KC Nakli Sonrasi HCV Tedavisi

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3. TKV-Azerbaycan Hepatoloji Kursu
30 Eylul 2017

HCV Recurrence after Liver Transplant

- **100% re-infection of new liver if detectable HCV RNA at the time of transplant**
- **10–50% of patients with recurrent infection progress to cirrhosis within 5 years[1]**
- **Once cirrhosis is established, the probability of liver graft failure is 42% within 12 months[2]**

1. Picciotto FP, et al. J Hepatol 2007;46:459-65; 2. Berenguer M, et al. Hepatology 2002;36:202-10.

Hepatitis C following Liver Transplantation

- Current treatment of HCV infection with all oral new direct-acting antivirals in the post liver transplant setting;
  - is easier, shorter, tolerable, and more effective with high-sustained virological response rates
  - some challenges remain, including the optimal timing of therapy, drug–drug interactions, renal insufficiency, HIV coinfection

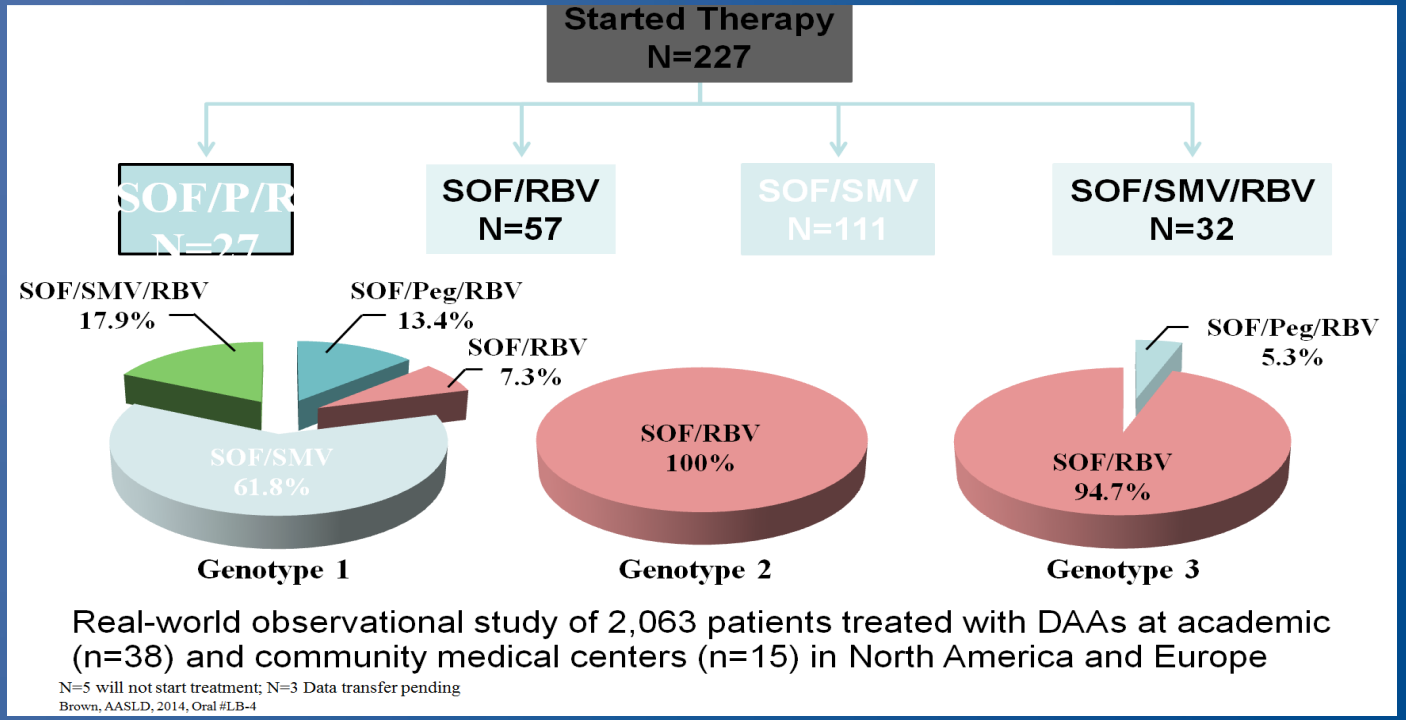
Timing of Therapy

- If a recipient achieves undetectable HCV RNA level for at least 30 days prior to liver transplantation, post LT HCV recurrence is very low
- This is the ideal scenario for Live Donor LT Recipients
- Delaying the treatment to the post LT period also allows candidates to receive allografts from HCV-infected donors
- During the first year of LT, presence of rapid progression indicators (such as *acute cholestatic hepatitis*, moderate to extensive fibrosis, or portal hypertension) is an urgent indication of antiviral treatment, for 12 or 24 weeks with or without ribavirin

Preemptive Treatment

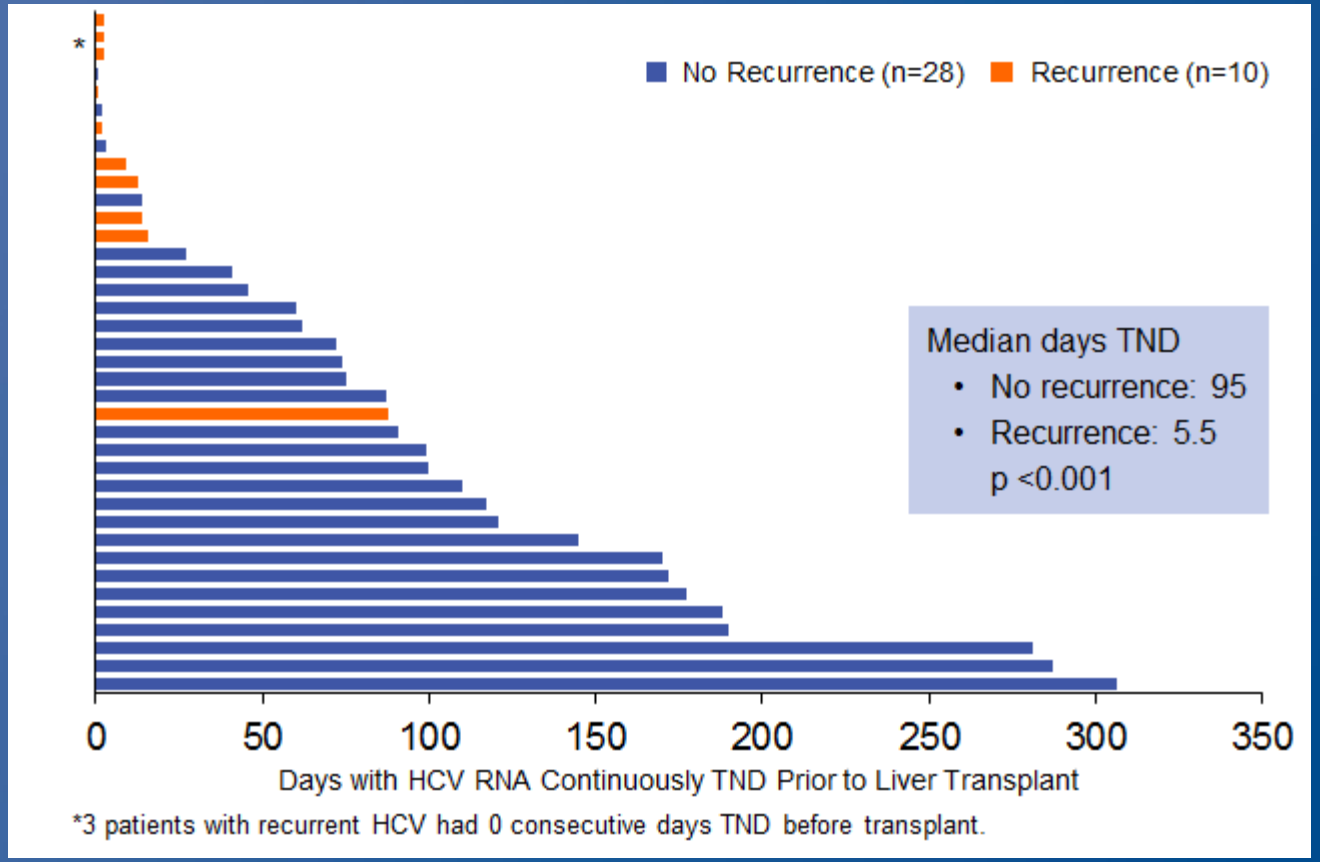
- Considered as the ideal treatment option
  - Start the genotype-specific DAA treatment a few days following the liver transplantation
  - In the case HCV positive donor is used, initiation of the treatment should be delayed until after the new genotype is obtained, 5–7 days following LT

Safety and Efficacy of Post-Transplant Patients Treated with SOF-Containing Regimens for HCV

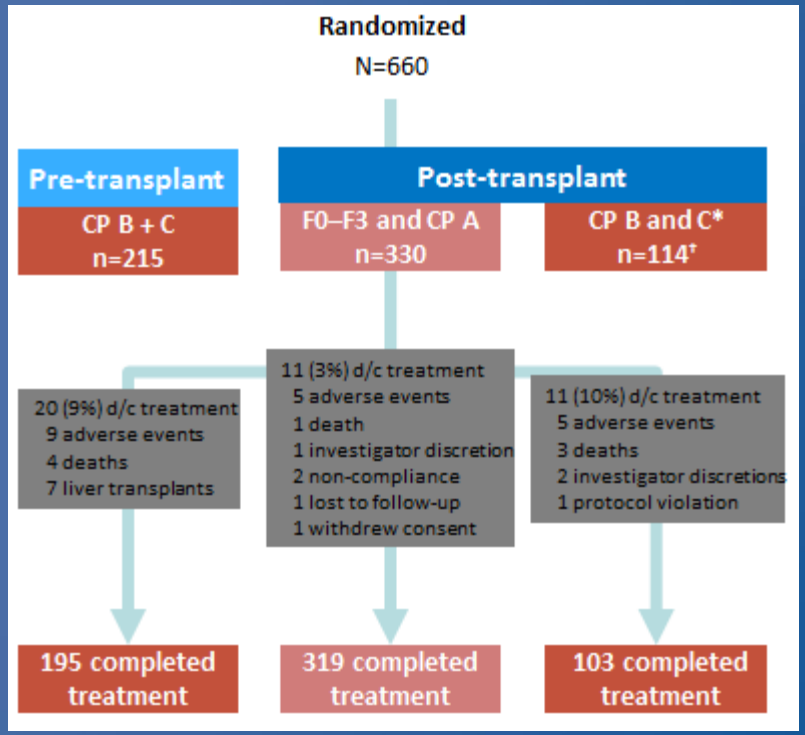


HCV-TARGET – Post Transplant

Sofosbuvir + Ribavirin: Days with HCV RNA not detected prior to transplant predicted likelihood of no infection post-transplant



Integrated safety analysis of SOLAR 1 and 2: LDV/SOF + RBV is safe in >600 decompensated and post-LT patients with HCV infection



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Samuel D, et al. EASL 2015, Vienna. #P0774

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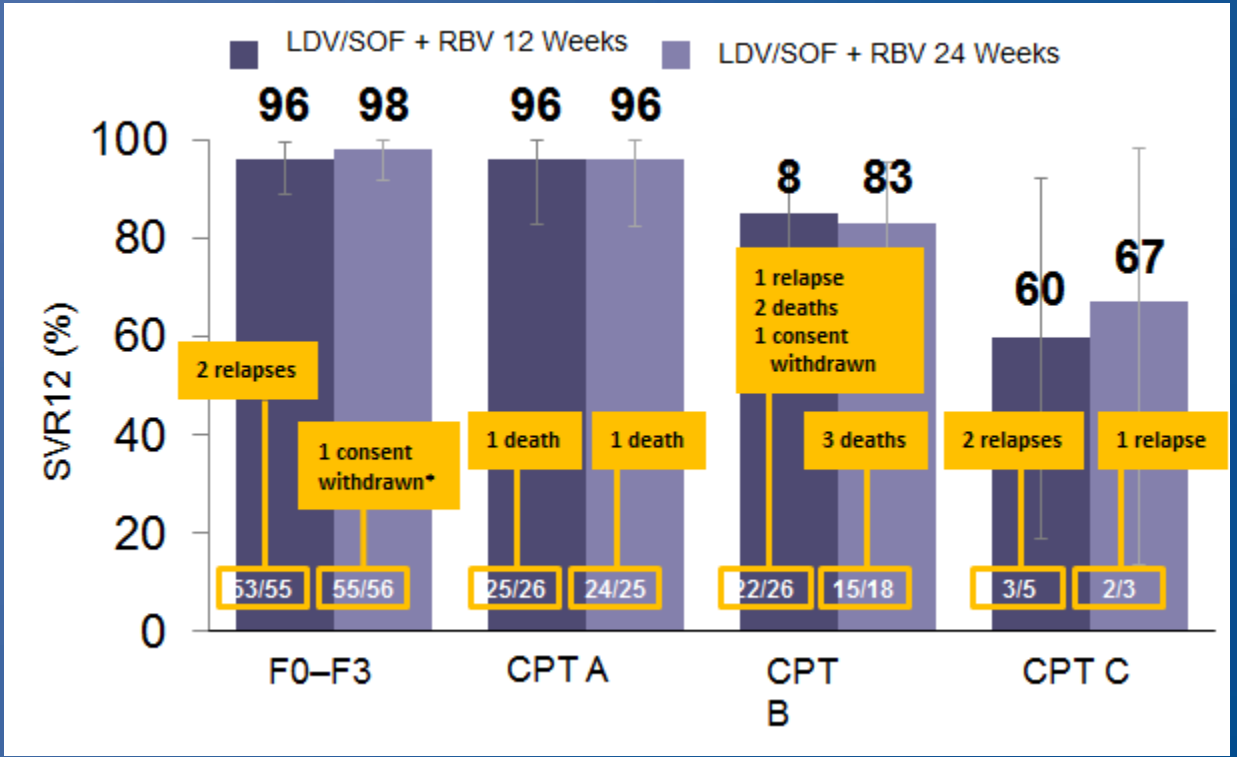
Multi-organ failure due to decompensated cirrhosis	Post	CP C

SOLAR-1: Ledipasvir/Sofosbuvir + RBV for 12 or 24 weeks in patient with liver transplant

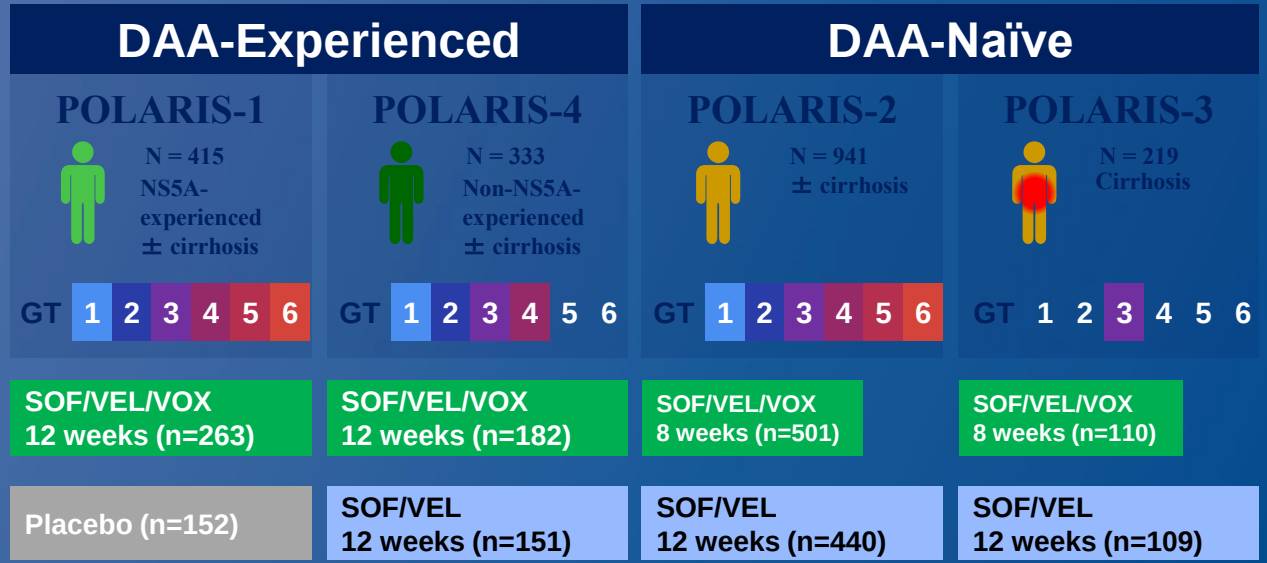


*Subject completed 8 days of treatment and withdrew consent

8 CPT B 24 Week and 1 CPT C 24 Week subjects have not reached the Week 12 post treatment visit.

Error bars represent 2-sided 90% exact confidence intervals.

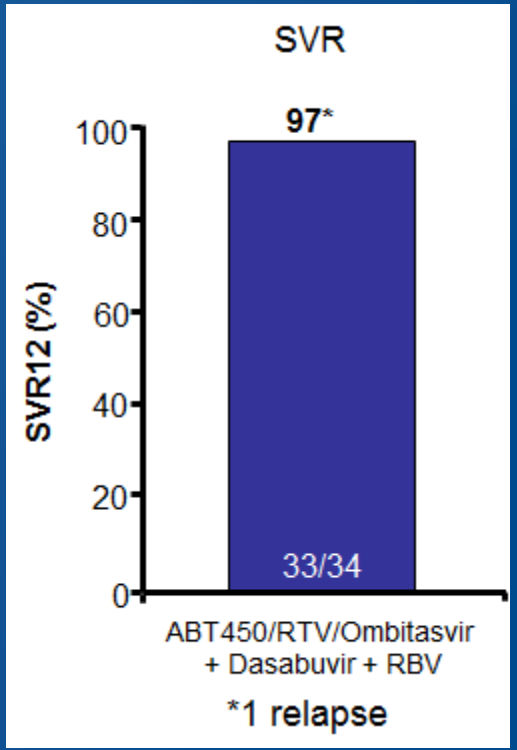
POLARIS Phase 3 Program



Bourliere M, et al. N Engl J Med 2017;376:2134-46; Jacobson I, et al. Gastroenterology 2017, doi: 10.1053/j.gastro.2017.03.047.

CORAL-1: Ombitasvir/Paritaprevir/r + Dasabuvir + RBV for 24 weeks in liver transplant recipients

- 34 patients with genotype 1 and METAVIR ≤ F2
- RBV dosed at discretion of treating physician
- Tacrolimus dose modified to 0.5 mg once weekly or 0.2 mg every 3 days.
- Cyclosporine dose modified to 20% of daily dose administered before study drugs.
- Prednisone ≤ 5 mg/day permitted.



Kwo P, et al. NEJM 2015

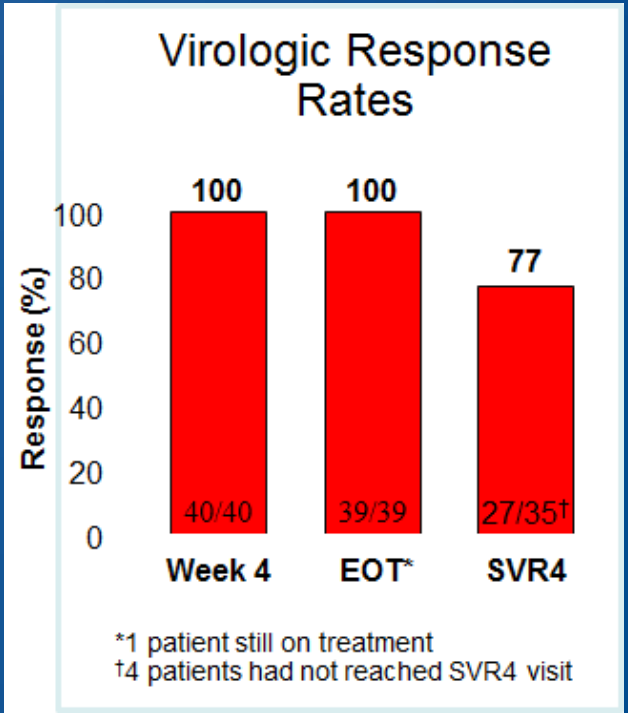
HCV DAAs and Immunosuppressives Drug–Drug Interactions

Drug Class	Drug	DDI With CNIs	
		Yes	No
Protease inhibitors	Boceprevir	✓	
	Telaprevir	✓	
	Simeprevir	CsA ✓	Tac ✓
	Paritaprevir/RTV	✔	
Nucleoside	Sofosbuvir		✔
Nonnucleoside	Dasabuvir		✔
NS5A	Ledipasvir		✓
	Daclatasvir		✓
	Ombitasvir	✔ (in combo)	✔

Tischer S, et al. J Hepatol. 2014;60:872-884.

Sofosbuvir + RBV for Treatment of Post-LT HCV Recurrence

- Prospective, multicenter, single-arm, open-label pilot study
  - Median time since LT: 4.3 years (range: 1.02-10.6)
  - CTP ≤ 7 and MELD ≤ 17
  - 83% GT1, 33% *IL28B* CC, 40% with complicated cirrhosis
- SOF 400 mg/day + RBV 400-1200 mg/day for ≤ 24 weeks
  - RBV started at 400 mg/day and increased based on hemoglobin levels



Charlton MR, et al. AASLD 2013. Abstract LB-2. NEJM 2014

HCV Antivirals in Patients with Renal and Hepatic Impairment

DAA	Primary Metabolic Pathway	Suitable in Patients With Cirrhosis			Suitable if Renal Impairment
		CTP-A	CTP-B	CTP-C	
Sofosbuvir	Renal	Yes	Yes	Yes	Not if CrCl < 30 mL/min
Simeprevir	Hepatic	Yes	No	No	Not if CrCl < 15 mL/min
Asunaprevir	Hepatic	Yes	No	No	Unknown
Paritaprevir/RTV	Hepatic	Yes	No	No	Unknown
Ledipasvir	Hepatic	Yes	Yes	Yes	Unknown
Ombitasvir	Hepatic	Yes	No (as combo)	No (as combo)	Unknown
Daclatasvir	Hepatic	Yes	Yes	Yes	Yes
Dasabuvir	Hepatic	Yes	No	No	Unknown

Bifano M, et al. AASLD 2011. Abstract 1362. Garimella K, et al. Clinical Pharm 2014. Abstract P43. Sofosbuvir [package insert]. Simeprevir [package insert]. Khatri A, et al. AASLD 2012. Abstract 758. German, et al. AASLD 2013. Abstract 467. Kirby R, et al. Clinical Pharm 2013. Abstract PO20.

Considerations in Patients with Renal Dysfunction

- Renal transplant candidate – willing to accept HCV + kidney?
- CrCl ≥ 30 mL/min: No dosage adjustment is required with sofosbuvir or ledipasvir/sofosbuvir FDC or simeprevir or paritaprevir/ritonavir/ombitasvir FDC + dasabuvir BID
- CrCl < 30 mL/min: Sofosbuvir is not recommended

Ribavirin dose adjustment in patients with renal dysfunction	
Creatinine clearance	RBV dose daily
> 50 mL/min	<75 kg = 1000 mg ≥75 kg = 1200 mg
30 – 50 mL/min	Alternate 200 mg & 400mg QD
< 30 mL/min	200 mg QD
Hemodialysis	200 mg QD

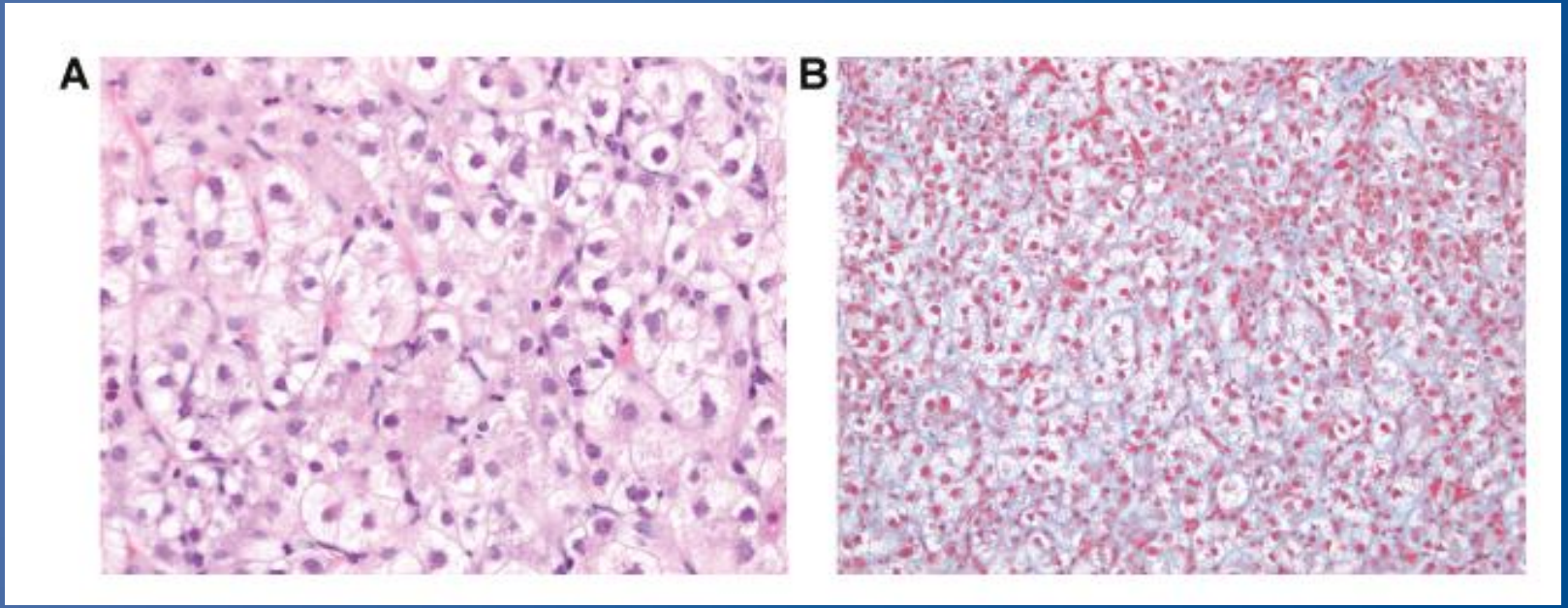
Case Report

Sofosbuvir and Daclatasvir Combination Therapy in a Liver Transplant Recipient with Severe Recurrent Cholestatic Hepatitis C

R. J. Fontana, E. A. Hughes, M. Bifano, H. Appelman, D. Dimitrova, R. Hindes, W. T. Symonds

American Journal of Transplantation 2013; 13: 1601-1605

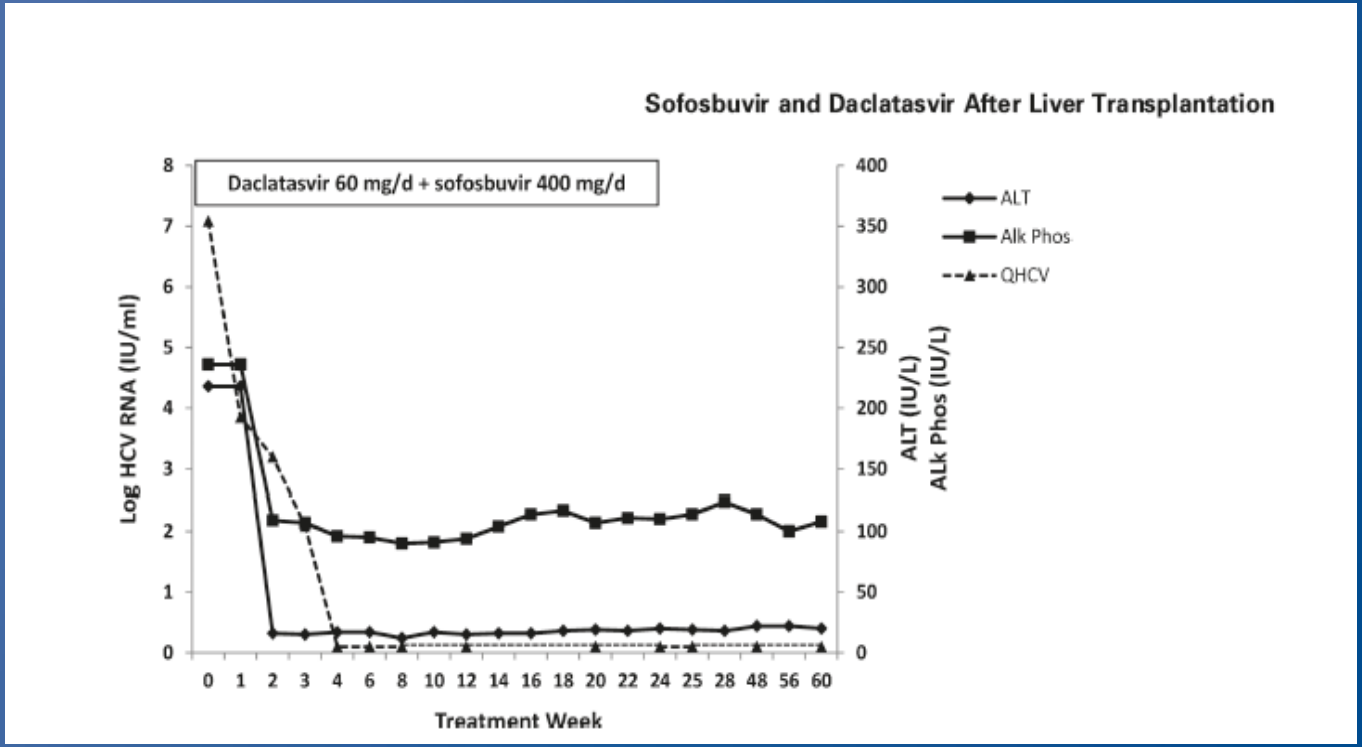
Figure 1: A: The hepatocytes are swollen with pale cytoplasm and arranged in clusters rather than cords, a common finding in fibrosing cholestatic HCV



The only evidence of inflammation is the few sinusoidal lymphocytes (hematoxylin and eosin 400×).
B: Fine blue collagen fibers separate the clusters of pale swollen hepatocytes (trichrome stain,200×).

American Journal of Transplantation 2013; 13: 1601–1605

Figure 2: Serum HCV RNA was 12 000 000 IU/mL, ALT 218 IU/L and alkaline phosphatase 236 IU/L prior to treatment



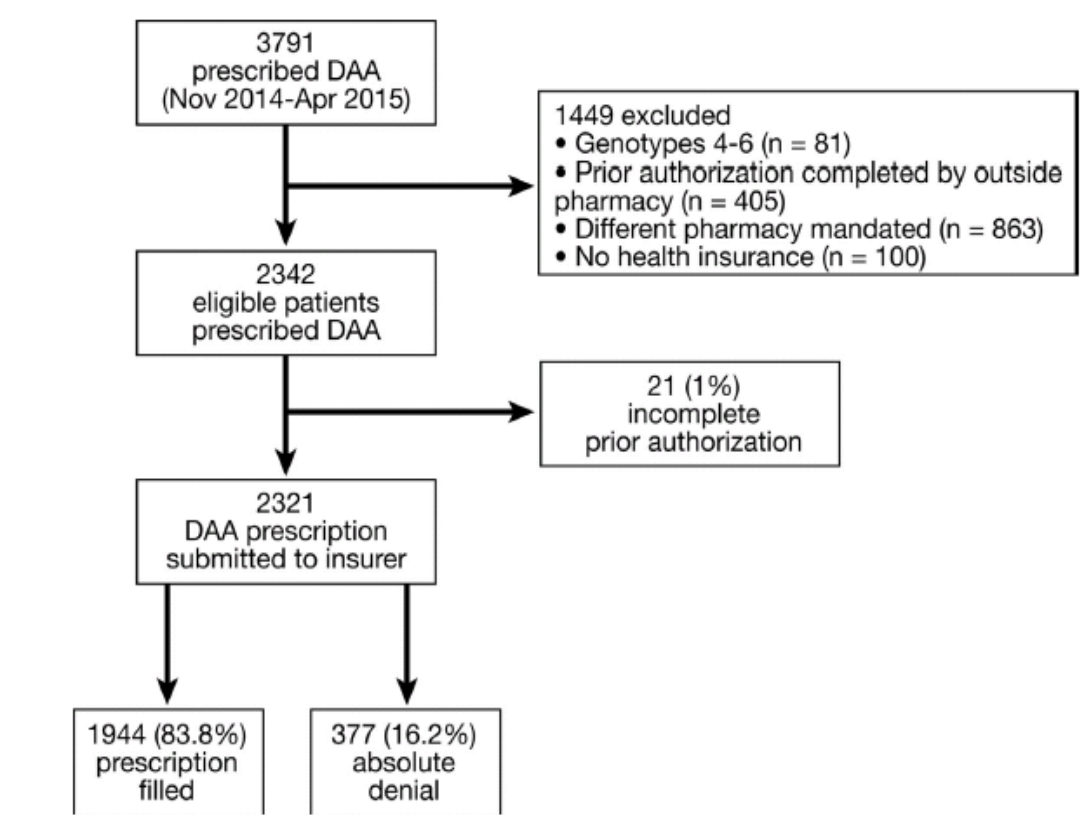
American Journal of Transplantation 2013; 13: 1601–1605

Disparities in Absolute Denial of Modern Hepatitis C Therapy by Type of Insurance

Vincent Lo Re III, Charitha Gowda, Paul N. Urick, Joshua T. Halladay, Amanda Binkley, Dena M. Carbonari, Kathryn Battista, Cassandra Peleckis, Jody Gilmore, Jason A. Roy, Jalpa A. Doshi, Peter P. Reese, K. Rajender Reddy, Jay R. Kostman

Clinical Gastroenterology and Hepatology 2016;14: 1035-1043

Figure 1. Selection flowchart of patients prescribed a DAA in the study cohort



Pre- Versus Post-transplant Treatment of Hepatitis C Virus With Direct-Acting Antivirals in Liver Transplant Recipients: More Issues to be Solved

Abdelhai Abdelqader,1 Gokhan Kabacam,2 Tinsay A. Woreta,2 James P. Hamilton,2 Harry Luu,2 Kawtar Al Khalloufi,2 Behnam Saberi,2 Benjamin Philosophe,3 Andrew M. Cameron,3 Ahmet Gurakar2

Experimental and Clinical Transplantation (2017)

Pre-LT HCV Untreated Group

- 12 of 46 untreated recipients (26%) developed biopsy-proven HCV recurrence in median of 87 days (range 55-383 days)
- In this untreated group, DAA therapy was initiated at a median of 81 days post LT
- Insurance Companies should revise their policies for rapid approval of preemptive DAA treatment Post LT

Abdelhai Abdelqader et al. Experimental and Clinical Transplantation (2017)

Table 1. Recipient Characteristics Related to Hepatitis C Virus Status at Time of Liver Transplant

	Treated Before LT (n = 21)	Not Treated Before LT (n = 46)	*P* Value
Mean age (SD; range), y	57.7 (8.8; 35-69)	58.1 (6.7; 34-69)	.78
Male, No. of patients (%)	15 (71.4)	34 (73.9)	1.00
White, No. of patients (%)	16 (76.2)	31 (67.4)	.57
DCD, No. (%)	2 (9.5)	6 (13.0)	1.00
HCC, No. (%)	15 (71.4)	29 (63.4)	.58
Donor graft, No . (%)			
HCV antibody (-), RNA (-)	20	21	
HCV antibody (+), RNA (-)	0	11	
HCV antibody (+), RNA (+)	0	11	
HCV antibody (-), RNA (+)	1	3	

Abbreviations: DCD, donation after cardiac death; HCC, hepatocellular carcinoma; LT, liver transplant; SD, standard deviation

Abdelhai Abdelqader et al. Experimental and Clinical Transplantation (2017)

Table 2. Recipient Characteristics Related to Hepatitis C Virus Status at Time of Liver Transplant

	Treated Before LT (n = 21)	Not Treated Before LT (n = 46)	*P* Value
Median allocation MELD (range)	28 (25-40)	28 (11-40)	.43
Median days on wait list (range)	287 (11-1066)	172 (3-923)	.02

Abbreviations: LT, liver transplant; MELD, Model for End-stage Liver Disease

Abdelhai Abdelqader et al. Experimental and Clinical Transplantation (2017)

Utilization of Hepatitis C RNA-positive Donor Liver for Transplant to Hepatitis C RNA-Negative Recipient.

- Saberi B Hamilton JP Durand CM Li Z Philosophe B Cameron AM Sulkowski MS Gurakar A

- Liver Transpl. 2017 Aug 5. doi: 10.1002/lt.24838. [Epub ahead of print]

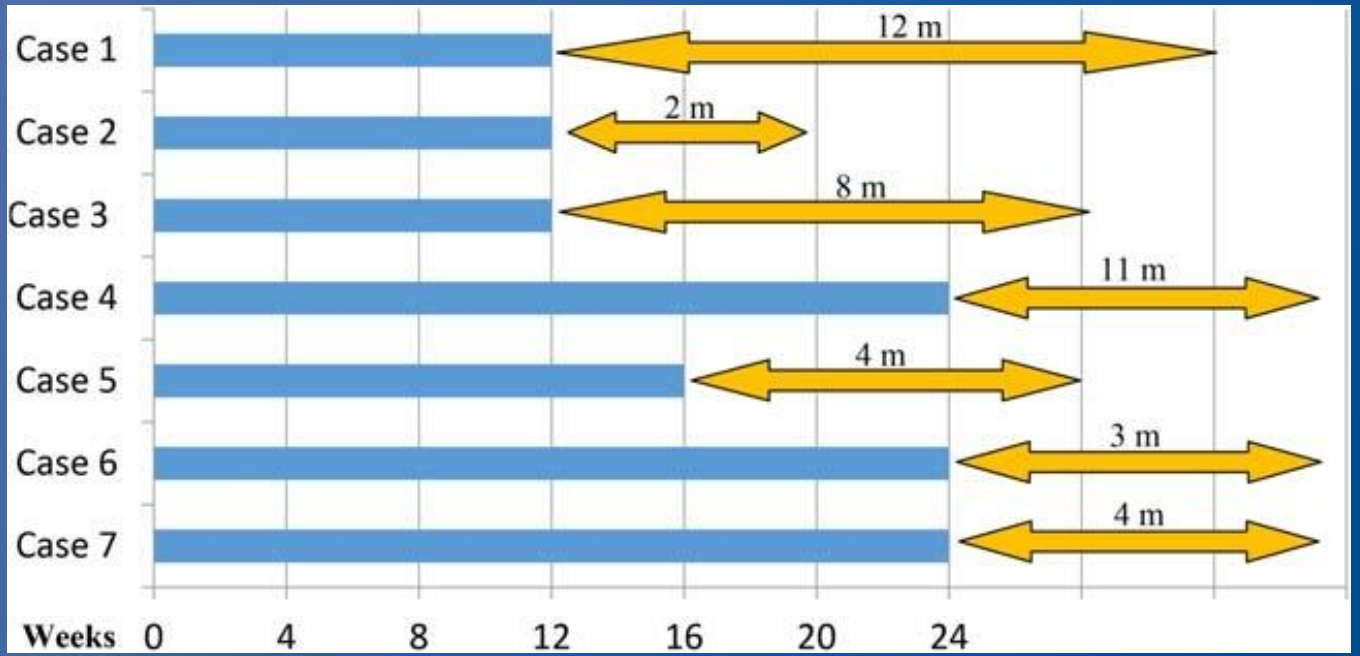
Challenges in treatment of hepatitis C among patients with hepatocellular carcinoma.

- Saberi B Dadabhai AS Durand CM Philosophe B Cameron AM Sulkowski MS Gurakar A

- Hepatology. 2017 Aug;66(2):661-663.

- 7 of the 21 patients (33.3%) relapsed following treatment with various DAA regimens, before the transplant
- 4 were genotype 1A, 1 genotype 2 and 2 genotype 3
- 2 with ledipasvir/sofosbuvir, 1 with simeprevir and sofosbuvir, and 4 with sofosbuvir and ribavirin
- 6 of the 7 patients had received locoregional therapy pre-LT

Timing of LT, relative to the end of treatment

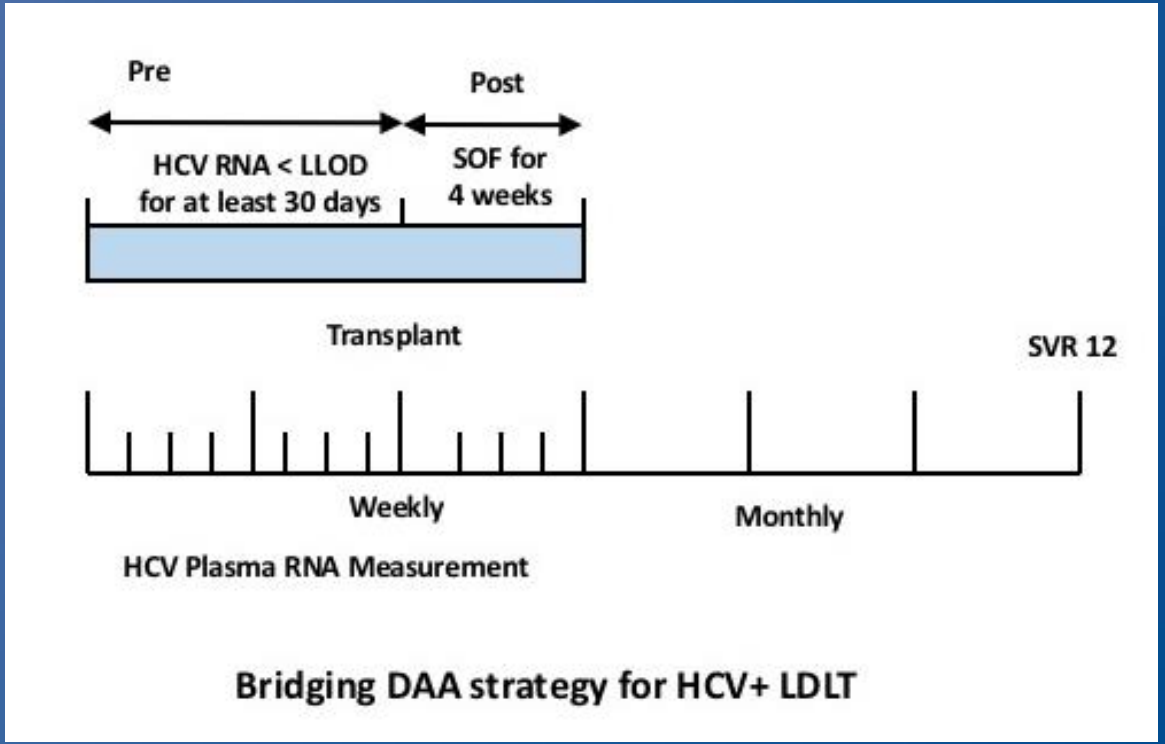


Single-Center Experience in Pre-transplant Hepatitis C Virus (HCV) Treatment Among Living Donor Liver Transplant Candidates: Bridging the Direct-Acting Antivirals (DAA)

- Niranjan-Azadi AM, Kabacam G, Durand CM, Anjum S, Saberi B, Dagher NN, Philosophe B, **Gurakar** A

- Ann Transplant, 2017 (Sep) ; 22: 570-574

Pre-transplant HCV Treatment Among Living Donor Liver Transplant Candidates; Bridging the DAA



Bridging DAA strategy for HCV+ LDLT

Niranjan-Azadi AM, Kabacam G Ann Transplant 2017


THE JOHNS HOPKINS HOSPITAL

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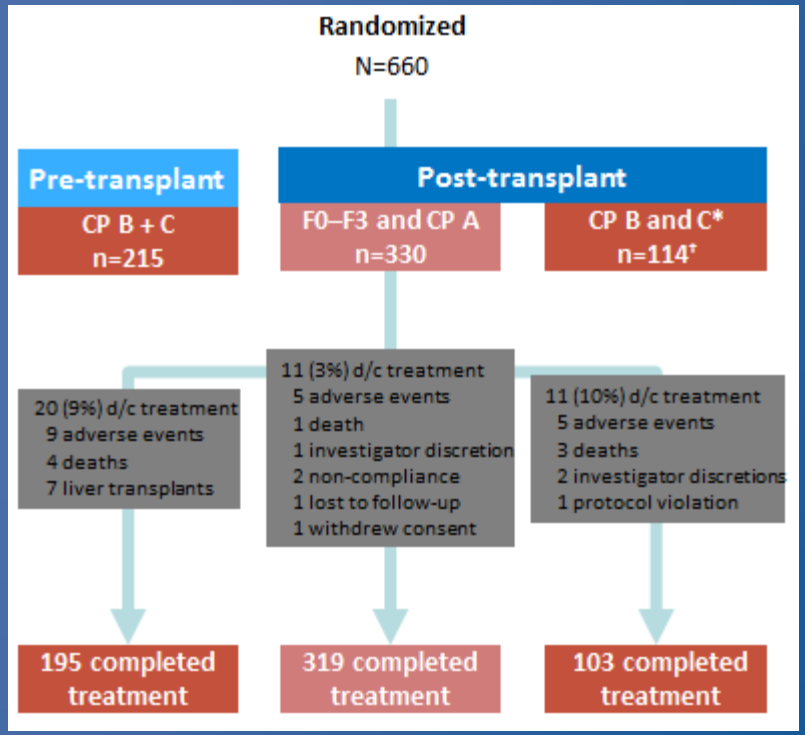

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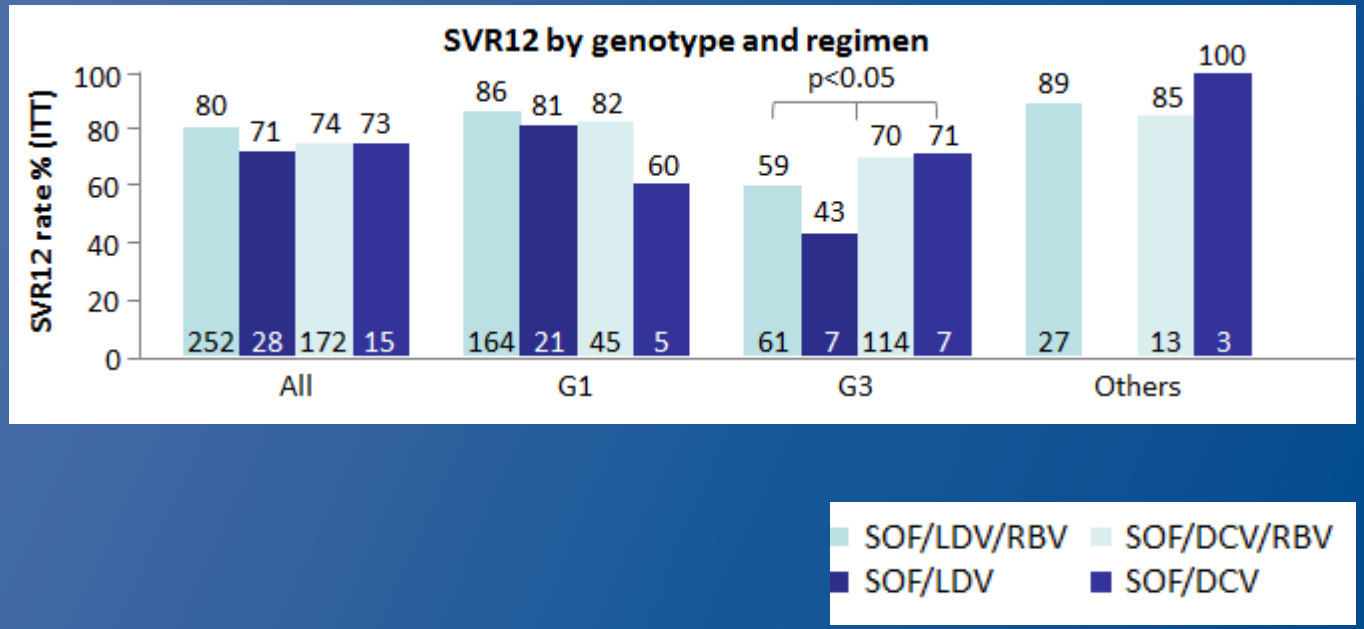
NHS Early Access for 467 patients with Childs B cirrhosis (≥7): 12 weeks SOF + NS5A inhibitors ± RBV for genotype 1 or 3



Foster GR, et al. EASL 2015, Vienna. #O002

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Risk : Benefit

	N (%)	Albumin >35	Albumin <35
Age <65	'Harmed' SAE/MELD worse by 2	14 (14%)	94 (33%)
	Helped MELD improved by 2	29 (28%)	53 (18%)
	Total	102	288
Age >65	'Harmed' SAE/MELD worse by 2	9 (32%)	14 (33%)
	Helped MELD improved by 2	4 (14%)	6 (14%)
	Total	28	43

- Restricted regimen: 12 weeks SOF only
- Encouraging results in G1 somewhat concerning G3
- G3 SVR favored by SOF + DCV vs SOF + LDV, compared with EC_{50}s
- Estimates of risk benefit may assist decision-making

Foster GR, et al. EASL 2015, Vienna. #O002

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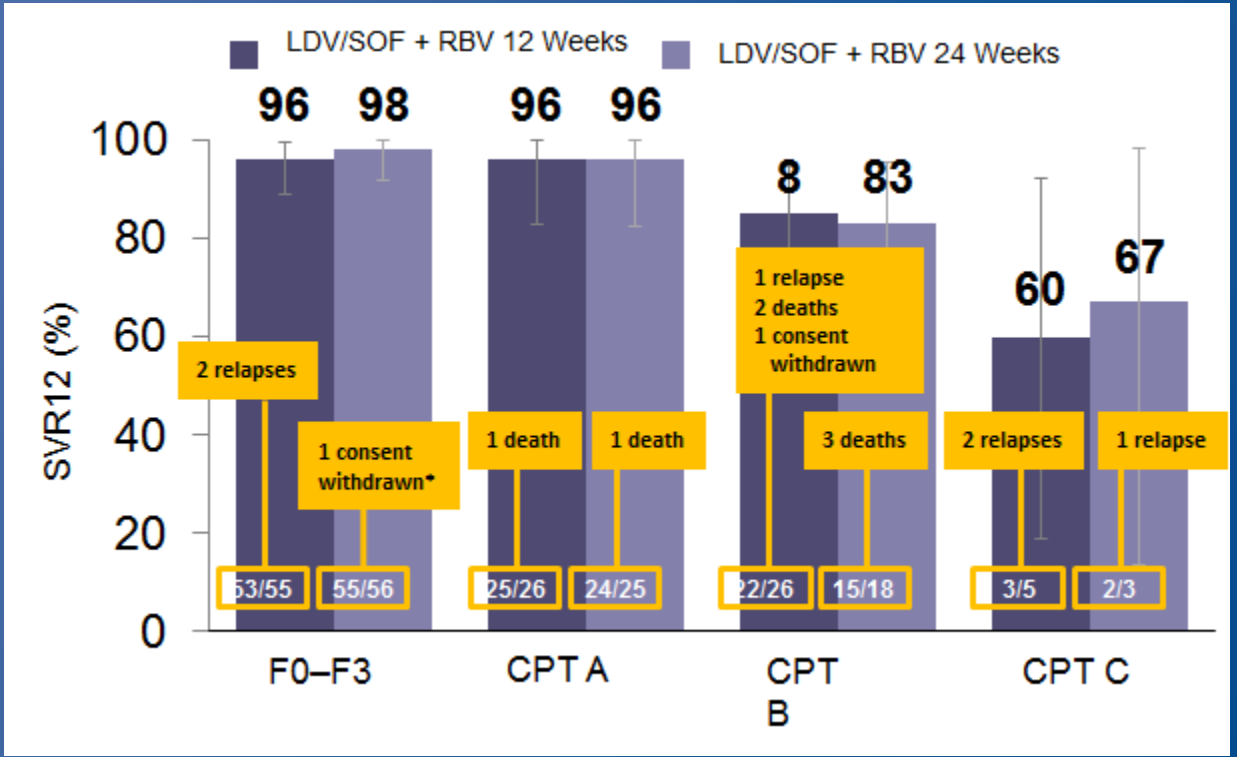

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