

HCV Treatment in 2016: Genotypes 1, 2, and 3

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Disclosures

- I have no financial disclosures.

Caveats

- I will only discuss treatment of GT 1-3.
 - Majority of US population infected with GT 1, 2, or 3
 - GT 4 treatment closely reflects GT 1 treatment
 - GT 5 and 6 are rare and treatment has relatively little clinical data
- We will discuss treatment naïve and PEG-IFN/RBV treatment experienced patients (not DAA treatment experienced patients).
 - Majority of patients who present for HCV care reflect these populations
 - Patients who have failed DAA-based regimens should be assessed by experienced HCV treatment providers.

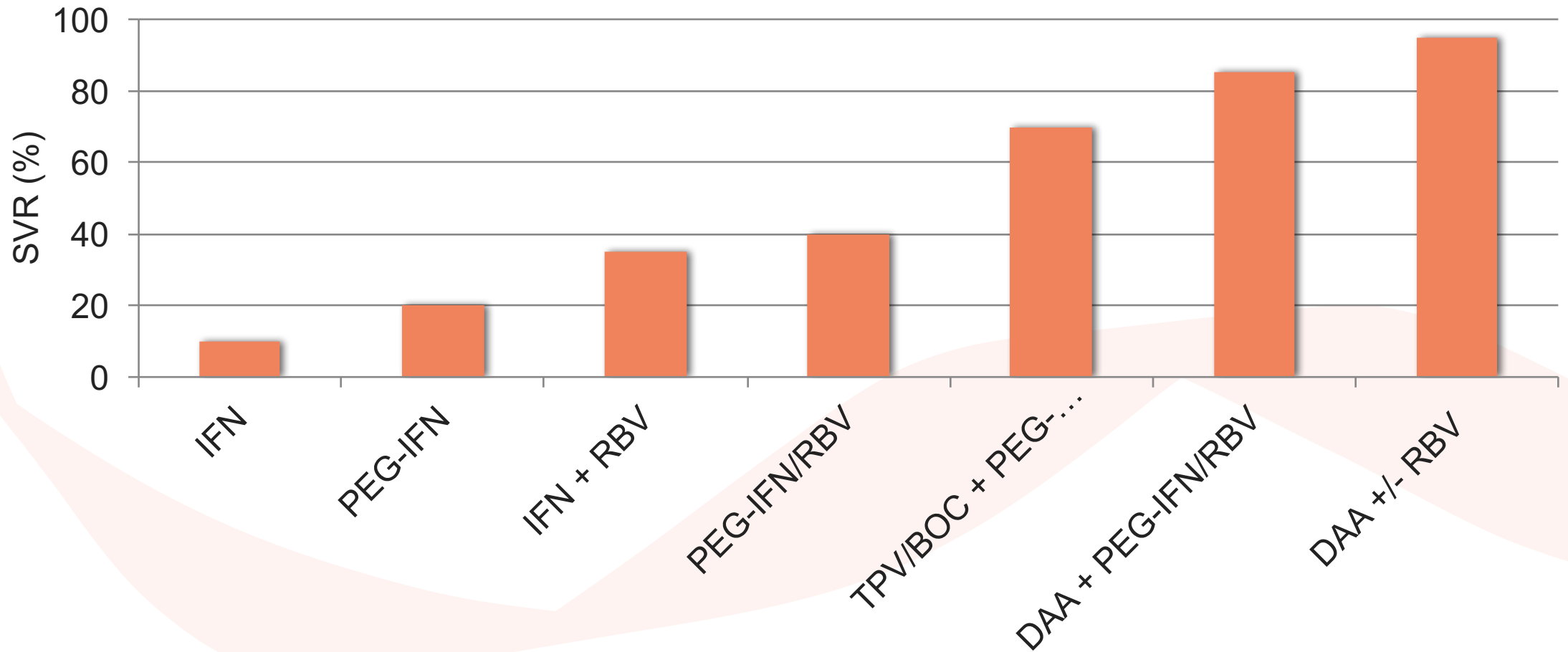
Overview

- Direct Acting Antiviral (DAA) Review
- Selecting HCV Treatment
- Genotype 1
- Genotype 2
- Genotype 3
- Resistance Associated Variants
- Case Discussions

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Treatment Response in Direct Acting Antiviral (DAA) Era



HCV Therapies: The Past, Present, and Future

<u>Pre-2011</u>	<u>July 2011</u>	<u>Nov-Dec 2013</u>	<u>Oct-Dec 2014</u>	<u>July 2015</u>	<u>Jan-Jun 2016</u>
IFN	IFN	IFN	IFN	IFN	IFN
PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN	PEG-IFN
RBV	RBV	RBV	RBV	RBV	RBV
	Telaprevir	Telaprevir	Telaprevir	Telaprevir	Telaprevir
	Boceprevir	Boceprevir	Boceprevir	Boceprevir	Boceprevir
		Simeprevir	Simeprevir	Simeprevir	Simeprevir
		Sofosbuvir	Sofosbuvir	Sofosbuvir	Sofosbuvir
			Ledipasvir	Ledipasvir	Ledipasvir
			Paritaprevir	Paritaprevir	Paritaprevir
			Ombitasvir	Ombitasvir	Ombitasvir
			Dasabuvir	Dasabuvir	Dasabuvir
				Daclatasvir	Daclatasvir
					Elbasvir
					Grazoprevir
					Velpatasvir

FDA Approved HCV Therapies (8/2016)

Nonspecific Antivirals

Interferon (IFN)

Ribavirin (RBV)

Pegylated Interferon (PEG-IFN)

NS3/4 Protease Inhibitors

Telaprevir (TPV)

Boceprevir (BOC)

Simeprevir (SMV)

Paritaprevir (PTV)

Grazoprevir (GZP)

NS5A Inhibitors

Ledipasvir (LDV)

Ombitasvir (OBV)

Daclatasvir (DCV)

Elbasvir (EBR)

Velpatasvir (VEL)

NS5B Polymerase Inhibitors

Sofosbuvir (SOF)

Dasabuvir (DBV)

Simeprevir (SMV; Olysio™)

- FDA Approval
 - 2013
- Class
 - NS3/4A protease inhibitor
- Genotypes (FDA approved for treatment)
 - 1 and 4
- Common Side Effects (≥10%)
 - Headache, fatigue, nausea, diarrhea, photosensitivity, rash, dizziness
- Notes:
 - No dose adjustment for renal function
 - Not recommended in patients with moderate/severe hepatic impairment
 - Negatively impacted by NS3/4A protease polymorphisms (Q80K)

Sofosbuvir (SOF; Sovaldi™; half of Harvoni™; half of Epclusa™)

- FDA Approval
 - 2013
- Class
 - NS5B polymerase nucleotide analogue inhibitor
- Genotypes (FDA approved for treatment)
 - 1-6
- Common Side Effects (≥10%)
 - None
- Notes:
 - Not recommended with severe renal impairment (GFR <30 ml/min/1.73m²)
 - Contraindicated with amiodarone

Ledipasvir (LDV; half of Harvoni™)

- FDA Approval
 - 2014
- Class
 - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
 - GT 1 and 4-6
- Common Side Effects ($\geq 10\%$)
 - Headache, fatigue
- Notes:
 - Caution with acid blocking agents

PTV/r /OBV + DBV (Viekira Pak/XR™ and Technivie™)

- FDA Approval
 - 2014, 2015, and 2016
- Class
 - Paritaprevir (PTV)
 - NS3/4A protease inhibitor
 - Ombitasvir (OBV)
 - NS5A replication complex inhibitor
 - Dasabuvir (DBV; in Viekira Pak/XR™)
 - NS5B RNA non-nucleoside polymerase inhibitor
- Genotypes (FDA approved for treatment)
 - 1 and 4
- Common Side Effects (≥10%)
 - Fatigue, nausea, pruritus, insomnia, asthenia, skin reactions
- Notes
 - No dose adjustment with renal dysfunction
 - Not recommended in moderate/severe hepatic impairment
 - Contraindicated with many drugs due to strong CYP3A inhibition by ritonavir

Daclatasvir (DCV; Daklinza™)

- FDA Approval
 - 2015
- Class
 - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
 - 1 and 3
- Common Side Effects ($\geq 10\%$)
 - Headache, fatigue
- Notes
 - No dose adjustment for renal impairment

Elbasvir/Grazoprevir (EBR/GZP; Zepatier™)

- FDA Approval
 - 2016
- Class
 - Elbasvir
 - NS5A replication complex inhibitor
 - Grazoprevir
 - NS3/4A protease inhibitor
- Genotypes (FDA approved for treatment)
 - 1 and 4
- Common Side Effects (≥10%)
 - Headache, fatigue, nausea
- Notes
 - No dose adjustment for renal impairment
 - Not recommended in moderate/severe hepatic impairment
 - Negatively impacted by NS5A polymorphisms at M28, Q30, L31, Y93

Velpatasvir (VEL; half of Epclusa™)

- FDA Approval
 - 2016
- Class
 - NS5A replication complex inhibitor
- Genotypes (FDA approved for treatment)
 - 1-6
- Common Side Effects ($\geq 10\%$)
 - Headache, fatigue
- Notes
 - First single-tablet, pangenotypic regimen available

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Primary Factors when Selecting HCV Treatment

- Genotype
- Degree of fibrosis
 - I.e. Non-cirrhotic vs. cirrhotic
- Treatment history
 - I.e. Treatment naïve vs. treatment experienced
 - Recommendations may differ depending on what therapies were used previously (i.e. PEG-IFN vs. DAA-based therapy)

Secondary Factors when Selecting HCV Treatment

- Efficacy
 - Relatively equal among recommended regimens
- Safety
- Side effect profile
 - Including need for PEG-IFN or RBV
- Drug-drug interactions
- Access
 - Cost
 - Formulary restrictions

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HCV GT 1a, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks*
	LDV/SOF (Harvoni™)	12 weeks**
	PrOD (Viekira Pak/XR™) + RBV	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

* - If no NS5A resistance-associated variants detected. ** - Consider 8 weeks in select patients.

HCV GT 1a, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks*
	LDV/SOF (Harvoni™)	12 weeks**
	PrOD (Viekira Pak/XR™) + RBV	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	EBR/GZP (Zepatier™)	12 weeks*
	LDV/SOF (Harvoni™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

* - If no NS5A resistance-associated variants detected. ** - Consider 8 weeks in select patients.

HCV GT 1a, P/R Treatment Experienced (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks*
	LDV/SOF (Harvoni™)	12 weeks
	PrOD (Viekira Pak/XR™) + RBV	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	EBR/GZP (Zepatier™)	12 weeks*
	LDV/SOF (Harvoni™) + RBV	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

* - If no NS5A resistance-associated variants detected.

HCV GT 1b, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks
	LDV/SOF (Harvoni™)	12 weeks*
	PrOD (Viekira Pak/XR™)	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

* - Consider 8 weeks in select patients.

HCV GT 1b, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks
	LDV/SOF (Harvoni™)	12 weeks*
	PrOD (Viekira Pak/XR™)	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	EBR/GZP (Zepatier™)	12 weeks
	LDV/SOF (Harvoni™)	12 weeks
	PrOD (Viekira Pak/XR™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

HCV GT 1b, P/R Treatment Experienced (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	EBR/GZP (Zepatier™)	12 weeks
	LDV/SOF (Harvoni™)	12 weeks
	PrOD (Viekira Pak/XR™)	12 weeks
	SOF (Sovaldi™) + SMV (Olysio™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	EBR/GZP (Zepatier™)	12 weeks
	LDV/SOF (Harvoni™) + RBV	12 weeks
	PrOD (Viekira Pak/XR™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

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HCV GT 2, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	SOF/VEL (Epclusa™)	12 weeks
	<i>Alternative:</i> SOF (Sovaldi™) + DCV (Daklinza™)	12 weeks

HCV GT 2, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	SOF/VEL (Epclusa™)	12 weeks
	<i>Alternative:</i> SOF (Sovaldi™) + DCV (Daklinza™)	12 weeks
F4 (Cirrhotic)	SOF/VEL (Epclusa™)	12 weeks
	<i>Alternative:</i> SOF (Sovaldi™) + DCV (Daklinza™)	16-24 weeks

HCV GT 2, P/R Treatment Experienced (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	SOF/VEL (Epclusa™)	12 weeks
	<i>Alternative:</i> SOF (Sovaldi™) + DCV (Daklinza™)	12 weeks
F4 (Cirrhotic)	SOF/VEL (Epclusa™)	12 weeks
	<i>Alternative:</i> SOF (Sovaldi™) + DCV (Daklinza™)	16-24 weeks

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HCV GT 3, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks

HCV GT 3, Treatment Naïve (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™) +/- RBV	24 weeks
	SOF/VEL (Epclusa™)	12 weeks

HCV GT 3, P/R Treatment Experienced (9/2016)

Fibrosis	Recommended Treatment	Treatment Duration
F0-F3 (Non-cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™)	12 weeks
	SOF/VEL (Epclusa™)	12 weeks
F4 (Cirrhotic)	DCV (Daklinza™) + SOF (Sovaldi™) + RBV	24 weeks
	SOF/VEL (Epclusa™) + RBV	12 weeks

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Resistance Associated Variants

- Present in variable amounts at baseline in the population
- May be selected in cases of treatment failure
- Evolving role in timing of testing and impact on DAA selection

Resistance Associated Variants: When to Test?

- Genotype 1
 - Simeprevir treatment
 - Elbasvir/grazoprevir treatment
 - Prior NS5A DAA treatment failure (who have cirrhosis or have urgent indications for treatment)
- Genotype 3
 - Treatment-naïve patients with cirrhosis OR treatment-experienced patients without cirrhosis when considering:
 - Daclatasvir and sofosbuvir treatment
 - Sofosbuvir/velpatasvir treatment
- Consider discussion with HCV treatment expert in other situations

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Case 1: Alfred

- 58 y/o man presents to clinic for primary care f/u.
- PMH: Hypertension, diabetes
- Medications: lisinopril, glipizide
- Allergies: NKDA
- Family History: Coronary artery disease, “liver disease”
- Social History: smokes 1 ppd; drinks 2-3 beers on weekends; experimental inhaled drug use in distant past but no IVDU

Case 1: Alfred

- HCV antibody is positive; subsequent RNA testing reveals 850,000 copies/ml. Genotype testing reveals 1a.
- Labs reveal:
 - CBC within normal limits (of note, Plt 178)
 - CMP: within normal limits except AST 85 and ALT 155
 - INR: 1.0
 - HAV IgG positive and HBV cAb and sAb positive
 - HIV negative
- He undergoes liver ultrasound and elastography. No HCC is noted and F2 fibrosis is predicted.

Question #1

- Per AASLD/IDSA Guidelines, should treatment be pursued on this patient's behalf?
 - A. Yes
 - B. Wait for more advanced disease
 - C. Wait for higher efficacy therapies
 - D. Wait for safer HCV treatments

Question #2

- Based on available information, what treatment would you select on this patient's behalf?
 - A. EBR/GZP x 12 weeks
 - B. LDV/SOF x 8 weeks
 - C. PrOD x 12 weeks
 - D. SOF + DCV x 12 weeks
 - E. SOF + SMV x 12 weeks

Case 1: Alfred

- Alfred is started on LDV/SOF x 8 weeks.
- He has mild fatigue and intermittent headaches easily managed with over-the-counter therapies.
- He completes therapy and achieves SVR12.

Case 2: Beth

- 53 y/o woman who presents for HCV evaluation (treatment naïve).
- PMH: Endometriosis s/p hysterectomy, back pain, HCV
- Medications: Aspirin, OTC NSAIDs
- Allergies: NKDA
- Family History: Breast cancer, ovarian cancer
- Social History: does not smoke or drink alcohol; prior opioid abuse including IVDU but no use x 5 years

Case 2: Beth

- HCV testing testing reveals RNA 10,500,000 copies with genotype 3.
- Labs reveal:
 - CBC within normal limits except Hgb 12, Hct 36 (of note, Plt 145)
 - CMP: within normal limits except AST 55 and ALT 93
 - INR: 1.0
 - HBV cAb negative and sAb positive
 - HIV negative
- She undergoes liver ultrasound and elastography. No HCC is noted and elastography is consistent with F1 fibrosis.

Question #3

- Based on available information, what treatment would you select on this patient's behalf?
 - A. EBR/GZP x 12 weeks
 - B. LDV/SOF x 12 weeks
 - C. SOF + RBV x 12 weeks
 - D. SOF + DCV x 12 weeks
 - E. SOF/VEL x 12 weeks

Case 2: Beth

- Beth is started on SOF/MEL x 12 weeks.
- She has no significant side effects.
- She completes therapy and achieves SVR12.

Case 3: Carl

- 61 y/o man referred for HCV evaluation and treatment.
- Diagnosed 10 years ago. Treated with PEG-IFN x 48 weeks but relapsed after treatment.
- PMH: MVA with polytrauma in 1985 (multiple pRBC transfusions), arthritis, severe coronary artery disease
- Medications: ASA, carvedilol, lisinopril, atorvastatin
- Allergies: NKDA
- Family History: coronary artery disease, lung cancer
- Social History: does not smoke or drink alcohol; no history of drug use

Case 3: Carl

- HCV testing testing reveals RNA 5,250,000 copies with genotype 1a.
- Physical exam unremarkable with no evidence of decompensated disease.
- Labs reveal:
 - CBC within normal limits except Plt 103
 - CMP: within normal limits except Cre 1.5, AST 50 ,and ALT 65
 - INR: 1.0
 - HBV serology negative and HIV serology negative
- He undergoes liver ultrasound and elastography. No HCC is noted and elastography is consistent with F4 fibrosis.

Question #4

- Based on available information, what treatment would you select on this patient's behalf?
 - A. EBR/GZP + RBV x 16 weeks
 - B. LDV/SOF x 12 weeks
 - C. PrOD + RBV x 12 weeks
 - D. SOF + DCV x 12 weeks
 - E. SOF/VEL x 12 weeks

Case 3

- Carl is treated with an appropriate HCV regimen and attains SVR12.
- He continues to receive HCC screening with an ultrasound every 6 months.

Summary

- HCV treatment has transformed over the past several years.
- High efficacy therapies with limited side effects are available for all genotypes.
- Selecting HCV treatment is based on primary and secondary factors.
- Recommendations regarding treatment and duration are constantly evolving.