Treatment of Hepatitis C in Patients With Cirrhosis

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IAS–USA
International AIDS Society–USA

Disclosure

- Research grants
  - Abbvie, Achillion, BMS, Gilead, Hologic, Intercept, Janssen, Merck, NGM, Roche, Shire
- Advisory boards
  - Abbvie, Achillion, BMS, Gilead, Janssen, Merck
- Consultant
  - Theravance

Outline

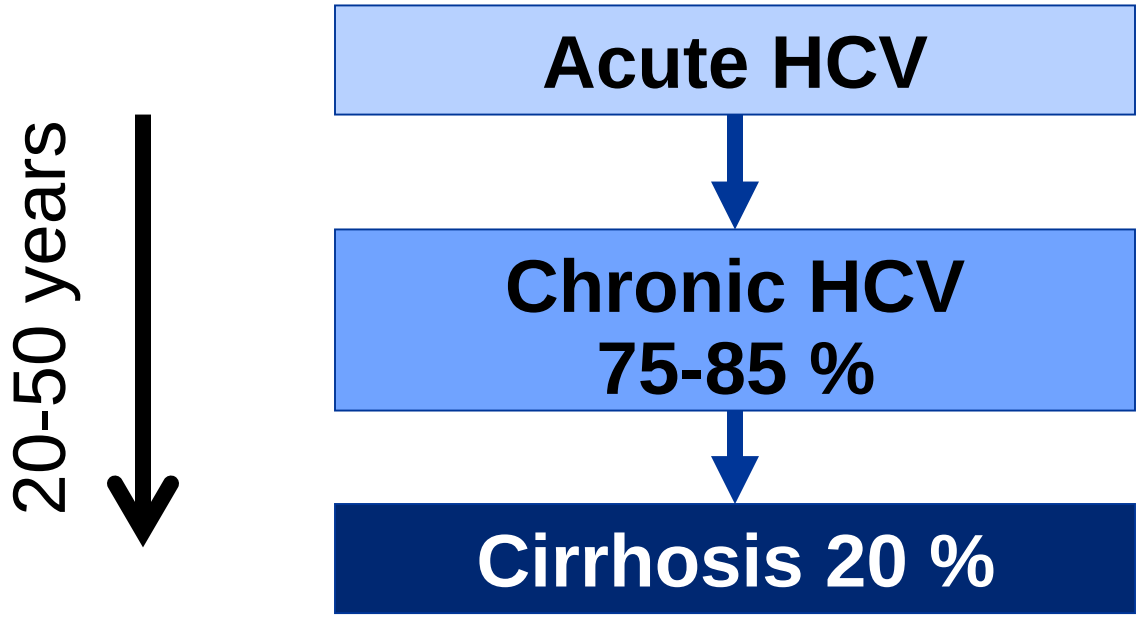
- Definitions and diagnostic approach
- Treatment
  - Candidacy
  - Efficacy
  - Adverse events
- Decompensated cirrhosis

Case

- 54-year-old man presents with new diagnosis
  - History: no ascites, encephalopathy, GI bleeding
  - Examination: mentally clear, no ascites or edema
  - Laboratory data:
    - AST 60 U/L, ALT 75 U/L, t bili 1.2 mg/dL
    - Albumin 3.9 gm/dL, creatinine 1.0 mg/dL
    - Platelet 110 x 10^9/L
    - PT-INR 1.1
    - HCV RNA 1,100,000 IU/mL
    - Genotype 1a
- Clinical questions
  - Does the patient need treatment?
  - What is the stage of liver disease?

Definitions and Diagnostic Approach

HCV natural history

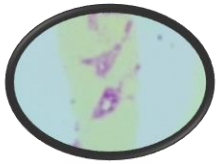


Faster progression with

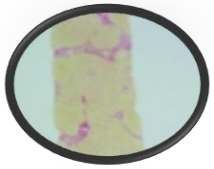
- older age at infection
- alcohol
- HIV infection
- post-transplant

DiBisceglie A. *Hepatology* 2000

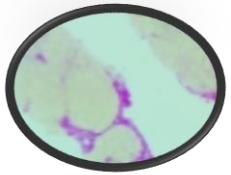
Liver fibrosis staging



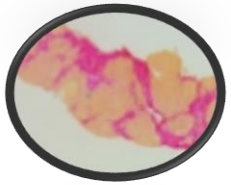
F1: portal fibrosis



F2: portal fibrosis with few septa



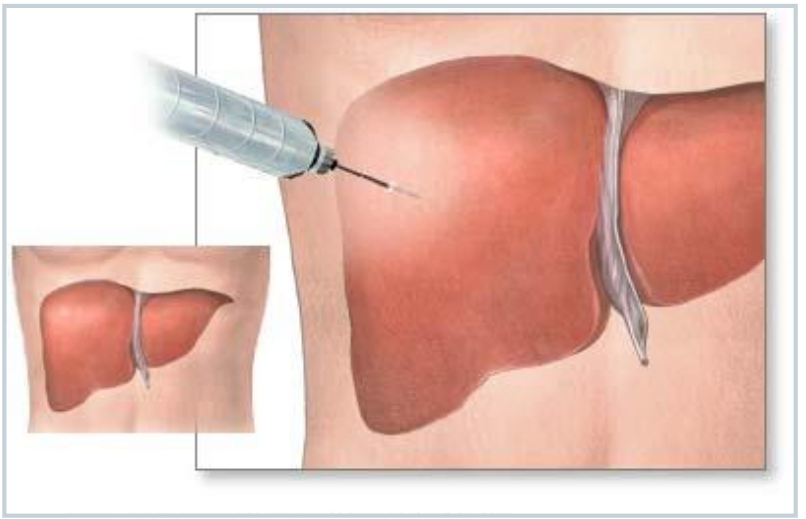
F3: septal fibrosis (bridging)



F4: cirrhosis

Liver biopsy

- Gold standard
- Invasive
  - Morbidity (3/1,000)
  - Mortality (1/10,000)
- Observer variability
- Sampling error
- Costly



Rockey DC. *Hepatology* 2009; Regev A. *Am J Gastroenterol* 2002

Alternatives to liver biopsy

- Alternative approaches
  - Serum markers
    - Standard laboratory tests: APRI, FIB-4
    - Commercial assays
  - Radiographic tests
    - Elastography
- Limitations
  - Ability to distinguish F1 versus F2, etc
    - Better to differentiate advanced versus early
  - Serologies impacted by inflammation
  - Indeterminate outcomes common

Lin ZH. *Hepatology* 2011; Vallet-Pichard. *Hepatology* 2007; Myers RP. *Dig Dis Sci* 2003; Friedrich-Rust M. *Gastroenterology* 2006

Recommendations

- AASLD/IDSA/IAS–USA Guidance
  - www.hcvguidelines.org

- An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.
- Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.

Treatment

IAS–USA
International Antiviral Society–USA

Who needs treatment?

- AASLD/IDSA/IAS–USA Guidance
  - www.hcvguidelines.org

- "Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert."

Genotype 1: **AASLD/IDSA Guidance Oct 2015**

Genotype	Sofosbuvir + peginterferon + ribavirin	Ledipasvir + sofosbuvir +/- ribavirin	Paritaprevir/r + ombitasvir + dasabuvir +/- ribavirin	Simeprevir + sofosbuvir +/-ribavirin	Daclatasvir + sofosbuvir +/- ribavirin
1		Recommended Naïve PEG failures PI failures SOF/RBV failure SOF/PEG/RBV SIM/SOF failures	Recommended Naïve PEG failures	Recommended Naïve PEG failures	Recommended Naïve PEG failures PI failures SIM/SOF failures

Ledipasvir + Sofosbuvir

- SIRIUS
- Patients:
  - Treatment-experienced, failure of both PEG/RBV and PI + PEG/RBV regimens
  - Compensated cirrhosis
- Design
  - Randomized, double-blinded
- Regimens
  - Placebo 12 weeks followed by LDV/SOF + RBV for 12 weeks
  - LDV/SOF + Placebo RBV for 24 weeks

- Adverse events
  - 2 AEs higher with LDV/SOF vs placebo: headache and fatigue

Safety Outcome	LDV/SOF + RBV 12 wks (n = 77)	LDV/SOF 24 wks (n = 78)
SAE	5%	10%
AE leading to d/c	1%	0
Headache	21%	35%
Fatigue	4%	17%

Bourlière M. Lancet Infect Dis 2015

Ledipasvir + Sofosbuvir

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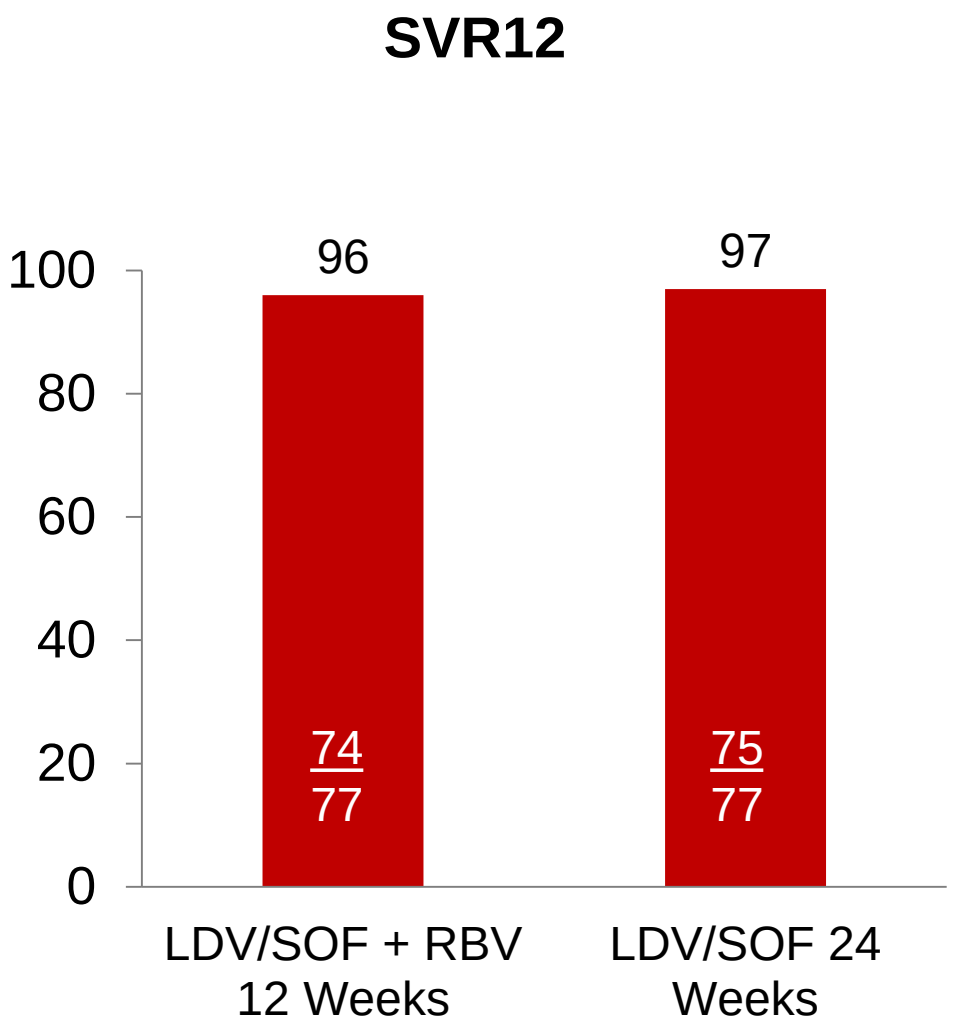
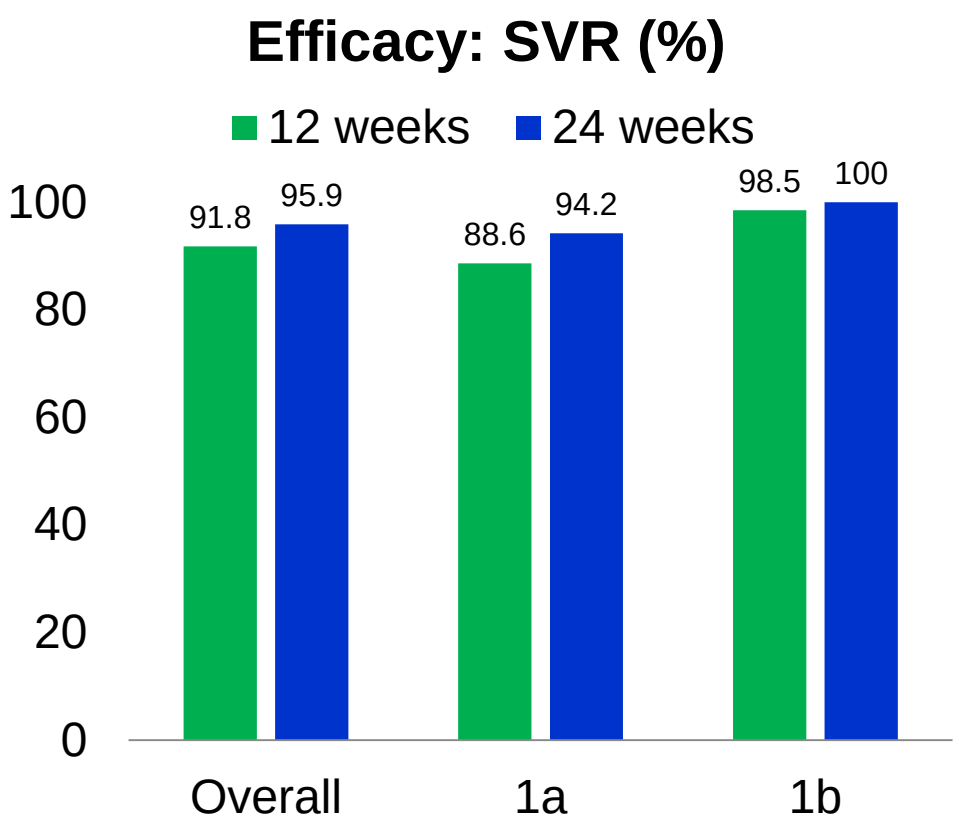


Paritaprevir/ritonavir + ombitasvir + dasabuvir

- Population
  - 380 Child Pugh Class A cirrhosis (compensated)
  - Treatment naive and previously treated
- Regimen
  - Paritaprevir/ritonavir, dasabuvir, ombitasvir, ribavirin
- Design
  - Phase 3, randomized, open label
  - Duration 12 vs 24 weeks

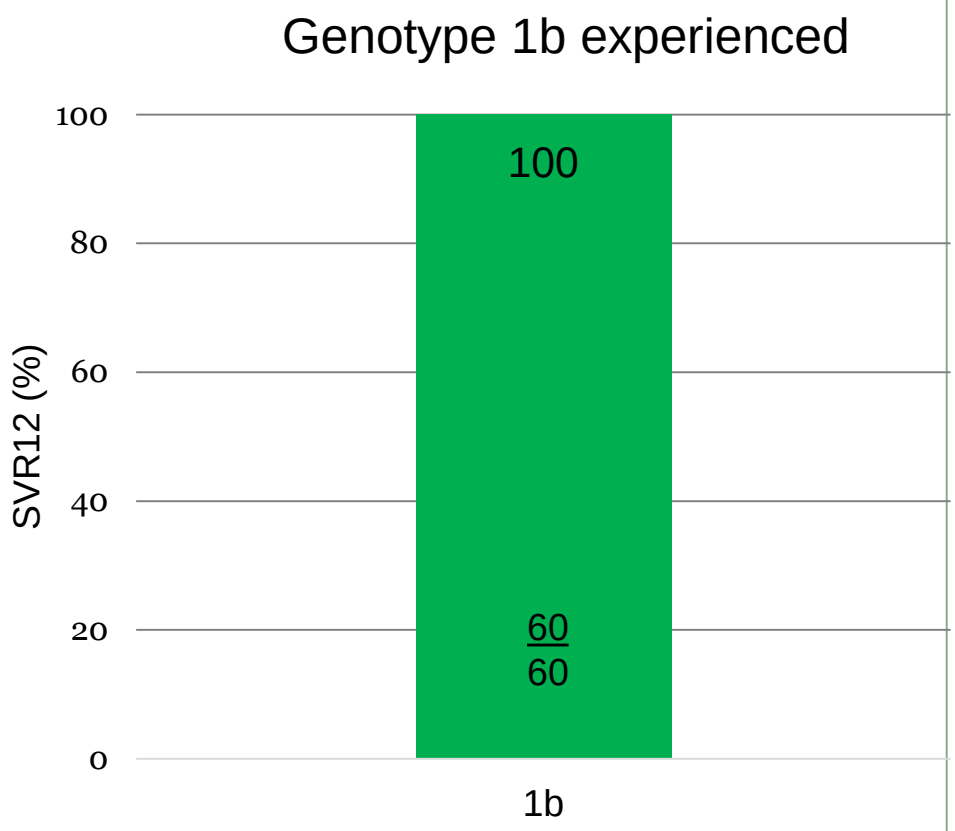


Paritaprevir/ritonavir + ombitasvir + dasabuvir

Variable	12-week group (N = 208)	24-week group (N = 172)
Any adverse event	191 (91.8%)	156 (90.7%)
AE leading to discontinuation	4 (1.9%)	4 (2.3%)
Serious adverse events	13 (6.2%)	8 (4.7%)
Deaths	1 (0.5%)	0

Paritaprevir/ritonavir + ombitasvir + dasabuvir
Genotype 1b, cirrhosis

- Paritaprevir/r, ombitasvir + dasabuvir
- NO RIBAVIRIN
- Duration: 12 weeks
- Naïve and experienced patients (55%)
- All compensated cirrhosis
- Sample size 60



Paritaprevir/ritonavir + ombitasvir + dasabuvir

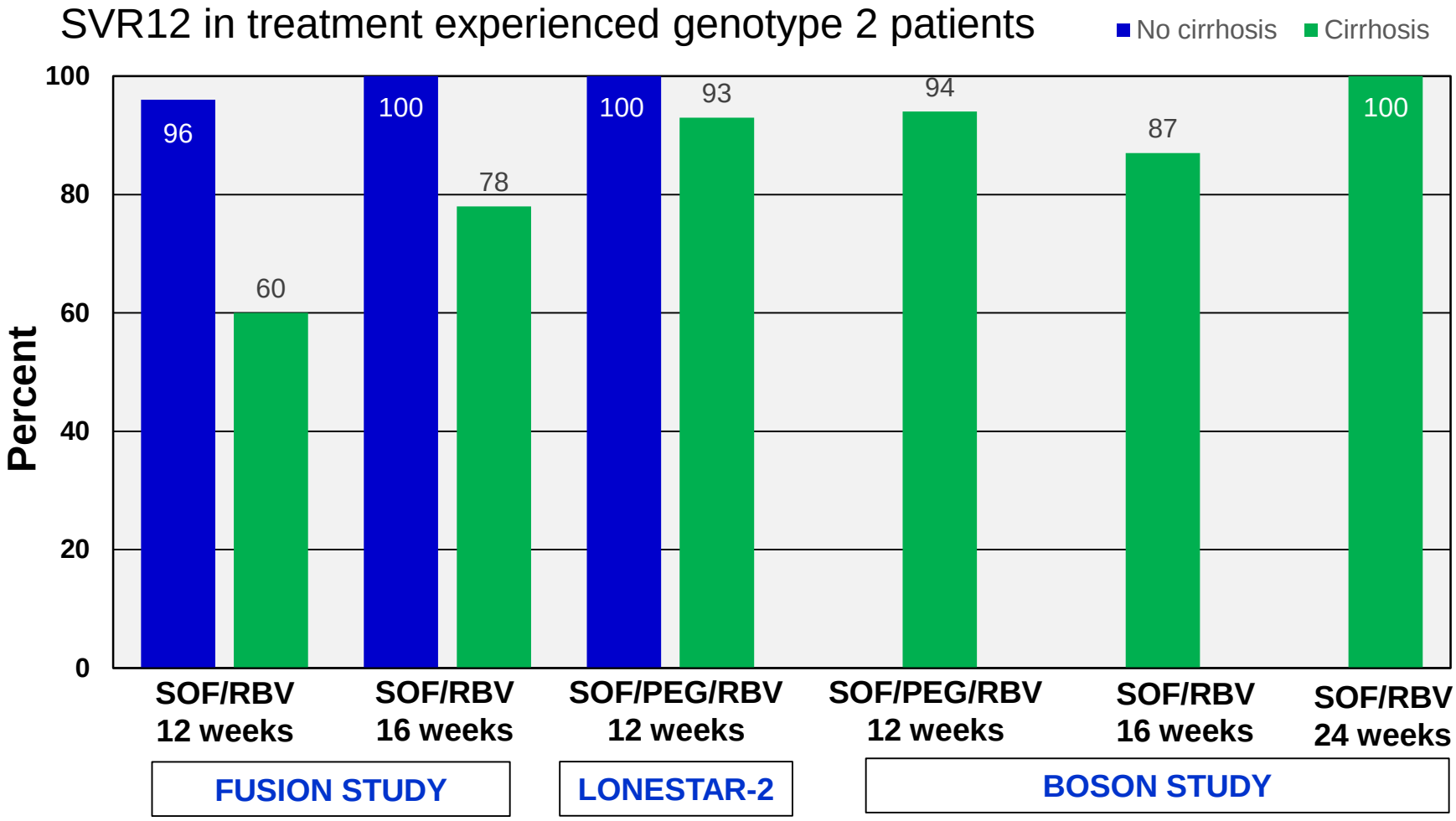
- FDA letter
- 26 worldwide cases
  - 10 hepatic failure resulting in transplantation or death
  - 16 patients with liver dysfunction
- In most, liver injury within 1 to 4 weeks of starting
- Some patients contraindicated or not recommended
- “Transaminase elevations did not appear to be a predominant presentation in the cases with advanced liver disease”
- Contraindicated in Child Pugh B and C

Genotype 2

- AASLD/IDSA/IAS–USA Guidance
  - www.hcvguidelines.org

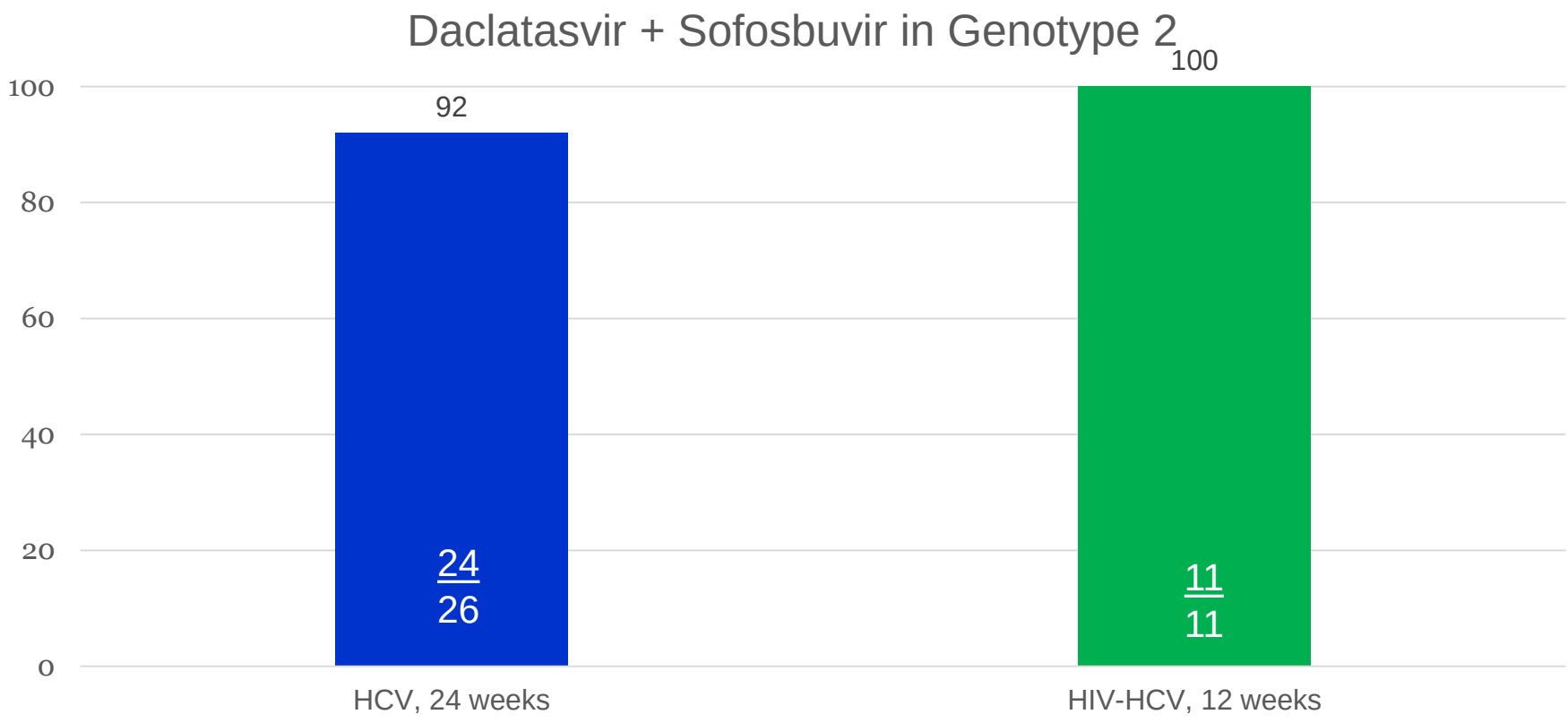
	Sofosbuvir + ribavirin	Peginterferon-α, ribavirin + sofosbuvir	Daclatasvir + sofosbuvir
Treatment naive	Recommended 12 wks (cirrhosis 16 wks)		Recommended 12 weeks RBV ineligible
PEG/RBV nonresponders	Recommended 16-24 weeks	Alternative 12 weeks	
Sofosbuvir failures		Recommended IFN eligible 12 weeks	Recommended IFN ineligible +/- RBV 24 weeks

Genotype 2



Jacobson IM. *NEJM* 2013; Lawitz 2015; Foster 2015

Genotype 2



- Minimal data in genotype 2 cirrhosis
- AASLD/IDSA: consider 24 weeks and ribavirin if cirrhosis

Sulkowski *NEJM* 2014; Wyles *NEJM* 2015

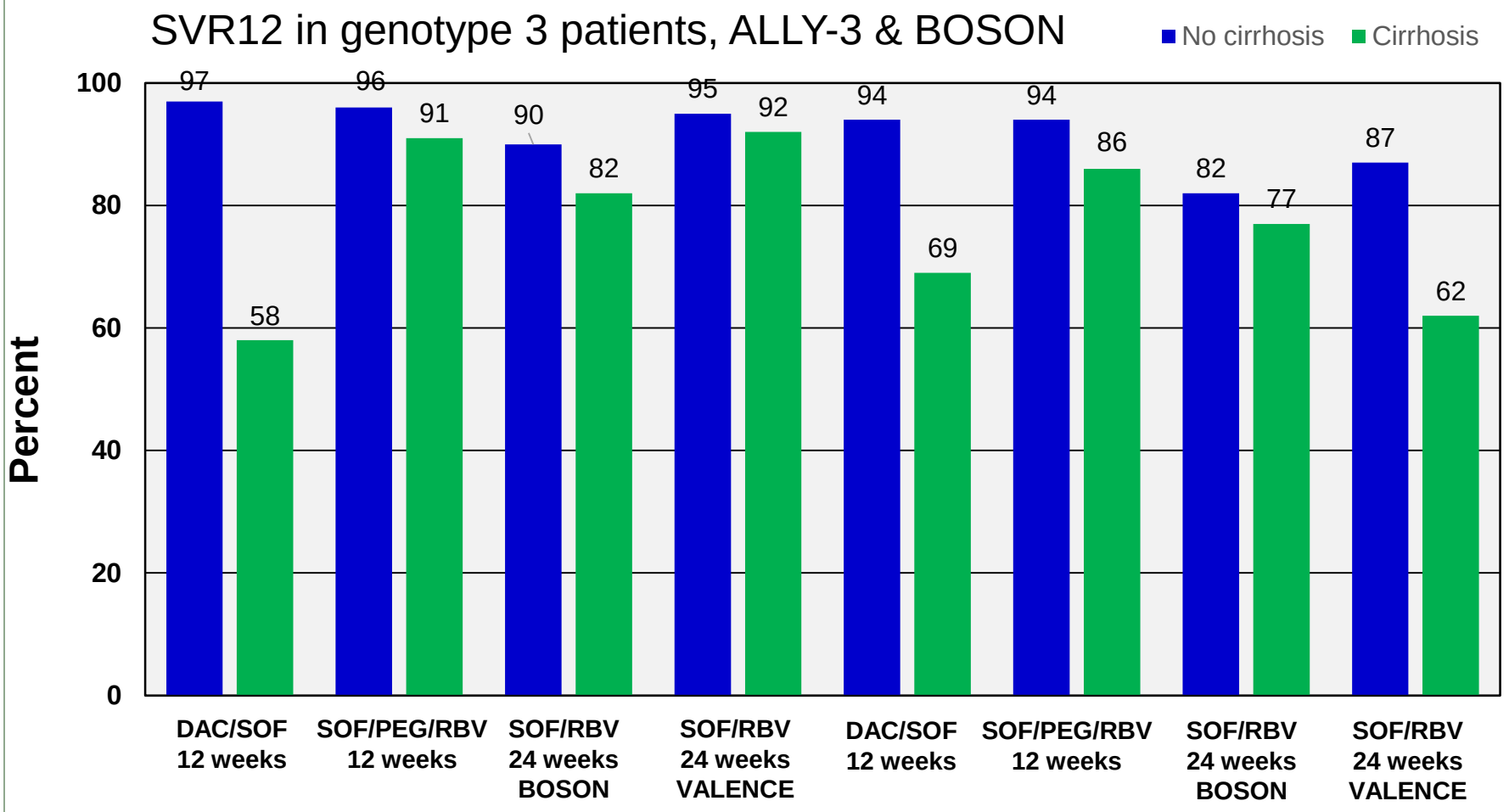
Genotype 3

- AASLD/IDSA/IAS–USA Guidance
  - www.hcvguidelines.org

American Association for the Study of Liver Diseases
AASLD
IDSA
Infectious Diseases Society of America

	Sofosbuvir + ribavirin	Peginterferon-α, ribavirin + sofosbuvir	Daclatasvir + sofosbuvir
Treatment naive	Alternative, 24 weeks	Recommended, 12 weeks	Recommended, 12 weeks Cirrhosis: 24 wks +/- RBV
PEG/RBV nonresponders		Recommended, 12 weeks	Recommended, 12 weeks Cirrhosis: 24 wks + RBV
Sofosbuvir failures		Recommended, 12 weeks	Recommended, 24 weeks + RBV

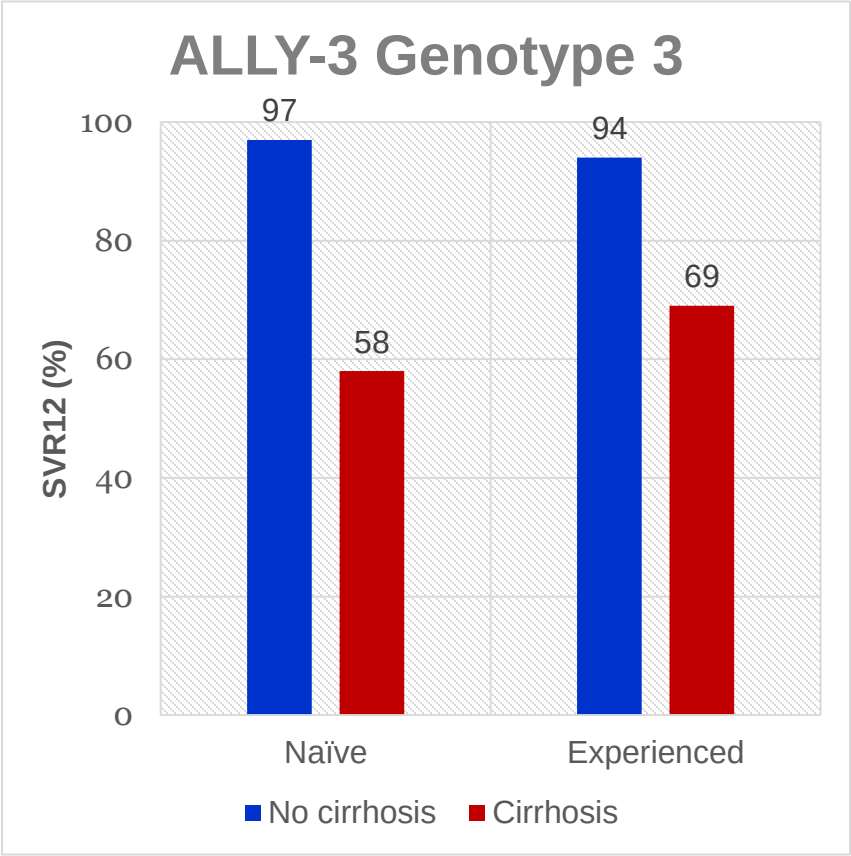
Genotype 3



Lawitz 2015; Foster 2015

Genotype 3: daclatasvir + sofosbuvir

- ALLY-3
- Population:
  - Genotype 3
  - Treatment naïve and experienced
- Regimen
  - Daclatasvir 60 mg + sofosbuvir 400 mg for 12 weeks



Nelson D. *Hepatology* 2015

Genotype 3: daclatasvir + sofosbuvir

- ALLY-3+
- Population:
  - 50 patients
  - Genotype 3
  - Advanced fibrosis (28%) and cirrhosis (72%)
  - Treatment naïve (26%) and experienced (74%)
- Design: RCT
- Regimen
  - Daclatasvir 60 mg + sofosbuvir 400 mg + ribavirin
- Arms: 12 vs 16 weeks

	12 weeks n=24	16 weeks n=26
SVR4	21 (88%)	25 (96%)
Adv fibrosis	6/6 (100%)	8/8 (100%)
Cirrhosis	15/18 (83%)	17/18 (94%)
Breakthrough	0	0
Relapse	2 (8%)	1 (4%)

Decompensated Cirrhosis

Decompensated cirrhosis

Is treatment safe?

With decompensated cirrhosis, how much better can the liver get?

Will this be like HBV?

AASLD/IDSA: Patients with decompensated cirrhosis (Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).

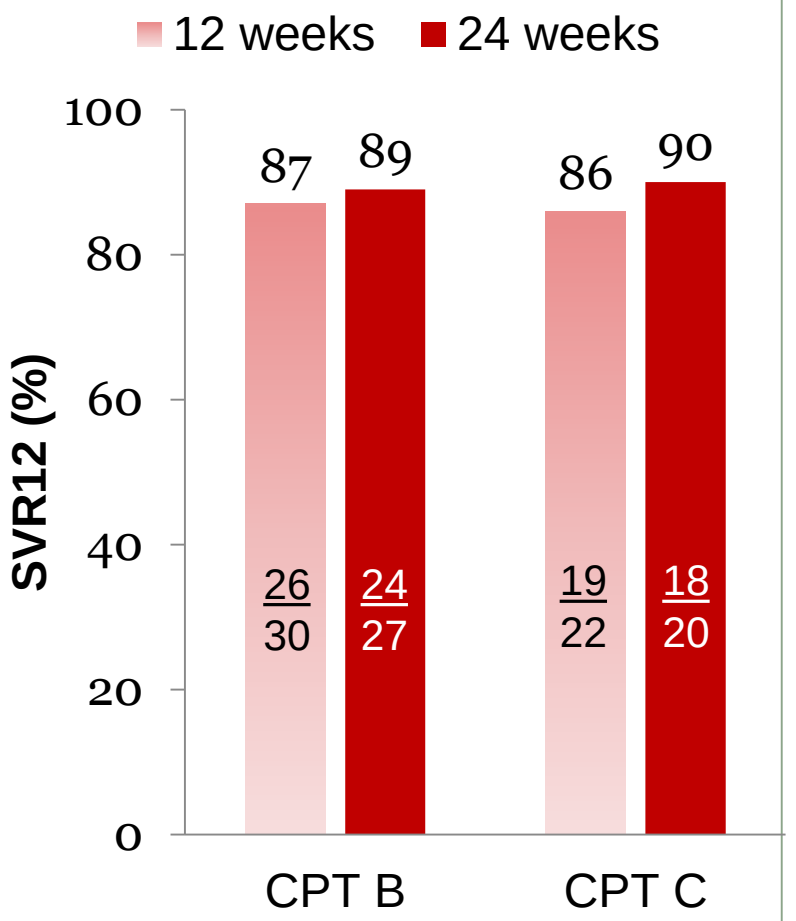
DAAs with hepatic impairment

Regimen	FDA recommendation for hepatic impairment
Sofosbuvir + ribavirin	No dose adjustment for CTP A, B, C
Sofosbuvir + peginterferon + ribavirin	Contraindicated if decompensated
Sofosbuvir/ledipasvir	No dose adjustment for CTP A, B, C
Paritaprevir/ritonavir + ombitasvir + dasabuvir	Contraindicated in CTP B, C
Simeprevir + sofosbuvir	Not recommended in CTP B, C
Daclatasvir + sofosbuvir	No dose adjustment for CTP A, B, C

CTP: Child Turcotte Pugh score

Decompensated cirrhosis

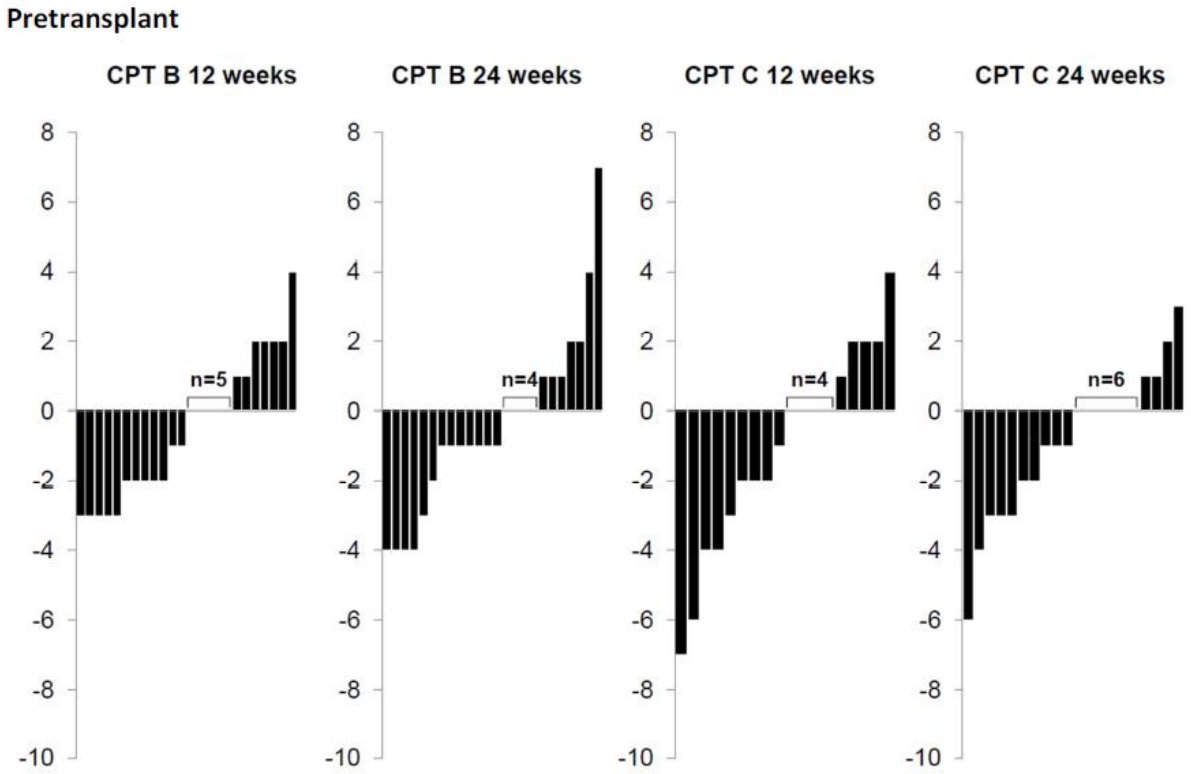
- SOLAR study
- Patients
  - 108 GT 1 or 4
  - Treatment naïve or experienced
  - CPT class B or C
- Inclusion/exclusion
  - Total bili ≤10 mg/dL
  - Creatinine clearance ≥40 mL/min
  - Platelets >30,000 x 10^3/uL
- Design: RCT
- Regimen
  - Ledipasvir + sofosbuvir
  - Ribavirin 600 mg daily, titrated up if tolerated
  - Duration: 12 or 24 weeks



Charlton M. *Gastroenterology* 2015.

What does cure of HCV mean?

- SOLAR study MELD scores



Charlton M. *Gastroenterology* 2015.

What does cure of HCV mean?

- Decompensated cirrhosis:
  - Is there a threshold where we cannot avoid a transplant?

  - Should HCV+ patients defer and take a HCV+ organ?
  - Outcomes post-transplant are excellent

Summary

- All patients with HCV need an assessment of fibrosis
  - Patients with advanced fibrosis or cirrhosis should be prioritized for treatment
- HCV treatment is safe and effective in patients with compensated cirrhosis
- Patients with decompensated cirrhosis
  - Should be referred to an experienced clinician and preferably a liver transplant center
  - Antiviral treatment can be effective but must consider transplant options
  - Some agents are not recommended or contraindicated in patients with decompensated cirrhosis