
2021
NCSCG
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HCV in Special Populations

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Disclosure

- I have nothing to disclose

Objectives

- Review the most recent guidance for the management of some special HCV populations, highlighting the Simplified HCV Treatment Algorithm and pangenotypic Direct Acting Antiviral (DAA) regimens
- Review guidance from societies in the management of kidney or liver transplant candidates and how that intersects with the timing of HCV treatment
- Explore considerations for the treatment of complex HCV patients with decompensated cirrhosis and known HCC

Pan-genotypic DAAs have led to simplified HCV treatment

- High efficacy and safety has simplified treatment for a duration of 8-12 weeks, with SVR ≥ 95%, even in compensated cirrhosis
- Simplified HCV Treatment Algorithm is targeted to primary care providers, emphasizing the use of simple non-invasive tools for fibrosis staging (FIB-4, APRI), and minimizing barriers to treatment
- Guidelines emphasize "Test and Treat" strategy in acute HCV to decrease incidence and prevalence of HCV

www.hcvguidelines.org accessed 26Dec2020

Simplified HCV Treatment Algorithm-Who?

ELIGIBLE

- Adults without cirrhosis, treatment naïve, with any GT
- Adults with compensated cirrhosis, treatment naïve, with any GT*

  ** for GT 3, NS5a RAS testing needed to determine if Y93H is present if using SOF/VEL*

NOT ELIGIBLE

- Prior HCV treatment (any)
- Current or prior decompensated cirrhosis
- HIV or HBsAg positive
- Pregnancy
- Known or suspected HCC
- Prior liver transplantation

www.hcvguidelines.org accessed 26Dec2020

Current FDA Approved DAAs

"previr" "buvir" "asvir"

PROTEASE INHIBITOR	NS5B INHIBITOR	NS5A INHIBITOR	Trade Names	genotype
	Sofosbuvir (SOF)	Ledipasvir (LDV)	Harvoni	1,4-6
Grazoprevir (GRZ)		Elbasvir (ELB)	Zepatier	1, 4
	Sofosbuvir (SOF)	Velpatasvir (VEL)	Epclusa	1-6
Glecaprevir (GLE)		Pibrentasvir (PIB)	Mavyret	1-6
Voxilaprevir (VOX)	Sofosbuvir (SOF)	Velpatasvir (VEL)	Vosevi	1-6

Simplified Treatment algorithm regimens

"previr" **"buvir"** **"asvir"**

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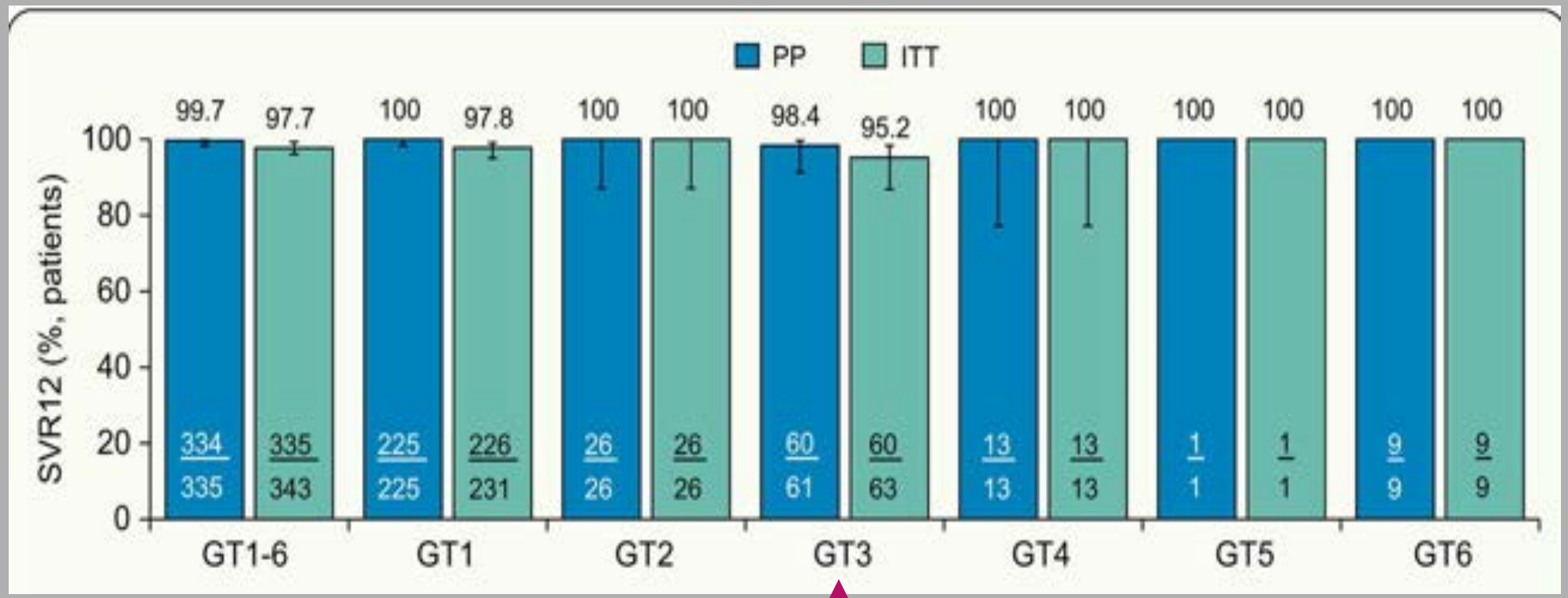
	Sofosbuvir (SOF)	**Velpatasvir (VEL)**	**Epclusa**	**1-6**	→ ***12 wks***
Glecaprevir (GLE)		**Pibrentasvir (PIB)**	**Mavyret**	**1-6**	→ ***8 wks***
Voxilaprevir (VOX)	Sofosbuvir (SOF)	Velpatasvir (VEL)	Vosevi	1-6	

GLE/PIB x 8 weeks is sufficient for all genotypes in treatment naïve cirrhosis

Adults with chronic HCV GT 1-6, treatment naïve, cirrhosis CPA



Brown et al. J Hepatol 2020, 72

Acute HCV management
AASLD/IDSA "Test and Treat" strategy

Recommendations for Medical Management and Monitoring of Acute HCV Infection	
RECOMMENDED	RATING ⓘ
After the initial diagnosis of acute HCV with viremia (defined as quantifiable RNA), HCV treatment should be initiated without awaiting spontaneous resolution.	I, B
Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults, including hepatotoxic drugs (eg, acetaminophen) and alcohol consumption, and to reduce the risk of HCV transmission to others.	I, C
Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.	I, B

What about TREATMENT?

- Treat like chronic HCV
- Emerging data on shortened course of DAAs in acute HCV is not sufficient

www.hcvguidelines.org accessed 26Dec2020

HCV and renal disease

- Prevalence of HCV in CKD and in persons receiving dialysis is high (3-20%), and routine screening of long-term HD patients recommended
- KDIGO guidelines recommend that all CKD patients infected with HCV be evaluated for antiviral therapy
- HCV infection is associated with higher risk of progression of ESRD, and successful HCV treatment improves clinical outcomes in patients with renal disease

Patel et al. Am J Kidney Dis 2019; 56 371-378
KDIGO 2018 Clinical practice Guidelines 8(3) 2018

HCV and renal disease

Case 1: 60 y.o. man with CKD 4 and genotype 3, treatment naïve, referred by Nephrology.

Etiology of CKD is MPGN. He is HIV negative, and HBsAg negative/anti-HBs positive. FIB 4 is 1.5, APRI 1.0, estimating absence of cirrhosis. His nephrologist has referred the patient to GI for treatment to potentially improve his kidney function with CrCl of 20 ml/min.

What are his treatment options?

HCV with CKD 4, GT 3, TN, Non-cirrhotic

"previr" **"buvir"** **"asvir"**

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Voxilaprevir (VOX)	Sofosbuvir (SOF)	Velpatasvir (VEL)	Vosevi	1-6	

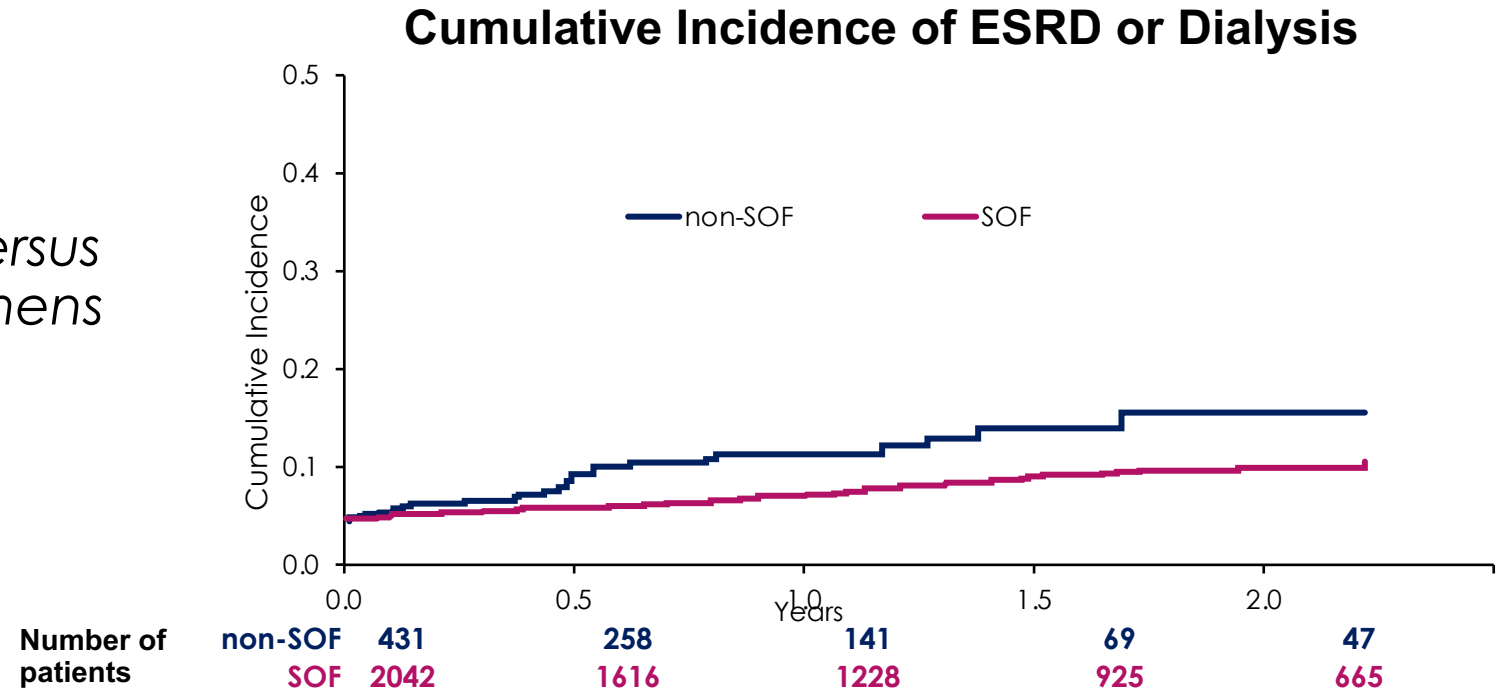
**** SOF/VEL label now indicates no dose adjustment needed for moderate-severe renal impairment.***

www.hcvguidelines.org accessed 26 Dec 2020

Risk of ESRD not different among HCV Patients with CKD Treated with or w/o SOF

Non-concurrent prospective observational cohort of 2473 patients with mild-severe CKD, treated with SOF-containing versus non-SOF-containing DAA regimens

- *70% male*
- *Median age 55-64*



Risk of ESRD or Dialysis with SOF-containing regimens: 0.85 aHR propensity score weighting

Telep L, et al. EASL 2020. FRI441

HCV and renal disease
What if patient were on dialysis?

Case 2: 60 y.o. gentleman ***on HD x 5 yrs, listed for kidney transplant without living donor.***

- genotype 3, treatment naïve
- FIB 4 is 1.5, APRI 1.0, estimating absence of cirrhosis

Prior to treating, consider:
- Use of HCV+ donor may substantially reduce patient's waiting time and treatment can be deferred until after kidney transplant

KDIGO 2018 Clinical Practice Guidelines 8(3) 2018

Management of patients with HCV cirrhosis

Case 3: 57 y.o. woman with HCV GT 1a, TN, radiologic evidence of cirrhosis

- PMHx + for HTN and GERD
- Hx of alcohol use disorder, abstinent x 1yr, 20 p.y. history of tobacco use, quit 1 year ago.

- ROS: forgetfulness, sleep reversal, + LE edema, no hx of ascites or GI bleed

- Meds: metoprolol, amlodipine, lasix/spirolonactone, omeprazole, lactulose

- U/S with nodular liver, splenomegaly and no focal lesion or ascites.

Considerations in cirrhosis

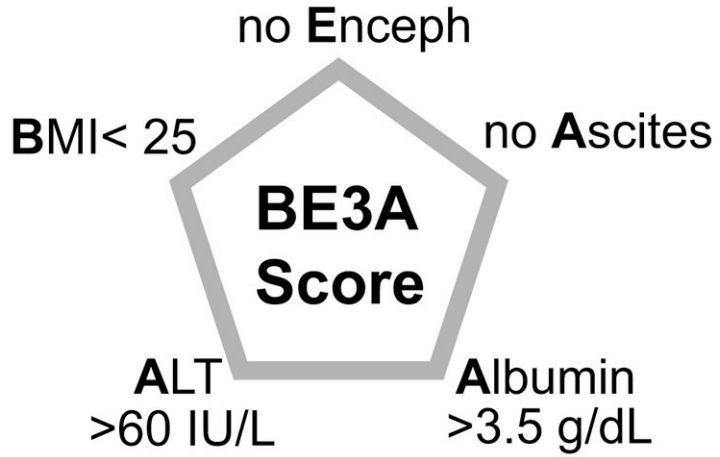
- Calculate Childs Pugh score to guide treatment decisions
- Calculate MELD-Na score if considering referral for liver transplant evaluation

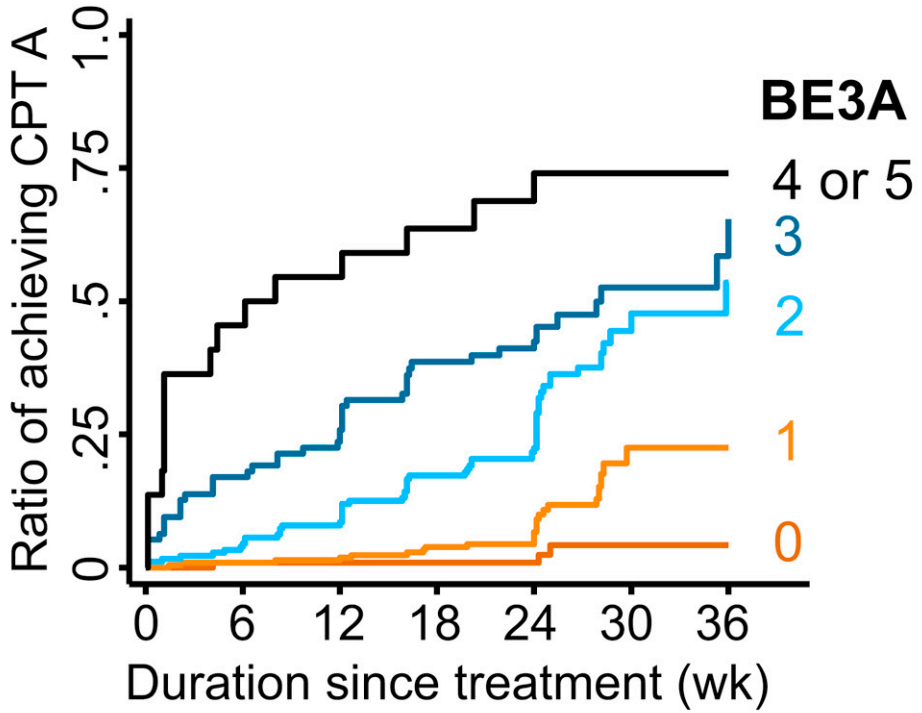
Given low MELD of 7, you proceed with HCV treatment

Lab	Result
HCV RNA	622,196
T Bili	0.7
Creat	0.7
INR	1.1
Albumin	3.2
Na	137
Hgb	10.9
Platelets	100
CPT Score	B (7)
MELD-Na	7

Clinical calculator to predict improvement from CTB/C to CTP A

Assign 1 point to each of the following





Gastroenterology

El-Sherif et al. Gastroenterology 2018.

Decompensated cirrhosis, TN, GT 1a

"previr" "buvir" "asvir"

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AASLD/IDSA Guidelines
Decompensated cirrhosis: add RBV if eligible

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose)	12 weeks	I, A[b]
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	12 weeks	I, A[d]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[c] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
[d] Only available data for genotype 6 are in patients with compensated cirrhosis.

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Ineligible

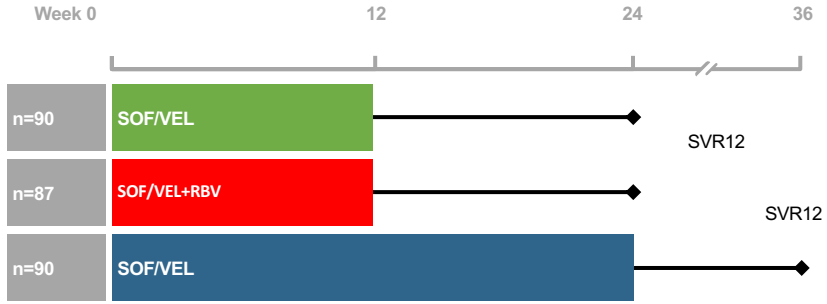
RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[c]

www.hcvguidelines.org
Accessed 26Dec2020

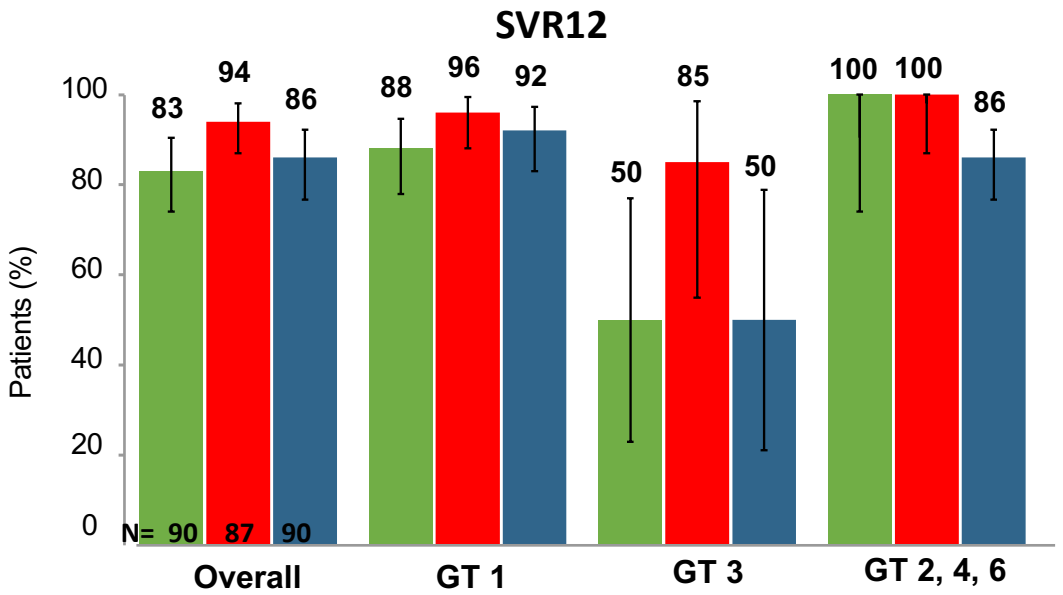
SOF-VEL ± RBV for G1-6 Patients with Child-Pugh B Cirrhosis: The Role of RBV

- **ASTRAL-4**
- **HCV GT 1-6 patients with CPT B cirrhosis**

Study Design



Conclusion:
Adding ribavirin increases SVR in patients with decompensated cirrhosis, especially in GT3



	GT1			GT3			GT2,4, 6		
Relapse	5	1	3	6	1	4			
VBT					1	1			
Death/LTFU	3	2	3	1		1			1

Charlton M, *N Engl J Med. 2015;373:2618-28*

Common Ribavirin Side Effects

- Hemolytic anemia- consider getting stress test in patients with CVD risk factors (HTN, DM, smoking, age)

  - Patients with renal impairment may experience more hemolysis, as RBV is renally cleared.

- Mood changes- screen for depression, irritability, anxiety

- Insomnia (not advised to take RBV after 5pm)

- Less frequent: GI distress (always take with food), rash, itching

- **Serious teratogen**

Ribavirin package insert. Drugs.com revised 11/2016
Te et al., Gastroenterol Hepatol (NY) 2007 Mar 3(3)

HCV and Decompensated Cirrhosis
*What if **ascites** is present with **higher** MELD?*

57 y.o. woman wih HCV GT 1a, treatment naïve. No current alcohol and no history of tobacco. PMHx + for HTN and GERD. Hx of alcohol use disorder and abstinent for a year, + 20 p.y. history of tobacco use, quit a year ago.

ROS: forgetfulness, sleep reversal, ***ascites***/LE edema, no hx of GI bleed

Meds: metoprolol, amlodipine, lasix/spirolonactone, omeprazole, lactulose

U/S with nodular liver, splenomegaly no focal lesion and ***ascites***

Labs: Na 131, TBil 3.5, creat 1.2, alb 2.9, INR 1.3

Child Pugh C (10), MELD-Na 19

Considering her MELD > 15 with significant portal hypertensive complications, you refer to a liver transplant center for evaluation.

HCV Treatment in liver transplant candidates should be individualized

Key question: will patient achieve clinical benefit from HCV cure?

Treatment goals for decompensated patients with HCV:

1. Stabilize liver disease, improve QOL
2. Prevent need for liver transplant or promote delisting
3. Prevent waitlist drop off/death due to worsening decompensation

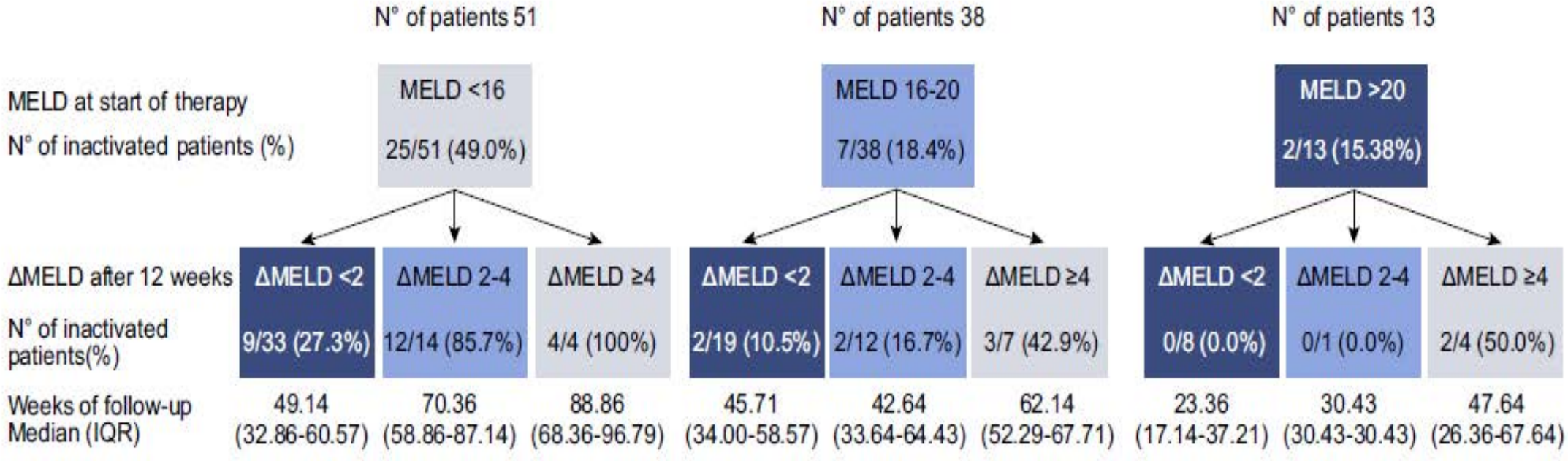
Treat selectively and individualized, considering:

- Anticipated time to transplantation
- Access to living donor LT

Terrault et al. *Transplantation* 107; 101: 945-955;
Belli et al *J Hepatol 2017; 101: 945-955*
EASL guidelines J Hepatol 2018 69: 461-511

Which patients may be able to avoid liver transplant after HCV cure?

Patients with a baseline MELD <16 have a 50% chance of delisting
Patients with a baseline MELD >20 with only 15% chance of delisting



Belli, et al. J Hepatology 2016; 65:524-531.

HCV and Hepatocellular Carcinoma

Case 4: 65 y.o. man with a new HCC

HCV GT 3, compensated cirrhosis with MELD-Na of 10. Prior to initiating treatment, you recommend abdominal imaging to rule out HCC. Abdominal ultrasound shows a hyperechoic lesion, and a quad-phase CT w/contrast characterizes it as a 2.7cm LR-5 lesion c/w HCC.

Do you proceed with HCV treatment now?

HCV and Hepatocellular Carcinoma

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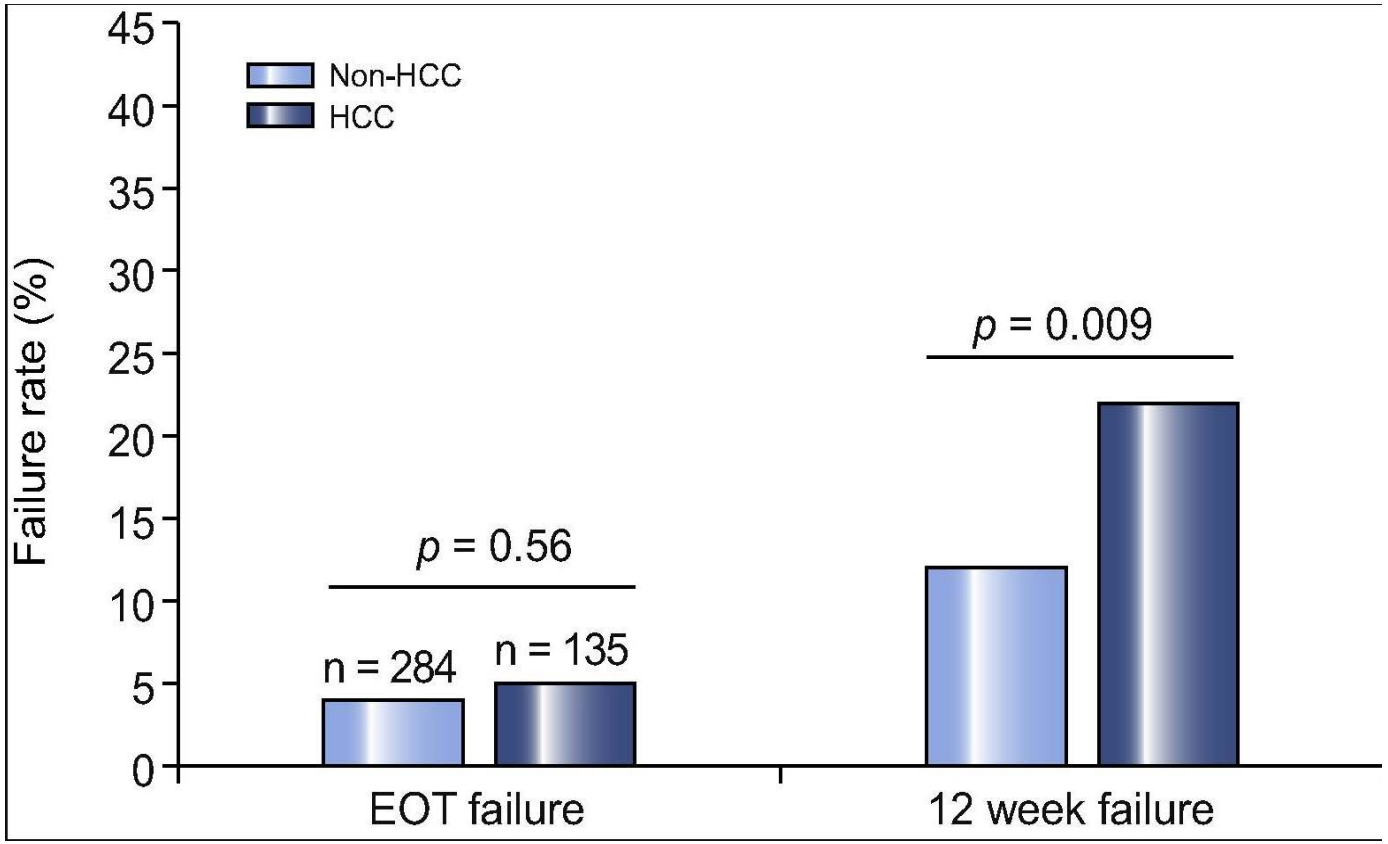
Do you proceed with HCV treatment now?

1. *Is there a higher risk of HCC recurrence with DAAs in the presence of HCC?*
   - *Debatable…*
2. *Does the presence of HCC affect the efficacy of DAAs?*
   - *Likely….*

Active HCC at time of HCV treatment initiation predicts 20% reduction in SVR

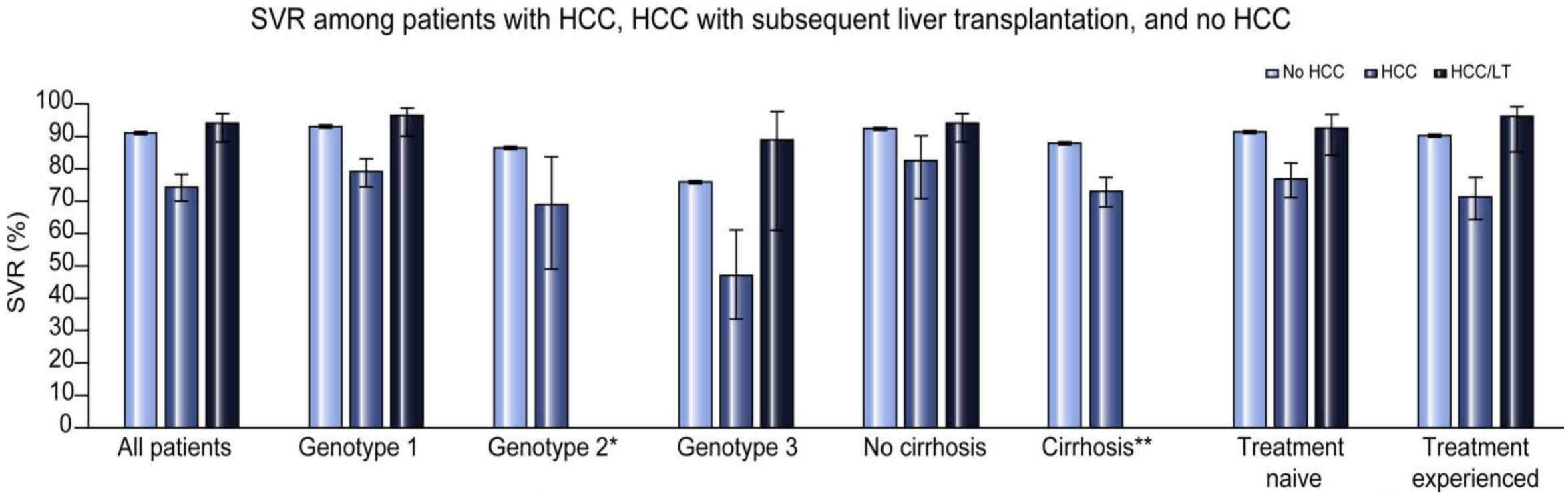


N = 421, single center study

Primary predictor of DAA failure: *Active HCC (AOR 8.49)*

Prenner et al J Hepatol 6 2017

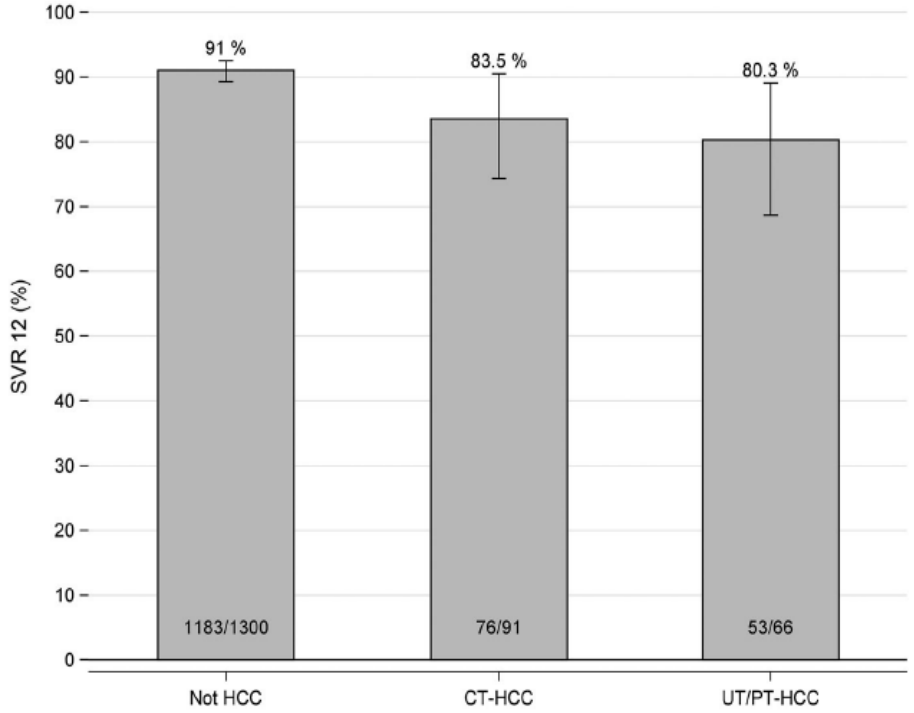
HCV can be cured in majority of patients with prior HCC and post liver transplant.



Patients currently listed for liver transplant and likely to receive offer soon may benefit from postponing treatment until after transplant

Beste et al., J Hepatol 2017 67

Presence of HCC reduces likelihood of SVR regardless of treatment status of HCC prior to DAAs



N= 1457, multi-center HCV-TARGET study
CT= completely treated HCC at the time of DAA therapy
PT/UT= partially/untreated HCC at time of DAA therapy

Multivariate analysis:
Lower odds of SVR:
Presence of HCC* vs no HCC (OR 0.51)
** Whether HCC was "active" or treated HCC did not influence SVR*

No need to delay DAA therapy for patients with active HCC who would benefit from HCV eradication prior to HCC treatment

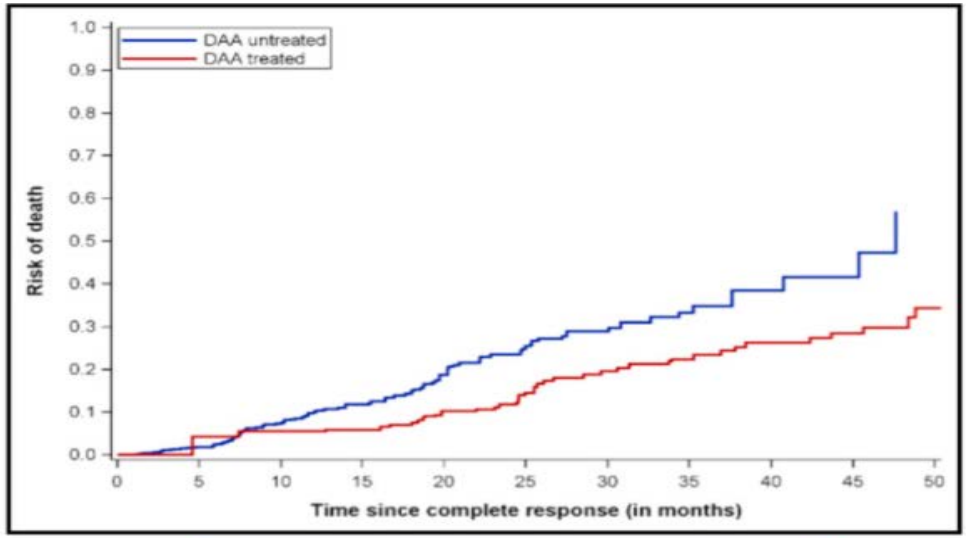
Radhakrishnan et al. *Hepatology communications* 2019; 3:1

DAAs associated with improved survival in patients with history of HCC

Results:

DAA Treated:
4.6 deaths per 100 person-years follow-up

DAA Untreated:
19.6 deaths per 100 person-years follow-up



Multivariable analysis
- Adjusted for site, age, sex Child Pugh score, AFP, tumor burden and HCC treatment modality

→ **DAA therapy associated with lower mortality: HR: 0.54; 95%CI: 0.33 – 0.90**

797 patients with *complete response* to HCC treatment prior to DAA therapy, 50% lower risk of death

Singal et al, Gastro 2019 157 (5)

HCC presents complex decision making on the timing of HCV treatment.

Case 4: 65 y.o man with HCV GT 3, compensated cirrhosis with MELD-Na of 10 and 2.7cm HCC lesion

Do you proceed with HCV treatment now?

- ***Discuss possible referral to transplant center (HCV + organ transplant?)***
- ***Prioritize HCC first, then address HCV***
  - If compensated: Defer DAA treatment until response to curative HCC treatment is known
  - If decompensated: Consider treating HCV to stabilize liver disease with goal to have more curative options for HCC and improve survival.

Key points

- High efficacy and safety of DAAs have led to simplified treatment with overall SVR of > 95% in most patient populations
- HCV patients with mild to severe renal dysfunction do not require dose adjustments in DAAs but consider HCV+ kidney option for transplant candidates
- Patients with CP B/C cirrhosis have more limited treatment options and ribavirin optimizes SVR
- DAA treatment in decompensated cirrhosis should be individualized, and poses challenges in considering option for LT versus stabilization of liver disease
- If HCC is known or suspected – prioritize HCC first, then treat HCV