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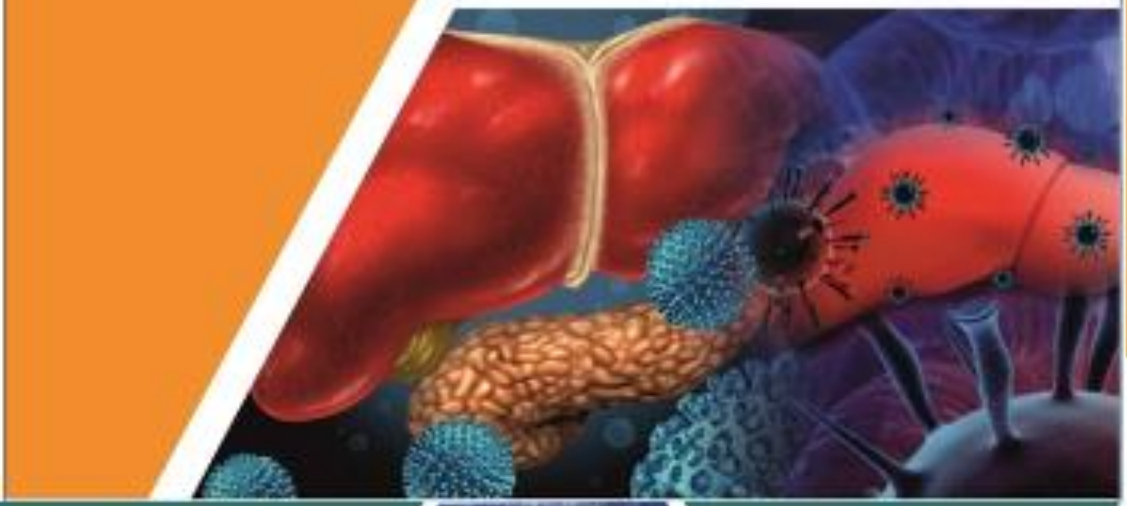
PROJECT PRAKASH

Programmed Approach to Knowledge and Sensitization on Hepatitis

HEPATITIS INDUCTION PROGRAM

FOR DOCTORS



DIAGNOSIS & MANAGEMENT OF HEPATITIS C

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WHERE HCV THERAPY STANDS NOW

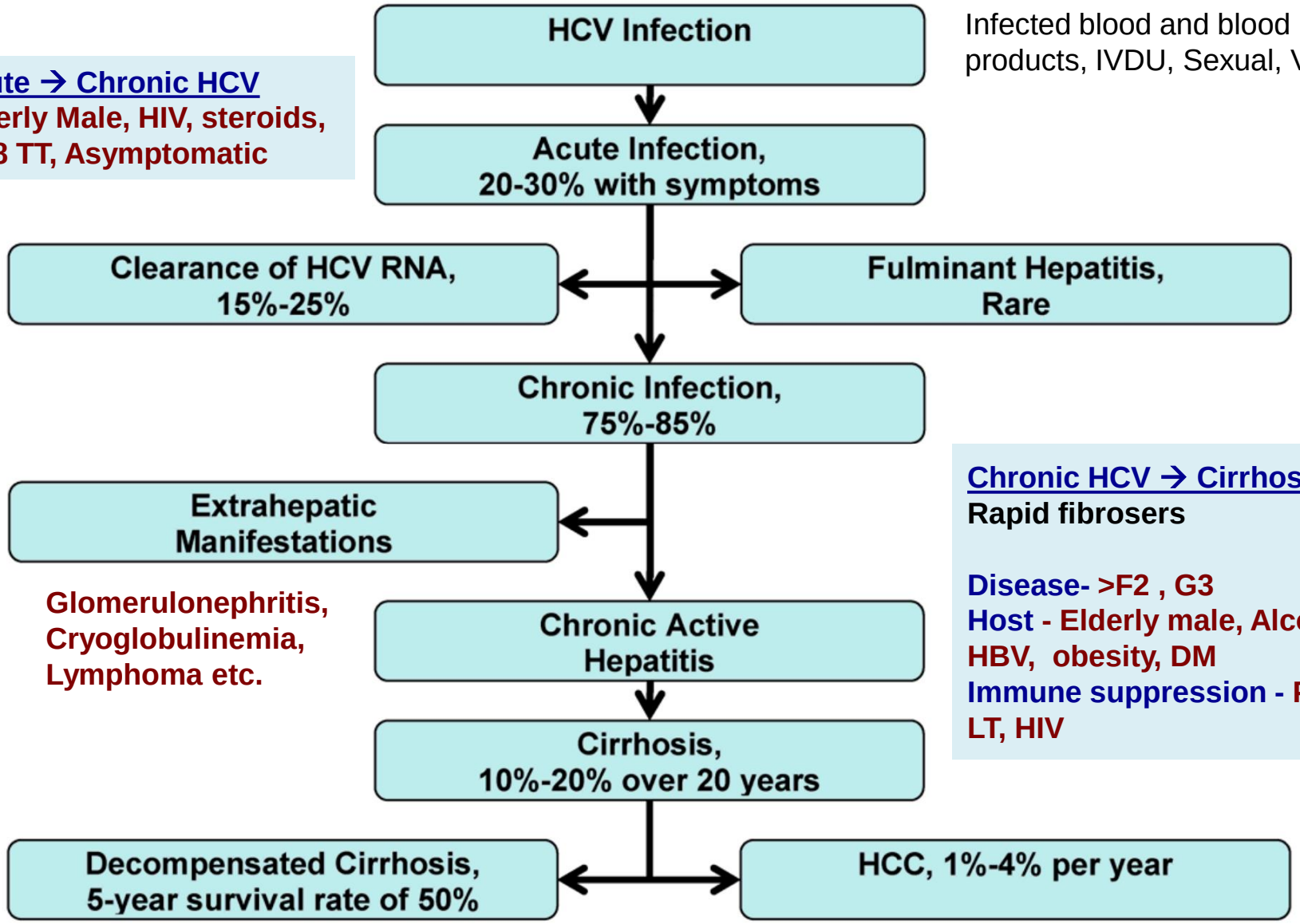
- Interferon is gone in the US; ribavirin . . . not quite
- SVR in > 95% of pts
- "Difficult-to-cure" populations no longer difficult
  - Black race
  - HIV coinfection *- Cirrhosis* *- Renal failure & kidney transplant*
    - Older age *- Liver transplant*
  - Persons who inject drugs (PWID)
  - Genotype 3 remains more challenging (but not by much)
- Emergent issues and controversies:
  - HBV reactivation
- Cost and access issues persist but improving

- HCC recurrence after DAA therapy

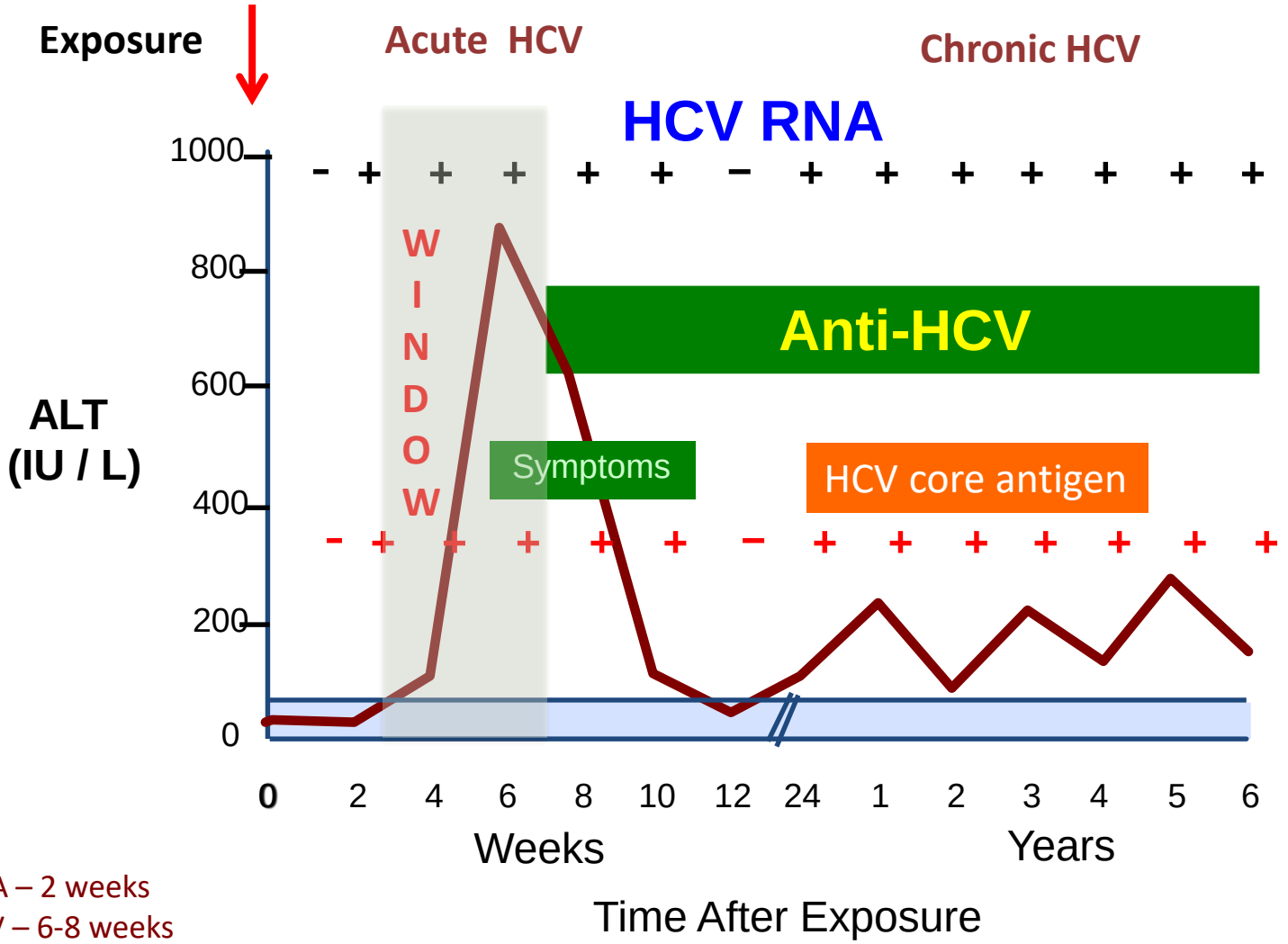
Outline

- Natural course of HCV infection and Diagnosis
- First time treatment
- Retreatment in DAA failures, drug resistance
- Special scenarios
  - Decompensated cirrhosis
  - HCV + Liver cancer
  - HCV + HBV
  - Acute hepatitis C
  - Pregnancy, children and adolescence
- Post treatment follow up

Natural history of HCV infection



Diagnosis of HCV infection



HCV RNA – 2 weeks
Anti HCV – 6-8 weeks
HCV core antigen – 2-4 weeks

Diagnosis of HCV: Requires Both Anti-HCV (Antibody) and HCV-RNA (Viral Load)

Anti-HCV	HCV RNA	Interpretation
Positive	Positive	• Chronic or acute HCV infection
Positive	Negative	• Resolution of HCV infection (spontaneous or with treatment)
Negative	Positive	• Early acute HCV infection (prior to antibody development) • HCV infection in severely immunocompromised setting (eg, HIV infection, organ transplant, chemotherapy)
Negative	Negative	• No HCV infection

Benefits of SVR (HCV cure)

* SVR – Undetected HCV RNA after 12 to 24 weeks of treatment completion

SVR

Decreased transmission

Improved clinical outcomes

Hepatic

↓ Cirrhosis
↓ Decompensation
↓ HCC
↓ Transplantation

Extrahepatic

↓ All-cause mortality
↑ QoL
↓ Malignancy
↓ Diabetes
↓ CVD
↓ Renal
↑ Neurocognitive

Smith-Palmer J, et al. BMC Infect Dis. 2015;15:19. Negro F, et al. Gastroenterology. 2015;149:1345-1360. George SL, et al. Hepatology. 2009;49:729-738.

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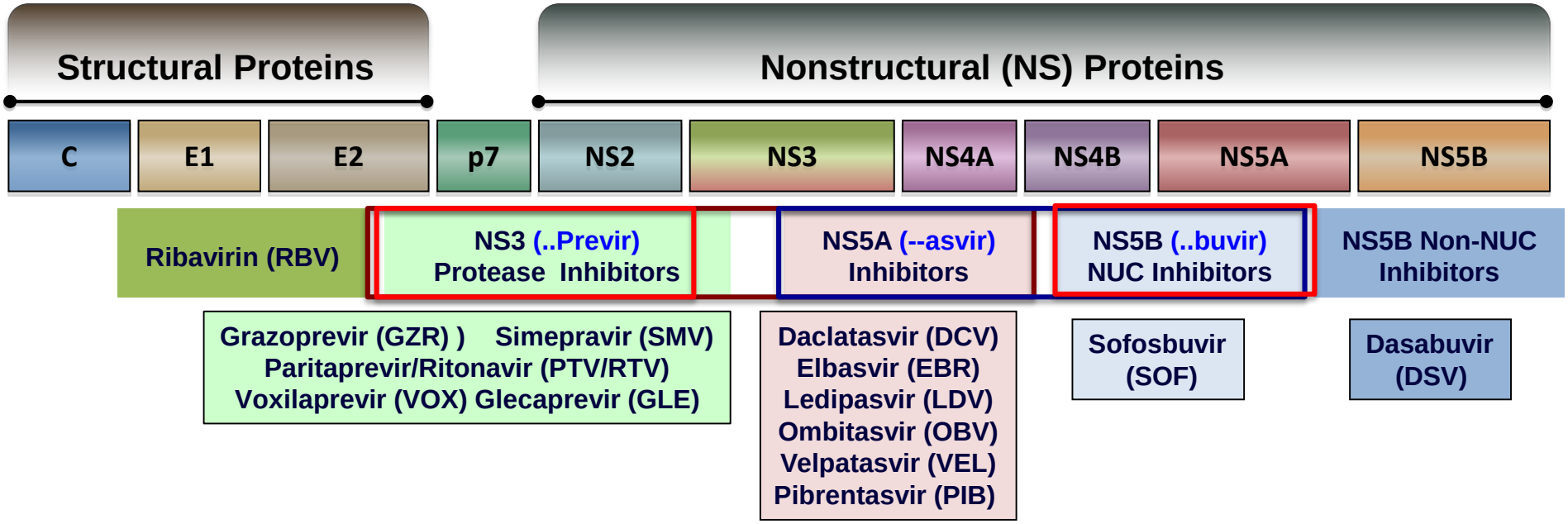
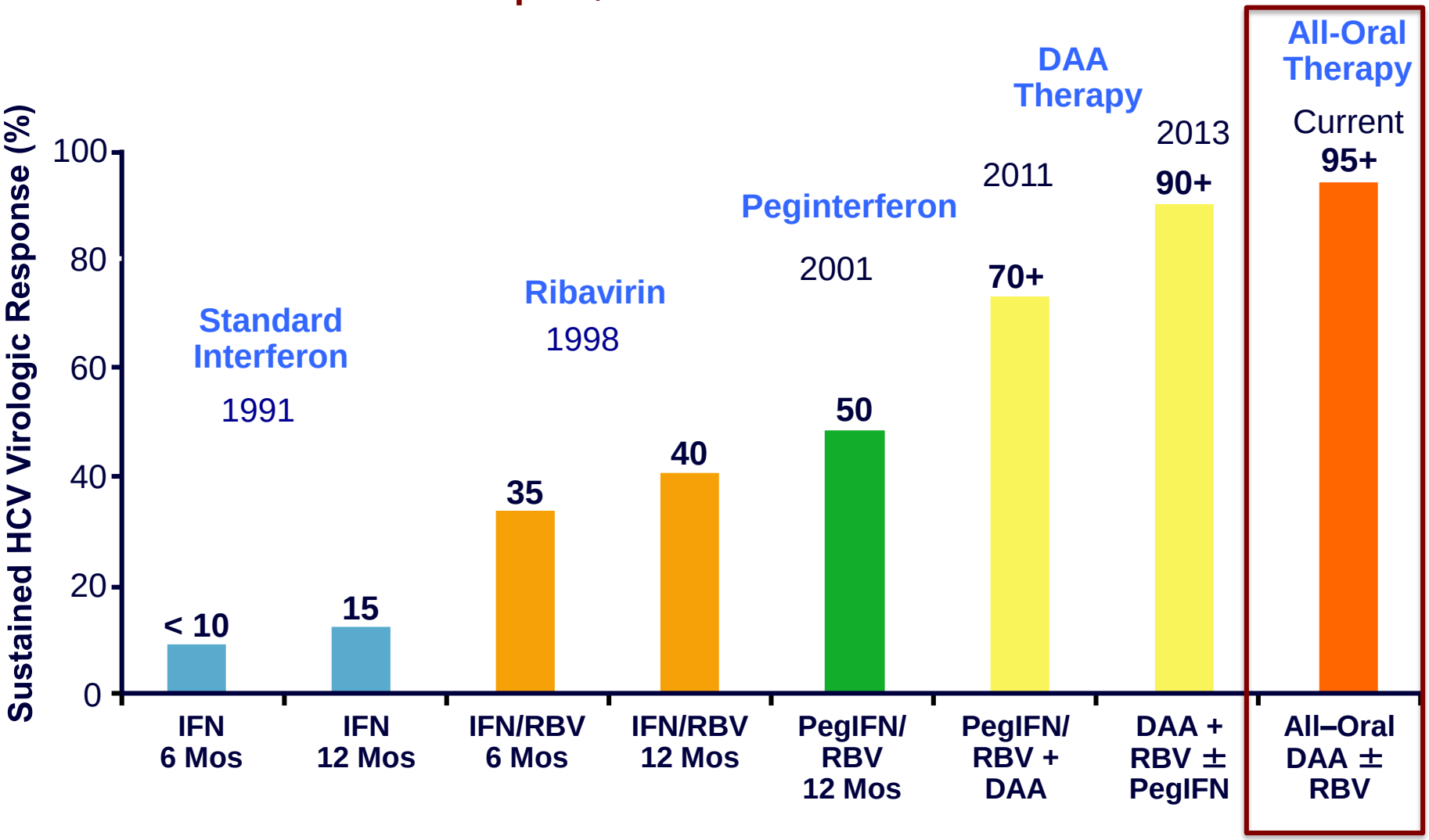
Directly acting agents (DAA) and targets



Antiviral class (DAA)	DAA regimen in use
NS3 PI + NS5A	Grazoprevir + Elbasvir Glecaprevir + Pibrentasvir Daclatasvir + Asunaprevir
NS5B + NS5A*	**Sofosbuvir + Ledipasvir (G1,4 > G3)** **Sofosbuvir + Daclatasvir (G3 > 1,4)** **Sofosbuvir + Velpatasvir (Pangenotype)**
NS5B + PI	Sofosbuvir + Simeprevir
NS5B (NUC) + PI + NS5A	Sofosbuvir + Velpatasvir + Voxilaprevir
NS5B (Non-NUC) + PI + NS5A	Ombitasvir + Paritaprevir/Ritonavir + Dasabuvir

* Available in India

Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



Development of HCV viral resistance

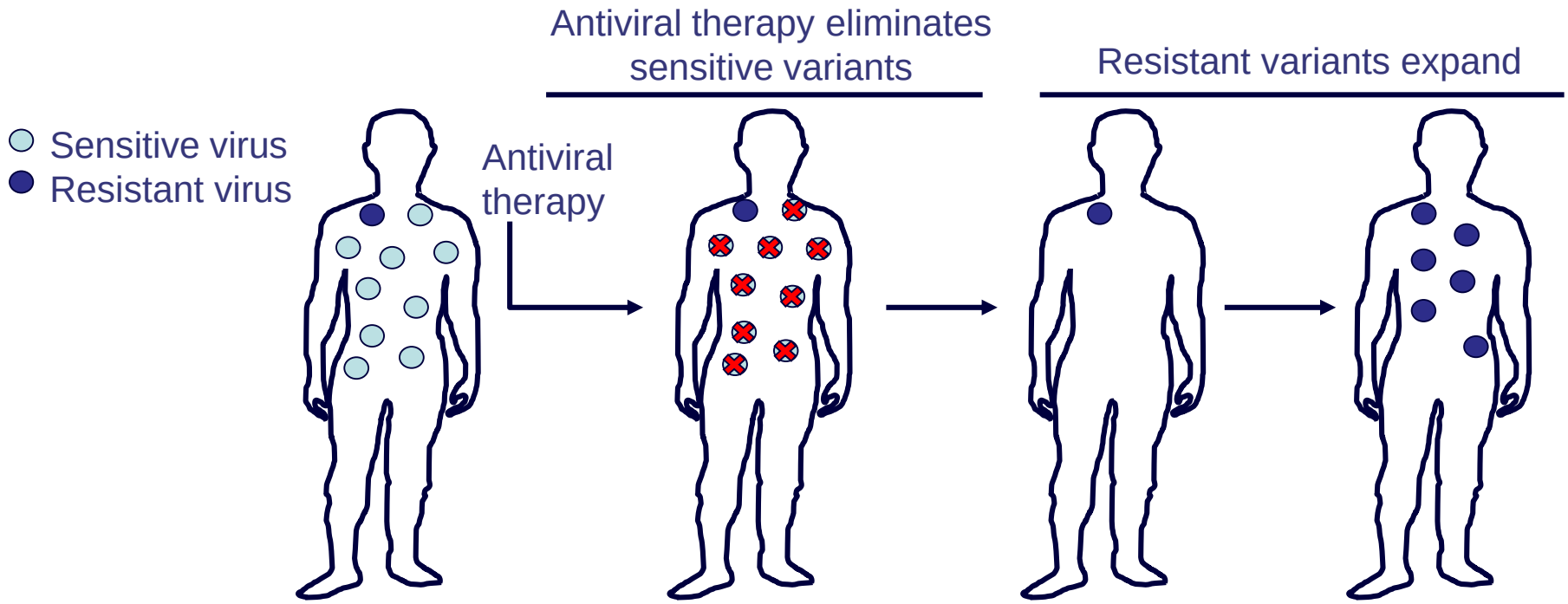
HCV RNA replicates at ~10^{12} virions/day

By chance, replication errors produce baseline RASs

RASs may also be selected for with treatment failure

Virological breakthrough (Rare)

Relapse (Most common cause of DAA failure)



RAS with Potential Clinical Significance

Wild-type Amino Acid (Sensitive)	Position	Variant Amino Acid
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	**93**	**C/H/N/S**

Example= Y93H = Y (Tyrosine) 93H (Histidine)

- NS5A RASs appear to have impact on treatment response with regimens that include an NS5A inhibitor; impact occurs primarily with GT1a and GT3
- New generation of DAAs less impacted by NS5A RASs but modification of treatment regimen is required in some circumstances

Zeuzam S, Pol S et al. J Hepatol 2018

Current management of hepatitis C

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Factors That Influence HCV Treatment Decisions

Category	Factors	
Viral	▪ HCV GT ▪ Viral load	
Treatment	▪ HCV treatment history – PegIFN + RBV – Protease inhibitor – Sofosbuvir, NS5A	▪ RBV eligibility ▪ Resistance
Fibrosis stage	▪ Cirrhosis? ✓ Liver biopsy (for mixed etiologies, invasive, sampling error) ✓ Fibroscan > 12.5 , NPV >90%, to r/o cirrhosis ✓ Plt count, APRI (AST, Plt) <1, Fib-4 (+ age) <1.9, high NPV ▪ If cirrhotic, any history of decompensation? ▪ Transplant evaluation if necessary	
Co-infection/ comorbidities	▪ HIV confection ▪ Cardiovascular, renal, metabolic, etc, concerns ▪ Drug–drug interactions	
Financial	▪ Cost issues, insurance	

AASLD/IDSA. HCV Guidelines. April 2017. EASL, et al. J Hepatol. 2015;63:237-264.

Recommendations for First-time HCV Treatment

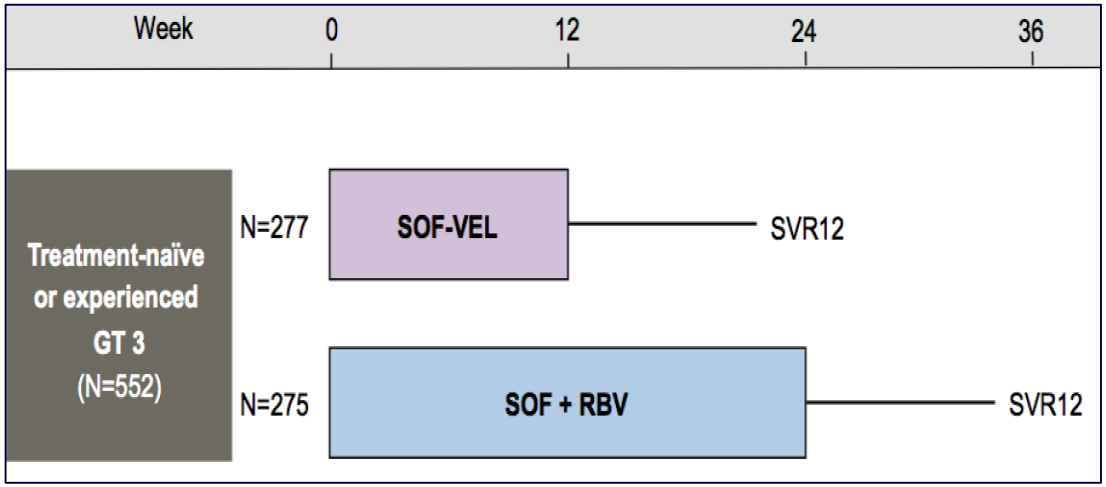
GT	Regimen	Duration, Wks: No Cirrhosis	Duration, Wks: Compensated Cirrhosis	SVR >95% Clinical Trial
1	Glecaprevir / Pibrentasvir	8	12	ENDURANCE 1, EXP 1
	Elbasvir / Paritaprevir	12 (G1b)	12 (G1b)	C-EDGE (TN)
	Sofosbuvir / Ledipasvir	8 or 12†	12	ION 1, 3
	Sofosbuvir / Velpatasvir	12	12	ASTRAL 1
3	Glecaprevir / Pibrentasvir	8	12	SURVEYOR 1;2
	Sofosbuvir / Velpatasvir	12	12 (No BL RAS)	ASTRAL 3
4	Glecaprevir / Pibrentasvir	8	12	ENDURANCE 4, EXP 1
	Elbasvir / Paritaprevir	12	12	ASTRAL 1
	Sofosbuvir / Ledipasvir	12	12	C-EDGE (TN)
	Sofosbuvir / Velpatasvir	12	12	ION 4

†If nonblack, no HIV, and HCV RNA < 6 million IU/mL, 8-wk duration recommended.

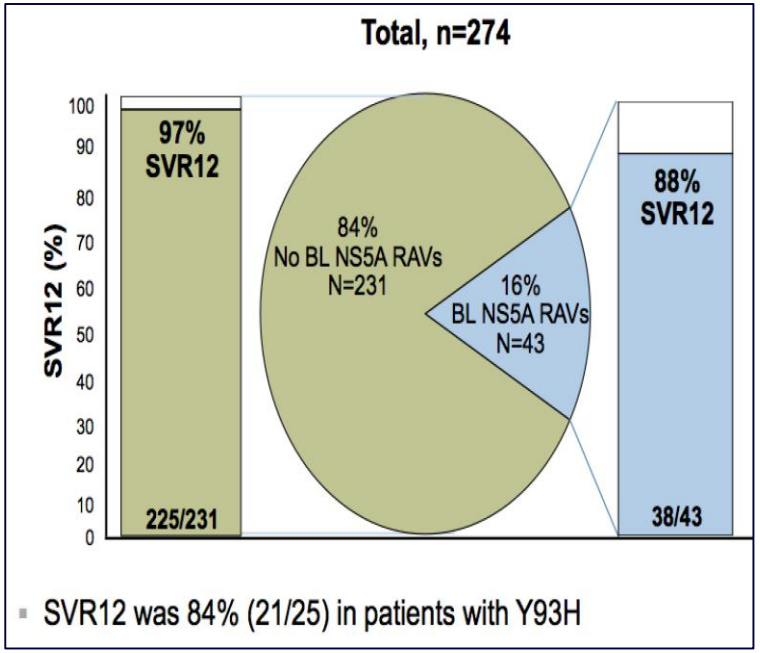
High Efficacy, No need for Genotype testing in Treatment naïve non-cirrhotics

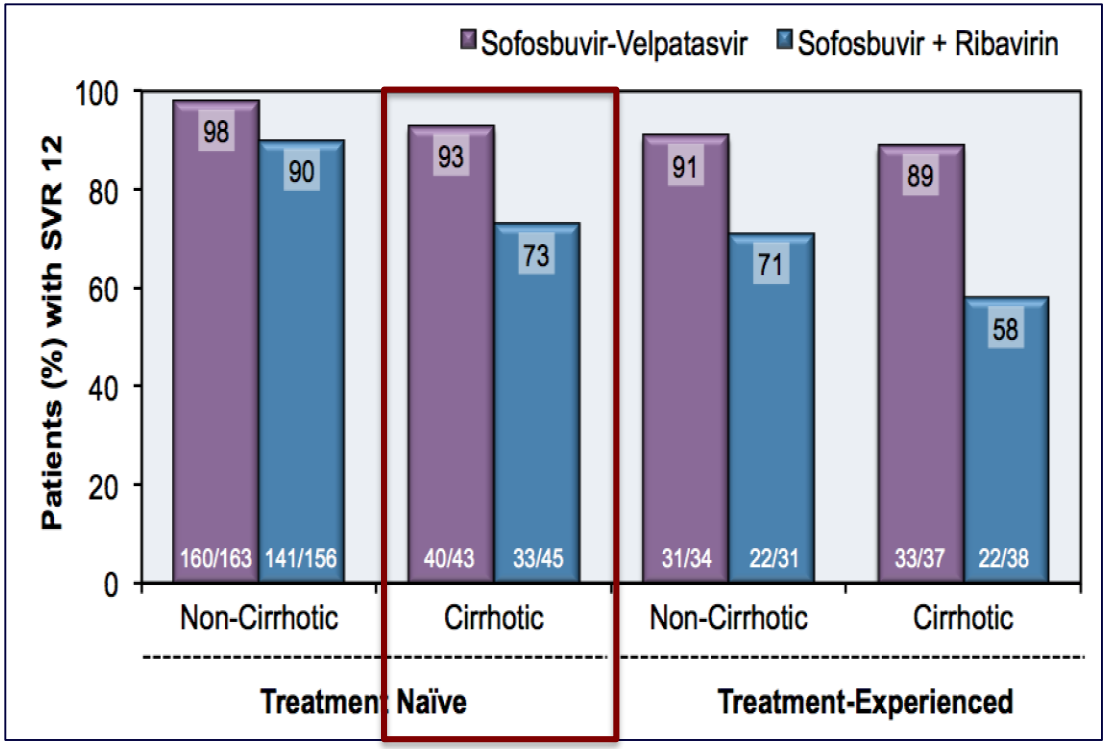
Modified from AASLD/IDSA. HCV guidelines 2018 (updated), EASL HCV guidelines 2018

ASTRAL 3 Study



Baseline NS5A RAS ~ 15%



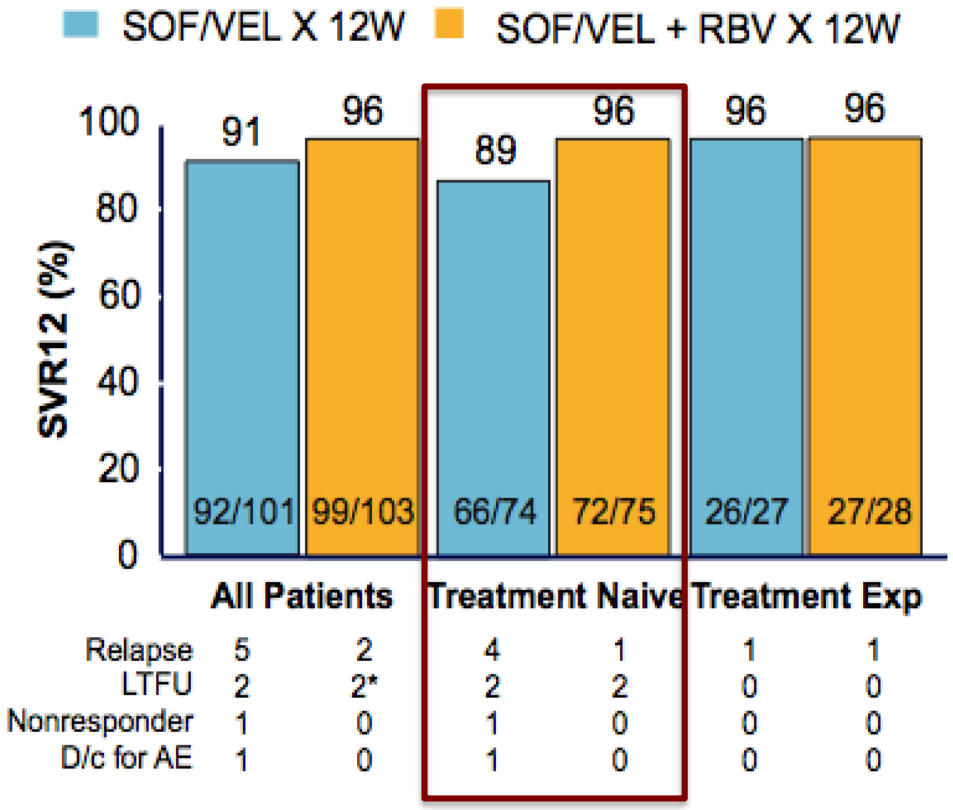


Baseline resistance variants (Y93H) hampering SVR in Treatment naïve G3 Compensated Cirrhosis

Foster GR, et al. NEJM 2015

No need for Baseline RAS testing, add RBV

Sofosbuvir/Velpatasvir +/- RBV for GT3 HCV with Cirrhosis



Patients with GT3 HCV infection and compensated cirrhosis*, prior SOF

RAS Analysis, n/N (%)	SOF/VEL	SOF/VEL + RBV
Detection of BL RAS		
▪ No	79/98 (81)	79/101 (78)
▪ Yes	19/98 (19)	22/101 (22)
SVR12		
▪ No BL RAS	76/79 (96)	78/79 (99)
▪ BL RAS	16/19 (84)	21/22 (96)
▪ BL Y93H	2/4 (50)	8/9 (89)

Adding Ribavirin to SOF/VEL in treatment naïve GT3 compensated cirrhosis improve SVR and compensates for testing baseline RAS

Buti M et al. EASL 2018

Regimens for Treatment Experienced Patients (Regimens with SVR >90%)

GT	Prior PegIFN/r or SOF/r or PegIFN/SOF/r based regimens
1a	**Sofosbuvir/Velpatasvir (SOF/VEL) x 12 w** Glecaprevir/Pibrentasvir x 8 w (No cirrhosis) Glecaprevir/Pibrentasvir x 12 w (cirrhosis) Elbasvir/Grazoprevir x 12 w (HCV RNA < 8L)
1b	**Sofosbuvir/Velpatasvir (SOF/VEL) x 12 w** Glecaprevir/Pibrentasvir x 8 w (No cirrhosis) Glecaprevir/Pibrentasvir x 12 w (cirrhosis) Sofosbuvir/Ledipasvir x 12 w Elbasvir/Grazoprevir x 12 w (HCV RNA < 8L)
3	**Sofosbuvir/Velpatasvir x 12 w (No cirrhosis)** Glecaprevir/Pibrentasvir x 12 w (No cirrhosis) Glecaprevir/Pibrentasvir x 16 w (cirrhosis) Sofosbuvir/Velpatasvir /Voxilaprevir x 12 w (only cirrhosis)

All G1 TE on NS5a (LDV/DCV) have suboptimal outcomes
All Genotype 3 treatment experienced cirrhotics patients have suboptimal response

Modified from AASLD/IDSA. HCV guidance 2018 (updated) EASL HCV guidelines 2018

Regimens for Treatment Experienced Patients (Regimens with SVR >90%)

GT	Prior PegIFN/r or SOF/r or PegIFN/SOF/r based regimens	Prior NS5a (DCV/LDV/VEL relapse) regimens
1a	**Sofosbuvir/Velpatasvir (SOF/VEL) x 12 w** Glecaprevir/Pibrentasvir x 8 w (No cirrhosis) Glecaprevir/Pibrentasvir x 12 w (cirrhosis) Elbasvir/Grazoprevir x 12 w (HCV RNA < 8L)	Sofosbuvir/Vel /Voxilaprevir (SOF/VEL/VOX) x 12 w ?? SOF/VEL/R X 24 W SOF/GLE/PIB x 12 w
1b	**Sofosbuvir/Velpatasvir (SOF/VEL) x 12 w** Glecaprevir/Pibrentasvir x 8 w (No cirrhosis) Glecaprevir/Pibrentasvir x 12 w (cirrhosis) Sofosbuvir/Ledipasvir x 12 w Elbasvir/Grazoprevir x 12 w (HCV RNA < 8L)	Sofosbuvir/Velpatasvir /Voxilaprevir (SOF/VEL/VOX) x 12 w SOF/GLE/PIB x 12 w
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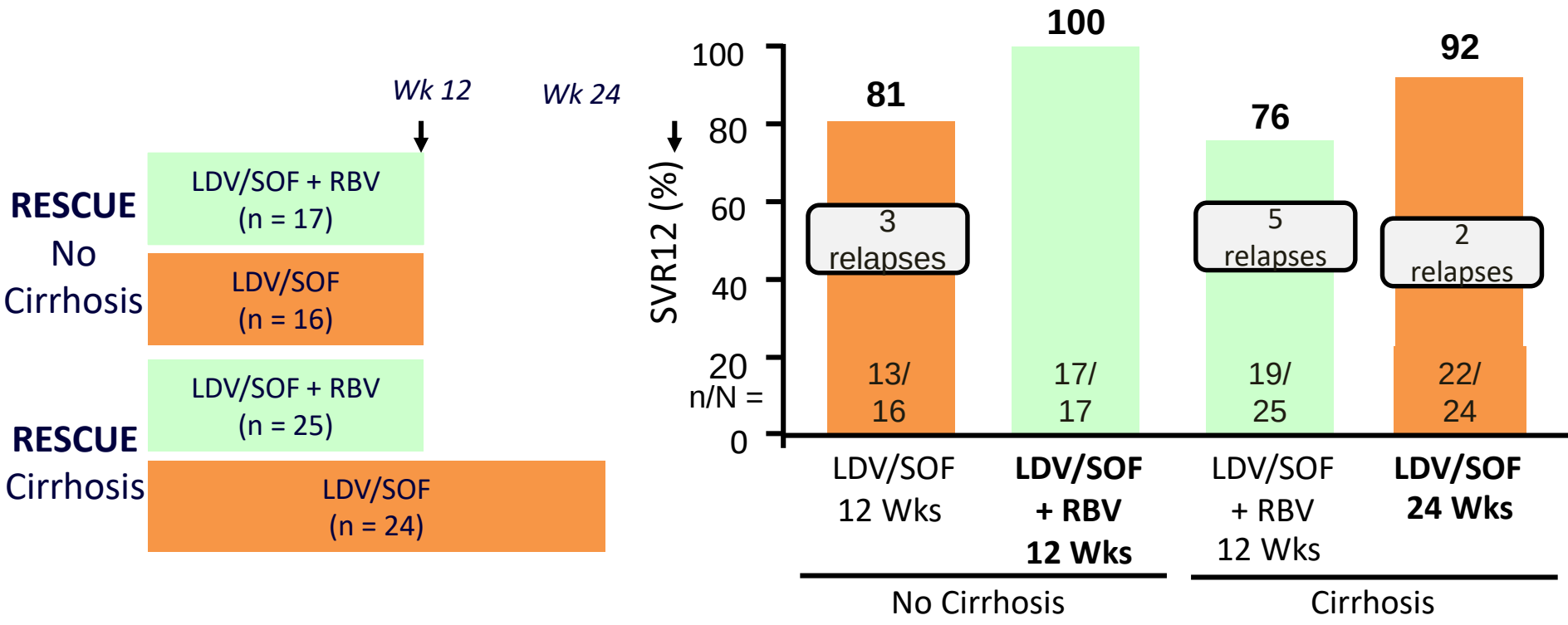
All Genotype 3 treatment experienced cirrhotics patients have suboptimal response

Modified from AASLD/IDSA. HCV guidance 2018 (updated) EASL HCV guidelines 2018

G1 Treatment experienced cirrhotic

No option for VEL → Add RBV or 24 w SOF + LDV

Previous SOF Failure Without NS5A (LDV/VEL) Exposure



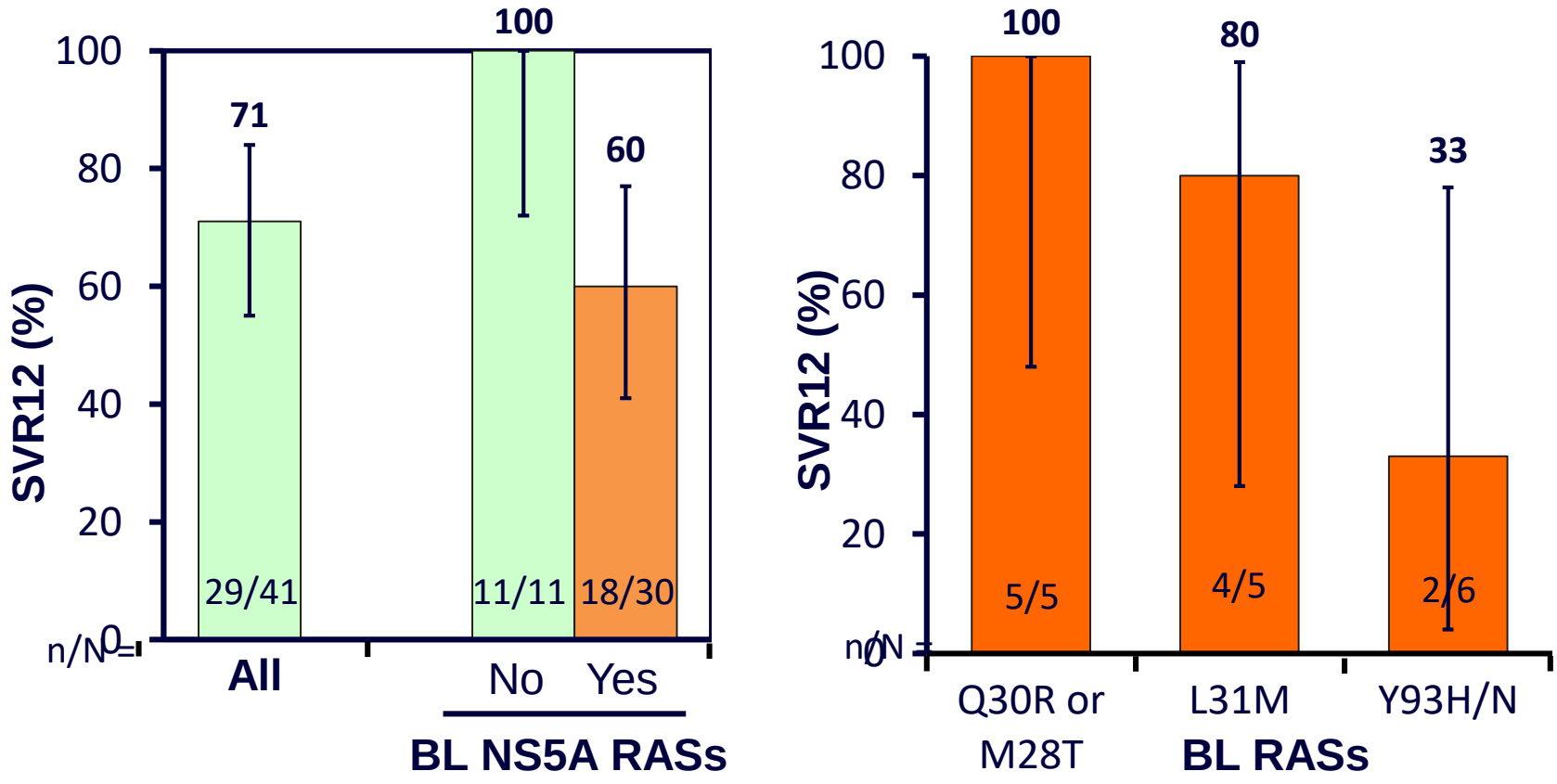
37% (30/82) with previous SMV + SOF failure

Adding ribavirin or increasing treatment duration to SOF + LDV improve SVR in TE (prior SOF/r or P/R) G1 patients

Tam E, et al. EASL 2017

Failure of SOF + LDV in GT1
Never reuse failed regimen

- 8-wk or 12-wk LDV/SOF-based treatment failures retreated with LDV/SOF for 24 wks (N = 41)



Repeating same failed regimen with extended duration does not improve SVR

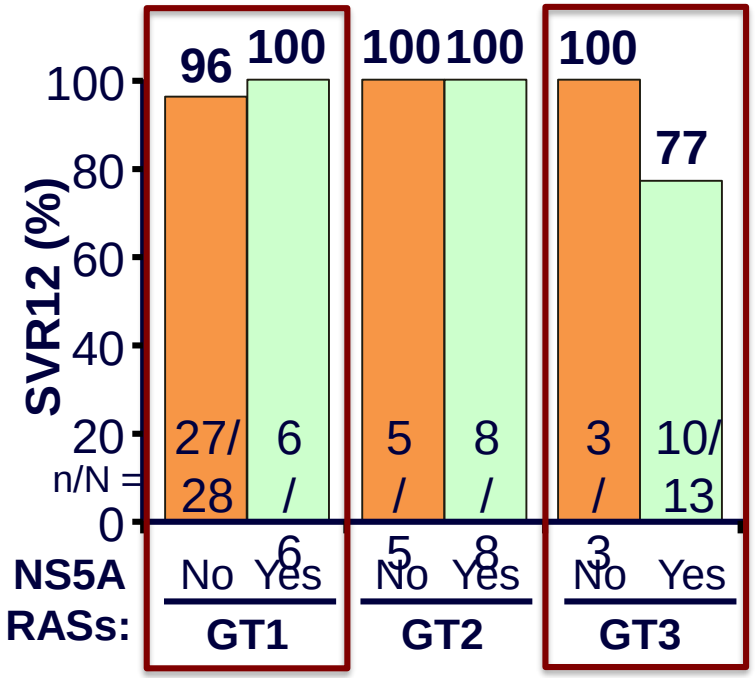
Lawitz E, et al. EASL 2015, Hepatology 2016.

Failure of SOF + LDV in GT1
May treat with SOF + VEL + R x 24 weeks

- Single-arm trial

HCV-infected pts without SVR in previous phase II trials of SOF/VEL (n = 41) or SOF/VEL + VOX (n = 28) → SOF/VEL 400/100 mg + RBV (N = 69)

Wk 24



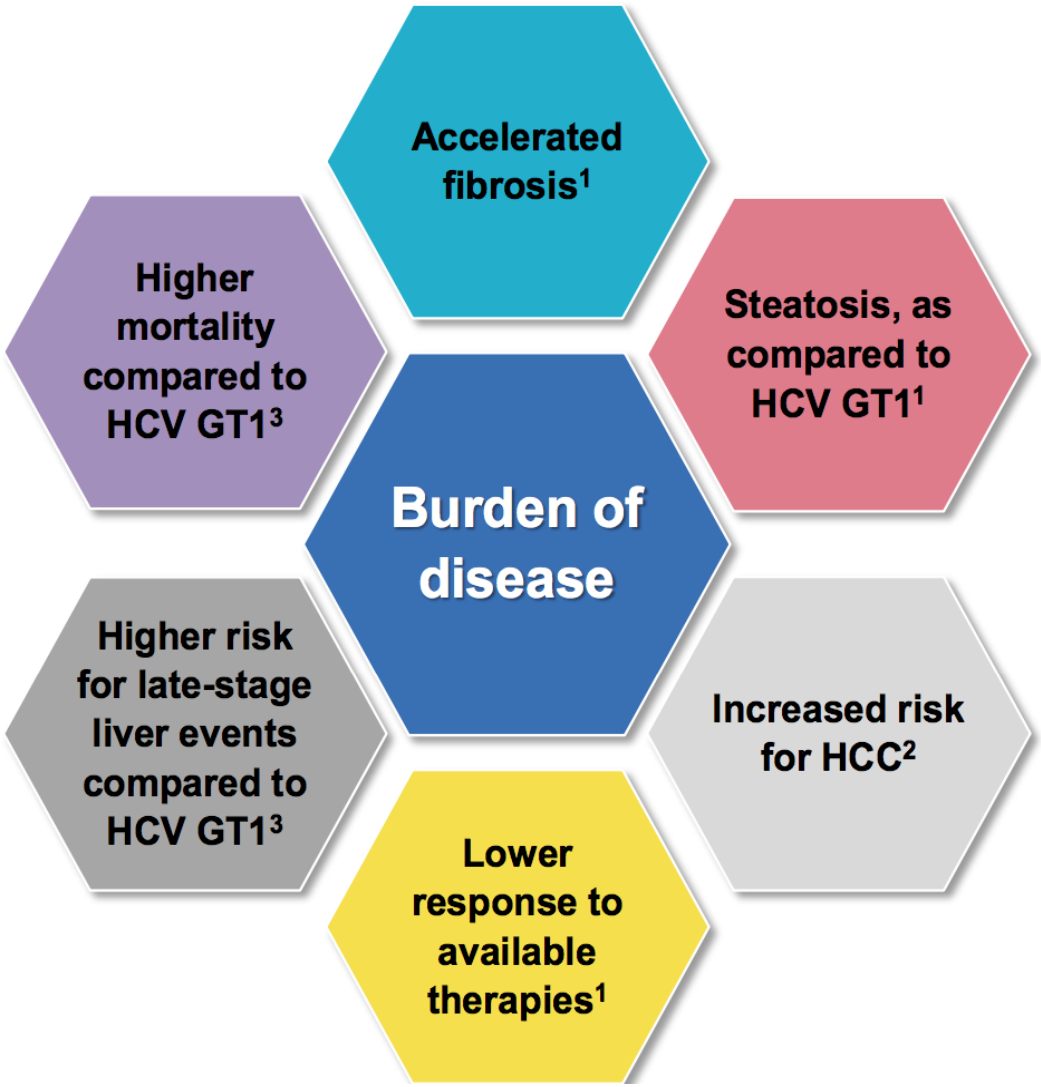
- Cirrhosis: 26%; previous relapse: 99%
- 20% GT2
- Only 18% of GT1 with NS5A RASs
- Overall SVR12: GT1 : 97%; GT2: 91%; GT3 : 76%

- 9/11 (82%) pts with GT3 HCV and Y93H achieved SVR12

Adding RBV to 24 w of SOF + VEL improves SVR in GT1 but remain suboptimal In GT3

Gane EJ, et al. EASL 2016.

HCV GT3 has a Unique Pathophysiology Compared to Other Genotypes



Difficult to treat HCV GT3

Treatment experienced and cirrhosis

DAA Regimen	Clinical Trial	Prior Treatment	All cirrhosis	Treatment experienced	Treatment experienced cirrhosis
SOF + R					
SOF + R X 12 W	FUSION	Peg-IFN/r	31		19
SOF + R X 16 W	FUSION	Peg-IFN/r	66		61
SOF + R X 24 W	VALENCE	Peg-IFN/r		79	62
SOF + DCV					
SOF + DCV X 12 W	ALLY 3 UK-EAP French cohort	Peg-IFN/r, SOF	63	86	58
SOF + DCV + R X 12 W	ALLY 3+	Peg-IFN/r, SOF	83		88
SOF + DCV + R X 16 W	ALLY 3+	Peg-IFN/r, SOF	89		86
Any SOF/DCV + NS5A RAV	Nelson et al. Hepatology 2016	Peg-IFN/r, SOF	67		25
SOF + VEL					
SOF + VEL X 12 W	ASTRAL-3	Peg-IFN/r, SOF	91	90	89

No study of SOF + VEL +/- R X 12-24 Week in TE (P/R or SOF/r) compensated cirrhotic

SOF + VEL failure in G3 cirrhotic (CTP A)

Test for NS5A RAS, if + → wait for new regimen
If - → SOF + VEL + R X 24 weeks

- Single-arm trial

HCV-infected pts without SVR in previous phase II trials of SOF/VEL (n = 41) or SOF/VEL + VOX (n = 28) → **SOF/VEL 400/100 mg + RBV** (N = 69)

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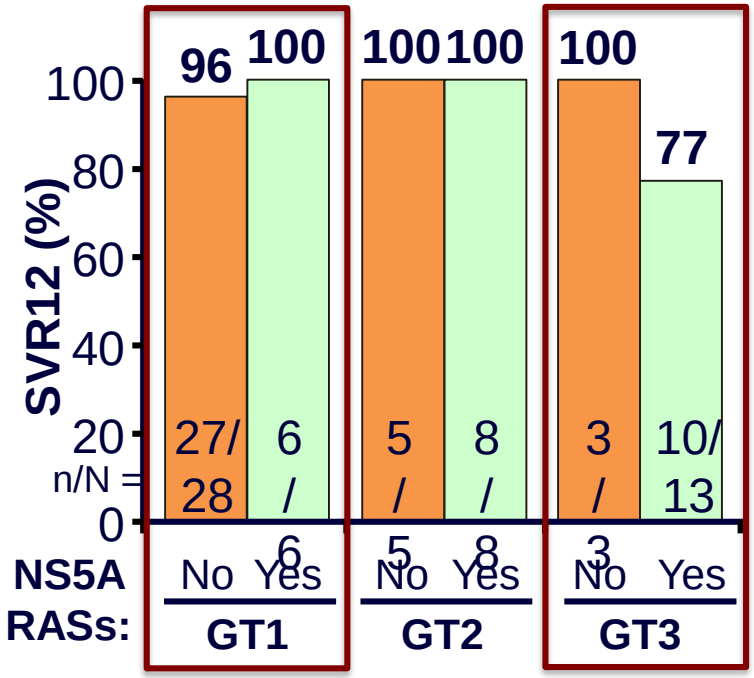

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Gane EJ, et al. EASL 2016.

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Decompensated HCV cirrhosis
To Treat or Not to Treat

Potential benefits with SVR

- Improved clinical outcomes (decompensation, HCC), QOL
- Delisting, better wait list survival, no re-infection of graft

Cons

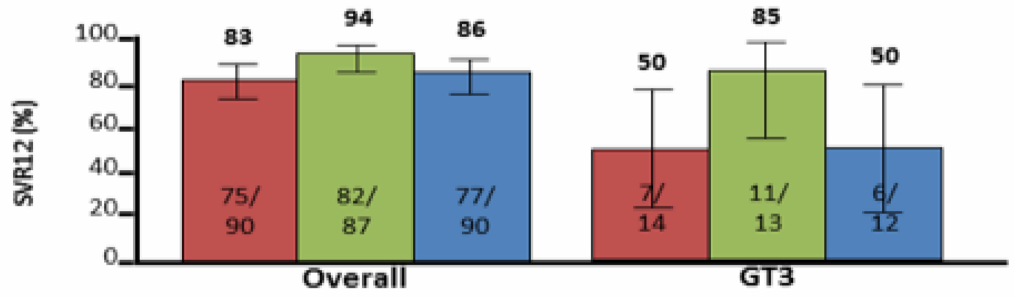
- DAA toxicity (NS3 PI contraindicated) or further decompensation
- If treatment fails; selection of resistance may impair future therapy
- MELD purgatory
- Lose access to HCV+ livers

Decompensated HCV cirrhosis
Pre-LT treatment : Questions ?

- Regimens ?? Role of RBV
- Futility vs benefit ?
- Delisting ? How long?
- Obstacles ? HCC, HBV Reactivation

Treatment Regimens in HCV decompensated cirrhosis

Trial	GT	MELD	DAA	Duration	SVR	SAE
CP-B cirrhosis treated with SOF/VEL x 12w +/- RBV or 24w					CTP B:94%	Overall 17%
						CTP C: 56%
					CTP B:87%	CTP B: 10%
					CTP C:86%	CTP C: 26%
					CTP B:89%	CTP B: 34%
					CTP C:87%	CTP C: 42%
					CTP B:87%	Overall 22%
						CTP C: 4%
					CTP B:96%	
					CTP C:78%	
ASTRAL-4	Any	Overall median 10	SOF/VEL	12 weeks	83%	19%
				24 weeks	86%	18%
			SOF/VEL+RBV	12 weeks	94%	16%



Lower SVR due to treatment discontinuations + true relapse CTP B > C

SAE – Bradyarrythmias, Worsened Renal functions, HBV reactivation, SOF related hepatotoxicity

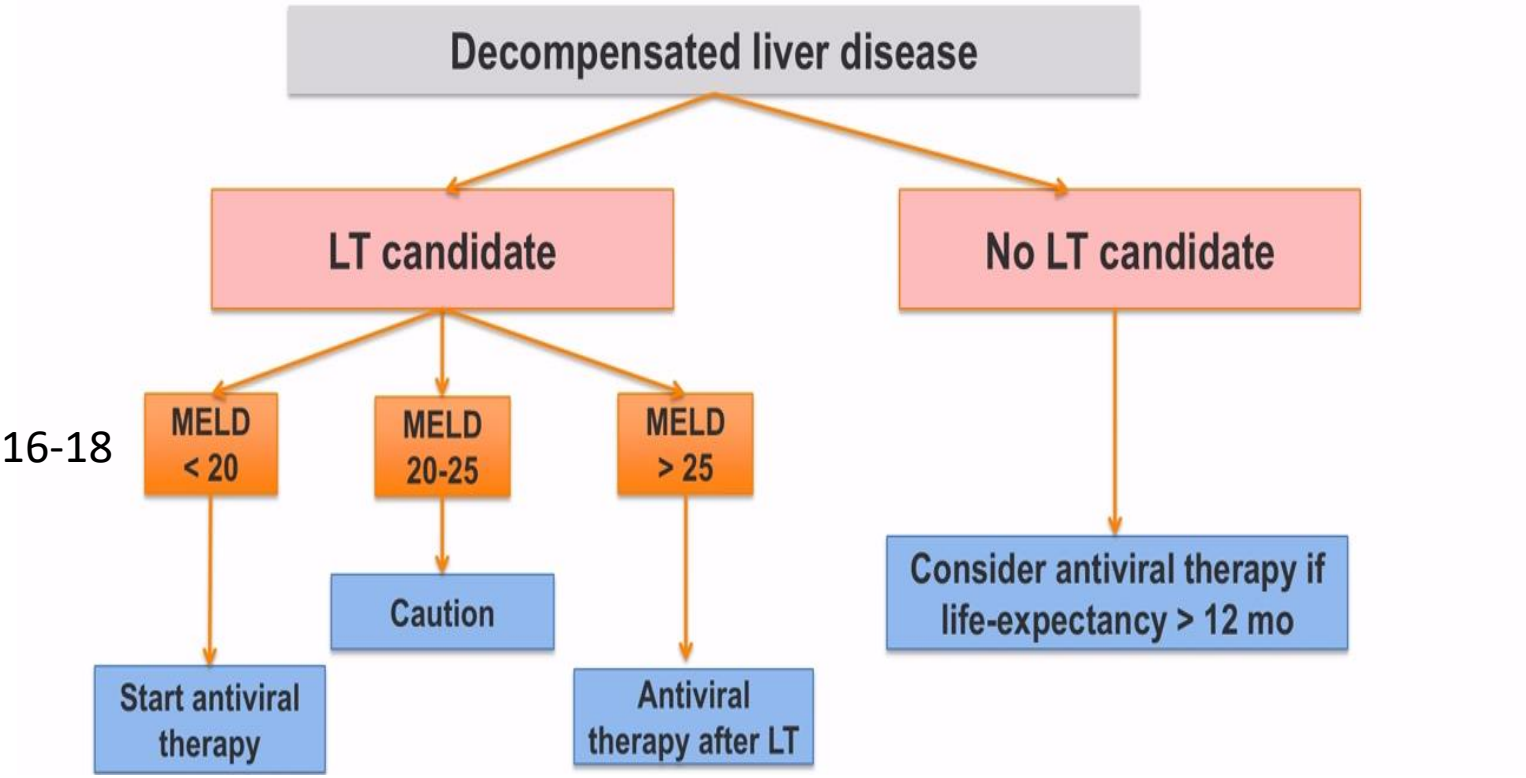
Liver disease severity post DAA in Decompensated Patients

	N	Overall SVR	Improved	Unchanged	Worsened
SOF + LDV + RBV (SOLAR-1)	94	87%	67%	16%	17%
SOF + LDV + RBV (SOLAR-2)	136	83%	71%	13%	16%
SOF + DCV + RBV (ALLY-1)	56	83%	45%	21%	34%
SOF + NS5A + RBV (UK EAP)	220	75%	61%	15%	24%
SOF + VEL +/- RBV (ASTRAL-4)	250	88%	54%	21%	25%
Total	**801**	**83.5%**	**480 (60%)**	**140 (17%)**	**181 (23%)**

~ 24% delisted (CTP B/C → CTP A, MELD < 15)
Predictors of delisting – Baseline MELD (<16), delta MELD and delta albumin
Time to delisting = minimum of 24 w after treatment start
MELD >20, Unlikely to delist → Focus on LT

Belli et al. J Hepatol 2016
Sharif El et al. Gastroenterology 2018

Suggested approach and treatment regimen in Decompensated cirrhosis



? < 16-18

	SOF + LDV	SOF + DCV	SOF + VEL
RBV eligible	12 weeks + low-dose RBV	12 weeks + low-dose RBV	12 Week + RBV (Weight based for CTP-B; Low dose CTP-C), ? 24w
RBV ineligible	24 Weeks	24 Weeks	24 Weeks

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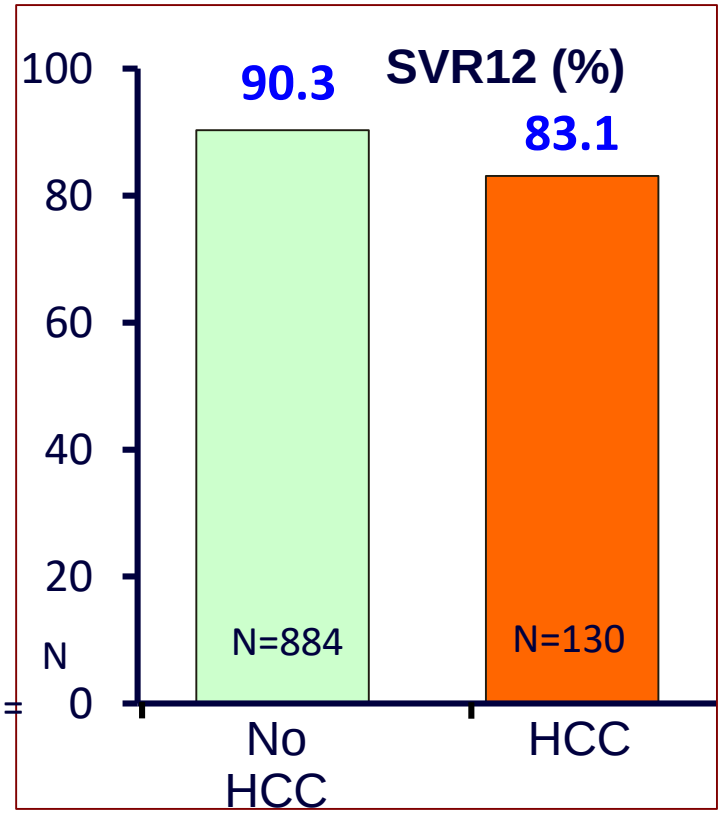
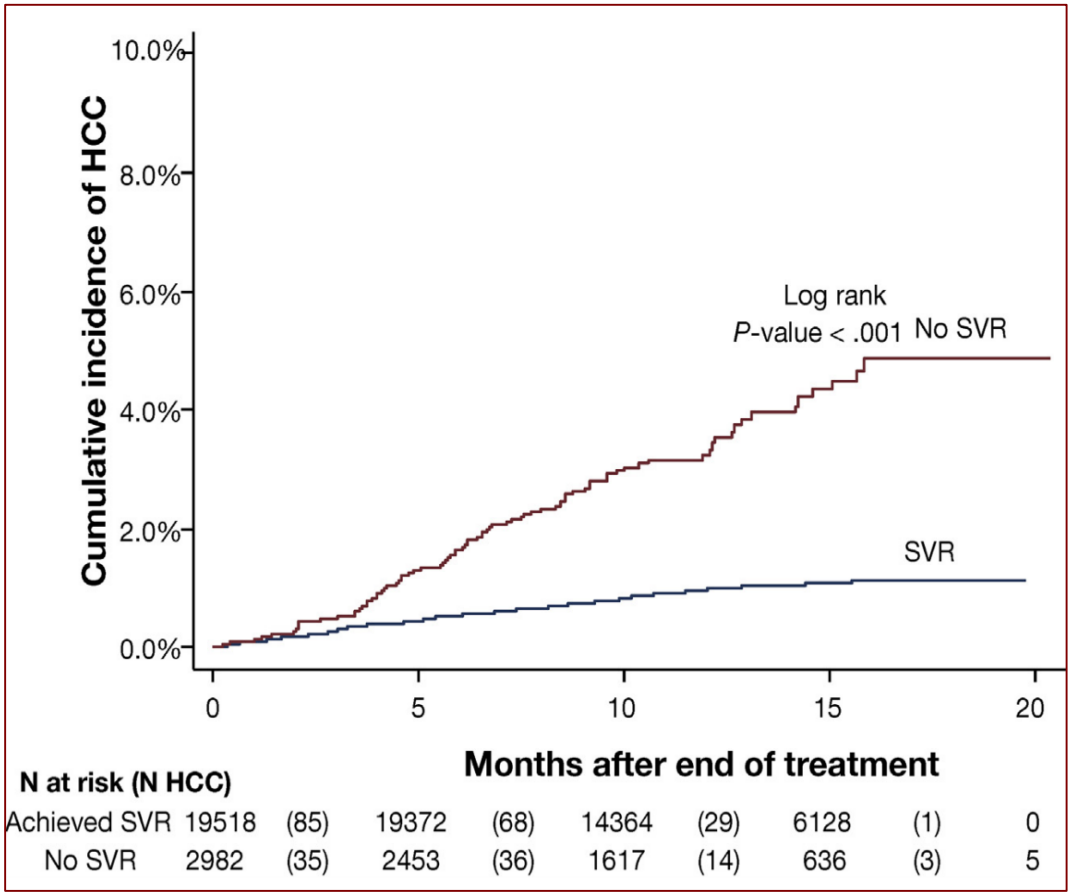
DAA antiviral therapy and HCC





SVR lower in HCC cirrhotic patients treated with DAA

Radhakrishnan K et al. AASLD 2017

DAA therapy and de-novo HCC

Kanwall et al. Gastroenterology 2017

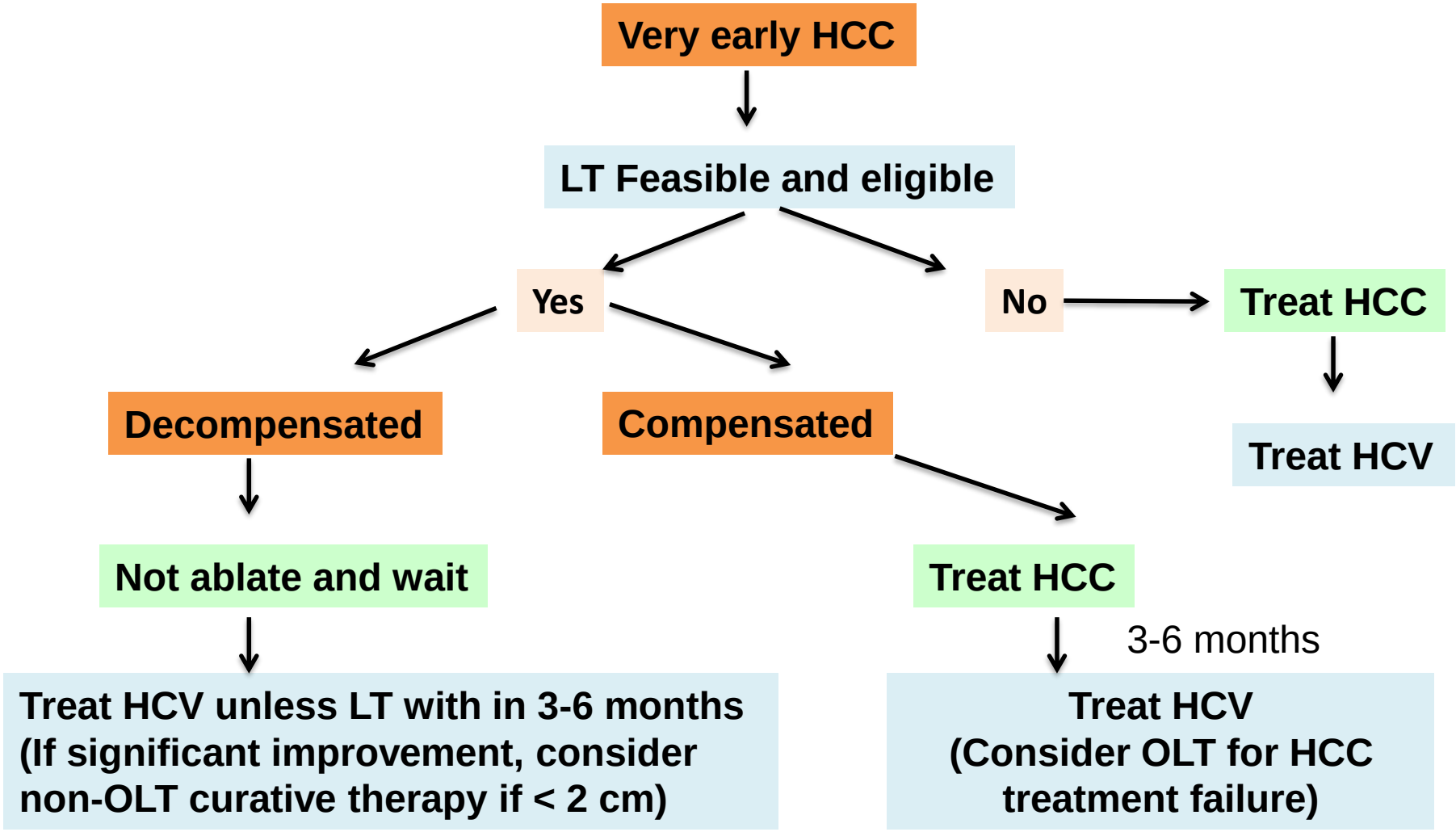
WILEY AP&T Alimentary Pharmacology & Therapeutics

Systematic review with meta-analysis: recurrence of hepatocellular carcinoma following direct-acting antiviral therapy

- 24 studies (n = 1820 patients)
- Proportion of patients with pooled HCC recurrence following DAA therapy was 21.9%
- Factors associated with recurrence
  - History of prior HCC recurrence
  - Shorter interval between HCC complete response and DAA initiation
- DAA-treated and interferon-treated or untreated patients - similar recurrence
- Limitations- heterogeneous cohorts, ascertainment bias for recurrence, and short durations of follow-up.
- **Acceptable HCC recurrence rates after DAA therapy, particularly if DAA therapy is delayed at least 6 months after HCC complete response.**

Saraiya N et al. Aliment Pharmacol Ther. 2018; 48:127–137.

Timing of HCV therapy in very early HCC



Safety and Efficacy of Current Direct-Acting Antiviral Regimens in Kidney and Liver Transplant Recipients With Hepatitis C: Results From the HCV-TARGET Study

Varun Saxena,[1*] Vandana Khungar,[2*] Elizabeth C. Verna,[3] Josh Levitsky,[4] Robert S. Brown Jr,[5] Mohamed A. Hassan,[6] Mark S. Sulkowski,[7] Jacqueline G. O'Leary,[8] Farrukh Koraishy,[9] Joseph S. Galati,[10] Alexander A. Kuo,[11] Monika Vainorius,[12] Lucy Akushevich,[12] David R. Nelson,[13] Michael W. Fried,[12] Norah Terrault,[1**] and K. Rajender Reddy, MD[2**]

HCV treatment post Transplant

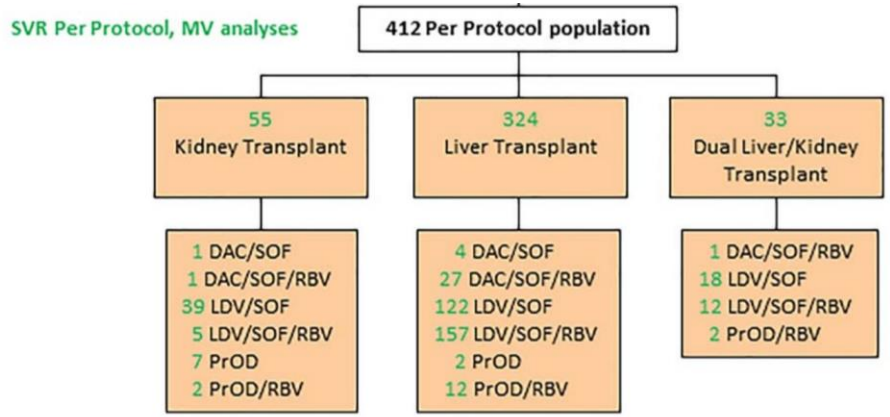
No major challenges with current DAA

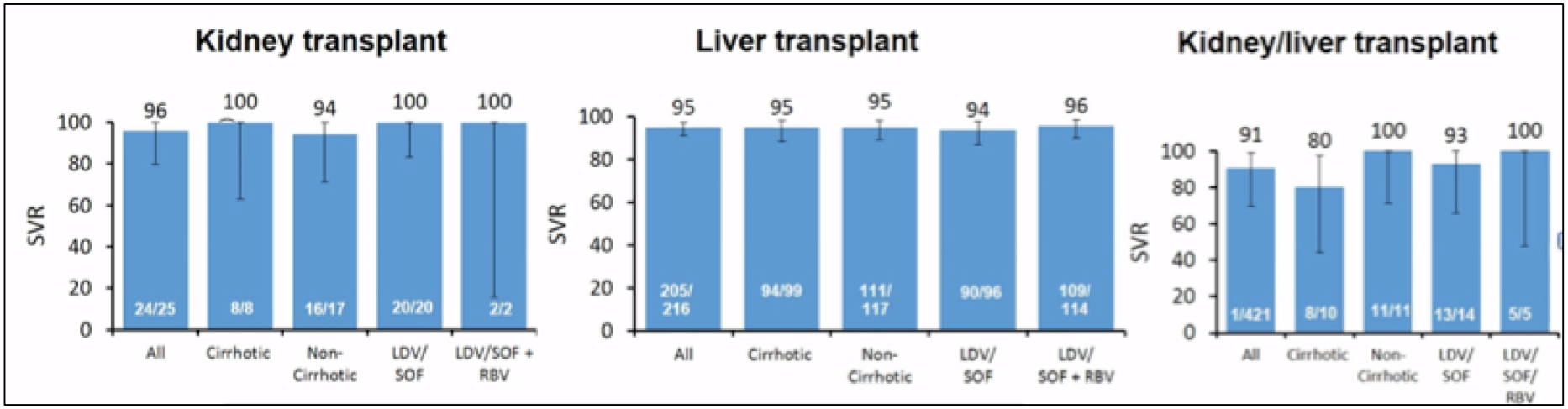
Velpatasvir efficacy and safety not studied in LT recipients

Renal insufficiency may restrict use of sofosbuvir

Ribavirin use may be restricted due to anemia

HCV+ Donor- Mixed GT, RAS





Saxena V et al. Hepatology 2017

HCV and Renal disease
Phenotypes and treatment approach

Type	Line of therapy
CKD Stage 4,5 +/- hemodialysis	SOF free DAA AASLD/IDSA recommendations ▪ **GT1-6: GLE/PIB** • No cirrhosis: 8 wks • Compensated cirrhosis: 12 wks ▪ **GT1 or GT4: EBR/GZR 12 wks**
Post Renal transplant	SOF + NS5A X 12 W ; SVR >95%
Cirrhosis with renal failure (HRS, AKI, ACLF)	Albumin, vasopressors, LT → DAA On stabilization
Post LT with CNI toxicity	Alternate Ix, reduce dose
Mixed essential cryoglobulinemia	DAA + Plasmapheresis / Immunosuppression (Rituximab)

HCV treatment in CKD
Indian studies – SOF + NS5a

- 65 CKD Stage 4/5
- 32% Cirrhosis
- Sofosbuvir [200 mg (half tablet of 400 mg)] plus full-dose Daclatasvir (60 mg) given daily for either 12 or 24 weeks given in patients with genotype 3 cirrhosis.

RESULTS:

- ETR- 98.5%
- SVR 12-100%
- No serious adverse events.

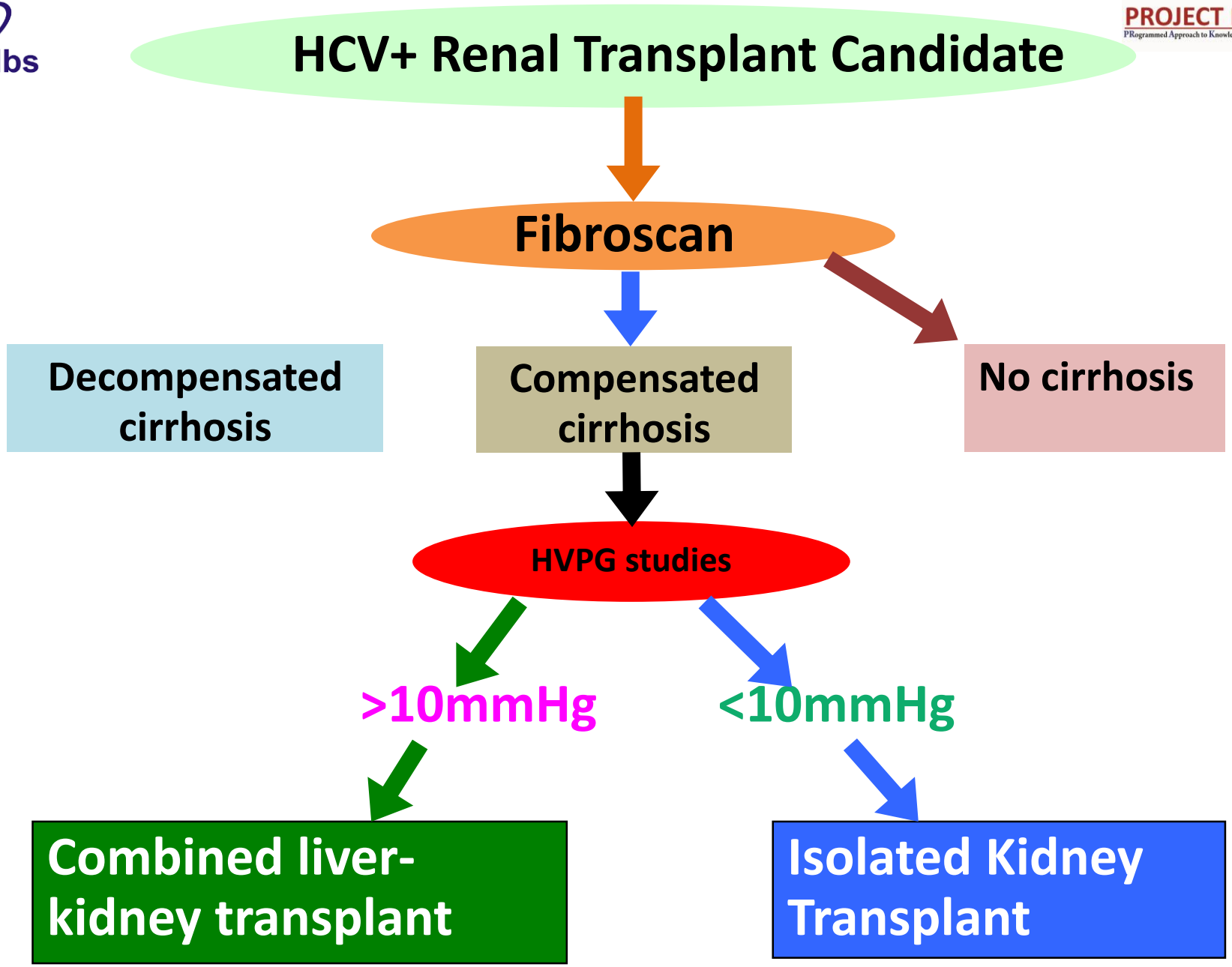
Taneja S et.al. Dig Dis May 2018

- 71 CKD (84.5% on MHD)
- 23.9% Cirrhosis
- Full-dose sofosbuvir was used in combination with
  - Ribavirin (n = 26, for 24 weeks, 69.2% genotype 1, 30.8% genotype 3),
  - Ledipasvir (n = 26, for 12 weeks, geno- 1)
  - Daclatasvir (n = 19, for 12 weeks, geno- 3).

RESULTS

- SVR 12 in 100%
- Relapse
  - 1- S+L, at 24 weeks
  - 1-S+R at 48 week

Sharma M et.al Liv Int April 2018

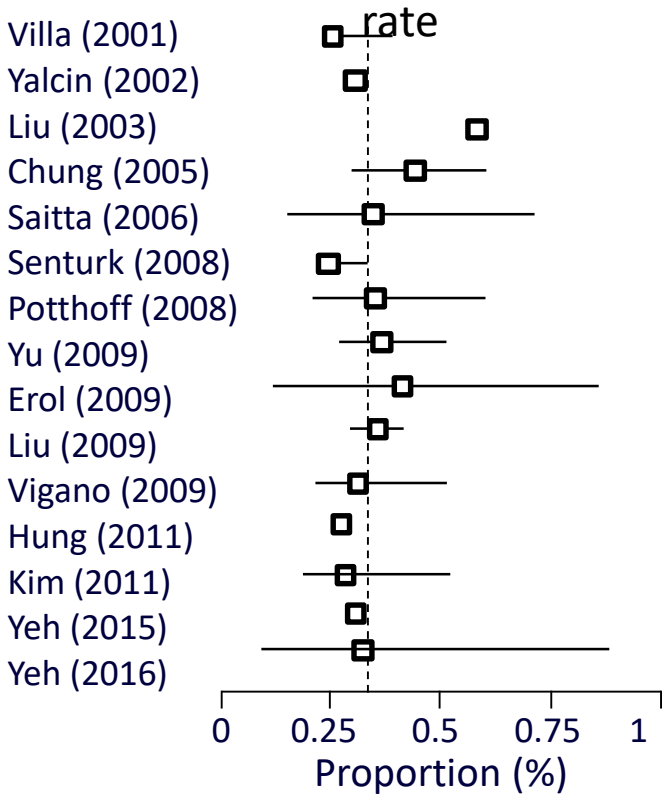


UNOS, ASN, ASTS, AST

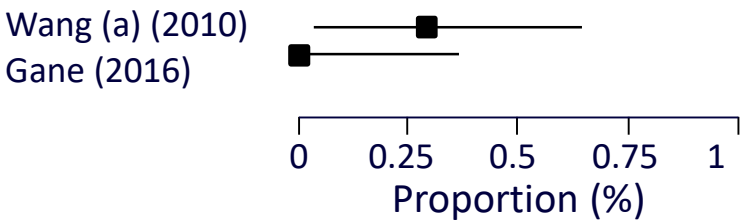
Hepatitis B reactivation in hepatitis B and C co-infected patients treated with antiviral agents: A systematic review and meta-analysis.

IFN-based regimens (n=1,037) vs. DAAs (n=148)

Reactivation rate: IFN-based regimens



Reactivation rate: DAAs



HBVr occurred earlier in DAA (4-12 weeks) versus IFN (at end of therapy or later)

- HBVr did not affect HCV SVR
- HBV DNA not associated with higher HBVr

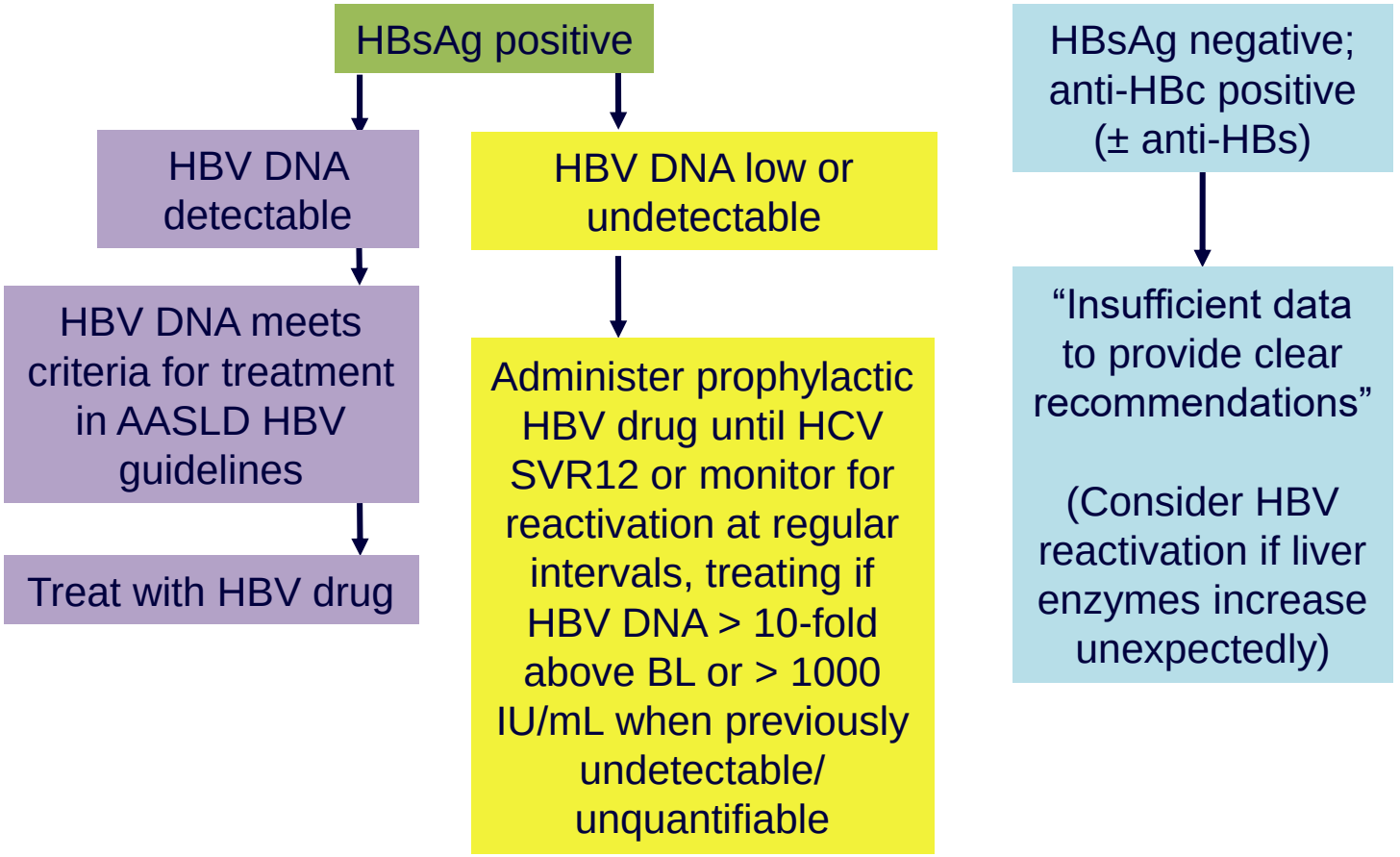
pooled incidence rate of HBV reactivation was significantly higher for DAAs (12.2%) vs. IFN

Chen G et al. Hepatology 2017

HBV Testing/Monitoring During HCV DAA Therapy

Risk of HBV reactivation

- Test all pts. initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



HCV treatment in Children and adolescence

- Mother to Child transmission- Uncommon, except HCV-HIV co-infection
- Maternal HCV therapy – IFN C/I, DAA not approved, small study from Kashmir
- Test anti HCV at 18 m, HCV RNA earlier if apprehensive
- IFN safe beyond 2-3 years , SVR suboptimal and require RBV (unsafe esp. in Thallesemics)
- Defer, Current trials on SOF + LDV, SOF + RBV at 12-17 years age
- Wait for ongoing trials of DAA use at Age 3-12 years

Outline

- Natural course of HCV infection and Diagnosis
- HCV life cycle, Antiviral drugs and targets
- First line treatment
- Retreatment in DAA failures, drug resistance
- Special scenarios
  - Decompensated cirrhosis
  - HCV + Liver cancer
  - HCV + HBV
  - Acute hepatitis C
  - Pregnancy, children and adolescence
- **Post treatment follow up**

Post SVR follow up

Risk of late relapse very low, *but* can happen

HCV RNA

N = 3004
SVR12

→ n = 2992
SVR24

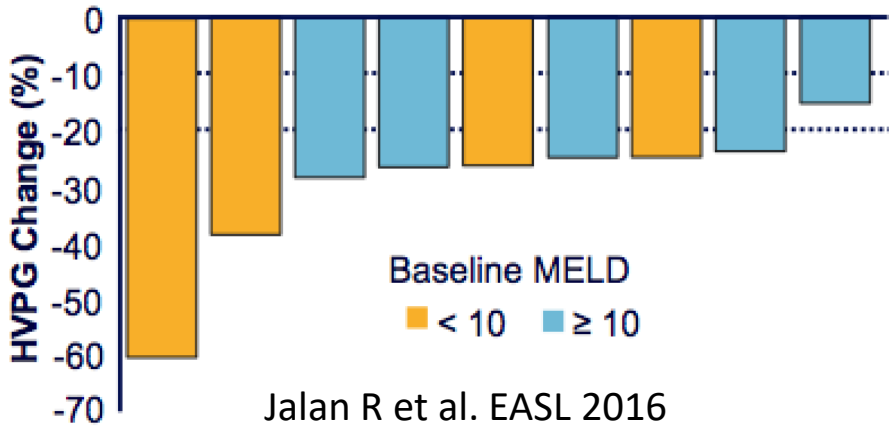
→ n = 12 (< 1%)
No SVR24

Phylogenetic analyses →

- 5/12 with late relapse
- 7/12 reinfected

HVPG

HVPG Reduction in Pts With Baseline HVPG ≥ 12 mm Hg Who Achieved SVR12 and Completed 48-Wk Follow-up (n = 9*)



Jalan R et al. EASL 2016

Fibroscan

33 pts with HCV and biopsy-proven cirrhosis who achieved SVR after IFN based therapy

FibroScan and biopsy ~ 60 mos post SVR

Biopsy

20 pts regressed (≤ F3)

13 pts had persistent cirrhosis (F4)

FibroScan

19 (95%) pts regressed (TE < 12 kPa)

5 (38%) pts regressed (TE < 12 kPa)

Conclusion

- DAA for HCV infection – a major breakthrough
- Stage of liver disease more important than SVR
- No Peg-IFN, LDV or DCV
- Use SOF + VEL = Easy to treat pts. 12 w
- Difficult patients –

  Optimize response – Add RBV, Extended treatment

  NS5A failure – Individualize, Wait for new DAA vs retreatment

  Decompensated cirrhosis – SOF + VEL + R X 12/24 wks

  Transplant candidates (LDLT) – Treat post transplant

  Monitor- HBV reactivation, de-novo HCC, recurrence

Thank you!