Imperial College London

Imperial College Healthcare NHS Trust

HCV Treatment Failure: What Next?

Dr Ashley Brown, Imperial College Healthcare NHS Trust, London

European HIV Hepatitis Co-infection Conference
QEII Conference Centre
10th December 2015

EUROPEAN HIV HEPATITIS CO-INFECTION (EHHC)

CONFERENCE

Dr Ashley Brown

Imperial College Healthcare NHS Trust, London, UK

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Ashley Brown	I have received research grants, have acted as an investigator for, or have received speaker honoraria from the following: Abbvie, Bristol Myers-Squibb, Gilead, Janssen, Merck
Date	

The goal of therapy: treat-to-cure

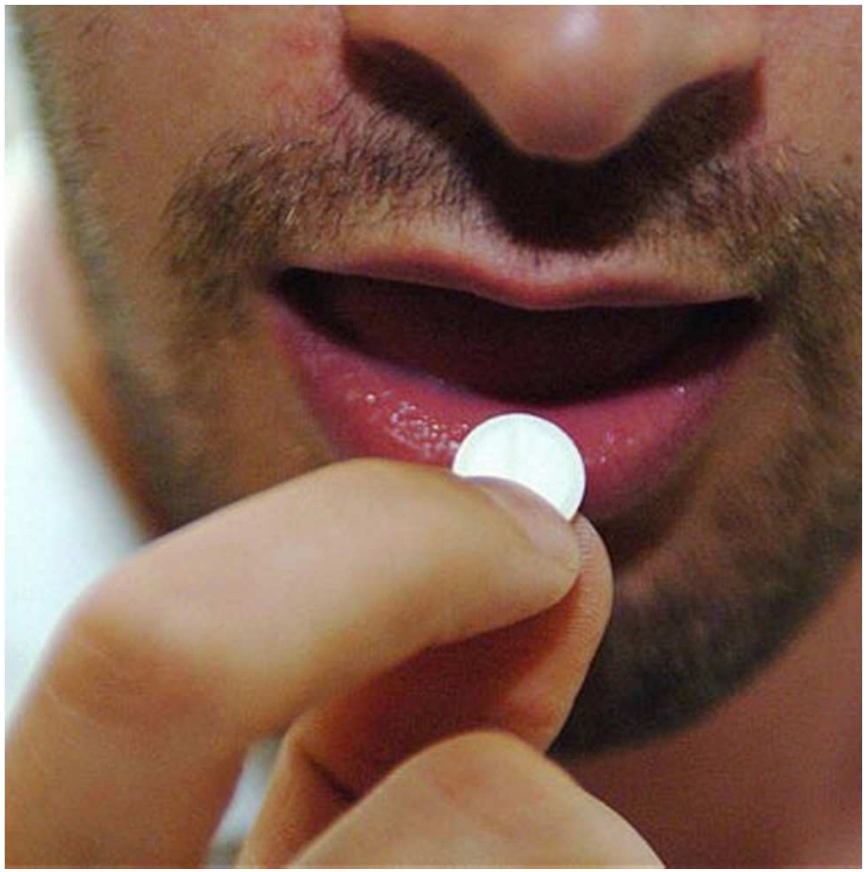
"The primary goal of HCV therapy is to cure the infection."
-EASL Guidelines 2015

"Currently, there is no data to firmly support retreatment recommendations…."
-EASL Guidelines 2015

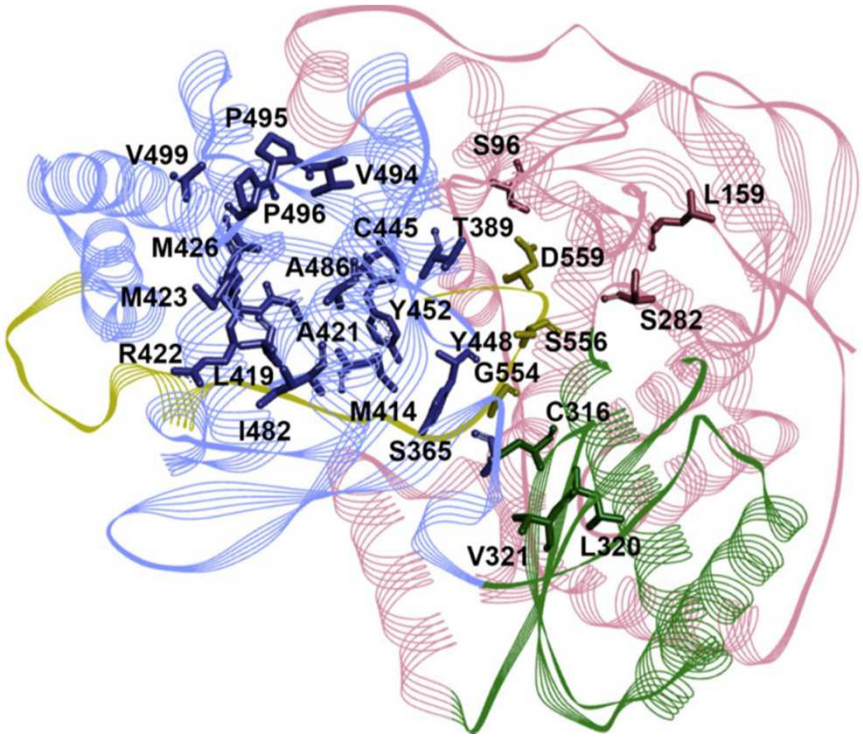
Why has treatment failed?

Human Factors

- Adherence issues?
- The wrong drugs??



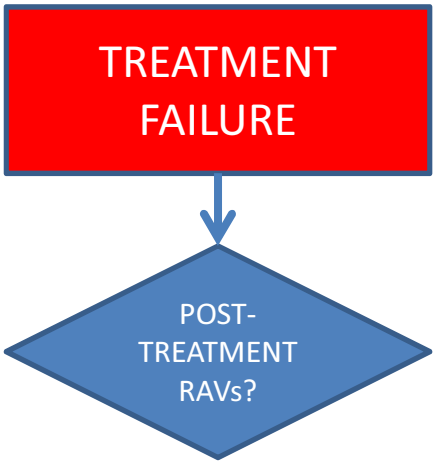
Why has treatment failed?



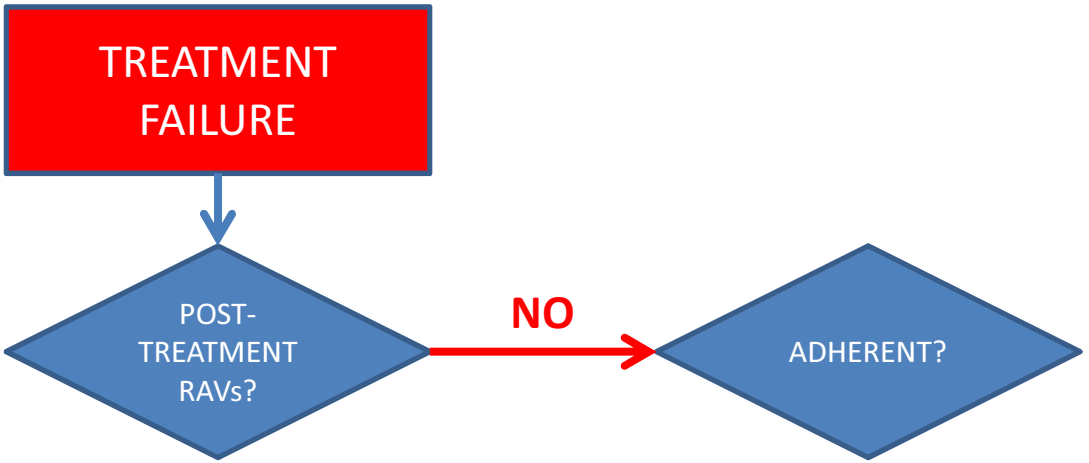
Virologic Factors

- Insufficient duration
- Baseline RAVs
- Drug-selected RAVs

Suggested Pathway for HCV Treatment Failure



Suggested Pathway for HCV Treatment Failure



Pill burden is not a predictor of adherence in short term treatment programmes

Table 2. HIV medication adherence over the first 12 weeks of treatment

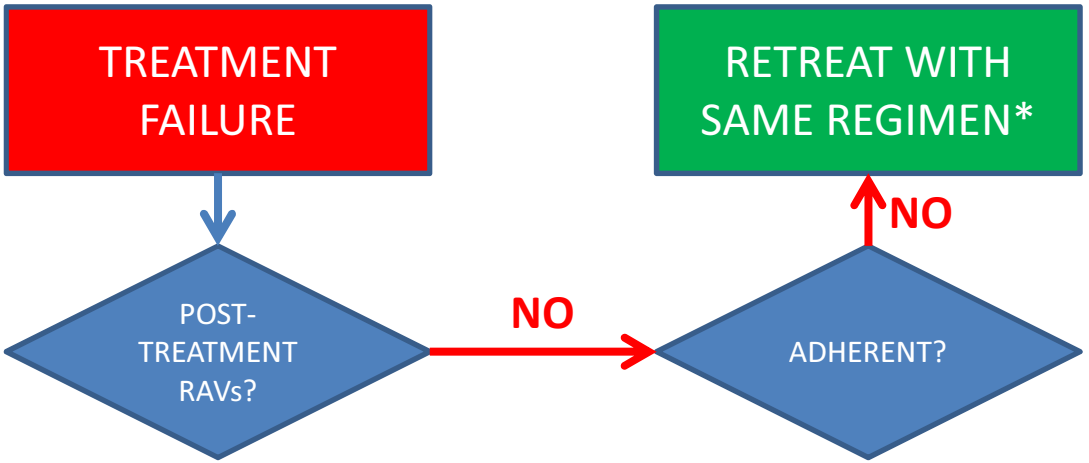
US Commercial Plans	Cohort 1** 1 pill/day	Cohort 2** 2 pills/day	Cohort 3** 3 pills/day
Sample size	6,533	496	75
Adjusted adherence rate*	81.4%	80.0%	80.4%

*Adjusted for age and gender. No statistically significant difference between cohorts.
**Cohort 1: TDF/FTC/EFV; Cohort 2: TDF/FTC+EFV; Cohort 3: TDF+FTC+EFV

Over a short-duration timeframe, pill count does not appear to impact medication adherence in treatment naïve HIV patients

ePoster P0741, EASL 2015

Suggested Pathway for HCV Treatment Failure

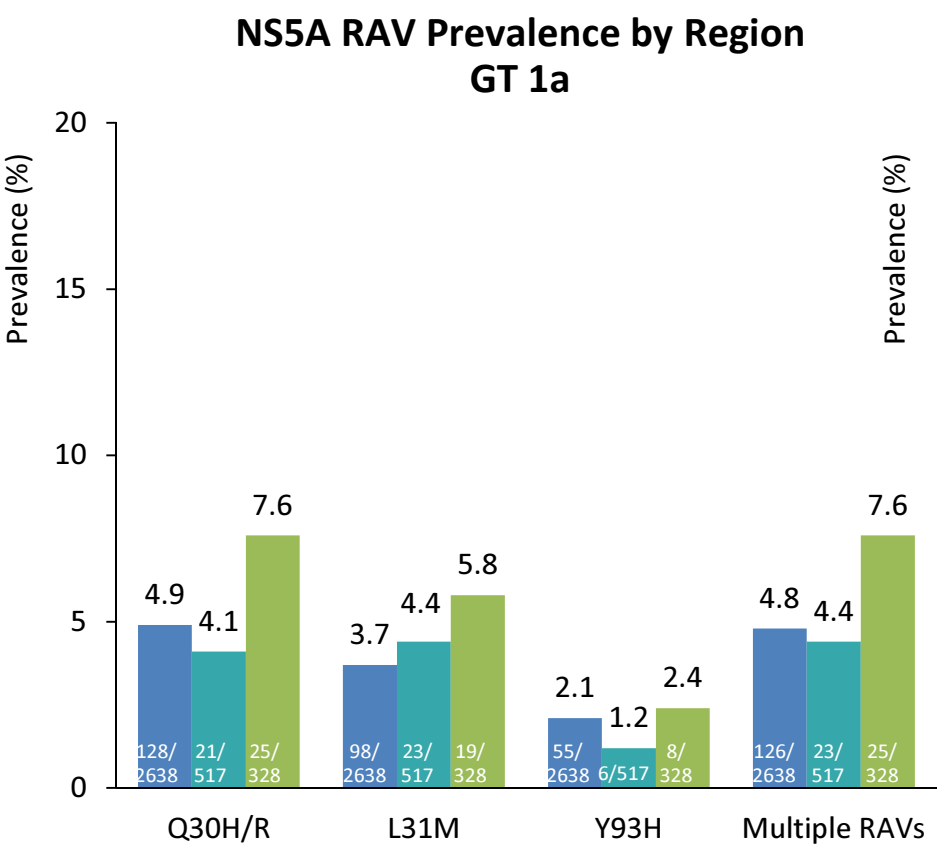


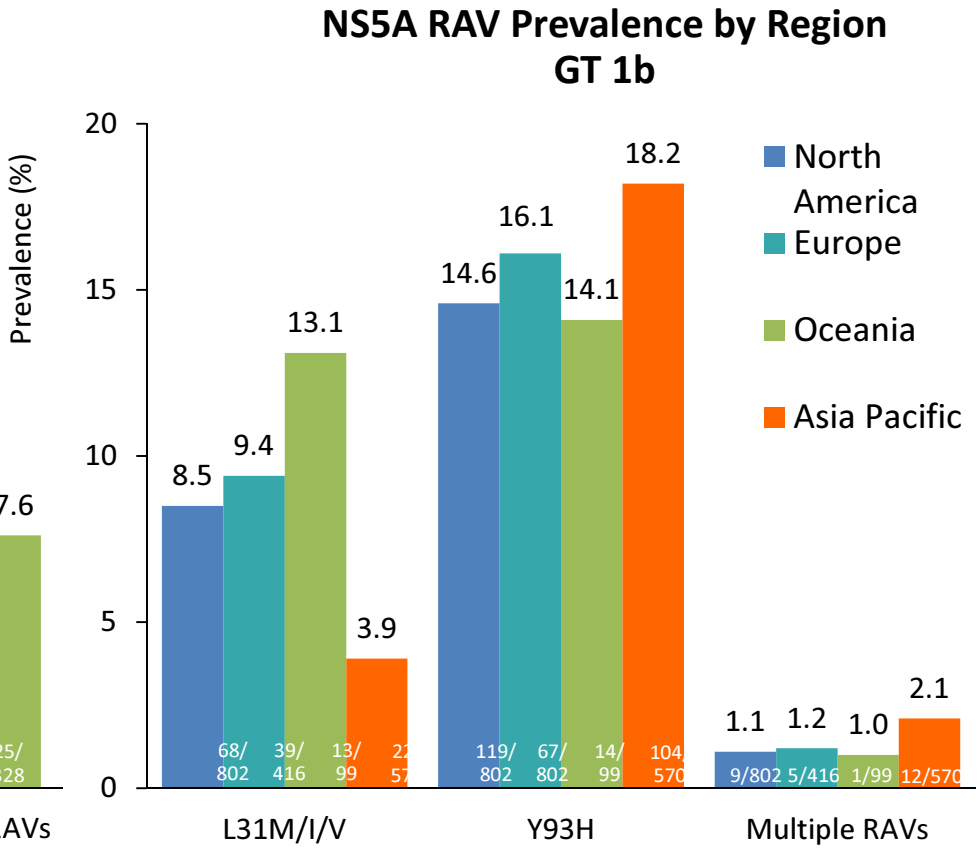
* Assuming availability and funding

What is the role of baseline resistance?

Prevalence of Pre-Treatment NS5A RAVs in GT1 patients

NS5A deep sequencing analysis (1% cut-off) on 5397 patients





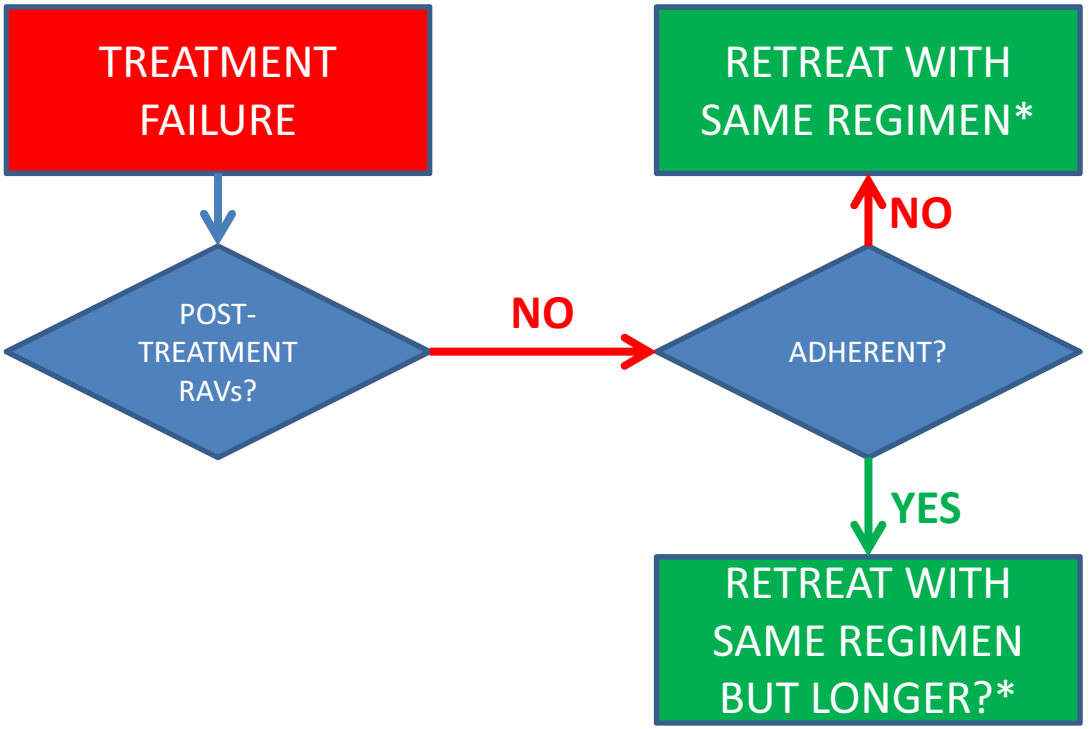
Q30H/R, L31M and Y93H RAVs confer >100 fold shift to LDV.

Asia Pacific not included due to low number of patients with GT1a (n=27)

Zeuzem, AASLD, 2015, 91

L31M/I/V confer 3-43 fold shift to LDV; Y93H confers >100 fold shift to LDV

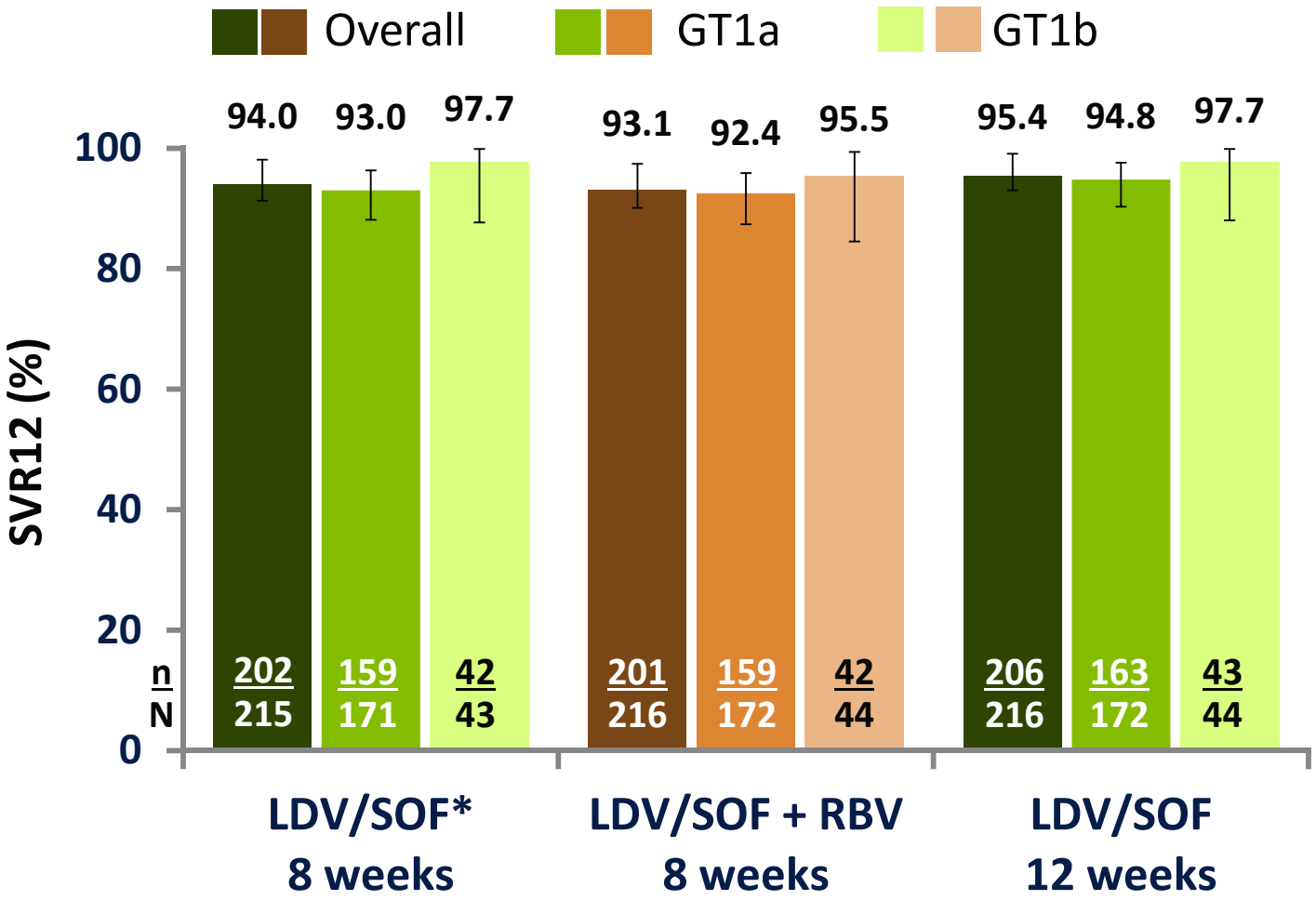
Suggested Pathway for HCV Treatment Failure



* Assuming availability and funding

Same Drugs Longer Duration?

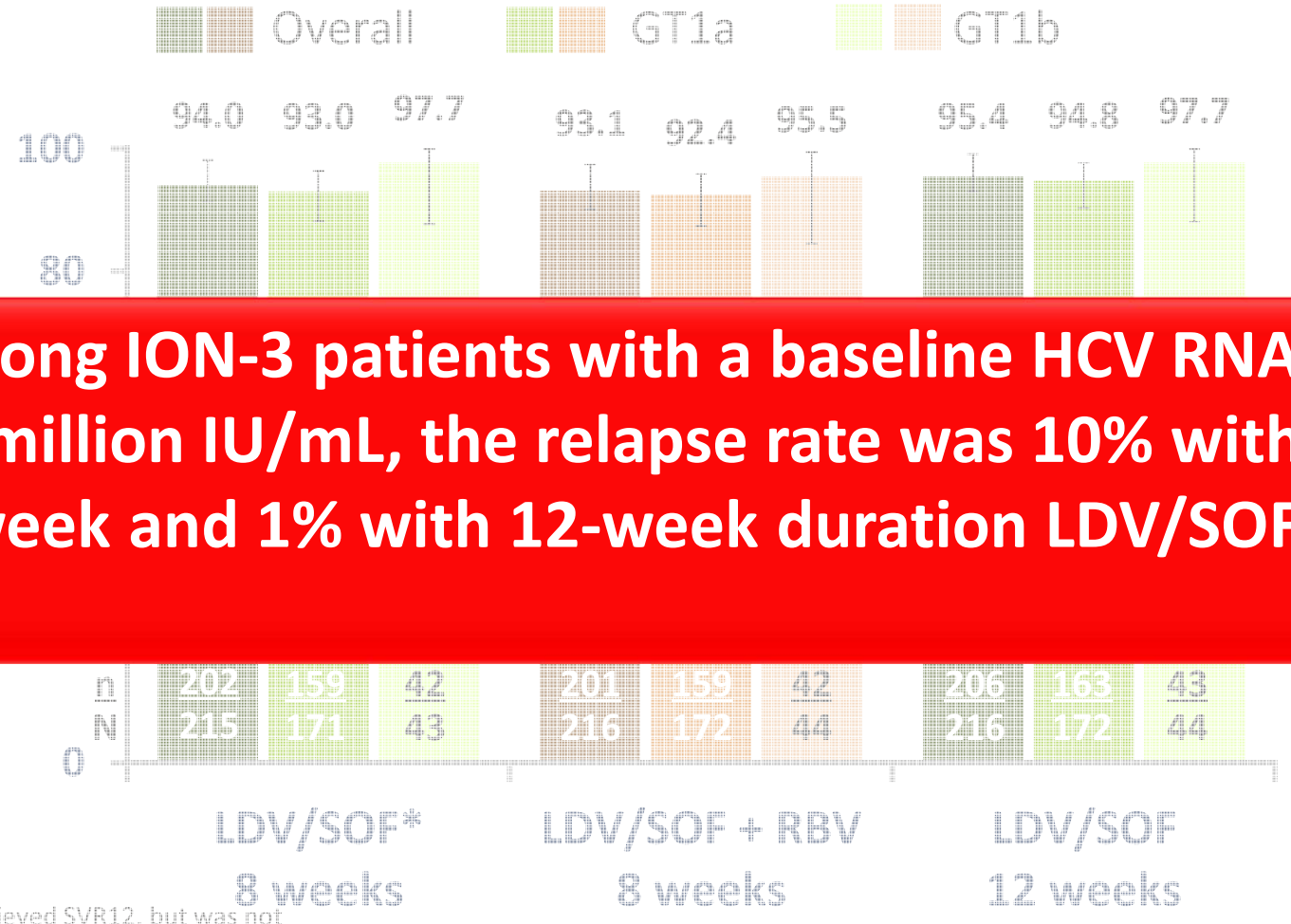
ION-3: LDV/SOF in GT1, naive, non-cirrhotics



* One patient achieved SVR12, but was not subgenotyped; error bars: 95% CI.

*Kowdley KV, et al. N Engl J Med 2014; **370**:1879–1888 (and supplement).*

ION-3: LDV/SOF in GT1, naive, non-cirrhotics

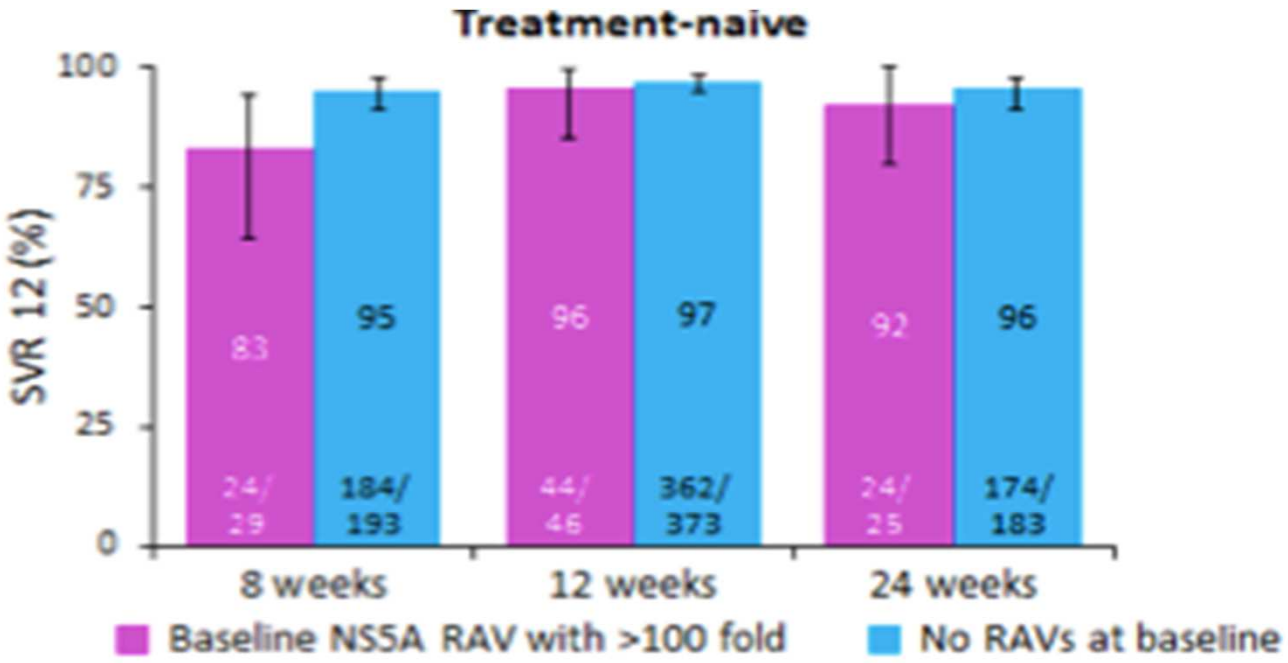


Among ION-3 patients with a baseline HCV RNA ≥6 million IU/mL, the relapse rate was 10% with 8-week and 1% with 12-week duration LDV/SOF

* One patient achieved SVR12, but was not subgenotyped; error bars: 95% CI.

Kowdley KV, et al. N Engl J Med 2014; 370:1879–1888 (and supplement).

NS5A baseline resistance analysis of Phase 2/3 LDV/SOF studies

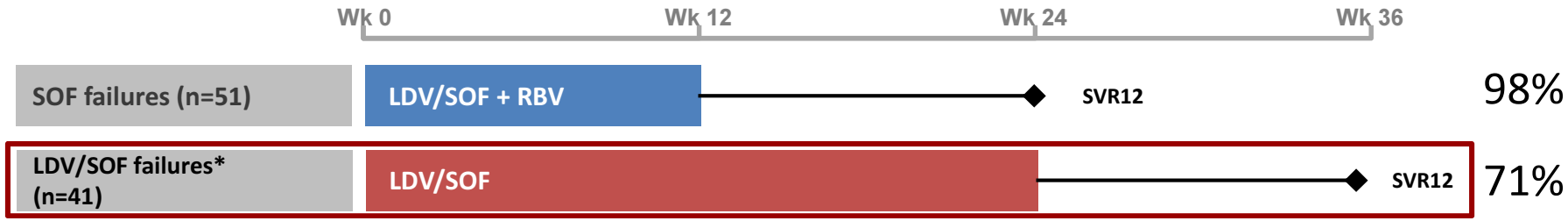


SVR was 83% (suboptimal) in GT1 Naïve non-cirrhotic patients treated with SOF/LDV for 8 weeks and who had baseline NS5A RAV with >100fold

Sarrazin et al, AASLD 2014

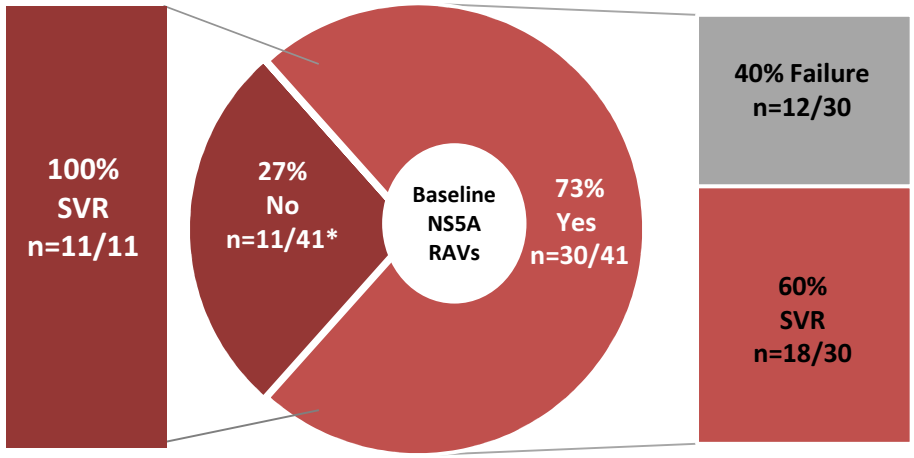
Patients Who Failed 8 or 12W LDV/SOF Retreated with LDV/SOF for 24 Weeks

‡



*LDV/SOF failures from ION1-3, LONESTAR and TRILOGY-1

	GT 1 (n=41)
Mean age, years (range)	58 (35-71)
Male, n (%)	34 (83)
Black, n (%)	10 (24)
Cirrhosis, n (%)	19 (46)
IL28B non-CC, n (%)	38 (93)
Mean HCV RNA, log_{10} IU/mL (range)	6.2 (4.5-7.4)



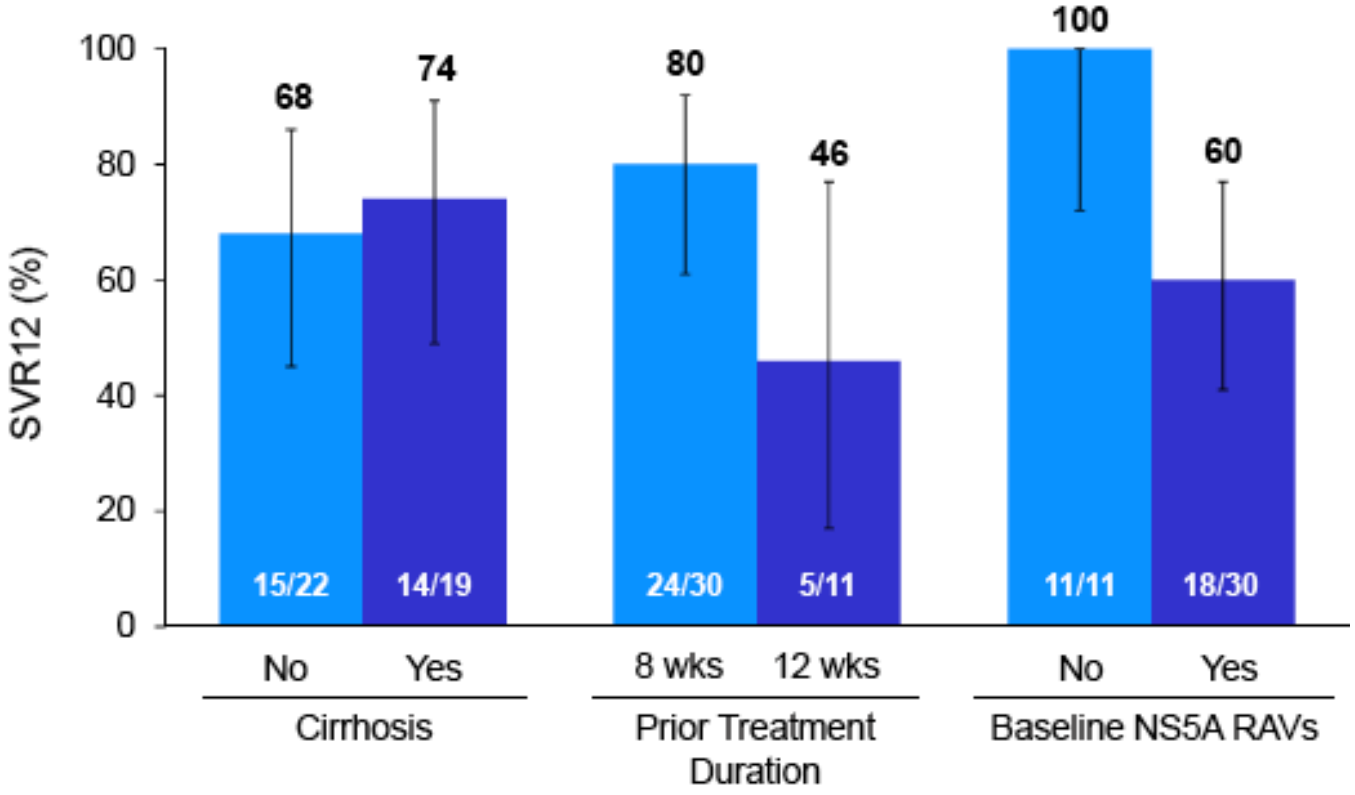
*All 11 had failed 8 weeks of LDV/SOF

- No NS5B SOF-associated variants (S282T, L159F, V321A) detected at baseline
- Of 12 patients with NS5A RAVs at baseline who failed treatment, NS5B and NS5A variants were detected in 4 and 12 patients, respectively

Wyles, AASLD, 2014, Oral #235; Lawitz, et al. EASL 2015, O005

LDV/SOF for Retreatment of HCV GT1 Previous LDV/SOF Failures

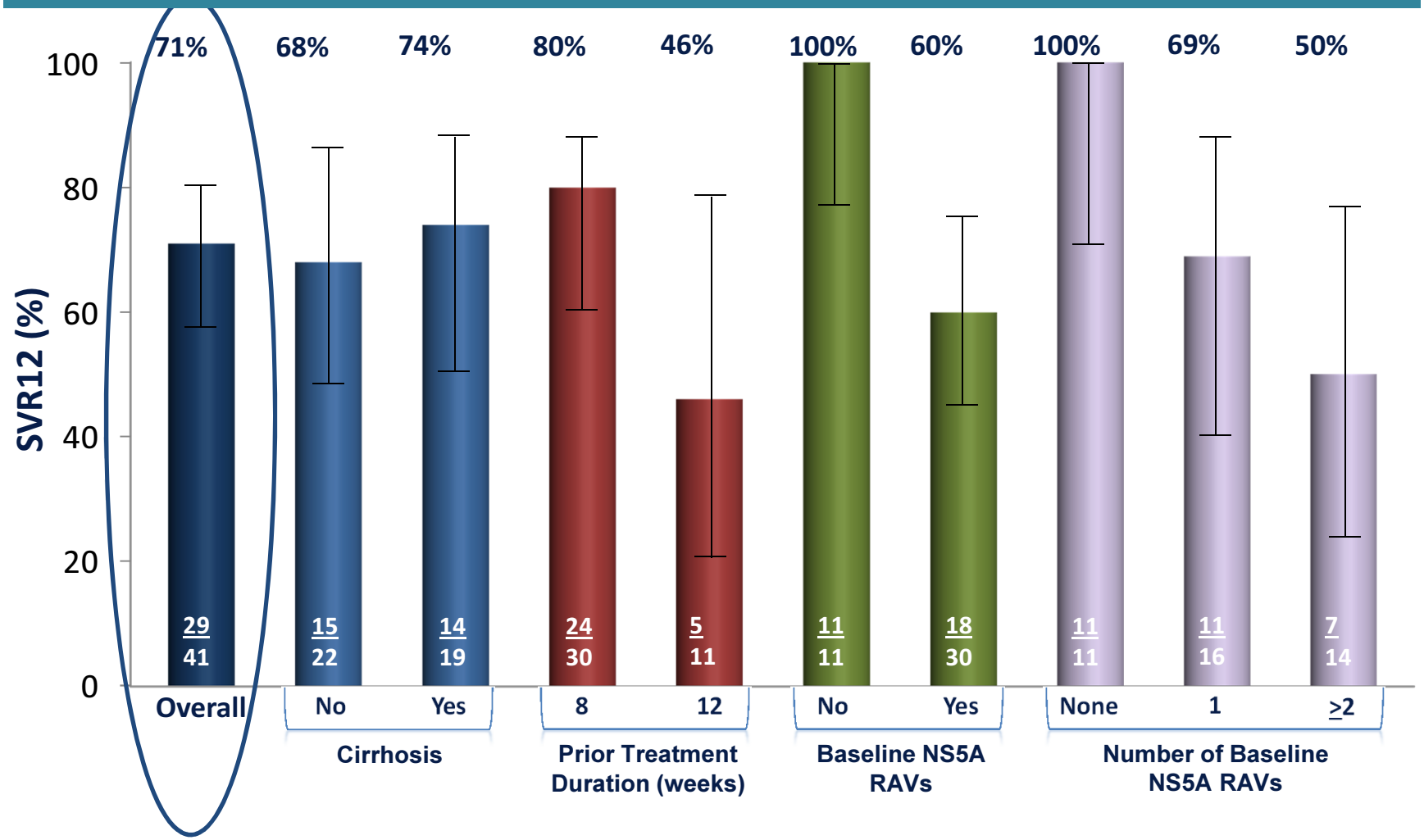
Overall 71% of patients achieved SVR12 when retreated with LDV/SOF for 24 weeks



- All 11 patients without NS5A RAVs received 8 weeks of prior treatment

Lawitz E, et al. J Hepatol. 2015;62(suppl 2):S192. Abstract O005.

LDV/SOF for Retreatment of HCV GT1 Previous LDV/SOF Failures

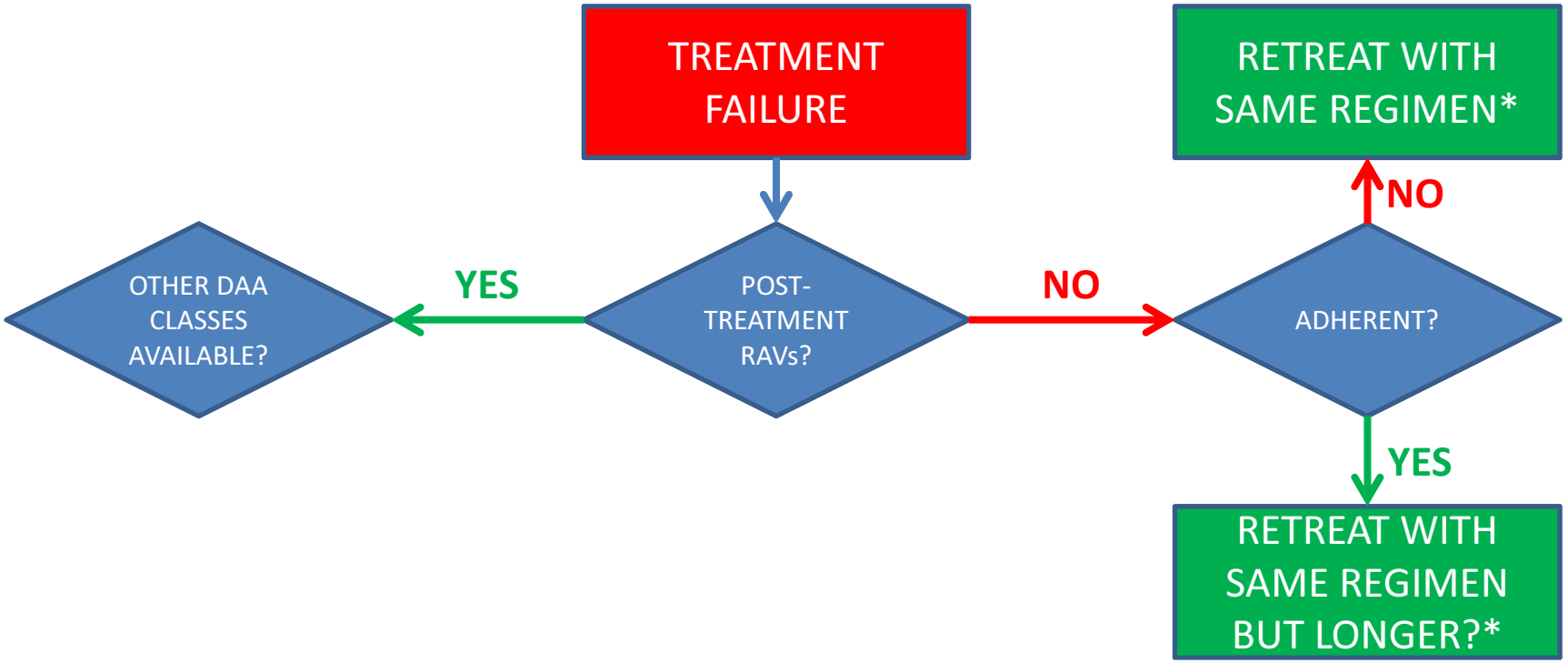


Lawitz E, et al. J Hepatol. 2015;62(suppl 2):S192. Abstract O005.

Successful Retreatment of GT1 With LDV/SOF After Initial Short Course of DAAs

- 34 participants with HCV (GT-1) and early-stage liver fibrosis who previously failed 4–6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks.
- Prior to retreatment, 29 patients (85%) had NS5A-resistant variants.
- The SVR_{12} rate by ITT analysis was 91% (2 patients withdraw and only one relapsed).

Suggested Pathway for HCV Treatment Failure



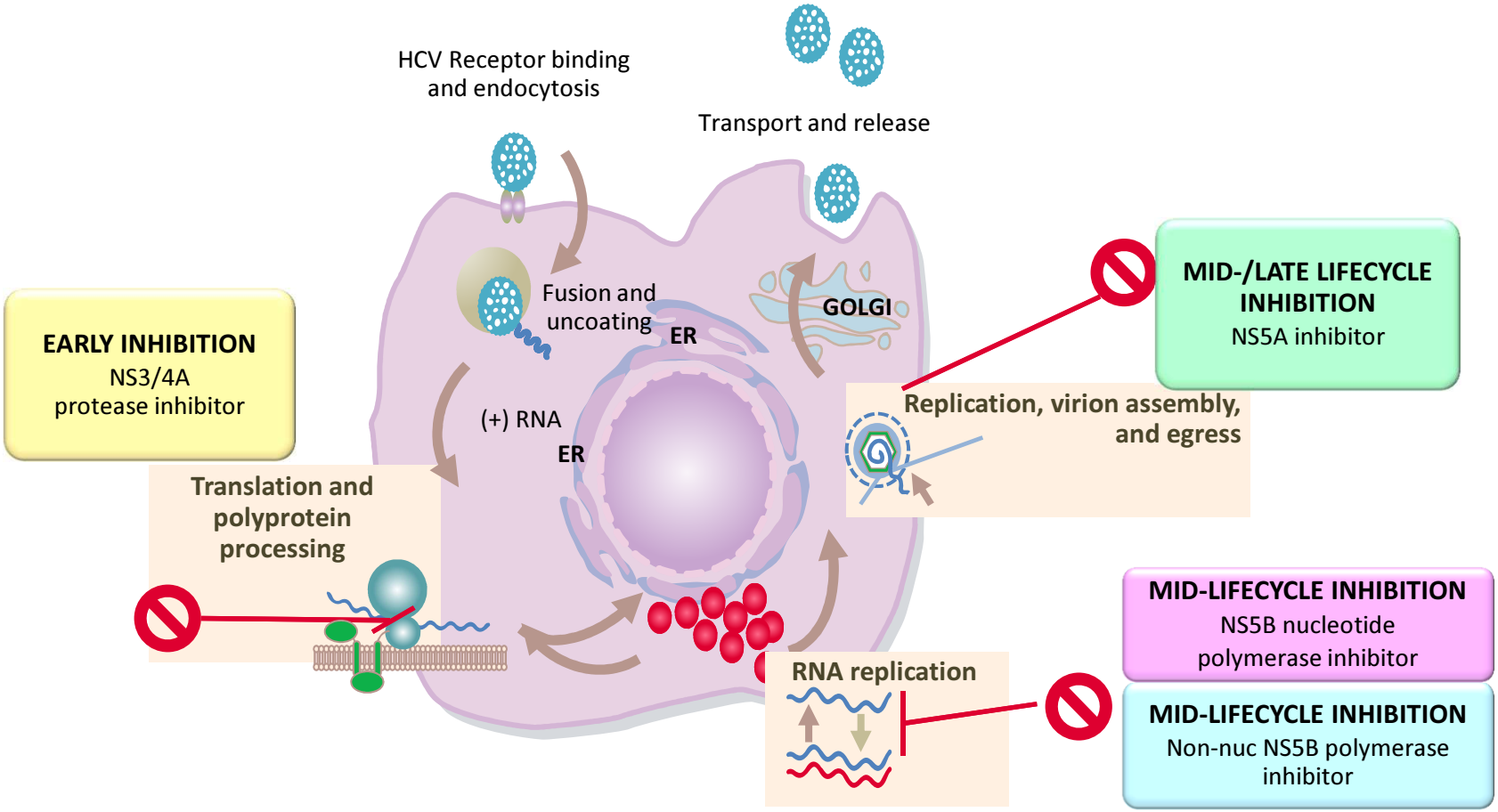
* Assuming availability and funding

Drug Classes

PROTEASE INHIBITORS	NS5A INHIBITORS	NON-NUC POLYMERASE INH	NUCLEOTIDE POLYMERASE INH

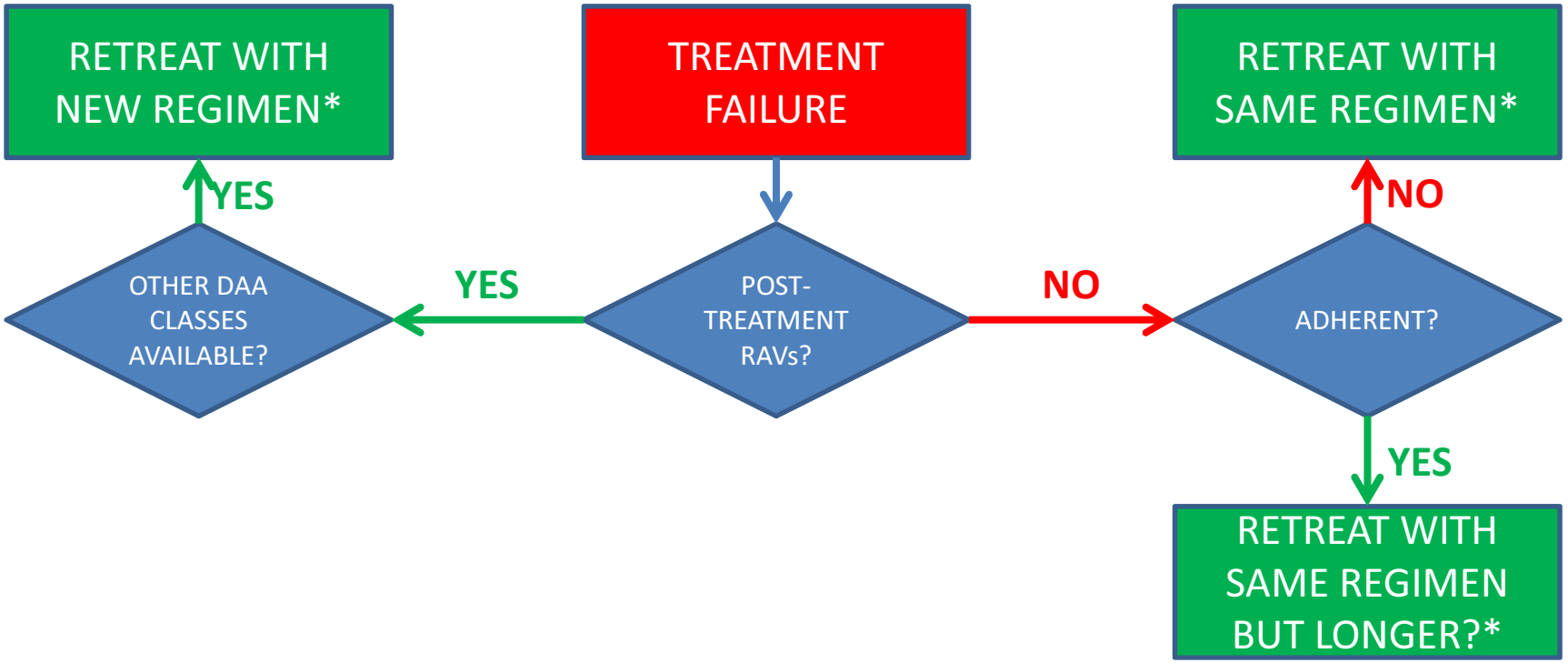
Drug Classes

PROTEASE INHIBITORS	NS5A INHIBITORS	NON-NUC POLYMERASE INH	NUCLEOTIDE POLYMERASE INH



Reference: Lindenbach & Rice. Nature 2005:436;933–38.

Suggested Pathway for HCV Treatment Failure



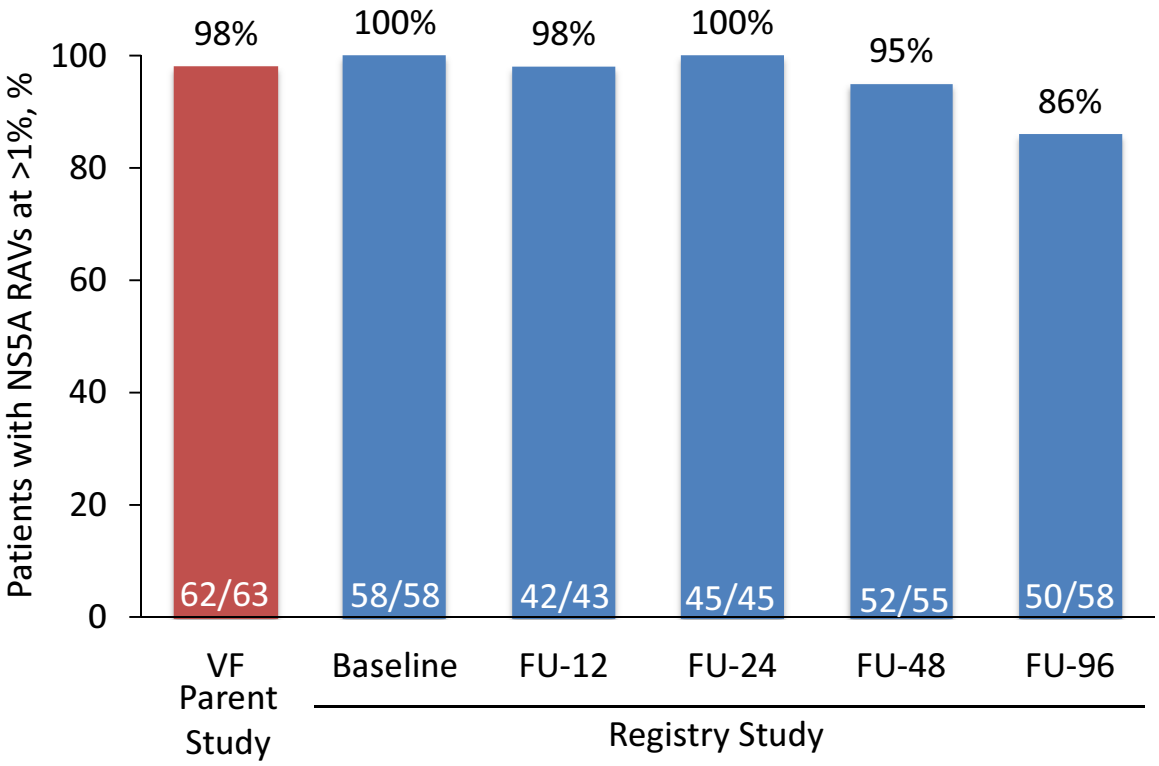
* Assuming availability and funding

Retreatment Using Different Drugs

Currently Available Drugs

PROTEASE INHIBITORS	NS5A INHIBITORS	NON-NUC POLYMERASE INH	NUCLEOTIDE POLYMERASE INH
(Boceprevir)	Ledipasvir	Dasabuvir	Sofosbuvir
(Telaprevir)	Daclatasvir		
Simeprevir	Ombitasvir		
Paritaprevir			

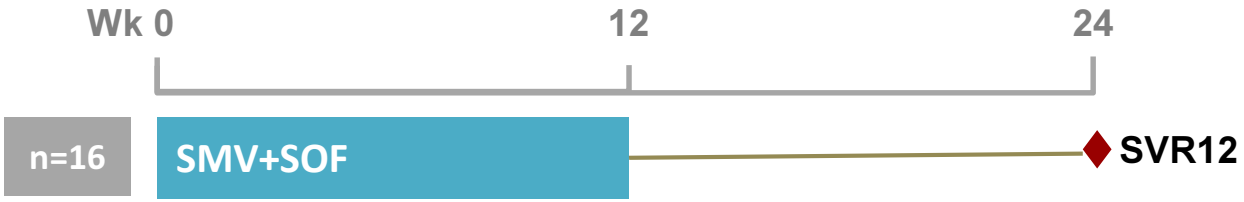
Persistence of NS5A RAVs following LDV Treatment



Once NS5A resistance develops, it very infrequently resolves on its own

Wyles et al, EASL 2015; Vienna, Austria. Abstract O059.

Retreatment with SMV+SOF in those who failed an NS5A-Inhibitor containing regimen

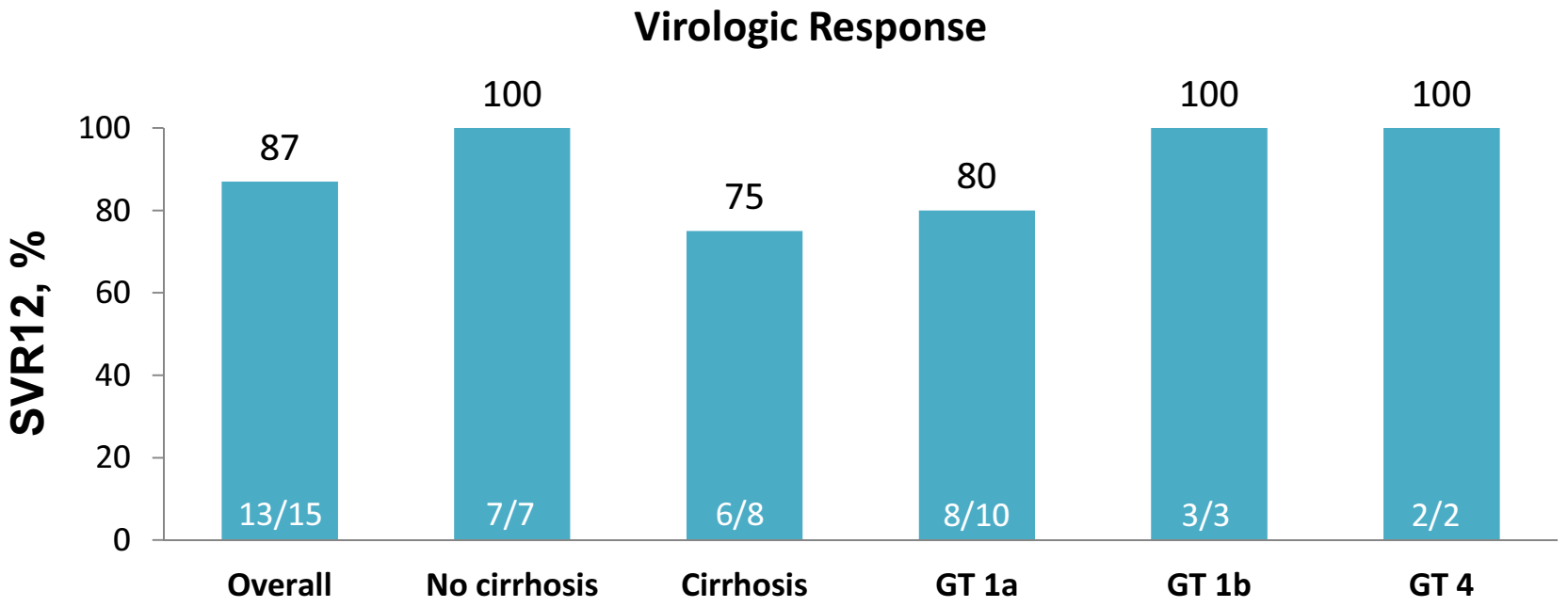


Baseline Demographics

	n=16
Mean age, years (range)	54 (43–73)
Male, n (%)	13 (81)
Genotype, n (%)	
GT 1a	11 (69)
GT 1b	3 (23)
GT 4	2 (13)
Severe fibrosis (FS 9.6–12.5 kPa), n (%)	7 (44)
Cirrhosis (FS > 12.5 kPa), n (%)	9 (56)
Previous regimen, n (%)	
DCV+PegIFN+RBV	13 (81)
DCV+ASV+PegIFN+RBV	3 (19)
Median baseline HCV RNA, 10^6 IU/mL	1.38
>800,000 IU/mL, n (%)	14 (88)

Hezode, AASLD, 2015, 1123

Retreatment with SMV+SOF in those who failed an NS5A-Inhibitor containing regimen



- No SAEs, premature D/Cs, or Grade 3/4 laboratory abnormalities
- Two treatment failures
  - One patient with advanced liver disease and one patient previously exposed to a PI

Hezode, AASLD, 2015, 1123

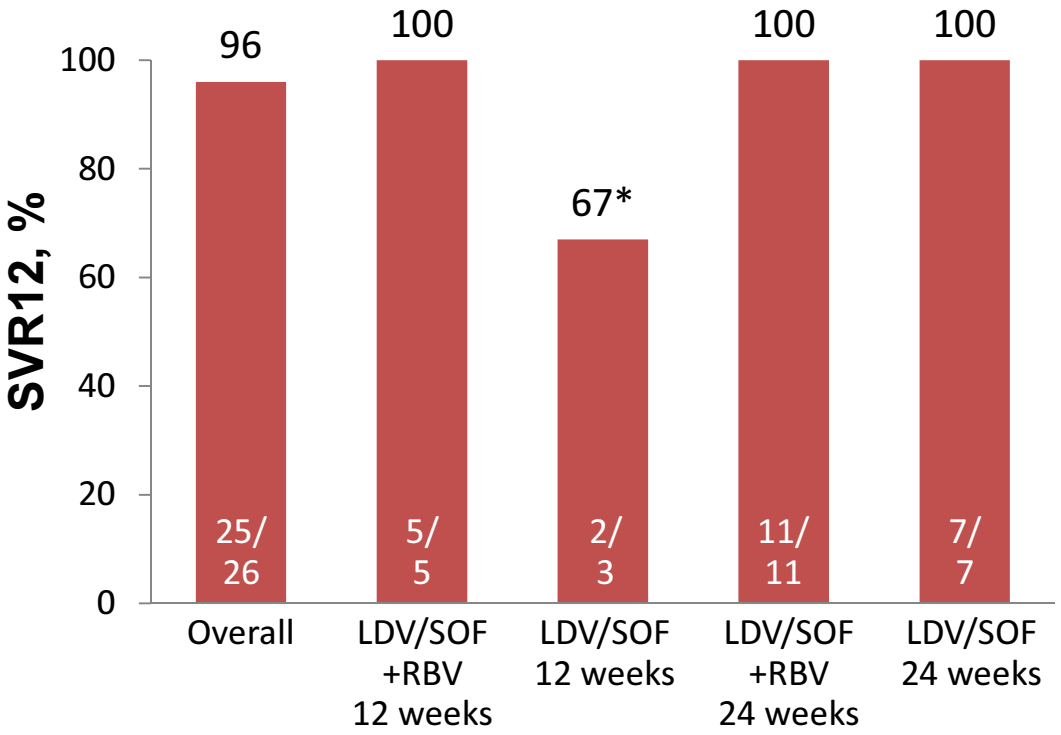
‡

LDV/SOF±RBV in GT1 Relapsers after SMV+SOF±RBV

Baseline Demographics

Patients	n=34
Average age, years (range)	59 (49–76)
Male, n (%)	28 (82)
Non-white, n (%)	5 (15)
GT 1a, n (%)	24 (71)
IL28B CT/TT, n (%)	21 (88)
Metavir F3–F4, n (%)	27 (79)
CPT Class B/C, n (%)	11 (32)
Post-liver transplant, n (%)	10 (29)
Median time since last dose of SMV+SOF, weeks (range)	23 (7–55)

Virologic Response



*Only failure was a post-transplant CPT B, MELD 16 patient who was only treated for 12 weeks of LDV/SOF because of insurance issues

Pungpapong, AASLD, 2015, 1038

LDV/SOF ± RBV for 12-24 Weeks in GT 1 Who Failed SMV+SOF

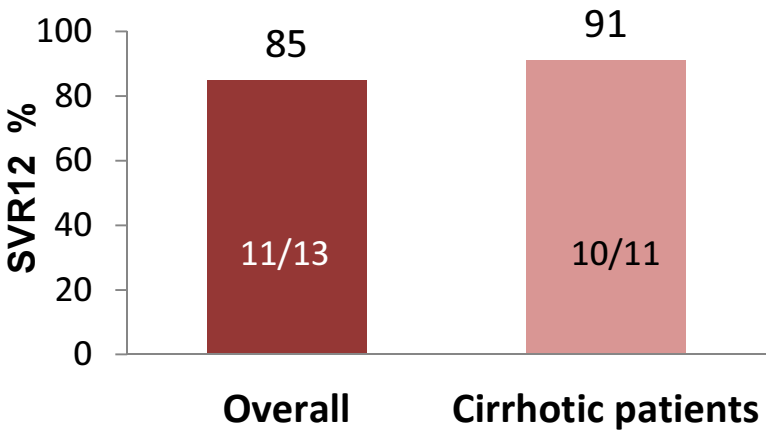
‡

Interim analysis from 2 hepatology referral centers in Texas, USA

Baseline Demographics

Patients	n=31
Male, n (%)	24 (77)
Median age, years (range)	58 (44–66)
GT 1a, n (%)	29 (93)
Compensated cirrhosis, n (%)	15 (48)
Decompensated cirrhosis, n (%)	10 (32)
Post-liver transplant, n (%)	3 (10)
LDV/SOF 12 weeks, n (%)	1 (3)
LDV/SOF+RBV 12 weeks, n (%)	11 (35)
LDV/SOF 24 weeks, n (%)	16 (52)
LDV/SOF+RBV 24 weeks, n (%)	3 (10)

Virologic Response



- 2 patients did not achieve SVR due to relapse
- 31% reported no AEs
- Most common AEs: fatigue, headache, insomnia, nausea, diarrhea
- 1 episode of decompensation with bleeding esophageal varices during treatment (patient on LDV/SOF 24 weeks)

Gonzales, AASLD, 2015, 1146

Retreatment of DAA failure patients with SOF+PegINF/RBV

- 80 GT1 patients who had participated in previous DAA trials of GS-9451 or GS-9256 with or without the non-nucleoside polymerase inhibitor, tegobuvir (TGV), and/or the NS5A inhibitor, ledipasvir (LDV)
- 51% of patients harbored NS3 RAVs, 84% harbored NS5A RAVs, and 28% had NS5B RAVs at time of virologic failure
- All patients treated with 12 weeks Sofosbuvir + P/R
- All patients undetectable at EOTR. 17 patients (21%) relapsed by PTW12 giving overall SVR of 79%

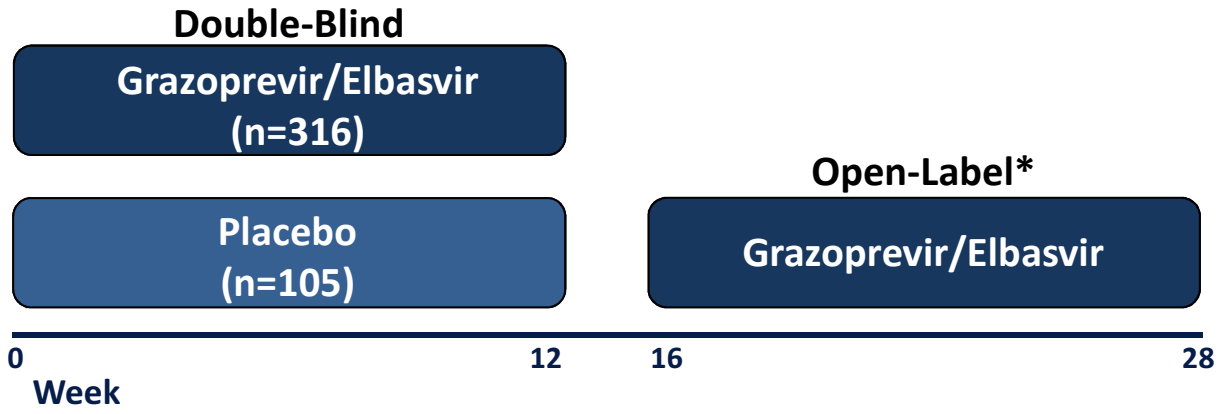
Pol et al, Hepatology. 2015 Jul;62(1):129-34

Soon to be Licensed Drugs

PROTEASE INHIBITORS	NS5A INHIBITORS	NON-NUC POLYMERASE INH	NUCLEOTIDE POLYMERASE INH
(Boceprevir) (Telaprevir) Simeprevir Paritaprevir	Ledipasvir Daclatasvir Ombitasvir	Dasabuvir	Sofosbuvir
Grazoprevir	Elbasvir Velpatasvir		

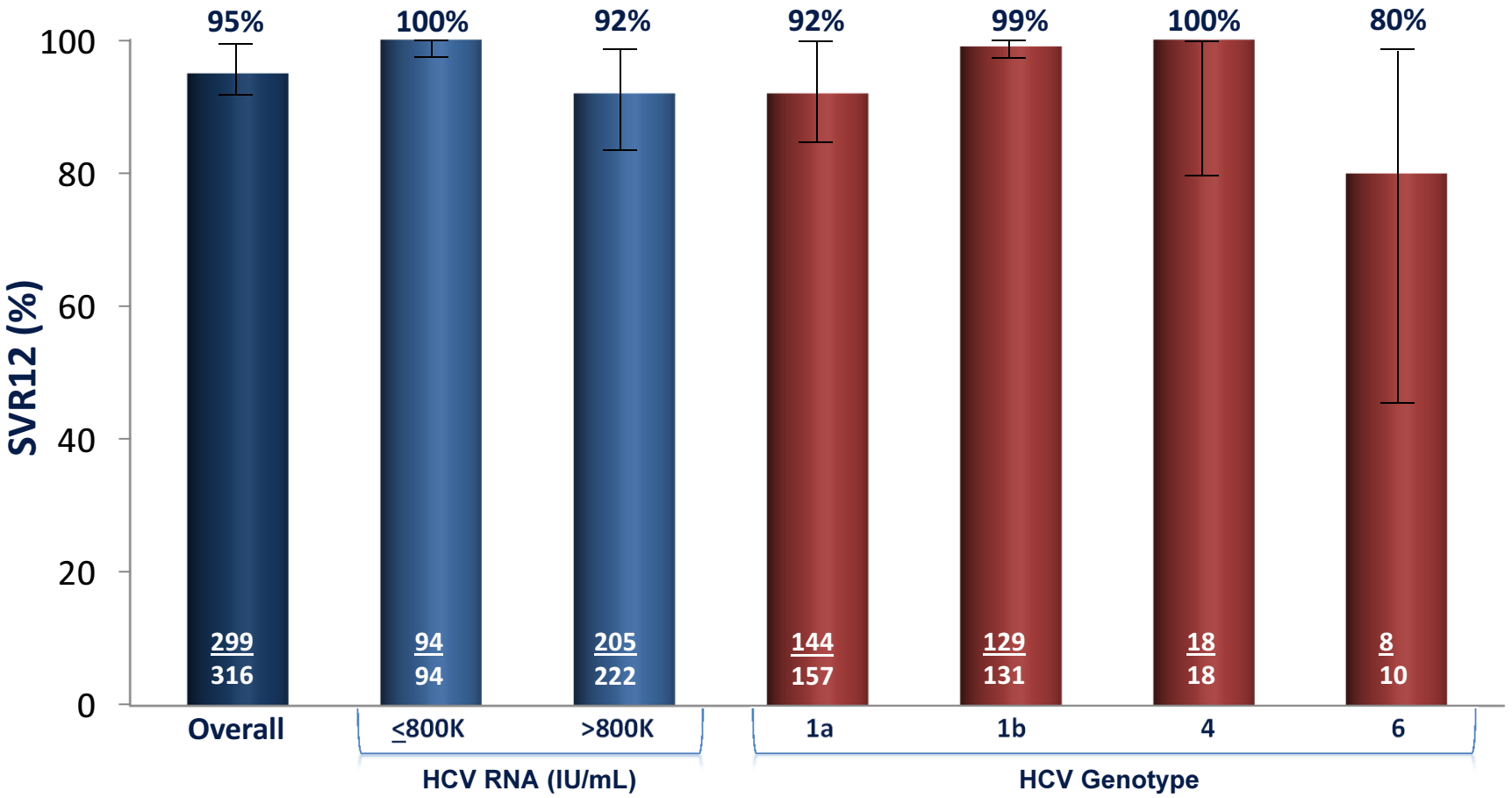
C-EDGE: Grazoprevir/Elbasvir in Treatment-Naïve, HCV Genotypes 1, 4, or 6

- Phase 3, Placebo-controlled trial of treatment-naïve GT1,4 and 6 patients.
- Cirrhosis allowed. HCC, HIV and HBV coinfection excluded.
- 54% male, mean age 52.6y, 18% African American
- GT1a (50%); GT1b (41%); GT4 (6%); GT6 (3%)
- HCV RNA > 800,000 IU/mL 68%
- 22% cirrhosis
- Platelets <100 in 8.1%



Zeuzem S, et al. J Hepatol. 2015;62(suppl 2):S213. Abstract G07.

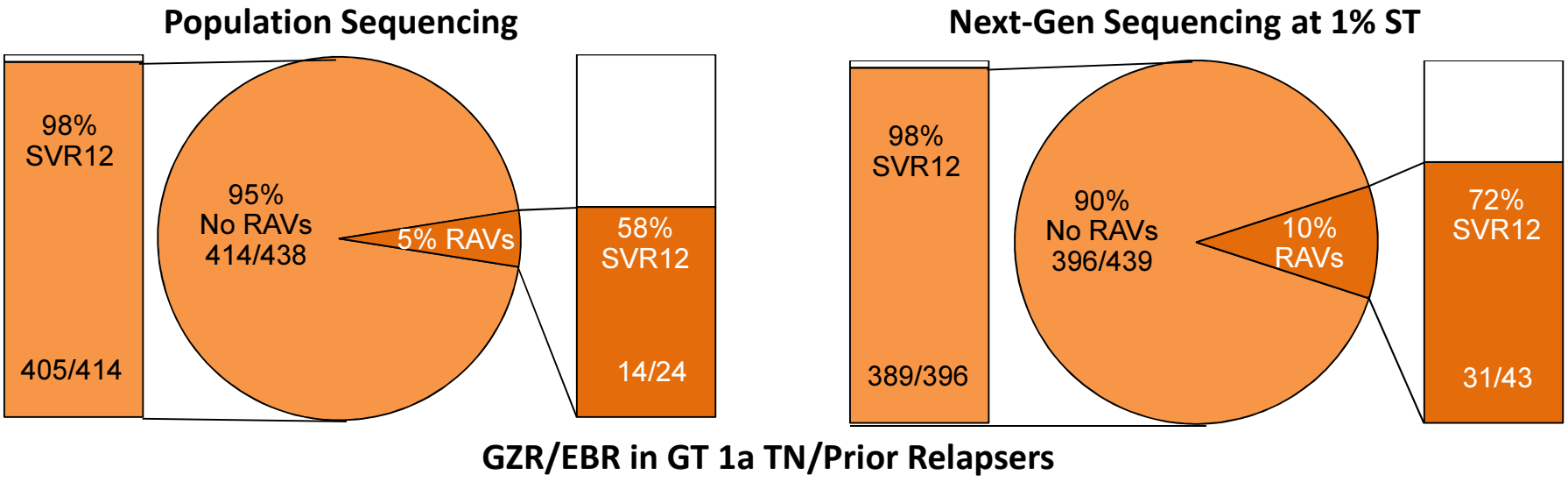
C-EDGE: SVR12 With GZV/EBV in Treatment-Naïve, HCV GT1, 4, or 6



All patients with virologic failure (n=12) had baseline HCV RNA >800K IU/mL (genotype 1a [n=9], 1b [n=1], 4 [n=0], 6 [n=2]).

Zeuzem S, et al. J Hepatol. 2015;62(suppl 2):S213. Abstract G07.

Prevalence and Impact of Baseline NS5A RAVs on Efficacy of GZR/EBR in HCV GT 1a



Effect of Baseline NS5A RAVs on SVR12

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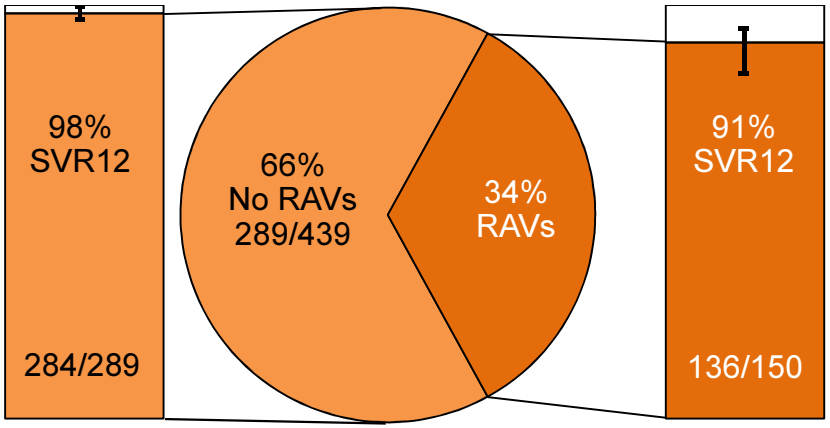
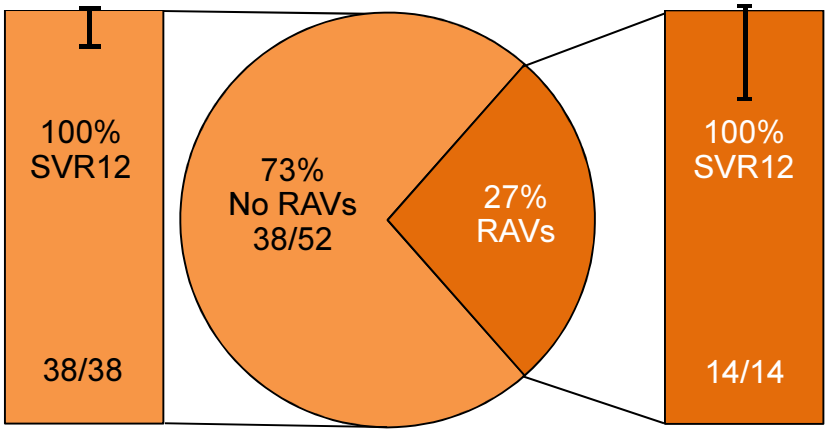
TN and prior relapse patients
12 weeks, no RBV

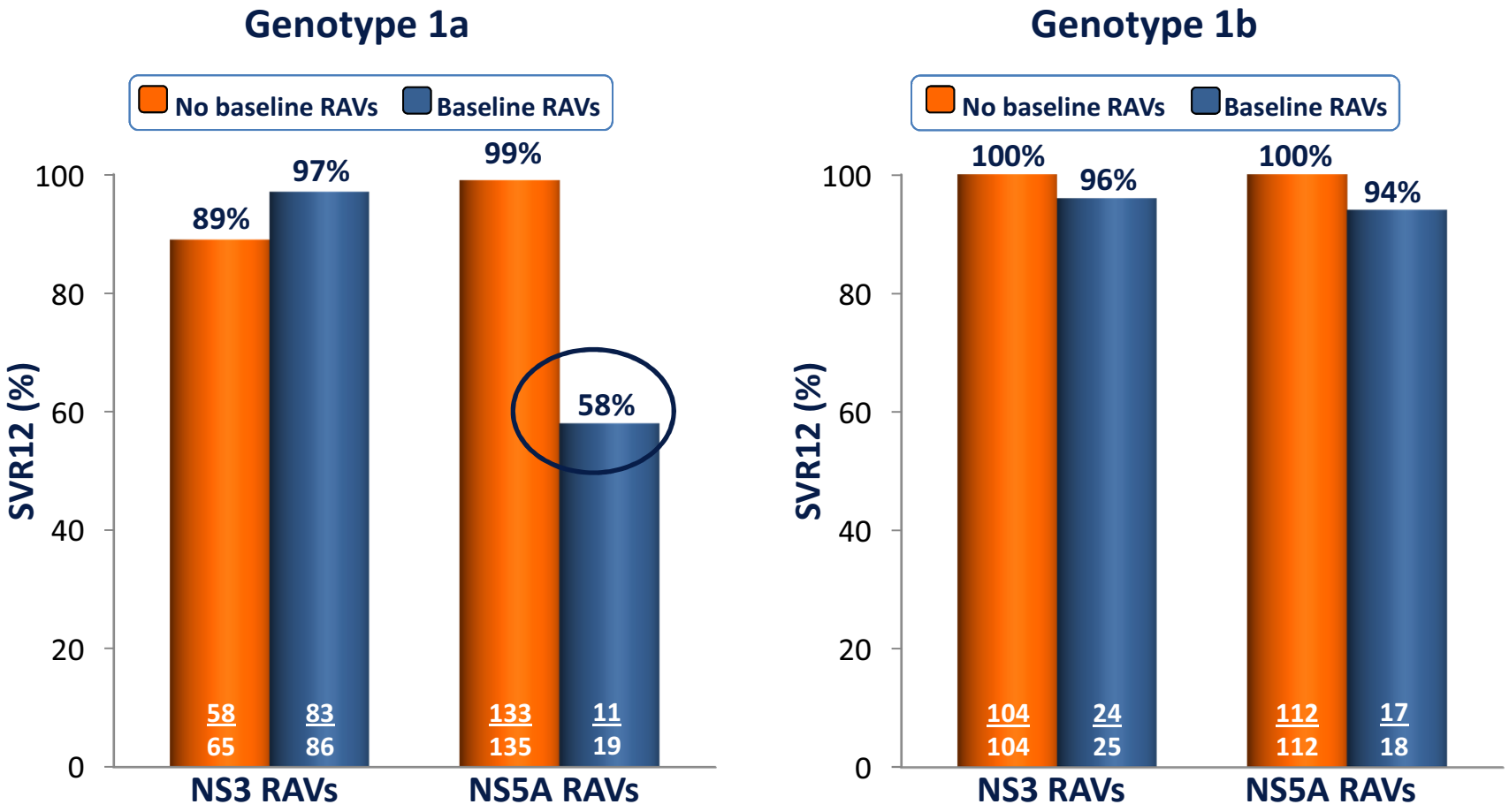


Prior on-treatment failure
16/18 weeks + RBV



Thompson, AASLD 2015, 703

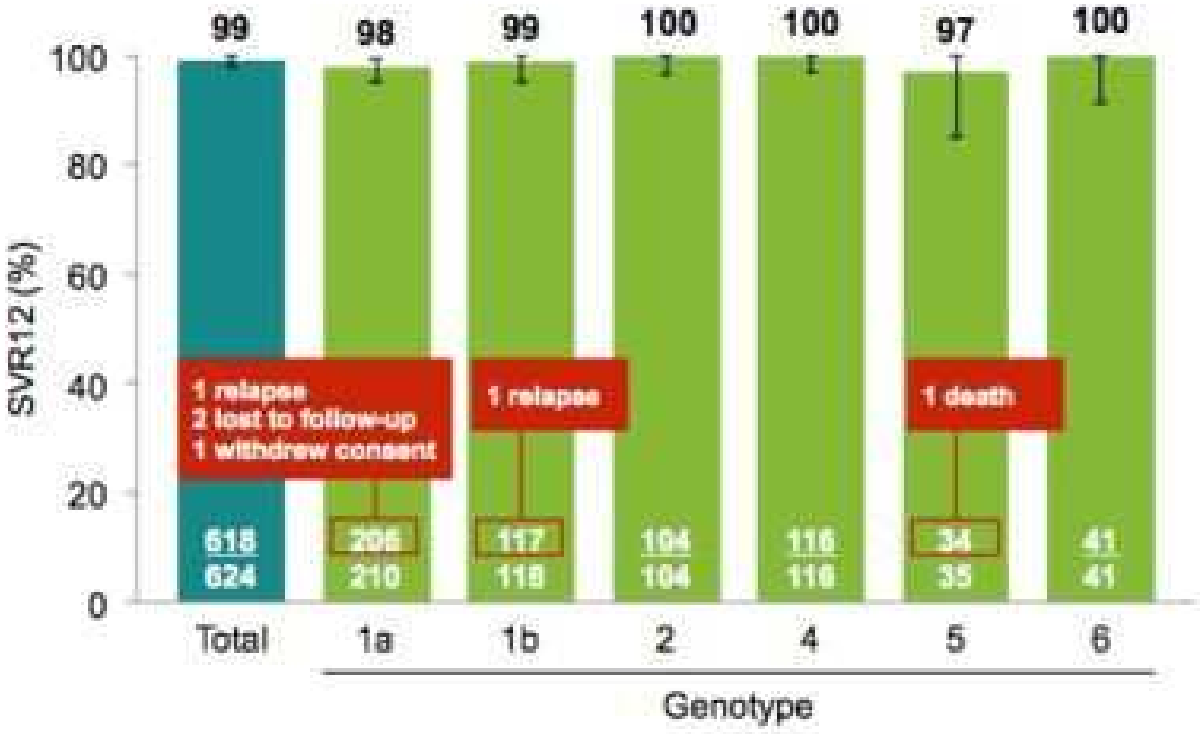
C-EDGE: GZR/EBR in Treatment-Naïve, HCV GT1 SVR12 by Baseline RAVs



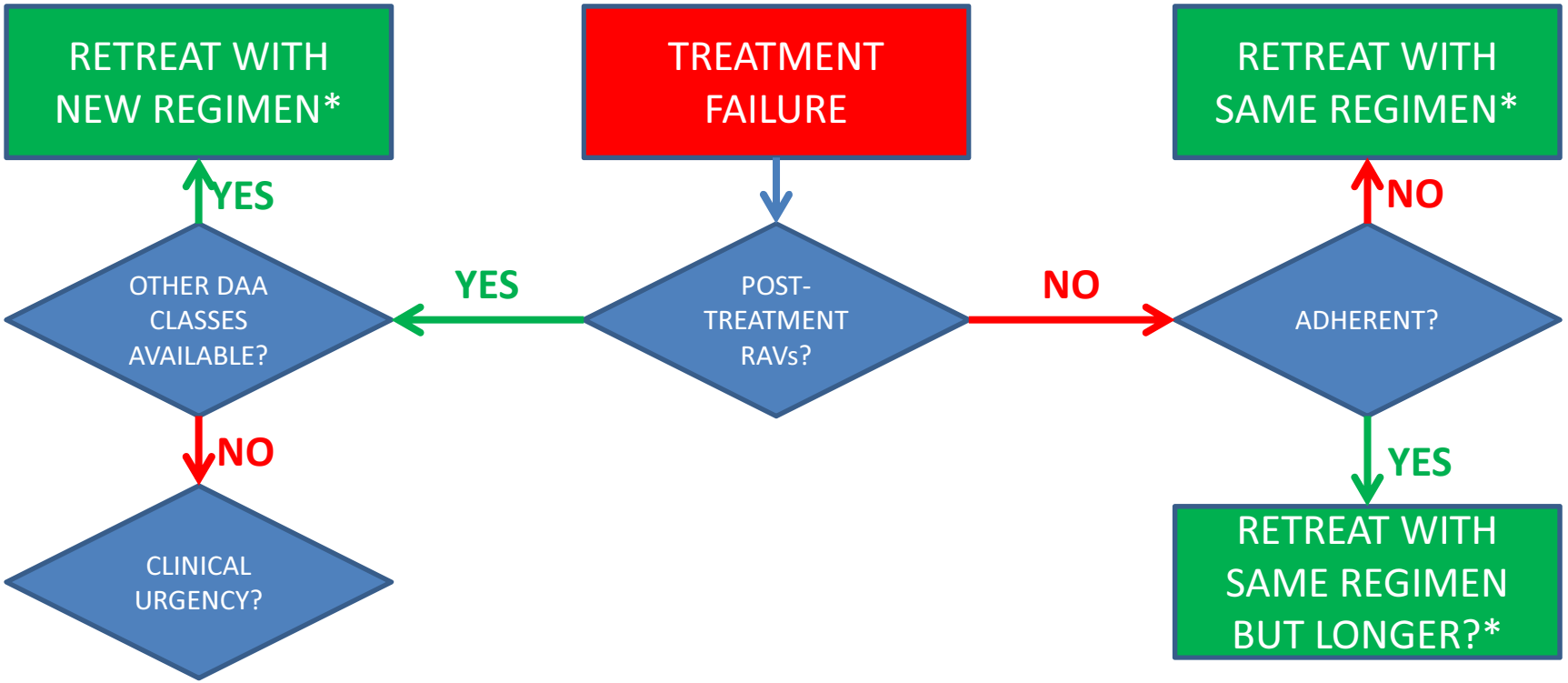
SVR12 rates with baseline NS5A RAVs: <5-fold potency (90%, 9/10); >5-fold potency (22%, 2/9).

Zeuzem S, et al. J Hepatol. 2015;62(suppl 2):S213. Abstract G07.

Astral Studies: 12 weeks
Sofosbuvir/Velpatasvir FDC

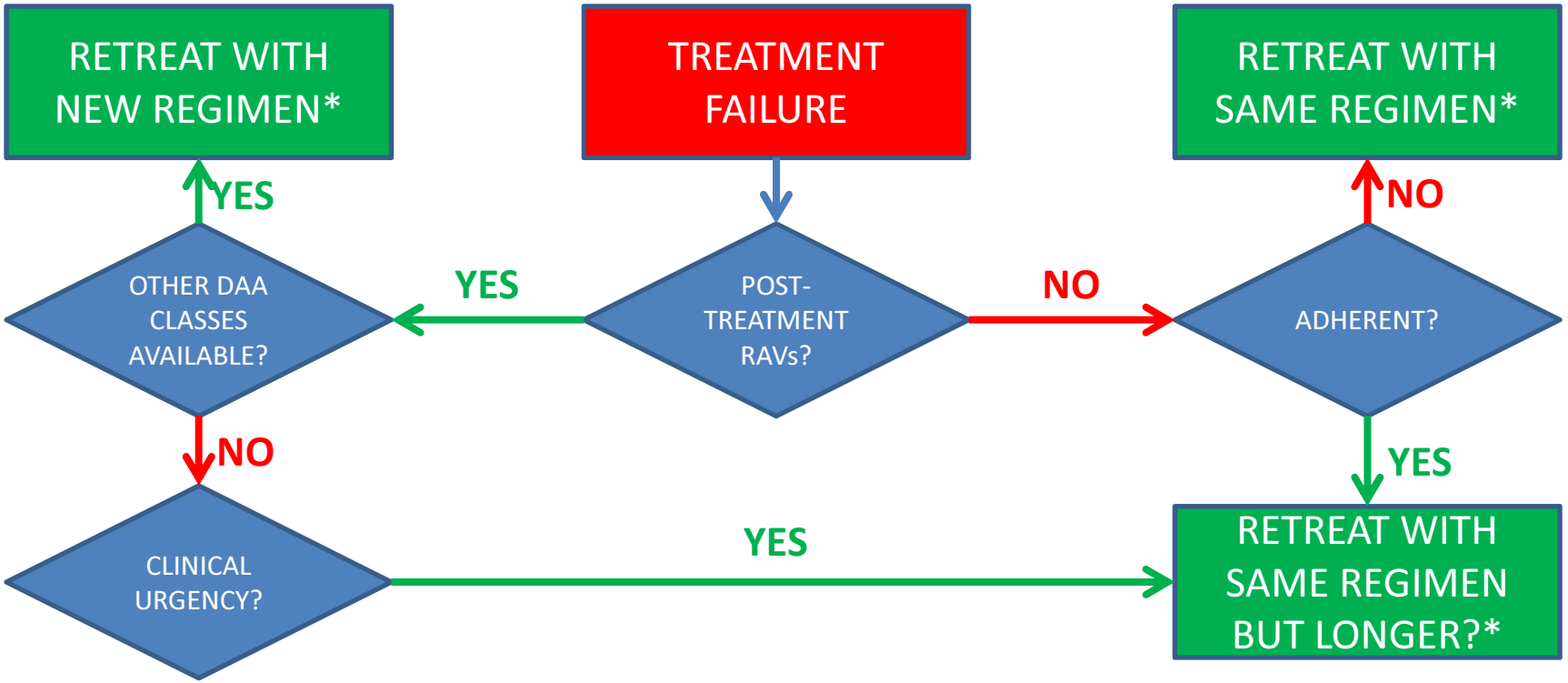


Suggested Pathway for HCV Treatment Failure



* Assuming availability and funding

Suggested Pathway for HCV Treatment Failure



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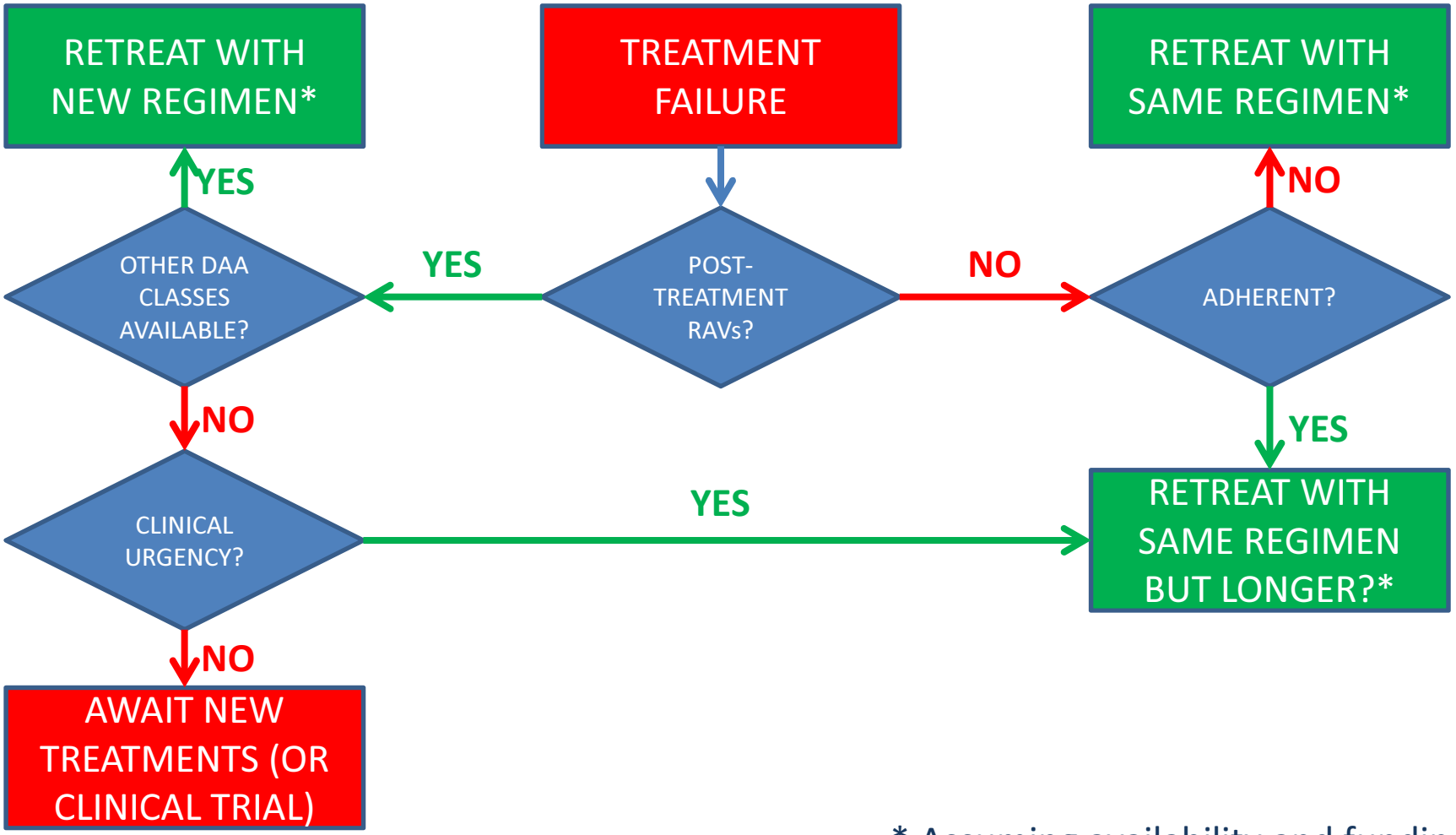


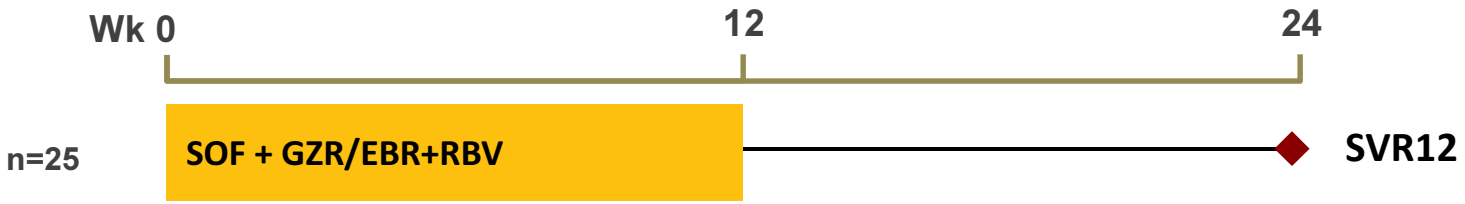
* Assuming availability and funding

Future Drugs

Future Drug Pipeline

PROTEASE INHIBITORS	NS5A INHIBITORS	NON-NUC POLYMERASE INH	NUCLEOTIDE POLYMERASE INH
(Boceprevir)	Ledipasvir	Dasabuvir	Sofosbuvir
(Telaprevir)	Daclatasvir		
Simeprevir	Ombitasvir		
Paritaprevir			
Grazoprevir	Elbasvir		
	Velpatasvir		
GS-9857	Odalasvir	Beclabuvir	AL-335
ABT-493	ACH-3102		MK-3682
	MK-8408		
	GS-5816		
	ABT-530		

Triple Therapy as the Ultimate Rescue?



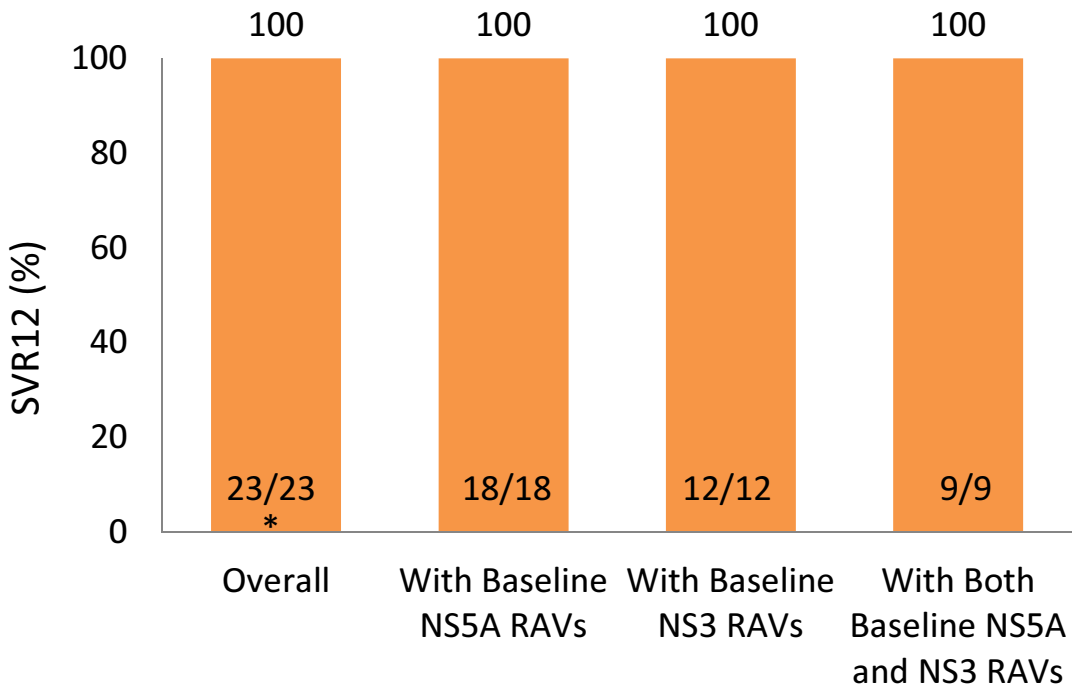
Patients	n=25
Male, n (%)	22 (88)
Mean age, years (range)	54 (23-66)
White, n (%)	25 (100)
IL28B CC, n (%)	5 (20)
Previous treatment failure, n 4 / 6/ 8 week treatment	17 / 7/ 1
GT 1a, n (%)	22 (88)
Cirrhosis, n (%)	5 (20)
Mean baseline viral load, $\log_{10}$ IU/mL	6.19
Baseline NS5A RAVs, n (%)	20 (80)
Baseline NS3 RAVs, n (%)	13 (52)

GZR, grazoprevir (NS3/4A inhibitor); EBR, elbasvir (NS5A inhibitor).
Lawitz, AASLD, 2015, LB-12

SOF + GZV/EBV+RBV for 12 Weeks in GT1 Patients Who Failed 4, 6 r 8 Weeks GZV/EBVDAA Therapy

‡

SVR12 by baseline RAVs, mFAS



Safety Summary

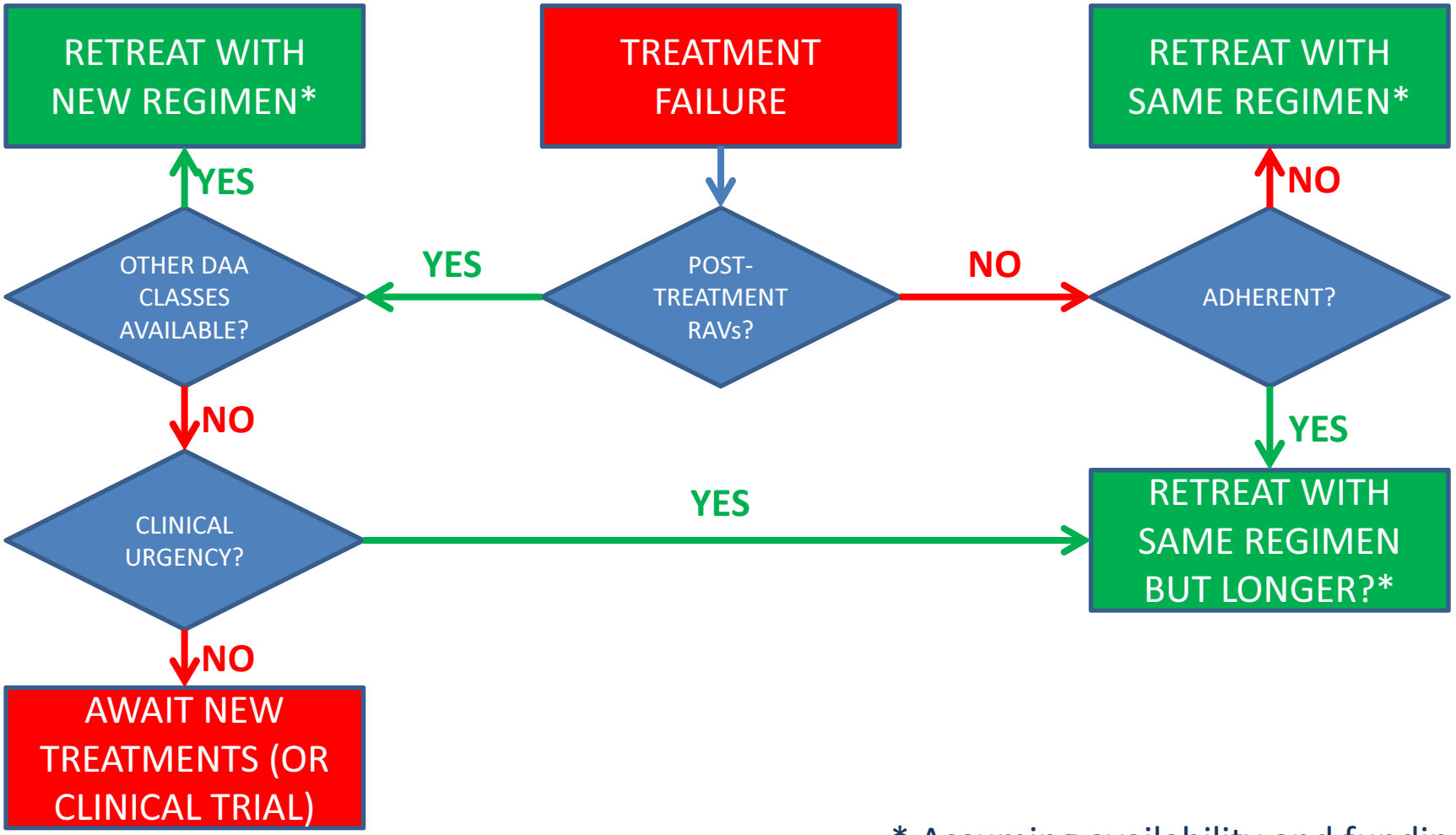
Patients	SOF + GZR/EBR+ RBV x 12 weeks n=25
≥ 1 AE, n (%)	13 (52)
SAE, n (%)	1 (4)
Drug-related AE, n (%)	9 (36)
Most common AEs >5%	
Rash	2 (8)
Fatigue	2 (8)
Nausea	2 (8)
UTI	2 (8)

*Excludes 2 patients lost to follow-up at Day 3 and Treatment Week 4

- NS3 RAVs: V36M (1/22), Q80K (12/22), S122G (2/22), D168E (1/22), and I170V (1/22)

Lawitz, AASLD, 2015, LB-12

THANK YOU



* Assuming availability and funding