Management of hepatitis C in special patient groups

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B. Müllhaupt
Gastroenterology and Hepatology
Swiss HPB- and Transplant-Center
University Hospital Zurich

What are special patient groups?

- Decreased sustained virological response rate
- Reduced tolerability and/or increased risk for side and/or drug-drug interaction
- Not well represented in clinical trials
- Reduced access to care

What are special patient groups?

- Renal insufficiency, Hemodialysis, Renal transplant
- Cirrhosis with portal hypertension / decompensation
- Liver transplant recipients
- HIV Co-infection
- Children
- Acute HCV infection
- Bleeding disorders
- Drug users / Methadone substitution
- Coexistent liver diseases (NAFLD, Autoimmune, HBV)
- Psychiatric disorders and Alcohol abuse
- Elderly patients
- Lymphoma / lymphoproliferative malignancies
- Prisoners

What are special patient groups?

Management of hepatitis C in special patient groups

- **Renal insufficiency, Hemodialysis, Renal transplant**
- Cirrhosis with portal hypertension / decompensation
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Renal Insufficiency and Dialysis

- HCV prevalence in dialysis patients
  - 2.6% (UK) – 22.9% (Spain)
- Infection source
  - Pre-existent infection unrelated to hemodialysis
  - New infections on dialysis: Inadequate safety precautions (desinfection of equipment and blood spills, re-use of multi-dose vials)
  - No need for dialysis on separate machines or in separate rooms

Ghany, Hepatology 2009;49(4):1335-1374;
Fabrizi, Nat Rev Nephrol 2010 Jul;6(7):395-403

Renal Insufficiency, Dialysis and Renal Transplantation

- ALT levels lower in ESRD
- Regular HCV screening recommended on dialysis
- Dialysis: Relative risk for
  - Overall mortality = 1.3[1],
  - Liver specific mortality = 5.9[1]
- Increased relative risk of death (1.79) and graft failure (1.56) after renal transplantation [2] (Chronic GN, Sepsis, Diabetes)

[1] Fabrizi, J Viral Hepatitis 2007;14:697-703;
[2] Fabrizi, J Transplant 2005;5:1452-1461

Challenges in anti-HCV Treatment

- Multiple comorbidities in end-stage renal disease (diabetes, coronary artery disease, hypertension)
- Frequent anemia worsened by ribavirin leading to 25% dropout[1]
- ~ 30% risk of acute renal graft rejection during IFN treatment[2]

1. Fabrizi, J Viral Hepat. 2004 Jan;11(1):84-7
2. Fabrizi, Nat Rev Nephrol 2010 Jul;6(7):395-403;

(Peg-)IFN in hemodialysis pts.

Meta-Analysis of 24 trials including 529 pts

SVR-Rates on INF montherapy: 39% SVR
19% Drop-out

Meta-Analysis of 16 trials including 254 pts

SVR on PEG-INF monotherapy: 33% SVR
23% Drop-out

Fabrizi, Nat Rev Nephrol 2010 Jul;6(7):395-403

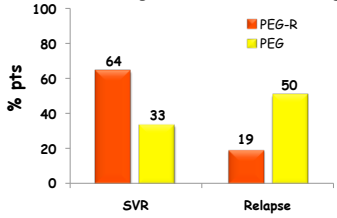
(Peg-)IFN + Ribavirin in hemodialysis pts

Study	Year	Patients	Gentyop 1	Treatment	Treatment duration	SVR %	Stop %
IFN + RBV							
Bruchfeld	2001	6	5	IFNa2b + RBV	28	17	33
Pegylated IFN + RBV							
Bruchfeld	2006	6	4	pegIFNa + RBV	24-48	50 (3/6)	33
Rendina	2007	35	16	pegIFNa2a + RBV	24-48	97 (34/35)	14
Carriero	2008	14	12	pegIFNa2a + RBV	48	29 (4/14)	71
Van Leusen	2008	7	4	pegIFNa2a + RBV	24-48	71 (4/7)	0
Hakim	2009	15	18	pegIFNa2a + RBV	48	7 (1/15)	33
Liu	2009	35	25	pegIFNa2a + RBV	24-48	60 (21/35)	17

Fabrizi, Nat Rev Nephrol 2010:6:395-403

Peg-IFN ± Ribavirin in hemodialysis pts

- 205 tx.-naive genotype 1 pts on hemodialysis
- 135ug PEG-INFa2a ± 200mg Riba



	P/R	P
SAE	5%	4%
Hb <8.5g/dl:	72%	6%
R dose red:	72%	

Liu et al Ann Intern Med 2013:159:729-738

AALSD treatment recommendations

Stage	Description	GFR (ml/min x 1.73m²)	Recommended Treatment
1	Normal or increased GFR	≥ 90	Routine combination therapy
2	Mild decreased GFR	60 - 90	Routine combination therapy
3	Moderate decreased GFR	30 - 59	PEG-IFNa-2b 1µg/kg, or Peg-IFNa-2a 135µg + Ribavirin 200 - 800 mg/d
4	Severe decreased GFR	15 - 29	
5	Kidney failure	< 15	
5D	Dialysis (hemo- or peritoneal)		Controversial if Standard- or Peg-IFN Dosage same as 5

Ghany, Hepatology 2009;49(4):1335-1374

Telaprevir and Boceprevir

- Mostly hepatic metabolization
  - Boceprevir: Aldoketoreductase & Cytochrome P450 → Feces
  - Telaprevir: Cytochrome P450 → Feces
- No significant alteration of pharmacokinetics for Boceprevir[1], 10-21% increased plasma levels for Telaprevir[2]
- Treatment without dose modifications feasible with intensified anemia management (Epo and transfusions; 5 cases)[3,4]
- Transient reduction in eGFR (~5% GFR<60 ml/min)[5,6]

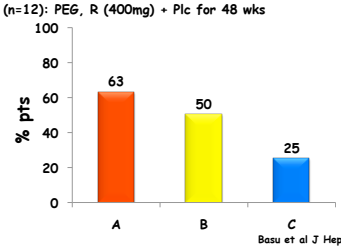
[1] Treitel et al, Clin Pharmacokinet. 2012;51:619-28; [2] Swissmedicinfo.ch (Telaprevir); [3] Knapstein et al, Dig Liver Dis. 2013 Sep 17 epub; [4] Dumortier et al, J Clin Virol. 2013;56:146-9; [5] Mauss et al, Hepatology. 2014:59:46-48, [6] Loustaud-Ratti, Hepatology in press

TVR, Peg-IFN ± Ribavirin in hemodialysis pts

Group A (n=12): PEG, R(200mg), TVR for 12w + PEG + R (400mg) for 12w

Group B (n=12): PEG, Plc + TVR for 12w + PEG + R (400mg) for 24 w

Group C (n=12): PEG, R (400mg) + Plc for 48 wks



Basu et al J Hepatol:58 Suppl 1: S30-S31

Directly Acting Antivirals

Drug	Target	Plasma exposure in ESRD	Adverse effects	Dose reduction in ESDR
Simeprevir	Protease	↑ +70%	±	no
Faldaprevir	Protease	↑ +50%	±	no
Asunaprevir	Protease	±	±	no
Sofosbuvir	Polymerase	↑	?	if GFR<30 ml/min
Ritonavir	Booster (Protease)	likely unchanged	?	?
ABT-450	Protease	No trials	No trials	No trials
ABT-267	NS5a	No trials	No trials	No trials
ABT-333	Polymerase	No trials	No trials	No trials
Daclatasvir	NS5a	Info from Trial AI444-063 pending		

Summary Renal Insufficiency

- HCV causes significant morbidity and mortality in patients with renal insufficiency or after renal transplantation
- Antiviral treatment is moderately effective and frequently causes side effects requiring intense management
- IFN treatment preferentially prior to renal transplant due to increased risk of acute allograft rejection
- Use of triple therapy feasible in end stage renal disease
- DAA may offer easier and more effective options for future treatment also after renal transplantation

Management of hepatitis C in special patient groups

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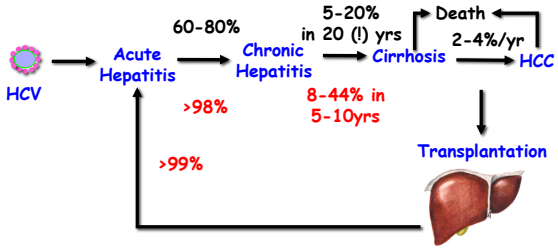
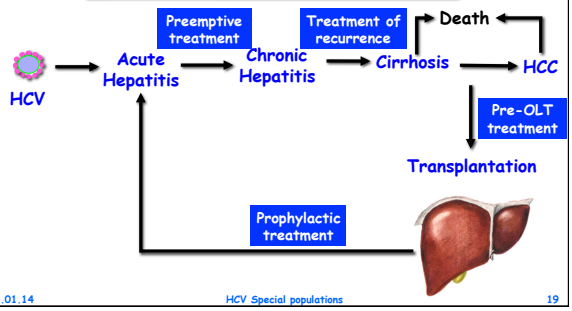
- **Cirrhosis with portal hypertension / decompensation**
- Liver transplant recipients

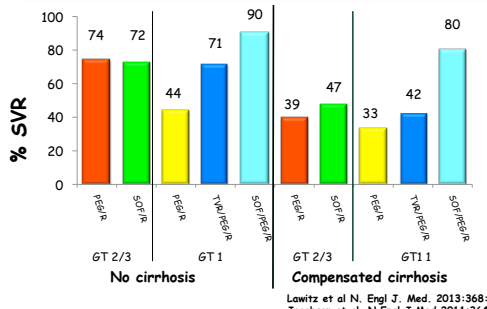
Natural history of HCV infection



Natural history of HCV infection



Impact of cirrhosis on SVR



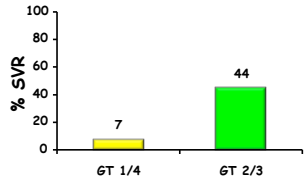
Lawitz et al N. Engl J. Med. 2013:368:1878-87,
Jacobson et al. N Engl J Med 2011;364:2405-16

Decompensated HCV cirrhosis

129 pts with decomp HCV cirrhosis, mostly Child B

66 Pts PEG-IFNa-2b (1.0μg) + Riba (800-1000mg) for 24 wks

63 controls, median f/up after Tx: 30 months



Full dose:	27 (41%)
Stop:	13 (20%)
	7 Infection
Reduction:	26 (39%)

Iacobellis et al. J Hepatol 2007;46;206-212

Decompensated HCV cirrhosis:

During treatment

	No. of patients (%)		Odds ratio (95% C.I.)
	Control ($n = 63$)	PEG-IFN + RIB ($n = 66$)	PEG-IFN + RIB ($n = 66$)
Patients with events	42 (66.6)	45 (68.2)	1.07 (0.52 – 2.23)
Types of events			
Ascites	15 (23.8)	12 (18.2)	0.71 (0.31–1.65)
Encephalopathy	12 (19)	8 (12.1)	0.59 (0.23–1.51)
Bleeding	6 (9.5)	4 (6.1)	0.62 (0.18–2.14)
Hepatocarcinoma	2 (3.2)	2 (3)	0.95 (0.16–5.58)
Infective: total	9 (14.3)	19 (28.8)	2.43 (1.02–5.77)
Severe	4 (6.4)	11 (16.6)	2.95 (0.93–9.30)
Deaths: total	4 (6.3)	5 (7.6)	1.21 (0.33–4.37)
Related to infection	2 (3.2)	4 (6.1)	1.97 (0.40–9.51)

RF for infection:
Child C
Neutro<900

	No. of patients (%)			Odds ratio (95% C.I.)	
	Control ($n = 59$)	No SVR ($n = 48$)	SVR ($n = 13$)	No SVR ($n = 48$)	SVR ($n = 13$)
Patients with events	52 (88.1)	33 (68.7)	3 (23.1)	0.29 (0.11 – 0.78)	0.04 (0.01 – 0.17)
Types of events					
Ascites	39 (66.1)	22 (45.8)	1 (7.7)	0.09 (0.02–0.65)	0.04 (0.01–0.28)
Encephalopathy	37 (62.7)	25 (52)	2 (15.4)	0.17 (0.04–0.76)	0.11 (0.02–0.48)
Bleeding	18 (30.5)	10 (20.8)	0 (0)	0.59 (0.25–1.44)	0 (0–0.70)
Hepatocarcinoma	6 (10.1)	5 (10.4)	0 (0)	0 (0–2.77)	0 (0–2.82)
Severe infections	20 (33.9)	12 (25)	1 (7.7)	0.25 (0.04–1.69)	0.16 (0.02–1.06)
Deaths: total	19 (32.2)	10 (20.8)	0 (0)	0.55 (0.23–1.32)	0 (0–0.65)
Liver failure	18 (30.5)	9 (18.7)	0 (0)	0.52 (0.21–1.29)	0 (0–0.70)

At the end of f/up

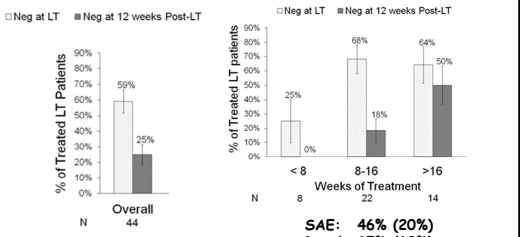
Iacobellis et al. J Hepatol 2007;46;206-212

CUPIC

Risk of death or severe complications

Factors	Platelet count >100,000/mm³	Platelet count ≤100,000/mm³
Serum albumin		
≥35 g/L	3.4% (10/298)	4.3% (3/69)
<35 g/L	7.1% (2/28)	44.1% (15/34)

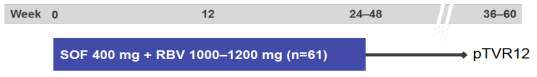
Preoperative PegIFN/RBV to prevent HCV recurrence (A2ALL)



SAE: 46% (20%)
Death: 15% (10%)

Everson et al. Hepatology 2013:57:1752-62

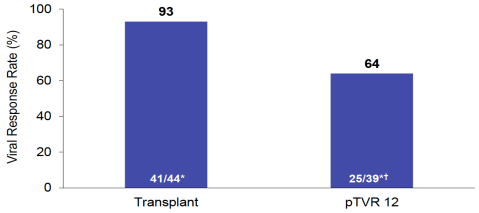
SOF + RBV before OLT



- DDLT candidates with HCC meeting MILAN criteria
- Genotypes 1-4
- CPT ≤7

Curry et al Hepatology 2013:58 S1:314A

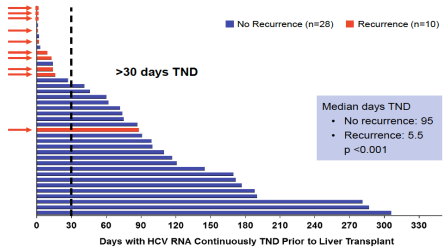
SOF + RBV before OLT



* 3 subjects were > LLOQ at transplant
†1 subject has not reached pTVR12, 1 subject lost to FU at Week 8 post transplant

Curry et al Hepatology 2013:58 S1:314A

Predictor for recurrence



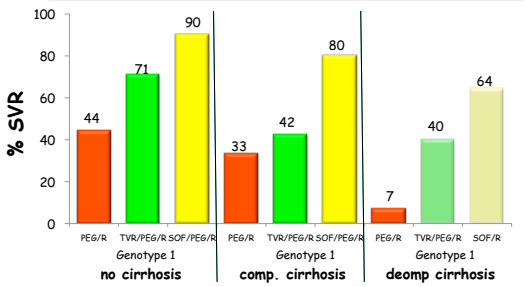
Curry et al Hepatology 2013:58 S1:314A

SOF + RBV before OLT

n (%)	SOF + RBV (N=61)
SAEs*	11 (18)
Deaths	
Pre transplant	2 (3)
Post transplant	3 (5)

Curry et al Hepatology 2013:58 S1:314A

Impact of cirrhosis on SVR



Jacobson et al. N Engl J Med 2011;364:2405-16; Lawitz et al N. Engl J. Med. 2013:368:1878-87; Iacobellis et al. J Hepatol 2007:46;206-212; Fontaine et al. EASL 2013;

Mortality in patients with cirrhosis

	MELD		Mortality (%)	
	Treatment	Control	Treatment	Control
Curry	8	n.a	3	n.a
Hezode	8	n.a	0.5-2.6	n.a.
Everson	12	12	15	10
Iacobellis	14	14	7.6	6.3

Curry et al Hepatology 2013:58 S1:314A
Hezode et al. J Hepatol 2013;59:434-441
Everson et al. Hepatology 2013:57:1752-62
Iacobellis et al. J Hepatol 2007:46;206-212

Summary Liver Cirrhosis

- SVR with Peg-IFN + RBV in genotype 1 pts with Child B cirrhosis as low as 7%
- BOC or TVR triple therapy achieves 40% SVR in a real life cohort in compensated cirrhosis
- Both options carry increased risks for serious adverse events including infections and death
- Prevention of HCV recurrence post-LTPL can be achieved by pre-transplant Peg-IFN + RBV in 25%, or Sofosbuvir + RBV in at least 64%

Management of hepatitis C in special patient groups

- Renal insufficiency, Hemodialysis, Renal transplant
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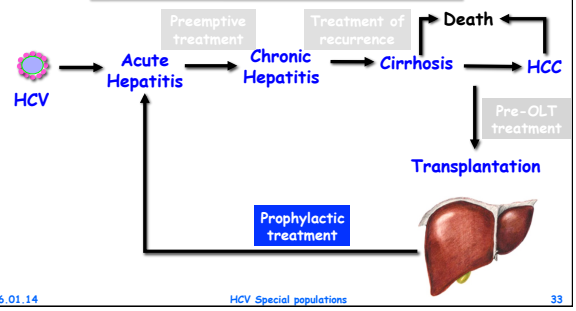
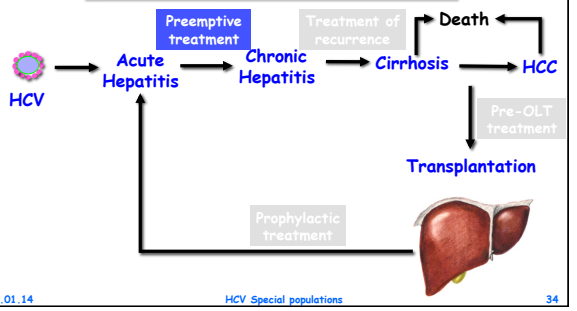
- **Liver transplant recipients**

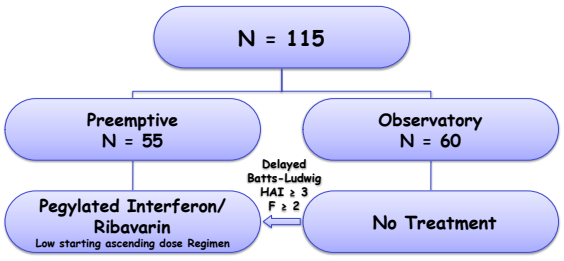
Natural history of HCV infection



Natural history of HCV infection



Preemptive Therapy



Bzowej et al Liver Transplantation 2011:17:528-38

Preemptive Therapy

Primary endpoint: Significant HCV recurrence after 120 weeks (Activity index≥3, fiborsis score ≥2; Batts & Ludwig)

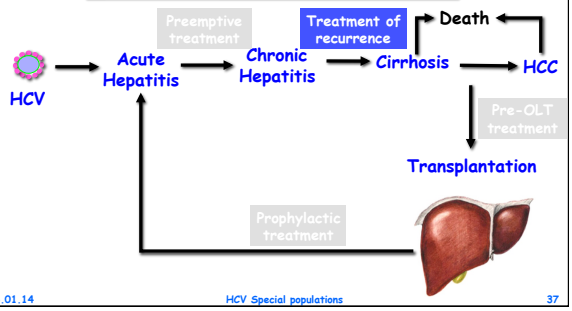
No difference in

- Significant HCV recurrence
- SVR rates (22%)
- Acute allograft rejection
- Frequency of adverse events

➡ Routine preemptive therapy NOT recommended

Bzowej et al Liver Transplantation 2011:17:528-38

Natural history of HCV infection



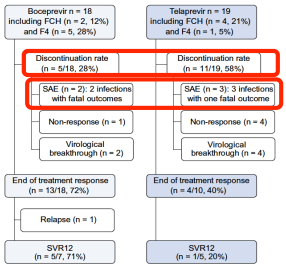
PEG-INF/RBV after OLT

- Uncontrolled, retrospective studies, small sample size
- 3 systematic reviews: SVR ~30-40% for PEG-IFN/RBV
- Pos. predictors: +EVR, genotype non-1, low viral load

Side effects:
Anemia 58%
Neutropenia 41%
Tc-penia 34%
Discont. 36%

Wang et al Am J Transplatation 2006;6:1586-99
Berenguer J Hepatol 2008:49;274-287
Rabie et al Liver Transplantation 2012 epub

Triple Therapy after OLT



Coilly et al, J Hepatol 2014:60:78-86

Triple Therapy after OLT

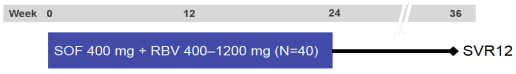
Table 3. Adverse events during triple therapy after liver transplantation.

	Boceprevir (n = 18)	Telaprevir (n = 19)
Death, No. (%)*	2 (11)	1 (5)
Infections, No. (%)*	5 (27)	5 (26)
Hematological toxicity, No. (%)		
Anemia		
<10 g/dl	18 (100)	16 (84)
<8 g/dl	7 (39)	5 (26)
Neutropenia (<1 g/L)	11 (61)	4 (21)
Thrombocytopenia (<50 g/L)	9 (50)	3 (15)
Dermatological toxicity, No. (%)^	1 (5)	1 (5)
Renal failure, No. (%)	1 (5)	4 (21)
Diabetes mellitus, No. (%)	2 (10)	0
Rehospitalization rate	6 (33)	6 (32)

*Context of septic shock.
*Community-acquired pneumonia (n = 2, W3 and W4), cytomegalovirus infection (n = 1, W2), pneumocystosis and aspergillosis (n = 1, W20), urinary tract infection (n = 4, W2, W4, W24, and W25), erysipelas (n = 1, W16), peritonitis (n = 1, W20).
^Anal itching (Grade 1).

Coilly et al, J Hepatol 2014:60:78-86

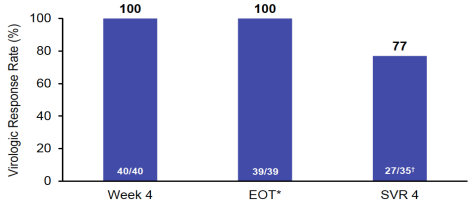
SOF + RBV after OLT



- Recurrent HCV after OLT, all genotypes
- RBV: starting at 400mg, escalating based on Hb
- Tx naïve or experienced
- CPT ≤7 und MELD ≤17
- No rejection

Charlton et al Hepatology 2012:58,1387A

Sofosbuvir + RBV after OLT



* 1 patient still on treatment; † 4 patients have not yet reached post-treatment week 4

Charlton et al Hepatology 2012:58,1387A

Daclatasvir after OLT

Liver Transpl. 2012 Sep;18(9):1053-9. doi: 10.1002/lt.23482.

Case report of successful peginterferon, ribavirin, and daclatasvir therapy for recurrent cholestatic hepatitis C after liver retransplantation.

Fontana RJ, Hughes EA, Appelman H, Hindes R, Dimitrova D, Bifano M.

Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI 48109-0362, USA. rfontana@med.umich.edu

Am J Transplant. 2013 Jun;13(6):1601-5. doi: 10.1111/ajt.12209. Epub 2013 Apr 17.

Sofosbuvir and daclatasvir combination therapy in a liver transplant recipient with severe recurrent cholestatic hepatitis C.

Fontana RJ, Hughes EA, Bifano M, Appelman H, Dimitrova D, Hindes R, Symonds WT.

Department of Internal Medicine, University of Michigan Medical Center, Princeton, NJ, USA. rfontana@med.umich.edu

24 weeks therapy → SVR & rapid normalization of liver function, no interaction with Tacrolimus or Cyclosporine

Drug interactions

CYP450 3-4A metabolism of Protease Inhibitors causes interaction with a wide variety of drugs

EPOCRATES an athenahealth company

Drug	Tacrolimus Exposure	Cyclosporine Exposure	MMF Exposure	Azathioprine Exposure	Prednisone Exposure
Telaprevir[1]	↑ x 70	↑ x 4.6	±	±	↑
Boceprevir[1]	↑ x 9.5	↑ x 2.7	±	±	↑
Sofosbuvir[2]	±	±	±	±	±
Daclatasvir[3]	±	±			
Dose reductions					
Telaprevir	- 23.8 x	- 3.4 x			
Boceprevir	- 5.2 x	- 1.8 x			

[1] Coilly et al, J Hepatol 2014:60:78-86
[2] Fontana, Liver Transplantation 2013;13:1601-1605;
[3] Fontana, Liver Transplantation 2012;18:1053-9

Summary Liver transplantation

- Recurrent HCV after LTPL significantly reduces graft and patient survival compared to other transplant indications
- Treatment success with PEG-IFN + Ribavirin in 8-33% improves prognosis and depends on IL28b genotype of donor and recipient
- Toxicity is high and despite manageable drug interactions is even further increased with triple therapy
- Inconsistent data on risk of rejection
- New DAA regimens may overcome both toxicity and efficacy limitations and facilitate management of drug interactions in the near future