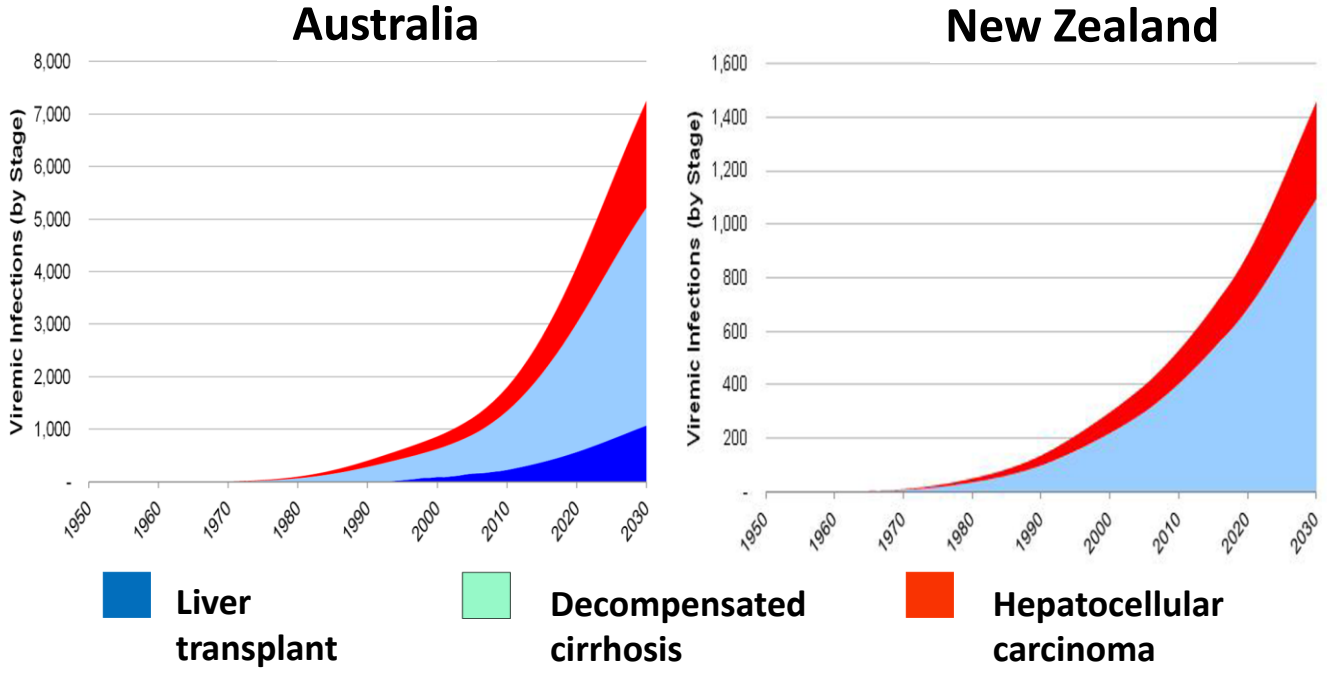
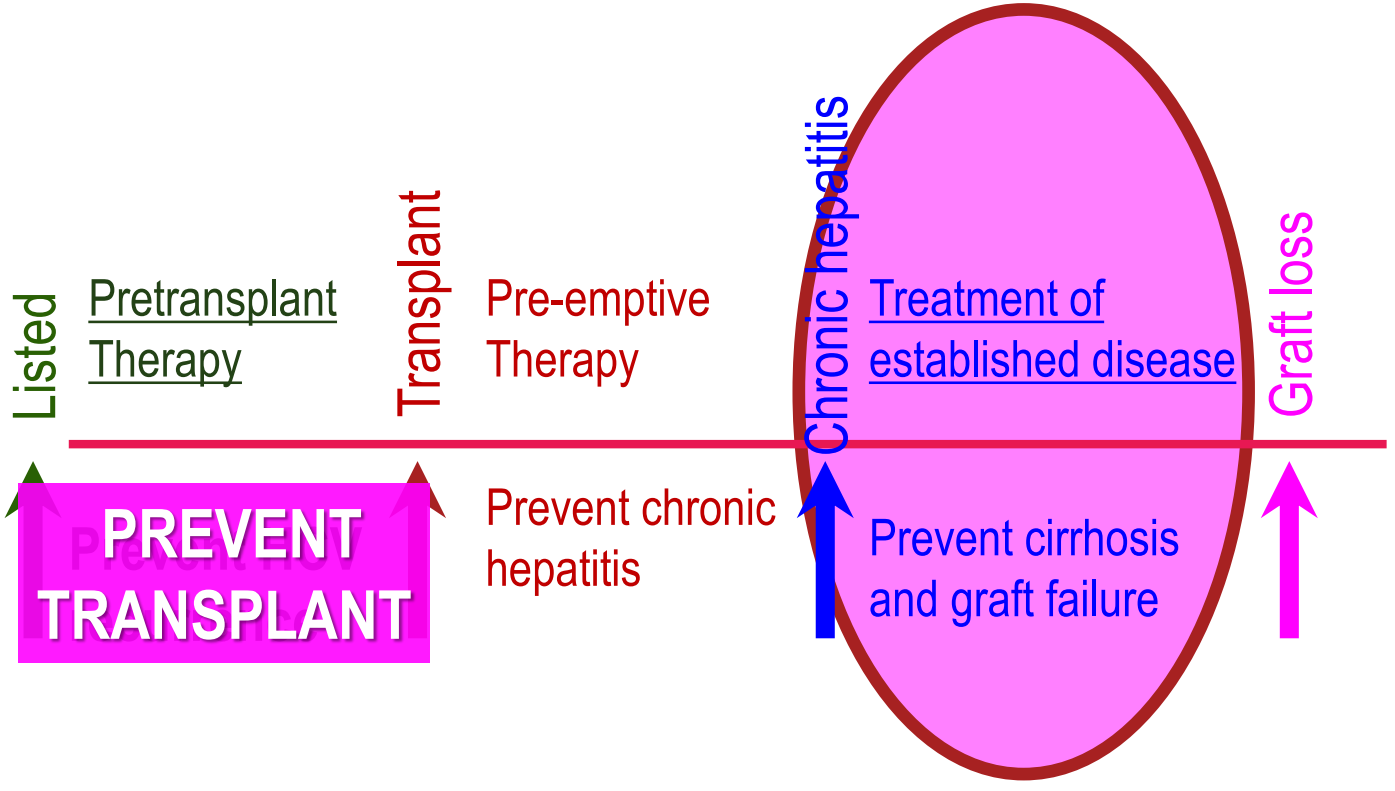
Treating patients with decompensated GT 3?

Hepatitis C – growing disease burden



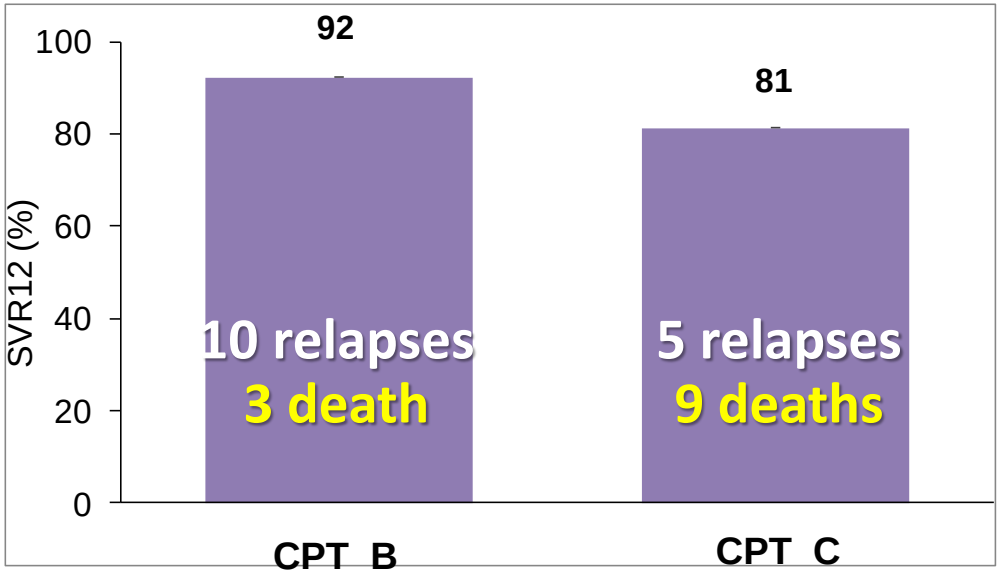
Razavi H, et al. J Viral Hepat 2014; 21 Suppl 1: 34-59.

Recurrent Hepatitis C: Antiviral Strategies



Treating decompensated cirrhosis
Reduced efficacy especially in CTP C

- **SOLAR 1/2 Studies of HARVONI + RBV for 12/24 weeks in 247 CTP B/C GT 1 Patients**

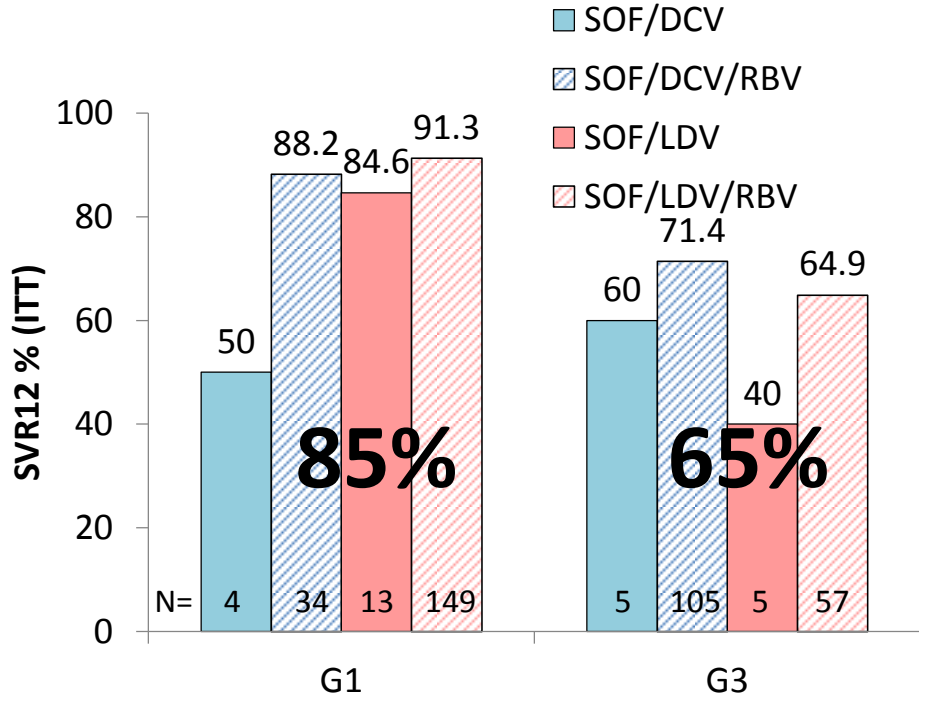


Analysis excluded 13 patients transplanted prior to posttreatment Week (FU) 12 with HCV RNA <LLOQ at last measurement prior to transplant, and 3 pretransplant patients who were CPT A at baseline. *Error bars* represent 95% confidence intervals (CIs).

Gane E, et al. APASL 2016

Treating decompensated cirrhosis
Reduced efficacy especially in GT 3

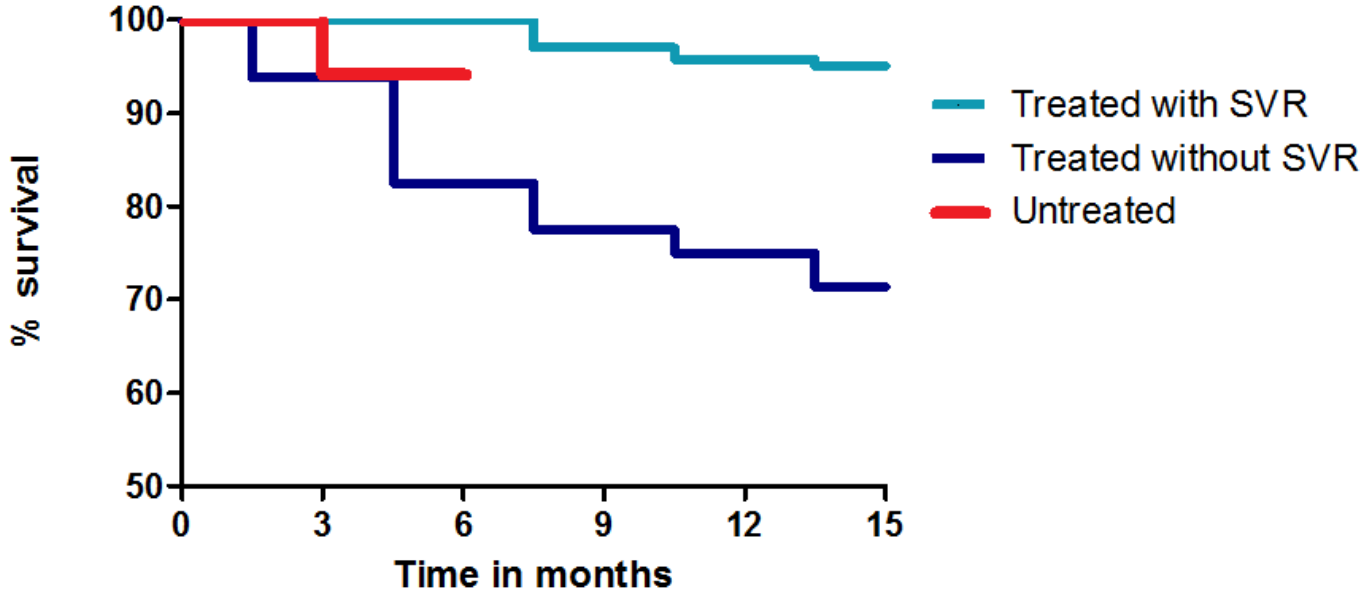
- UK EAP for 409 CTP B/C pts 12 wks
  - LDV/SOF±RBV or DCV/SOF±RBV for 12 weeks



Foster G et al. J Hepatol 2016

Treating decompensated cirrhosis
Is it worth it?

- **SVR is associated with rescue from death/transplant**

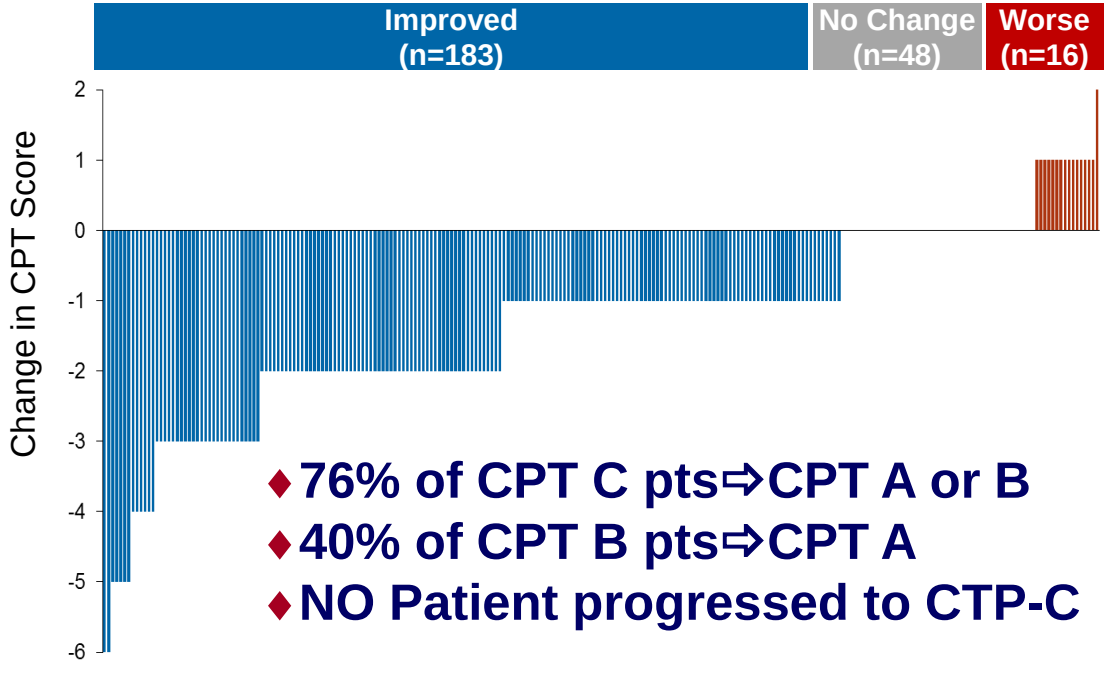


Foster G et al. J Hepatol 2016

Treating decompensated cirrhosis
Do we rescue patients?

- **DAAs improve liver synthetic function**

HARVONI + RBV fir 12 weeks in 247 CTP B/C patients

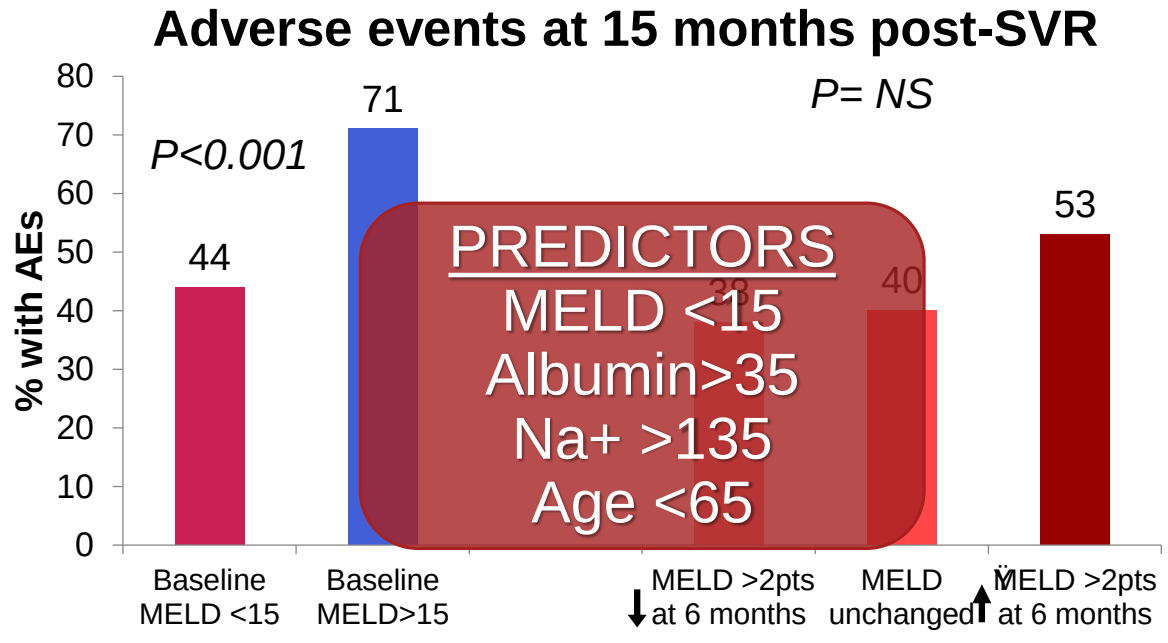


- **76% of CPT C pts⇨CPT A or B**
- **40% of CPT B pts⇨CPT A**
- **NO Patient progressed to CTP-C**

Gane E, et al. AASLD 2015 Poster #1049

Treating decompensated cirrhosis
Is there a point of "no return"

- **Baseline MELD but NOT Δ MELD predicts outcome**



Foster G et al. J Hepatol 2016

Foster G, et al. J Hepatol (in press)_

Treating decompensated cirrhosis
Is there a point of "no return"

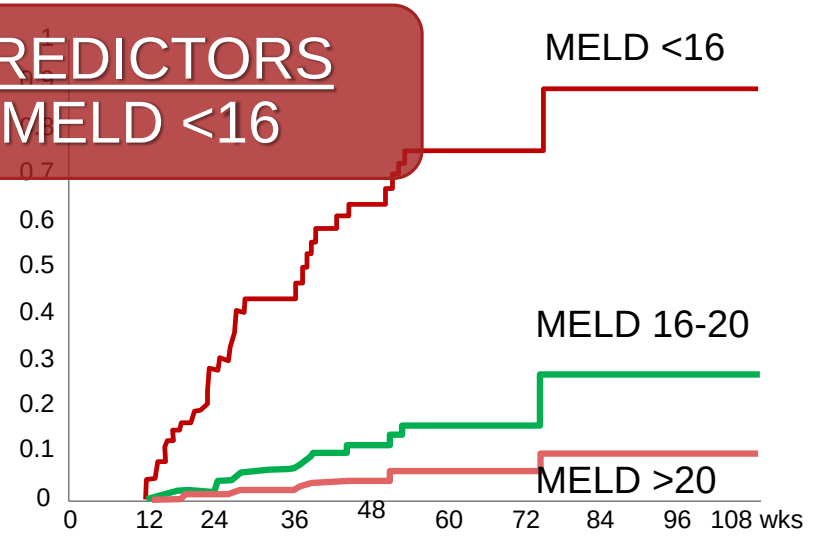
- 103 patients listed for decompensated HCV
- SOF/RBV, SOF/LDV, SOF/DCV
- 34 deactivated

Baseline Predictors

Variable	% Delisting
Baseline MELD	
<16	**25/51 (49%)**
16–20	**7/38 (18%)**
>20	**2/13 (15%)**

PREDICTORS
MELD <16

- **Cumulative incidence of inactivation**



elli L, et al. EASL 2016, Barcelona. #PS036

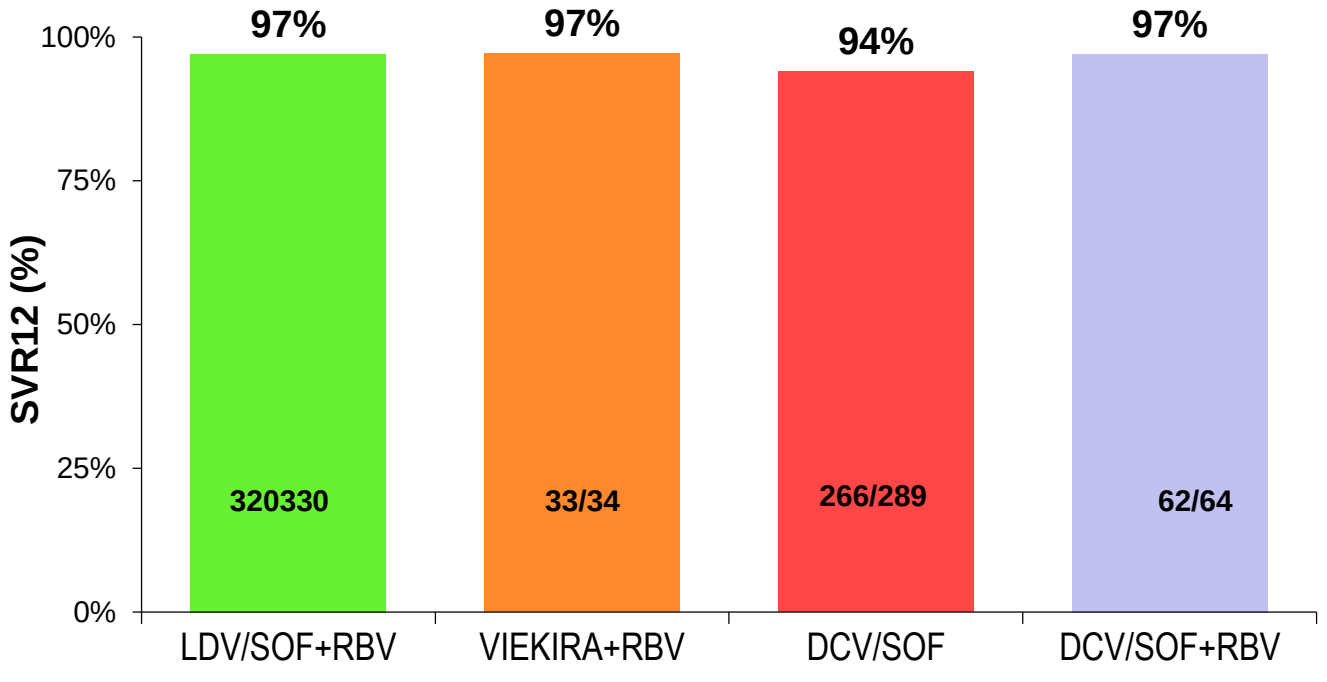
What is the Point of No Return?

HARM outweighs BENEFIT, if high MELD

- Low efficacy: 60% in GT 3
- Relapse with NS5A RASs – retreatment?
- Low safety of RBV (+ SOF? If renal dysfn)
- Even if achieve SVR, risk of MELD purgatory
  - lose priority on list and die

WAIT AND TREAT AFTER TRANSPLANT

Wait and treat after transplant
SVR rates are excellent after transplant



Charlton M. Gastroenterology 2015;149:649-59
Kwo P. N Engl J Med. 2014;371:2375-82
Pungpapong S. Hepatol 2015; 61:1880-6.
Houssel-Derby P, et al. EASL 2016, Barcelona. #PS018
Coilly A, et al. EASL 2015. Abstract G15

11

What is the Point of No Return?

ILTS CONSENSUS RECOMMENDATION 2:

- HCV-infected patients with advanced decompensated cirrhosis with MELD >25 should not undergo antiviral therapy

Strength of recommendation: *Conditional*

Quality of Data: *Very Low*

Acute Hep C
Treat or wait?

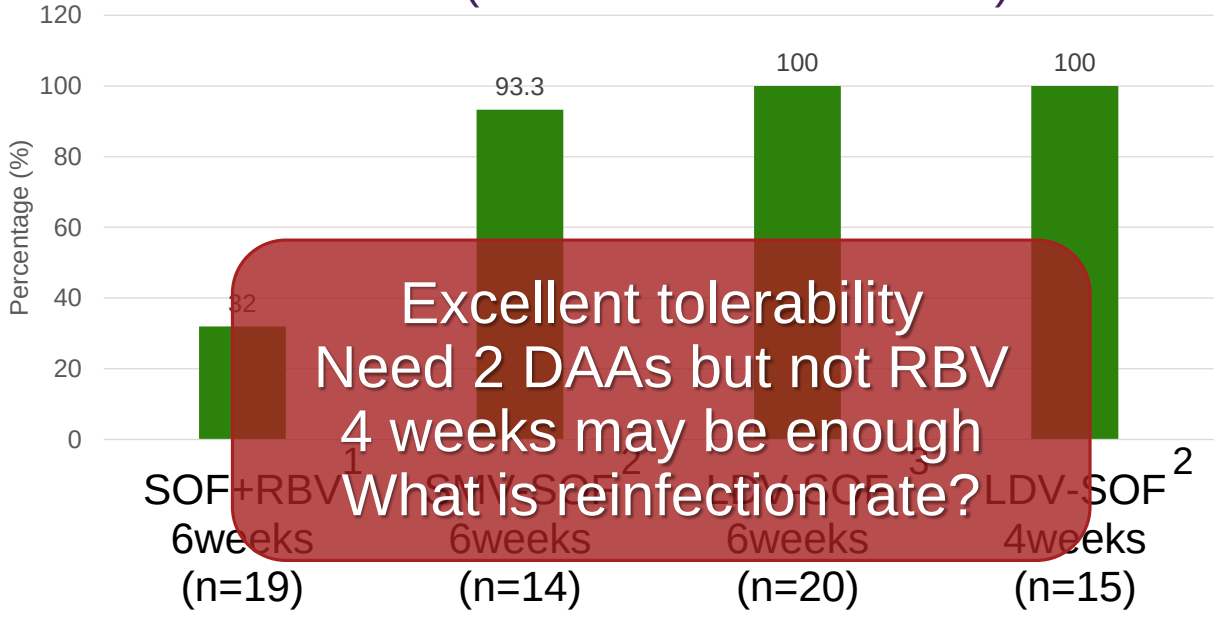
Acute Hepatitis C: Treat now or wait?

NO	YES
Peg-IFN ± RBV ▪ Poor tolerability ▪ Difficult to monitor ▪ 12-24 weeks duration ▪ Poor adherence ▪ High risk of reinfection ▪ Wait until chronic – DAAs ⇨95% SVR – Stable harm reduction	All DAA therapy ▪ Excellent tolerability ▪ No need to monitor ▪ Shorter duration? ▪ Adherence? ▪ Low risk of reinfection ▪ Prevent transmission – Public Health benefit

Ultrashort duration DAA therapy for acute HepC

DARE-C II, HepNet, SLAM-C

- 3 studies in acute HepC
  - Only one was all genotypes (DARE-C)
  - Different definitions (acute vs. recent infection)

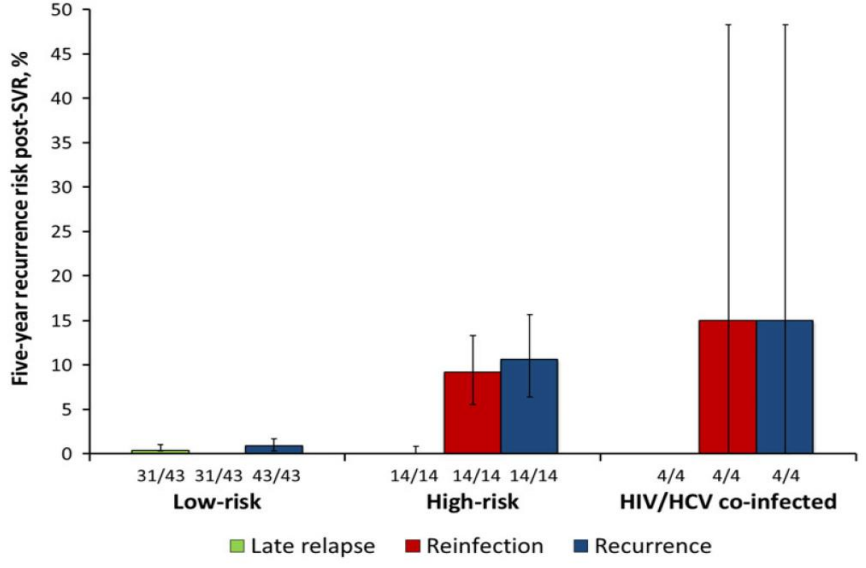


[1]Martinello M, et al. Hepatology 2016; Sept 17 (on line)
[2]Basu P, et al. EASL 2016, Barcelona. #SAT-234
[3]Deterding K, et al. EASL 2016, Barcelona. #LB08

What is the Risk of Reinfection?

Meta-analysis of 61 studies to determine reinfection

- 7969 Low-risk patients → 1% HCV recurrence at 5 years
- 771 High-risk IDU/prisoners → 11% HCV recurrence at 5 years
- 309 HIV coinfected patients → 15% HCV recurrence at 5 years



Active IDU, prisoners and HIV+ patients should be monitored for reinfection

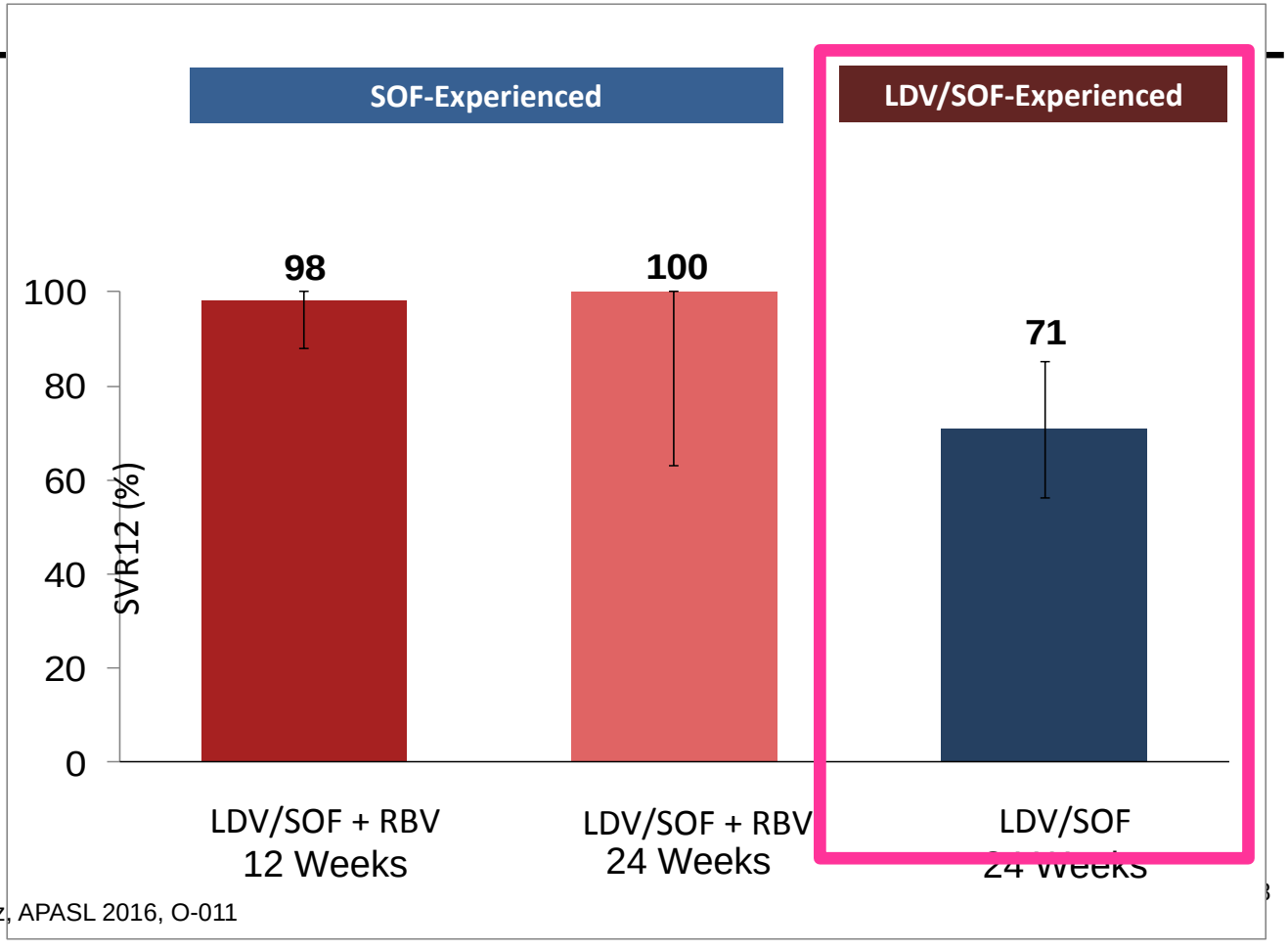
Simmons B et al, Clin ID March 2016 [16]

The patient who has failed HARVONI, DAC/SOF or VIEKIRA PAK

Treat now or wait?

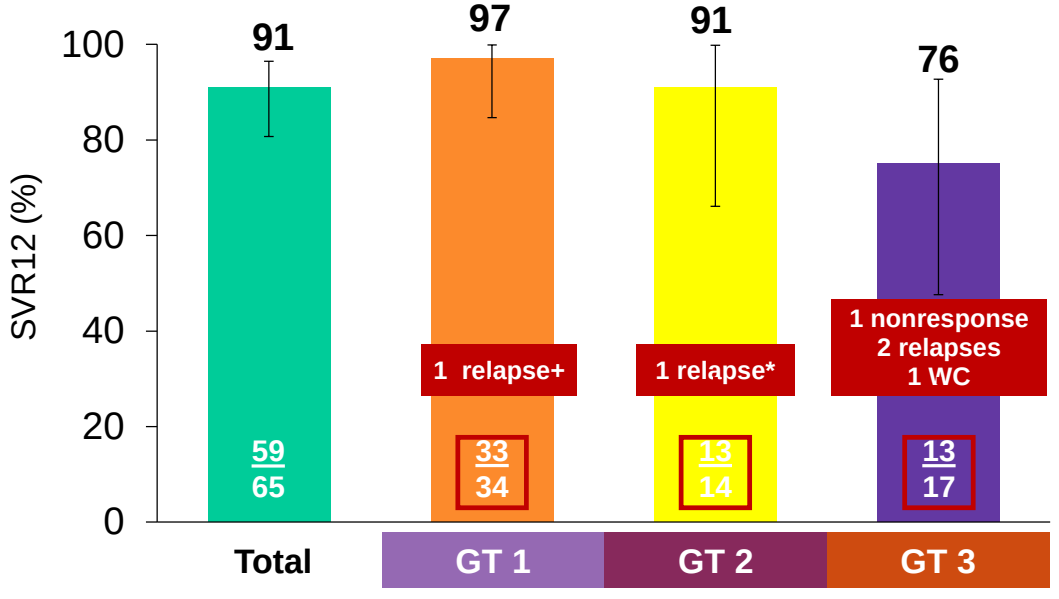
Phase II LDV/SOF ± RBV for 12-24 weeks in GT 1

Patients who have failed prior SOF therapy



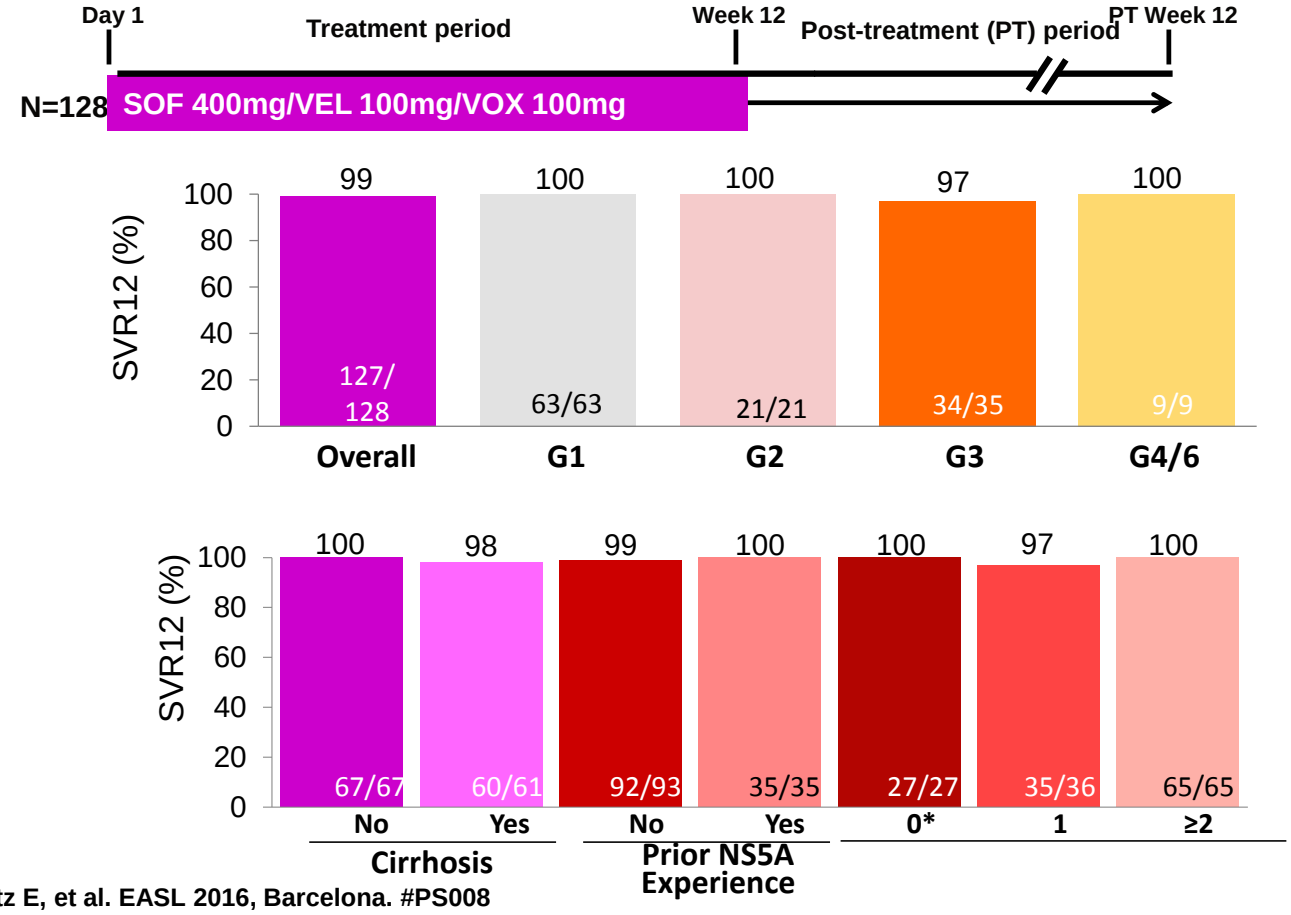
Lawitz, APASL 2016, O-011

Phase II SOF/VEL+RBV for 24 weeks in GT 1–6
Patients who have failed prior DAA therapy



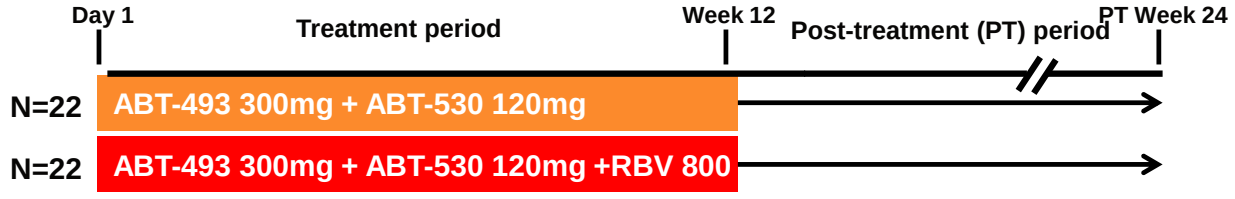
Gane E et al. EASL 2016, Barcelona

Phase II SOF/VEL/VOX for 12 weeks in GT 1–6
Patients who have failed prior DAA therapy

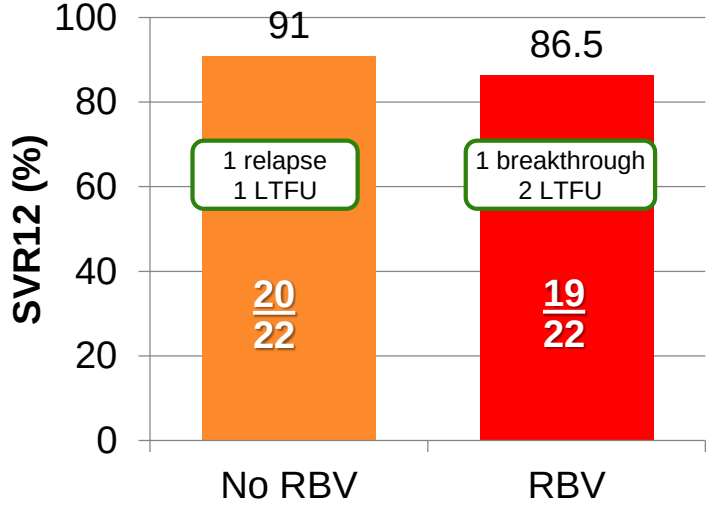


Lawitz E, et al. EASL 2016, Barcelona. #PS008

Phase II Data on GLE/PIB for 12 weeks in GT 1–6
Patients who have failed prior DAA therapy



ITT



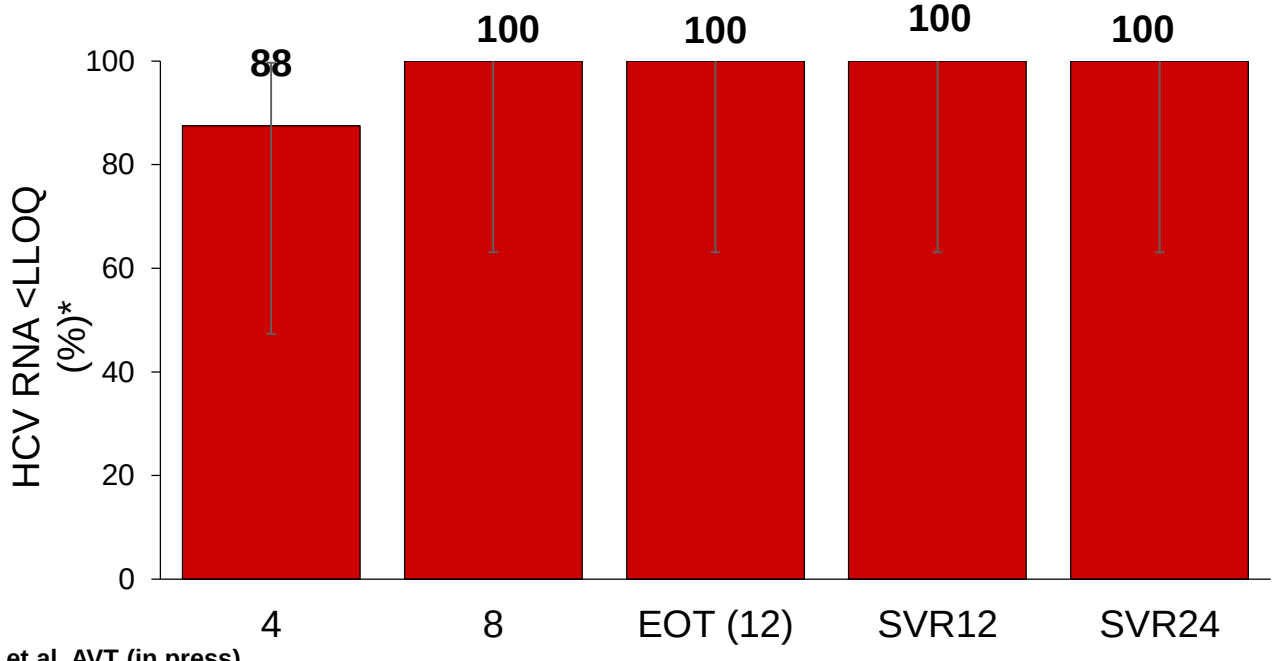
Poordad F et al. EASL 2016, Barcelona. #GS11

The Patient with HBV coinfection

Treat HBV as well to prevent HBV Flare?

HARVONI for 12 weeks in GT 1 with HBV coinfection
LEPTON Phase II Pilot Study

- **All HBsAg+, HBV DNA <3 log IU/mL**

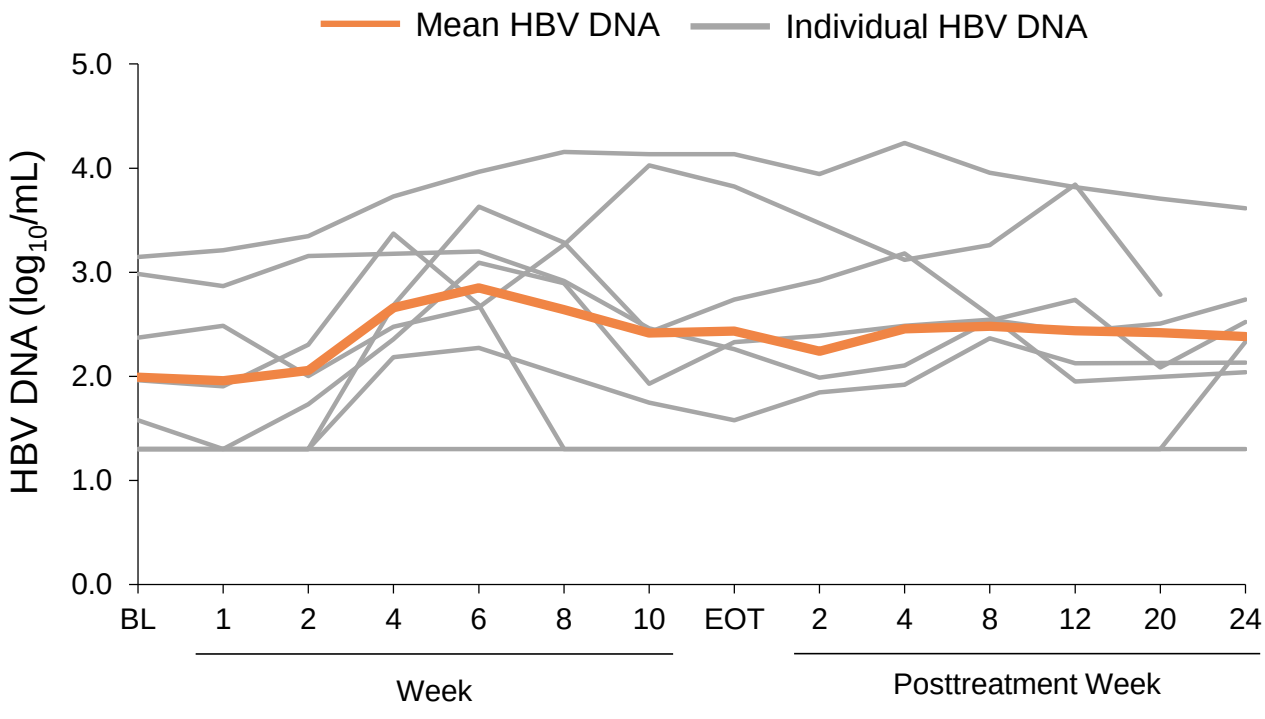


Gane E, et al. AVT (in press)

23

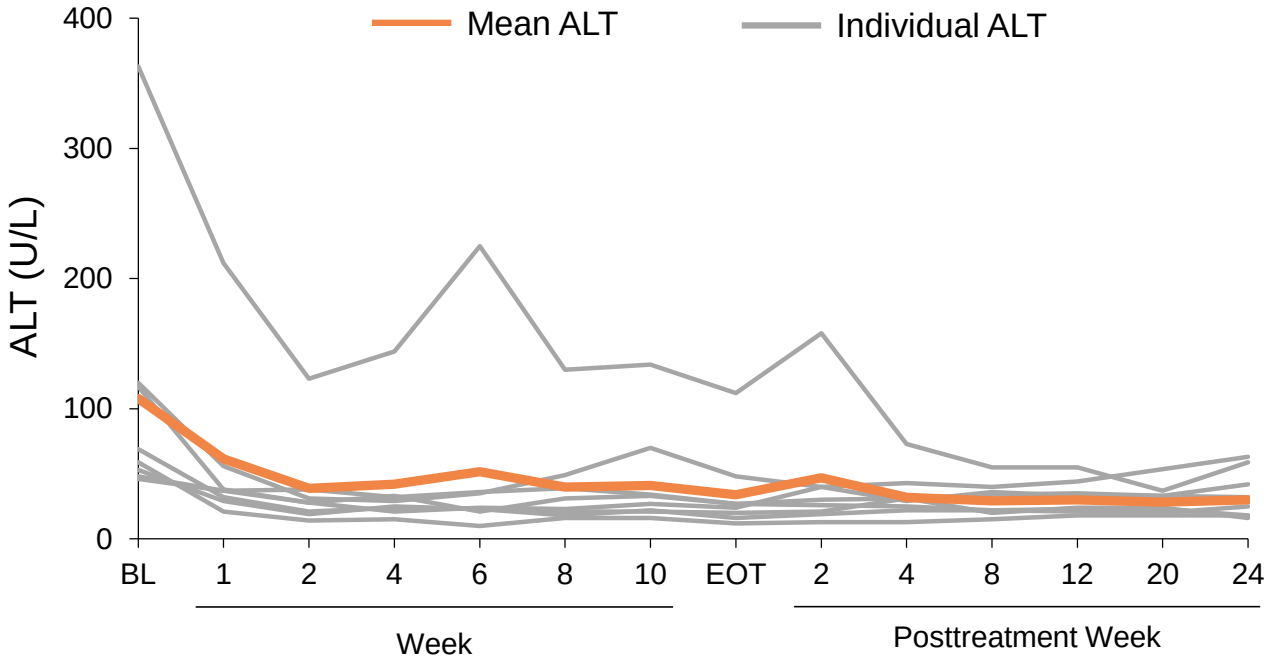
Mean and Individual HBV DNA Profiles

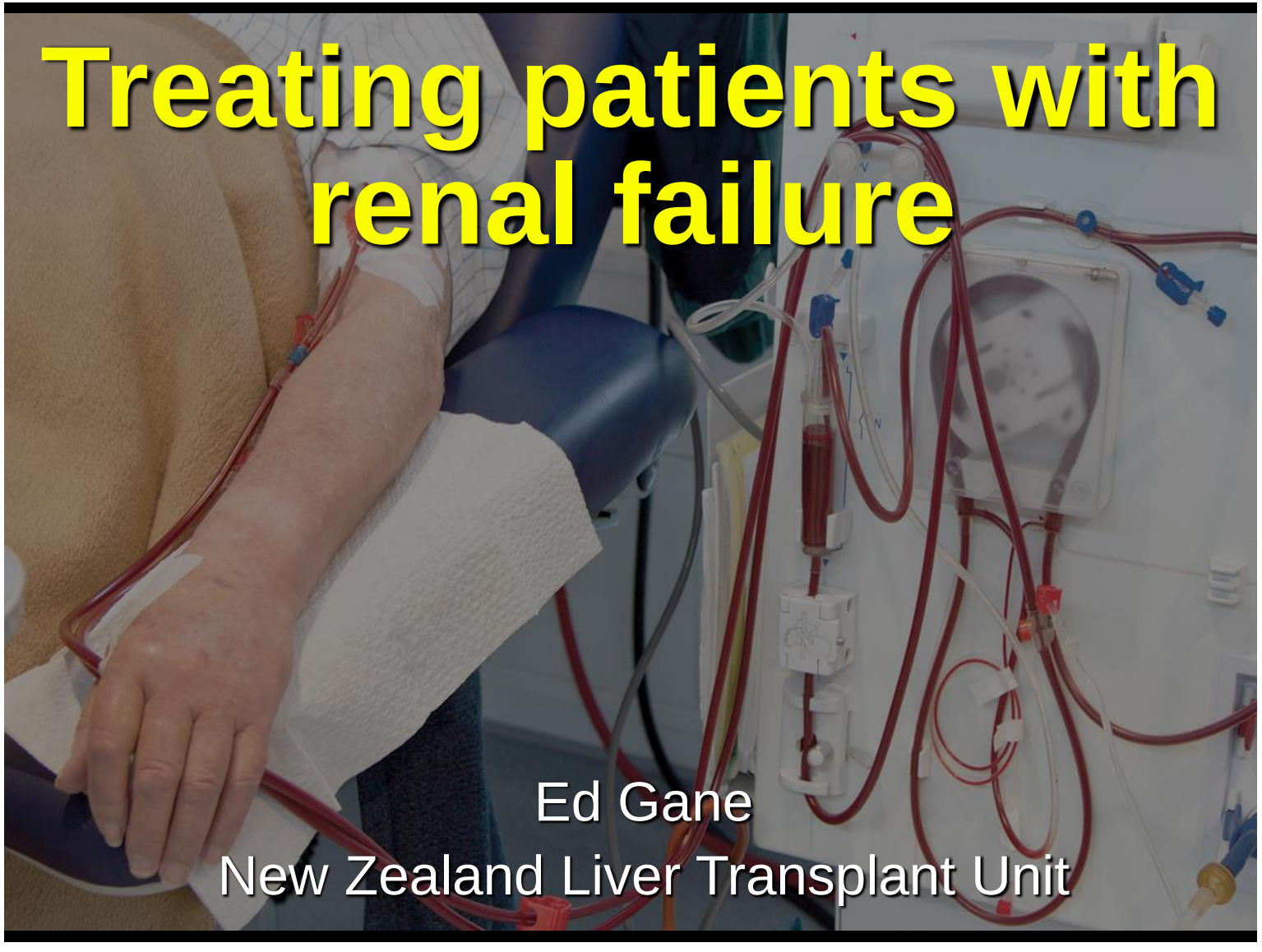
HBV/HCV Co-infection



Mean and Individual ALT Profiles

HBV/HCV Co-infection




Treating patients with renal failure
Ed Gane
New Zealand Liver Transplant Unit

Treatment of HCV in Renal Impairment

What drugs are safe?

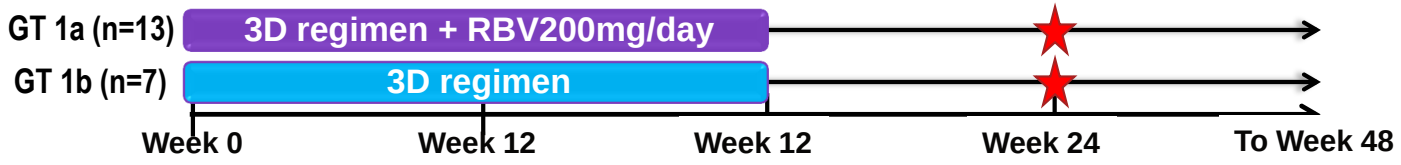
DAA Class	Name	AUC_{24} if eGFR <30 ml/min
NS3 Protease inhibitor	Paritaprevir[3]	1.5
	Grazoprevir[4]	1.4
	ABT-493	1
NS5A inhibitor	Daclatasvir[5]	1
	Ledipasvir[6]	1
	Ombitasvir[3]	1
	Elbasvir	1.5
	ABT-530	1
Non-NUC NS5B	Dasabuvir[3]	1.5
NUC NS5B Inhibitor	Sofosbuvir[1]	6x
	Ribavirin	>10x

27

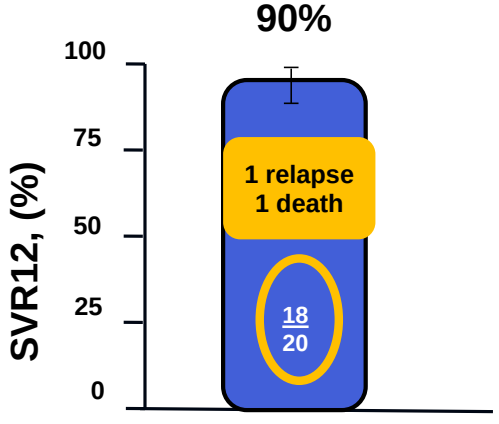
VIEKIRA PAK Phase II Trials in Renal Failure

RUBY-1 Study

- 20 GT1 patients with eGFR <30ml/min, include HD, no cirrhosis



(i) Efficacy



(ii) Safety

	Viekira Pak + RBV (G 1a)	Viekira Pak (Gt 1b)
AE	62%	29%
SAE	22%	14%
RBV reduced	69%	0
Hb <100	54%	29%
Death	1	0

- Only safety issue is RBV
- RUBY-II removes RBV in all patients and includes cirrhotics

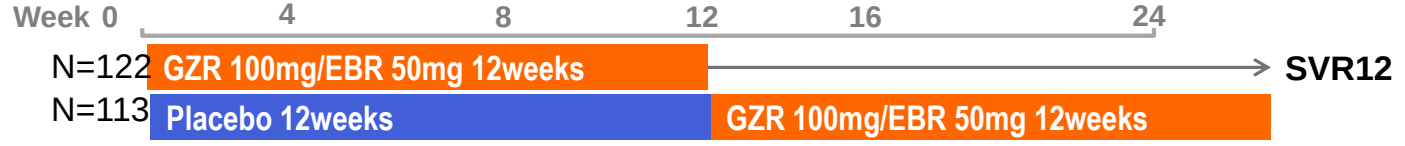
Pockros PJ, et al. AASLD 2015, San Francisco. #1039

28

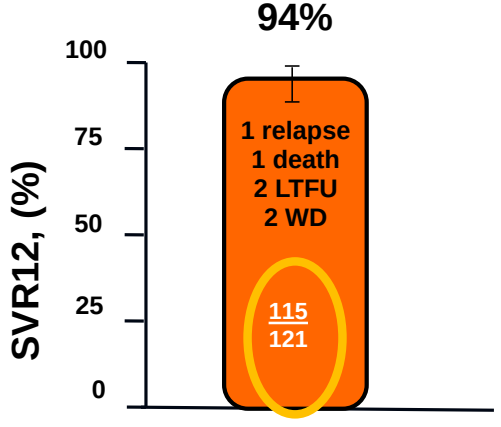
Grazoprevir/Elbasvir (ZEPATIER) in HCV GT 1

C-SURFER: Efficacy in ESRD

- 235 GT1 patients with eGFR <30ml/min, include HD, cirrhosis



(i) Efficacy



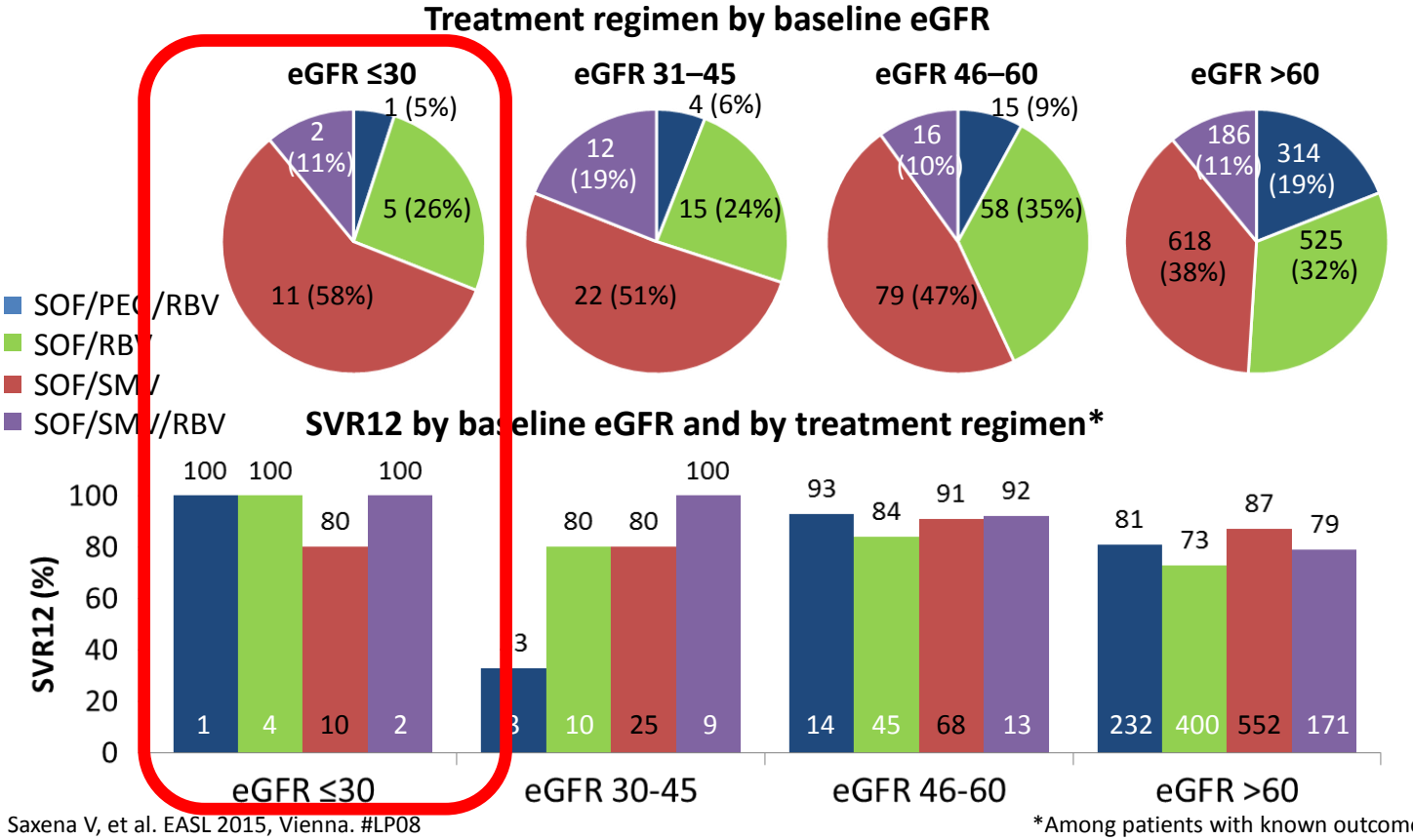
(ii) Safety

	GZR/EBR	Placebo
Rx-related AE	34%	35%
SAE	14%	17%
DC from AE	0%	4%
Hb <100	24%	27%
ALT>5xULN	0	1
Death	1	3

Roth D, et al. Lancet. 2015;386:1537-45

Sofosbuvir in Renal Impairment

HCV TARGET Real World Study

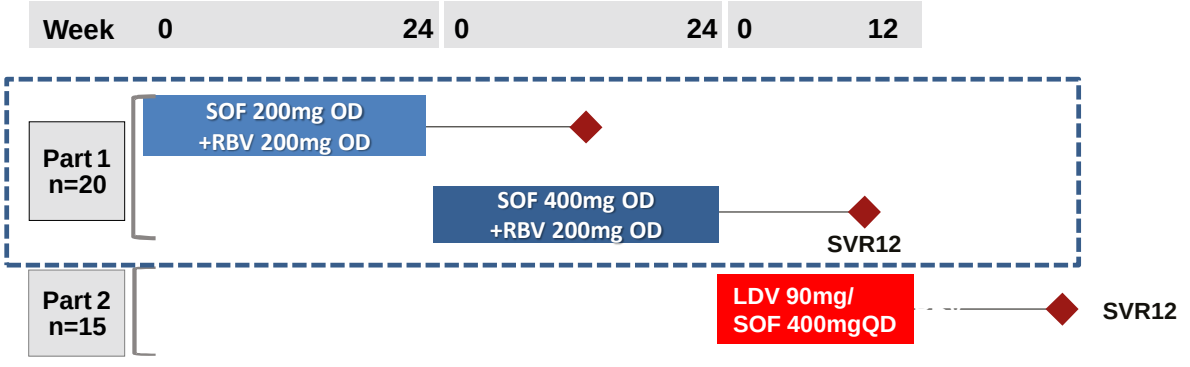


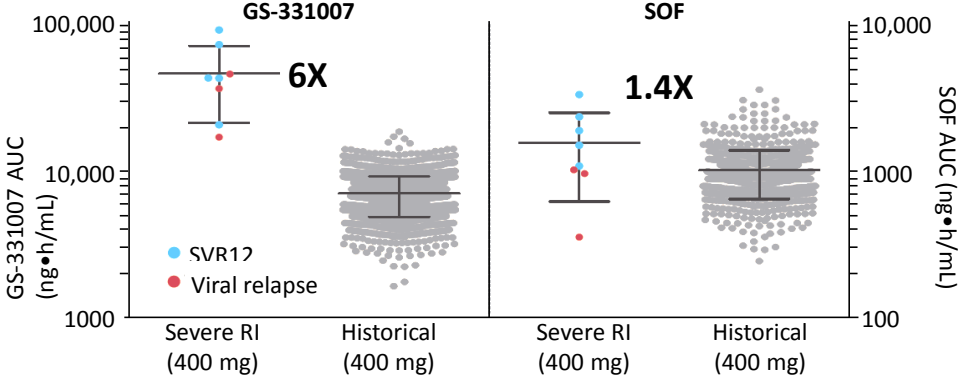
Saxena V, et al. EASL 2015, Vienna. #LP08

*Among patients with known outcome

Sofosbuvir in Renal Impairment

Open-label study in HCV pts with GFR <30





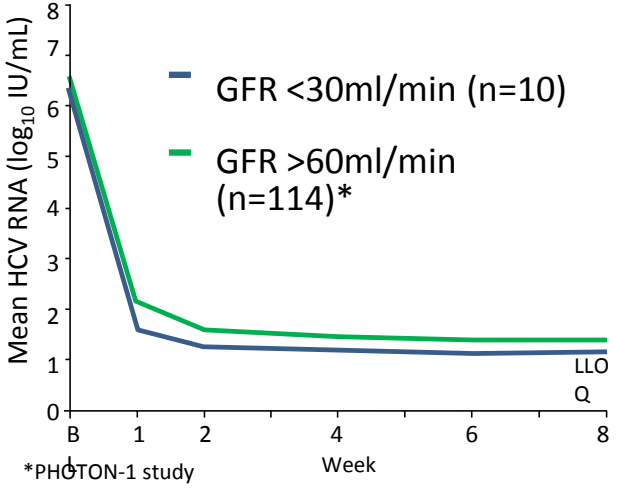
Martin P et al. AASLD 2015, San Francisco. #1128
Gane E, et al. AASLD 2014, Boston. #966

QD: once-daily; RBV: ribavirin; SOF: sofosbuvir

Sofosbuvir in Renal Impairment

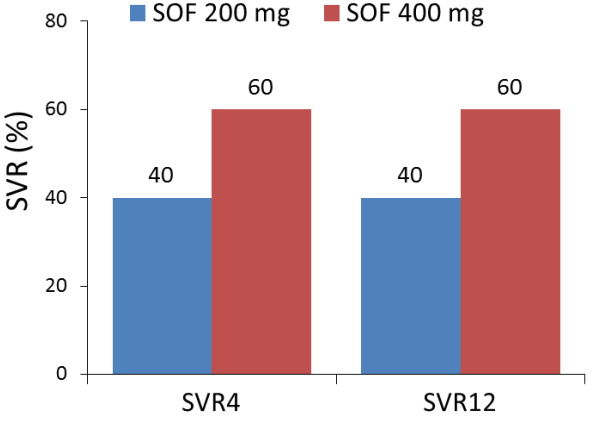
Open-label study in HCV pts with GFR <30

- **On treatment suppression**



*PHOTON-1 study

- **SVR12**



- AEs all due to RBV toxicity. NO evidence of SOF toxicity
- eGFR improved during treatment (26⇨36 mL/min)
- Next group is LDV/SOF for 12 weeks without RBV (GT 1)

Martin P et al. AASLD 2015, San Francisco. #1128
Gane E, et al. AASLD 2014, Boston. #966