Cases: Management of Hepatitis C in Prior Treatment Failure

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe need for resistance testing
- Describe rates of resistance selection following treatment failure and describe the most common resistance-associated substitutions (RASs)
- Recognize non-viral factors that may contribute to treatment failure
- Select effective re-treatment regimens for NS5A-containing initial treatment failures.

Case 1: EJ

- 63 AA male HTN, BPH and HCV GT1a
  - Cirrhosis based on FIB-4 and nodular liver on imaging with splenomegaly
  - HCV RNA 1.5 million
- Exam and key labs:
  - Abd: No ascites.
  - No asterixis
  - PLT 78 ALB 3.4 INR 1.1 Tbili 0.9 AST 63 ALT 52 Cr 0.8 (CTP A6)
- Meds:
  - Tamsulosin, omeprazole 20 mg QD, HCTZ, rosuvastatin 5mg

Case continued

- Treated with G/P for 12 weeks
  - HCV RNA: 55@wk4, 98@wk8
  - Viral breakthrough by EOT: RNA 25,034 IU/ml
- Pharmacy refills were on time.
  - Pt states maybe missed 2 or 3 doses.
- 4 weeks post EOT: HCV RNA 423,743 IU/mL

ARS Question #1: Would you do any additional testing prior to deciding on a retreatment regimen?

1. NS5A RAS testing
2. NS3 RAS testing
3. NS3 + NS5A RAS testing
4. No, re-treat without it
5. I would refer out for a second opinion

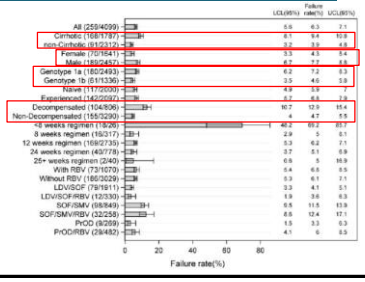
Considerations for treatment failures after DAAs

- Was initial therapy appropriate?
- Was staging accurate? Is it needed again?
- Was adherence adequate?
- Were drug interactions present?
- What medication classes were used?

HCV Target cohort: Who is failing?

4099 GT1 patients treated with all-oral DAA regimens

- 259 (6.3%) failed therapy



Key HCV Resistance Concepts

1. HCV resistance associated substitutions (RASs) may be present without drug exposure
2. HCV RASs impact treatment responses in specific situation
   - Depends on regimen and patient characteristics
3. HCV is resistance is NOT absolute
4. Patient characteristics are more important than RASs
   - Cirrhosis seems to be the major one
5. New regimens **have** obviated the need for most (all?) resistance testing

Back to our patient

- RAS testing was done
  - NS3: A156A/T
    - VOX: >1000x
    - GLE: >1000x
  - NS5A: Q30E, Y93S
    - VEL: 20x, 60x; dual?
    - PIB: <3x, <10; dual?

GLE	Resistance Possible
GZR	Resistance Possible
PTV/r	Resistance Possible
SMV	Resistance Possible
VOX	Resistance Possible

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Ledipasvir Resistance: Predicted
Elbasvir Resistance: Predicted
Ombitasvir Resistance: Possible
Daclatasvir Resistance: Possible
Velpatasvir Resistance: Not Predicted
Pibrentasvir Resistance: Not Predicted
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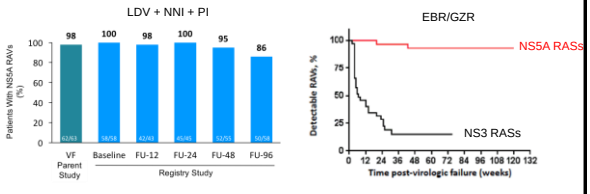
Characteristics of Direct Acting Antiviral (DAAs)

Drug	Class	Activity	Potency	Resistance Barrier
Simeprevir	NS3 PI	GT 1, 4	High	Low (1a<1b)
Paritaprevir				
Grazoprevir		GT 1, 4 & 6 (3)		Moderate
Voxilaprevir*		GT 1-6		High
Glecaprevir*				
Daclatasvir	NS5A	GT 1 - 6	High	Low (1a<1b)
Ledipasvir		GT 1, 4 & 6		
Ombitasvir				
Elbasvir		GT 1,4 & 6		
Velpatasvir		GT 1 - 6		Moderate
Pibrentasvir*				Very high
Sofosbuvir	NS5B Nucleotide	GT 1 - 6	High	Very High

*FDA approval in 2017

Durability of Treatment-Emergent HCV RASs



Week 144:

Wyles D et al. Antiviral Ther 2017. Lahser F. AASLD 2016.

Baseline versus selected RASs

Baseline	Selected
Single variants	Multiple variants (w/ "linkage")
Variable fold change	High fold change
Variable prevalence in viral population	High prevalence in viral population
Any patient	"Difficult to treat" populations

Most common RAS profiles in DAA failure

Regimen	NS5A RASs	NS3 RASs
LDV/SOF	GT1a:Q30H/**R**>Y93**H**/N>L31M Dual: Q30H+Y93H	--
EBR/GZR	GT1a: Q30H/**R**>Y93**H**/N	A156T≈D168**A**/G/V>Y56H
SOF/VEL	GT1a: Y93H/N GT3: Y93H Dual: A30K+Y93H	--
GLE/PIB*	GT1a: Q30G/H/K/dual or triple mutants (K24, M28, L31, H58 or Y93); P32del GT3: Y93H>A30K; A30K+Y93H	1a:A156G/T/**V**> D168**A**/E>Y56H GT3:Q168L/R>Y56H/N

*most of GT1a resistance data from retreatment of DAA failures

Most common RAS profiles in DAA failure

Regimen	NS5A RASs	NS3 RASs
LDV/SOF	GT1a:Q30H/**R**>Y93**H**/N>L31M Dual: Q30H+Y93H	--
EBR/GZR	GT1a: Q30H/**R**>Y93**H**/N	A156T≈D168**A**/G/V>Y56H
SOF/VEL	GT1a: Y93H/N GT3: Y93H Dual: A30K+Y93H	--
GLE/PIB*	GT1a: Q30G/H/K/dual or triple mutants (K24, M28, L31, H58 or Y93); P32del GT3: Y93H>A30K; A30K+Y93H	1a:A156G/T/**V**> D168**A**/E>Y56H GT3:Q168L/R>Y56H/N

*most of GT1a resistance data from retreatment of DAA failures

ARS Question #2: Based on his RAS testing and history how would you proceed?

GT1a, cirrhosis (compensated- CTP A6) failed G/P 12 wks. NS5A RASs: Q30E + Y93S. NS3: A156T

1. SOF/VEL/VOX for 12 weeks
2. SOF/VEL/VOX + RBV for 12 weeks
3. SOF/VEL/VOX for 24 weeks
4. GLE/PIB + SOF for 12 weeks
5. GLE/PIB + SOF + RBV for 12 weeks
6. GLE/PIB + SOF for 16 weeks
7. GLE/PIB + SOF + RBV for 16 weeks

Polling Open

Recommendations for Testing, Managing, and Treating Hepatitis C

AASLD / IDSA

Recommended and alternative regimens for:

NS5A Inhibitor DAA-Experienced, Genotype 1 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] except NS3/4 protease inhibitor inclusive DAA combination regimens	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

- Resistance testing is generally not recommended for these regimens

Taken from http://hcvguidelines.org, September 26, 2017

Improved resistance profile of "Next Generation" NS5As

Fold Change	Genotype 1a				Genotype 1b		GT3a	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H	A30K	Y93H
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000		> 100x	N/A	N/A
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x/ > 10,000x	< 10x	20x	N/A	N/A
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1,000x/ > 10,000x	< 10x	20x	>1000x	>1000x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x/ > 1000x	< 10x	> 100x	N/A	N/A
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x	>50x	>700x
Pibrentasvir	< 3x	< 3x	< 3x	7x/7x	< 3x	< 3x	<3x	<3x

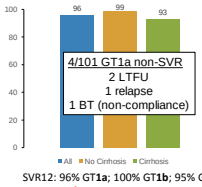
Wang C. AAC 2012. Wang C. AAC 2014. Cheng G, et al. EASL 2012. Abstract 1172. Zhao Y, et al. EASL 2012. Abstract A845. Yang G, et al. EASL 2013. Abstract 1199. Ng T, et al. CROI 2014. Abstract 639. Asante-Appiah E, et al. AASLD 2014. Abstract 1979. Ng T. THU-305 EASL 2017. Lawitz E. AAC 2016. Ng. AAC 2018 Hezode J Hepatol 2018

Triple DAA therapy for re-treatment

Regimen: SOF/VEL/VOX for 12 weeks

POLARIS-1 (n=263)

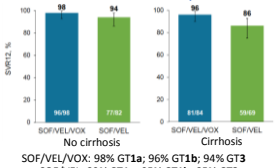
NS5A experienced (g3: 3/4 RAS)
46% cirrhosis



SVR12: 96% GT**1a**; 100% GT**1b**; 95% GT**3**
VF: 6/6 relapses with cirrhosis

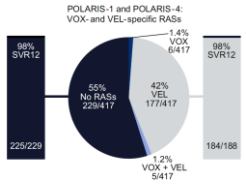
POLARIS-4 (n=182)

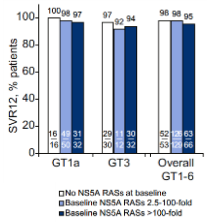
NO NS5A exposure
46% cirrhosis
97% SVR vs 90% SOF/VEL



SOF/VEL/VOX: 98% GT**1a**; 96% GT**1b**; 94% GT**3**
SOF/VEL: 89% GT**1a**; 95% GT**1b**; 85% GT**3**

Any way you slice it: no significant impact of pre-treatment RASs

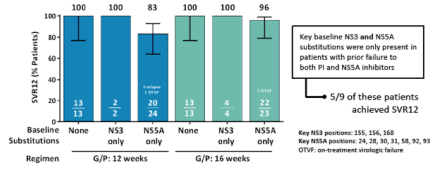




Glecaprevir / pibrentasvir for re-treatment of NS5A failures - MAGELLAN 1

GLE
PIB

SVR12 by Key NS3 and NS5A Baseline Substitutions



Y93H/N at baseline: 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

Poordad et al. EASL 201

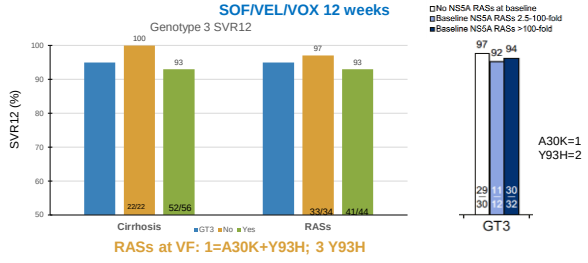
Case 2: GT3

- 53 Hispanic male with DM and HCV GT3a infection
  - History of EtOH
  - Borderline fibrosis stage (F3 vs F4)
    - Elastography 11.7 kPa (18% IQR)
    - PLT 152 ALB 3.5 INR 1.0
    - No RAS testing done
- Failure after SOF/VEL for 12 weeks in 2018
  - HCV RNA: week 4- <15 IU/mL (detected); week 6 0
  - SVR12: 187,000 IU/mL

ARS Question #3: How would you proceed?

1. RAS testing and restage then decide
2. GLE/PIB for 16 weeks
3. SOF/VEL/VOX for 12 weeks
4. SOF/VEL/VOX + RBV for 12 weeks
5. SOF + GLE/PIB + RBV for 16 weeks
6. SOF/VEL + RBV for 24 weeks

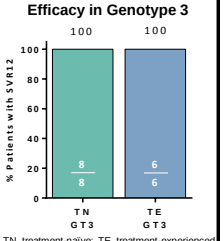
Revisiting GT3 NS5A failures



RASs at VF: 1=A30K+Y93H; 3 Y93H

G/P + SOF + RBV 16 weeks: GT3 details

	Treatment-naïve Genotype 3 N=8	Treatment-exp Genotype 3 N=6
8/12/16-week treatment in APS	5 (63) / 3 (38) / 0	0 / 4 (67) / 2 (33)
Subtype 3a	7 (88)	6 (100)
With cirrhosis	2 (25)	1 (17)
Relapse with G/P	6 (75)	4 (67)
NS3 RAS at G/P failure in APS	4 (50)	3 (50)
NS5A RAS at G/P failure in APS	8 (100)	6 (100)
Time from G/P VF to retreatment, mean months (range)	9.8 (4.6–13.2)	10.8 (6.2–21.8)
NS3 RAS at BL (MAGELLAN-3)	3 (38)	0
NS5A RAS at BL (MAGELLAN-3)	8 (100)	6 (100)
A30K alone	1 (13)	2 (33)
Y93H alone	2 (25)	2 (33)
A30K + Y93H	4 (50)	2 (33)
Y93H + other	1 (13)	0



TN, treatment-naïve; TE, treatment-experienced

Wyles D. EASL 2018

What do the labels say?

	Prior treatment	SOF/VEL/VOX	GLE/PIB
GT1	NS5A (+/- SOF)	12 (also 2-6)	16
GT1	NS3 (+/- SOF)	12 (1a only)	12
GT1-6	NS3+NS5A	12	NR
GT3	SOF (no NS5A)	12	16

AASLD/IDSA Guidelines: GT3 NS5A-experienced with compensated cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg)	12 weeks	I, A
For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.	12 weeks	IIa, C

Reminder: HCV PIs (including VOX and GLE) are either not recommended or contraindicated in CTP B/C cirrhosis

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

RECOMMENDED	RATING
Elbasvir/grazoprevir NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, a different regimen should be considered.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important* resistance is present, a different recommended therapy should be used. NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If clinically important* resistance is present, a different recommended therapy should be used.	I, A
Sofosbuvir/velpatasvir NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis and treatment-experienced patients (with or without cirrhosis) being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added or sofosbuvir/velpatasvir/voxilaprevir should be used.	I, A
Daclatasvir plus sofosbuvir NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added. NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.	I, B

* Clinically important = greater than 100-fold resistance

When should one test for RASs?

Different regimen if: RAS
G1a ELB/GRZ + NS5A

G 1a LDV/SOF (TE) + NS5A

G3 Y93H if F4 or TE (any)
- If using SOF/VEL add VOX or add RBV
- If using DAC/SOF add RBV

http://hcvguidelines.org
September 26, 2018

NOT RECOMMENDED	RATING
Elbasvir/grazoprevir RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy.	I, A
Glecaprevir/pibrentasvir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load <6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy.	I, A
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively.	I, A
Sofosbuvir/velpatasvir RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy.	I, A
Sofosbuvir/velpatasvir/voxilaprevir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy.	I, A

When should one NOT test for RASs?

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Key principles of HCV resistance-associated substitutions (RASs)

- **Viruses with RASs may exhibit variable "fitness" compared to wildtype**
  - Higher fitness last longer, lower fitness may be transient
- **RAS are present at baseline in the absence of drug exposure, but may or may not be detected**
  - Possibility of transmission
- **RASs may impact treatment responses in select situations**
  - Situation is often worse in presence of other treatment characteristics
- **Resistance is NOT futile**
  - May be overcome by longer durations, addition of ribavirin, or later-generation agents
- **For newly approved regimens detection of RASs is most often NOT necessary**

Summary

- New regimens have addressed unmet medical need for DAA experienced patients
- Resistance testing does not have a significant role in deciding on DAA failure retreatment
  - Prior drug class exposure history is important
  - Appropriate staging of liver fibrosis
- There is limited date on re-treatment after G/P failure
  - Complex resistance patterns- impact on retreatment?
- When in doubt in patients with cirrhosis I still add RBV

Question-and-Answer

Remember to raise your hand and wait until you have the microphone before you ask your question—we are recording!

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