Hepatitis C Post-OLT
Who, What, When?

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Disclosures

- Grant Support/Consultant for Abbvie, BMS, Genentech, Gilead, Janssen, Merck, Vertex

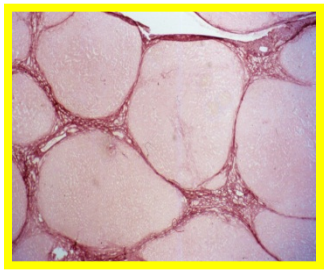
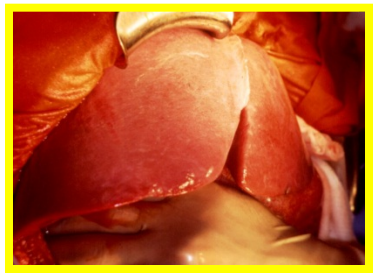
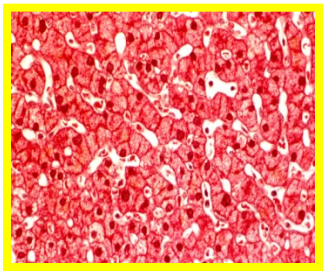
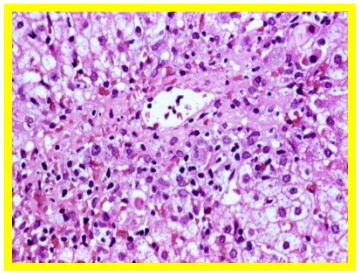
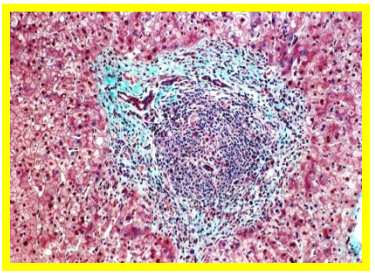
Recurrent HCV Infection Post-LT

When to treat?

Cirrhosis

Transplant

Normal histology

Pre-LT

Preemptive

0

4-6 weeks

6 months

Years

Acute hepatitis

Chronic hepatitis

Prevent recurrent HCV

PHOENIX study showed no benefit w/ PEG+RBV. No studies of new DAA in this setting.

Established recurrence

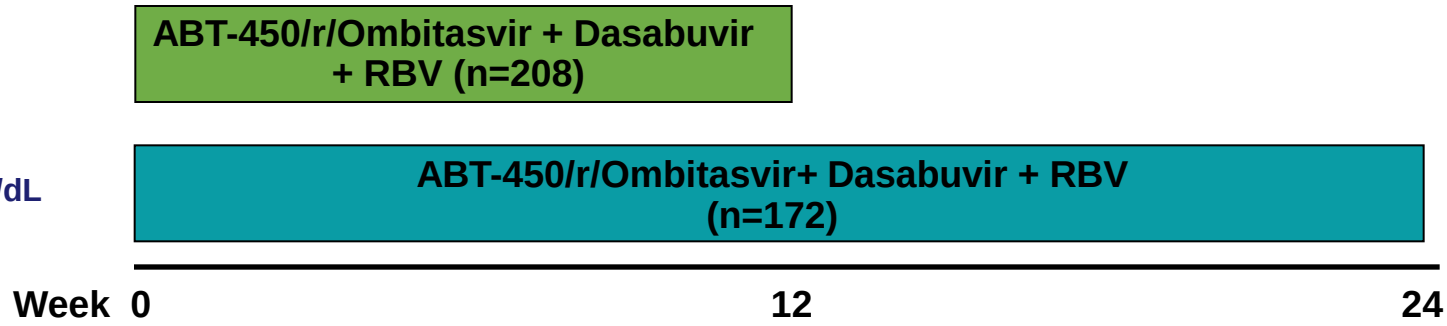
When/Who to Treat

- Will all patients be HCV RNA (-) going into OLT?
  - HCC upgrades, LDLT-Possible
  - Patients treated earlier with SVR who develop HCC
  - Decompensated, high MELD-Not at the current time, ? Soon
- Will decrease risk of early recurrence but may have decreased response and access to HCV + livers

TURQUOISE-II: ABT-450/r/Ombitasvir + Dasabuvir + RBV in HCV Genotype 1, Compensated Cirrhotics

Phase 3

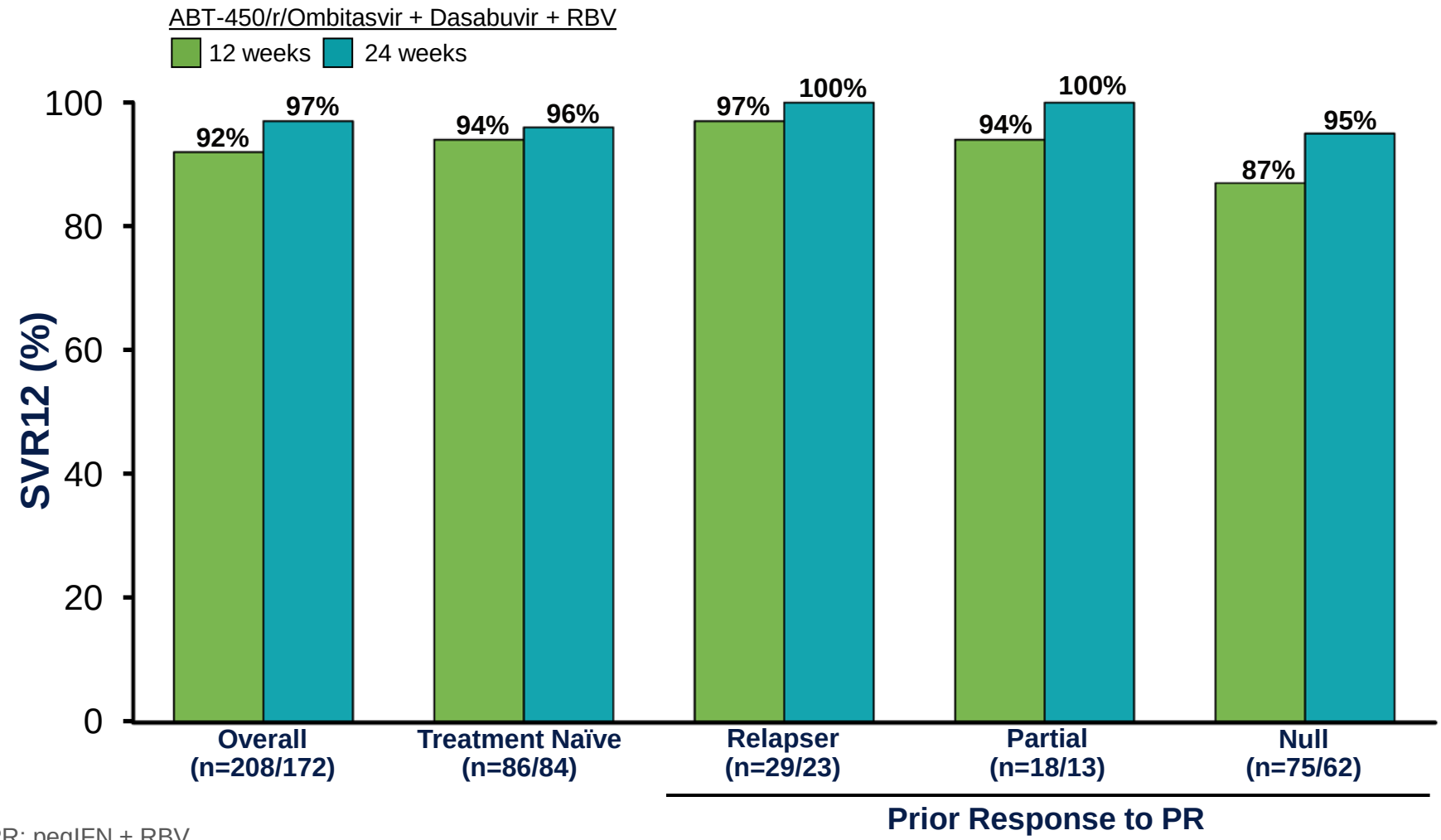
Open-label
Genotype 1
Treatment-naïve and PR experienced
Child-Pugh A
Platelets: ≥60K/mL
Serum albumin: ≥2.8 g/dL
Total bilirubin: <3 g/dL
INR: ≤2.3
AFP: ≤100 ng/mL



ABT-450/ritonavir/ombitasvir 150/100/25 mg qd; dasabuvir 250 mg bid. RBV (1000-1200 mg). PR: pegIFN + RBV.
Primary endpoint: SVR12 versus historical control SVR rate: 43% and 54% for non-inferiority and superiority, respectively (telaprevir + PR).
Baseline demographics and disease characteristics:
- Male: 70%; age: 57 years; black: 4%-6%.
- Genotype 1a: 67%-70%.
- IL28B non-CC: 80%-83%.
- Treatment naïve: 41%-43%.
- Prior PR response:
  - Relapse: 13%-14%.
  - Partial response: 8%-9%.
  - Null response: 36%.
- Child-Pugh score >5: 18%-19%.

Fried MW, et al. *Hepatology.* 2014;60(suppl 1):238A. Abstract 81.
Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982.

TURQUOISE-II: SVR12 Rates With ABT-450/r/Ombitasvir + Dasabuvir + RBV in HCV Genotype 1, Compensated Cirrhotics



PR: pegIFN + RBV.

Fried MW, et al. *Hepatology.* 2014;60(suppl 1):238A. Abstract 81.

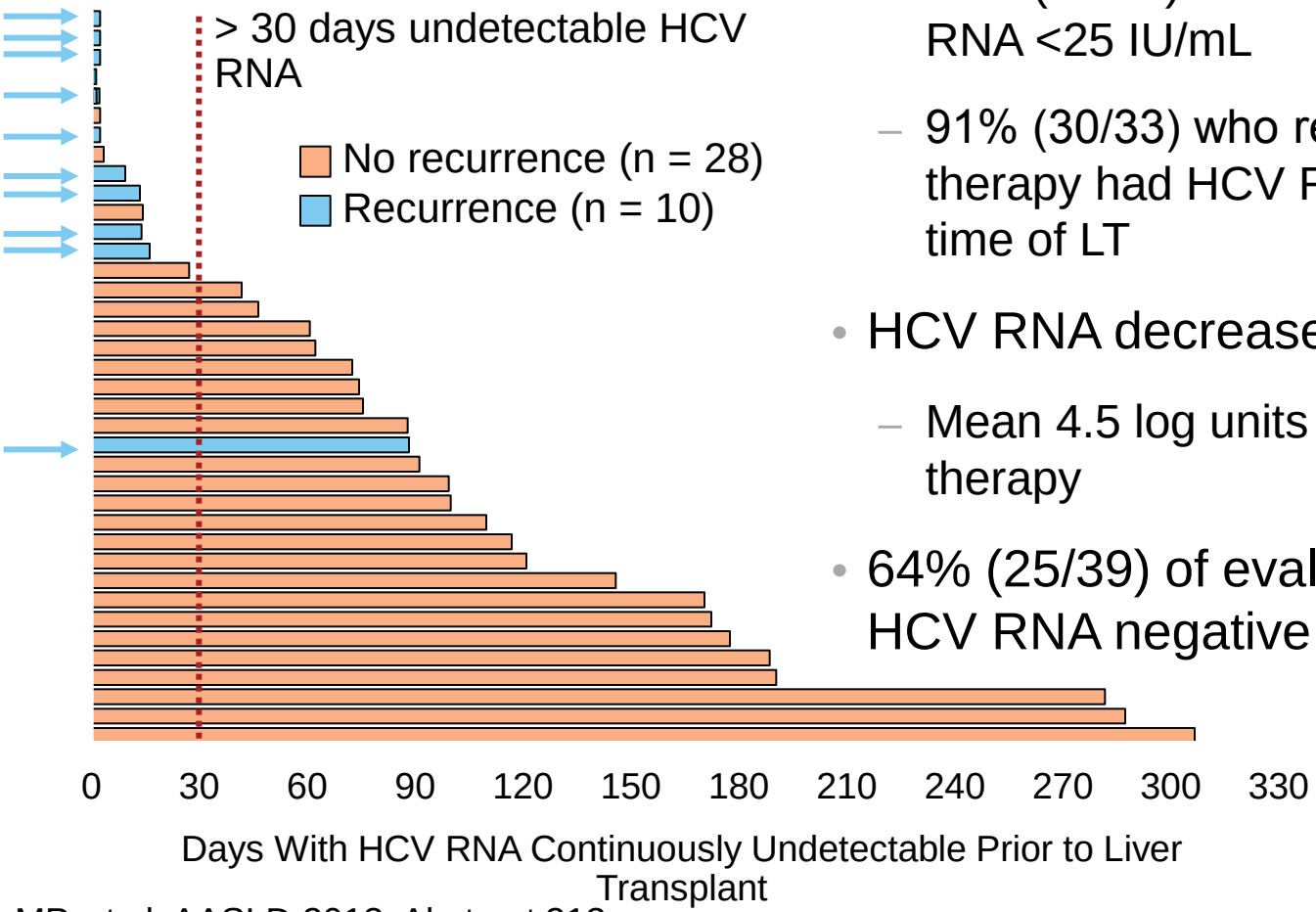
Pre-LT Antiviral Therapy with Sofosbuvir + Ribavirin

- **Single-arm, open-label phase II study from 16 liver transplantation sites**
  - **HCC with MELD upgrades**
- **Excluded:**
  - **LDLT**
  - **Decompensated cirrhosis (CTP >8)**
  - **Renal impairment (CrCl <60 cc/min)**
- **Pre-LT therapy for 48 weeks or until LT:**
  - **Sofosbuvir 400 mg/day**
  - **Ribavirin 1000-1200 mg/day**
- **Post-LT immunosuppression:**
  - **Tacrolimus (≥12 weeks)**
  - **Prednisone**
  - **MMF**

Characteristic	SOF + RBV (N = 61)
Median age, yrs (range)	59 (46-73)
HCV genotype, %	
▪ 1a	39
▪ 1b	34
▪ 2	13
▪ 3a	12
▪ 4	2
Non-CC *IL28B* genotype, %	78
CTP score, %	
▪ 5-7	96
▪ 8	5
Previous HCV treatment, %	75

Curry MP, et al. AASLD 2013. Abstract 213.

Pre-LT Sofosbuvir + Ribavirin to Prevent Post-LT HCV Recurrence

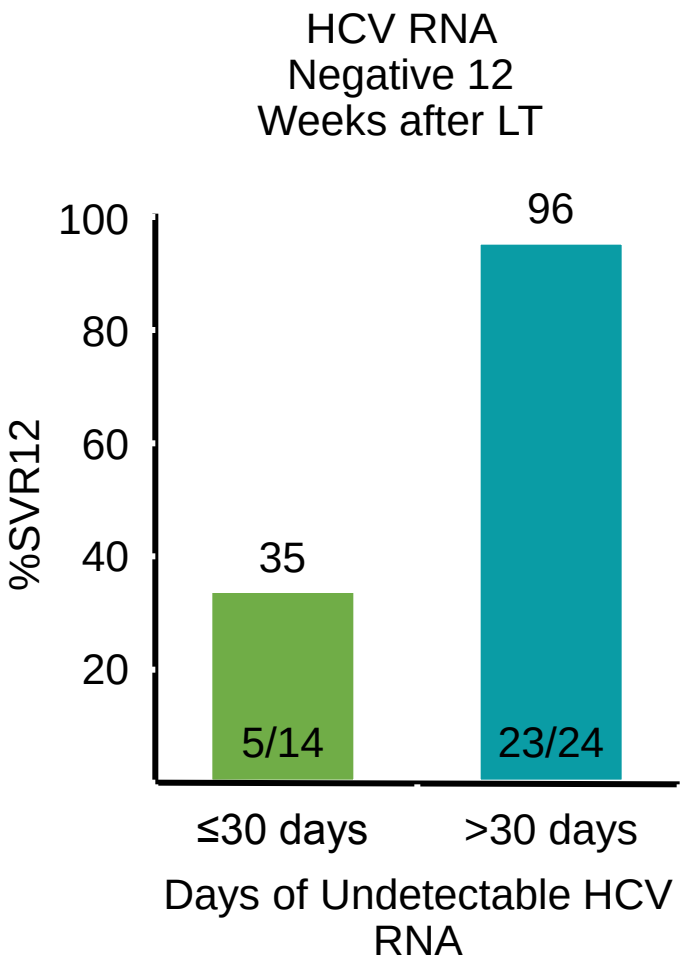


- 61 pts enrolled in study;
  - 67% (41/61) received LT with HCV RNA <25 IU/mL
  - 91% (30/33) who received ≥12 wks therapy had HCV RNA <25 IU/mL at time of LT
- HCV RNA decreased rapidly
  - Mean 4.5 log units after 2 weeks of therapy
- 64% (25/39) of evaluable pts had HCV RNA negative 12 wks post-LT

Curry MP, et al. AASLD 2013. Abstract 213.

Duration of Undetectable HCV RNA Before Transplant Predicted Lack of Recurrence

- Continuous days of undetectable HCV RNA pre-LT only factor predicting HCV recurrence in multivariate analysis
- Median days TND ($p<0.001$)
  - No recurrence 95 days
  - Recurrence 5.5 days

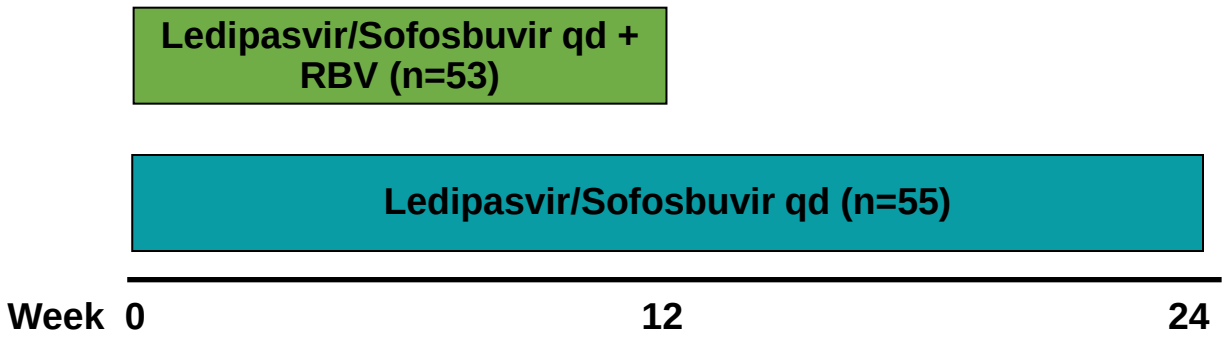


Curry MP, et al. AASLD 2013. Abstract 213.

Ledipasvir/Sofosbuvir + RBV in HCV Genotype 1 or 4 with Decompensated Cirrhosis

Phase 2

Open-label
Genotype 1 or 4
CPT class B or C
Treatment-naïve or experienced
No organ transplantation or HCC
Total bilirubin ≤10 mg/dL
Hemoglobin ≥10 g/dL
CrCl: ≥40 mL/min
Platelets: >30K x 10^3/μL



CPT: Child-Pugh-Turcotte.
PR: pegIFN + RBV.
Ledipasvir/sofosbuvir 90/400 mg qd + weight-based RBV(1000-1200 mg).
Primary endpoint: SVR12.
Baseline demographics:
- Male: 61%-73%.
- Mean age: 58-60 years
- White: 90%-97%
- Genotype 1a: 63%-76%.
- HCV RNA (log_{10} IU/mL): 5.6-5.9.
- IL28B non-CC: 73%-87%.
- BMI >30 $kg.m^2$: 33%-57%.

Flamm SL, et al. *Hepatology.* 2014;60(suppl 1):320A-321A. Abstract 239.

Ledipasvir/Sofosbuvir + RBV in HCV Genotype 1 or 4: Baseline Liver Status

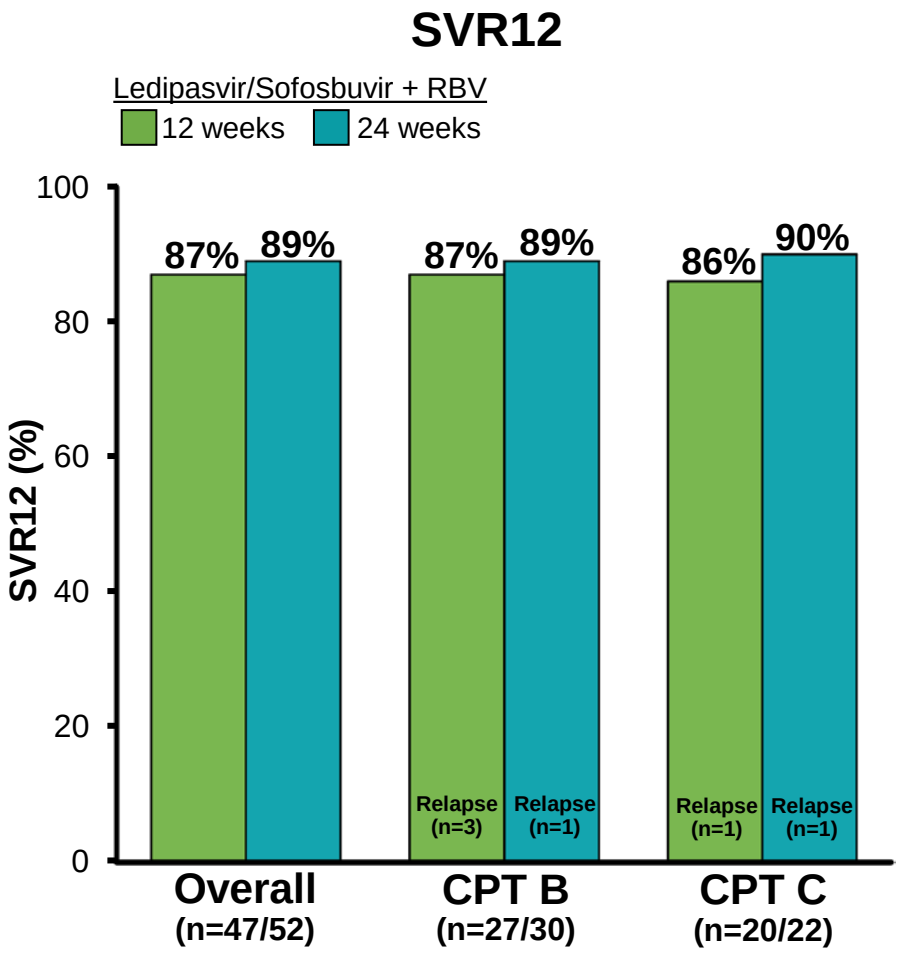
	CPT B		CPT C	
	12 Weeks (n=30)	**24 Weeks (n=29)**	**12 Weeks (n=23)**	**24 Weeks (n=26)**
MELD score (%)				
<10	20	28	0	0
10-15	70	55	70	50
16-20	10	17	30	46
21-25	0	0	0	4
Ascites (%)	57	59	96	96
Encephalopathy (%)	67	55	91	88
Median bilirubin (mg/dL)	2.0	1.4	2.9	3.8
Median albumin (g/dL)	2.9	3.0	2.6	2.6
Median INR	1.3	1.3	1.4	1.4
Median platelets (x 10^3/µL)	88	73	81	71
Median hemoglobin (g/dL)	13.1	13	12.3	12.6
Median creatinine clearance (mL/min)	98	81	77	78

CPT: Child-Pugh-Turcotte.

Flamm SL, et al. *Hepatology.* 2014;60(suppl 1):320A-321A. Abstract 239.

Ledipasvir/Sofosbuvir + RBV in HCV Genotype 1 or 4: Preliminary Results

- High SVR12 rates in HCV patients with advanced liver disease
- CPT B and C patients at post-treatment week 4
  - Significant improvements in median total bilirubin and albumin
  - Change in CPT scores
    - Improved: 70%
    - Stable: 21%
    - Worsened: 9%
  - Change in MELD score (CPT B/C)
    - Improved: 64%/70%
    - Stable: 19%/13%
    - Worsened: 17%/18%



Flamm SL, et al. *Hepatology.* 2014;60(suppl 1):320A-321A. Abstract 239.

Ledipasvir/Sofosbuvir + RBV in HCV Genotype 1 or 4: Preliminary Safety Summary

	CPT B		CPT C	
	12 Weeks (n=30)	**24 Weeks (n=29)**	**12 Weeks (n=23)**	**24 Weeks (n=26)**
Grade 3/4 adverse events (%)	7	28	26	42
Serious adverse events (%)	10	34	26	42
Treatment-related serious adverse event (%)	7	0	0	8
Treatment discontinuations due to adverse events (%)	0	3	0	8
Death (%)	3	7	9	4

CPT: Child-Pugh-Turcotte.
Treatment-related serious adverse events: anemia (n=2), hepatic encephalopathy (n=1), peritoneal hemorrhage (n=1).
Early discontinuations (n=1 for each): sepsis, hepatic encephalopathy, peritoneal hemorrhage.
Deaths: septic shock (n=2), multi-organ failure and shock (n=2), oliguric renal failure (n=1), cardiac arrest (n=1).

Flamm SL, et al. *Hepatology.* 2014;60(suppl 1):320A-321A. Abstract 239.

When/Who to Treat

- **Pre-emptive/prophylactic post-OLT is ideal, but…**
  - **No clear established regimen or duration**
  - **Higher levels of immunosuppression**
  - **Off-label**
  - **IMS and liver function is changing, DDI's will be more difficult and toxicity difficult to interpret (DILI, rejection, etc)**
  - **What is benefit vs waiting until stable?**

When/Who to Treat

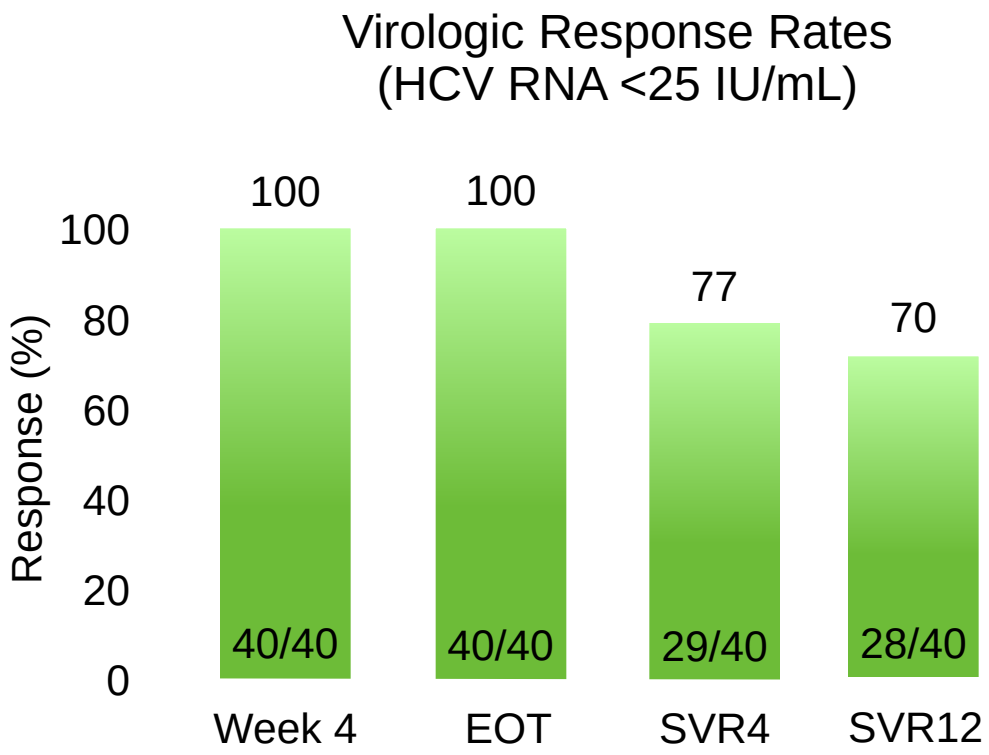
- Reactive post-OLT is current standard for most
  - Graft stabilized but VL higher
  - IMS lower and stable
  - Identifies those who can wait for better Rx or maybe may do not need Rx?
  - Histologic trigger may be milder as therapies improve--F2 any time? Any fibrosis in 1st year(s)?, ALT or grade on bx?
- As treatments improve earlier, universal Rx likely to be the rule

Sofosbuvir + RBV for Treatment of Post-LT HCV Recurrence

- Prospective, multicenter, single-arm, open-label pilot study
  - CTP ≤ 7 and MELD ≤ 17
  - 40% with compensated cirrhosis
- Treatment:
  - SOF 400 mg/day
  - RBV 400-1200 mg/day for ≤ 24 wks
    - RBV started at 400 mg/day and increased based on hemoglobin levels

Characteristic	SOF+RBV (N=40)
Median Age, yrs (range)	59 (49-75)
Male, %	78
White, %	85
Mean time from LT, yrs (range)	4.3 (1.02-10.6)
HCV genotype, %	
- 1a	55
- 1b	28
- 2	0
- 3	15
- 4	3
Non-CC IL28B genotype, %	67%
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.55 (4.49-7.59)
Previous HCV treatment, %	88
Fibrosis stage (F3-F4), %	63

Sofosbuvir + RBV for Treatment of Post-LT HCV Recurrence

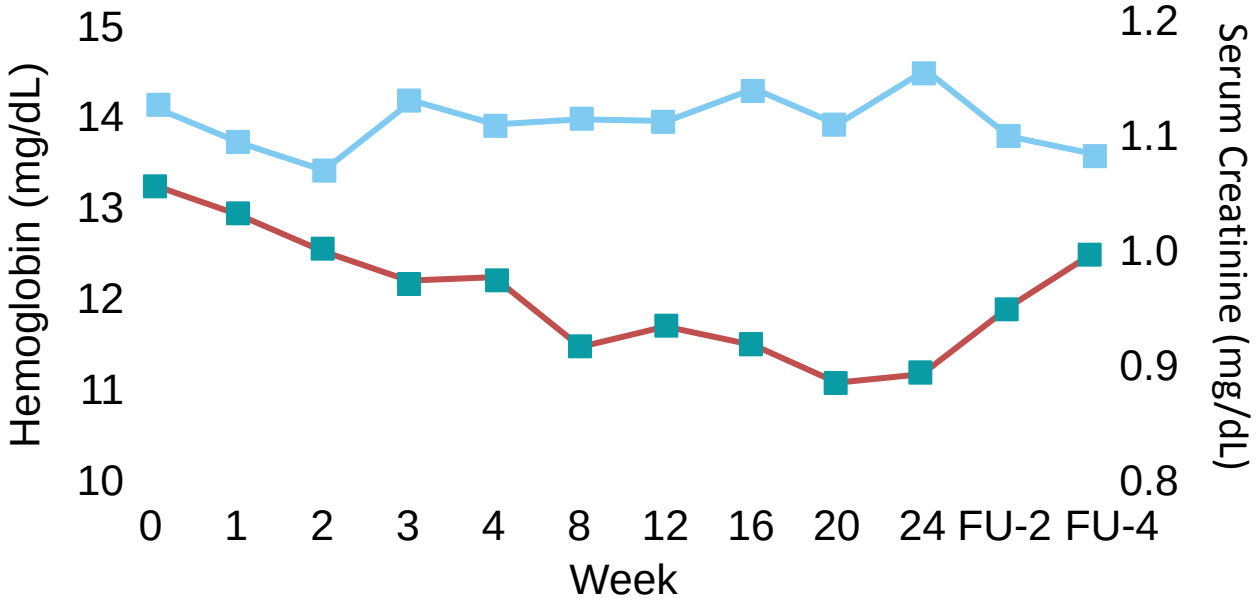


Baseline characteristics similar in patients with and without virologic relapse

Samuels D, et al. EASL 2014. Abstract P1232.

Sofosbuvir + RBV for Post-LT HCV Recurrence: Safety Outcomes

- No deaths, graft loss, or rejection
- No drug–drug interactions with immunosuppressive agents
- RBV dose reduction in 28%; 20% received epoetin and/or blood products



Median RBV dose, mg/day	400	400	600	600	800	800	600	800	800

Samuels D, et al. EASL 2014. Abstract P1232.
Charlton MR, et al. AASLD 2013. Abstract LB-2.

Real-World Use of Sofosbuvir-Based Regimens in Recurrent HCV Post-Liver Transplantation: HCV TARGET Study

- Ongoing longitudinal, observational study of DAA-based therapy in recurrent HCV post-liver transplant (n=245)
  - 38 academic and 15 community medical centers in the US, Germany, and Canada
  - HCV treatment is administered according local standard of care
    - Regimen selection made by health care provider
- Interim results for sequentially enrolled patients who started therapy with sofosbuvir-containing regimens
  - Genotype 1 (n=179): sofosbuvir + simeprevir + RBV (79.7%), sofosbuvir + PR (13.4%), sofosbuvir + RBV (7.3%)
  - Genotype 2 (n=20): sofosbuvir + RBV (100%)
  - Genotype 3 (n=19): sofosbuvir + RBV (94.7%), sofosbuvir + PR (5.3%):

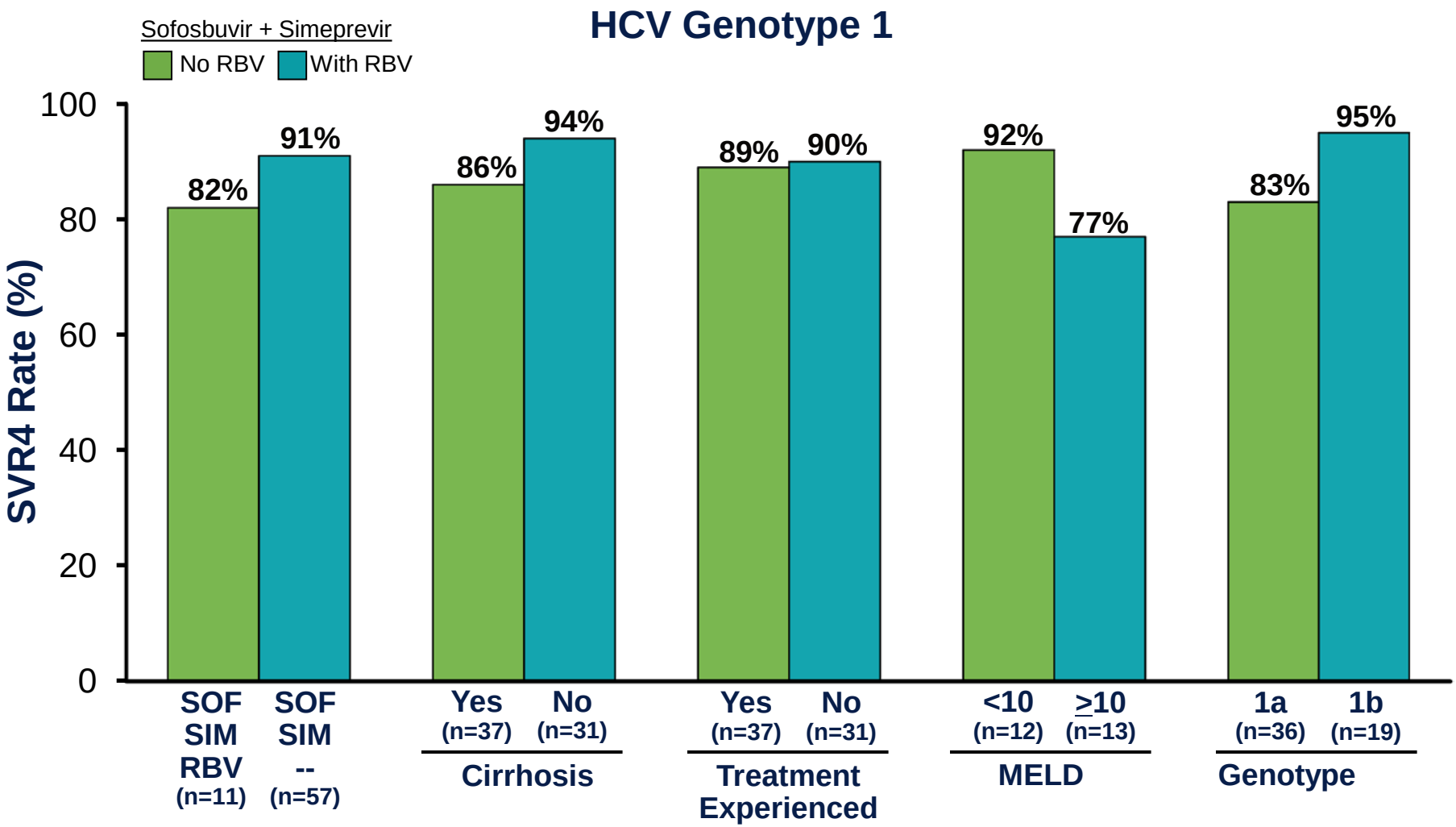
PR: pegIFN + RBV.

Baseline Characteristics

	Patients (n=227)
Male (%)	73.6
Mean age (years)	60.0
≥65 years (%)	19.8
Black (%)	8.4
Treatment experienced (%)	
Naïve	42.7
Experienced	57.3
PI failure	11.5
Cirrhosis (%)	56.4
MELD >10 (%)	31.3
Immunosuppression (%)	
TAC	76.7
CSA	12.3
Everolimus/sirolimus	15.9
MMF/MPA	42.3

Brown RS, et al. *Hepatology.* 2014;60(suppl 1). Abstract LB-4.

HCV TARGET Study (Interim Results): Crude SVR4 Rates With Sofosbuvir + Simeprevir ± RBV in Recurrent HCV Post-Liver Transplantation



Brown RS, et al. *Hepatology.* 2014;60(suppl 1). Abstract LB-4.

HCV TARGET Study (Interim Results): Treatment Outcomes With Sofosbuvir + Simeprevir ± RBV in Recurrent HCV Post-Liver Transplantation

- Additional SVR4 rates
  - Sofosbuvir + PR: 83% (10/12 genotype 1); 100% (1/1 genotype 3)
  - Sofosbuvir + RBV: 90% (9/10 genotype 2), 60% (3/5 genotype 3)
- Predictors of SVR4 (adjusted for cirrhosis status, previous treatment, prior decompensation)
  - For: baseline hemoglobin, age
  - Against: baseline total bilirubin
- Safety
  - ≥1 adverse event (82%, most deemed mild in severity)
  - Discontinuations due to adverse events (2.2%)
  - Serious adverse events (8.5%)
  - No episodes of acute cellular rejection
  - Renal failure (n=3; sofosbuvir + simeprevir [2], sofosbuvir + simeprevir + RBV [1])

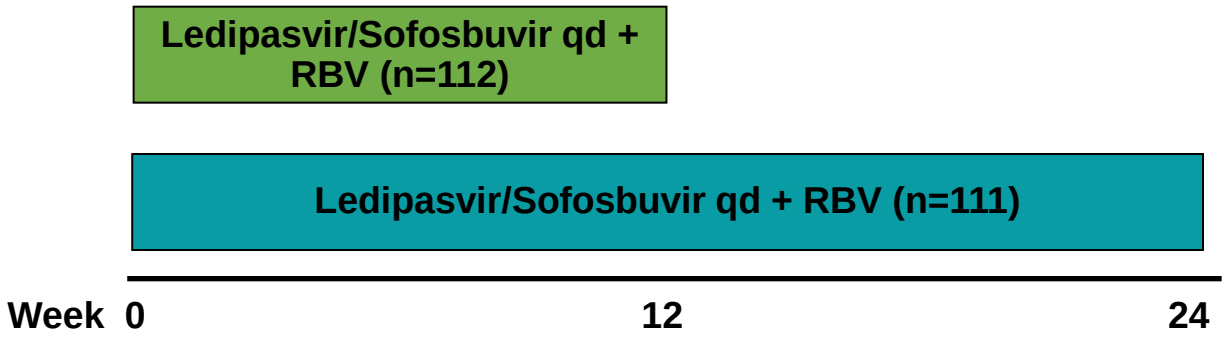
PR: pegIFN + RBV.

Brown RS, et al. *Hepatology.* 2014;60(suppl 1). Abstract LB-4.

Ledipasvir/Sofosbuvir + RBV for Post-Transplantation HCV Recurrence (Genotype 1 or 4)

Phase 2

Open-label
Genotype 1 or 4
CPT class A, B, or C
Treatment-naïve or experienced
No HCC
Total bilirubin ≤10 mg/dL
Hemoglobin ≥10 g/dL
CrCl: ≥40 mL/min
Platelets: >30K x 10^3/μL



CPT: Child-Pugh-Turcotte.
Ledipasvir/sofosbuvir 90/400 mg qd.
RBV (F0-F3 and CPT A cirrhosis: weight based; CBT B and C: continuous dose escalation 600-1200 mg).
Primary endpoint: SVR12.
Baseline demographics:
- Male: 80%-100%.
- Mean age: 59-61 years
- White: 80%-89%
- Genotype 1a: 67%-78%.
- HCV RNA (log_{10} IU/mL): 6.3-6.6.
- IL28B non-CC: 67%-85%.
- Median time from orthotopic liver transplantation: 2.9-8.1 years
- Prior HCV treatment: 78%-90%.

Reddy KR, et al. *Hepatology.* 2014;60(suppl 1):200A-201A. Abstract 8.

Ledipasvir/Sofosbuvir + RBV for Post-Transplantation HCV Recurrence (Genotype 1 or 4): Baseline Liver Status

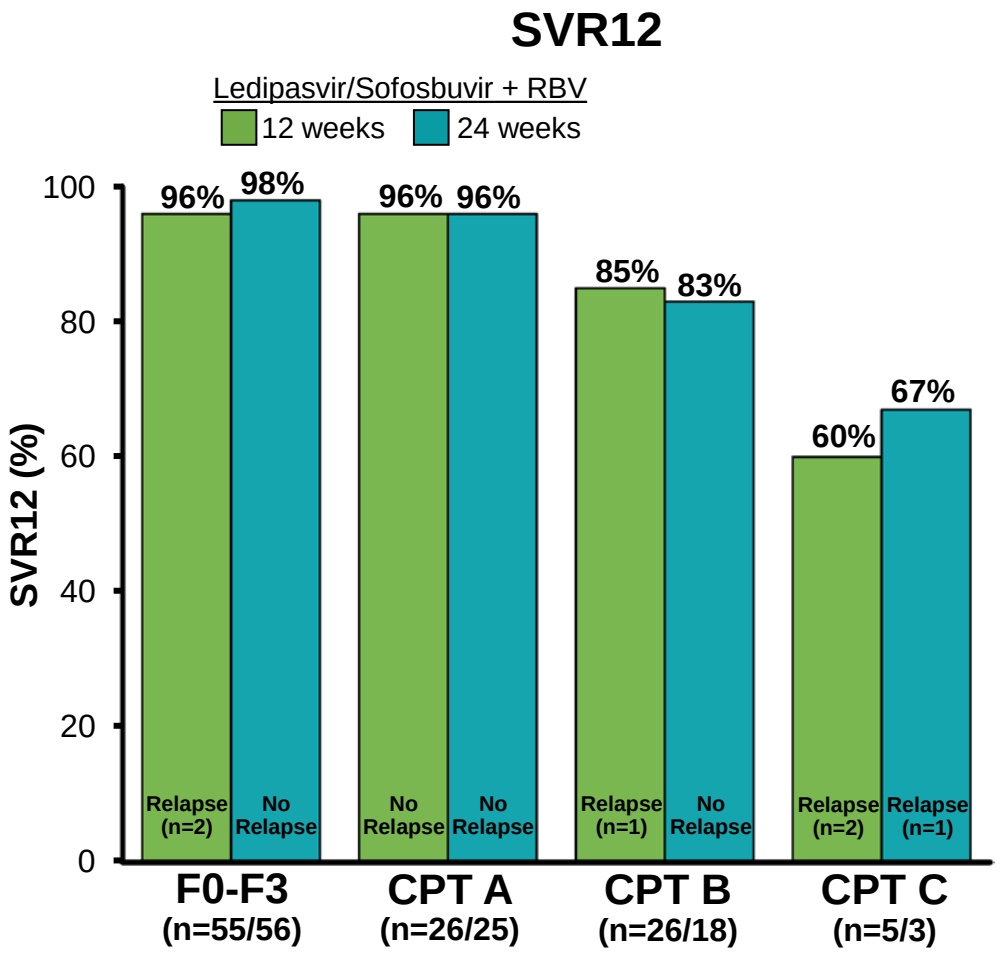
		CPT		
	F0-F3 (n=111)	**A (n=51)**	**B (n=52)**	**C (n=9)**
MELD score (%)				
<10	--	55	25	11
10-15	--	39	63	56
16-20	--	6	8	22
21-25	--	0	4	11
Ascites (%)	2	4	77	100
Encephalopathy (%)	1	6	44	78
Median bilirubin (mg/dL)	0.7	0.8	1.2	2.1
Median albumin (g/dL)	3.8	3.7	3.2	2.4
Median INR	1.0	1.1	1.2	1.3
Median platelets (x 10^3/µL)	146	108	93	79
Median hemoglobin (g/dL)	14.0	13.6	12.9	11.5
Median creatinine clearance (mL/min)	65	62	59	67

CPT: Child-Pugh-Turcotte.

Reddy KR, et al. *Hepatology.* 2014;60(suppl 1):200A-201A. Abstract 8.

Preliminary Outcomes: Ledipasvir/Sofosbuvir + RBV for Recurrent HCV Post-Transplantation (HCV Genotype 1 or 4)

- High SVR12 rates in HCV patients with advanced liver disease
- CPT A and B patients at post-treatment week 4
  - Significant improvements in median total bilirubin and albumin
  - Change in MELD score (CPT A/B)
    - Improved: 42%/68%
    - Stable: 27%/12%
    - Worsened: 32%/20%



CPT: Child-Pugh-Turcotte.

Reddy KR, et al. *Hepatology.* 2014;60(suppl 1):200A-201A. Abstract 8.

Ledipasvir/Sofosbuvir + RBV for Post-Transplantation HCV Recurrence (Genotype 1 or 4): Preliminary Safety Summary

	F0-F3		CPT A		CPT B		CPT C	
	12 Weeks (n=30)	24 Weeks (n=29)	12 Weeks (n=30)	24 Weeks (n=29)	12 Weeks (n=30)	24 Weeks (n=29)	12 Weeks (n=23)	24 Weeks (n=26)
Grade 3/4 adverse events (%)	27	25	15	28	23	35	20	25
Serious adverse events (%)	11	21	12	16	19	42	20	100
Treatment-related serious adverse event (%)	4	2	8	8	0	4	0	0
Treatment discontinuations due to adverse events (%)	0	4	4	0	0	12	0	0
Death (%)	0	0	4	0	4	8	0	0

CPT: Child-Pugh-Turcotte.
Adverse events leading to discontinuation (n-1 for each): shortness of breath, hemoperitoneum, thoracis aorta aneurysm, seizure, elevated ALT/AST, dyspnea.
Treatment-related serious adverse events: anemia (n=4), hemolytic anemia (n=2), portal vein thrombosis (n=1), sicks sinus syndrome (n=1), sinus arrhythmia (n=1).
Treatment emergent deaths (n=1 for each): progressive multifocal leukoencephalitis, thoracic aorta aneurysm, internal bleeding, complications of cirrhosis.

Reddy KR, et al. *Hepatology.* 2014;60(suppl 1):200A-201A. Abstract 8.

CORAL-I Study: ABT-450/r/Ombitasvir + Dasabuvir + RBV for HCV Genotype 1 After Liver Transplantation

- Ongoing phase 2 study
  - HCV genotype 1 (n=34)
  - Liver transplantation due to HCV infection
    - PR permitted prior to transplantation
    - Treatment-naïve post transplantation
  - METAVIR ≤F2
- On stable immunosuppression
  - Tacrolimus (85%)
  - Cyclosporine (15%)
- Primary outcome: SVR12

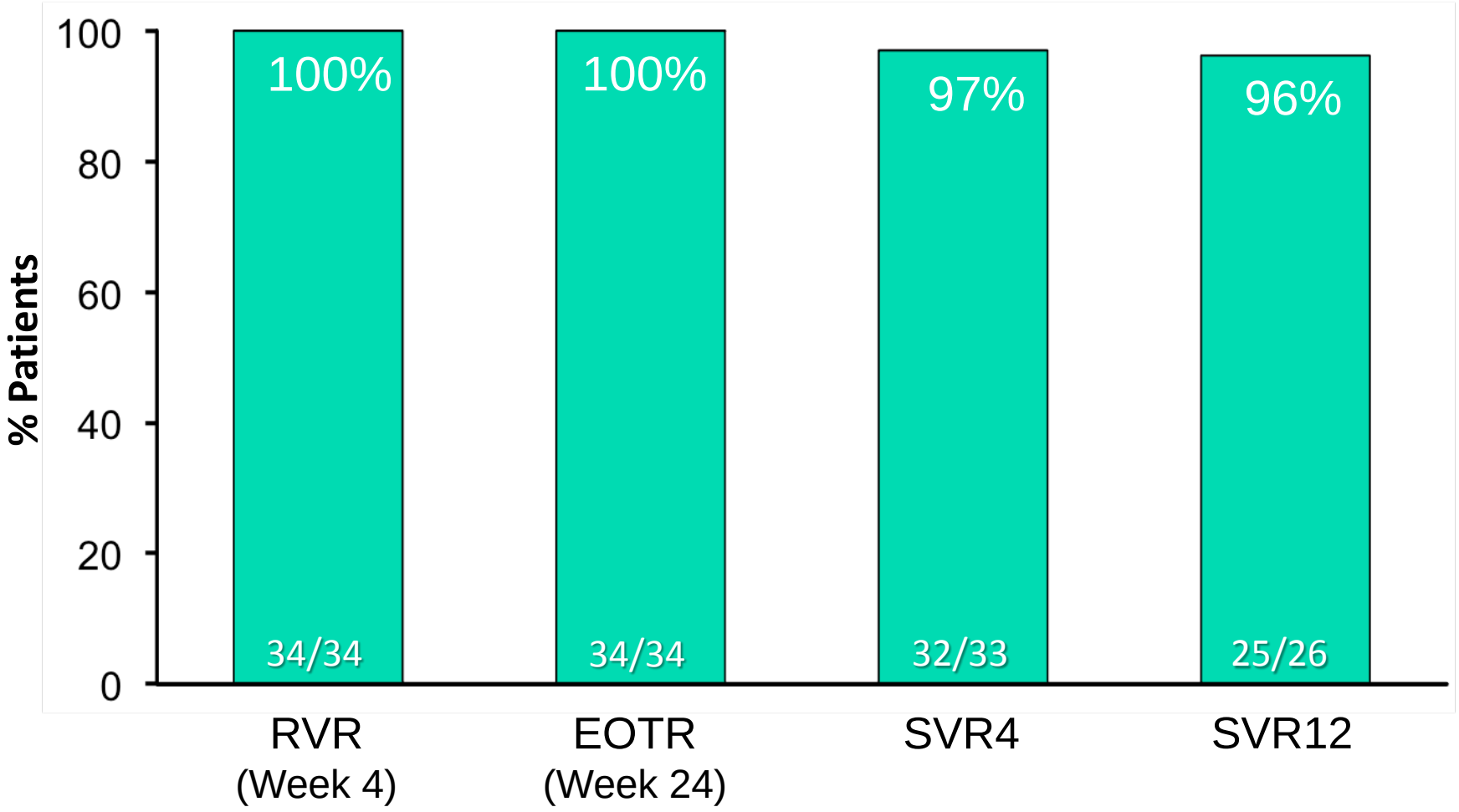
Baseline Characteristics

	Patients (n=34)
Male (%)	79
Mean age (years)	59.6
Fibrosis stage (%) F0/F1/F2	18/38/44
Median time since liver transplantation (months)	39.5
Genotype 1a (%)	85
IL28B non-CC (%)	77
HCV RNA (log_{10} IU/mL)	6.6
Creatinine clearance (mL/min)	90.5
ALT/AST (U/L)	78.9/63.9

ABT-450/ritonavir/ombitasvir 150/100/25 mg qd; dasabuvir 250 mg bid. RBV (1000-1200 mg).
Tacrolimus: 0.5 mg once weekly or 0.2 mg every 3 days.
Cyclosporine: 1/5 of daily dose given once daily prior to HCV therapy.

Mantry PS, et al. *Hepatology.* 2014;60(suppl 1):298A-299A. Abstract 198.

ABT-450/r/Ombitasvir+Dasavuvir+RBV for Treatment of Recurrent HCV GT1



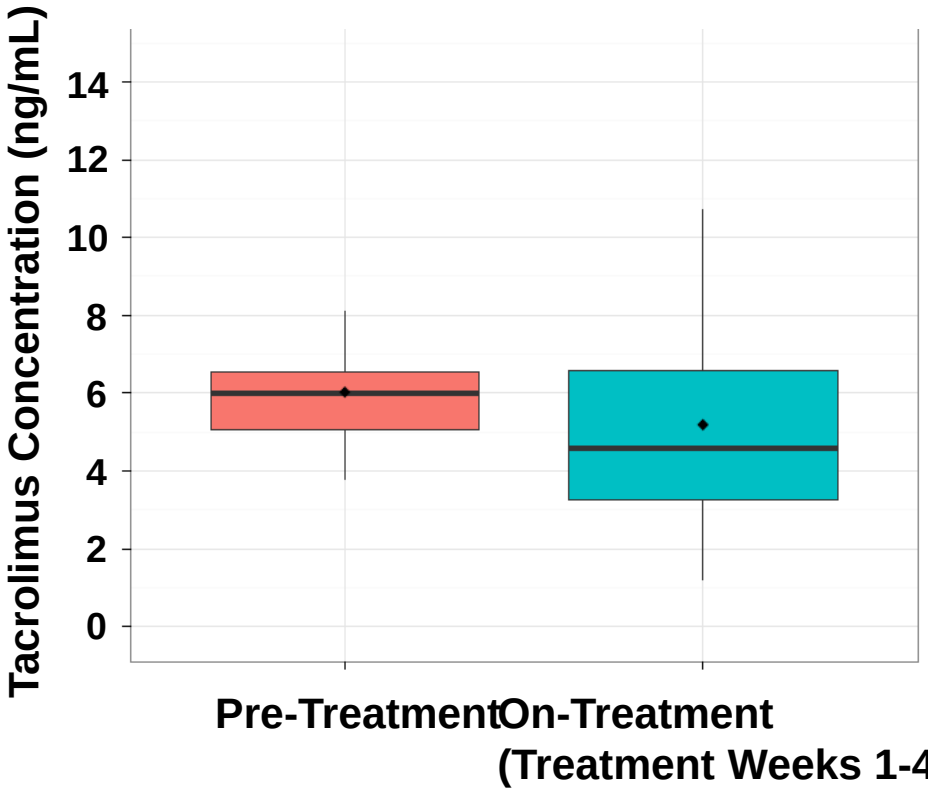
Kwo et al. EASL 2014. Abstract O114.

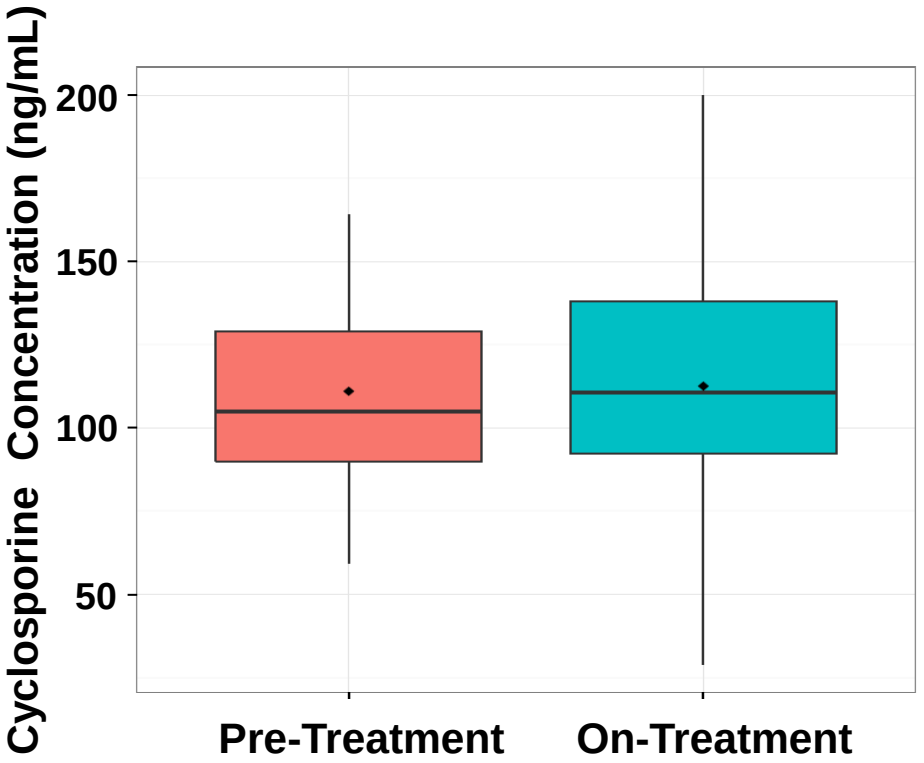
CORAL-I Study: Treatment Outcomes

- SVR12 and SVR24: 97%
  - No virologic breakthroughs
  - Relapse (n=1)
    - Emergent RAVs at time of relapse: R155K, M28T+Q30R, G554S
- No deaths, graft losses, or episodes of acute or chronic rejection
- Discontinuations due to adverse events (n=1)
- Serious adverse events (n=2)
  - Hypotension and tachycardia associated with tamsulosin
  - Moderate peripheral edema and pain in extremities in a diabetic patient
- All patients who required RBV dose reduction achieved SVR12

Mantry PS, et al. *Hepatology.* 2014;60(suppl 1):298A-299A. Abstract 198.

ABT-450/r/Ombitasvir+Dasavuvir+RBV for Treatment of Recurrent HCV GT1





- TAC dose 0.5-1.0 mg at 1-2 week intervals for most
- 4 patients had TAC >15 ng/mL, all due to dosing errors

- CsA levels maintained within desired range in all 5 patients
- On treatment CsA dose was 1/5 of pre-treatment dose in these patients

Kwo, P et al. EASL 2014. Abstract O114.

Hepatitis C and Liver Transplantation

- Clearance of HCV post transplant is achievable with either a pre- or post-transplant approach
- DAA's offer high rates of viral clearance
- Major issues will safety and efficacy in advanced liver disease pre-OLT and DDI post-OLT
- The near-term future offers
  - Early clearance post-OLT with IFN-free, ? Riba free therapy for decompensated disease
  - Pretransplant clearance for LDLT and HCC as well as low MELD waiting list candidates
- Better treatment strategies are needed for CPT C patrients particularly if it can stabilize/improve disease