Hepatitis Web Study

Treatment of Hepatitis C following Liver Transplantation

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Hepatitis web study

Disclosures

- **Research Support**
  - AbbVie, BMS, Boehringer-Ingelheim, Genfit, Gilead, Idenix, Ikaria, Intercept, Janssen, Merck, NGM, Novartis, Salix, Sundise, Vital Therapies
- **Speaker's Honorarium**
  - AbbVie, Gilead, Salix
- **Consultant**
  - AbbVie, BMS, Gilead, Janssen

Post Transplant Hepatitis C Recurrence

- HCV cirrhosis is most common indication (~40% of all recipients) for liver transplantation (LT) in the US
- Compared to other etiologies, survival rates are inferior[1]
  - HCV recurrence in the allograft is immediate and universal
  - Associated with accelerated progression to cirrhosis (25-40% within 5 years), graft loss and death[2]
- With treatment, achievement of sustained virologic response (SVR) is associated with improved graft and patient survival
- Recent evolution of HCV treatment has created new approaches to managing post transplant HCV recurrence

1) Gane EJ, et al. Long-term outcome of hepatitis C infection after liver transplantation. N Engl J Med 1996;334:815-820.
2) Gane EJ. The natural history of recurrent hepatitis C and what influences this. Liver Transpl 2008;14(suppl 2):S36-S44.

Post LT Recurrence of HCV

- Variable severity of HCV recurrence post LT
  - Modest increase in AST/ALT with mild fibrosis
  - Progressive fibrosis to cirrhosis over 3-5 years (25%)
  - Rapidly progressive, cholestatic hepatitis evolving to graft loss in <1 year (2%- 5%)
- Predictors of more severe post LT HCV recurrence [1-3]
  - Advanced donor age
  - High HCV RNA titer at time of LT
  - Multiple episodes of rejection
    - Use of anti-lymphocyte Rx and/or
    - High doses of steroid to treat rejection post LT
  - HIV/HCV co-infection

1. Charlton M, et al. Hepatology 1998;28:823-830.
2. Lake JR, et al. Am J Transplant 2005;5:549-557.
3. Sheiner PA, et al. Hepatology 1995;21:30-34.

Interferon-Free Regimens to Treat Recurrent HCV Infection after Liver Transplantation

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Currently Available Interferon Free HCV Treatments^

- Sofosbuvir *with ribavirin* {pan-genotypic}
- Sofosbuvir plus simeprevir (*without and with ribavirin*) {genotype 1}
- Sofosbuvir plus ledipasvir fixed dose combination (*without and with ribavirin*): Harvoni® {genotypes 1,4,6}
- Paritaprevir/ritonavir, ombitasvir and dasabuvir (*without and with ribavirin*) VieKira Pak® {genotypes 1,4}
- Sofosbuvir plus daclatasvir* {pan-genotypic}

^Per AASLD/IDSA Guidance document (www.hcvguidelines.org)

*** Anticipate 08/2015 FDA approval of daclatasvir**

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Sofosbuvir + Ribavirin

Sofosbuvir + Ribavirin in Recurrent HCV Post Liver Transplant

Sofosbuvir + Ribavirin Post Liver Transplant: Features

- **Design**: Open-label, prospective, single-arm, phase 2 trial of 24-week course of sofosbuvir + ribavirin in patients with HCV recurrence post-liver transplantation
- **Setting**: Multicenter, International Study
- **Entry Criteria**
  - N = 40 patients with chronic hepatitis C
  - Recurrent HCV infection post liver transplantation
  - Any genotype included
  - CTP score ≤ 7 and MELD score ≤ 17
  - Excluded if decompensated liver disease
- **Regimen (24 weeks**)
  - Sofosbuvir: 400 mg once daily
  - Ribavirin: started at 400 mg/day and increased up to 1200 mg/day
- **Primary End-Point**: SVR12

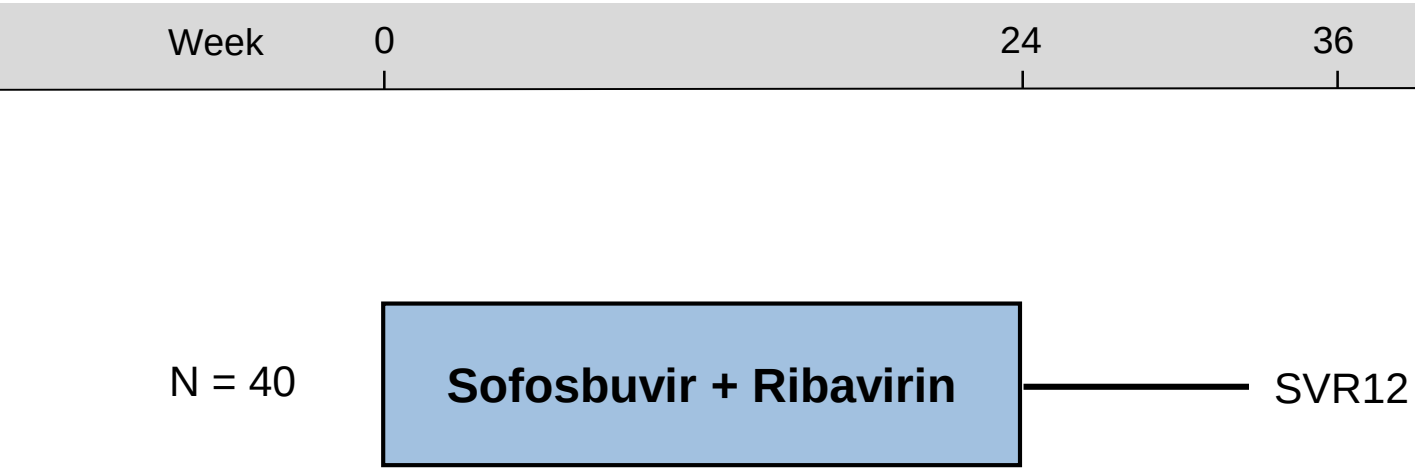
Source: Charlton M, et al. Gastroenterology. 2015;148:108-17.

Sofosbuvir + Ribavirin in Recurrent HCV Post Liver Transplant

Baseline Characteristic (n = 40)	Sofosbuvir + Ribavirin x 12 weeks
Median Age, years (range)	59 (49 to 75)
Male sex, %	78
White, %	85
Median Body Mass Index (BMI) <30 kg/m^2 (%)	75
HCV genotype 1 (%)	83
IL28B genotype CC, (%)	33
Median baseline HCV RNA, log_{10} IU/ml (range)	6.74 (4.49-7.59)
METAVIR-equivalent fibrosis (F3 or F4), %	F1-F2= 35%; F3=23%; F4=40%
Previous HCV treatment, %	88
Median time since liver transplantation, years (range)	4.3 (1.0-10.6)

Source: Charlton M, et al. Gastroenterology. 2015;148:108-17.

Sofosbuvir + Ribavirin in Recurrent HCV Post Liver Transplant
Design



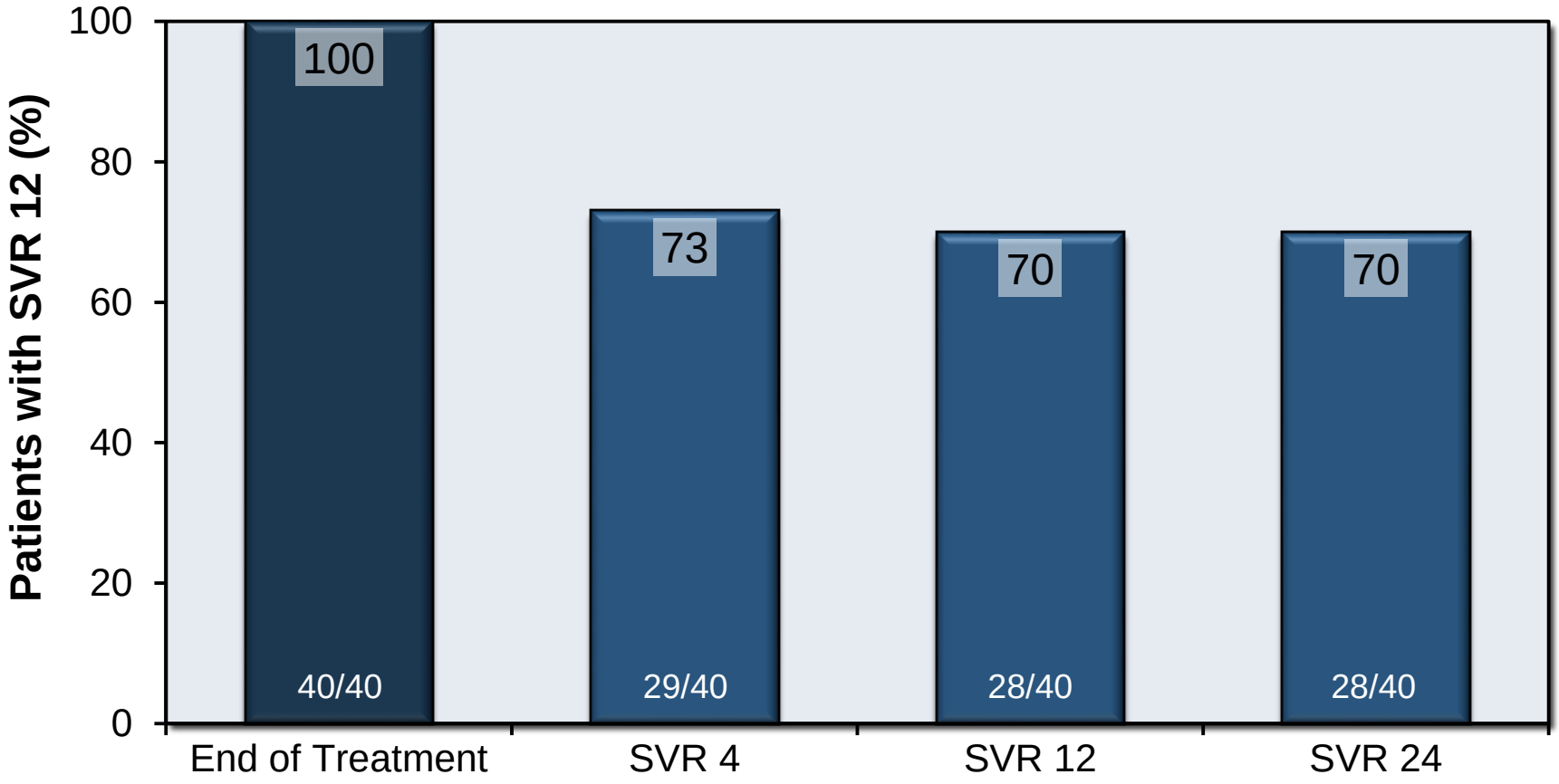
Drug Dosing

Sofosbuvir: 400 mg once daily

Ribavirin: administered in two divided daily doses (started at 400 mg/day and increased up to 1200 mg/day based on hemoglobin, creatinine clearance, and weight)

Source: Charlton M, et al. Gastroenterology. 2015;148:108-17.

Sofosbuvir + Ribavirin in Recurrent HCV Post Liver Transplant Results



Source: Charlton M, et al. Gastroenterology. 2015;148:108-17.

Sofosbuvir + Ribavirin in Recurrent HCV Post Liver Transplant
Adverse Effects

Event	**Sofosbuvir + Ribavirin** (n=40)
Any adverse event (%)	39 (98%)
Any serious adverse event	6 (15%)
Adverse event leading to discontinuation	2 (5%)
Adverse event occurring in >10% of patients	
Fatigue	12 (30%)
Diarrhea	11 (28%)
Headache	10 (25%)
Arthralgia	9 (23%)
Nausea	8 (20%)
Anemia	8 (20%)
Cough	7 (18%)
Insomnia	5 (13%)
Anxiety	5 (13%)

Source: Charlton M, et al. Gastroenterology. 2015;148:108-17.

Ledipasvir + Sofosbuvir + Ribavirin
SOLAR-I

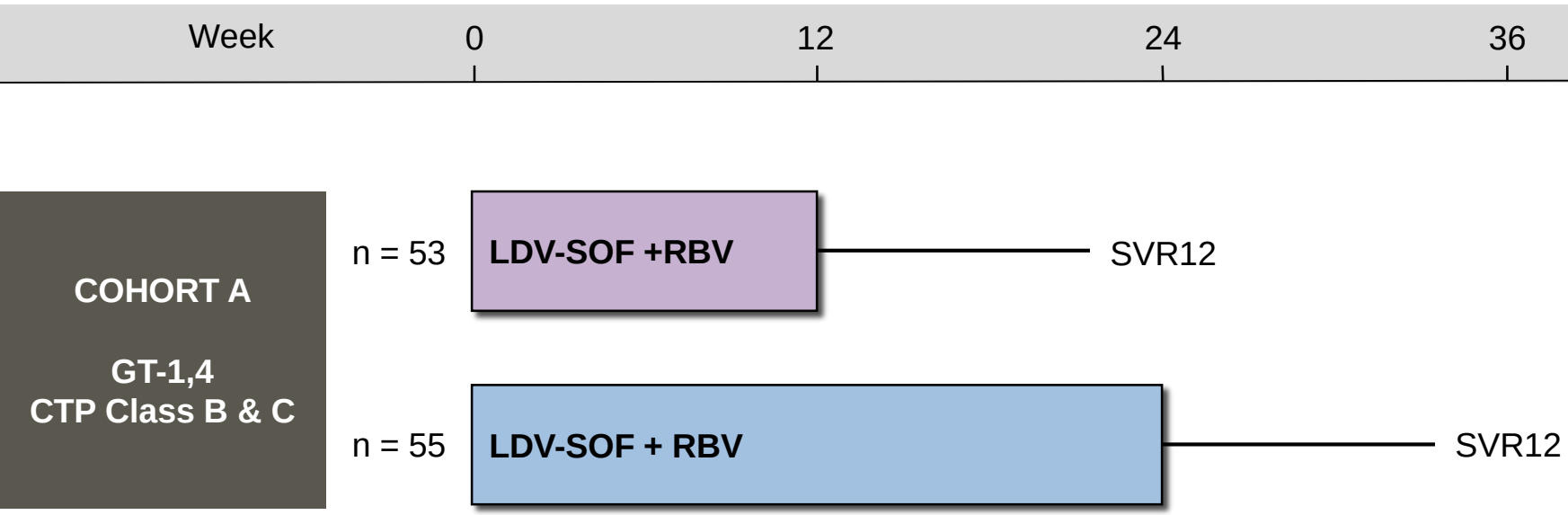
Ledipasvir-Sofosbuvir + Ribavirin in Advanced Liver Disease
SOLAR-1 (Cohorts A and B): Features

SOLAR-1 (Cohorts A and B): Design

- **Design**: Phase 2, open label, randomized prospective, trial, using fixed-dose combination of ledipasvir-sofosbuvir plus ribavirin for 12 or 24 weeks in treatment-naïve and treatment-experienced patients with HCV GT 1 or 4.
- **Cohorts**
  Cohort A = cirrhosis and moderate to severe hepatic impairment who had not undergone liver transplantation
  Cohort B = post liver transplantation
- **Setting**: multicenter study in United States
- **Entry Criteria**
  - Adults with Chronic HCV Genotype 1 or 4
  - Treatment-naïve or treatment experienced
  - Total bilirubin ≤ 10 mg/dL; Creatinine clearance ≥ 40 mL/min
  - Hemoglobin ≥ 10 g/dL; Platelet count > 30,000/mm^3
  - Exclusion: hepatitis B or HIV coinfection or prior receipt of NS5a inhibitor
- **Primary End-Point**: SVR12

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort A = Pre-transplantation): Study Design



Abbreviations: LDV= ledipasvir; SOF = sofosbuvir; RBV = ribavirin

Drug Dosing
Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily
Ribavirin: started at 600 mg/day and then escalated as tolerated up to maximum of 1200 mg/day

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort A = Pre-transplantation): Baseline Characteristics

Cohort A Characteristic	CTP B		CTP C	
	12-Weeks n=30	**24-Weeks** n=29	**12-Weeks** n=23	**24-Weeks** n=26
Median age, years	60	58	58	59
Male, n (%)	22 (73)	18 (62)	14 (61)	18 (69)
White, n (%)	29 (97)	26 (90)	21 (91)	24 (92)
HCV RNA, $\log_{10}$ IU/mL	5.9	5.8	5.6	5.8
IL28B genotype CC, n (%)	4 (13)	5 (17)	6 (26)	7 (27)
HCV Genotype				
1a, n (%)	19 (63)	22 (76)	15 (65)	18 (69)
1b, n (%)	10 (33)	7 (24)	6 (26)	8 (31)
4, n (%)	1 (3)	0	2 (9)	0
Prior Treatment	22 (73)	19 (66)	11 (48)	18 (69)

Abbreviations: CTP=Child-Turcotte-Pugh

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort A = Pre-transplantation): Baseline Liver Status

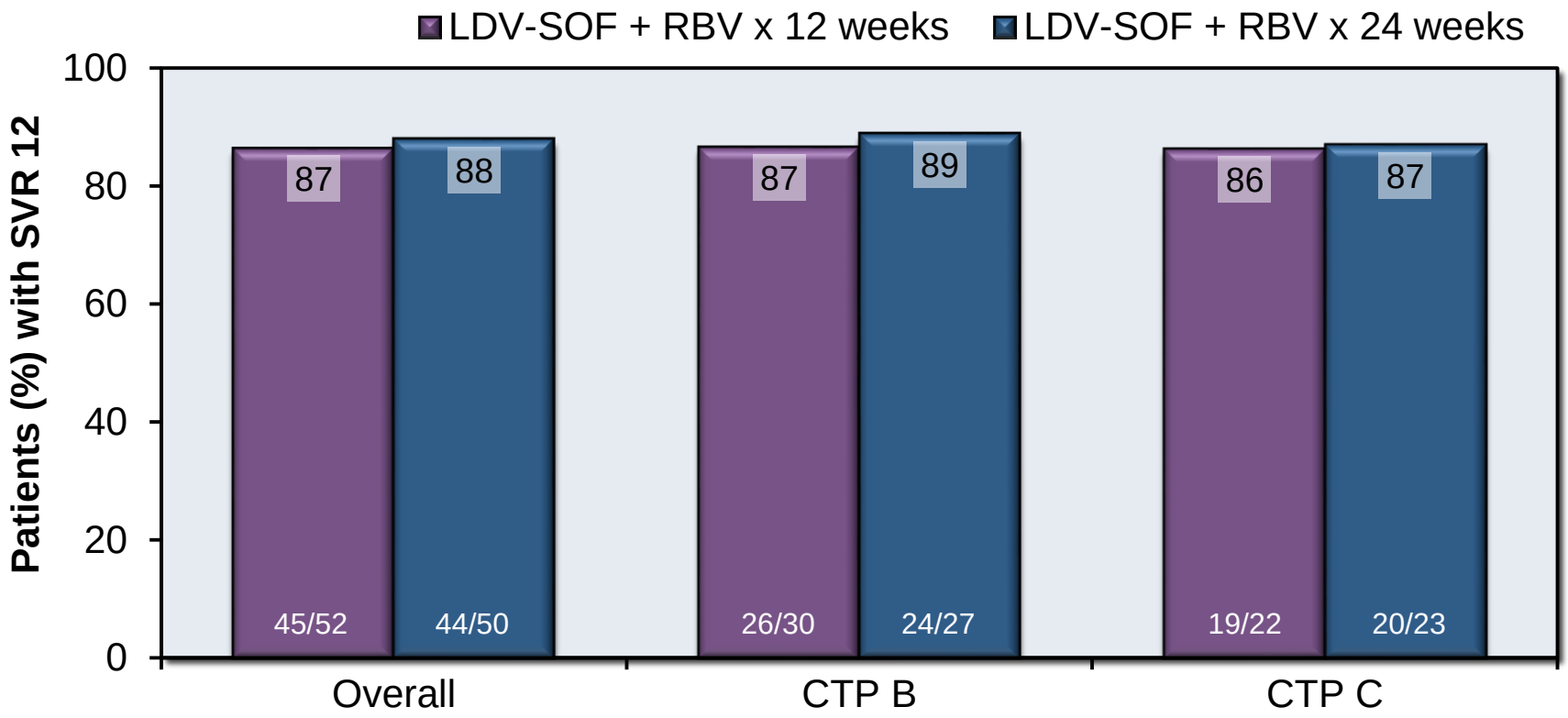
Cohort A Characteristic	CTP B		CTP C	
	12-Weeks n=30	24-Weeks n=29	12-Weeks n=23	24-Weeks n=26
Child-Turcotte-Pugh				
Class A (5-6)	0	1 (3)	0	0
Class B (7-9)	27 (90)	27 (93)	7 (30)	4 (15)
Class C (10-12)	3 (10)	1 (3)	16 (70)	22 (85)
MELD Score, n (%)				
<10	6 (20)	8 (28)	0	0
10-15	21 (70)	16 (55)	16 (70)	13 (50)
16-20	3 (10)	5 (17)	7 (30)	12 (46)
21-25	0	0	0	1 (4)
Median eGFR, mL/min	98	81	77	78
Median platelets, x 10^3 µL	88	73	81	71

Abbreviations: CTP=Child-Turcotte-Pugh

Source: Charlton M, al. Gastroenterology. 2015; [Epub ahead of print]

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4 SOLAR-1 (Cohort A= Pre-transplantation): Results

SOLAR-1 Cohort A (Pre-Transplantation): SVR12 Results

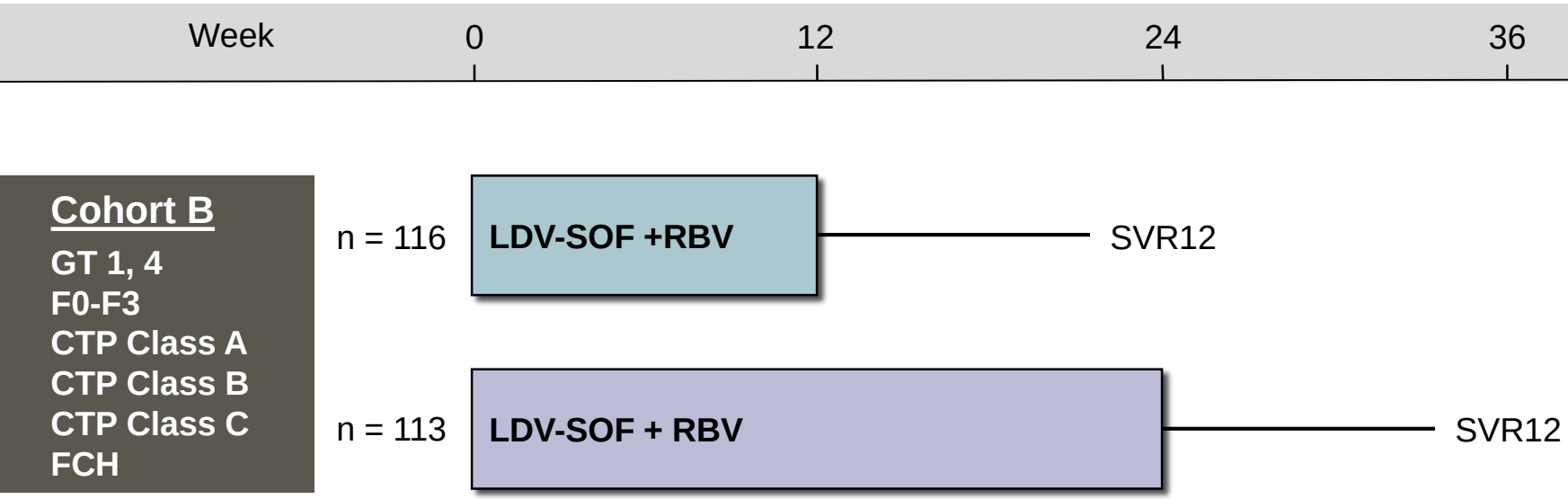


Abbreviations: CTP=Child-Turcotte-Pugh

6 subjects excluded because received transplant while on study: (2 CTP B/24 week; 1 CTP 2/12 week; 3 CTP C/24 week

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort B = Post Transplant): Study Design



Abbreviations: CTP=Child-Turcotte-Pugh; FCH=fibrosing cholestatic hepatitis; LDV=ledipasvir; SOF=sofosbuvir; RBV=ribavirin

Drug Dosing

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ribavirin Dosing

- No cirrhosis; FCH: weight-based and divided bid (1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg)
- CTP B, C: started at 600 mg/day and escalated up to maximum of 1200 mg/day

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort B = Post-transplantation): Baseline Characteristics

Cohort B Characteristic	No Cirrhosis		CTP A		CTP B		CTP C		FCH	
	12w n=55	24w n=56	12w n=26	24w n=25	12w n=26	24w n=26	12w n=5	24w n=4	12w n=4	24w n=2
Median age, years	59	58	60	61	61	61	58	61	62	58
Male, n (%)	45 (82)	46 (82)	19 (73)	22 (88)	22 (85)	23 (88)	5 (100)	4 (100)	4 (100)	2 (100)
White, n (%)	50 (91)	49 (88)	21 (81)	20 (80)	21 (81)	24 (92)	4 (80)	4 (100)	4 (100)	2 (100)
HCV RNA, $\log_{10}$ IU/mL	6.5	6.4	6.2	6.7	6.3	6.2	6.4	6.3	6.5	7.1
IL28B GT CC, n (%)	11 (20)	10 (18)	7 (27)	1 (4)	3 (12)	5 (19)	12 (40)	1 (25)	0	0
HCV Genotype										
1a, n (%)	40 (73)	40 (71)	17 (65)	17 (68)	20 (77)	18 (69)	4 (80)	3 (75)	3 (75)	2 (100)
1b, n (%)	14 (25)	16 (29)	9 (35)	8 (32)	6 (23)	7 (27)	1 (20)	1 (25)	1 (25)	0
4, n (%)	1 (2)	0	0	0	0	1 (4)	0	0	2 (9)	0
Prior Treatment	39 (71)	48 (86)	22 (85)	24 (96)	22 (85)	22 (85)	4 (80)	4 (100)	4 (100)	1 (50)

Abbreviations: CTP=Child-Turcotte-Pugh

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort B = Post-transplantation): Baseline Characteristics

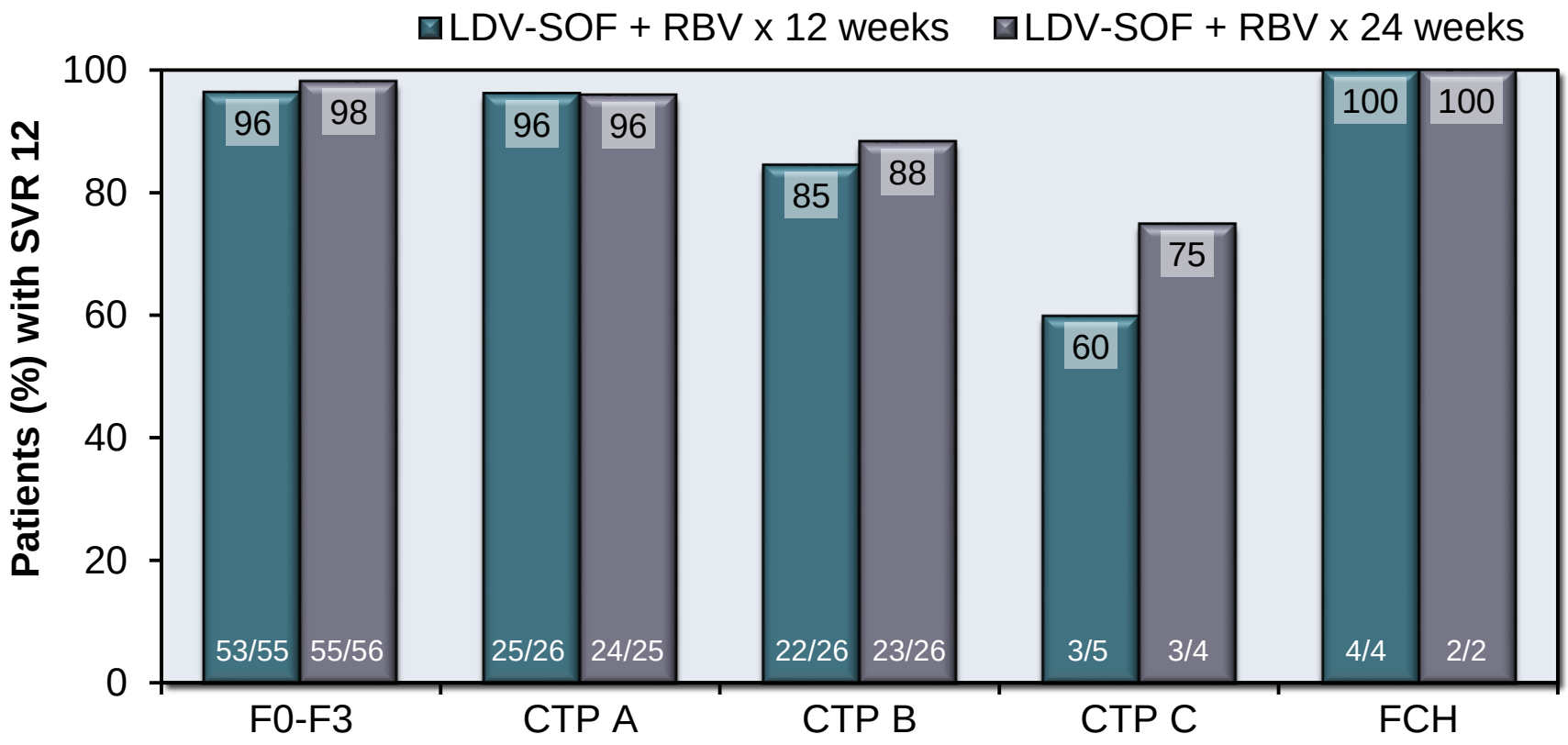
Cohort B Characteristic	F0-F3		CTP A		CTP B		CTP C		FCH	
	12w n=55	24w n=56	12w n=26	24w n=25	12w n=26	24w n=26	12w n=5	24w n=4	12w n=4	24w n=2
Median yrs post transplant	2.9	2.8	8.8	6.6	5.1	6.3	5.2	5.7	1.1	0.3
Child-Turcotte-Pugh										
Class A (5-6)	-	-	25 (96)	22 (88)	0	2 (8)	0	0	-	-
Class B (7-9)	-	-	1 (4)	3 (12)	24 (92)	24 (92)	2 (40)	1 (25)	-	-
Class C (10-12)	-	-	0	0	2 (8)	0	3 (60)	3 (75)	-	-
Meld Score, n (%)										
<10	-	-	15 (58)	13 (52)	8 (31)	5 (19)	1 (20)	0	-	-
10-15	-	-	10 (38)	10 (40)	14 (54)	19 (73)	3 (60)	2 (50)	-	-
16-20	-	-	1 (4)	2 (8)	2 (8)	2 (8)	1 (20)	1 (25)	-	-
21-25	-	-	0	0	2 (8)	0	0	1 (25)	-	-
Median eGFR, mL/min	61	71	59	68	68	56	67	62	90	69
Median platelets x 10^3 µL	143	152	106	112	93	97	106	65	45	196

Abbreviations: CTP=Child-Turcotte-Pugh

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

Ledipasvir-Sofosbuvir + Ribavirin in HCV GT 1,4
SOLAR-1 (Cohort B = Post-transplantation): Results

SOLAR-1 Cohort B (Post-Transplantation): SVR12 Results



CTP = Child-Turcotte-Pugh; FCH = fibrosing cholestatic hepatitis; 8 subjects CPT B 24 weeks

Source: Charlton M, al. Gastroenterology. 2015;149:649-59.

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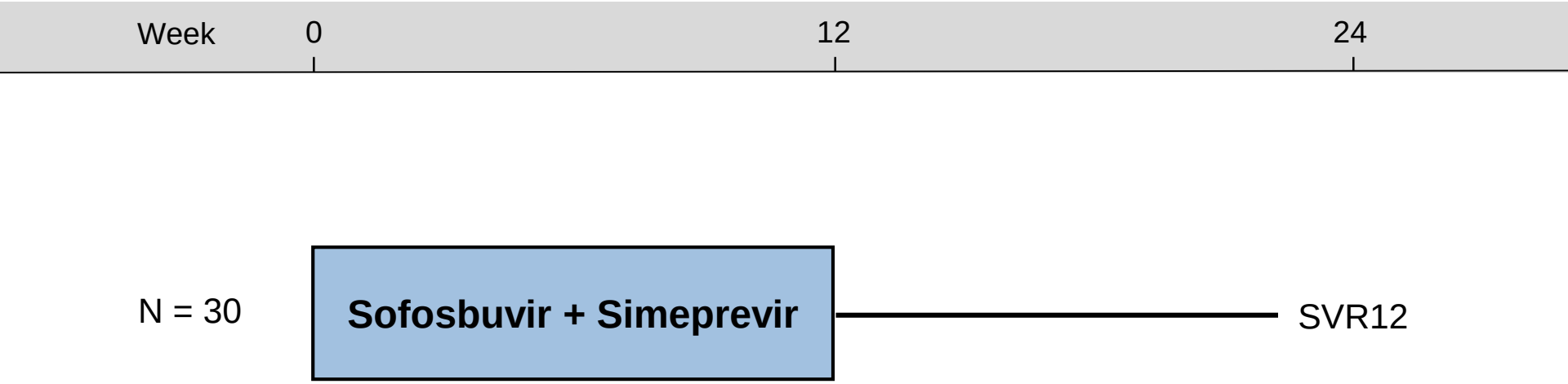
Sofsobuvir + Simeprevir
UCLA Study

Hepatitis
web study

Sofosbuvir + Simeprevir in Recurrent HCV Post Liver Transplant
UCLA Liver Transplant Study: Design

Sofosbuvir + Simeprevir in Recurrent HCV Post Liver Transplant: Design

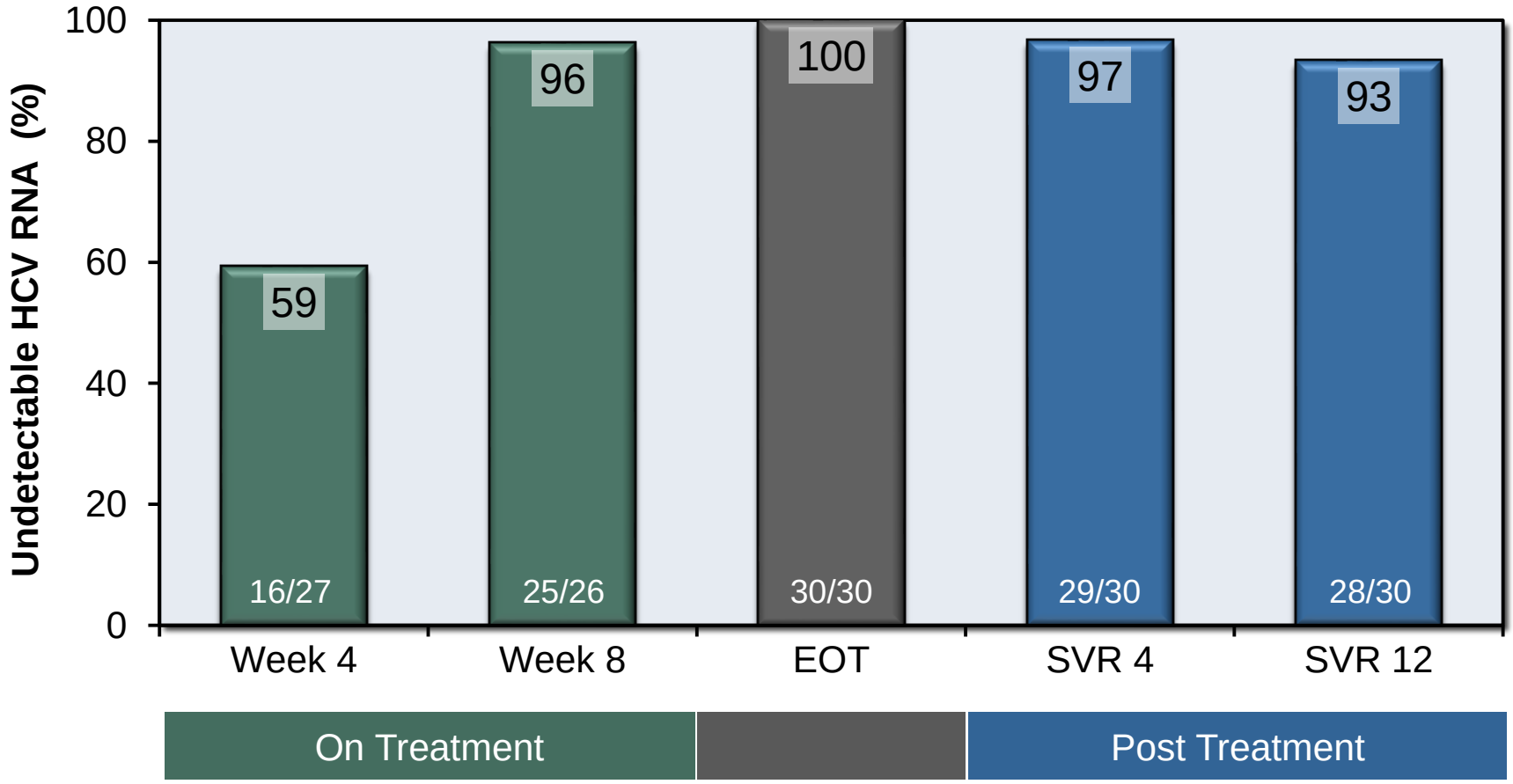


Drug Dosing
Sofosbuvir: 400 mg once daily
Simeprevir: 150 mg once daily

Source: Saab S, et al. Liver Int. 2015 Apr 24. [Epub Ahead of Print]

Sofosbuvir + Simeprevir in Recurrent HCV Post Liver Transplant
UCLA Liver Transplant Study: Results

Treatment with Sofosbuvir + Simeprevir Post Liver Transplant



Source: Saab S, et al. Liver Int. 2015 Apr 24. [Epub Ahead of Print]

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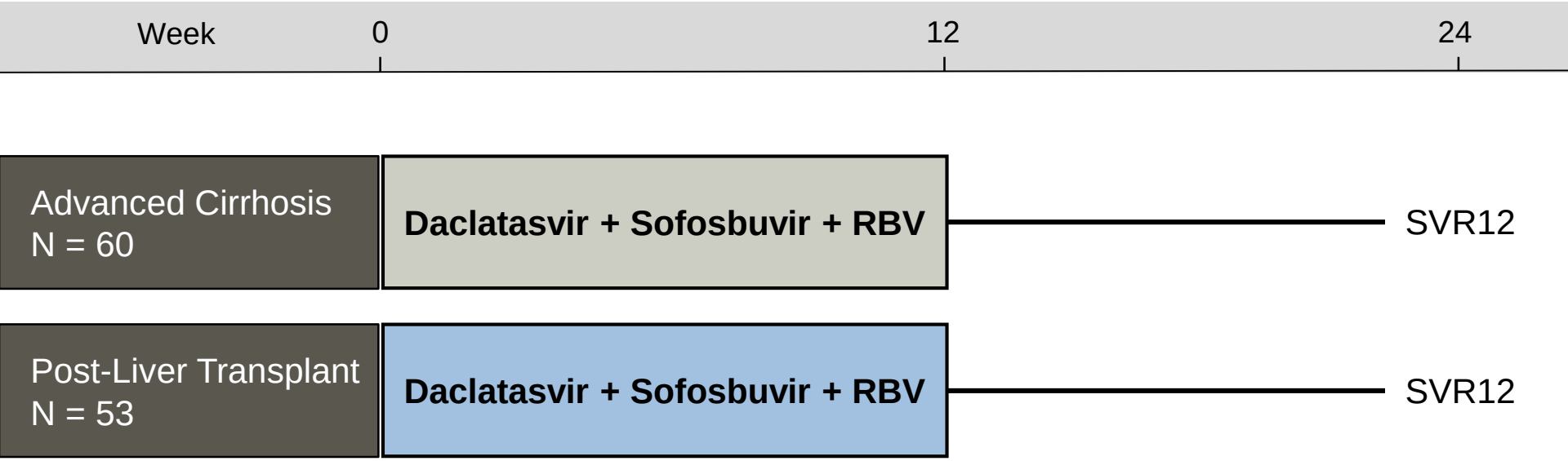
Daclatasvir + Sofosbuvir + Ribavirin
ALLY-1

Hepatitis
web study

Daclatasvir + Sofosbuvir + RBV in Recurrent HCV Post Liver Transplant
ALLY-1:Results

ALLY-1: Study Design



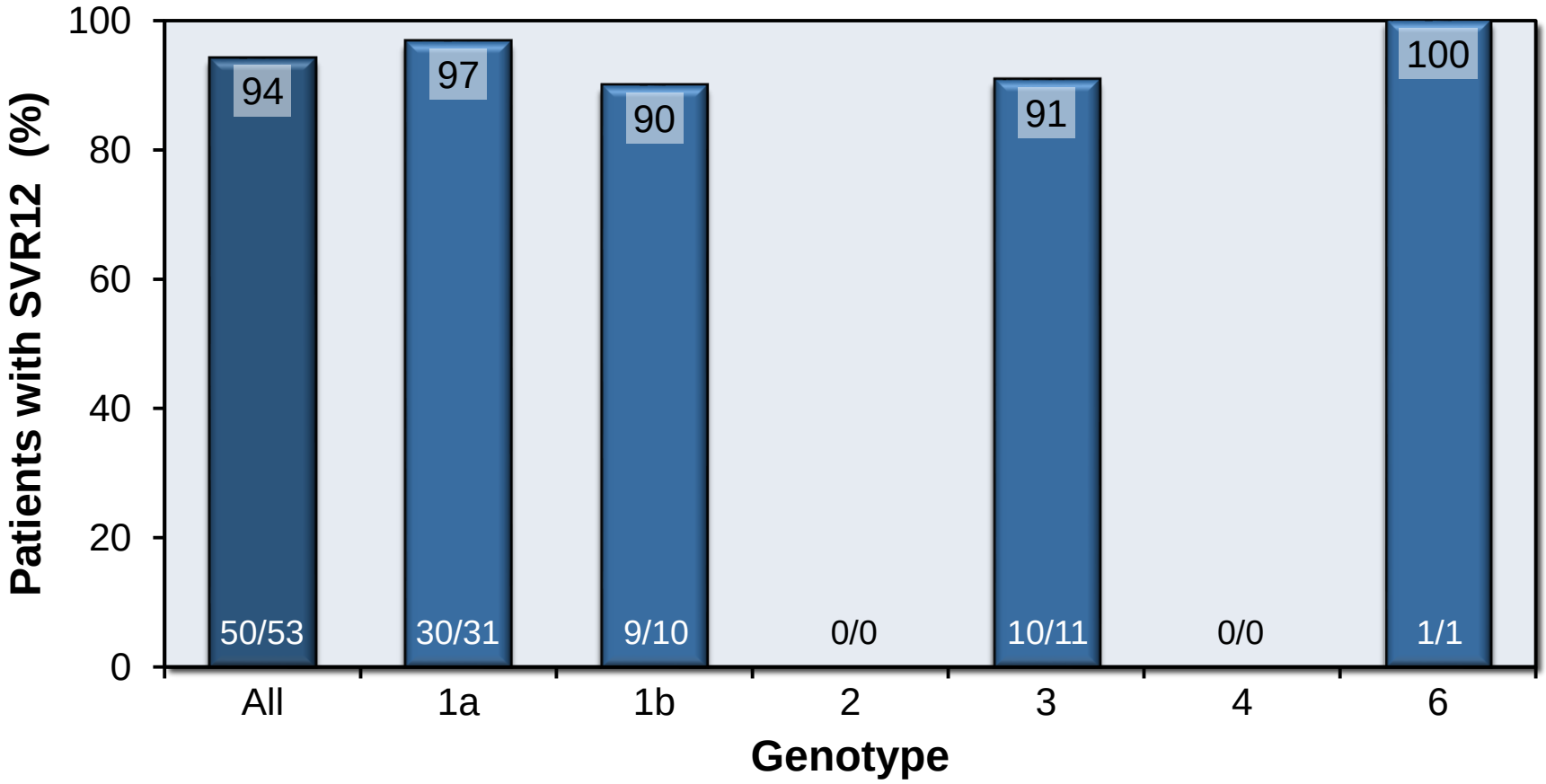
Drug Dosing
Daclatasvir: 60 mg once daily
Sofosbuvir: 400 mg once daily
Ribavirin: 600 mg daily, adjusted to 1000 mg/day based on Hemoglobin levels and renal function

Source: Saab S, et al. Liver Int. 2015 Apr 24. [Epub Ahead of Print]

Daclatasvir + Sofosbuvir + RBV in Recurrent HCV Post Liver Transplant

ALLY-1:Results

ALLY-1: SVR12 Results, by Genotype



Source: Poordad F, et al. 2015 EASL;LB08.

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Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir + R
CORAL-I

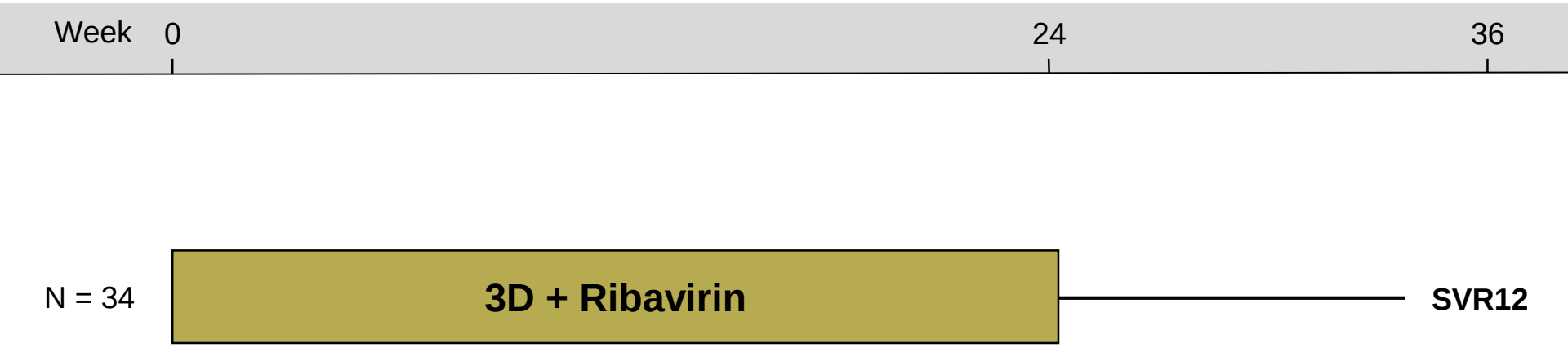
3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
CORAL-I Trial: Study Design

CORAL-I: Features

- **Design**: Phase 2, open-label, single-arm trial evaluating safety and efficacy of 3D (ombitasvir-paritaprevir-ritonavir + dasabuvir) + ribavirin x 24 weeks in liver transplant recipients with recurrent HCV GT 1
- **Setting**: International
- **Entry Criteria**
  - Chronic HCV infection with genotype 1
  - Liver transplantation due to HCV at least 12 months prior
  - Treatment-naïve after transplantation
  - Pre-transplant treatment with peginterferon + ribavirin allowed
  - Age 18-70
  - Metavir score ≤F2 confirmed by liver biopsy
- **Use of Immunosuppressants**
  - Receiving stable immunosuppressant regimen (tacrolimus or cyclosporin)
  - Tacrolimus or cyclosporin dose based on phase I pharmacokinetic study
  - Prednisone at dose ≤ 5 mg/day permitted but not use of mTOR inhibitors
- **Primary End-Point**: SVR12

Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
CORAL-I Trial: Regimen



3D = Ombitasvir-Paritaprevir-Ritonavir + Dasabuvir

Drug Dosing

Ombitasvir-Paritaprevir-Ritonavir- (25/150/100 mg once daily) + Dasabuvir: 250 mg twice daily

Ribavirin (RBV): dosing managed per investigator discretion; most patients received 600-800 mg/day

Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

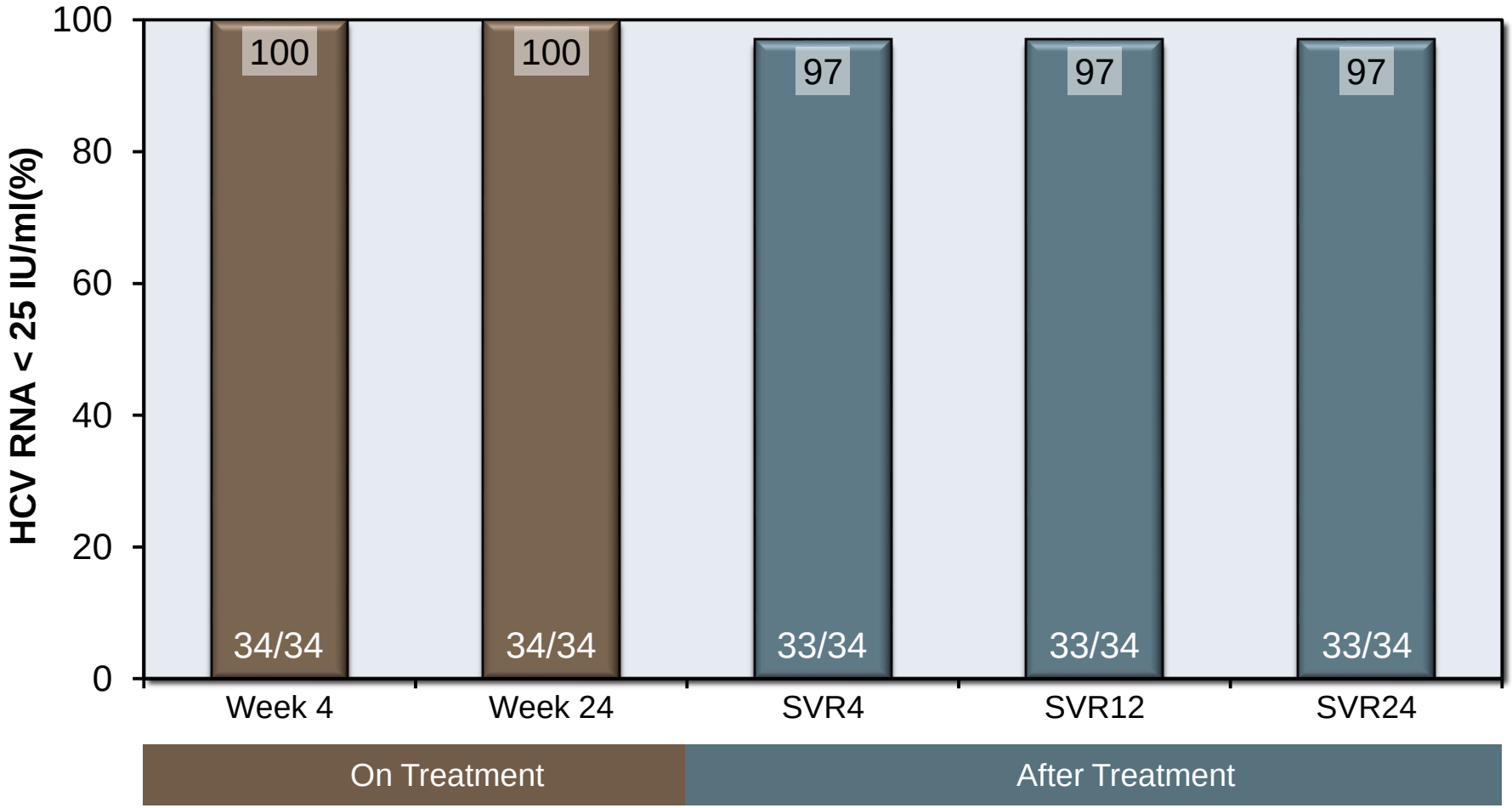
3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
CORAL-I Trial: Baseline Characteristics

Baseline Characteristic	**3D + Ribavirin** (n=34)
Age (years), Mean	59.6
Male sex–no. (%)	27 (79)
Race–no. (%) White Black Multiple	 29 (85) 4 (12) 1 (3)
Body Mass Index (kg/m^2) Mean	29.7
HCV genotype–no. (%) 1a 1b	 29 (85) 5 (15)
IL28B, non-CC genotype–no. (%)	26 (76)
HCV RNA, $\log_{10}$ IU/ml	6.6
Fibrosis stage (%) F0 F1 F2	 6 (18) 13 (38) 15 (44)

3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
CORAL-I Trial: Results



Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

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3D + RBV in Liver Transplant Recipients with Recurrent HCV GT1
CORAL-I Trial: Adverse Events

Adverse Event Occurring in > 15% of the 34 Patients Receiving 3D + RBV	
Event	**N (%)**
Any adverse event	33 (97)
Fatigue	17 (50)
Headache	15 (44)
Cough	11 (32)
Anemia	10 (29)
Diarrhea	9 (26)
Insomnia	9 (26)
Asthenia	8 (24)
Nausea	8 (24)
Muscle spasms	7 (21)
Rash	7 (21)
Back pain	6 (18)
Dizziness	6 (18)
Peripheral edema	6 (18
Rhinorrhea	6 (18)

3D = Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir; **RBV** = ribavirin

Source: Kwo PY, et al. N Engl J Med. 2014;371:2375-82.

Treatment Strategies

Timing of Treatment: Pre-Transplant

- Prevention would seem to be preferred strategy:
  - Difficult and dangerous in decompensated cirrhotic in the interferon era
  - Now safer, but cirrhosis remains negative predictor of SVR
- Abbreviated course of interferon free, direct acting antiviral (DAA) therapy that results in virus free state pre-transplant prevents recurrence in 64%[1]
- Concerns:
  - Pre-LT SVR would delay ultimately inevitable transplant
  - Remove the option of using an HCV positive donor liver.

Source: Manns MP, et al. [Abstract]. Hepatology 2013;58:86A.

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations
Decompensated Cirrhosis: Genotypes 1-4 HCV Infection

Treatment of HCV in Patients with Decompensated Cirrhosis
Genotype 1 and 4 HCV Infection: Initial Therapy
Daclatasvir + Sofosbuvir + Ribavirin (low Initial dose) x 12 weeks
Ledipasvir-Sofosbuvir x 12 weeks
Daclatasvir + Sofosbuvir x 24 weeks (for ribavirin intolerant/ineligible)
Genotype 1 and 4 HCV Infection: Prior Failure with Sofosbuvir
Ledipasvir-Sofosbuvir + Ribavirin (low Initial dose) x 24 weeks
Genotype 2 and 3
Daclatasvir + Sofosbuvir + Ribavirin (low Initial dose) x 12 weeks
Sofosbuvir + Ribavirin (weight-based) for up to 48 weeks
Note: patients with decompensated cirrhosis should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center)

Source: AASLD/IDSA/IAS-USA (www.hcvguidelines.org).

Post LT HCV Treatment Strategies

- **Response to post LT fibrosis (*Horse is out of barn*)**
  - Peginterferon/Ribavirin post LT: SVR- 27%[1]
    - 26% discontinuation rate
  - 1st generation Protease Inhibitor plus Peginterferon/Ribavirin: SVR- 63%[2]
    - Severe anemia, drug-drug interactions, renal failure, death
  - Sofosbuvir + Ribavirin (24 wk) post LT- 70%
  - Sofosbuvir /Simeprevir post LT: SVR 92% (F0-2) to 65% (F3-4) [3,4]
  - Sofosbuvir /Ledipasvir + Ribavirin post LT: SVR 96% to 80% (F4 Decomp.)
- **Pre-emptive post LT Rx (*Barn door is still closed*)**
  - Early ("Immediate") post LT in setting of universal recurrence
    - HCV RNA titer lowest level
    - Fibrosis minimal
    - Avoid Fibrosing Cholestatic Hepatitis

1. Wang CS, et al. Am J Transplant. 2006;6:1586-99.
2. Burton JR Jr, et al. J Hepatol. 2014;61:508-14.
3. Gutierrez J GA, et al. [Abstract]. Hepatology. 2014;60:545A.
4. Pungpapong S, et al. [Abstract]. Hepatology. 2014;60:201A.

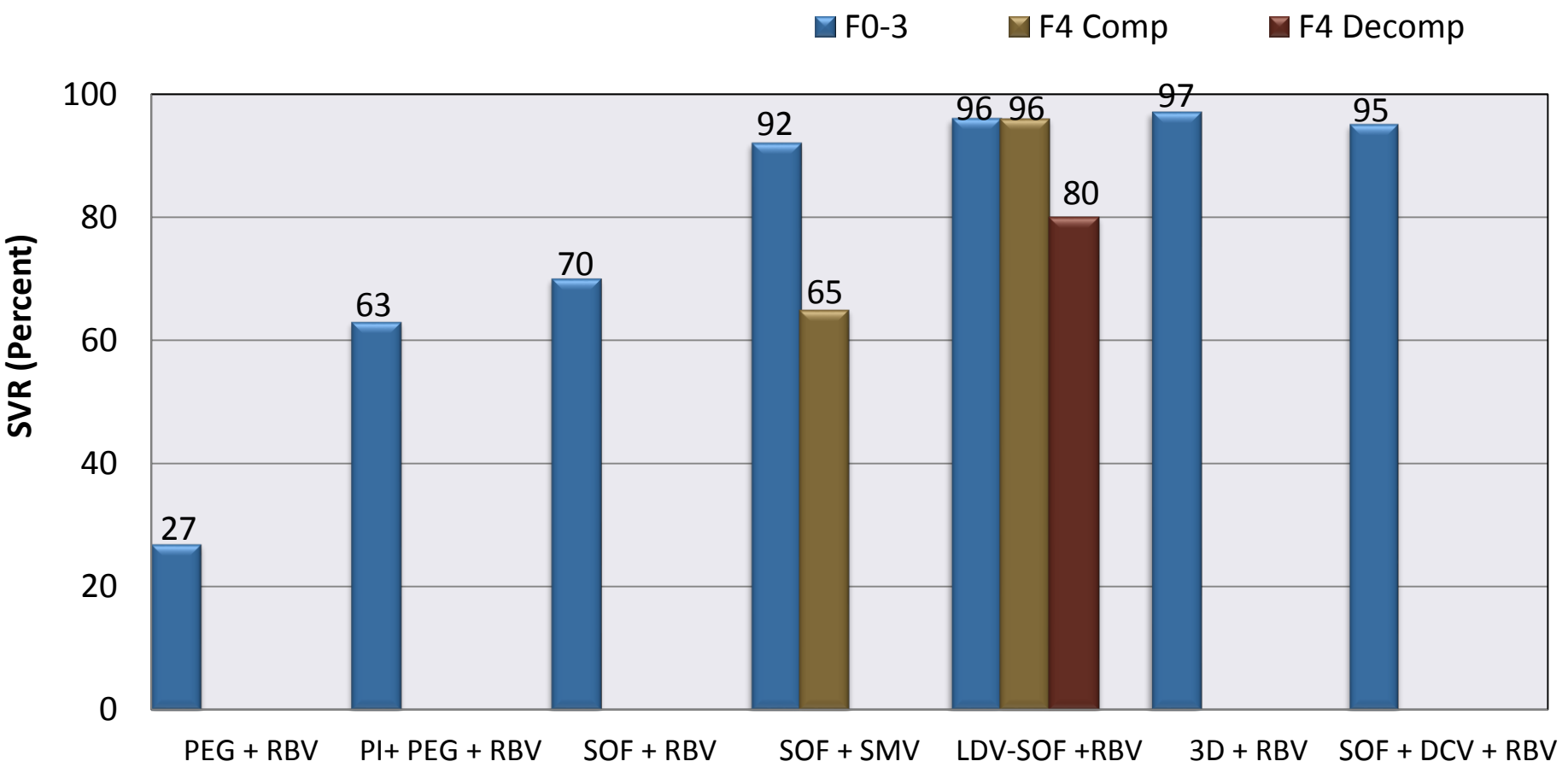
“Immediate” Post LT HCV Treatment

- Soon to become the Standard of Care?
  - No interferon related risks
  - Reduced DDI’s
  - Well tolerated
  - Highly effective
- Benefits of post LT SVR[1,2]
  - Increased graft survival
  - Regression of fibrosis
  - Improved long-term survival

1. Berenguer M, et al. J Hepatol. 2012;56:1310-16.
2. Crespo G, et al. J Gastroenterol. 2013;48:762-9.

Outcomes of Post LT HCV GT1 Therapies

SVR Related to Regimen and Fibrosis



Source: Peyton A, Bhamidimarri KR. Clin Liver Dis. 2015;5:145-9.

Hepatitis web study

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online

www.hepatitisc.uw.edu

Hepatitis Web Study

http://depts.washington.edu/hepstudy/

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