Hepatitis C and Liver Transplantation: Indications and Outcomes for Treatment

3rd GCC Organ Transplantation and Nephrology Congress

January 19, 2017

John J. Fung, M.D., Ph.D.
University of Chicago

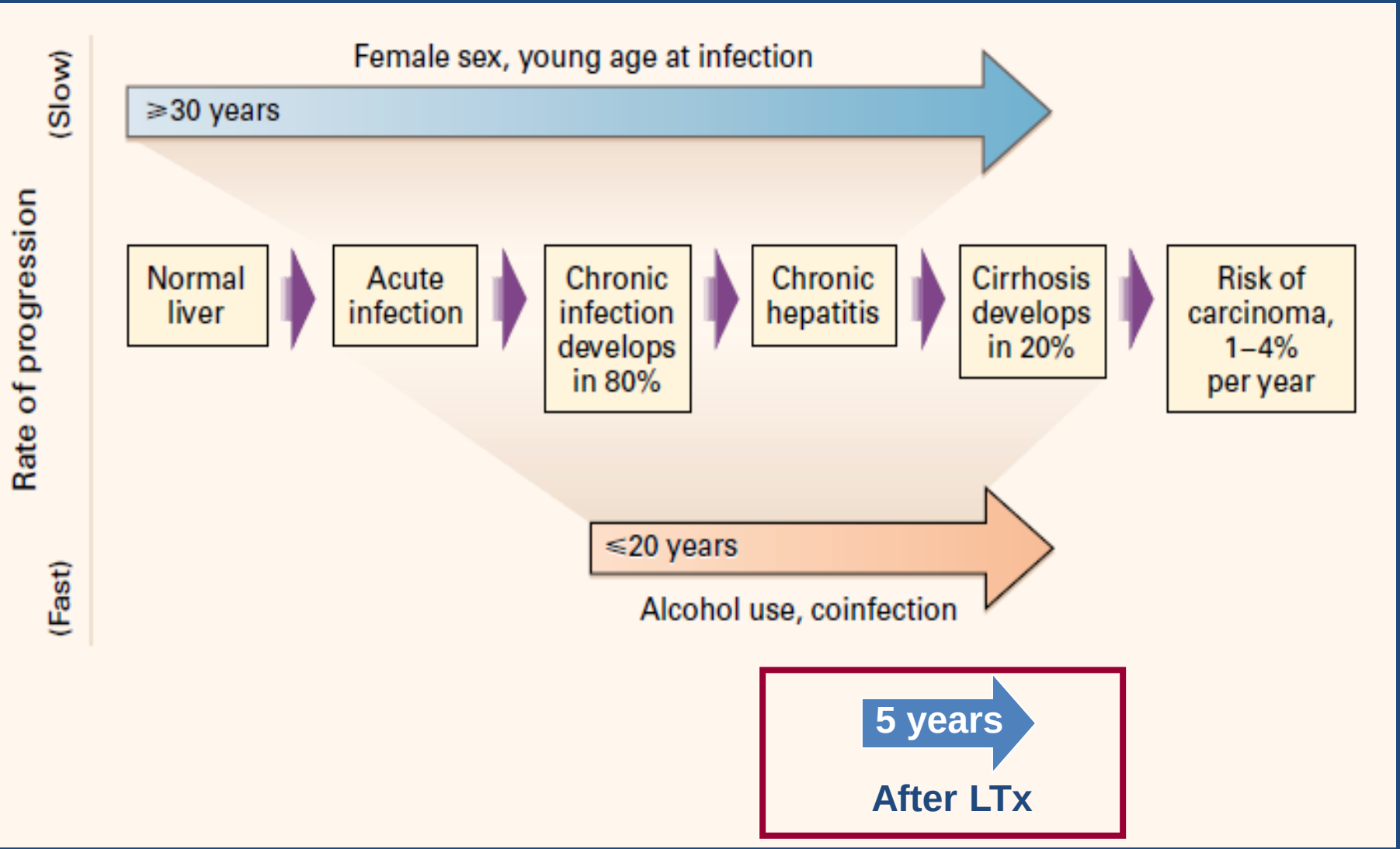
Indications for Adult Liver Transplantation

	% Transplants
Cirrhosis	68.2
Hepatitis C	22.9
Alcoholic liver disease	15.8
NASH/NAFLD	11.4
Autoimmune	4.9
Hepatitis B	4.0
ALD + hepatitis C	7.4
Cholestatic liver disease	16.6
Primary biliary cirrhosis	7.9
Primary sclerosing cholangitis	8.0

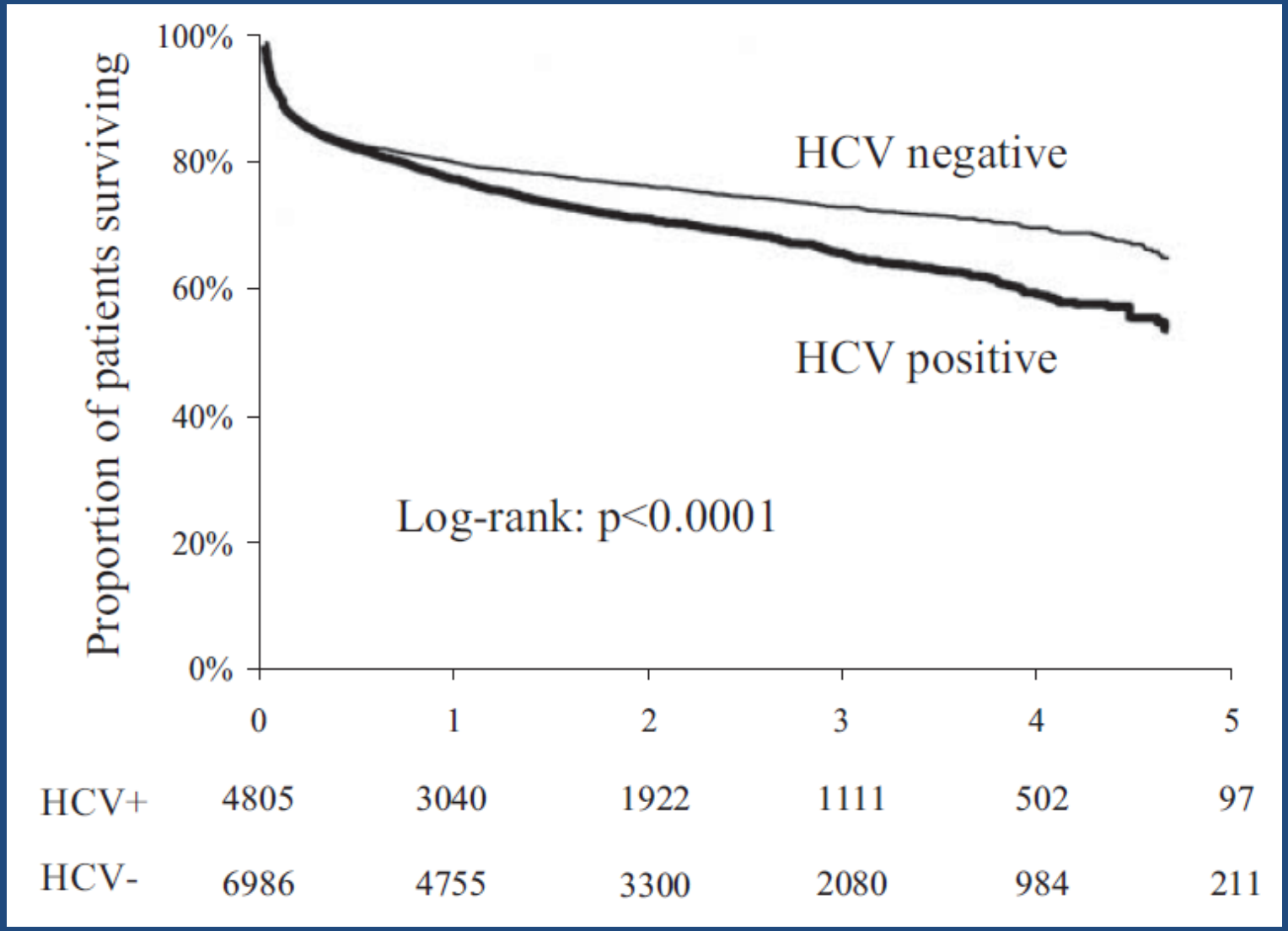
N = 12,908

Seaberg E.C. et al. 1999. Clinical Transplants 1998. Chapter 2

Natural History of HCV infection

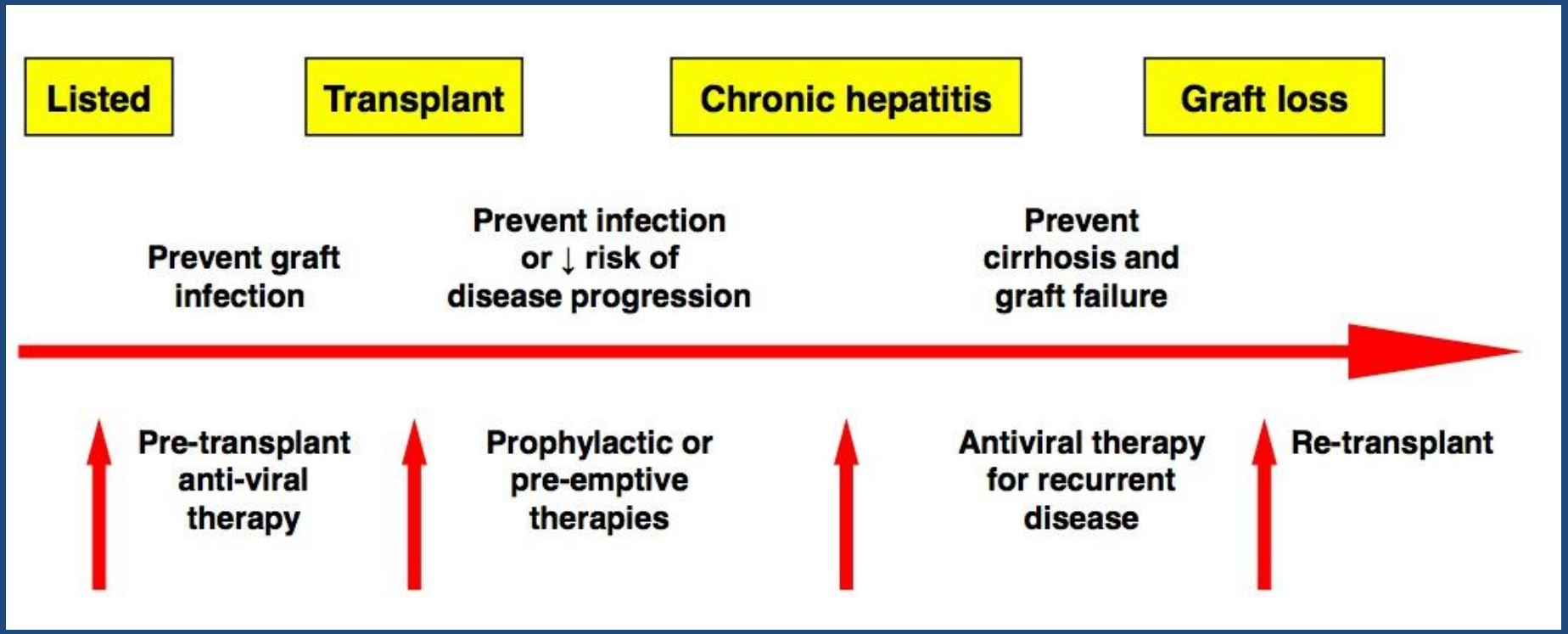


Post-transplant Graft Survival- UNOS, 1992-1999



HCV+	4805	3040	1922	1111	502	97
HCV-	6986	4755	3300	2080	984	211

Opportunities to Intervene with Antiviral Therapy



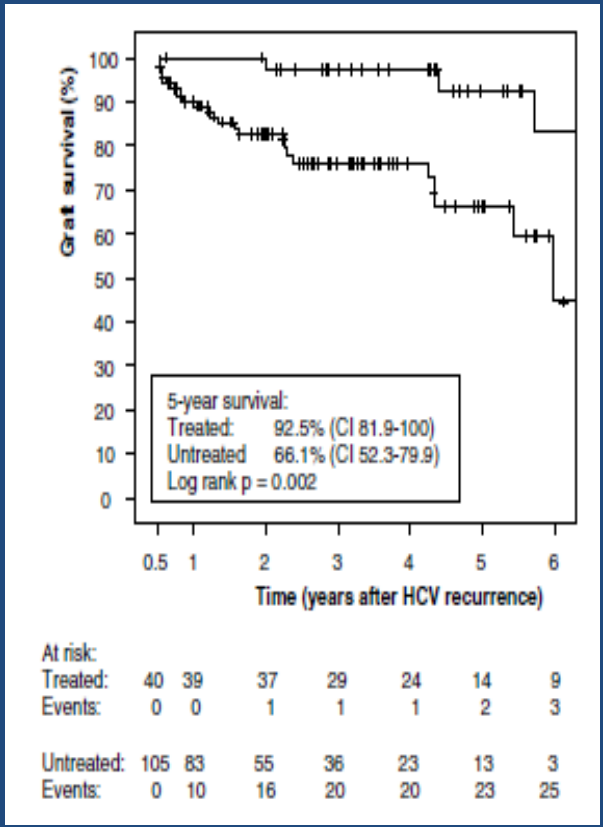
Biggins SW, Terrault NA. Infect Dis Clin N Am 2006; 20:155

Evolution of HCV Therapy

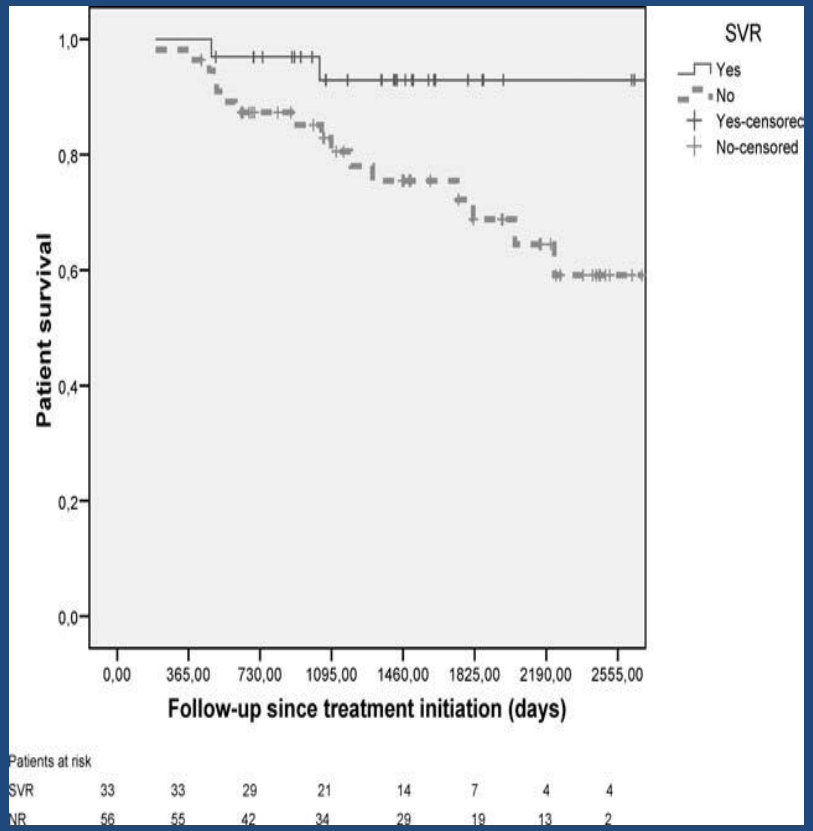
Independent of the treatment regimen used, sustained virological response (SVR) is the ultimate goal of therapy

SVR Associated With Improved Post-LTX Outcomes

HCV eradication leads to improvements in outcome

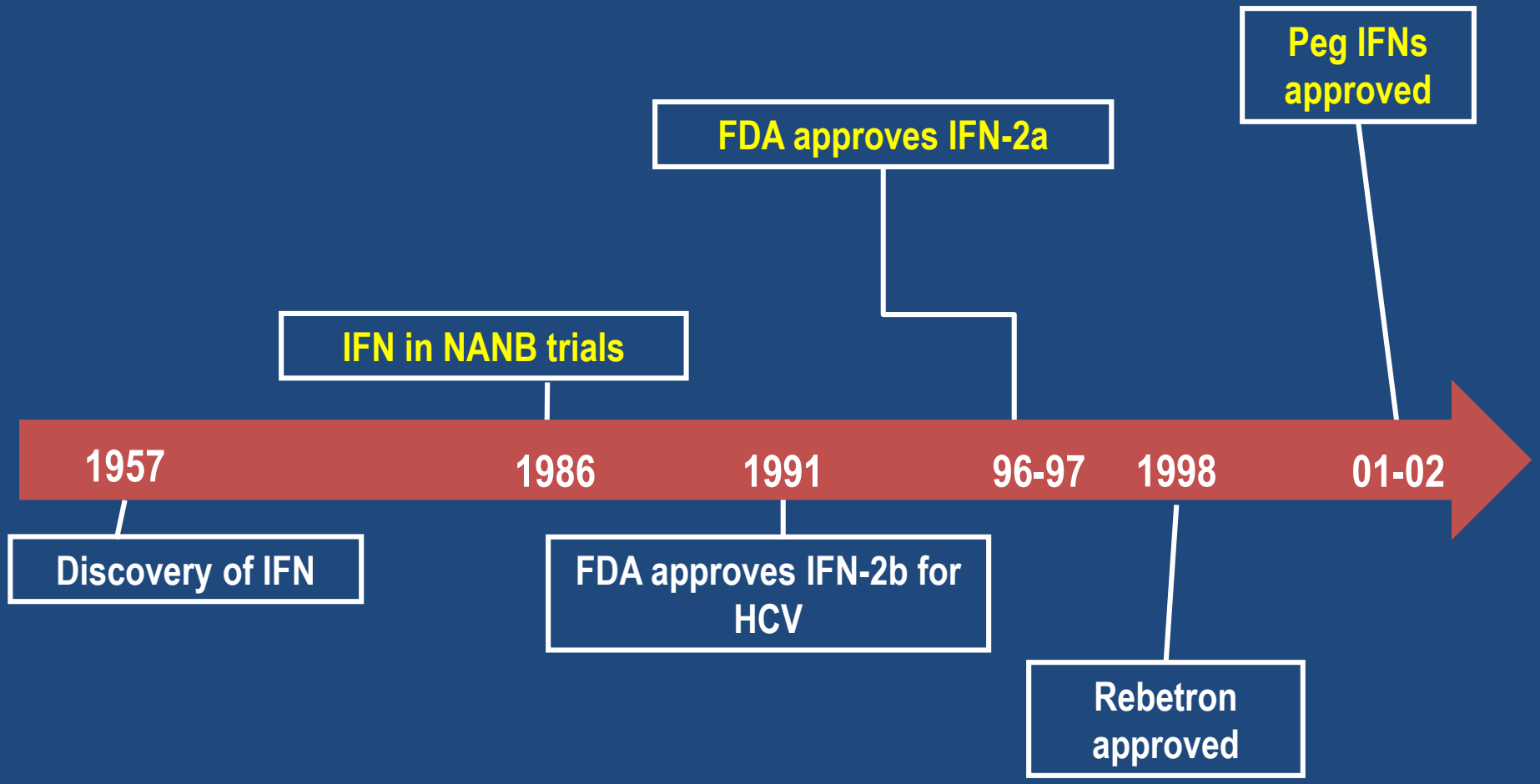


Veldt BJ et al. Am J Transplant 2008;8:2426–2433.

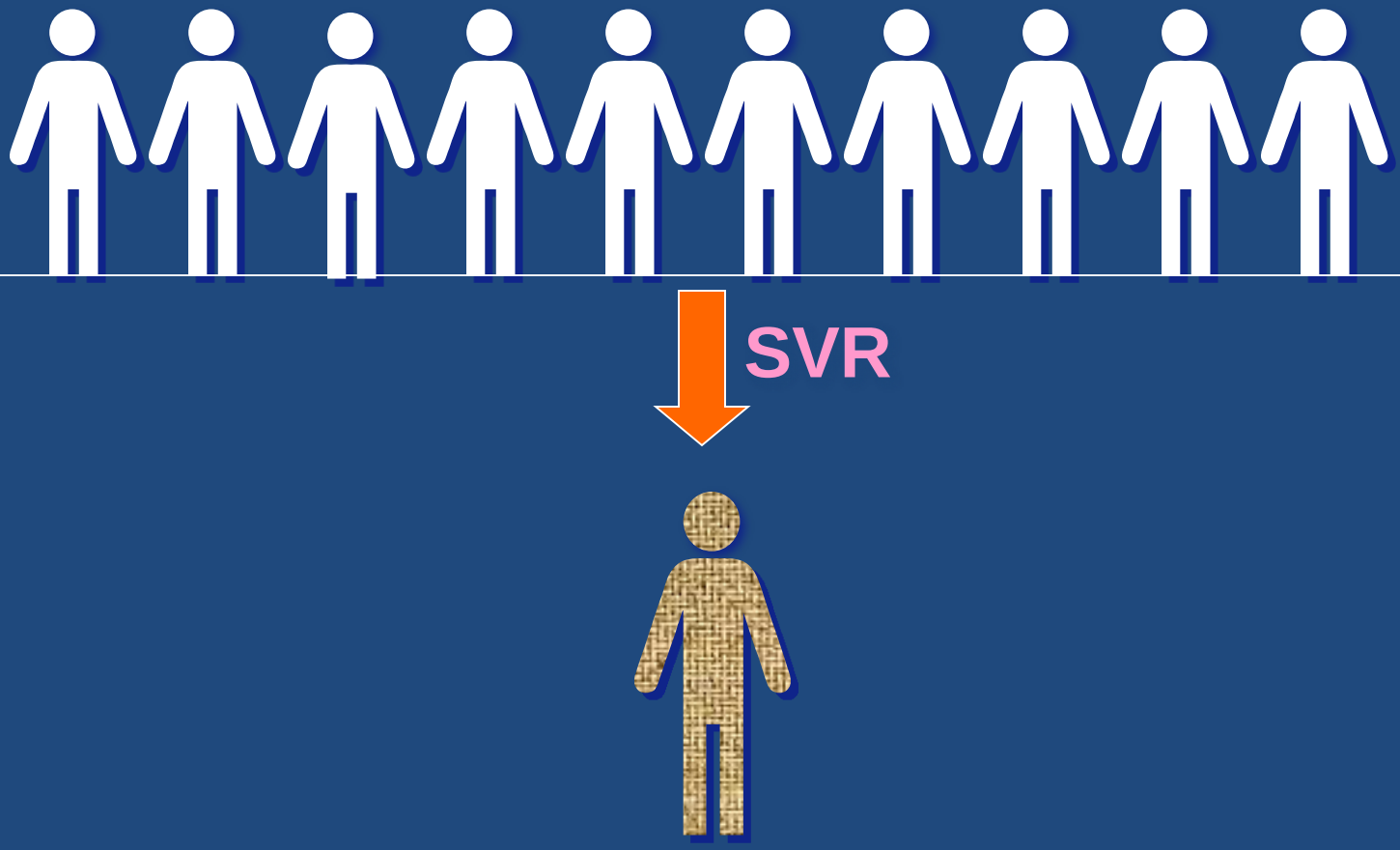


Berenguer M et al. Am J Transplant 2008;8:679–687.

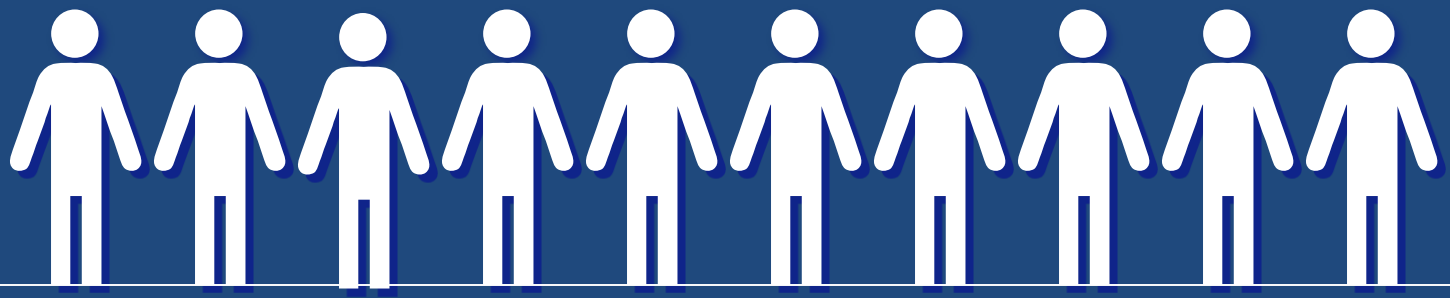
Evolution of Approved HCV Therapy – Interferon Based Therapy



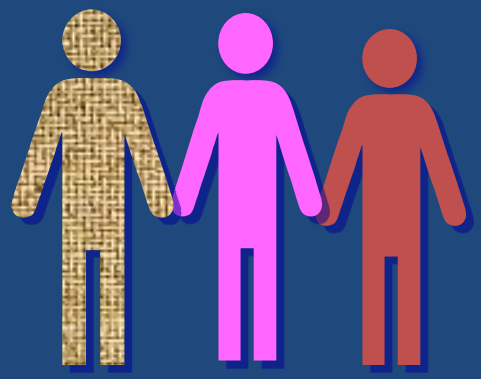
HCV G1: IFN Monotherapy x 6 months (1990-1993)



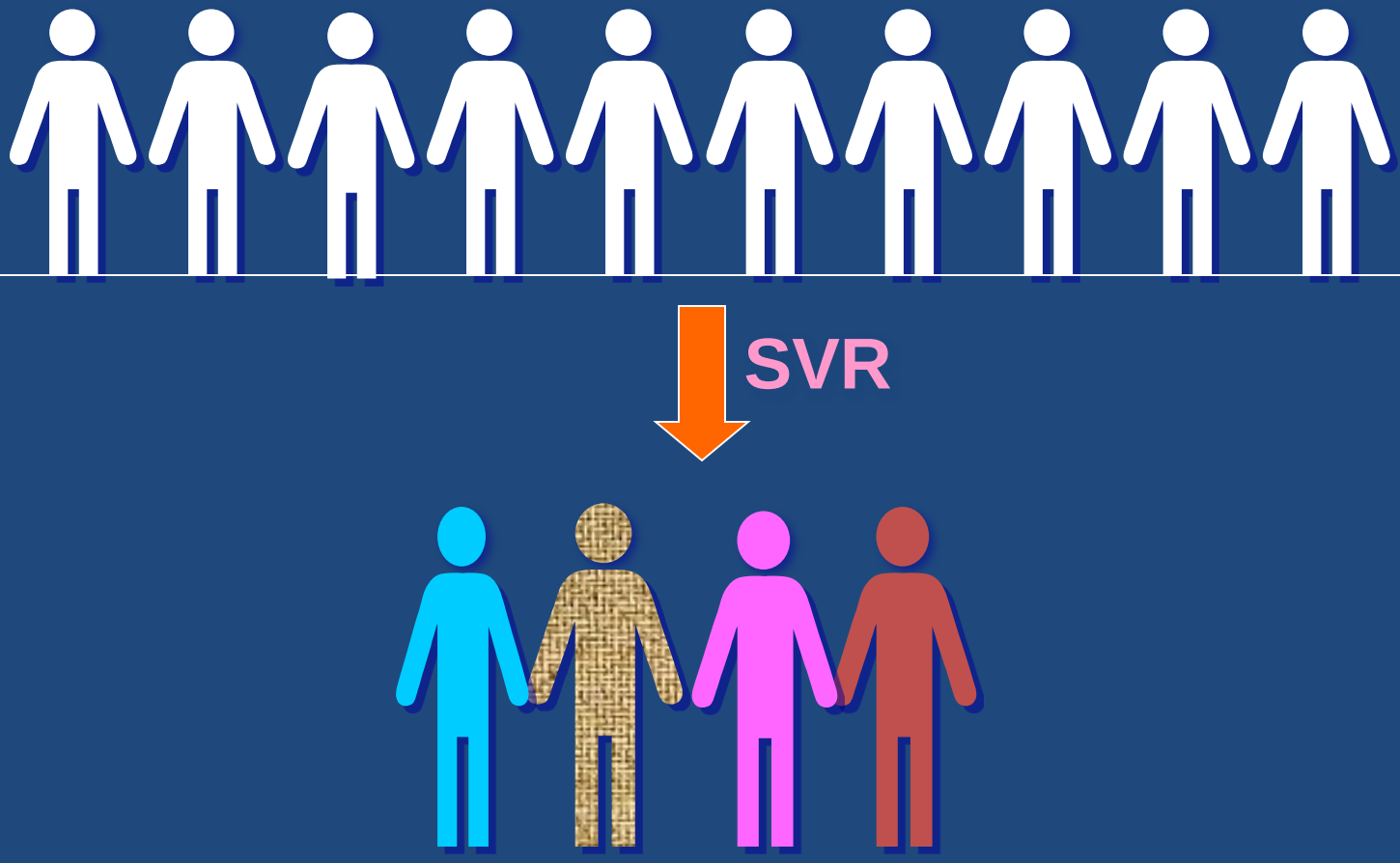
HCV G1: IFN+RBV x 12 months (1998-2001)



SVR



HCV G1: PEG IFN+RBV x 12 months (2002-2010)



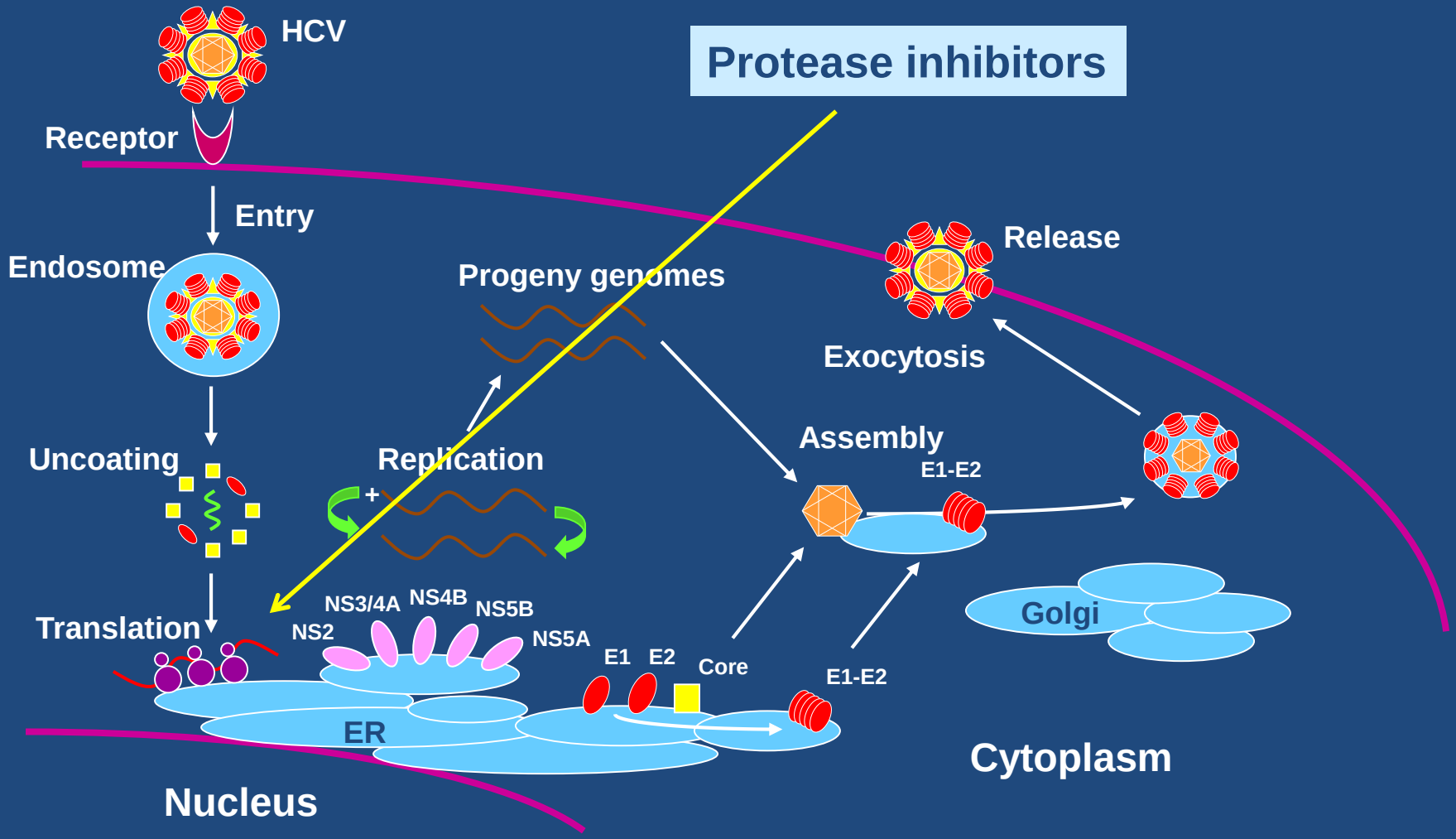
Issues with Interferon Based Rx Pre-LTX

- Therapy is significantly less effective in established cirrhosis
- High prevalence of genotype 1
- Problems in administering full doses of IFN and RBV because of side effects
- Risk of complications:
  - Life-threatening infection
  - Acceleration of hepatic decompensation
- As a result of severe cytopenias at baseline, 26–75% of screened patients are excluded for antiviral therapy

Management of HCV Disease Prior to 2014

- Antiviral therapy is primarily given post-LT
  - Annual biopsies used to monitor for fibrosis change
  - Treat early severe recurrence and those with progression (F2 or more)
- Mainstay of treatment = peg-IFN, ribavirin with later addition of Protease inhibitors (PIs)

Model of HCV Replication



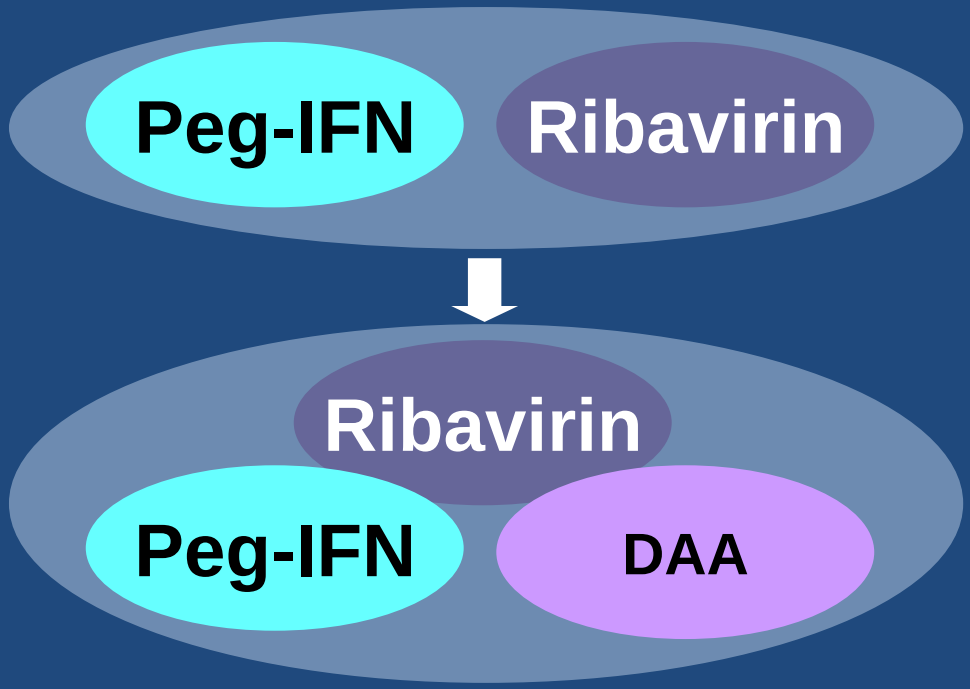
Racanelli V, et al. *Trends Immunol.* 2003;24:456-463.

Protease Inhibitors: First Generation DAA

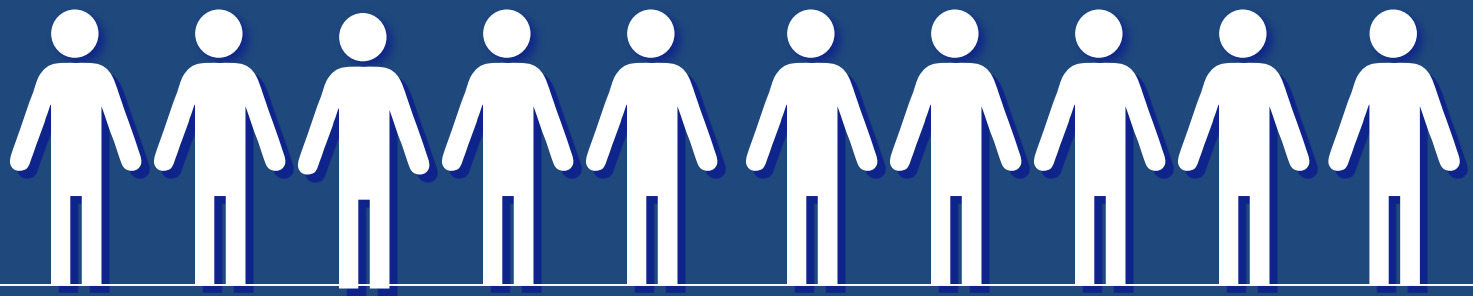
05/23/2011

05/14/2011

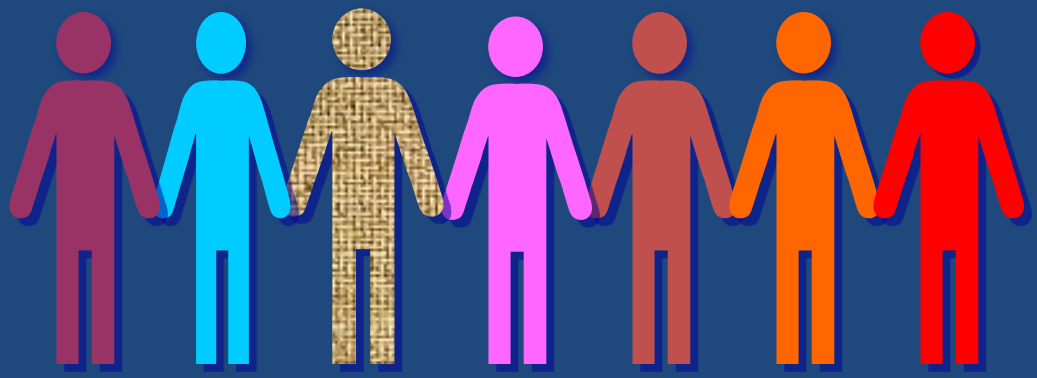
First-Generation Protease Inhibitors: Boceprevir And Telaprevir In Triple Combination



Triple Therapy with Telaprevir and Boceprevir (2011-2013)

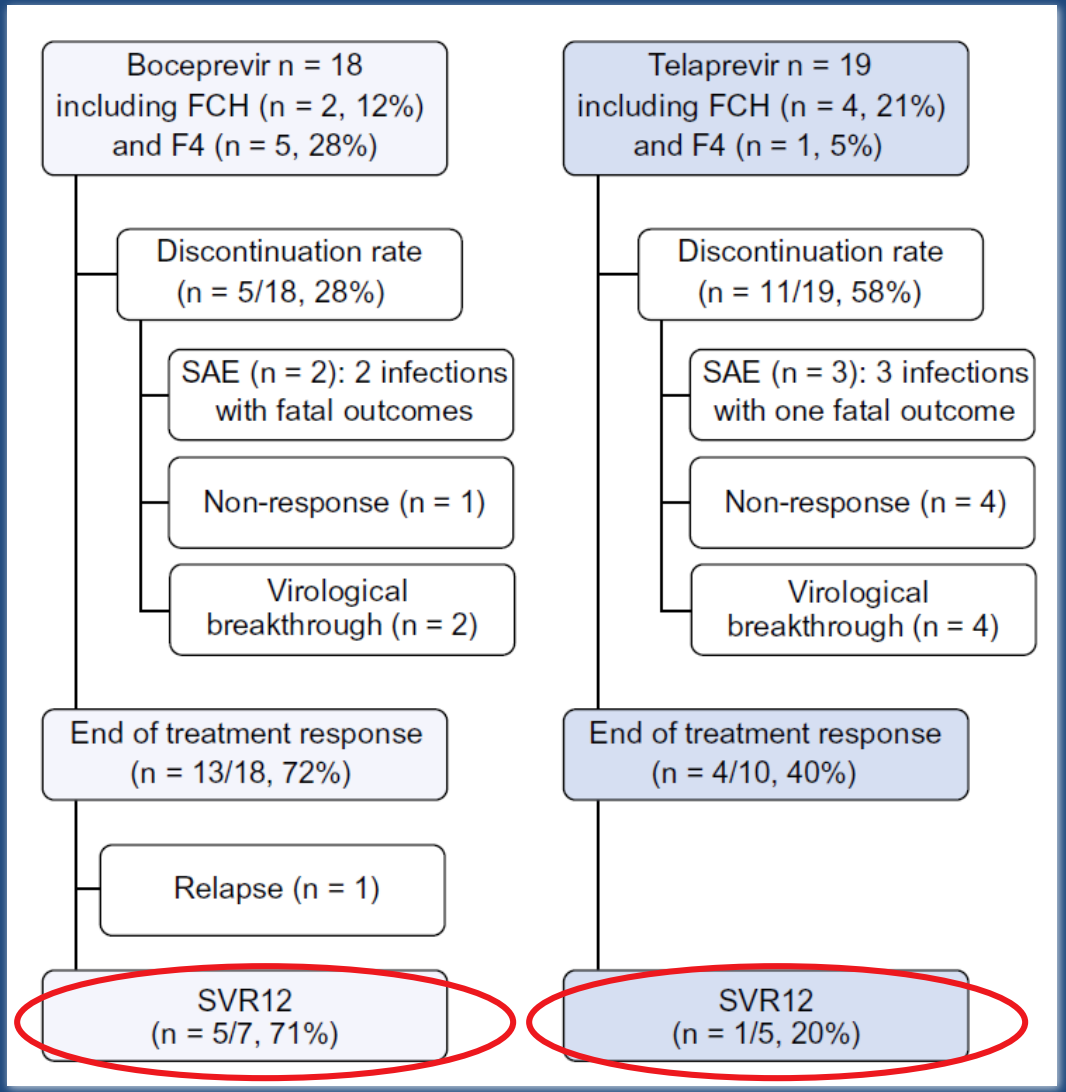


SVR



A very short lived era

Safety and efficacy of protease inhibitors to treat hepatitis C after liver transplantation: A multicenter experience



- Regimen complexity
  - High pill burden
  - Long duration, complex RGT rules
  - Multiple drug-drug interactions
  - Overlapping toxicities
  - With/without food dosing requirements
- Tolerability
  - Additional AEs beyond pegylated interferon/ribavirin

Coilly A et al. J of Hepatol. 2013

Adverse Events

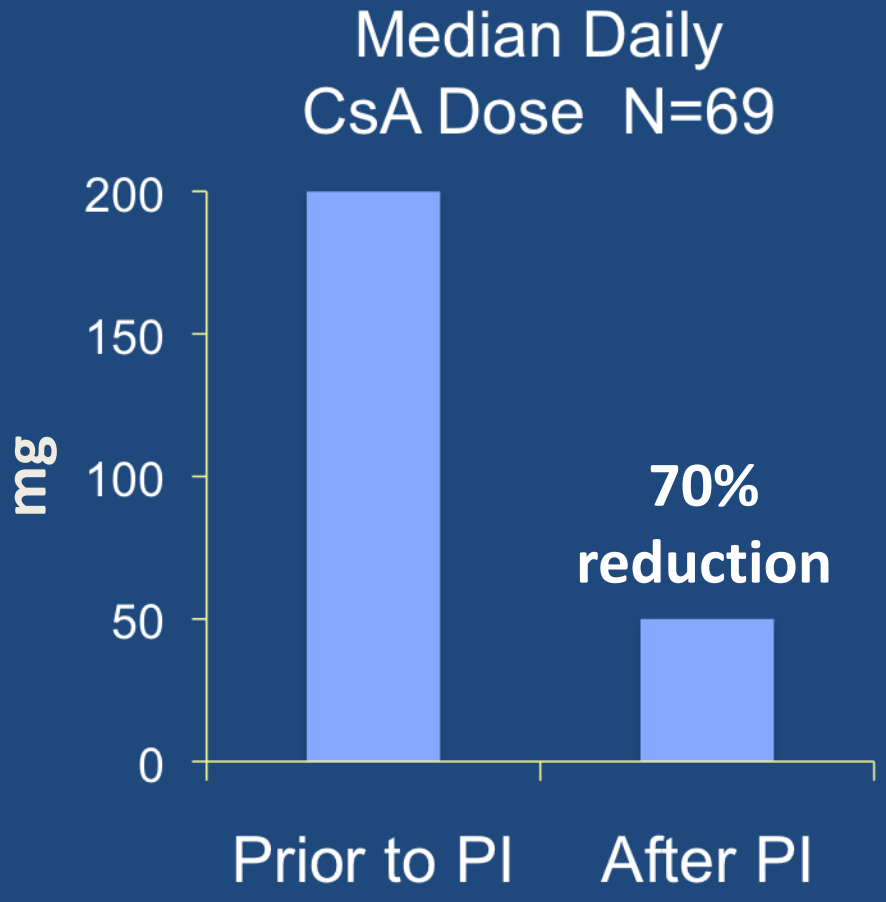
Adverse Event	All Patients (n=95)
AE requiring Rx discontinuations	18%
Hospitalization (%)	28%
Transfusion (%) Number of units** (IQR)	59 4 (2-8)
Rash (%)*	9%
Cr increase >0.5 mg/dl (%)	33%
Liver rejection**	3%
Death Liver-related	8% 8%

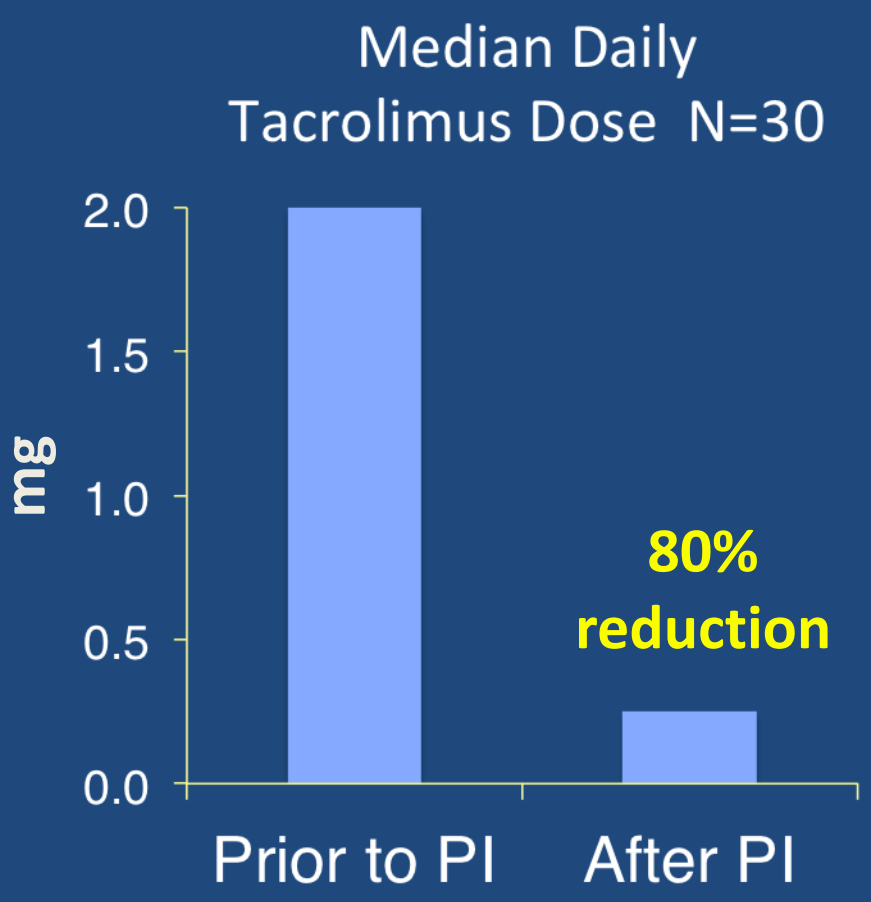
*Rash requiring more than topical therapy

**Any treated rejection during or after TT

Burton J, J Hepatol 2014

Calcineurin Inhibitor Dosing



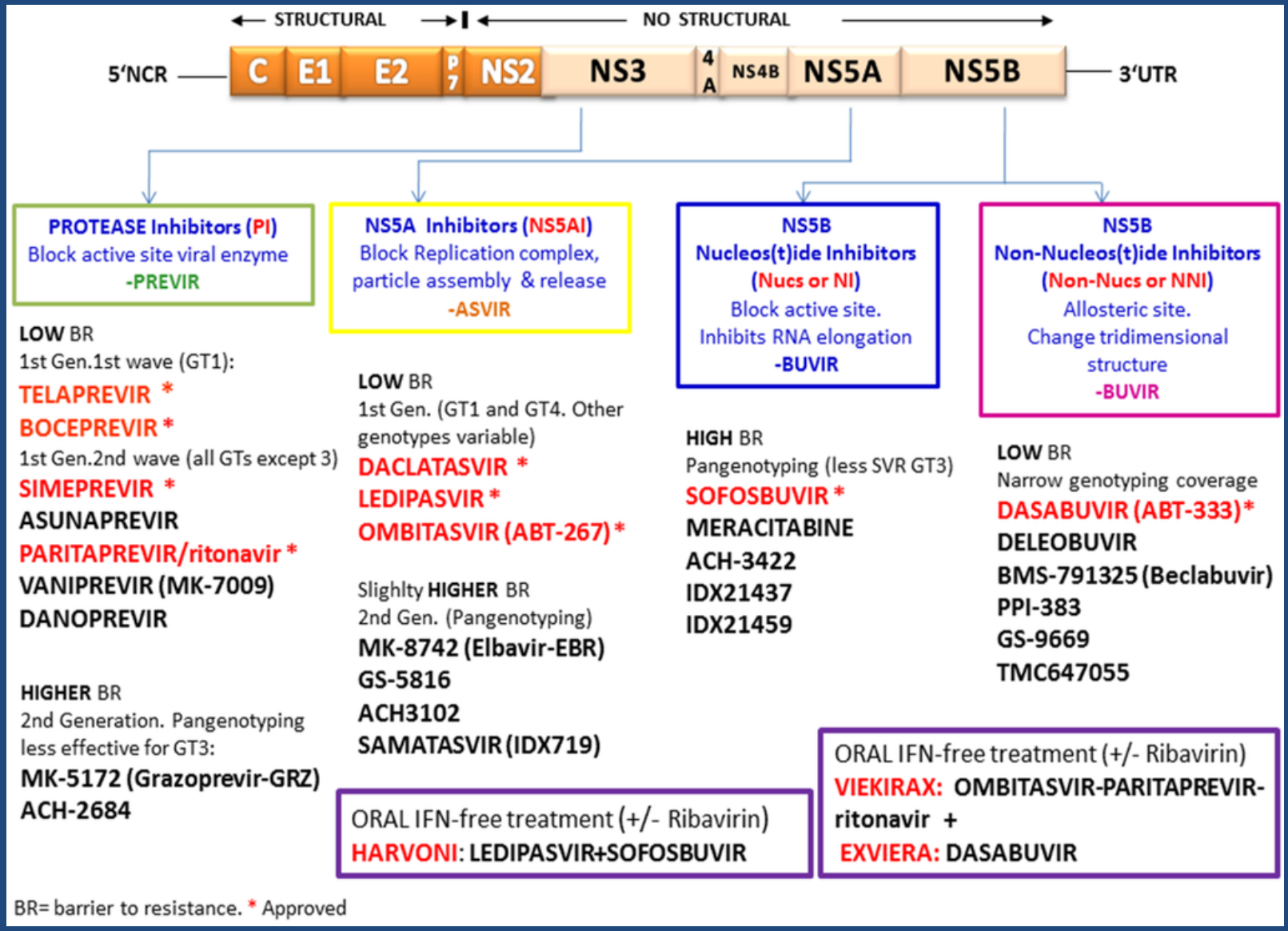


Burton J, J Hepatol 2014

PI-Triple Therapy
Why this Experience is Important

- First therapy to provide SVR rates >50% for genotype 1 patients
  - Major advance → many patients/ grafts saved
  - In countries with limited access to new DAAs, this remains an effective treatment option

Every Step of HCV Replication Can be Targeted

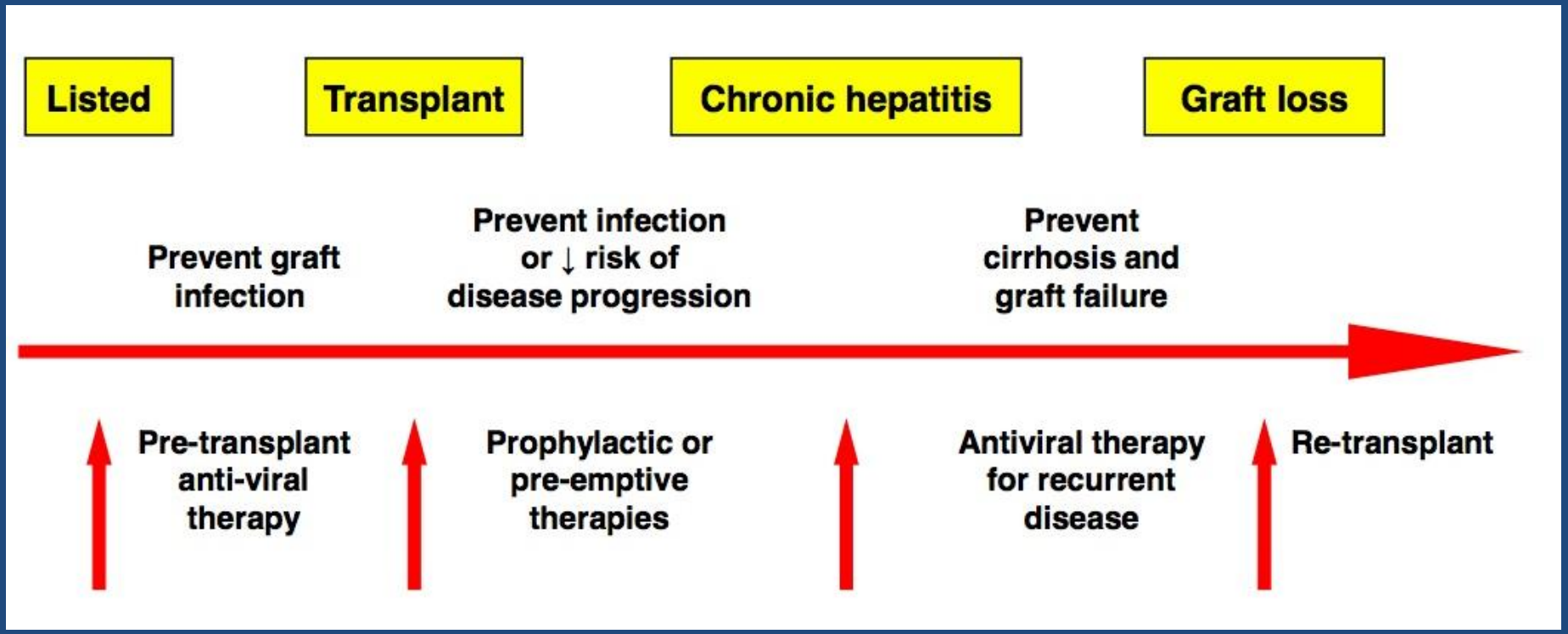


BR= barrier to resistance. * Approved

Sofosbuvir: A "Game Changer" For Management of Recurrent HCV Disease

- Positives
  - Excellent tolerability
  - No DDI with immunosuppression
  - Consistent HCV RNA suppression on treatment
- Negatives
  - Renal insufficiency requires dose reduction
    - Unknown dosing if on dialysis
  - Cost and access

Opportunities to Intervene with Antiviral Therapy



Biggins SW, Terrault NA. Infect Dis Clin N Am 2006; 20:155

The Arguments For/Against Treating Waitlisted Patients

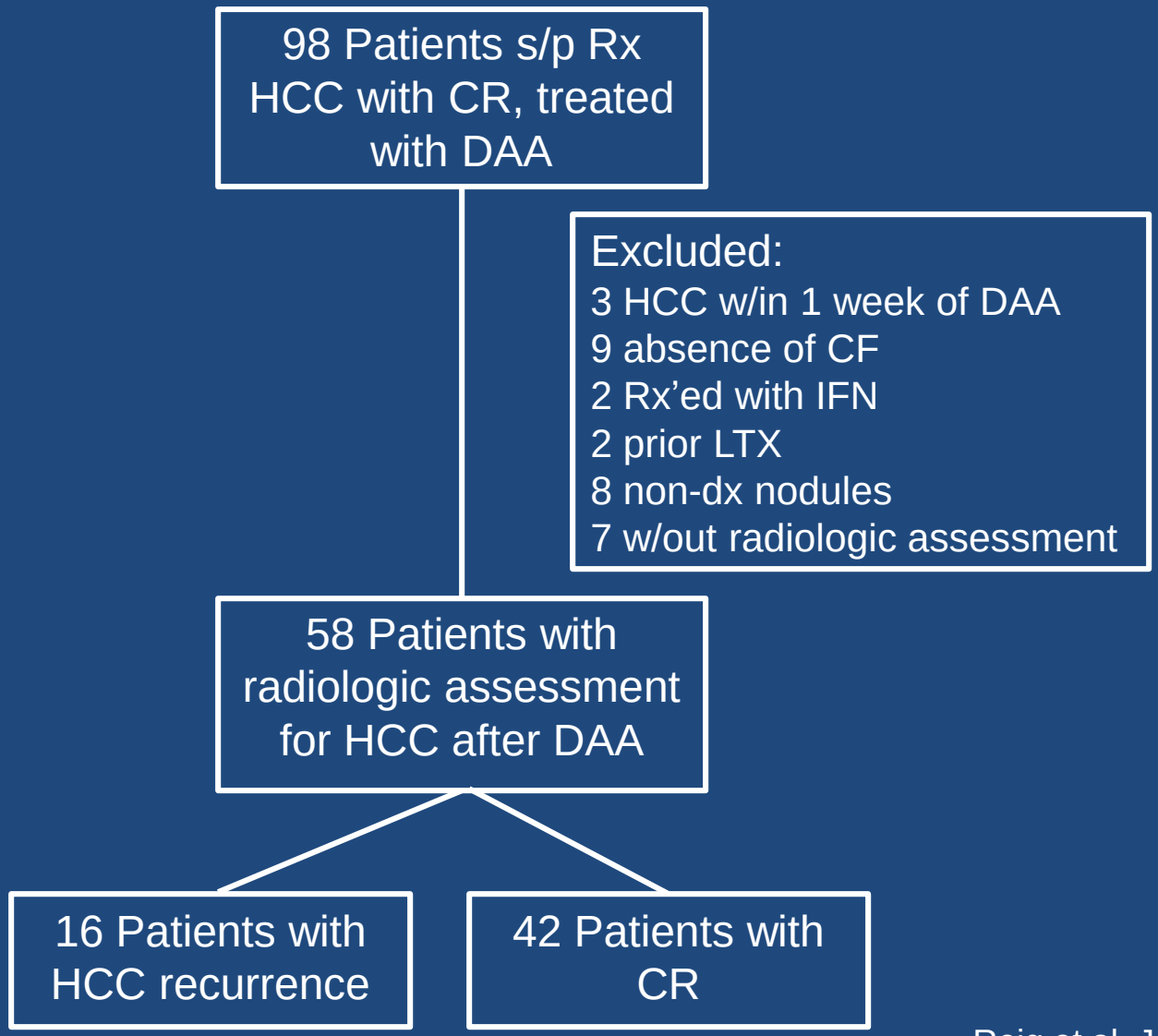
For Treatment Pre-Transplant:

1. Treatment of HCV is simpler pre-transplant, less DDI;
2. Practice guideline consensus for early treatment;
3. May allow patients to improve sufficiently to be removed from WL

Against Treatment Pre-Transplant:

1. Some waitlisted patients are sicker than their MELD score – unknown impact on waitlist mortality;
2. HCV clearance does not improve non-MELD complications, e.g. ascites, encephalopathy;
3. Clearance of HCV disqualifies candidate for HCV positive liver;
4. Success rate for HCV treatment is greater post-transplant;
5. Greater cost effectiveness (death on WL, HCC dropout)
6. Association of DAA therapy and HCC?

Unexpected HCC After HCV Clearance With DAA



- 7/16 initially Rx'ed with resection - 9/16 initially Rx'ed with RFA
- Median time from HCC Rx to DAA Rx was 11.2 months
- Median time from CR to HCC recurrence was 3.5 months
- Recurrence rate higher than center's historical non-DAA treated controls.

Reig et al. J Hepatol, 2016 [Epub ahead of print]

Risk Of Liver Decompensation Regardless Of Treatment Response in Face of Portal Hypertension

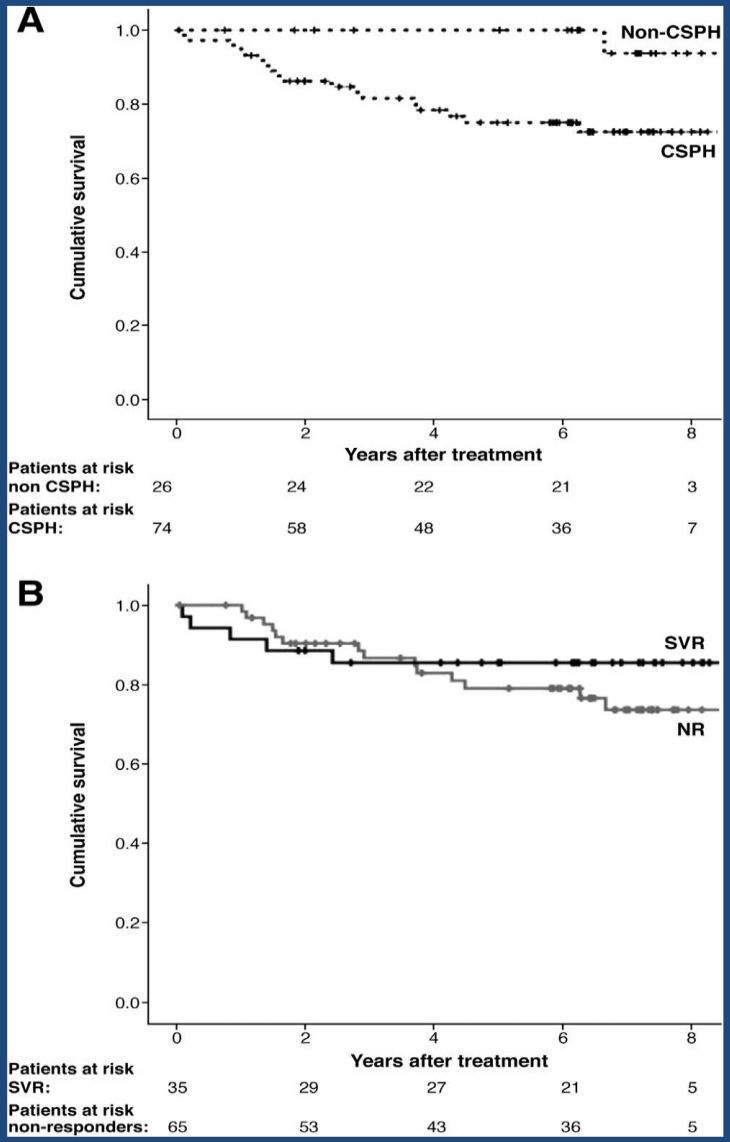


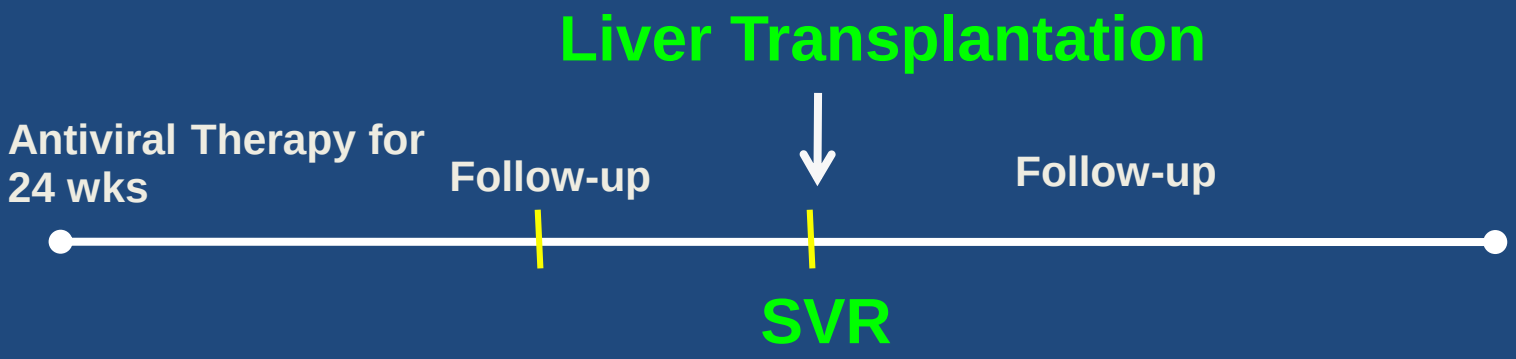
Table 3. Univariate and Multivariate Analyses of Variables Associated With the Development of Liver Decompensation

	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
Platelet count	0.97 (0.94–0.99)	.02		
Child–Pugh score	3.3 (1.4–3.3)	.08		
Esophageal varices	5.1 (1.8–14.4)	.002		
SVR	0.6 (0.2–1.8)	.42		
Baseline HVPG	1.1 (1.03–1.2)	.007	1.2 (1.1–1.6)	.05
Baseline CSPH	7.5 (1–56)	.04		

Patients with CSPH (Cirrhosis with severe portal hypertension, HVPG ≥ 10 mm Hg), regardless of an SVR to therapy for hepatitis C, remain at risk for liver decompensation within the first 5 years after treatment

Lens S et al. Clin Gastroenterol Hepatol 2015;13:1846–1853.

Treatment Strategies in Wait-Listed Patients with Chronic HCV



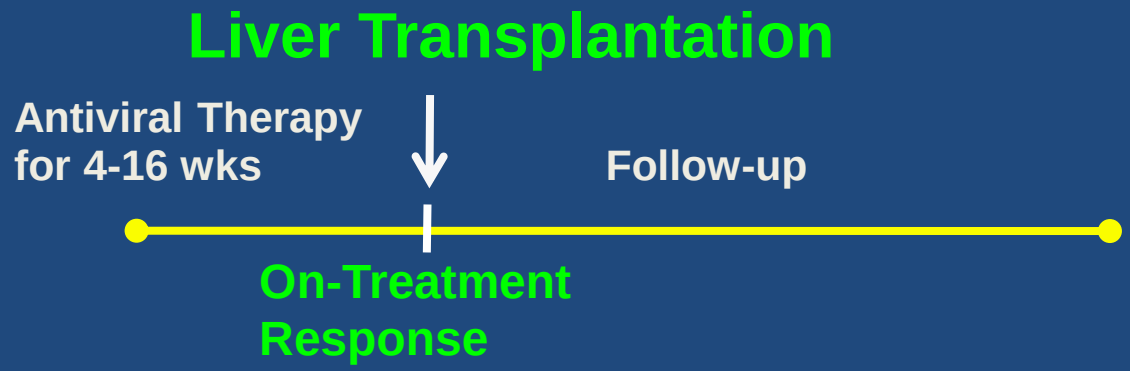
Pros

- Uniformly prevent post-LT HCV infection
- May reverse / improve liver function allowing avoidance of liver transplantation

Cons

- Treatment of patients who may not survive to LT
- Improvement insufficient to avoid LT but reduces MELD to range less likely to get LT

Treatment Strategies in Wait-Listed Patients with Chronic HCV



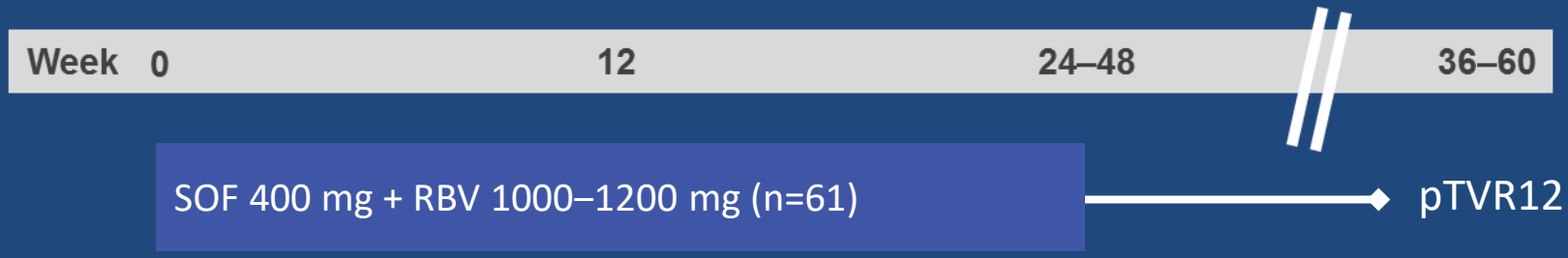
Pros:

- Shorter duration therapy (reduced adverse events)
- Higher rates of virologic response

Cons:

- Will not prevent need for LT
- Timing of treatment can be difficult
- Variable pTVR

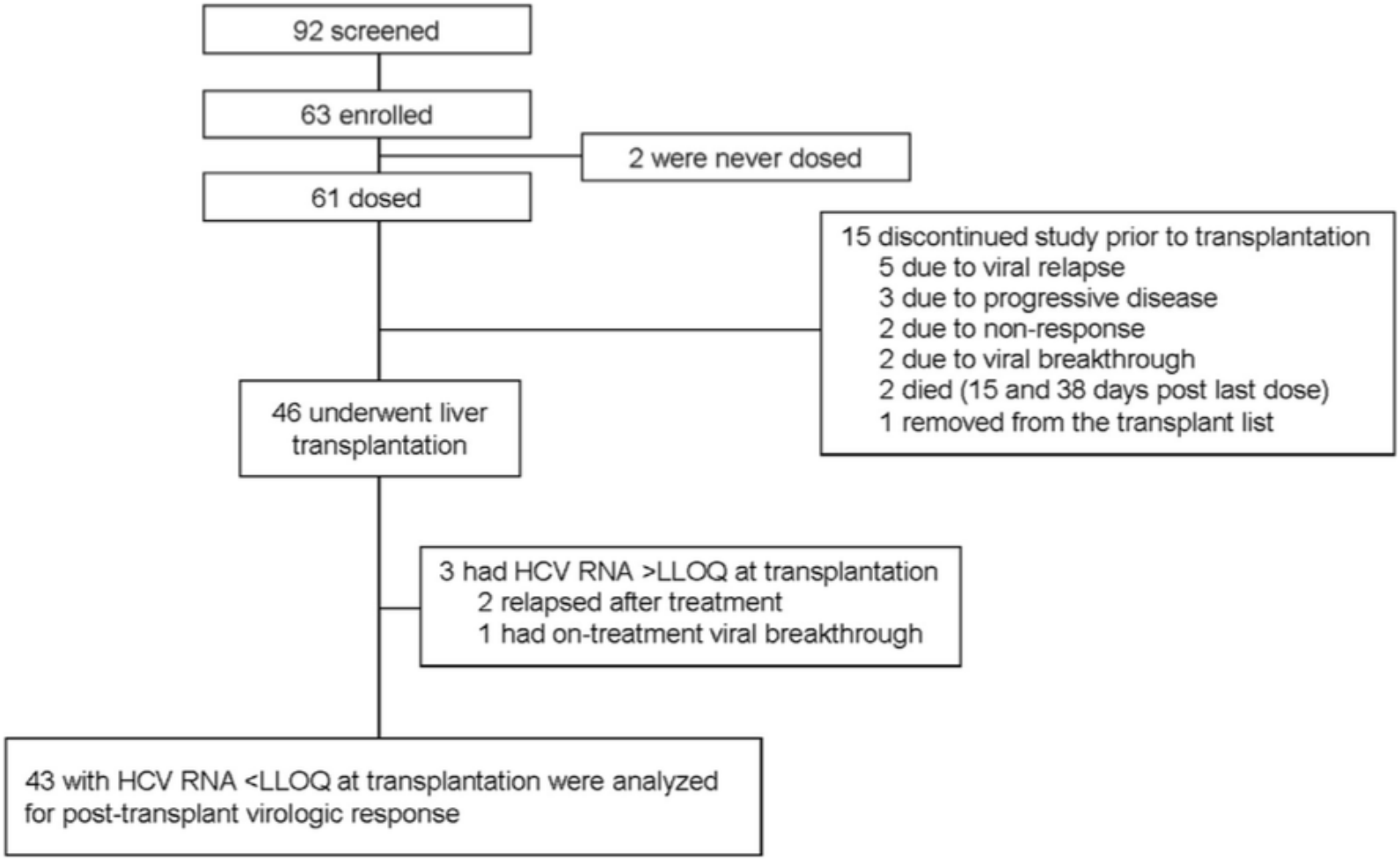
SOF + RBV in Wait-Listed HCV Patients (G1-4)



- N=61 DDLT candidates with MELD exception for HCC
  - CPT ≤8 (43% CP=5, 73% CP-A)
  - Median MELD =8 (8-14)
  - CrCl ≥60 mL/min
  - Rx- naïve (25%) or experienced (75%)
  - Absence of HIV or HBV

Curry M et al. Gastroenterology 2015

Patient Disposition



Safety of SOF + RBV in Compensated Cirrhotics on Wait-List

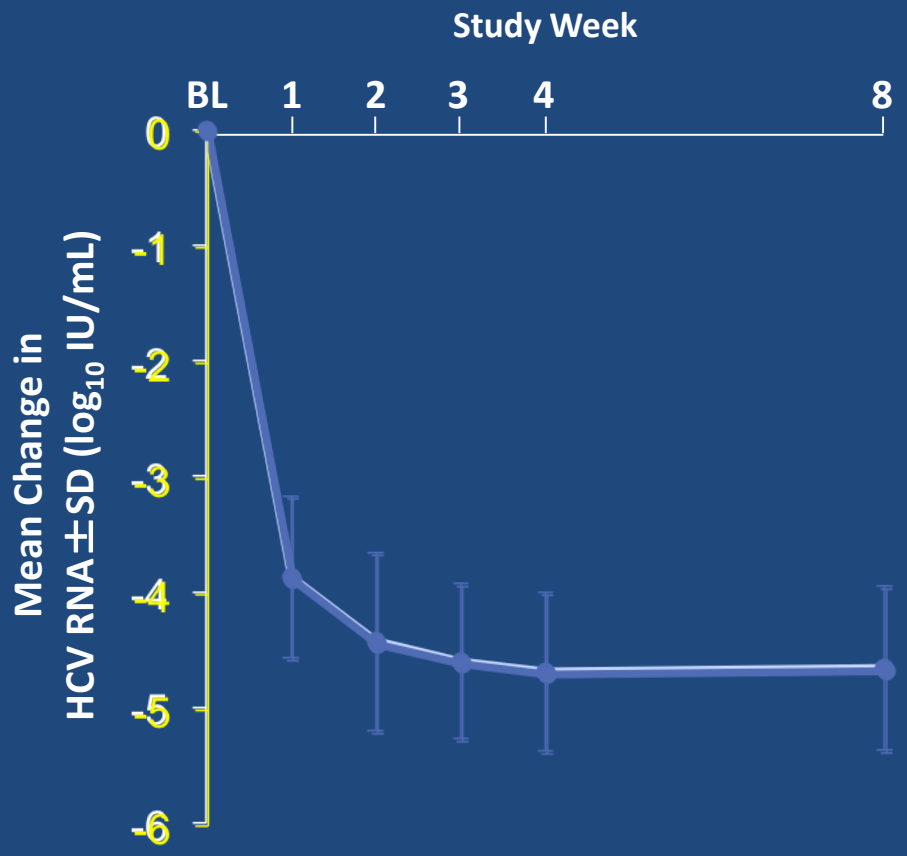
SAEs*	11 (18)
Deaths pre-LT	2 (3)
AEs leading to DC of study treatment	2 (3)
AEs in ≥10% of patients	
Fatigue	23 (38)
Anemia	14 (23)
Headache	14 (23)
Nausea	10 (16)
Rash	9 (15)
Dyspnea	7 (11)
Insomnia	7 (11)

*No SAEs were deemed related to SOF.

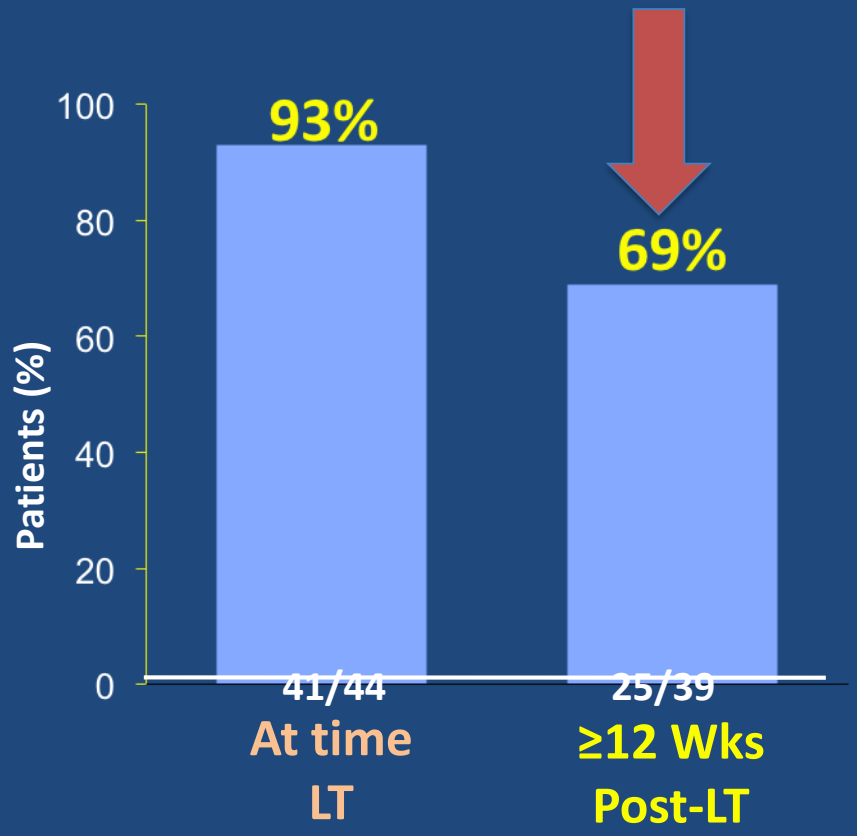
Curry M et al, Gastroenterology 2015

Viral Responses with SOF-RBV

HCV RNA Change from Baseline (n=61)



HCV RNA <LLOQ at Transplant

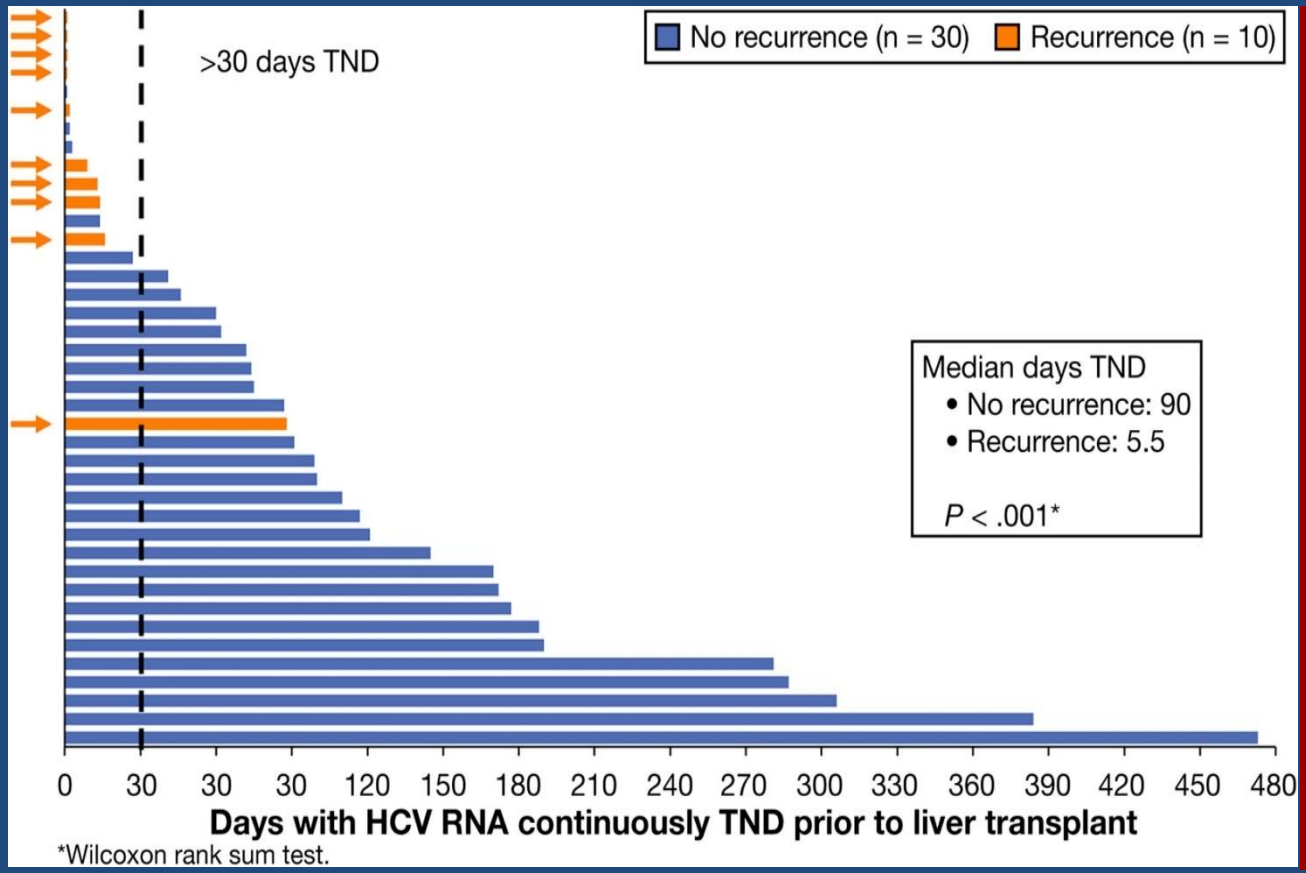


*3 subjects were >LLOQ at transplant.

†1 subject has not reached pTVR12, 1 subject LTFU at Week 8 post transplant.

Curry M et al, Gastroenterology 2015

Prevention Of HCV Recurrence Is Feasible

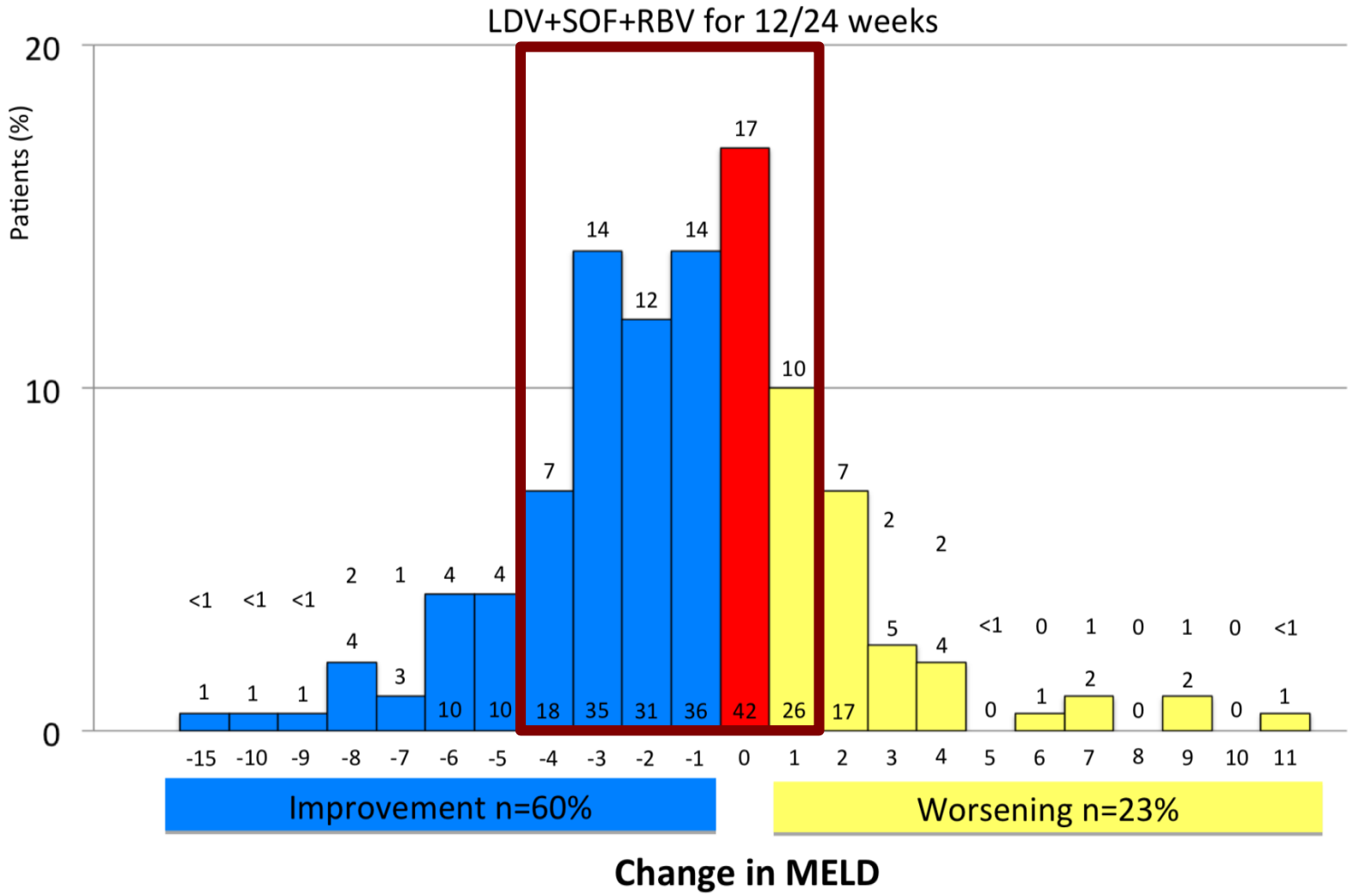


- **93% had HCV RNA < LLOQ at LTX**
- **pTVR12: 70%**
- **Continuous days TND pre-LT strongest predictor of HCV recurrence in multivariate analysis**
  - **Only 1/27 (4%) pts with > 30 days TND experienced recurrence (vs 9/13 – 69% <30 days TND)**

Open study, phase II, SOF + RBV for the prevention of recurrence of HCV infection patients on waiting list for LTX with preserved liver function (CTP ≤7, MELD <22). Decompensated cirrhosis, renal failure, and LDLT excluded. Patients treated for up to 48 weeks or until LTX

Curry MP et al. Gastroenterology 2015;148:100–107.

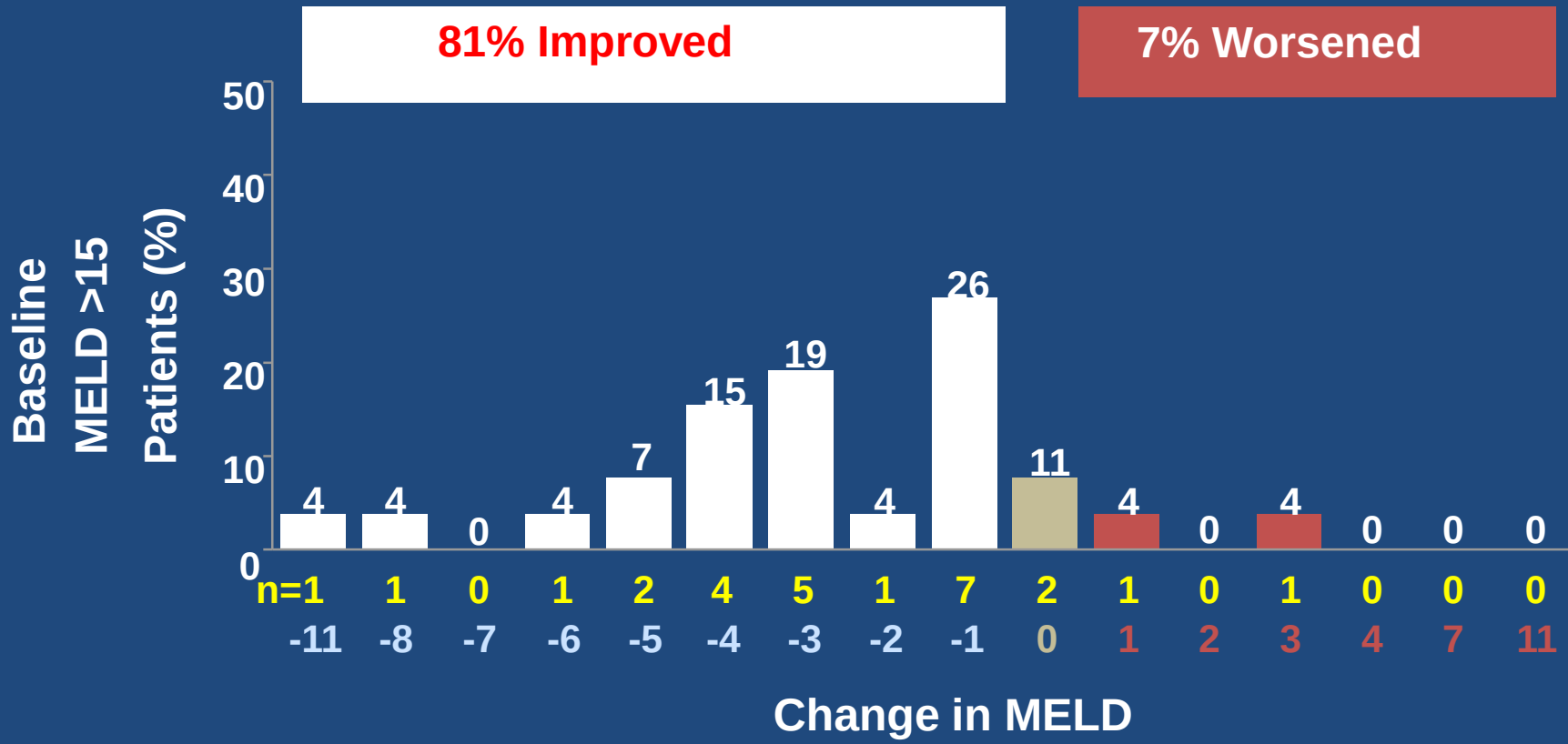
Combined Efficacy from the SOLAR-1 and SOLAR-2



Total n=250

Gane EJ et al. presented at: AASLD 2015

ASTRAL-4 Study: SOF/VEL in Patients with Decompensated Liver Disease
MELD Change: Baseline to Follow-up Week 12 Patients With SVR12



Curry MP et al. N Engl J Med 2015;373:2618–2628

ASTRAL-4: Improvements in Liver Function

Improvement in CPT Component % (n/N)	SVR 12 wk N=229 Baseline: CPT A: 29% (4/14) CPT B: 48% (98/205) CPT C: 60% (6/10)	SVR 24 wk N=213 Baseline: CPT A: 46% (6/13) CPT B: 53% (102/191) CPT C: 78% (7/9)
Albumin	34% (79/229)	39% (35/213)
INR	2% (5/229)	2% (5/213)
Total bilirubin	18% (41/229)	16% (35/213)
Encephalopathy	5% (12/229)	9% (20/213)
Ascites	8% (18/229)	15% (32/213)

Curry MP et al. N Engl J Med 2015;373:2618–2628;
Curry MP et al: Poster 2016 ILTS

Pre-Transplant Treatment HCV Summary

- Treatment decisions require consideration of:
  - Time to LT
  - Severity of liver disease (CPT)
- If aiming for prevention of post-LT HCV, need at least 4 weeks of HCV RNA negativity
  - SOF + RBV appears safe for CP-A, B & C patients
  - Requirement for RBV can be limiting in sick patients
- If aiming for SVR → limited current options for Childs B(+) and C patients
  - SOF + RBV for 24-48 weeks

The Arguments For/Against Treating Post-Transplant Patients

For Treatment Post-Transplant:

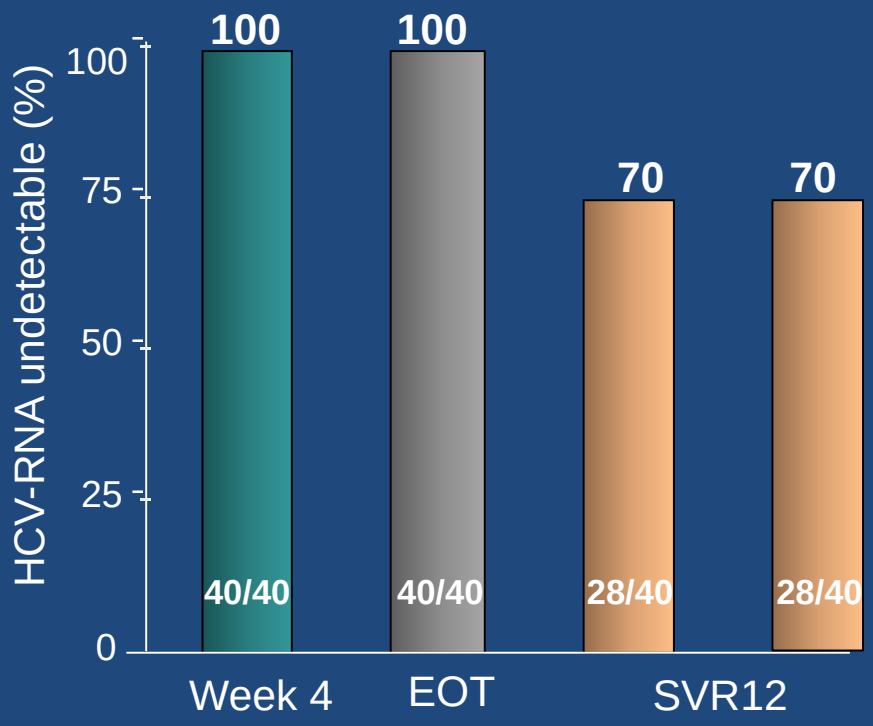
1. Treatment of HCV is more effective post-transplant;
2. More efficient, since only survivors of LTX are transplanted;
3. Allows consideration for HCV positive donor liver

Against Treatment Post-Transplant:

1. Potential for more complex drug-drug interactions (DDI);
2. High incidence of post-transplant renal dysfunction affects safety of DAA therapy;
3. Differential diagnosis of liver allograft dysfunction will include the possibility of recurrent HCV

Sofosbuvir And Ribavirin In LTX Recipients

Efficacy



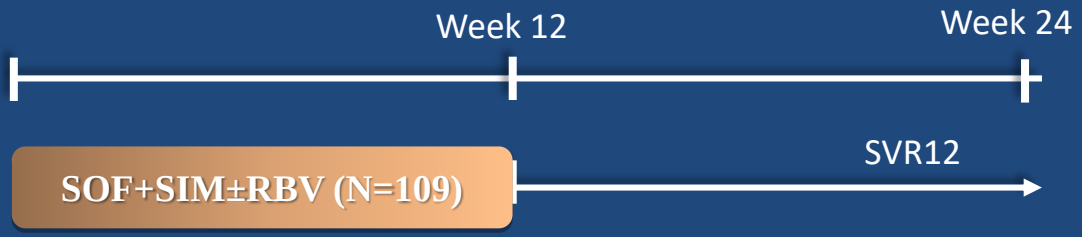
Safety

Anemia	20%
Rejection	0
Renal Impairement	0
Early Discontinuation	5%
SAEs	15%
Deaths	0

No DDI reported

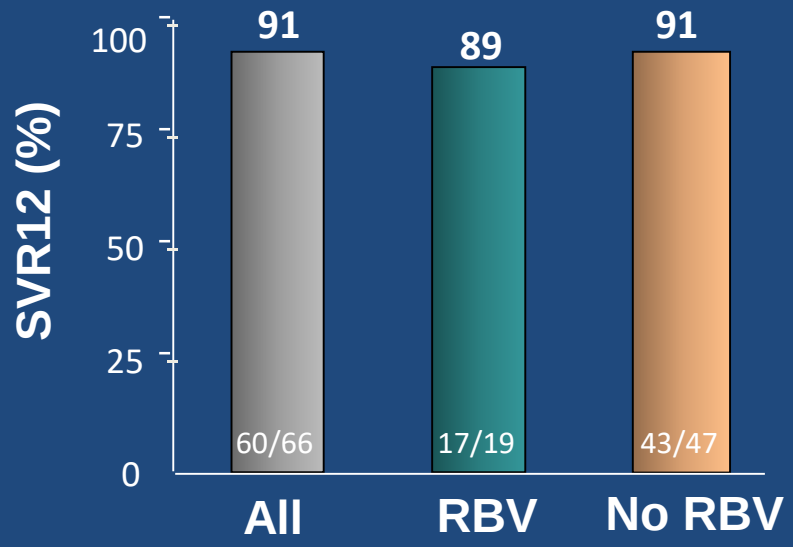
Charlton et al. Gastroenterology 2015

Simiprevir, Sofosbuvir +/- Ribavirin In LTX Recipients



Multicenter experience
(non randomized study)

G1 (G1a 62%), F3-F4 29%, Cholestatic recurrence 11%, Failed PR 69%, Failed PR+PI 12%



Safey: well tolerated
Anemia in RBV group 42% vs 2% non RBV group
1 death (drug-induced lung injury?)

Pungpapong et al AASLD 2014

PK/PD Studies In Patients With Renal & Hepatic Impairment

DAA	Primary metabolic pathway	Suitable in patients with cirrhosis			Suitable if renal impairment
		CTP-A	CTP-B	CTP-C	
Sofosbuvir[1]	Hepatic	Yes	Yes	Yes	Not if CrCl < 30 mL/min
Simeprevir[2]	Hepatic	Yes	No	No	Not if CrCl < 15 mL/min
Asunaprevir[3]	Hepatic	Yes	No	No	Unknown
ABT-450/RTV[4]	Hepatic	Yes	No	No	Yes
Ledipasvir[5,6]	Hepatic	Yes	Yes	Yes	Yes
Ombitasvir[7]	Hepatic	Yes	No (as combo)	No (as combo)	Yes
Daclatasvir[8,9]	Hepatic	Yes	Yes	Yes	Yes
Dasabuvir[7]	Hepatic	Yes	No	No	Yes

1. Sofosbuvir 2013 prescribing information; 2. Simeprevir 2013 prescribing information; 3. Asunaprevir 2015 prescribing information; 4. Khatri A et al. Abstract 758 presented at: AASLD 2012; 5. German P et al. Abstract 467 presented at: AASLD 2013; 6. Kirby R et al. Abstract Clinical Pharm 2013; 7. Ombitasvir/dasabuvir 2014 prescribing information; 8. Bifano M et al. Abstract 1362 presented at: AASLD 2011; 9. Garimella K et al. Abstract P43 presented at: Clinical Pharm 2014;

Drug-Drug Interactions

Drug Class	Drug	DDI with CNIs and mTORi YES	NO
Protease inhibitors	Boceprevir	✔	
	Telaprevir	✔	
	Simeprevir		✔
	ABT450/r	✔	
NUC	Sofosbuvir		✔
Non-NUC PoL Inh	Dasabuvir		✔
NS5Ai	Ledipasvir		✔
	Daclatasvir		✔
	Ombitasvir		✔

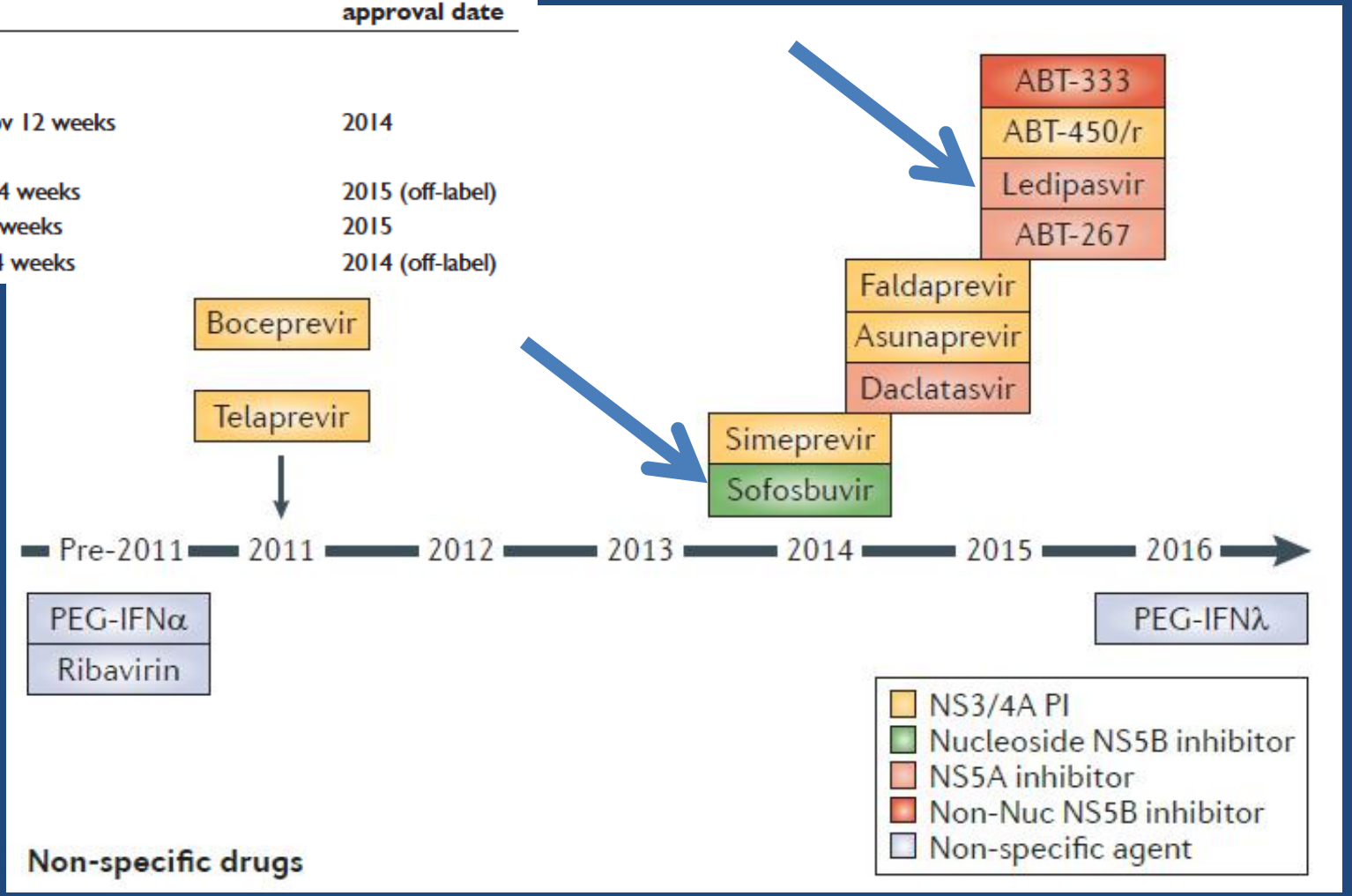
Tischer and Fontana, J Hepatol 2014

Current HCV Treatment Post-LTX

- IFN-free, all oral therapy quickly are becoming the norm
  - High efficacy and significantly improved tolerability
- Anticipate more IFN-free and RBV-free options in near future (within the year in U.S.)
- As choices increase the factors that are likely to influence treatment choices are:
  - DDIs
  - Renal function
  - Availability
  - Cost

Sofosbuvir and Ledipasvir Fixed Dose: 2014

Regimen	Expected FDA approval date
HCV-1	
IFN sparing	
• SOF + PegIFN/Rbv 12 weeks	2014
IFN free	
• SOF + DCV 12/24 weeks	2015 (off-label)
• SOF + LDV 8/12 weeks	2015
• SOF + SMV 12/24 weeks	2014 (off-label)

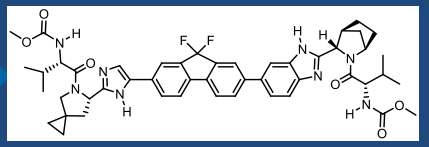


Manns MP et al. Nat Rev Drug Discov. 2013

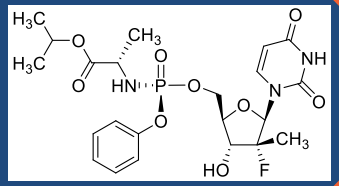
Ledipasvir/Sofosbuvir: A Single Tablet

- **Ledipasvir**
  - NS5A is essential for RNA replication and post-replication assembly and secretion
  - Picomolar potency against HCV GT 1a and 1b
  - Effective against NS5B RAV S282T
  - Once-daily, oral, 90 mg

LDV
NS5A
inhibitor



- **Sofosbuvir**
  - Potent antiviral activity against HCV GT 1–6
  - High barrier to resistance
  - Once-daily, oral, 400-mg tablet



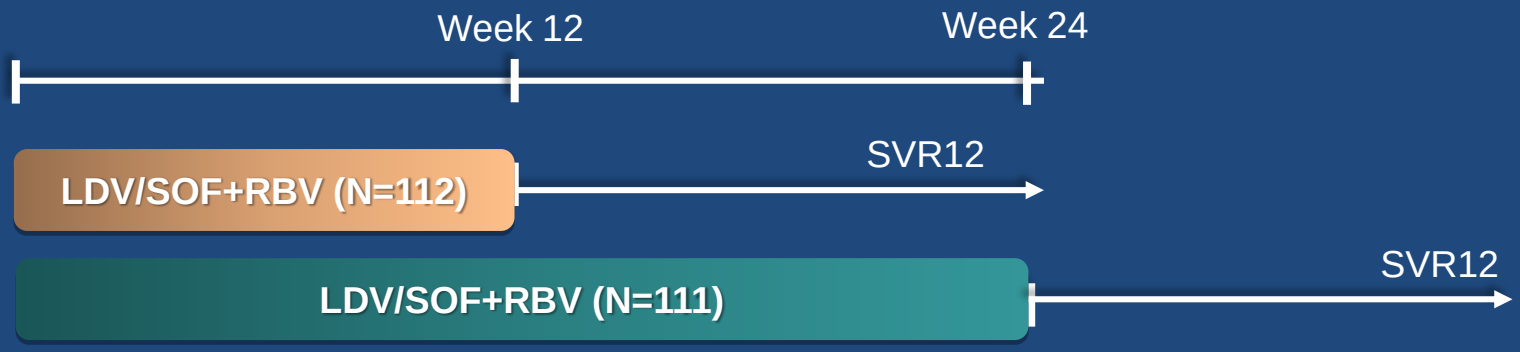
SOF - NS5B
nucleotide
polymerase
inhibitor

- **Ledipasvir/Sofosbuvir STR**
  - Once-daily, oral fixed-dose (90/400 mg) combination tablet
  - No food effect

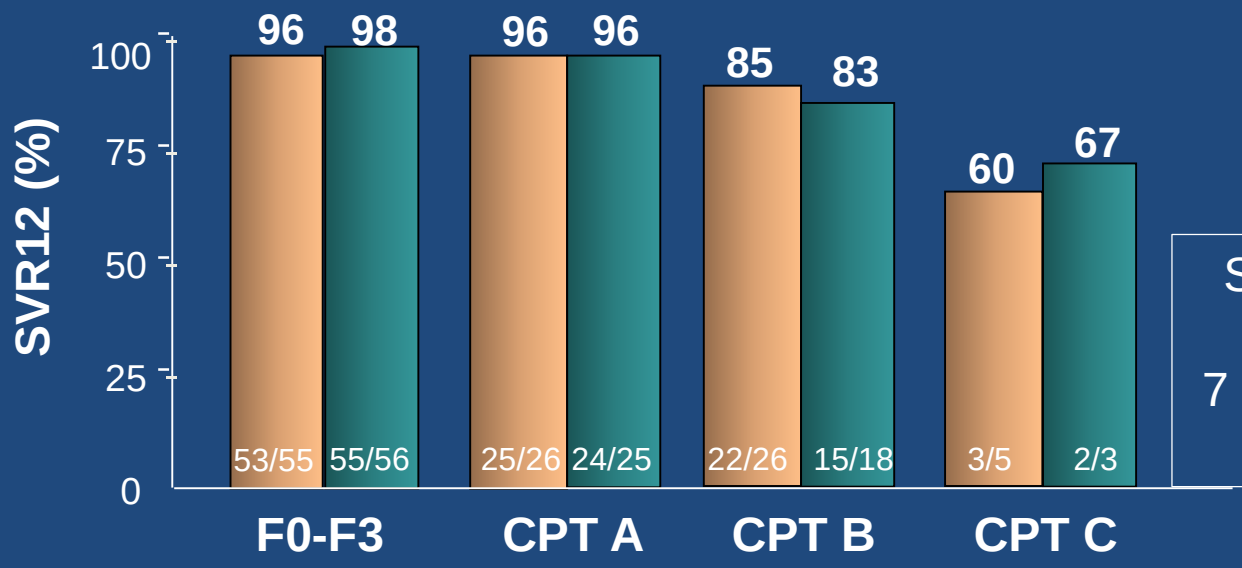
LDV
NS5A
inhibitor

SOF - NS5B
nucleotide
polymerase
inhibitor

Lawitz E, et al. EASL 2011, poster 1219
Cheng G, et al. EASL 2012, poster 1172



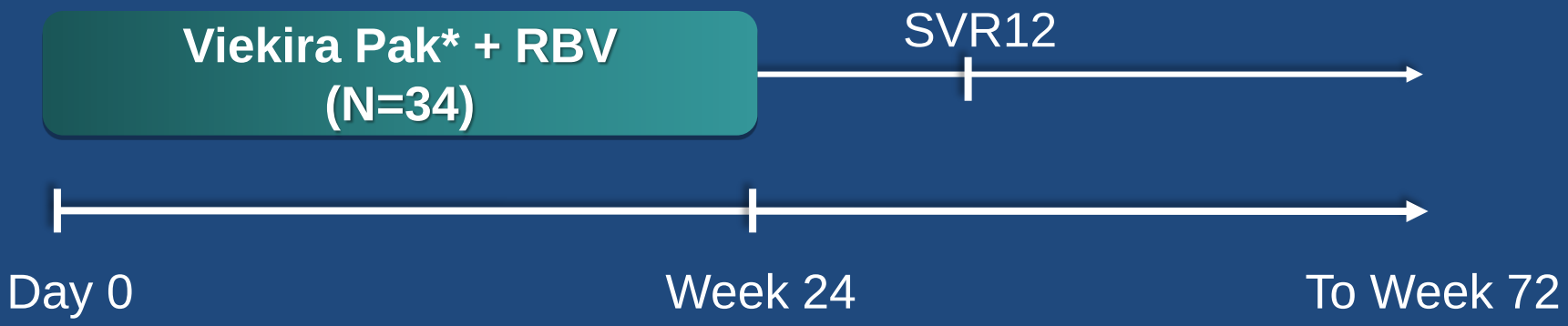
G1 or G4 treatment naïve or treatment experienced post-LT. F0-F3, CPT A, B C



Safety: Treatment generally safe
7 deaths (2 CPT A, 5 CPT B), diverse causes

Reddy et al AASLD 2014

Study M12-999 (CORAL-1): Design



- Ombitasvir (ABT-267): NS5A inhibitor
- Paritaprevir (ABT-450): NS3/4A serine protease inhibitor
- Ritonavir: HIV protease inhibitor used as pharmacologic booster
- Dasabuvir (ABT-333): Non-nucleoside NS5B polymerase inhibitor

▪ G1 Patients, Naïve after LT, F0-2, stable immunosuppression with TAC or CsA.

▪ TAC adjusted to 0.2-0.5 mg/week and CsA to 1/5 pre-3D dosing

Kwo et al, NEJM 2014

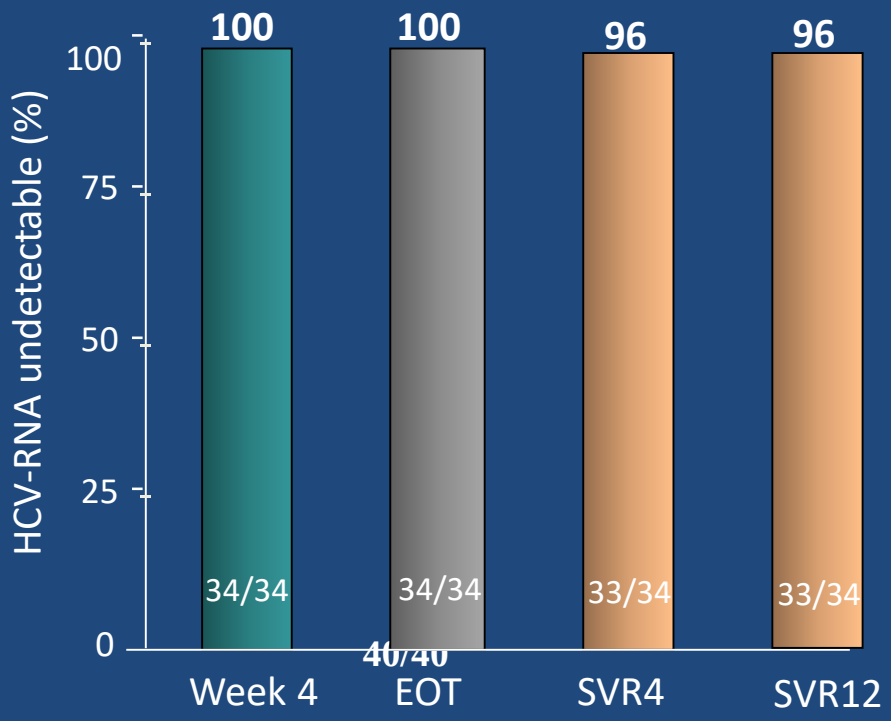
Paritaprevir/R(ombitasvir) + Dasabuvir + RBV In LTX Recipients

Mean time since transplantation, months	47.9
Male (%)	79.4
Mean age (years)	59.6
Fibrosis stage (%)	
F0-F1	53
F2	47
IL28B non-CC (%)	76.5
HCV subtype (%)	
GT1a	85.3
G1b	14.7
Mean HCV RNA (log_{10} IU/mL)	6.6
Immunosuppressive medication (%)	
Tacrolimus	85.3
Cyclosporine	14.7
Mean creatinine clearance (mL/min)	90.5
Mean ALT/AST/GGT (U/L)	78.9 / 63.9 / 170.3

Kwo et al, NEJM 2014

Viekira Pak + RBV for 24 Weeks

Efficacy



Safety

Anemia	**17%**
Rejection	0
Renal Impairment	0
Early Discontinuation	**3%**
SAEs	**6%**
Deaths	0

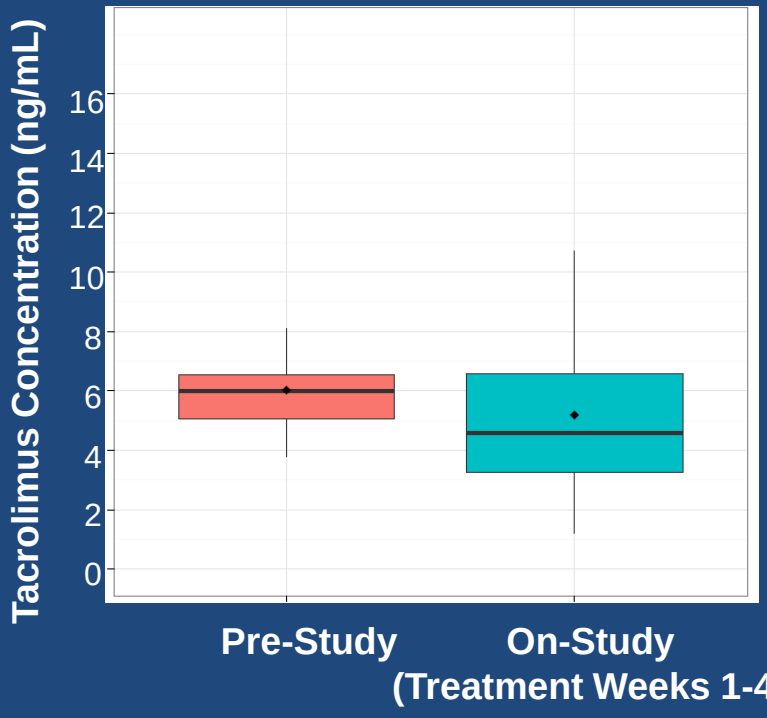
- No patient had breakthrough
- One patient had a relapse; at the time of relapse, this patient had R155K in NS3 protease, M28T+Q30R in NS5A, and G554S+G557R in NS5B, none of which were present at baseline

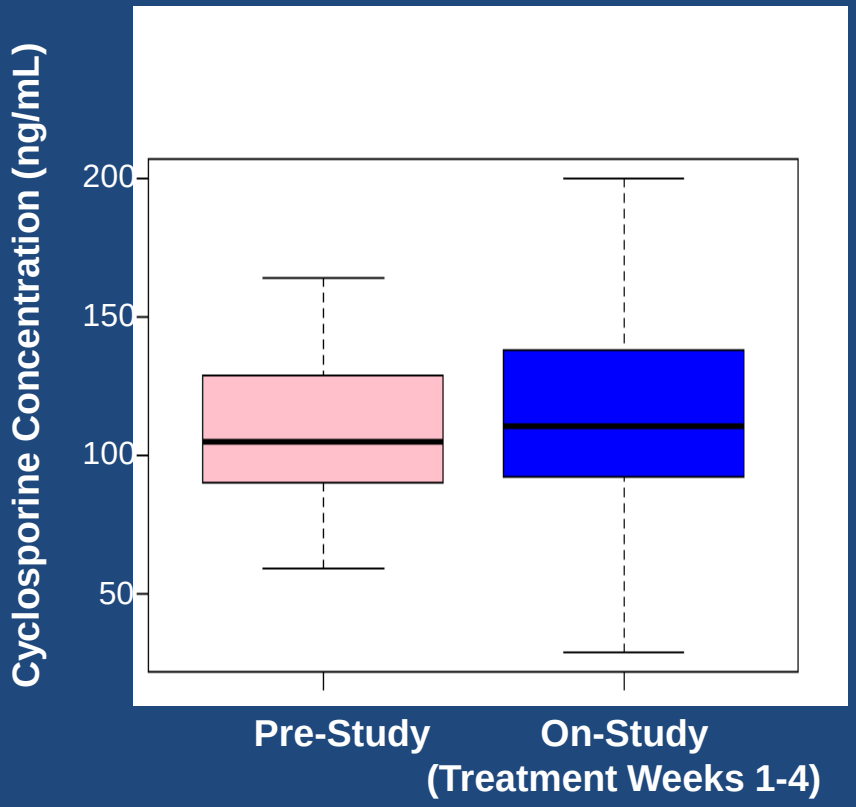
Kwo et al, NEJM 2014

Viekira Pak + RBV - DDI

TAC dose adjustments: 0.5mg once weekly or 0.2mg at every 3 days

CsA dose adjustments. 1/5 of the daily prestudy dose given once daily





Kwo et al. NEJM 2014

Conclusions

✓Phase II and III studies using **IFN-free regimens after LT** are encouraging. Their safety profile and virological results suggest that these combinations will lead to safe and very effective treatments in the post-LT setting

✓Data in patients with **severe hepatitis C recurrence**, including FCH, are good and importantly, clinical outcomes improve in those achieving viral clearance

✓ In the next few years, the **current scenario of hepatitis C in the transplant setting will radically change**, as we will be able to cure almost all patients on the waiting list, or easily after LT