Treatment of Hepatitis C in Special Populations

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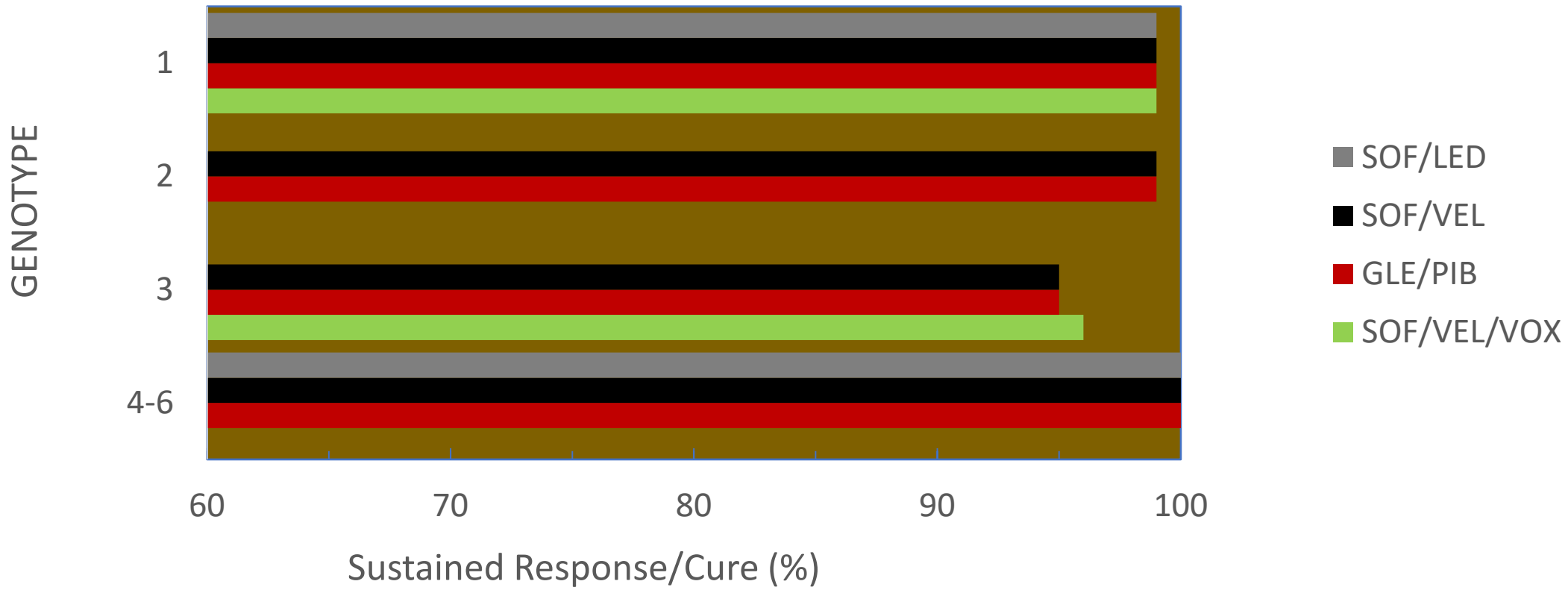
Hepatitis C: Commonly used DAA Medications

DRUG NAME	INHIBITOR TYPE	SHORT NAME	GENOTYPES	WEEKS OF TREATMENT
Ledipasvir Sofosbuvir	NS5A Polymerase	SOF/LED	1,4,5,6	8 or 12
Glecaprevir Pibrentasvir	Protease NS5A	GLE/PIB	All	8
Sofosbuvir Velpatasvir	Polymerase NS5A	SOF/VEL	All	12
Elbasvir Grazeprevir	NS5A Protease	ELB/GRZ	1,4	12
Sofosbuvir Velpatasvir Voxilaprevir	Polymerase NS5A Protease	SOF/VEL/VOX	All	12

HEPATITIS C: CURE RATES



- https://www.hcvguidelines.org/treatment-naive

HCV Special Populations

Late 2010'x

- HIV
- Renal failure
- HCC
- HBV co-infection
- Decompensated Cirrhosis
- Liver transplant

2020 to present

- Renal failure
- Decompensated disease
- HCC
- HBV co-infection
- Acute hepatitis C
- Transplantation
- Pediatrics

HCV – Renal disease

High prevalence of HCV in hemodialysis patients

- USA 4 %
- Middle East 20%

No dose adjustment when using recommended regimens

- Elbazvir/grazeprevir
  - cyclosporine
- Glecaprevir/Pibrentsavir
  - cyclosporine
- SOF/LED
- SOF/VEL
- SOF/VEL/VOX
  - cyclosporine

HEPATITIS C UPDATE: CKD AND ESRD

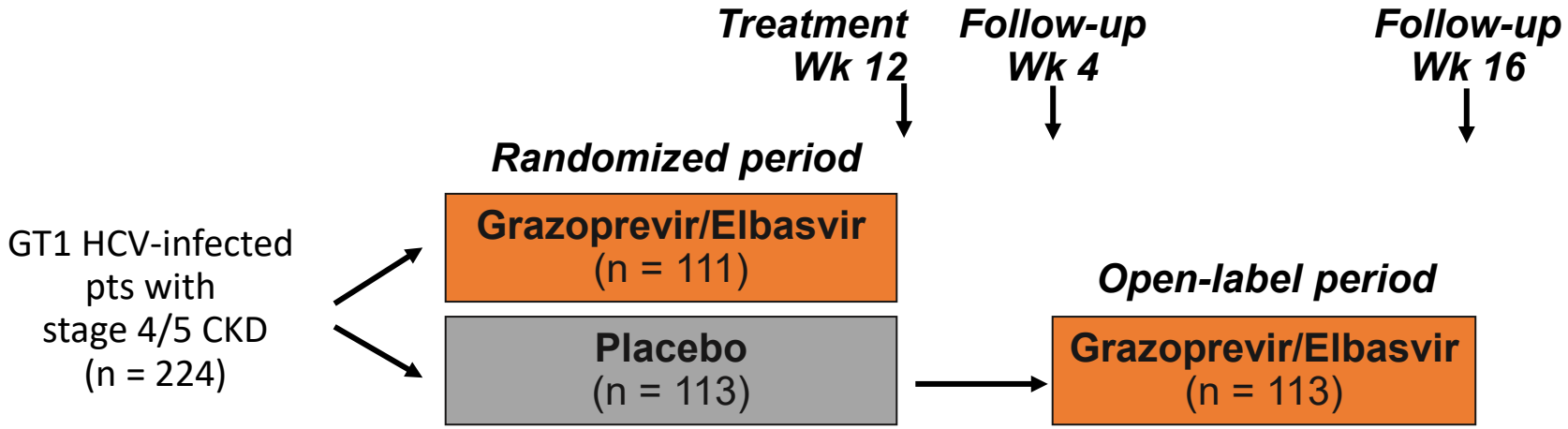
- GLE/PIB is not metabolized by kidney
- No dosing adjustments needed
- Same SVR rates as patients with normal renal function

- SOF metabolites excreted by kidney
- SOF regimens recently evaluated in patients with GFR < 30 cc/min
- Treatment well tolerated
- No metabolite toxicity
- Same SVR rates as patients with normal renal function
- Approved by FDA for use in patients with ESRD on dialysis

A Desnoyer et al. J Hepatol. 2016;65:40-47.

C-SURFER: Grazoprevir/Elbasvir in Pts With GT1 HCV and Stage 4 or 5 CKD

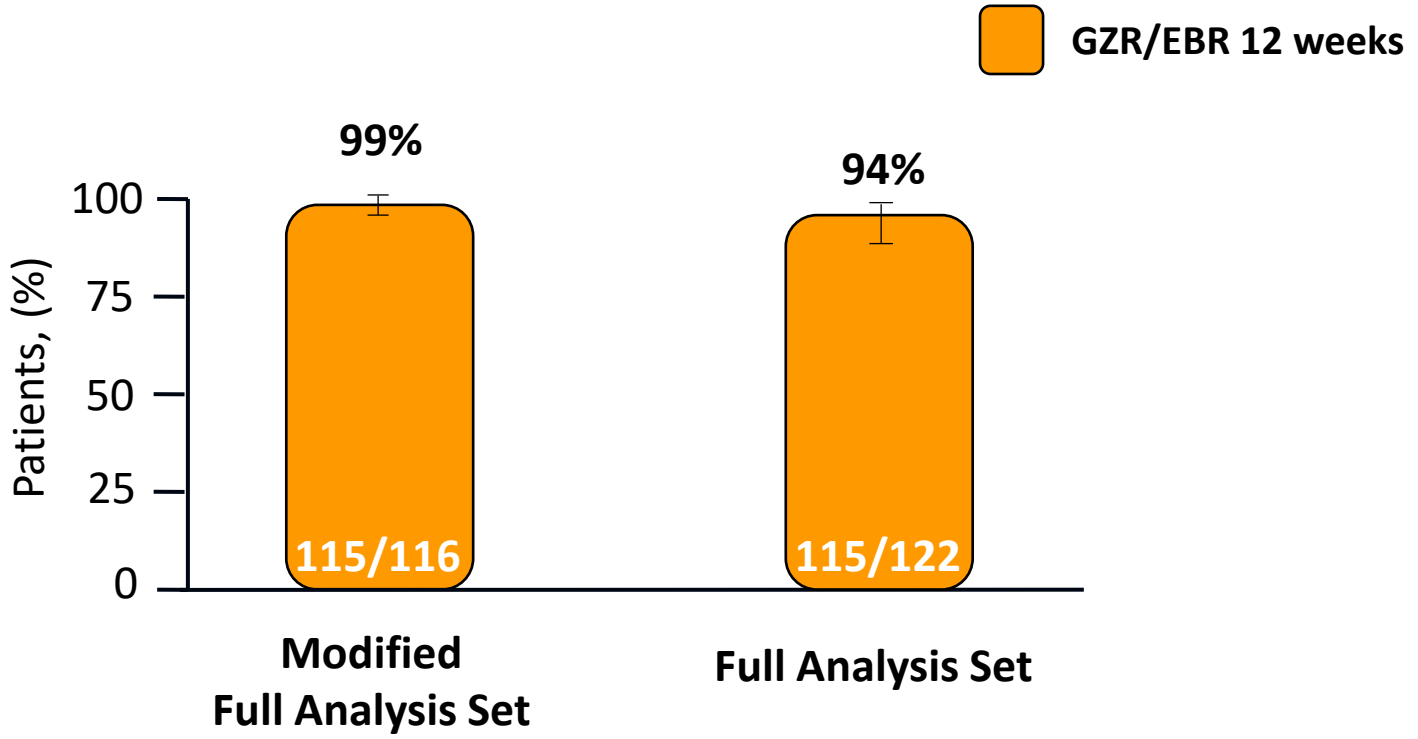
- Multicenter, part-randomized, parallel-group, placebo-controlled phase III trial



Grazoprevir/elbasvir dosed orally 100 mg/50 mg once daily.

Roth D, et al. EASL 2015. Abstract LP02.

SVR12: IMMEDIATE TREATMENT GROUP (ITG)



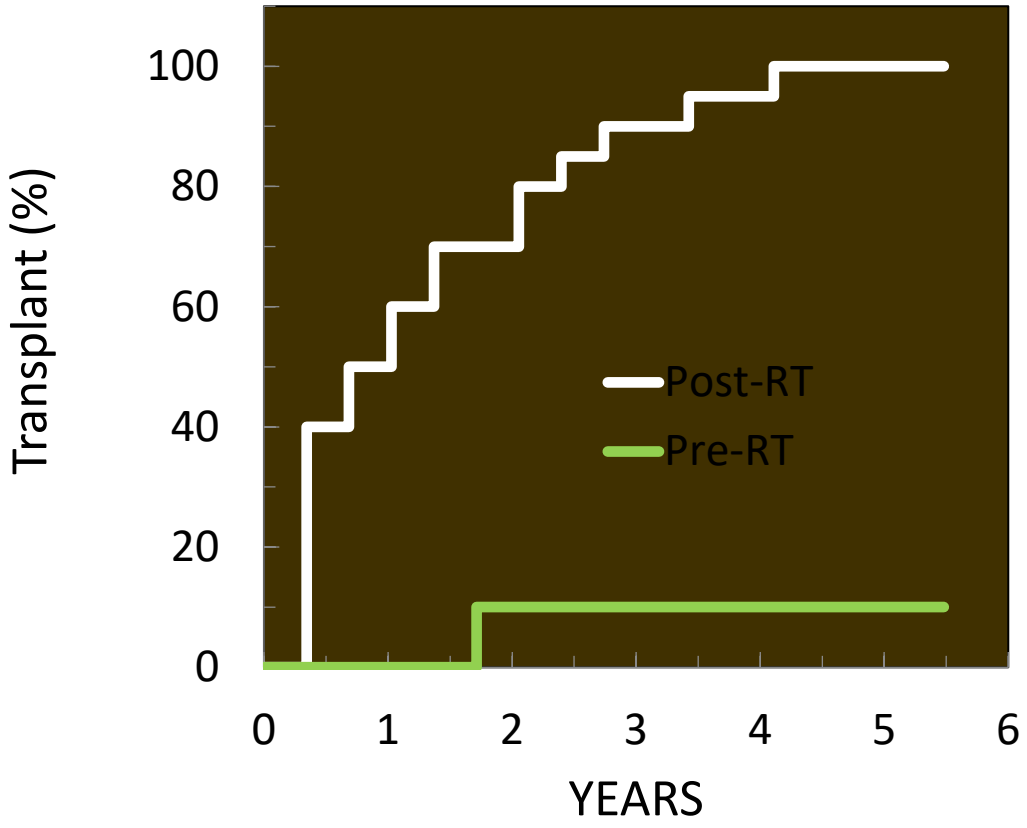
Relapse	1*	1
Discontinued unrelated to Tx	0	6†

MFAS = primary efficacy analysis; FAS was a secondary analysis
*Noncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at FW12
†lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)

Roth et al. 2015

CHRONIC HCV IN ESRD
WAITING TIME FOR KIDNEY TRANSPLANT

	HCV treatment	
	Pre-RT	Post-RT
N	21	33
No difference age, gender, race, %HCV GT1, % cirrhosis		
Renal Transplant	1	33
HCV (+) Kidney	0	21
Died prior to RT	1	0
Wait time to RT (d)	650	167
Time to DAA tx (d)		77



DM Chascsa et al
Am J Transplant 2018;18:2559-2565.

Recommendations post –kidney transplant

- https://www.hcvguidelines.org/accessed July 29, 2021

Post Kidney Transplantation: Genotype 1-6

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and Non-DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, C
ALTERNATIVE	**DURATION**	**RATING**
Genotype 1 or 4 only: Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg) for patients without baseline NS5A RASs[e] for elbasvir	12 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.

[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

[c] Based on evidence for patients without cirrhosis.

[d] Based on evidence for patients with compensated cirrhosis.

[e] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

DAA experienced Kidney transplant patients

Recommended regimen for:

DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg), with or without ribavirin[b]	12 weeks	IIa, C

[a] Excludes CTP class B and class C patients. For decompensated cirrhosis, please refer to the appropriate section.

[b] For patients with cirrhosis and multiple negative baseline characteristic, consideration should be given to adding ribavirin. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d for patients who weigh <75 kg and 1200 mg/d for those who weigh ≥75 kg.

- https://www.hcvguidelines.org/accessed July 29, 2021

Patients with renal impairment, including haemodialysis

Recommendations	Grade of evidence	Grade of recommendation
Mild to moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2)		
• Treat according to the general recommendations • No dose adjustments are needed • Patients should be carefully monitored	A	1
Severe renal impairment (eGFR <30 mL/min/1.73 m^2 or ESRD*)		
• Treat in expert centers with close monitoring by a MDT	B	1
• GLE/PIB for 8 or 12 weeks (all GT)	A	1
• GZR/EBR for 12 weeks (GT 1a, 1b and 4)†	A	1
• OBV/PTV/r + DSV for 12 weeks (GT 1b)	A	1
• Use SOF with caution, only if an alternative treatment is not available	B	1
• Risk/benefit of treating patients with ESRD and an indication for kidney transplant before or after renal transplantation require individual assessment	B	1

*ESRD on haemodialysis (CKD stage 4/5) without an indication for liver transplant; †With HCV RNA level ≤800,000 IU/mL (GT 1a/4)

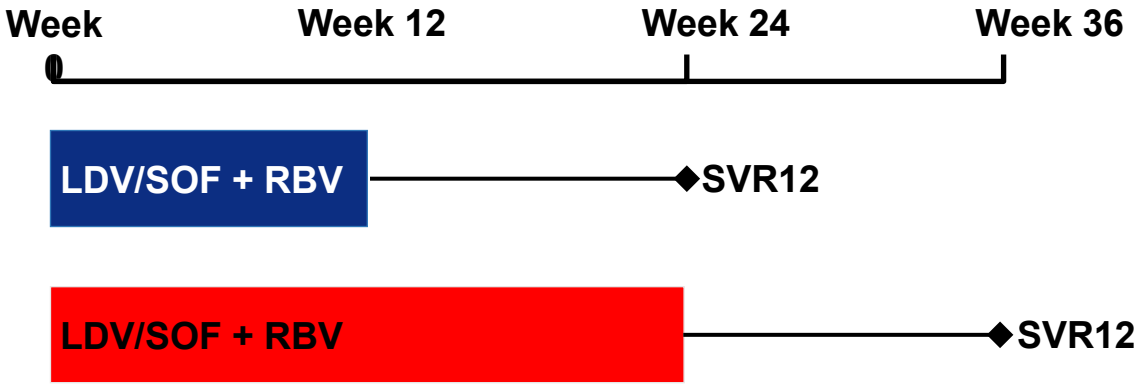
EASL CPG HCV. J Hepatol 2018;69:461–511.

HCV and decompensated disease

- Cannot use protease containing regimens
- Advanced cirrhosis with MELD $\geq$ 10, SVR ~ 90%
- Treatment indicated for non-transplant candidates
- Treatment may be delayed or withheld in transplant candidates listed in high median MELD areas

Verna et al, J Hep 2020

LDV/SOF + RBV: Genotype 1 and 4 with Decompensated Cirrhosis

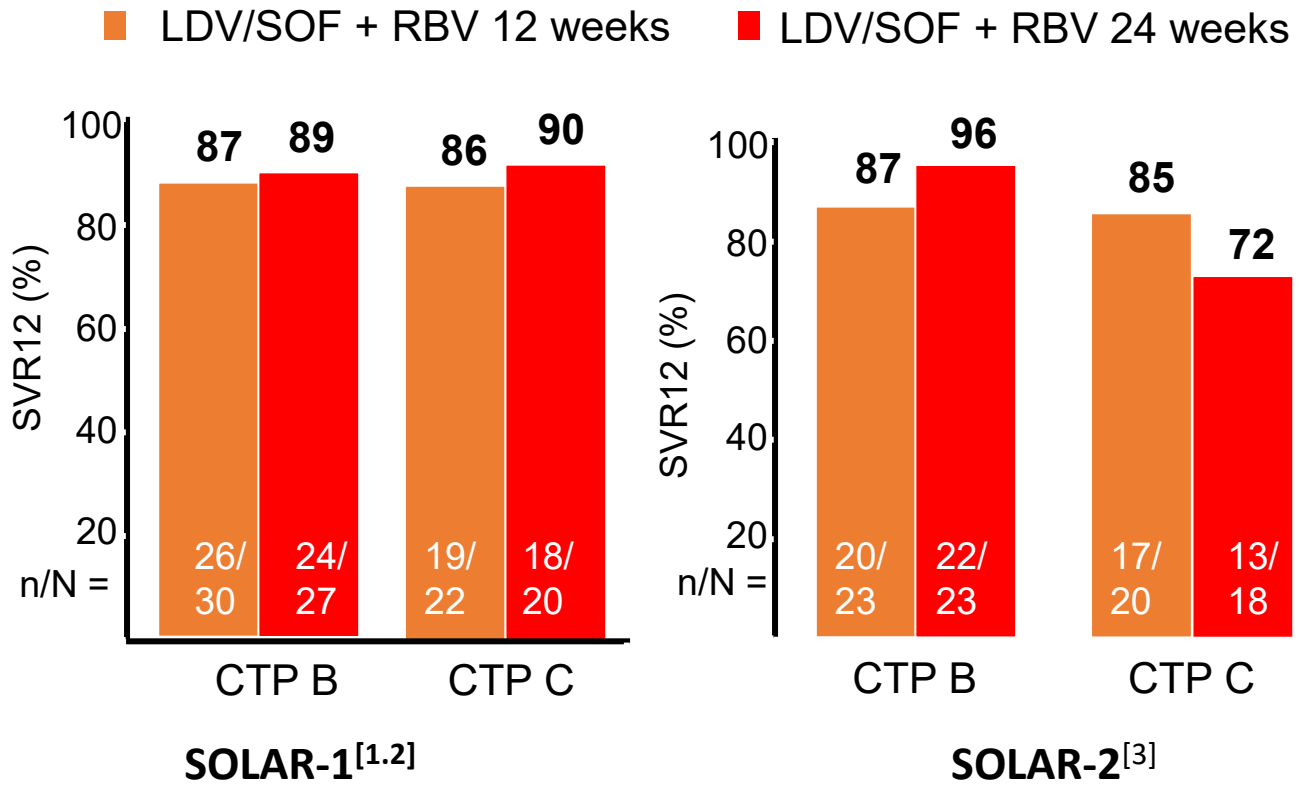


SOLAR-1
Treatment naïve or experienced
CPT Class B
CPT Class C
Post liver transplantation

SOLAR-2: (greater G4 population)
Treatment naïve or experienced
CPT Class B
CPT Class C
Post liver transplantation

Charlton M, et al. *Gastroenterology*, 2015
Reddy RT, et al. Presented at: AASLD; November 7-11, 2014; Boston, MA. Abstract 8.
Manns M, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract G02.

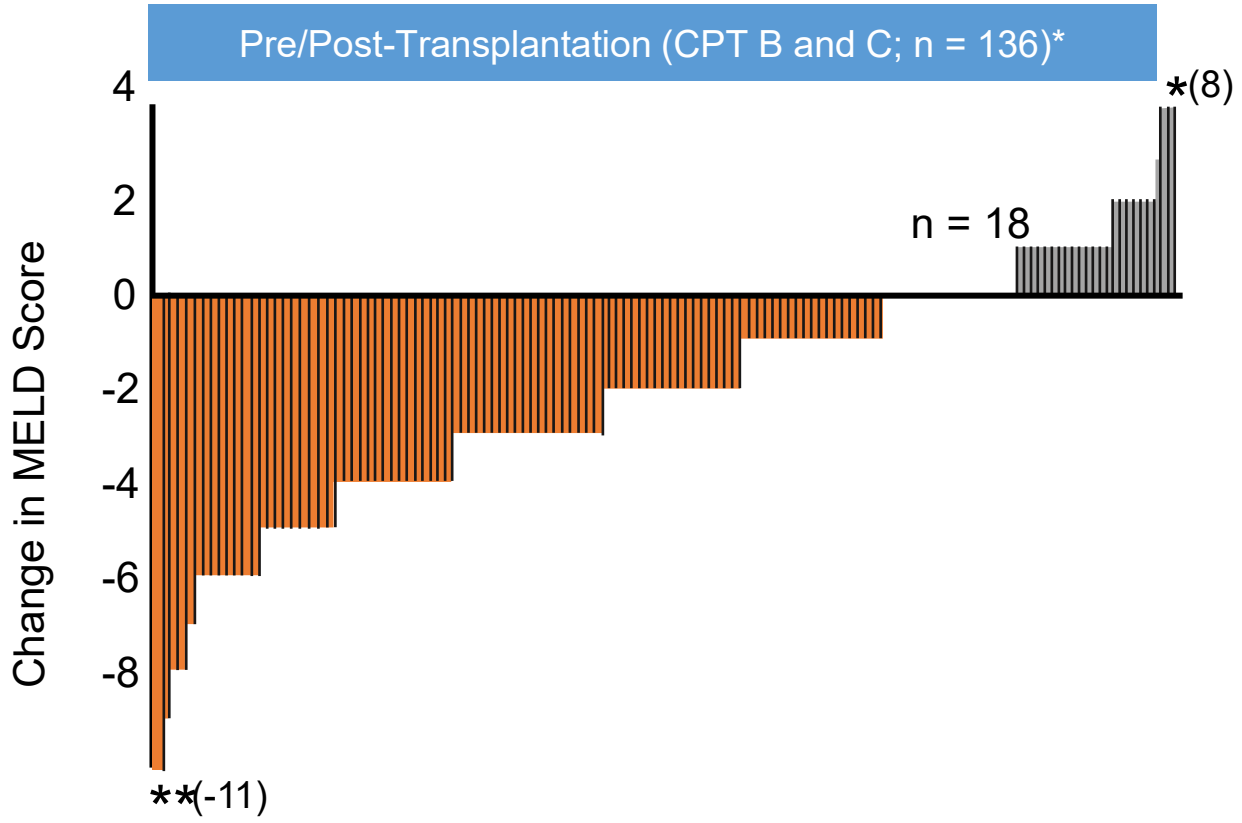
LDV/SOF + RBV: SVR12 in Genotype 1 or 4 with Decompensated Cirrhosis



AE, adverse event; CTP, Child-Turcotte-Pugh; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir.

1. Charlton M, et al. *Gastroenterology*, 2015
2. Flamm SL, et al. Presented at: AASLD; November 7-11, 2014; Boston, MA. Abstract 239.
3. Manns M, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract G02.

Solar 2: LDV/SOF + RBV: Change in MELD Score from Baseline to Follow-up Week 4 in CPT B or C Disease



*Missing FU-4: n = 24.

Manns M, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract G02.

Controversy: To treat or not treat patients waiting for liver transplantation

FOR

- Eradicate HCV
- Improve MELD score
- Prevent further decompensation

AGAINST

- Improve MELD score
  - MELD purgatory
- Unclear effect of development of HCC

Patients with severe liver disease (1)

- Due to efficacy, ease of use, safety and tolerability, IFN-free regimens are the only options in patients with decompensated (Child–Pugh B or C) cirrhosis without HCC awaiting liver transplantation (A1)

Recommendations	Grade of evidence	Grade of recommendation
Indications for treatment		
• MELD score <18–20: treat prior to liver transplantation	A	1
• MELD score ≥18–20:		
– Transplant first without antiviral treatment and treat HCV infection after transplantation	B	1
– Treat before transplant if waiting time exceeds 6 months (depending on the local situation)	B	2
Treatment (MELD score <18–20)		
• SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all genotypes) + RBV* for 12 weeks	A	1
• PI-containing regimens are contraindicated	A	1
• Contraindications/poor tolerance to RBV: SOF/LDV (GT 1, 4, 5, 6) or SOF/VEL (all genotypes) for 24 weeks	A	1

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance

EASL CPG HCV. J Hepatol 2018;69:461–511.

Patients with severe liver disease (2)

Recommendations	Grade of evidence	Grade of recommendation
Post-liver transplant recurrence		
• All patients with post-transplant recurrence should be considered for therapy	A	1
• Treatment should be initiated early after transplantation (≥3 months)	A	1
• Treatments include:		
– SOF/VEL for 12 weeks (all genotypes)	A	1
– SOF/LDV for 12 weeks (GT 1, 4, 5, 6)	A	1
– GLE/PIB for 12 weeks (eGFR ≤30 mL/min/1.73 m^2; all genotypes)*	B	1
– SOF/LDV or SOF/LDV + RBV for 24 weeks (decompensated cirrhosis)†	B	1
HCC with an indication for liver transplant		
• Liver transplantation must be considered the main therapeutic goal	A	1
• Make treatment decisions on a case by case basis through MDT discussion	A	1
• HCV treatment can be initiated before or delayed until after transplantation, depending on circumstances	A	1/2
HCC without an indication for liver transplant		
• HCV treatment should not be withheld but HCC surveillance should be carried out post-SVR	A	1
• Use the same DAA regimens as for patients with decompensated cirrhosis without HCC awaiting liver transplantation		

*Monitor immunosuppressant drug levels and dose adjust;
†Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance
EASL CPG HCV. J Hepatol 2018;69:461–511.

HCV and HCC

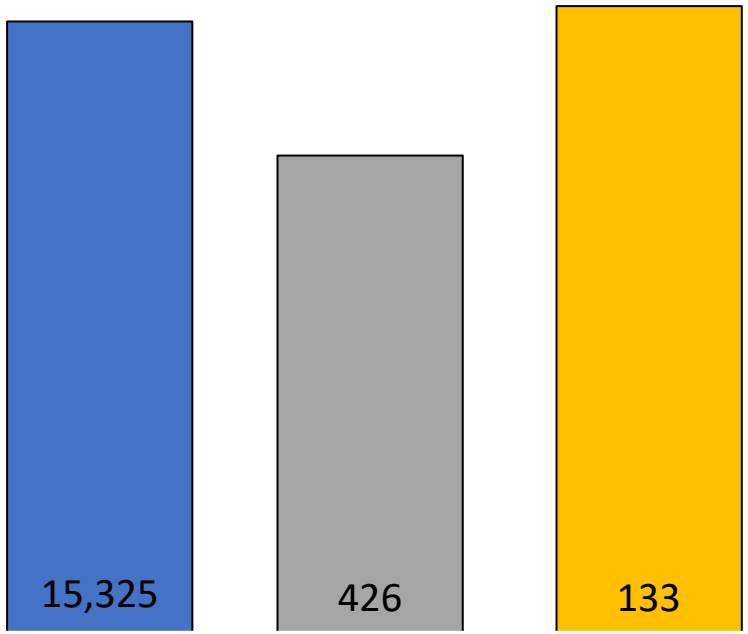
Controversy:

- Should patients with HCV and HCC be treated?

Real world data show decreased SVR rates in patients with HCC

Beste et al. J Hep 2017; Prenner et al. J Hep 2017

Should We Treat HCV in Patients With Active HCC?

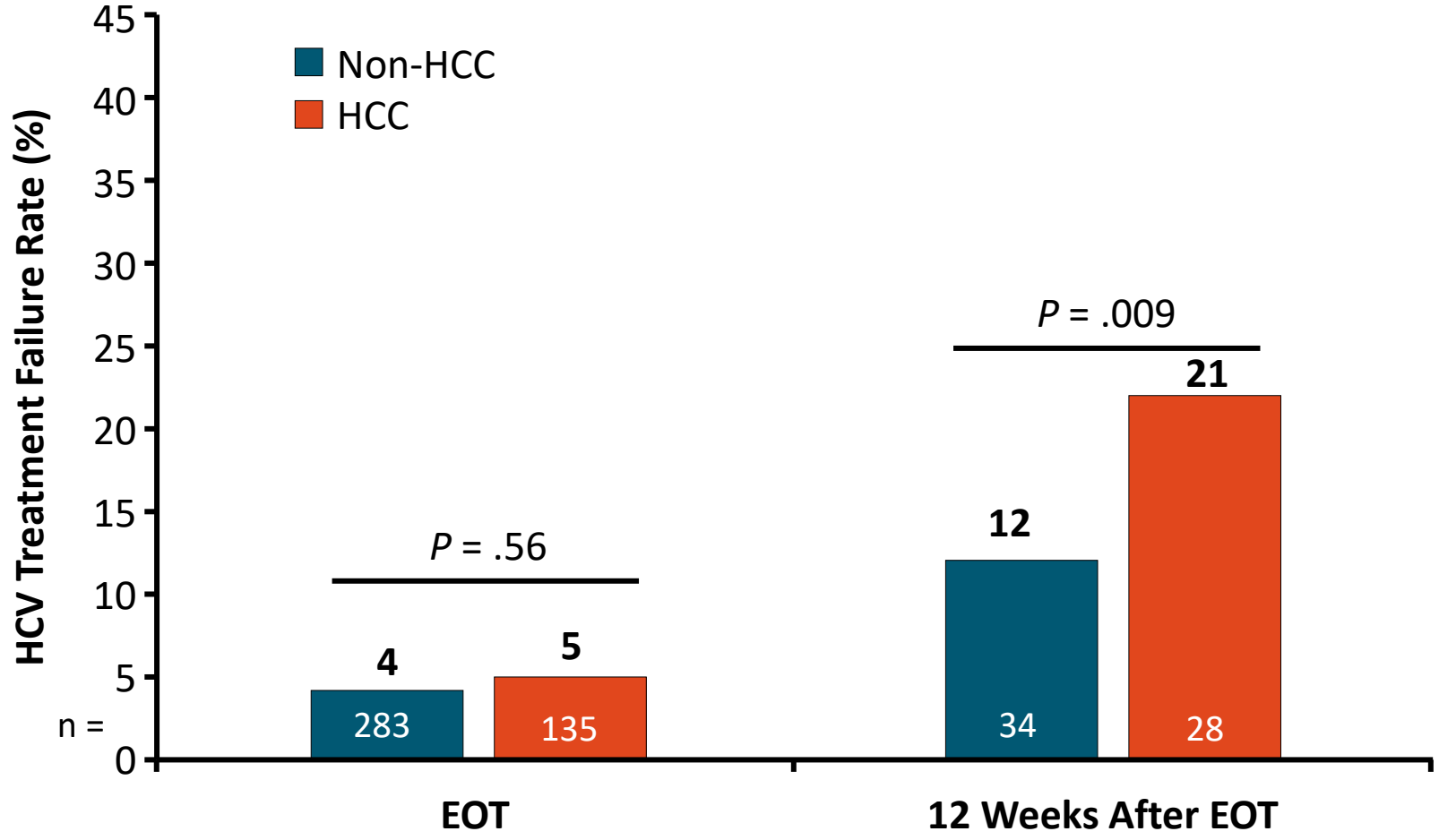


- Similar effect seen in other smaller studies
- HCC may affect vasculature – DAA exposure in the liver
- ***Bottom line: treat HCC first (including OLTx), then treat HCV***

Beste. J Hepatol. 2017;67:32

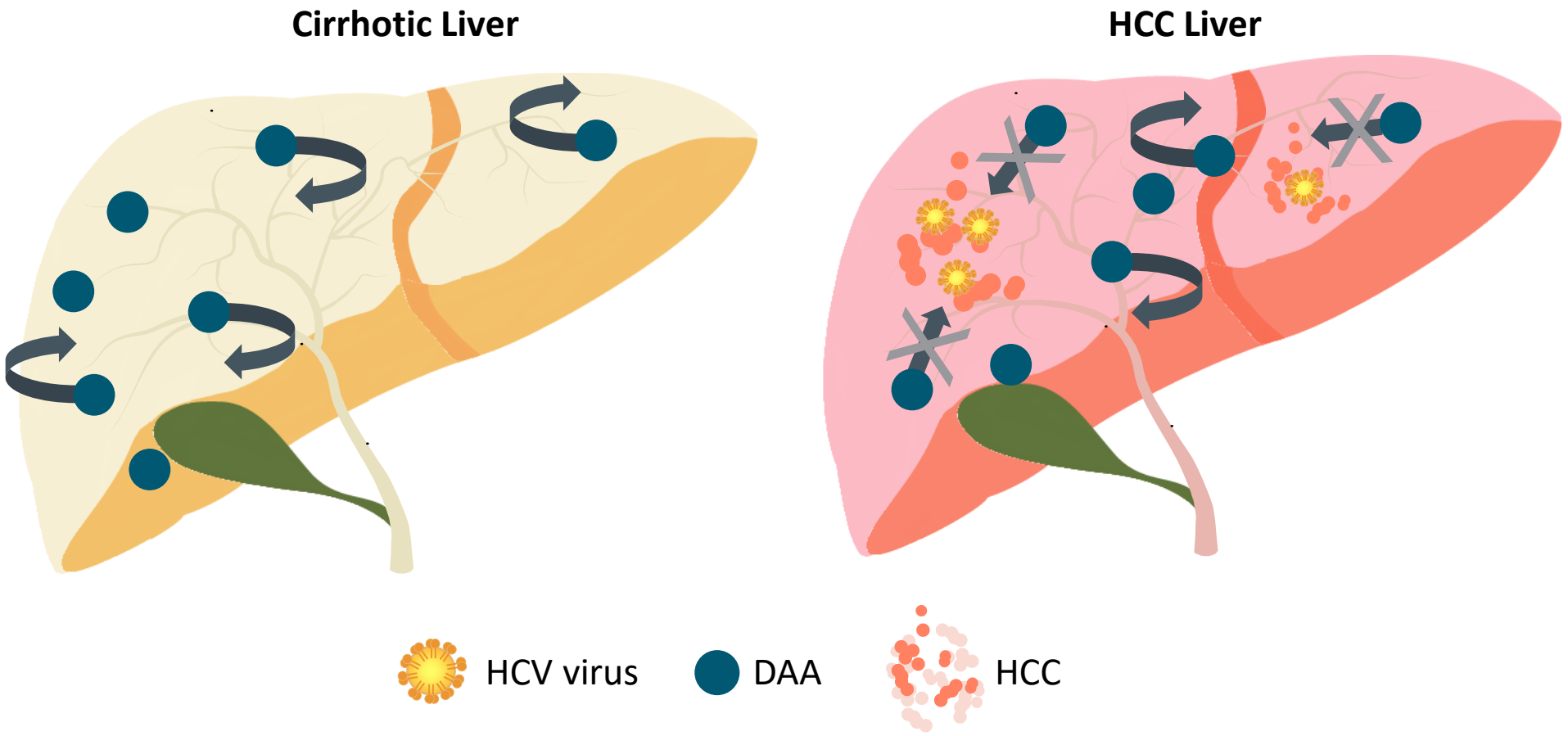
Confirmatory Study: Active HCC Associated With HCV Treatment Failure

- Retrospective study of people with cirrhosis and DAA-treated HCV (N = 421)



Prenner. J Hepatol. 2017;66:1173.

Why HCC May Affect SVR Rates



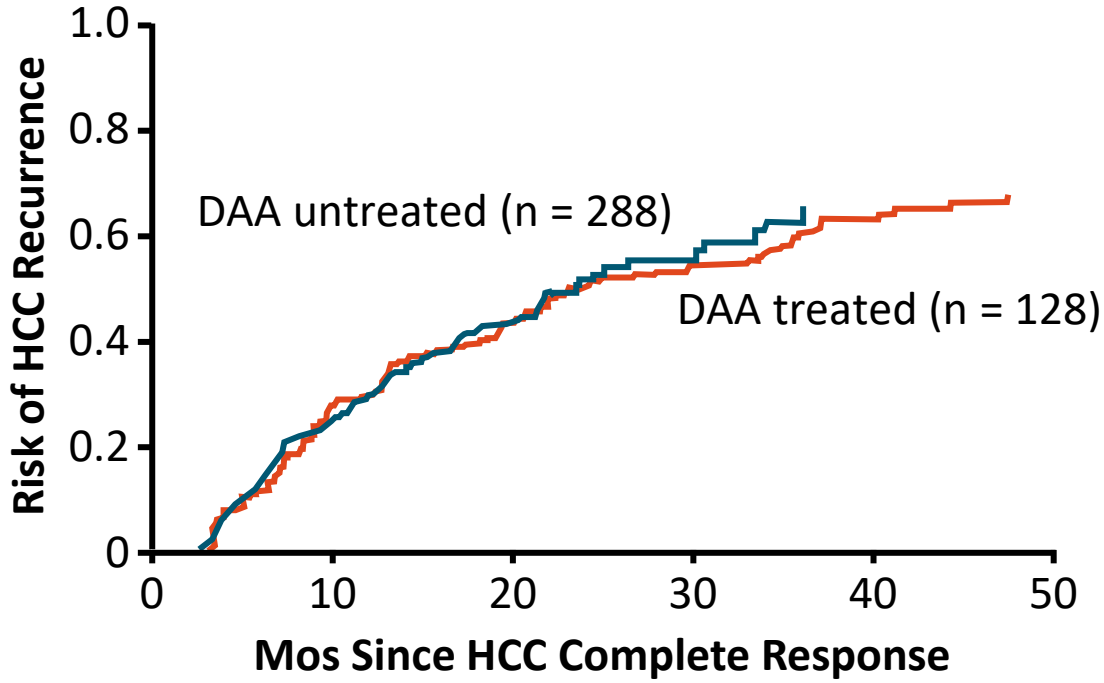
Prenner. J Hepatol. 2017;66:1173.

The Final Word? HCC Recurrence Rate After HCV DAA Therapy Among Patients With HCC Complete Response

- Retrospective multicenter cohort study in North American patients achieving cure for HCV-related HCC between January 2013 and December 2017 (N = 793)

HCC Recurrence	aHR (95% CI)	
	Overall Recurrence	Early Recurrence
Time-dependent exposure*	0.90 (0.70-1.16)	0.96 (0.70-1.34)
DAA start time after HCC CR		
▪ ≤ 6 mos	0.90 (0.67-1.21)	1.04 (0.74-1.47)
▪ > 6 mos	0.90 (0.64-1.27)	0.55 (0.22-1.38)

Median 10.4 mos of follow-up, adjusted for age, sex, site, CP, AFP, tumor burden, HCC therapy. Study excluded those with recurrent HCC within 30 days of cure.
*Stratified by receipt of DAA therapy.



No increased risk of HCC recurrence with DAA therapy after CR for HCV-related HCC

Singal. Gastroenterol. 2019;[Epub]. Singal. AASLD 2018. Abstr 92.

Conclusion

People Who Never Had HCC

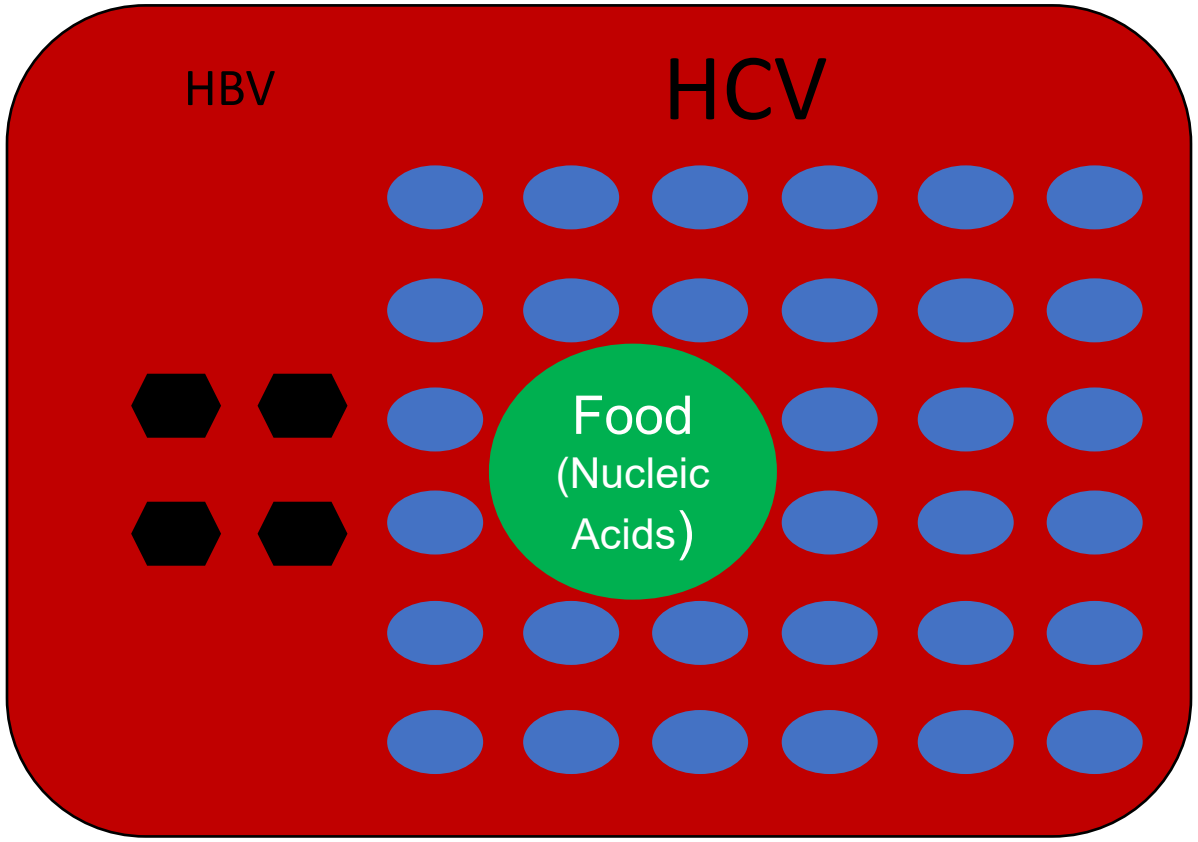
- **de novo HCC** is not caused by DAAs, but may occur more than with IFN because DAA patients are sicker, especially decompensated
- **Consider limiting surveillance** after SVR to those with cirrhosis

People Who Have Had HCC

- **HCC recurrence rate** may be higher with DAAs than with IFN
- **Treat HCC** (including OLTx) before treating HCV
  - Treat HCV *after* observation period of 3-6 mos to confirm no HCC recurrence[1]
  - Discuss with patients—image before treatment
  - Close surveillance

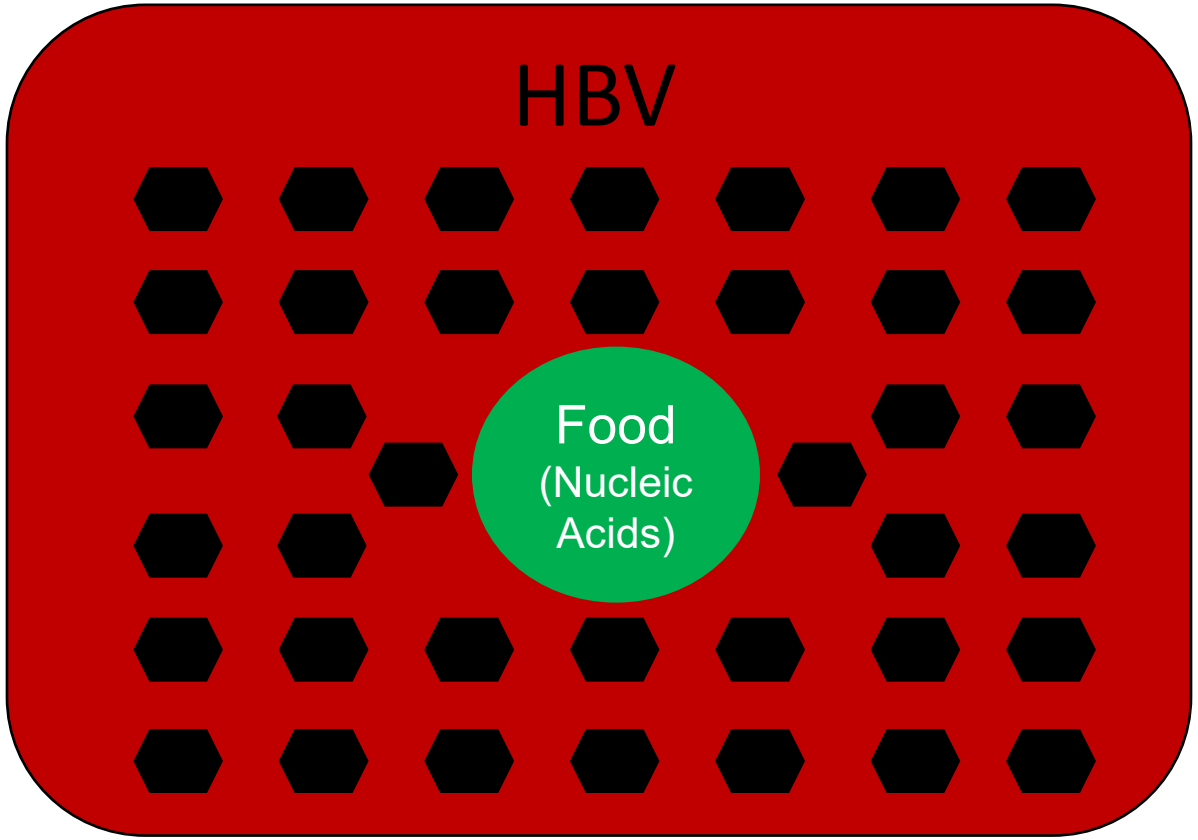
1. Marrero. Hepatol. 2018;68:723.

TREATMENT OF HCV WITH DAA
HBV REACTIVATION

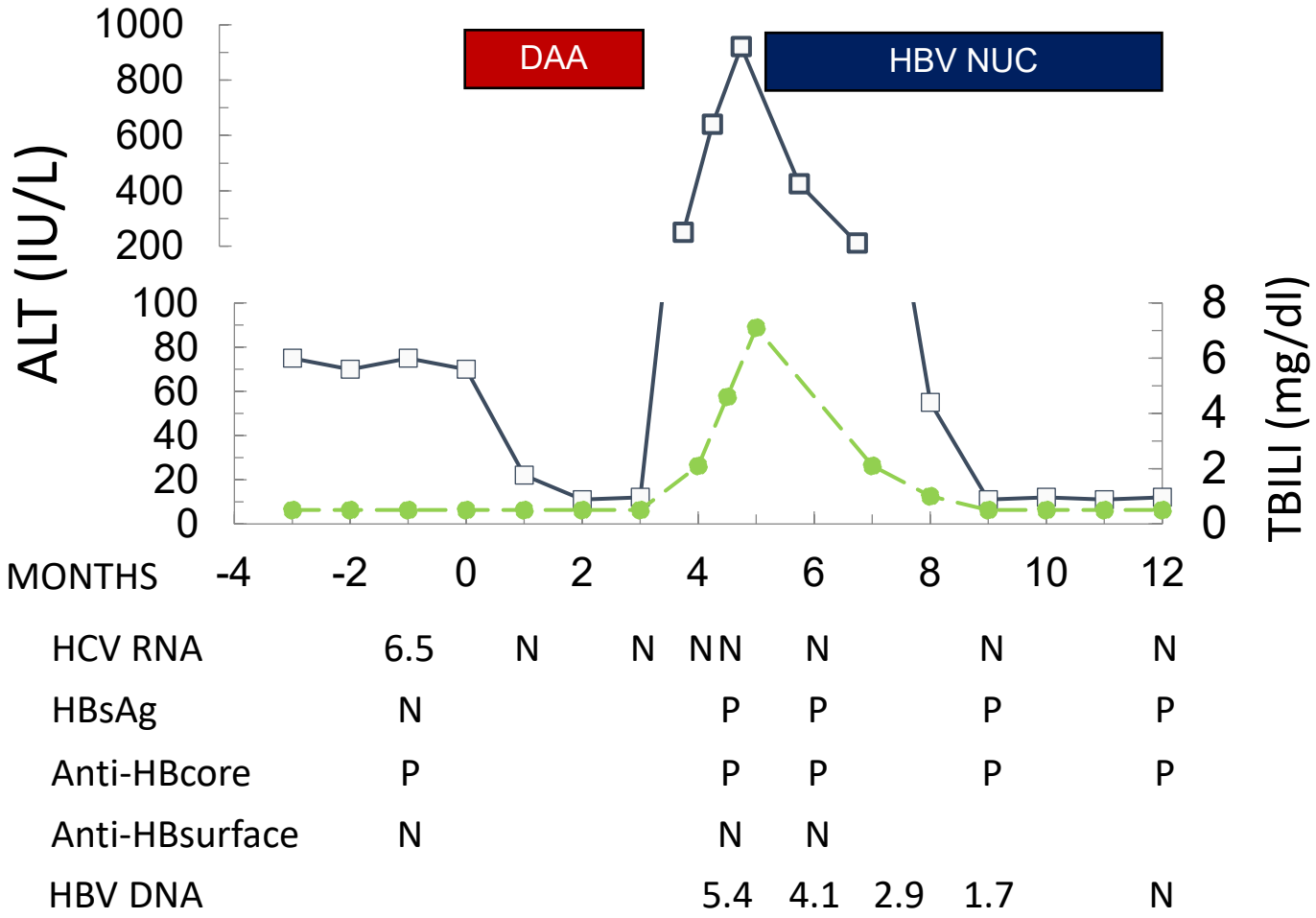


- HCV replicates faster than HBV
- HCV dominates HBV for food
- HCV grows
- HBV is relatively suppressed
- HCV is eradicated

TREATMENT OF HCV WITH DAA
HBV REACTIVATION



- HCV replicates faster than HBV
- HCV dominates HBV for food
- HCV grows
- HBV is relatively suppressed
- HCV is eradicated
- HBV has all the food
- HBV starts to replicate
- HBV DNA increases
- Liver enzymes flair



HBV REACTIVATION

- ML Shiffman, NT Gunn. Curr Hepatology Rep 2017;16:169-177.

Author	# patients	Description	Rate of HBV Reactivation
Yeh	57 7	HBsAg +, HBV DNA - HBsAg -, anti-HBcore +	14% 0%
Belperio	377 ?	HBsAg + HBsAg -, anti-HBcore +	2% <1%
Kawagishi	87	HBsAg -, anti-HBVcore +	1%
Wang	10 124	HBsAg +, HBV DNA + HBsAg -, anti-HBcore +	30% 2%
Londono	10 64	HBsAg +, HBV DNA + HBsAg -, anti-HBcore +	50% 2%

TREATMENT OF HCV WITH DAA HBV REACTIVATION

- ML Shiffman, NT Gunn Curr Hepatology Rep 2017;16:169-177.

TREATMENT OF HCV: HBV REACTIVATION

Reactivation of HBV occurs in patients with:

- HBsurface antigen - common
- Anti-HCV core - uncommon

Flare of HBV occurs during or after HCV treatment has been completed

Deaths from acute liver failure have been reported

Screen all patients for HBV

- Treat active HBsAg+ (HBV DNA >2,000 IU)
- Prophylaxis for inactive HBsAg+ (HBV DNA <2,000 IU) until 6 months after HCV treatment is complete
- Monitor closely if anti-HBcore positive

ML Shiffman, NT Gunn Curr Hepatology Rep 2017;16:169-177.

HBV-HCV coinfection

Recommendations		
Treat with the same anti-HCV regimens, following the same rules as HCV monoinfected patients	B	1
Patients fulfilling the standard criteria for HBV treatment should receive NA treatment according to EASL 2017 CPG on the management of HBV infection	A	1
Patients who are HBsAg+ should receive NA prophylaxis at least until Week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped	B	1
In patients who are HBsAg–, anti-HBc Ab+ on anti-HCV therapy • Monitor serum ALT levels monthly • Test HBsAg and HBV DNA if ALT levels do not normalise or rise • Initiate NA therapy if HBsAg and/or HBV DNA are present	B	1

EASL CPG HCV. J Hepatol 2018;69:461–511.

HCV after Liver Transplantation

Post Liver Transplantation: Genotype 1-6

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, C

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

AASLD Practice Guidance. Accessed July 30, 2021

HCV after Liver Transplantation

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft and Decompensated Cirrhosis[a]

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)[b]	12 to 24 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ ribavirin starting at 600 mg and increased as tolerated[b]	12 to 24 weeks[c]	I, B

[a] Includes CTP class B and class C patients.
[b] The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.
[c] 24-week treatment duration is recommended if treatment experienced.

Recommended regimen for:

DAA-Experienced Patients With Genotype 1-6 Infection in the Allograft, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)[b]	12 weeks	I, C

[a] Excludes CTP class B and class C patients.
[b] For patients with cirrhosis plus multiple negative baseline characteristic, consideration should be given to adding ribavirin. The starting dose of ribavirin should be 600 mg/d and increased or decreased as tolerated. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d if <75 kg and 1200 mg/d if ≥75 kg body weight.

AASLD Practice Guidance. Accessed July 30, 2021

Non-hepatic solid organ transplant recipients*

Recommendations	Grade of evidence	Grade of recommendation
Treat HCV infection before or after transplantation, provided that life expectancy exceeds 1 year	A	1
Before transplantation, while on waiting list, patients can receive HCV treatment according to general recommendations for GT, liver disease severity and prior anti-HCV treatment	A	1
After transplantation, • Treat with fixed-dose SOF/LDV (GT 1, 4, 5 and 6) or SOF/VEL (all GT) according to the general recommendations† • Treat patients with an eGFR <30 mL/min/1.73 m^2 with GLE/PIB for 12 weeks‡	A B	1 1

*Including kidney, heart, lung, pancreas or small bowel recipients;

†Without the need for immunosuppressant drug dose adjustments;
‡Immunosuppressant drug levels need to be monitored and adjusted as needed during and after EOT
EASL CPG HCV. J Hepatol 2018;69:461–511.

Recipients of an HCV+ organ transplant

Recommendations		
Organs from anti-HCV Ab+, HCV RNA+ donors can be transplanted to HCV RNA+ recipients	B	1
Use of anti-HCV Ab+, HCV RNA+ organs for HCV RNA– recipients is possible, provided that: • It is allowed by local regulations • Rigorous informed consent is obtained • Rapid post-transplant DAA therapy is guaranteed	C	2
Use of liver grafts with moderate (F2) or advanced (F3) fibrosis is not recommended	B	2

EASL CPG HCV. J Hepatol 2018;69:461–511.

AASLD HCV Guidelines: DAA DDI with Calcineurin Inhibitors

	Cyclosporine (CSA)	Tacrolimus (TAC)
Sofosbuvir (SOF)	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Elbasvir/grazoprevir (EBR/GZR)	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; combination is not recommended	43% ↑ in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir/pibrentasvir (GLE/PIB)	5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ↑ in TAC AUC; no a priori dose adjustment; monitor TAC levels and titrate TAC dose as needed
Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX)	9.4 fold ↑ in VOX AUC; combination is not recommended	No data; no a priori dose adjustment

AUC=area under the curve

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed July. 28, 2020

Treatment of Acute Hepatitis C

- Pre-exposure or post-exposure prophylaxis not recommended
- HCV infections spontaneously clears in 20-50% of cases
  - Most clear within 6 months
- Viral clearance can be transient
- Predictors of spontaneous clearance
  - Jaundice
  - Elevated ALT
  - HBsAg positive
  - Female
  - Genotype 1

Kamal et al. AJG 2008

Management of Acute HCV

Medical Management and Monitoring of Acute HCV Infection

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

http://www.hcvguidelines.org. Accessed July. 28, 2021

Management of Acute Hepatitis C

Antiviral Therapy

Recommended Regimens for Patients With Acute HCV Infection	
RECOMMENDED	RATING
Owing to high efficacy and safety, the same regimens that are recommended for chronic HCV infection are recommended for acute infection.	IIa, C

http://www.hcvguidelines.org. Accessed July. 28, 2021

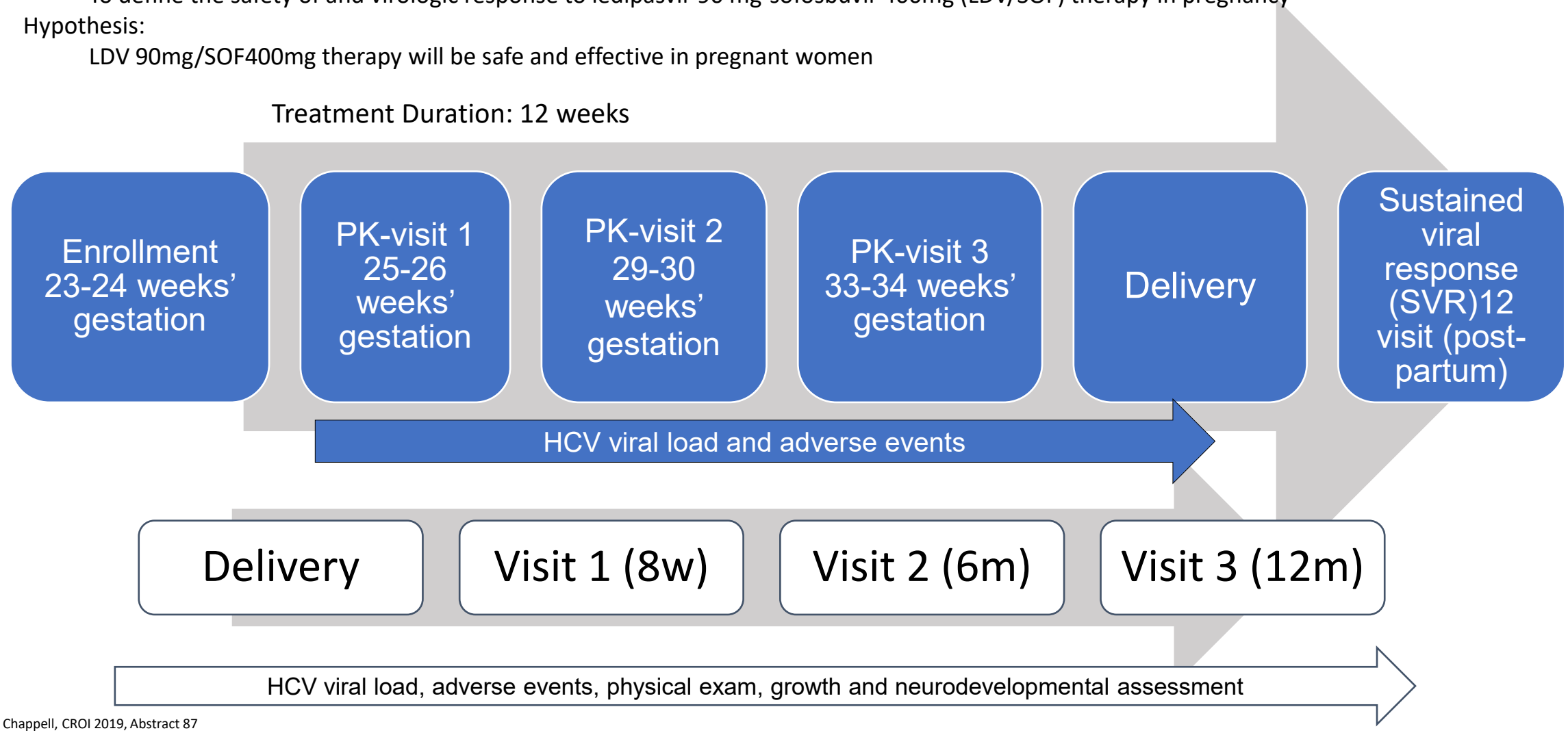
A Phase I Study of Ledipasvir/Sofosbuvir (LDV/SOF) in Pregnant Women with Hepatitis C Virus

Primary Objective:

To define the safety of and virologic response to ledipasvir 90 mg-sofosbuvir 400mg (LDV/SOF) therapy in pregnancy

Hypothesis:

LDV 90mg/SOF400mg therapy will be safe and effective in pregnant women



Chappell, CROI 2019, Abstract 87

Conclusions

In this first study of HCV treatment during pregnancy, LDV/SOF administration was safe for pregnant women

- 100% of participants were cured of HCV and all infants are negative to date
- LDV/SOF was well tolerated in pregnant women; any AEs were mild or moderate

No infant safety concerns following LDV/SOF in utero exposure at 12 months of follow up

A larger study using a pan-genotypic agent is planned

http://www.hcvguidelines.org. Accessed July. 28, 2021

Timing of HCV Treatment Around Pregnancy

During pregnancy to cure mother and prevent MTCT

- Maternal HCV may contribute to adverse fetal outcomes such as prematurity* and low birth weight.** Treatment in pregnancy might improve outcomes even in the 95% of infants who would not be infected.
- Pregnancy is a condition that increases access to health insurance coverage.
- Placebo controlled clinical trials of DAA in pregnancy may help discern natural effects of HCV on pregnancy outcomes as well as safety of DAAs in pregnancy.

After delivery

- Treatment is approved after breastfeeding is completed
- Multiple challenges exist: loss of health insurance, busyness of new mothers, focus on child's health, maternal guilt, lack of coordination of care between obstetric and ID/hepatology.

* Defined as birth prior to 37 weeks' gestation
**Low birth weight is defined as 2,499 g or less at birth regardless of gestational age

Society for Maternal-Fetal Medicine. HCV in pregnancy. Am J Obst & Gynecol 2017. Murray, EASL 2017, PS-101. Harvoni Product Insert. Data on file. Schwartz, AASLD 1028, 0184.Mavyret Product insert. Accessed online July 3, 2019.. Rezk, M. & Omar, Z. Arch Gynecol Obstet (2017) 296: 1097. https://doi.org/10.1007/s00404-017-4550-2 Wherry LR. Health Serv Res. 2018 Oct;53(5):3569-3591. Kushner and Terrault. Hepatology Communications, VOL. 3, NO. 1, 2019. Krans EE et al. *Subst Abus*. 2016;37(1):88–95. Chappell CA et al. Pediatrics. 2018;141(6):e20173273. Epstein R, JPediatrics 2018, 203:34-40, https://www.who.int/news-room/fact-sheets/detail/preterm-birth, https://www.who.int/nutrition/publications/globaltargets2025_policybrief_lbw/en/

AASLD/IDSA Guidance: HCV and Pregnancy

- **Universal HCV screening in pregnancy** (recommendation rating: IIb, C)
  - All pregnant women should be tested for HCV infection with each pregnancy, ideally at initial visit
- **HCV treatment and pregnancy** (recommendation rating: I, B)
  - For women of reproductive age with known HCV infection, antiviral therapy recommended before considering pregnancy

- **HCV treatment during pregnancy**
  - No large-scale clinical trials evaluating the safety of DAAs in pregnancy
  - 2 small studies reported 100% SVR12 and no early safety concerns with LDV/SOF or SOF; no data on pangenotypic regimens in pregnancy
  - *"Despite the lack of a recommendation, treatment can be considered during pregnancy on an individual basis, after a patient–physician discussion about the potential risks and benefits"*

AASLD/IDSA. HCV guidance. 2021

HCV and Breastfeeding

Postpartum Issues

Recommendations Regarding Breastfeeding and Postpartum Care for HCV-Infected Women	
RECOMMENDED	RATING
Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples, or in the context of HIV coinfection.	I, B
Women with HCV infection should have their HCV RNA reevaluated after delivery to assess for spontaneous clearance.	I, B

http://www.hcvguidelines.org. Accessed July. 28, 2021

HCV and Children

Possibility of spontaneous clearance up to age 3

Long term outcomes show that HCV acquired in infancy progresses slowly

Majority of children grow and develop normally with no symptoms

Few studies large studies of fibrosis progression in children

- Biopsies from PEDS-C trial included 121 samples from children ages 2-16
  - 78% acquired HCV perinatally
  - 14% had no fibrosis
  - 80% had portal-periportal fibrosis
  - 4% had bridging fibrosis
  - 2% were cirrhotic

Jara et al CID 2003; Goodman et al Hepatology 2008

HCV Antiviral Therapy for Children and Adolescents,

Without Cirrhosis or With Compensated Cirrhosis (Child-Pugh A)

Recommended regimens listed by age:

Treatment-Naive or Interferon-Experienced Children and Adolescents Without Cirrhosis or With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Combination of ledipasvir/sofosbuvir (weight-based dosing; see Table 1) for children aged ≥3 years with genotype 1, 4, 5, or 6	12 weeks	I, B
Combination of sofosbuvir/velpatasvir (weight-based dosing; see Table 2) for children aged ≥6 years or weighing ≥17 kg with any genotype	12 weeks	I, B
Combination of glecaprevir (300 mg)/pibrentasvir (120 mg) for adolescents aged ≥12 years or weighing ≥45 kg with any genotype	8 weeks	I, B

[a] Child-Pugh A

http://www.hcvguidelines.org. Accessed July. 28, 2021

Weight Based Dosing in Children

Table 1. Weight-Based Dosing of Ledipasvir/Sofosbuvir for Children Aged ≥3 Years

Body Weight	Once Daily Dose of Ledipasvir/Sofosbuvir
<17 kg	33.75 mg/150 mg
17 to <35 kg	45 mg/200 mg
≥35 kg	90 mg/400 mg per day

Table 2. Weight-Based Dosing of Sofosbuvir/Velpatasvir for Children Aged ≥6 Years or Weighing ≥17 kg

Body Weight	Once Daily Dose of Sofosbuvir/Velpatasvir
17 kg to <30 kg	200 mg/50 mg
≥30 kg	400 mg/100 mg

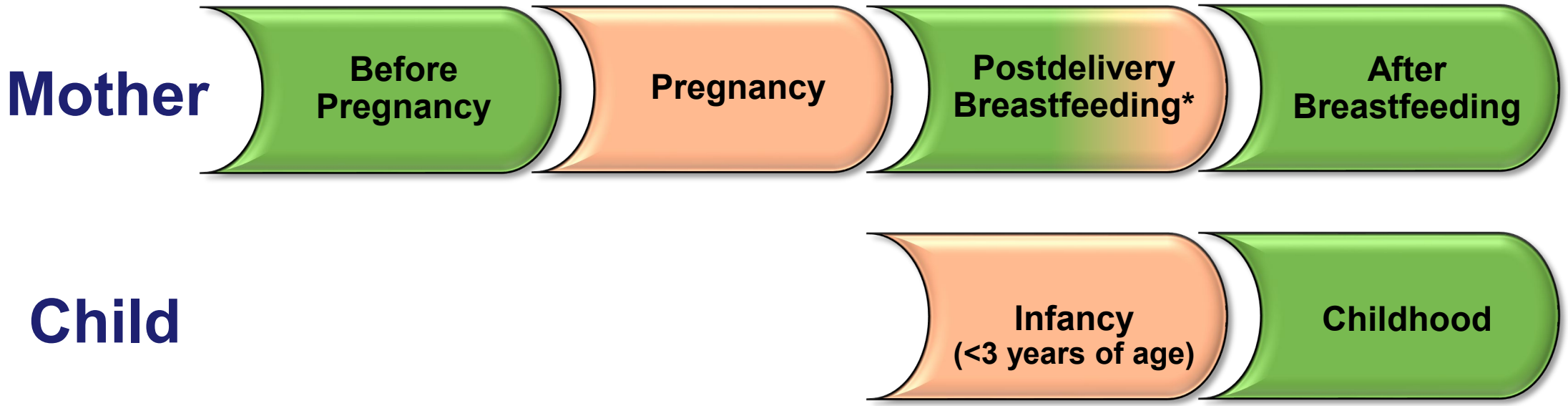
http://www.hcvguidelines.org. Accessed July. 28, 2021

Adolescents and children

Recommendations		
Adolescents aged ≥12 years • TN or TE, without cirrhosis or with compensated cirrhosis • GT 1, 4, 5 or 6: fixed-dose SOF/LDV for 12 weeks	B	1
• GT 2 or 3: other regimens approved for adults, with caution pending more safety data in this population	C	2
Children <12 years Defer treatment until DAAs, including pangenotypic regimens, are approved for this age group	B	1

- EASL CPG HCV. J Hepatol 2018;69:461–511.

Potential Times During the Pregnancy Care Cascade for DAA Therapy



*AASLD-IDSA, ACOG, CDC, Society for Maternal-Fetal Medicine:
Breastfeeding is safe in women with HCV infection, but recommend women abstain from breastfeeding if their nipples are damaged, bleeding, or cracked, or in the context of HIV coinfection.

HCV Special Populations

Late 2010'x

- HIV
- Renal failure
- HCC
- HBV co-infection
- Decompensated Cirrhosis
- Liver transplant

2020 to present

- Renal failure
- Decompensated disease
- HCC
- HBV co-infection
- Acute hepatitis C
- Transplantation
- Pediatrics

HEPATITIS C: TREATMENT

NOT TO TREAT

- Advanced malignancy including HCC
- Limited life expectancy
- Liver transplant candidates with MELD score >20

CHALLENGING TO TREAT

- Active drug users
- Homeless with poor social support systems

TO TREAT

- Everyone else