DAA FAILURES

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DISCLOSURES

Speaker Bureaus:

Gilead (former)

Intercept

Allergan

OBJECTIVES

As a result of this presentation, learners should be able to:

1. Identify barriers to DAA treatment response for patients diagnosed with HCV.
2. Determine best treatment plans for DAA nonresponders.
3. Improve ability to treat all patients diagnosed with HCV.
4. Improve patient outcomes by increasing treatment response rates for all patients who have been diagnosed with HCV.

TREATMENT PAST & PRESENT

Past	*Present*
• Interferon-based • Low efficacy against the most common HCV genotype (treatment often was not curative) • Patients often experienced significant side effects	• Direct-acting Antivirals (DAAs) • Curative (95%) for most patients and most genotypes • Provide improved patient quality of life: fewer side effects and shorter treatment duration (8-24 weeks)

Treatments are evolving with new medications, making it important to stay up-to-date with the latest guidelines

1. CDC. Hepatitis C FAQs for Health Professionals. http://www.cdc.gov/hepatitis/hcv/hcvfaq.htm
2. U.S. Food and Drug Administration / FDA: Harvoni (ledipasvir / sofosbuvir) Label Updated. http://content.govdelivery.com/accounts/USFDA/bulletins/1253f05
3. FDA: FDA Hepatitis C Update – Approval of Zepatier for Treatment of Chronic Hepatitis C Genotypes 1 and 4 http://content.govdelivery.com/accounts/USFDA/bulletins/1383e51

BENEFITS OF TREATMENT & CURE

- Curative treatment **reduces**:
  - Risk of liver cancer by 75%
  - Risk of all-cause mortality by 50%
- Curative treatment **improves**:
  - Cost-effectiveness compared to past treatment regimens
  - Cost-effectiveness compared to long-term treatment of HCV-associated conditions
  - Patient quality of life
  - Health outcomes for individuals co-infected with HIV
- Curative treatment **prevents** future transmission of HCV
  - Rates of reinfection among persons who inject drugs are relatively low, especially with behavioral support, and should not be a justification for withholding curative treatment

1. CDC. CDC Fact Sheet: Why Hepatitis and Liver Cancer. http://www.cdc.gov/nchhstp/newsroom/docs/factsheets/why-hep-liv-ca-cancer.pdf
2. Saab, et al. Cost-effectiveness Analysis of Sofosbuvir Plus Peginterferon/ribavirin in the Treatment of Chronic Hepatitis C Virus Genotype 1 Infection. *Alimentary Pharmacology & Therapeutics*. 2014;40(6):657-675.
3. Moorn, K. Reinfection after hepatitis C cure: Prevention may require long-term support for people who have injected drugs. 2015. http://www.aidsmap.com/Reinfection-after-hepatitis-C-cure-prevention-may-require-long-term-support-for-people-who-have-injected-drugs/page/2973522/

FICTIONAL CASE: GARY DAA FAILURE

56-yr-old black male patient with GT 1a HCV, DM, GERD, HTN and HLD, treated with pegIFN + RBV in 2009 (null response)

Physical Exam: BMI 38, no ascites, edema, palmar erythema or jaundice

Cirrhosis confirmed by elastography in 2015 (22.6 kPa; IQR 11%; CAP 300)

2015 treated with LDV/SOF + RBV for 12 wks

Tx week 4: HCV RNA < 15 IU/mL

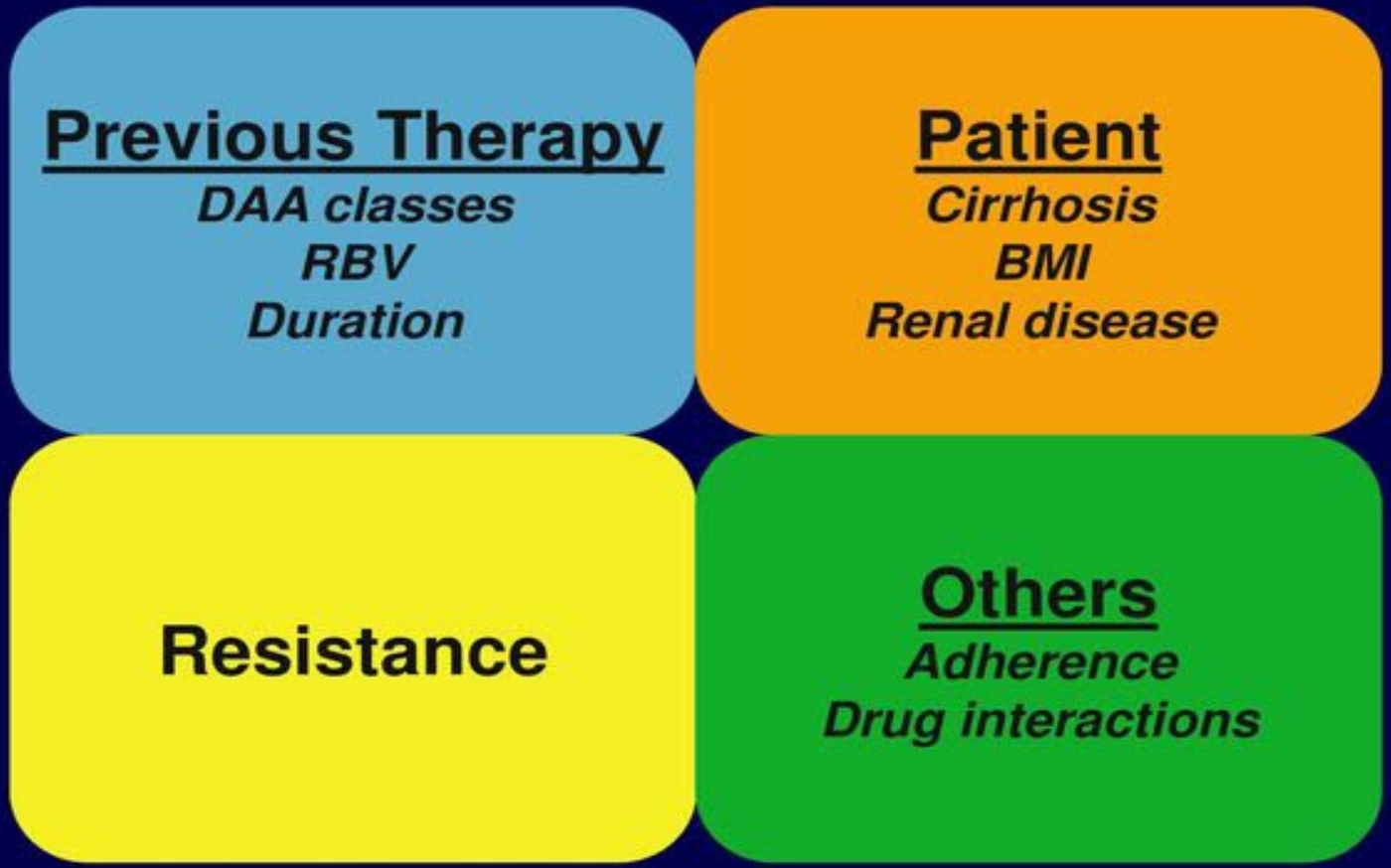
Relapse 4 weeks post treatment HCV RNA 176,000 IU/mL

Current meds: amlodipine, atorvastatin 40 mg, omeprazole 20 mg bid

GARY'S CURRENT RESULTS

Platelet count	98,000
Albumin	3.7
ALT	47
AST	56
Total bilirubin	0.9
INR	1.2
MELD	9

Considerations for DAA Regimen Failure



Slide credit: clinicaloptions.com

DRUG–DRUG INTERACTIONS

Recommendations	Grade of evidence	Grade of recommendation
Numerous and complex DDIs are possible with HCV DAAs A thorough risk assessment is required in all patients prior to starting DAAs and before starting other medications during treatment*	A	1
DDIs are a key consideration in treating HIV-HCV coinfected patients Close attention must be paid to anti-HIV drugs that are contraindicated, not recommended or require dose adjustment with particular DAA regimens	A	1
Patients should be educated on the importance of: • Adherence to therapy • Following dosing recommendations • Reporting the use of: – Other prescribed medications – OTC medications – Medications bought via the internet – Use of party or recreational drugs	A	1

- A summary of data on key interactions can be found in **Appendix 1** in this document
- Key internet resource: www.hep-druginteractions.org

*Based on the PI for each DAA

EASL CPG HCV. J Hepatol 2018;69:461–511.

Drug-Drug Interactions With HCV Treatments

- No clinically significant interaction expected
- Potential interaction that may require dose adjustment, altered administration timing, or additional monitoring
- Should not be coadministered

Lipid-Lowering Drug	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Atorvastatin					
Bezafibrate					
Ezetimibe					
Fenofibrate					
Fluvastatin					
Gemfibrozil					
Lovastatin					
Pitavastatin					
Pravastatin					
Rosuvastatin					
Simvastatin					

Illicit/Recreational Drug	SOF	SOF/VEL	SOF/VEL/VOX	GLE/PIB	GZR/EBR
Amphetamine					
Cannabis					
Cocaine					
Diamorphine					
Diazepam					
Fentanyl					
γ-hydroxybutyrate					
Ketamine					
MDMA					
Mephedrone					
Methadone					
Methamphetamine					
Oxycodone					
Phencyclidine					
Temazepam					

Pawlotsky. J Hepatol. 2020;73:1170.

Slide credit: clinicaloptions.com

Was Our Pt Set up for Treatment Failure?

- Negative predictors in our pt:
  - Black race and male
  - Treatment experienced
  - High BMI, diabetes (?)
  - Cirrhosis with portal HTN
  - Drug–drug interaction: omeprazole 20 mg BID and LDV

Slide credit: clinicaloptions.com

RETREATMENT OF DAA FAILURES

- Retreatment strategy depends on initial regimen

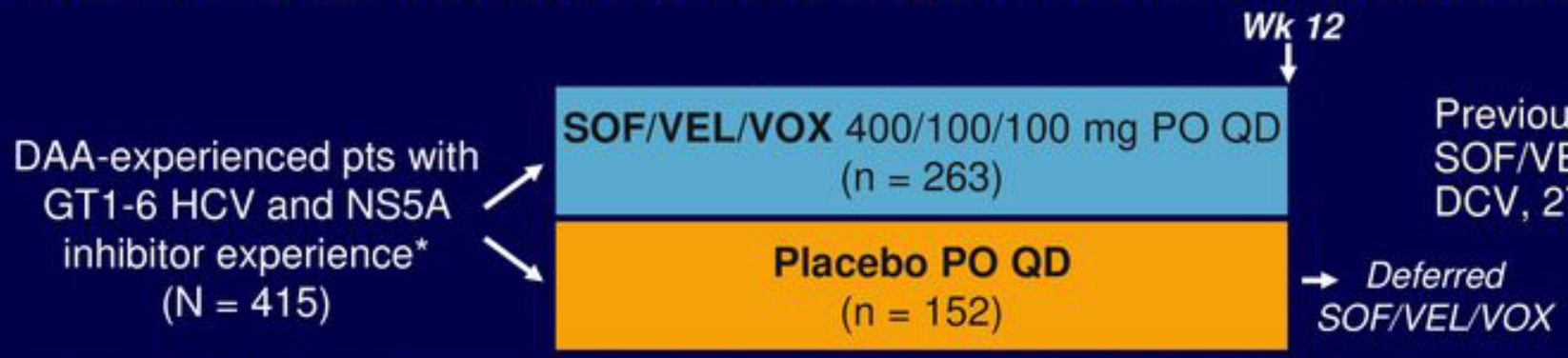
Recommendations	Grade of evidence	Grade of recommendation
After failure of PEG-IFNα + RBV, SOF + PEG-IFNα/RBV or SOF + RBV • Retreat according to recommendations for TE patients, by HCV genotype	A	1
HCV resistance testing after failure of any DAA-based regimen (excluding regimens with SOF as the only DAA) is a useful guide to retreatment	B	2
After failure of DAA (PI and/or NS5A inhibitor)-containing regimen		
• First-line retreatment		
– SOF/VEL/VOX for 12 weeks (without cirrhosis/with compensated cirrhosis)	A	1
– SOF/VEL + RBV* for 24 weeks (decompensated cirrhosis)	B	2
• Patients with predictors of poor response, SOF + GLE/PIB for 12 weeks: – Advanced liver disease – Multiple courses of DAA-based treatment – Complex NS5A RAS profile	B	2
• Very difficult-to-cure patients:† SOF/VEL/VOX + RBV or SOF + GLE/PIB + RBV for 12 weeks or for 16 or 24 weeks	C	2

*Daily weight-based RBV (1,000 mg or 1,200 mg in patients <75 kg or ≥75 kg, respectively); start RBV at a dose of 600 mg daily and adjust dose depending on tolerance;
†Patients with NS5A RASs who failed twice to achieve SVR after a combination regimen including a PI and/or an NS5A inhibitor

EASL CPG HCV. J Hepatol 2018;69:461–511.

POLARIS-1, -4: SOF/VEL/VOX for 12 Wks After DAA Failure in GT1-6 HCV

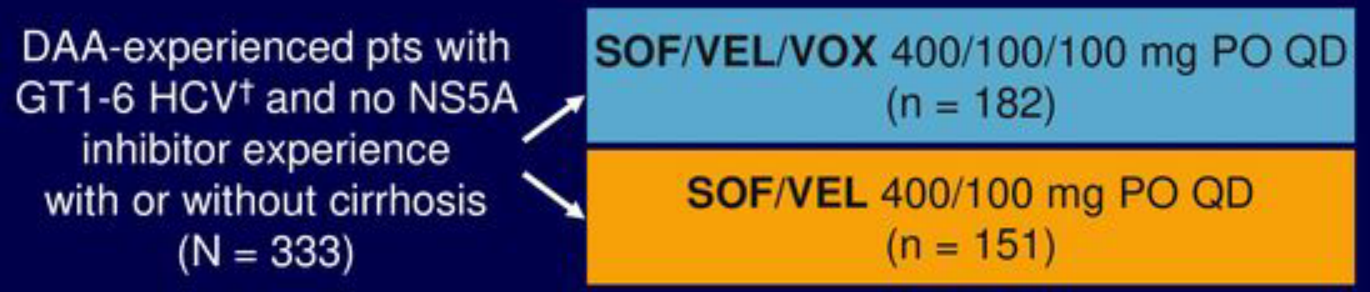
POLARIS-1: randomized, double-blind, placebo-controlled phase III trial[1]



Previous NS5A treatment in SOF/VEL/VOX group LDV, 51%; DCV, 27%; OBV, 11%; other, 13%

*Pts with GT1 HCV at screening equally randomized between arms; pts with GT2-6 HCV assigned to active treatment arm.

POLARIS-4: randomized, open-label, active-controlled phase III trial[2]



Previous HCV treatment: SOF, 69%; other NS5B inhibitor, 4%; SOF + SMV, 11%; other NS5B/NS3 inhibitor combinations, 14%

†Pts with GT1-3 HCV randomized 1:1 between arms. Pts with GT4-6 HCV assigned to SOF/VEL/VOX.

1. Bourlière M, et al. AASLD 2016. Abstract 194. 2. Zeuzem S, et al. AASLD 2016. Abstract 109.

QUESTIONS?