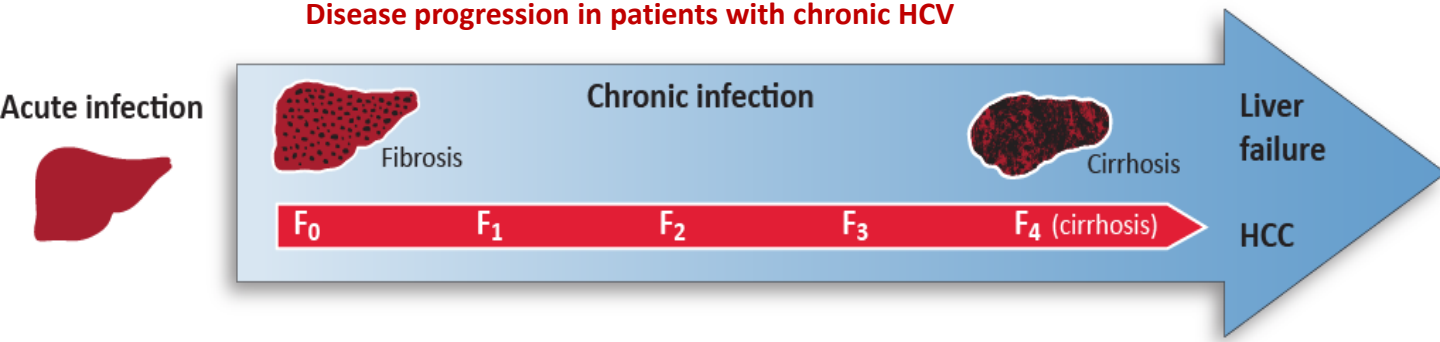
HCV TREATMENT IN DECOMPENSATED CIRRHOSIS

Ghanaei O,MD

Gastroenterologist

DISEASE PROGRESSION AND MORBIDITIES

Disease progression in patients with chronic HCV

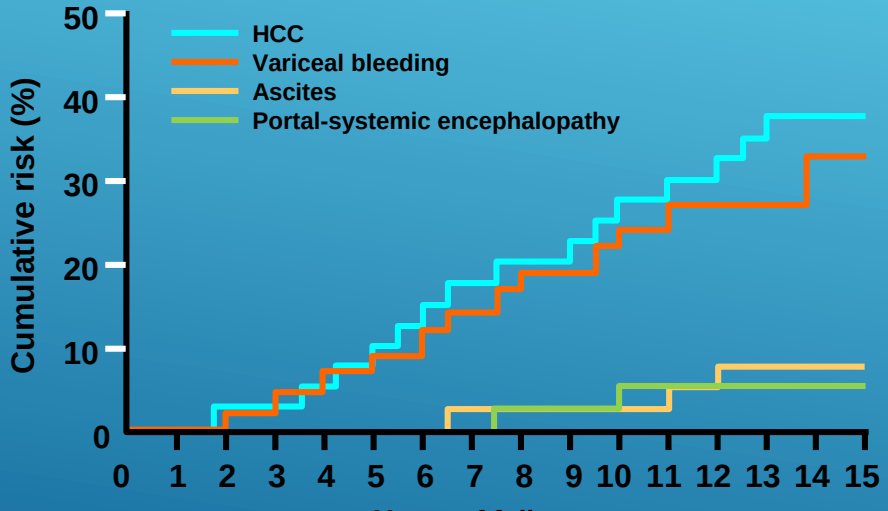


Morbidities associated with chronic HCV infection[1,2]

- Cirrhosis
- Decompensated cirrhosis: Ascites, varices, Encephalopathy
- Hepatocellular carcinoma (HCC)

CIRRHOTIC PATIENTS AT RISK OF SERIOUS MORBIDITY

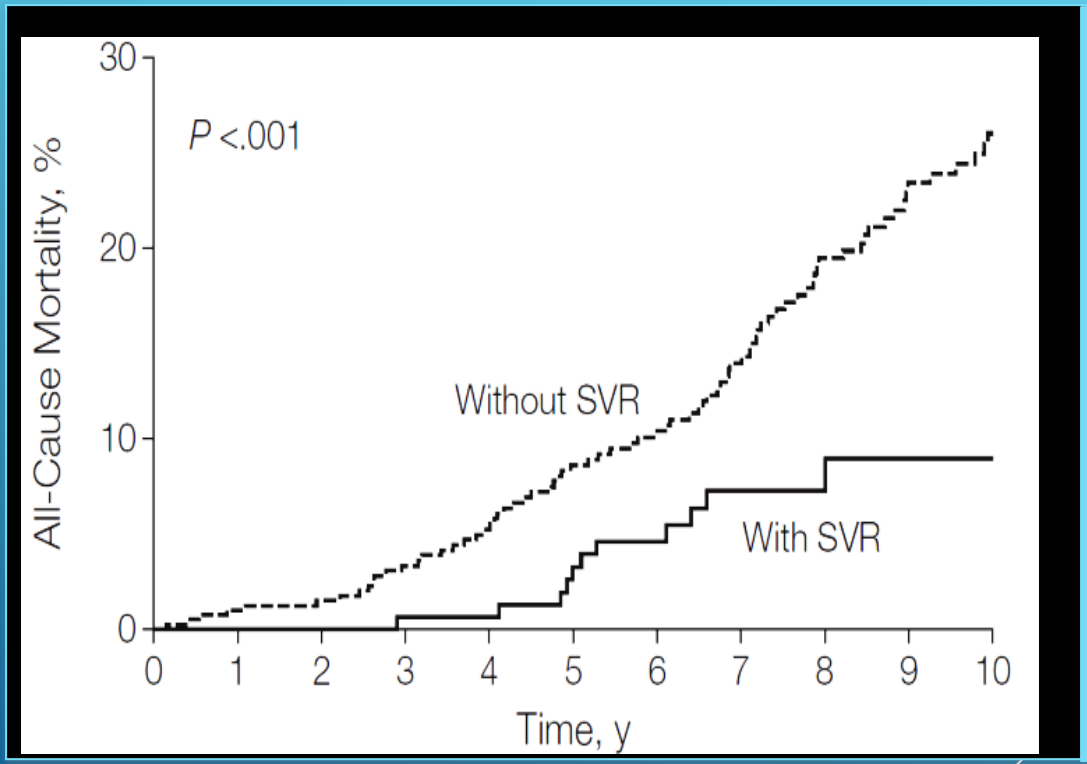
- **312 patients with initially compensated cirrhosis of viral etiology**



Patients at risk																
HCC	312	311	310	303	297	268	226	189	153	129	94	65	45	27	11	5
Variceal bleeding	312	312	312	309	301	269	237	190	163	131	97	71	44	29	13	7
Ascites	312	311	312	305	296	259	223	181	152	125	93	60	48	30	15	9
Encephalopathy	312	312	312	309	300	270	235	192	161	127	95	65	43	30	13	7

Benvegnù L, et al. Gut 2013; 53: 744

VIRAL ERADICATION IMPROVES ALL-CAUSE MORTALITY



Patient survival outcomes with and without SVR

- **Primary goal of treatment is to eradicate the virus**

- Slow disease progression
- Minimize risk of liver cancer
- Improve liver damage
- Enhance quality of life
- Prevent transmission of virus
- Reduce extra-hepatic manifestations

SVR IN DECOMPENSATED CIRRHOSIS

1. SVRs can be achieved in the majority of these individuals, and short-term follow-up from these studies has shown that SVR is often accompanied by improvement in measures of decompensation including MELD and Child- Pugh scores.

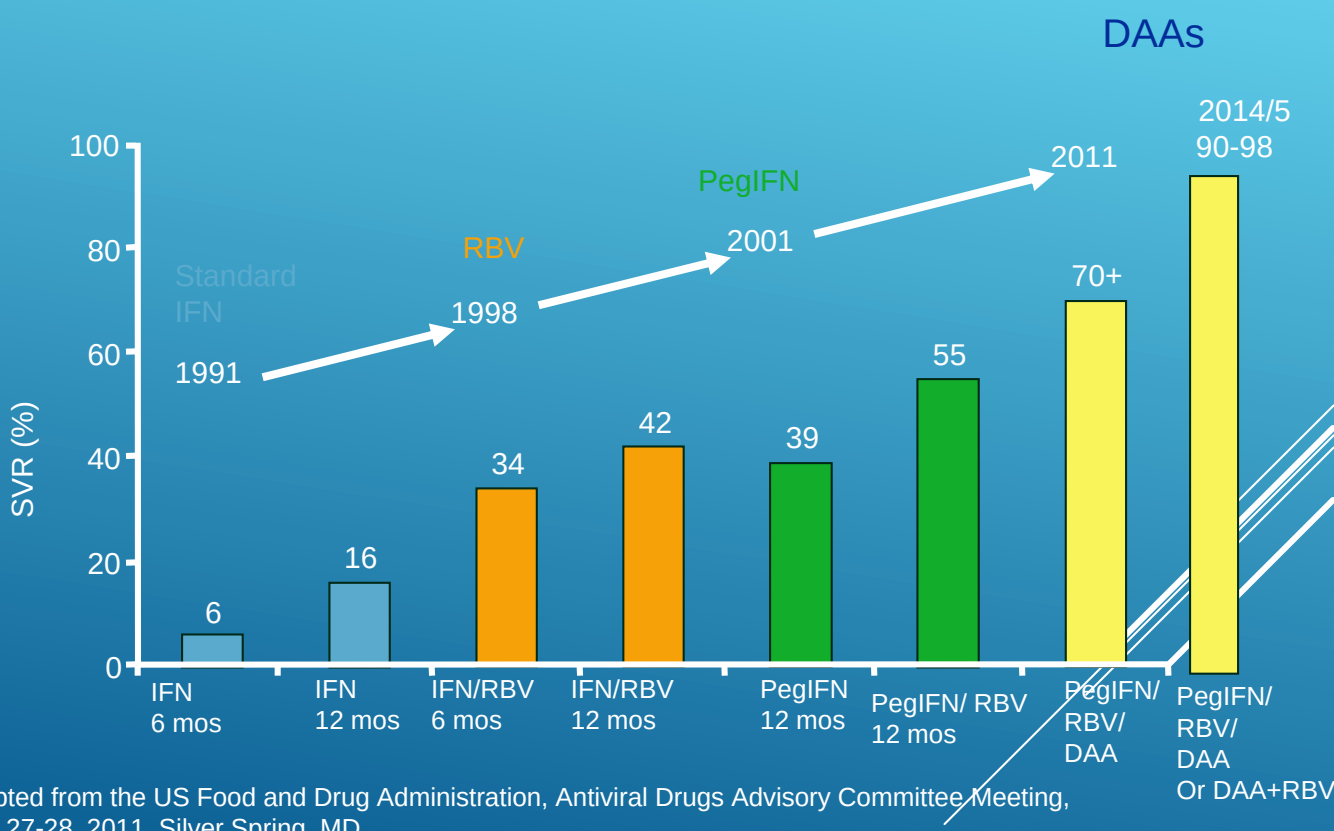
2. Achieving SVR before transplant in a decompensated population with chronic hepatitis C will likely allow these patients to achieve long-term outcomes not different from non–HCV-infected populations.

BACKGROUND HISTORY

1. Antiviral therapy, with a PEG-IFN/RBV component, has limited applicability peri- and post-LT because of poor tolerability and efficacy in patient with decompensated cirrhosis.

2. The improved efficacy of first-generation PIs, boceprevir and telaprevir, in the treatment of recurrent hepatitis C is offset by increased toxicity in LT recipients, especially anemia, and significant drug–drug interactions, especially with tacrolimus.

THE ADVANCING PRESENT



Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

THE PRESENT

1. In present, the NS5B inhibitors and the NS5A inhibitors lack toxicity and significant drug interactions with either cyclosporine or tacrolimus and seem ideally suited for Cirrhosis and post-LT treatment of recurrent HCV infection.

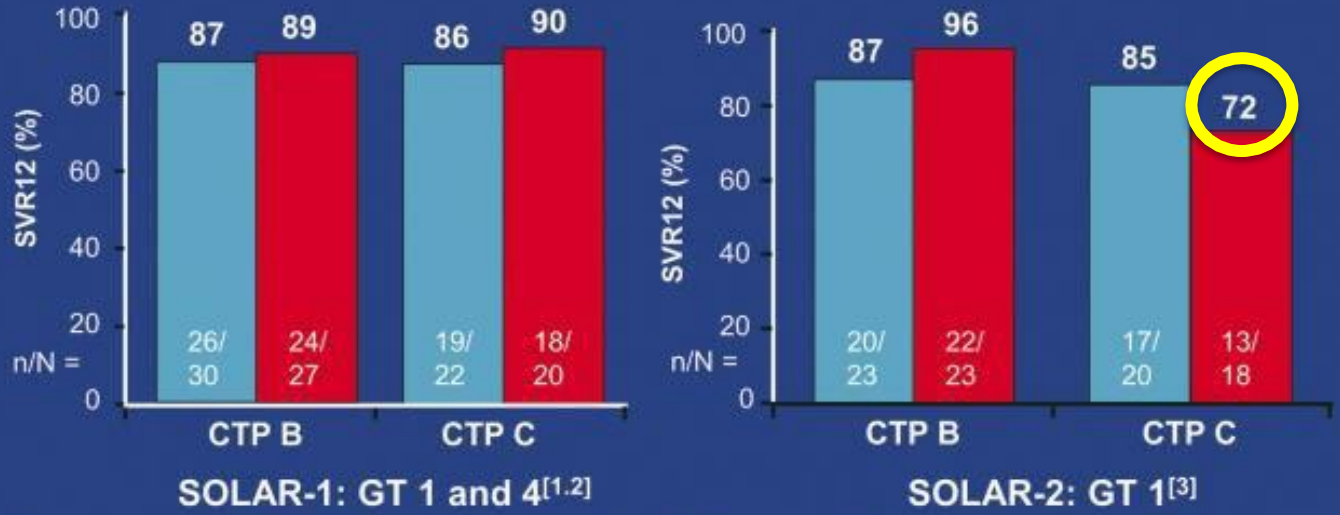
2. Recent studies of DAA combinations (SOF plus ledipasvir, or ABT-450/ABT-333/BT-267) are expected to achieve almost 97% response with shorter duration of therapy.

THE 2015 HCV TREATMENT OPTIONS

	Acute HCV	F0-F3	F4	Decompensated	LT
HCV-1					
SOF/LDV					
SOF + DCV					
HCV-4					
SOF/LDV					
SOF + DCV					
HCV-2					
SOF + Rbv					
HCV-3					
SOF + RBV					
SOF + DCV					

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

Comparable efficacy between SOLAR-1 and SOLAR-2 studies

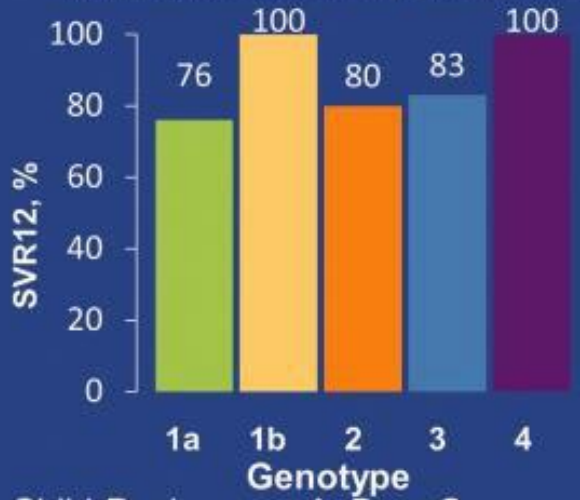


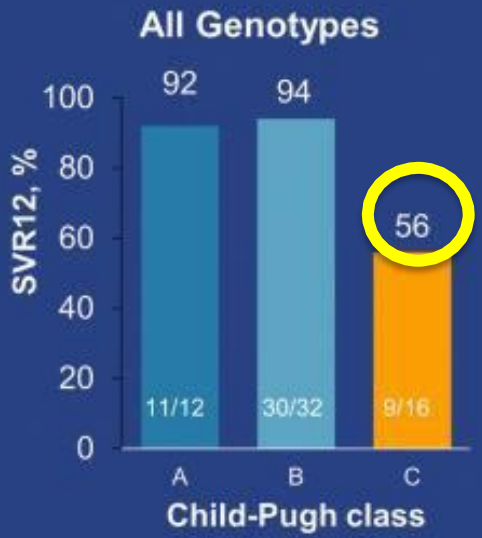
AE, adverse event; CTP, Child-Turcotte-Pugh; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir.

1. Charlton M, et al. *Gastroenterology*. 2015 [epub ahead of print]
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.

ALLY-1: SOF + DCV + RBV for 12 Weeks in Patients With Genotype 1 HCV and Cirrhosis

- Treatment naïve or treatment experienced adults with any HCV genotype
- DAA failures allowed, except NS5A





- Child-Pugh score: A, B, or C
- MELD scores 8-40
- Hepatocellular carcinoma allowed

Poordad F, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract LO8.

ALLY-1

SOLAR 1-2 and ALLY-1 in Decompensated Cirrhosis

No difference was seen in SVRs in the 12- or 24-week arms, and the therapy was well tolerated (SOLAR 1-2).

Similar results in the ALLY-1 study where the combination of sofosbuvir/daclatasvir and low-dose ribavirin for 12 weeks in cirrhotic patients was described across all genotypes.

Both studies reported improvement in MELD and CPT scores 4 weeks after therapy had been stopped with longer-term follow-up results expected.

TREATMENT IN DECOMPENSATED CIRRHOSIS

- In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between baseline and post-treatment week 4.
- As expected, the frequency of serious adverse events increased with treatment duration in both the CTP class B group (10% week 12; 34% week 24) and the CTP class C group (26% week 12; 42% week 24).

- Most of the serious adverse events were related to ribavirin

LOWER SVR IN DECOMPENSATED CIRRHOSIS

- The most common adverse events were anemia ,asthenia, headache, and pruritus; the frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups

LOWER SVR IN DECOMPENSATED CIRRHOSIS

1.The reasons for the lower SVRs in patients with decompensated cirrhosis compared with compensated liver disease are not well defined.

2.The presence of clinically significant portal hypertension may reduce hepatic exposure of DAAs by significant porto-systemic shunting.

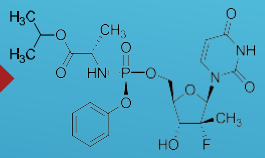
3.The presence of cirrhosis may alter the metabolism of DAAs in the liver as well, although for protease inhibitors, higher area under the curve values have been observed in those with decompensated cirrhosis.

KEY CONSIDERATIONS FOR DECOMPENSATED CIRRHOSIS

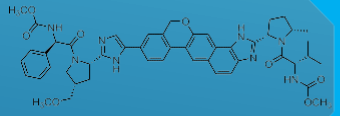
- Treatment options are more limited than for pts without cirrhosis or with compensated cirrhosis
  - SVR rates are generally lower
- Protease inhibitors are not recommended for CTP B or C
- Continuing role for ribavirin
  - Low dose for CTP C; weight based for CTP B with SOF/VEL
- Extend duration to 24 wks if RBV ineligible

Sofosbuvir + Velpatasvir: A Potent Pangenotypic Regimen

SOF
Nucleotide NS5B polymerase inhibitor



- Sofosbuvir (SOF)[1,2]
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet



VEL
NS5A inhibitor

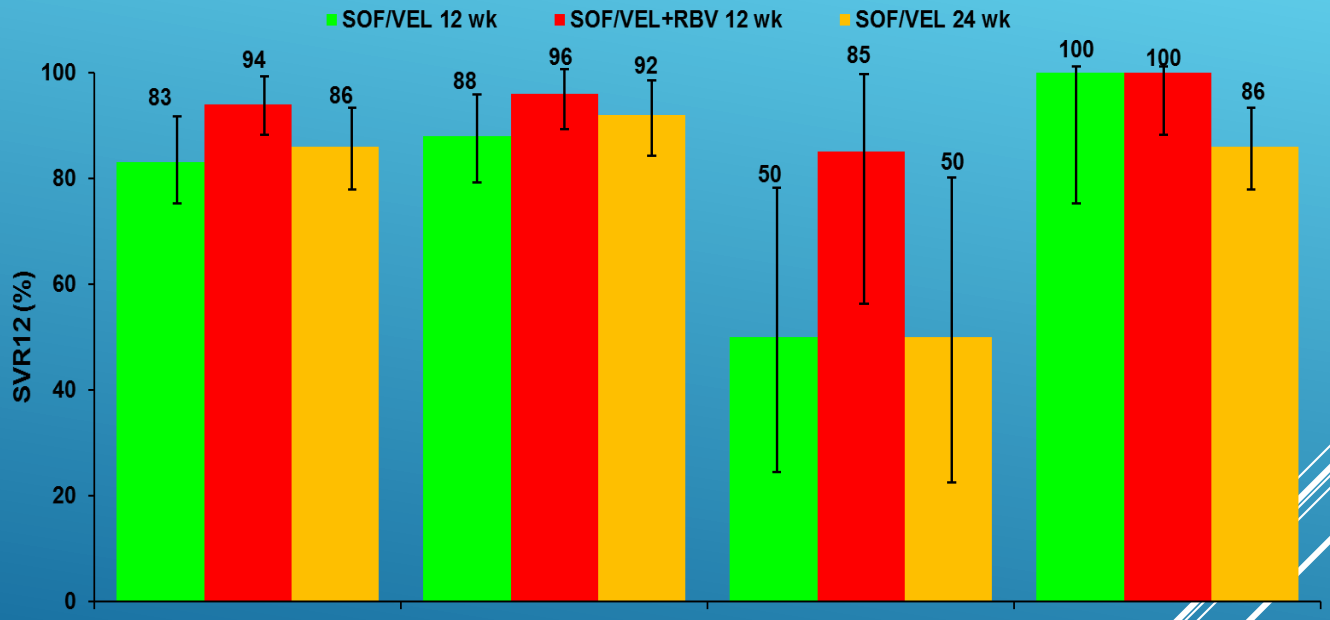
- Velpatasvir (VEL; GS-5816)[3-5]
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

SOF + VEL

- SOF/VEL Single Tablet Regimen (STR)
  - Once daily, oral, STR (400/100 mg)

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191;
4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. EASL 2013, poster 1082.

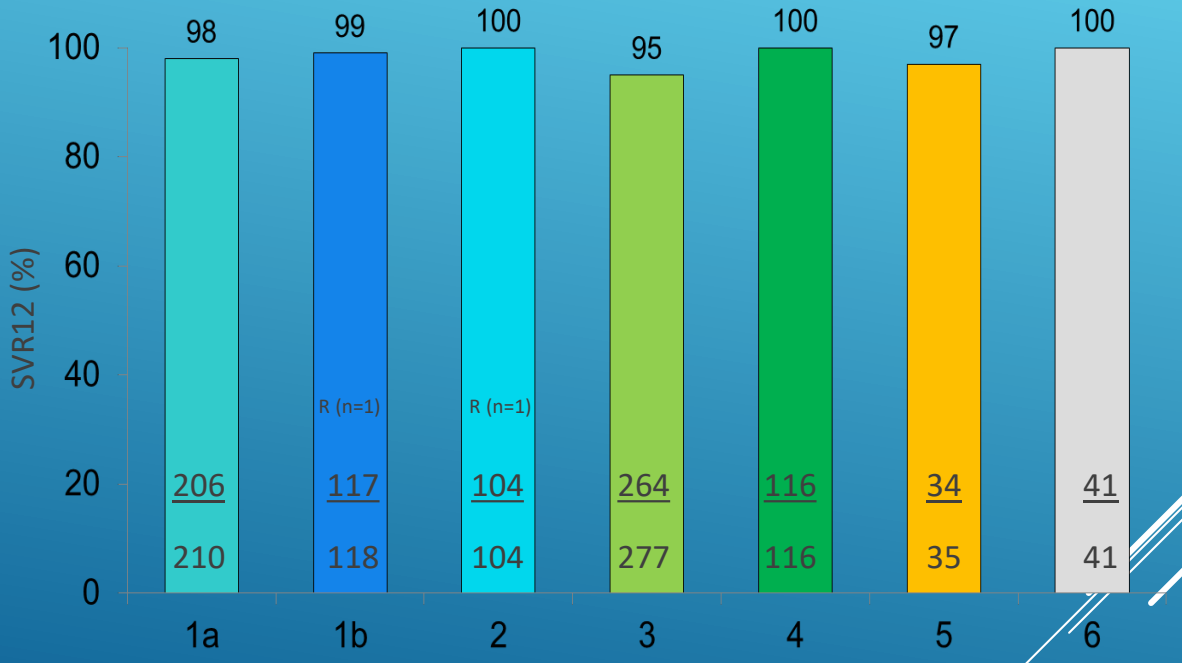
ASTRAL-4: SOF/VEL ± RBV IN HCV PATIENTS WITH DECOMPENSATED LIVER DISEASE



	Overall			GT 1			GT 3			GT 2, 4, and 6		
Breakthrough, n	—	1	1	—	—	—	—	1*	1	—	—	—
Relapse, n	11	2	7	5	1	3	6	1*	4	—	—	—
Lost to follow up, n	1	—	3	1	—	3	—	—	—	—	—	—
Death, n	3	3	3	2	2	—	1	—	1	—	—	1

Charlton M, et al., NEJM 2015

ASTRAL-1&3. IN SEARCH OF A PANGENOTYPIC REGIMEN



Feld JJ, et al. N Engl J Med. 2015. Foster GR, et al. N Engl J Med. 2015

ACHIEVING SVR: DOES THIS RESCUE PATIENTS AND PREVENT OLT?

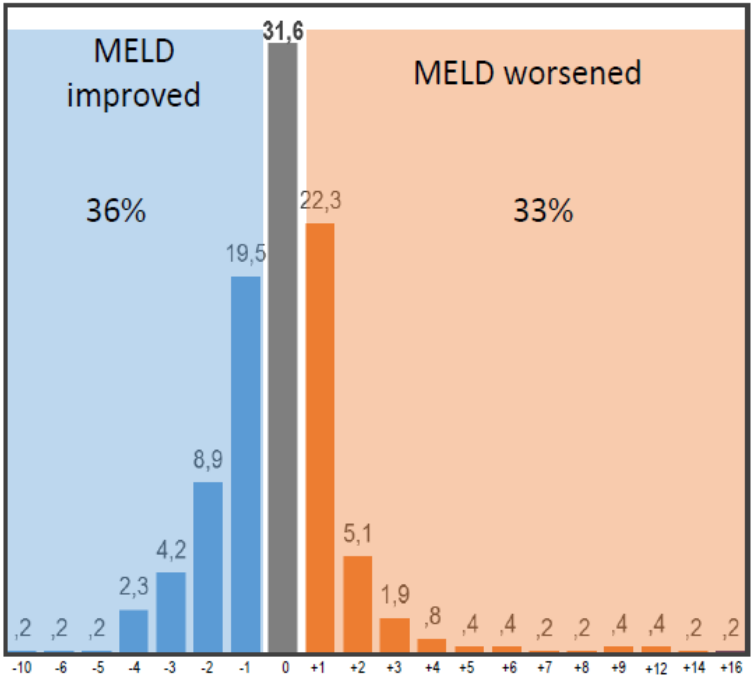
1. Achieving SVR is associated with improvement in albumin and bilirubin levels, as well improvements in MELD and CPT scores, although it is not yet clear what the long-term magnitude of improvement will be.

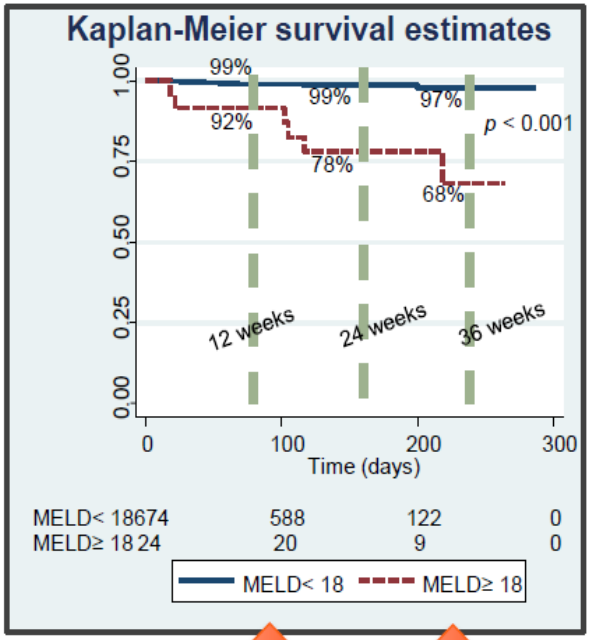
2.Studies from the interferon era suggest that it may take years to reverse clinically significant portal hypertension.

3.Improvement of MELD can wrongly lead to remove or downgrade the patient from the transplant list!

Treatment of Hepatitis C Virus in Patients With Advanced Cirrhosis. The Hepa-C Registry

Deaths 16 (2%), Breakthroughs 9 (1%), Relapses 45 (7%)





Fernàndez-Carrillo, et al. ILC2016 Barcelona

UK Expanded Access Program of NS5B + NS5A +/- Rbv in Decompensated Cirrhosis: First 6 months of treatment

Event	All treated (n=409)	Untreated (n=261)
Deaths	13 (3.2%)	15 (5.7%)
Decompensation	72 (17.6%)	73 (28%)
New HCC	19 (4.6%)	21 (8%)
Sepsis	27 (6.6%)	15 (5.7%)
New OLT	27 (6.6%)	10 (3.8%)
Hospital admissions	133 (32.5%)	83 (31.8%)
MELD worsening >2	94 (23%)	99 (37.9%)*
Total adverse outcomes	213 (52.1%)	166 (63.6%)*

**** P<0.05 between treated and untreated***

Foster & Irving et al, J Hepatol 2016; Cheung et al, ILC2016 Barcelona

- Improvements may be insufficient to avoid liver-related death or the need for liver transplantation , highlighting that not everyone benefits from DAA therapy.
- Most deaths among those receiving DAA therapy relate to the severity of underlying liver disease.

Belli LS. Journal of Hepatology. 2016;65(3):524 - 531.

- The predictors of improvement or decline have not been clearly identified, though patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than treatment

Terrault NA. Transplantation. 2017;101(5):945 - 955.

- Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotics without HCC

Prenner SB. Journal of Hepatology. 2017;66(6):1173 - 1181

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis

Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center. I, C

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	12 weeks	I, A[d]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[e] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	I, B

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1, 4, 5, or 6 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[c]
Genotype 1 or 4 infection only: Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg)	24 weeks	II, C

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 1, 4, 5, or 6 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Prior sofosbuvir-based treatment failure only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C[b]
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[c]	24 weeks	II, C[d]

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended Regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 2 or 3 Infection and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated)	12 weeks	II, B

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 2 or 3 Infection and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	24 weeks	II, C

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Recommended regimens listed by evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 2 or 3 Infection in Whom Prior Sofosbuvir- or NS5A-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[b]	24 weeks	II, C

AASLD/IDSA GUIDANCE FOR PTS WITH GT1 HCV AND DECOMPENSATED CIRRHOSIS

- Refer to experienced HCV provider (ideally liver transplant center)

GT1,3 Population	DCV + SOF	LDV/SOF	SOF/VEL
RBV eligible	12 wks + low-dose RBV*	12 wks + low-dose RBV*	12 wks + RBV (weight based for CTP B; low dose* for CTP C)
RBV ineligible	24 wks	24 wks	24 wks

*Initial dose: 600 mg/day, increase as tolerated.

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Regimens not recommended for:

Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C)

NOT RECOMMENDED	RATING
Paritaprevir-based regimens	III, B
Simeprevir-based regimens	III, B
Elbasvir/grazoprevir-based regimens	III, C
Glecaprevir/pibrentasvir	III, C
Sofosbuvir/velpatasvir/voxilaprevir	III, C

Potential algorithm for management of decompensated patients with hepatitis C

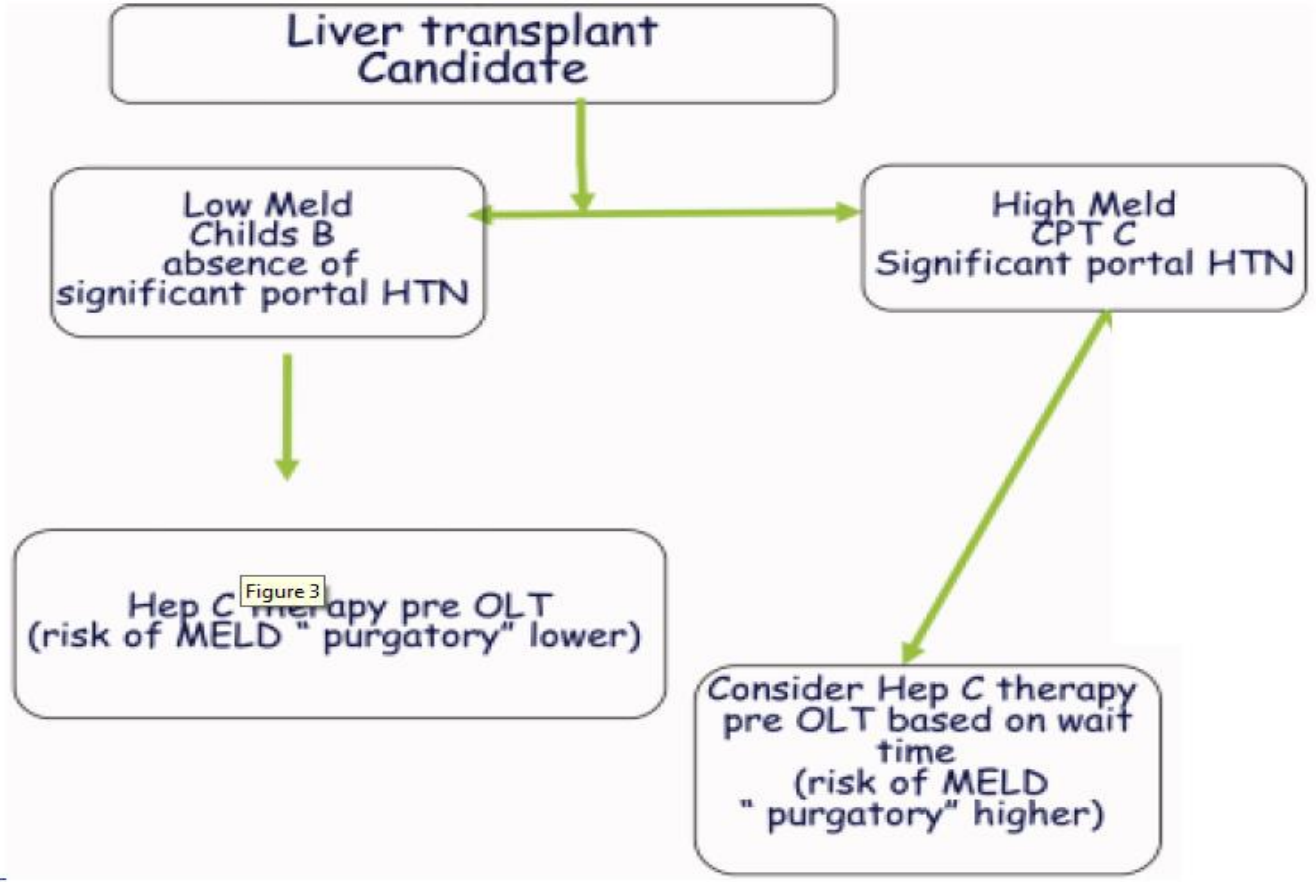
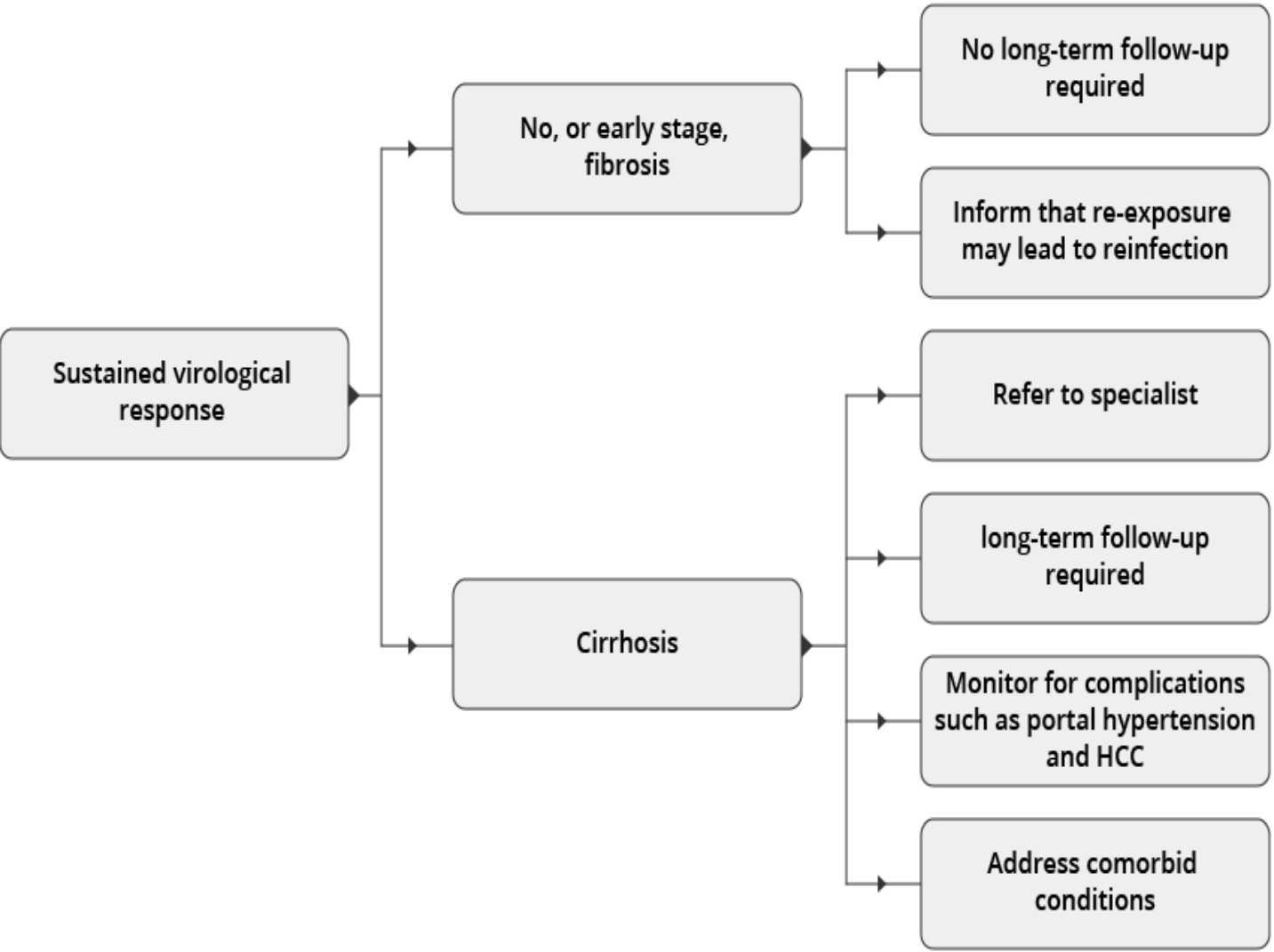


Figure 3


Sustained virological response
No, or early stage, fibrosis
No long-term follow-up required
Inform that re-exposure may lead to reinfection
Cirrhosis
Refer to specialist
long-term follow-up required
Monitor for complications such as portal hypertension and HCC
Address comorbid conditions