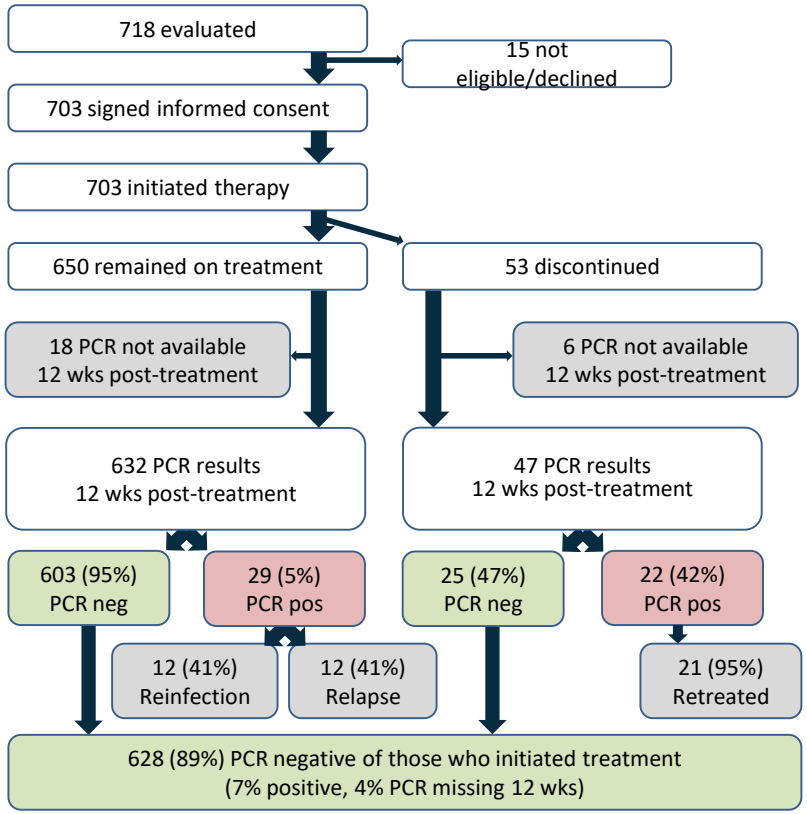
Characteristic	N=703
Age, years, mean (IQR)	44 (34–54)
Male, n (%)	474 (67)
Route of infection, IDU Recent IDU[a]	84% 33%
Homeless	7%
Incarcerated	5%
Stimulants used Opioids used	85% 13%
Genotype 3a Genotype 1	58% 40%
Cirrhosis[b]	7%

[a]within 6 months; [b]hepatic stiffness >12.5 kPa

Increase in HCV testing compared to previous years



Patient status during first 3 years of TraP HepC



Olafsson S, et al. AASLD 2019, Boston, USA. #1516

Challenge No. 2

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.

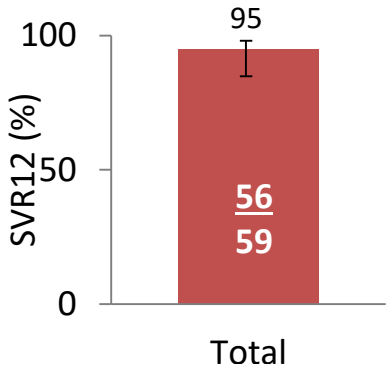
Challenge No. 3

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/m^2)	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 (log_{10} 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

Borgia S, et al. AASLD 2018, San Francisco, USA. #LB-15

Sofosbuvir-based regimen is safe and effective for HCV-infected patients with CDK4,5 disease

- Meta-analysis of 21 studies, including 717 HCV infected patients with CDK stage 4 or 5 (58% HD)
- SVR12/24: 97.1%; no significant differences in SVR and SAE rates between full or decreased SOF doses
- Similar SVR rates in cirrhotic and non-cirrhotic patients
- No significant modifications of eGFR/serum creatinine levels pre- and post-treatment (4 studies)

Li et al., Virol J 2019;16:34

Challenge No. 4

TREATMENT OF PATIENTS WITH DECOMPENSATED CIRRHOSIS WITH TRANSPLANT OPTION

Consensus Statement for Treatment of Patients with Decompensated Cirrhosis

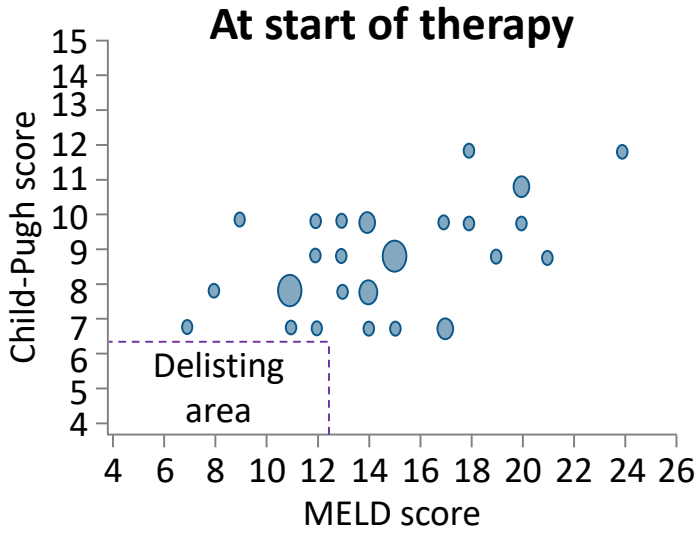
- *Recommendation 2.1*
  We suggest that HCV-infected patients with decompensated cirrhosis with CTP Class B and/or MELD less than 20 on the waiting list for liver transplantation, who are without refractory portal hypertensive symptoms or other conditions requiring more immediate transplantation, should 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.

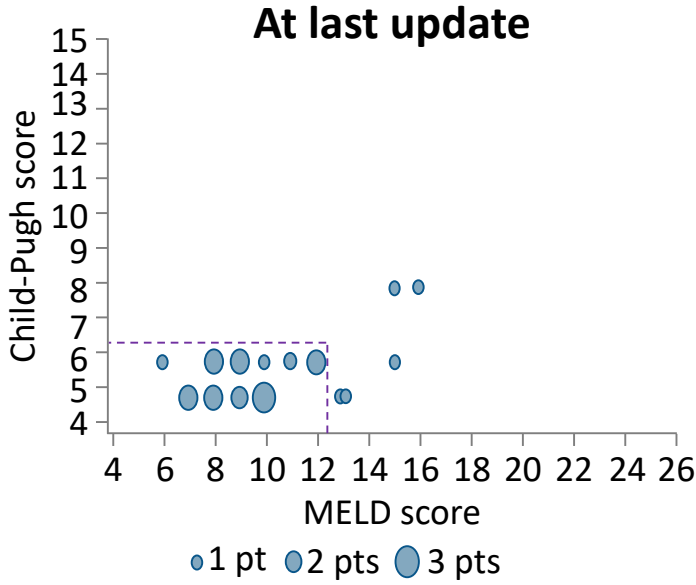
Terrault et al., International Liver Transplantation Society Consensus Statement on Hepatitis C Management in Liver Transplant Candidates. Transplantation 2017; 101: 945-955

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

- 142 patients listed for decompensated cirrhosis without HCC treated with DAAs
- 38/142 patients (26.8%) delisted due to clinical improvement
- Median (IQR) f/u from start of Tx = 28 months, from delisting = 15 months
- 37/38 delisted patients alive
- 2 pts were relisted for clinical re-decompensation (MELD at relisting were 16 and 15)

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



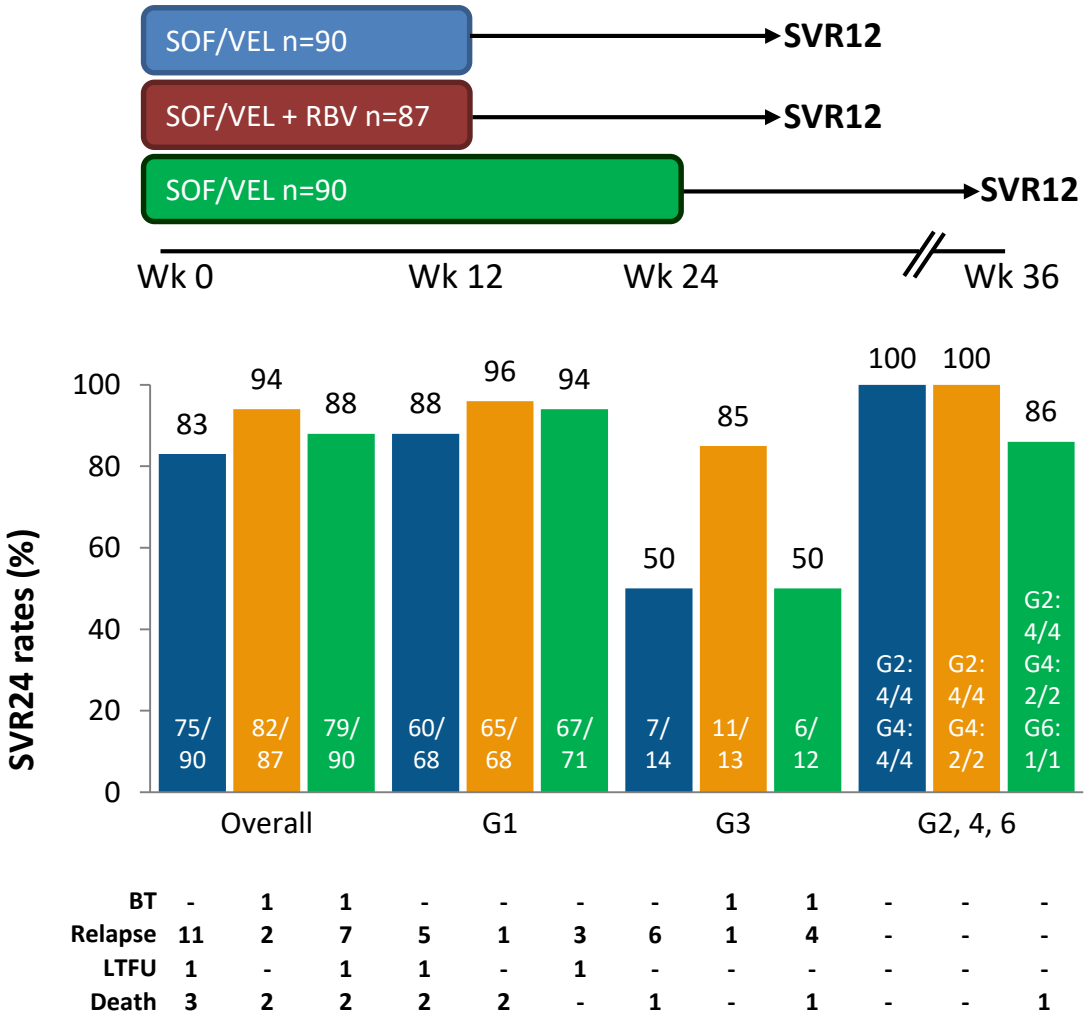


Belli LS, et al. EASL 2017, Amsterdam. #PS-063
Belli LS, et al., *J Hepatol* 2016;65:524-531

Challenge No. 5

TREATMENT OF PATIENTS WITH DECOMPENSATED CIRRHOSIS WITHOUT TRANSPLANT OPTION

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



Curry MP, et al., N Engl J Med 2015;373:2618-28

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

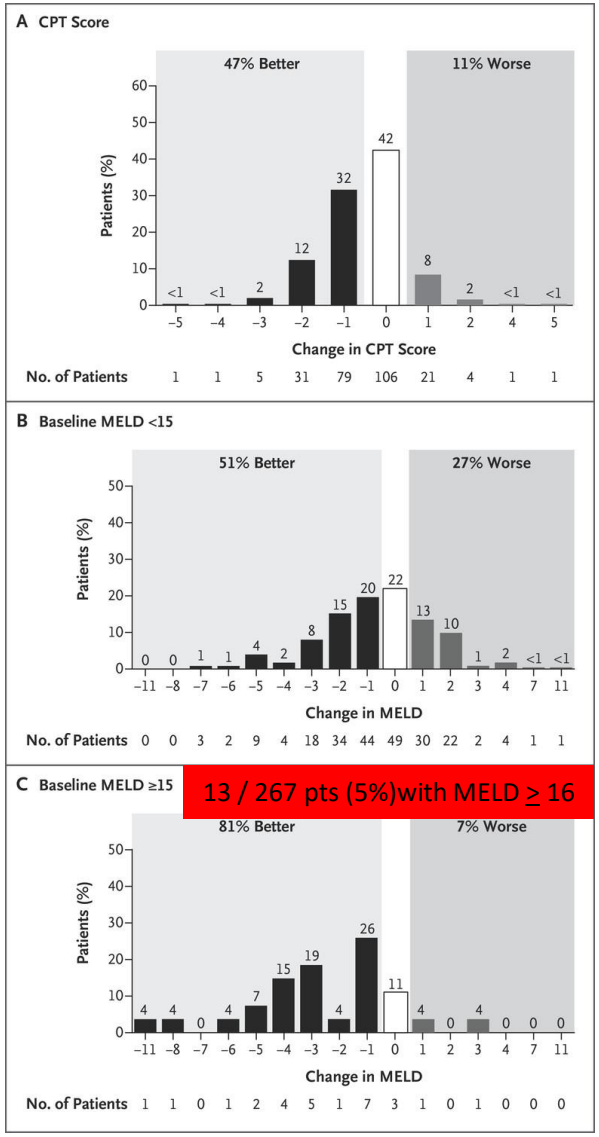


Table 3. Adverse Events and Hematologic Abnormalities.

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. 6

NON-RESPONDERS TO SOF/VEL/VOX

Safety and efficacy of sofosbuvir/velpatasvir/voxilaprevir-based regimens for the treatment of HCV genotype 1-6: Results of the HCV-TARGET cohort

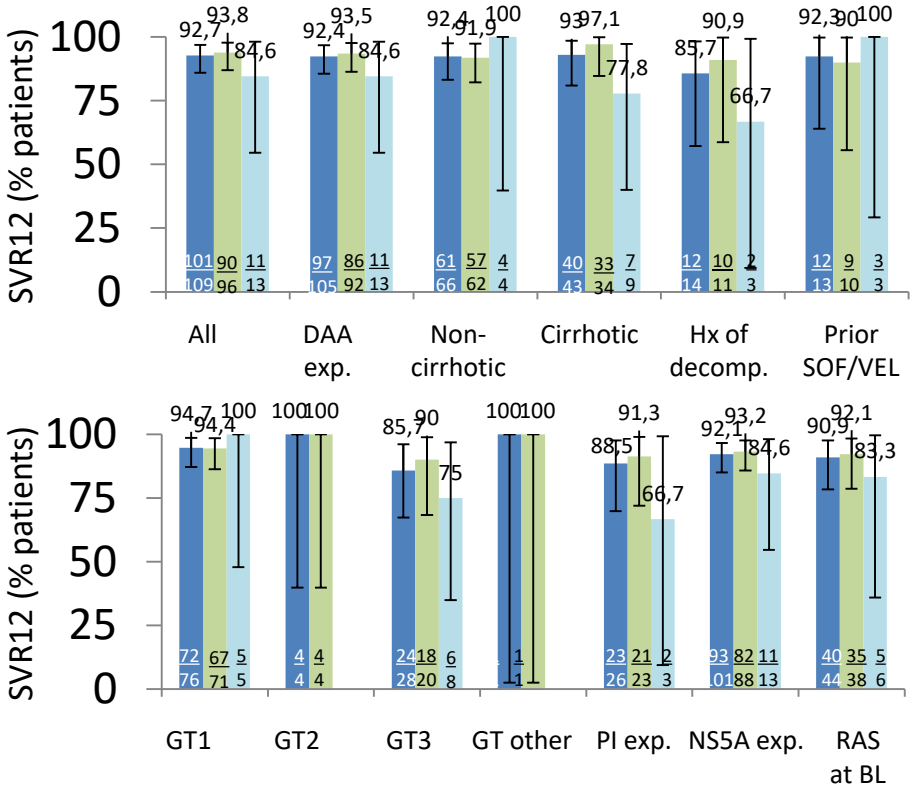
Disposition and Outcomes

Disposition, n (%)	SOF/VEL/VOX N=114	SOF/VEL/VOX/RBV N=14
Completed treatment	106 (93)	13 (93)
Lost to on Tx follow-up	3 (3)	1 (7)
Discontinued	5 (4)	0
AE[a]	3 (3)	
Non compliance	1 (1)	
Liver transplant	1 (1)	
Treatment outcome status, n (%)		
SVR12 available	98 (86)	13 (93)
Lost to on Tx follow-up	3 (3)	1 (7)
Lost to post Tx follow-up	13 (11)	0

[a]1 drug intolerance, 1 influenza-like illness, 1 schizophrenia; No deaths

BL, baseline; DAA, direct-acting antivirals; Hx of decomp, history of decompensation; PI, protease inhibitor; Tx, treatment

SVR12 Rates by Disposition



Zeuzem S, et al. AASLD 2019, Boston, USA. #1558

Safety and efficacy of sofosbuvir/velpatasvir/voxilaprevir-based regimens for the treatment of HCV genotype 1-6: Results of the HCV-TARGET cohort

Pt	Regimen	Prior DAA	Race	Tx weeks	GT	RAS at BL	Cirrhosis	Child Pugh	Decomp[a]
1	SOF/VEL/VOX	SOF/LDV	Black	6	1a	M28M/V+L31M	N	-	N
2	SOF/VEL/VOX	SOF/LDV	Black	12	1a	No RAS	N	-	N
3	SOF/VEL/VOX	SOF/LDV, G/P	Black	12	1a	Q30R+L31M+H58D	N	-	N
4	SOF/VEL/VOX	EBR/GZR	Other	12	1a	No RAS	Y	B	Y
5	SOF/VEL/VOX	SOF/LDV	White	12	1a	Q30R	N	-	N
6	SOF/VEL/VOX	SOF/VEL	White	12	3a	S62T+Y93H	N	-	N
7	SOF/VEL/VOX	SOF/DCV/RBV, SOF/LDV/RBV	White	13	3a	No testing done	N	-	N
8	SOF/VEL/VOX/RBV	SOF/RBV, SOF/DCV, EBR/GZR	Other	12	3a	S62T+Y93H	Y	A	Y
9	SOF/VEL/VOX/RBV	Naive	White	12	3a	No testing done	Y	A	N

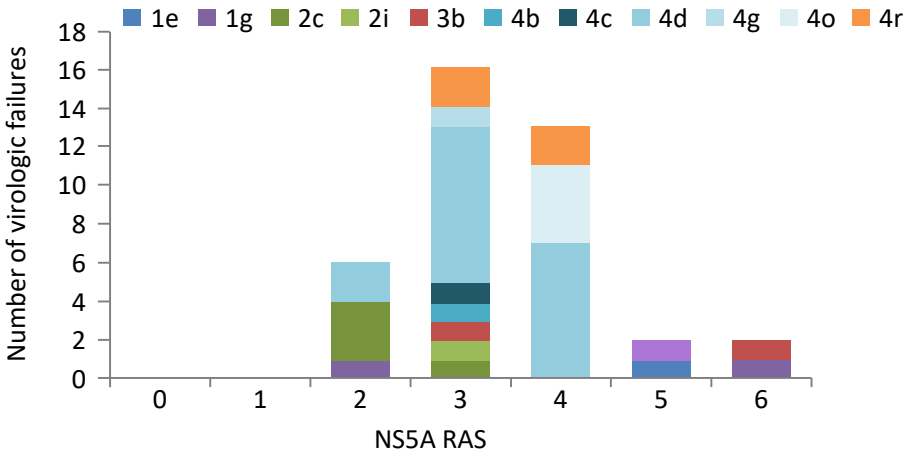
All but one of the patients who experienced a treatment failure with SOF/VEL/VOX/RBV regimen were treatment experienced. Only one patient is HIV-coinfected. None of the patients have history of liver transplant; [a]'Decomp' denotes history of decompensating events prior to treatment start

- Predominance of GT1 and GT3 was observed, only 6% of other GT infected patients
- SOF/VEL/VOX ± RBV is an effective rescue therapy for patients with prior DAA failure with 93% achieving SVR12
- Subgroups with numerically lower rates of SVR12 are those with history of decompensation and GT3
- Prior SOF/VEL treatment failure was not predictive of SOF/VEL/VOX treatment outcome
- Treatment was safe with no SAEs attributed to treatment
- Off label use in patients with history of current decompensation was evident in 13%

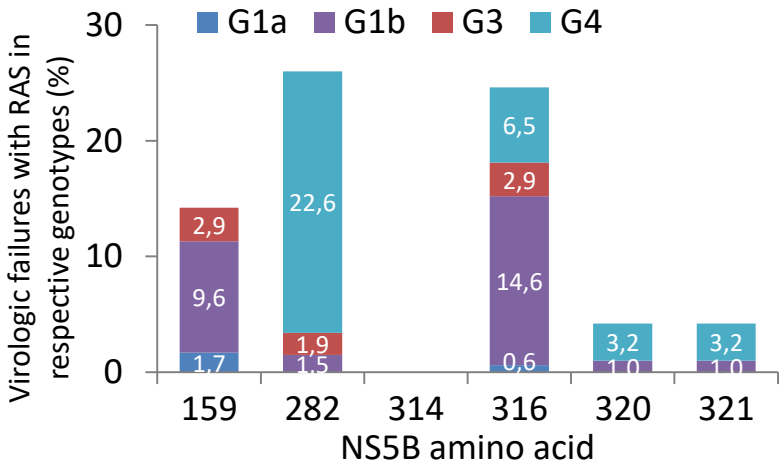
Zeuzem S, et al. AASLD 2019, Boston, USA. #1558

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 (confers 2- to 18-fold reduced drug susceptibility to SOF in HCV replicons)

Howe A, et al. AASLD 2018, San Francisco, USA. #204

Highly diverse HCV strains detected in sub-saharan Africa have unknown susceptibility to DAA treatments

- 7751 Ugandan patients screened for HCV
- 20 PCR-positive samples = NGS
- Genotypes 4k, 4p, 4q, 4s , and GT 7 prevalent
- NS3 and NS5A polymorphisms associated with resistance to DAAs
- Clinical trials are required where highly diverse GT4 and GT7 strains circulate

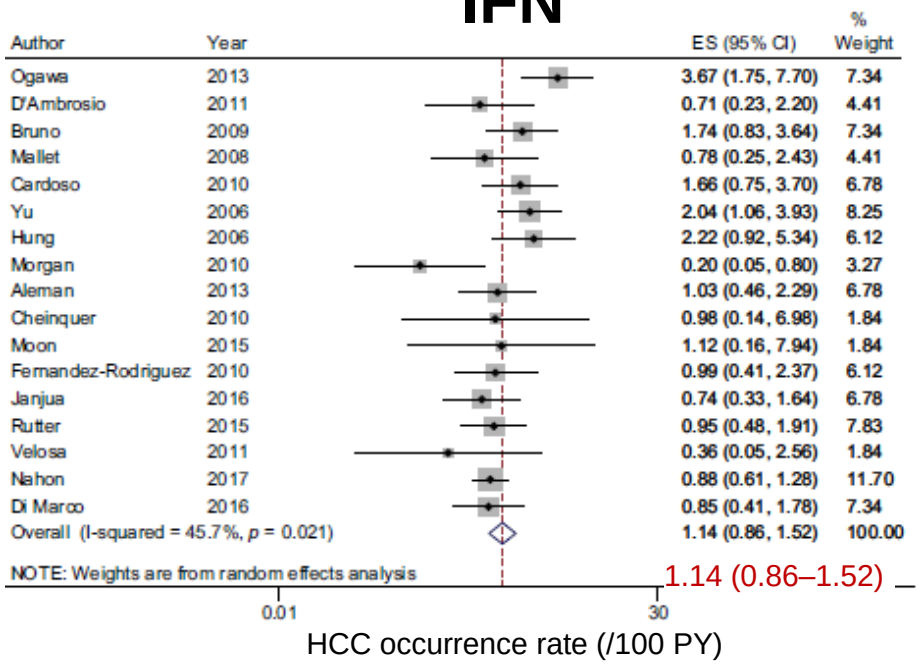
Davis et al., Hepatology 2019;69:1426-1441

Challenge No. 7

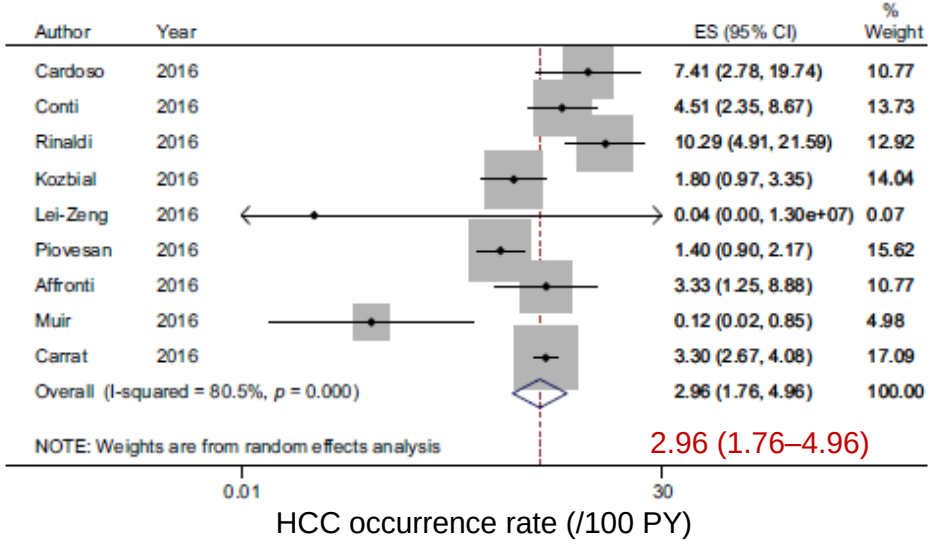
HCV TREATMENT IN PATIENTS WITH HCC, BCLC STAGE B / C

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

IFN



DAA



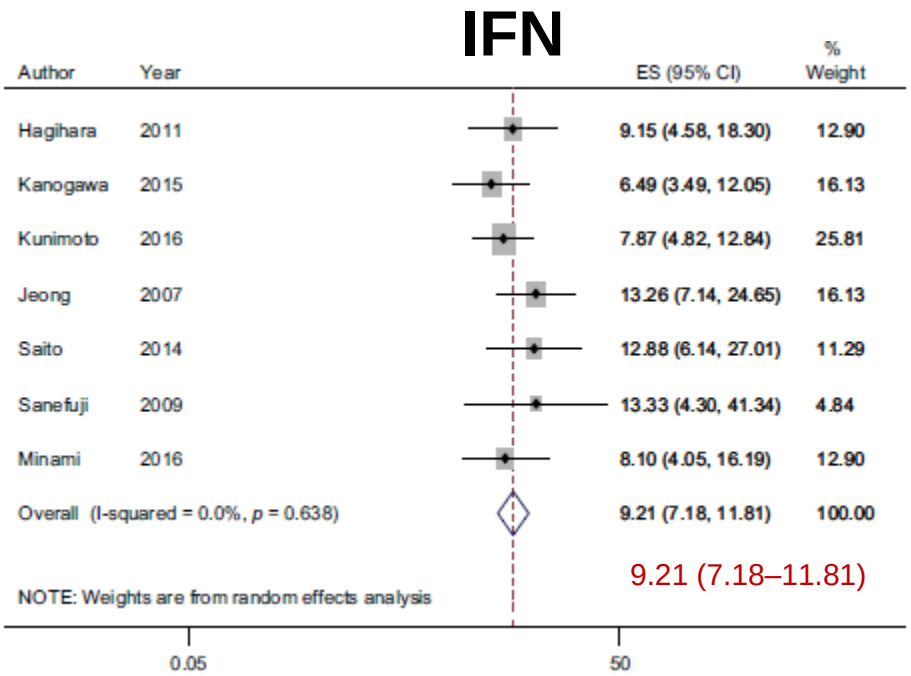
Meta regression of HCC occurrence

	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

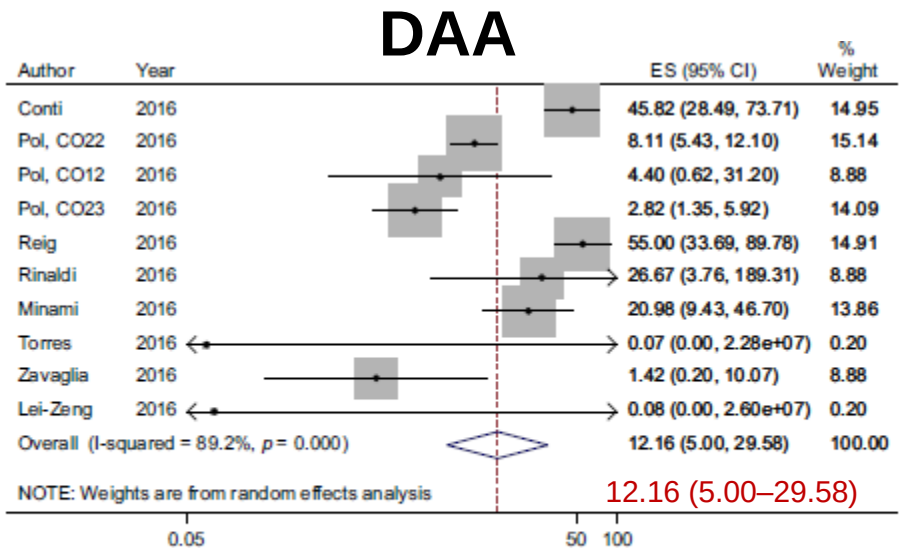
Waziry R, et al. J Hepatol 2017;67:1204–12

RR: risk ratio

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



HCC recurrence rate (/100 PY)



HCC recurrence rate (/100 person-years)

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

Challenge No. 8

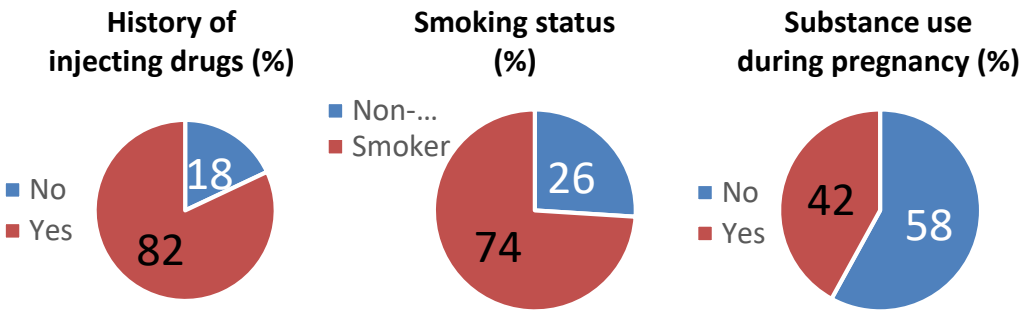
PREGNANT WOMEN

Hepatitis C infected pregnant women: Factors associated with linkage-to-care after delivery

- Kentucky policy mandates HCV testing in pregnant women
- A registry was developed to enable a nurse-led linkage-to-care navigation program for both mothers and infants
- HCV RNA detected in 89 (92%) of women; 78 (80%) women linked to care
- Women newly diagnosed with HCV infection (p=0.012) and/or not receiving prenatal care (p<0.001) were less likely to link to care
- No differences between linkage to care rates and substance abuse, current IDU, age, insurance status, marital status, educational attainment, or other factors

Demographics

n (%)	N=97
Race	
White	85 (88)
Black	12 (12)
Unmarried	85 (90)
Medicaid insured	78 (80)
Drug use	
Methamphetamine	25 (26)
Heroin	19 (20)



- Linkage to care could be facilitated by understanding the importance of the OBGYN
- HCV infection in pregnant women in Kentucky highly associated with a history of injection drug use and smoking
- New strategies needed to link women without prenatal care

Cave B, et al. AASLD 2019, Boston, USA. #606

A phase 1 study of LED/SOF in pregnant women with hepatitis C virus

- Pilot study on safety and efficacy in pregnancy
- Sofosbuvir 200 mg / Ledipasvir 90 mg x 12 wks
- HIV-negative women, GT 1, gestation week 23-24
- N=8, median age 32 (range 25-38) years
- All women achieved SVR, AEs $\leq$ grade 2
- All participants delivered at term
- One year follow-up of infants ongoing

Chappell et al., CROI 2019; A87

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
- Key challenges to reduce the burden of disease in geographic regions and populations:
  - Diagnosis rates
  - Linkage to care
  - Access to DAAs