NEW YORK STATE

HCV PROVIDER CLASSIFICATION TRAINING

Empire Liver FOUNDATION

New York State HCV Provider Webinar Series

Side Effects of Therapy

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Objectives

- Understand the basics of HCV therapy
- Review the currently available regimens for treatment of HCV
- Appreciate side effects related to specific medications
- Become aware of general side effects related to clearance of HCV


Case Presentation
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Case

- 56 year-old lady with Genotype 1A Hepatitis C, Treatment-naive
- Noninvasive fibrosis testing consistent with mild fibrosis
- Good candidate for treatment
- PMH: Atrial Fibrillation, Chronic Kidney Disease (GFR ~ 20 mL/min)
- Medications: ASA, Amiodarone

- **What elements of her history impact which regimen you choose to treat her with?**


Overview of Hepatitis C Therapy
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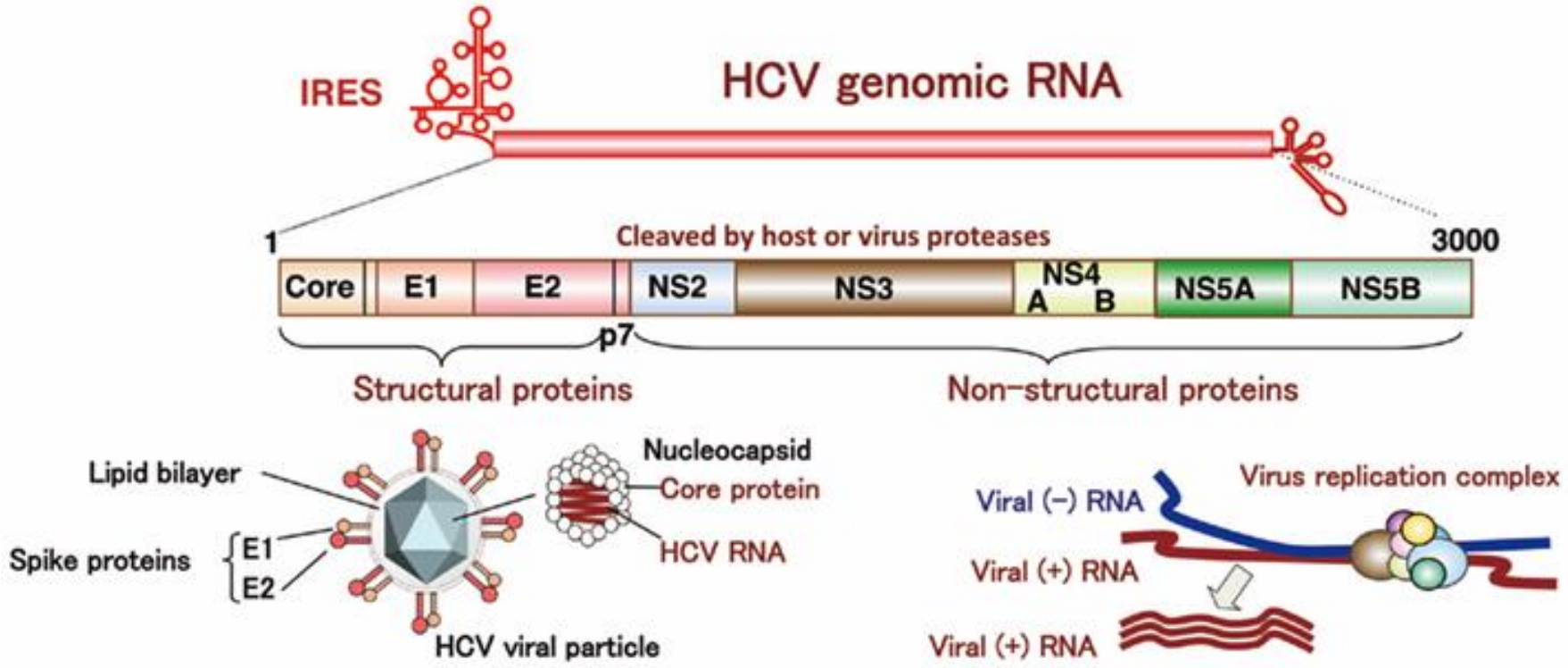
Hepatitis C Virology

- Enveloped, positive-strand RNA virus
- Family *Flaviviridae*
- Genotypes 1-6
  - 1, 2, 3 most common in U.S.
- RNA encodes a single polyprotein
- Processed by host and viral proteases to yield 10 viral proteins
- Include both structural and nonstructural proteins
- Nonstructural (NS) proteins NS3, NS4, NS5 are important components of viral replication complex

Lohmann V, et al. *Science*. 1999.

HCV Viral Replication



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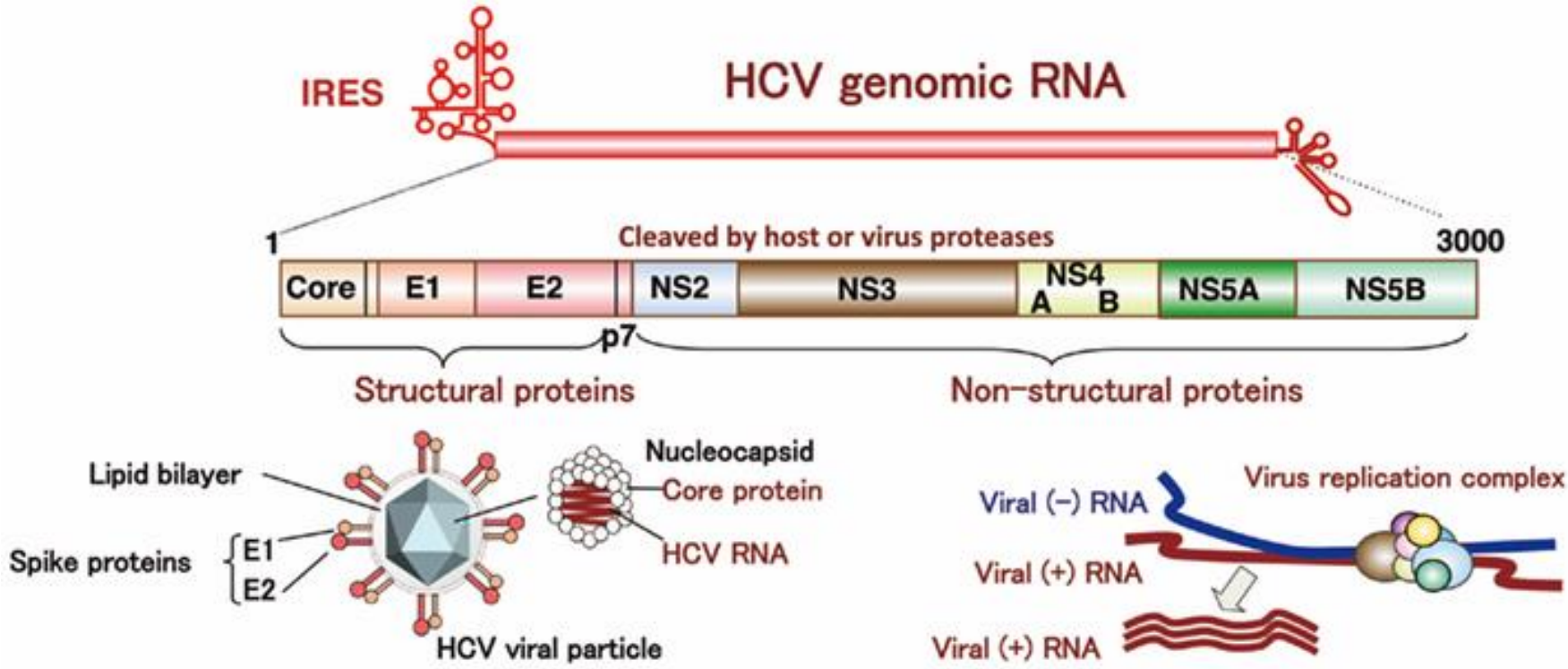
Direct Acting Antiviral (DAA) Therapy Targets



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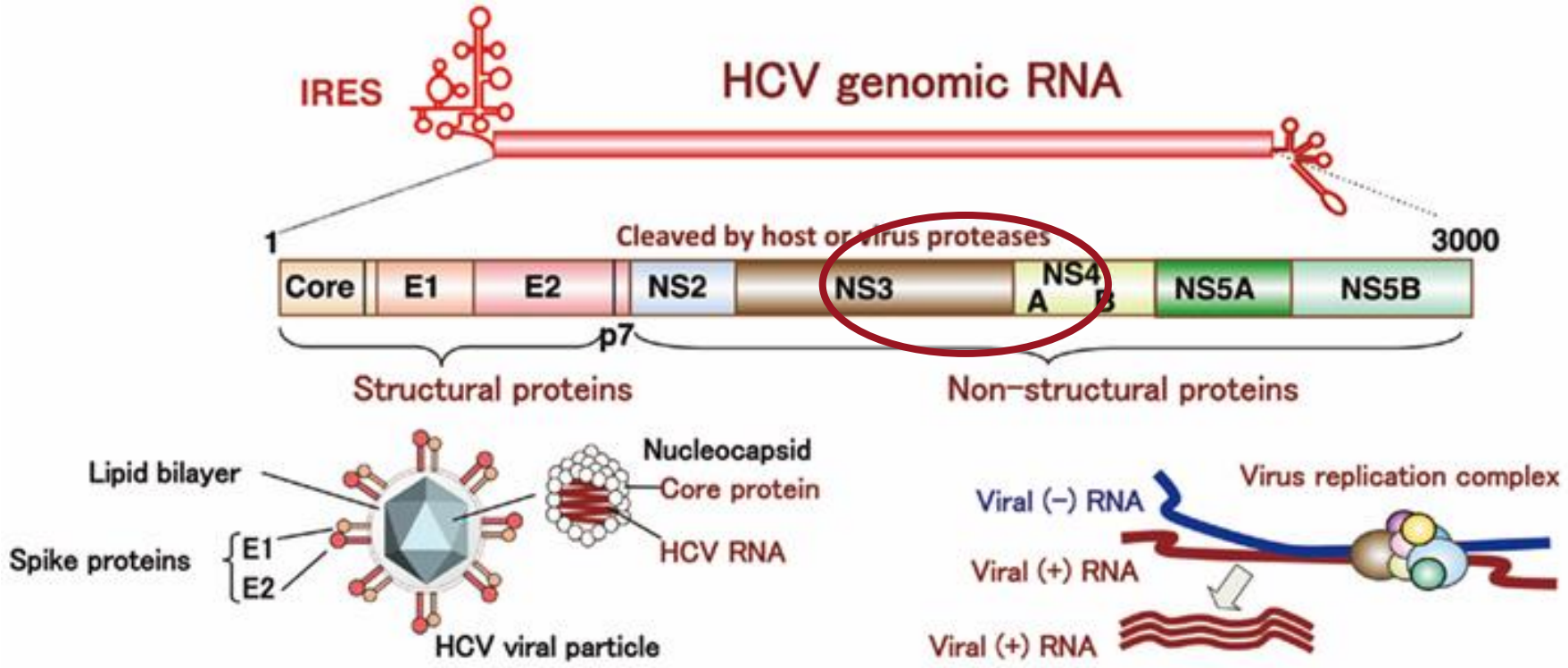

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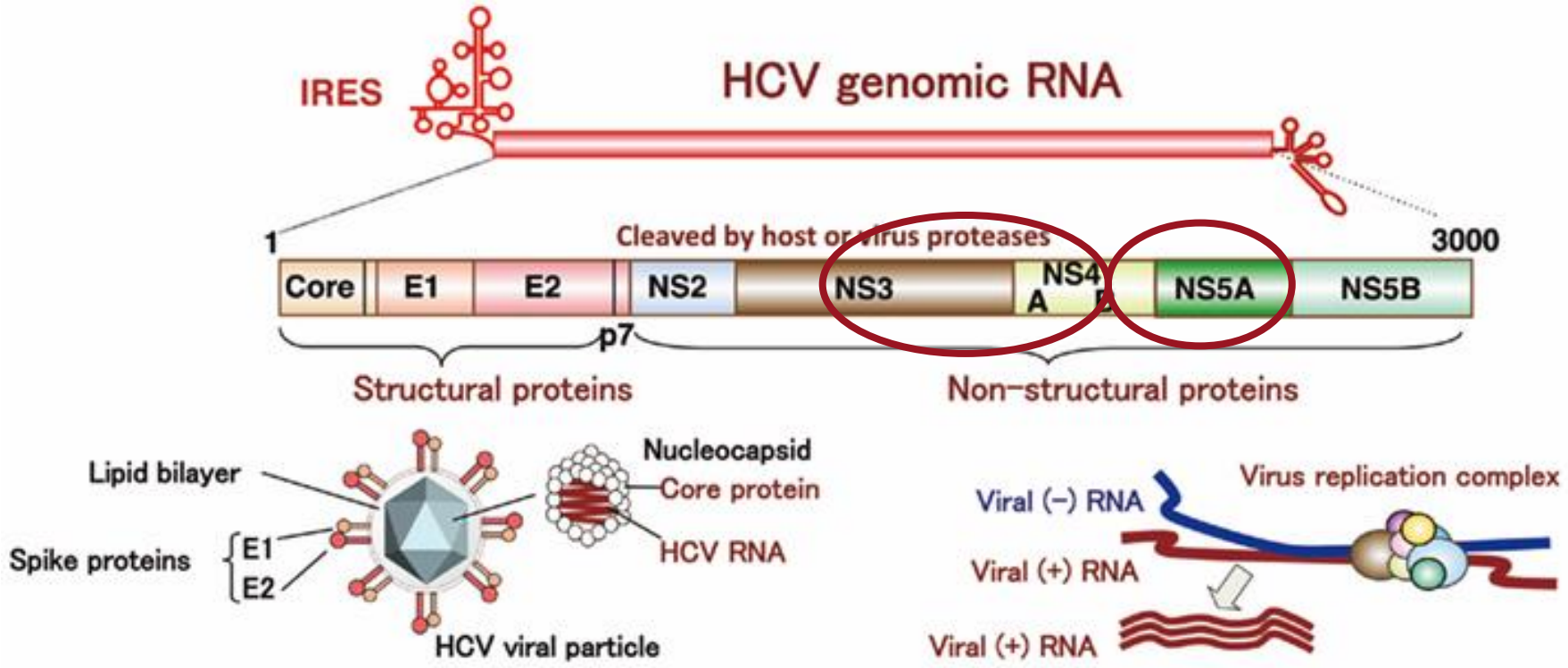

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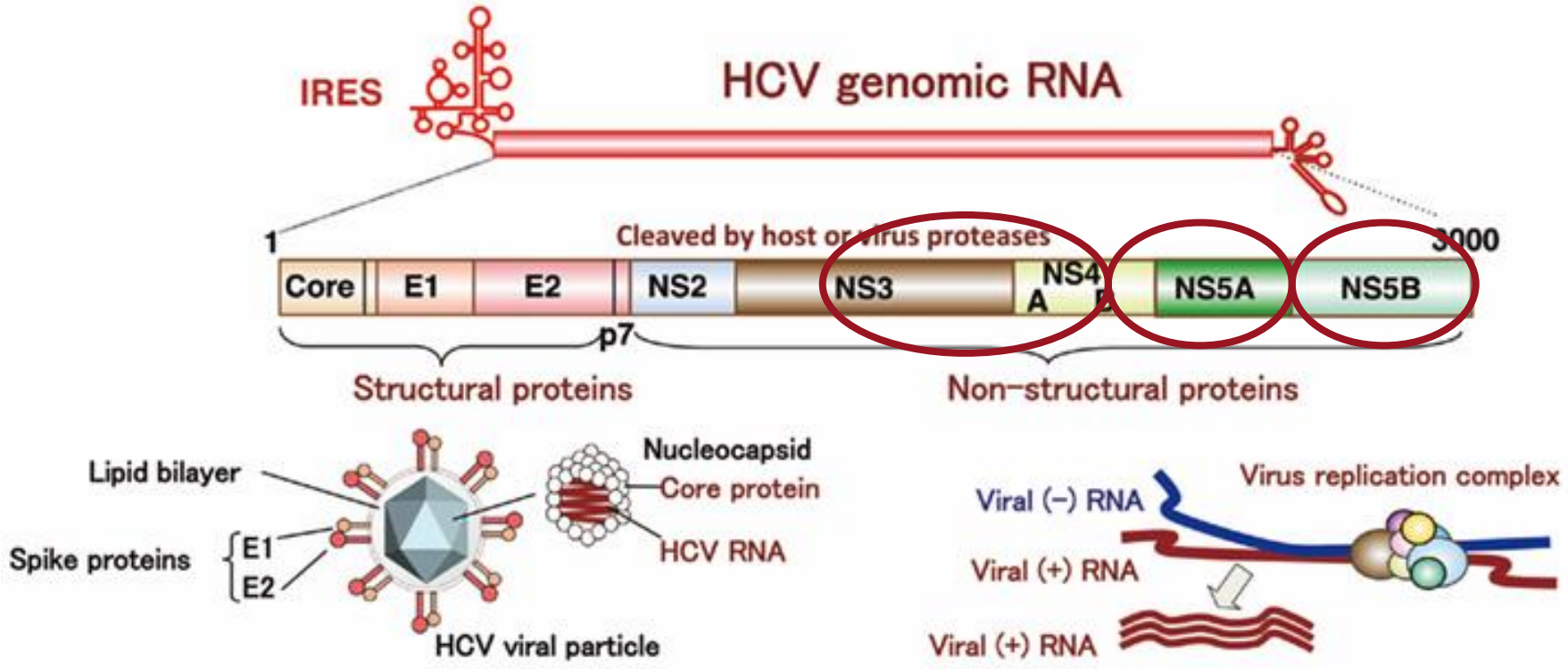

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DAA Classes

- NS3/4A Protease Inhibitor (“-previr”)
- NS5B Polymerase Inhibitor (“-buvir”)
  - Nucleotide analogs
  - Non-nucleotide analogs
- NS5A Inhibitor (-“asvir”)

NS3/4A Protease Inhibitors

- Grazoprevir
- Paritaprevir
- Simeprevir

NS5A Inhibitors

- Elbasvir
- Ledipasvir
- Ombitasvir
- Velpatasvir
- Daclatasvir

NS5B Polymerase Inhibitors

- Sofosbuvir (Nucleotide)
- Dasabuvir (Non-nucleotide)


Currently Available Therapies
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FDA Approved Combination Therapies

Combination Therapies	Trade Name
Grazeprevir/Elbasvir	Zepatier
Paritaprevir/Ombitasvir/Dasabuvir	Viekira XR
Sofosbuvir/Ledipasvir	Harvoni
Sofosbuvir/Velpatasvir	Epclusa

Ribavirin

- Largely replaced by newer DAA regimens
- Occasionally still used for difficult-to-treat patients
  - Nonresponders to DAA regimens
  - Post-solid organ transplant
- Oral antiviral agent
- Uncertain mechanism of action

Medication-Specific Side Effects

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Common DAA Side Effects Overview

Generic Name	Fatigue	Headache	Nausea	Diarrhea	Insomnia	Pruritus	Hemolytic Anemia	Cough	Rash	Teratogenicity
Sofosbuvir	X	X								
Ledipasvir/Sofosbuvir	X	X								
Sofosbuvir / Velpatasvir	X	X								
Daclatasvir	X	X	X	X						
Paritaprevir/ Ritonavir/ Ombitasvir/ Dasabuvir	X		X		X	X				
Elbasvir/Grazeprevir	X	X	X							
Ribavirin					X		X	X	X	X

Zepatier Package Insert MED Ireland 1/16; Viekira XR package insert Abbvie 7/16; Harvoni package insert Gilead 6/16; Epclusa package insert Gilead 6/16; Daklinza package insert BMS 4/16.

Ledipasvir/Sofosbuvir Side Effects*

- Serious adverse reactions
  - Symptomatic bradycardia when coadministered with amiodarone (sofosbuvir component)
- Adverse reactions reported in ≥ 5%
  - Fatigue 13-18%
  - Headache 11-17%
  - Nausea 6-9%
  - Insomnia 3-6%

(Package Insert)

Ledipasvir/Sofosbuvir Side Effects*

- Adverse Reactions in Cirrhotics
  - Asthenia (abnormal weakness) 31% vs. 23% placebo
  - Headache 29% vs. 16% placebo
  - Fatigue 18% vs. 1% placebo
  - Cough 5% vs. 1% placebo
  - Myalgia 9% vs. 0% placebo
  - Dyspnea 3% vs. 1% placebo
  - Irritability 8% vs. 1% placebo
  - Dizziness 5% vs. 0% placebo

(Package Insert)

Ledipasvir/Sofosbuvir Side Effects*

- Contraindicated in severe renal impairment (GFR < 30 or dialysis)
  - Causes increased exposure to sofosbuvir

(Package Insert)

Sofosbuvir/Velpatasvir Side Effects

- Serious adverse reactions
  - Symptomatic bradycardia when coadministered with amiodarone (sofosbvir component)
- Adverse reactions reported in ≥ 10%
  - Fatigue
  - Headache
- Contraindicated in severe renal impairment (GFR < 30 or dialysis)
  - Causes increased exposure to sofosbuvir

(Package Insert)

Elbasvir/Grazoprevir Side Effects

- Serious adverse reactions
  - ALT elevations, although usually mild and asymptomatic
    - Discontinuation advised if ALT persist > 10x ULN or if accompanied by signs/sx of liver inflammation, increasing conjugated bilirubin, alkaline phosphatase, or INR
- Adverse reactions reported in ≥ 5%
  - Fatigue 5%
  - Headache 11%
  - Nausea 11%
- Contraindicated in moderate-severe liver dysfunction, Child-Pugh B and C cirrhosis
  - Causes increased grazoprevir exposure

(Merck Package Insert)

Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir Side Effects

- Serious adverse reactions
  - Risk of hepatic failure or decompensation, including fatal outcomes
  - Contraindicated in moderate-severe liver dysfunction, Child-Pugh B and C cirrhosis
  - For patients with cirrhosis:
    - Monitor for clinical signs and symptoms of hepatic decompensation (such as ascites, hepatic encephalopathy, variceal hemorrhage).
    - Hepatic laboratory testing including direct bilirubin levels should be performed at baseline and during the first 4 weeks of starting treatment and as clinically indicated.
    - Discontinue in patients who develop evidence of hepatic decompensation
- ALT elevation >5x ULN in 1%

(AbbVie Package Insert)

Paritaprevir/Ritonavir/Ombitasvir/ Dasabuvir Side Effects

- Adverse reactions
  - Fatigue 34% vs. 26% placebo
  - Nausea 22% vs. 15% placebo
  - Pruritus 18% vs. 7% placebo
  - Skin reactions 16% vs. 9% placebo
  - Insomnia 14% vs. 8% placebo
  - Asthenia (abnormal weakness) 14% vs. 7% placebo

(AbbVie Package Insert)

Daclatasvir Side Effects

- Serious adverse reactions
  - None related to daclatasvir, but be aware of sofosbuvir-amiodarone interaction (symptomatic bradycardia)
- Adverse reactions reported in ≥ 5%
  - Fatigue 14%
  - Headache 14%
  - Nausea 8%
  - Diarrhea 5%

(BMS Package Insert)

Ribavirin Side Effects

- Common: Insomnia, cough, rash
- Serious: Hemolytic anemia (dose-dependent and increased risk with lower GFR/increased exposure)
- Also important: Teratogenic, contraindicated in pregnancy


Case Presentation Revisited
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Case

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- **What elements of her history impact which regimen you choose to treat her with?**

Case

- 56 year-old lady with Genotype 1A Hepatitis C, Treatment-naive
- Noninvasive fibrosis testing consistent with **mild fibrosis**
- Good candidate for treatment
- PMH: Atrial Fibrillation, **Chronic Kidney Disease (GFR ~ 20 mL/min)**
- Medications: ASA, **Amiodarone**

Case (Continued)

- **What elements of her history impact which regimen you choose to treat her with?**
- Mild fibrosis
  - *Protease inhibitors not contraindicated*
- GFR ~ 20 mL/min
  - *Sofosbuvir contraindicated*
- Amiodarone
  - *Sofosbuvir contraindicated*


General Side Effects
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Reactivation of Hepatitis B

- Patients with prior, resolved, or active HBV infection are at risk of reactivation on DAA therapy
- FDA issued black box warning in 2016
  - 24 reactivations reported since 2013
  - 2 died, 1 required liver transplant
- Mechanism of reactivation unknown

http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf

Reactivation of Hepatitis B

- Prior to initiating DAA therapy, test for HBV coinfection with HBsAg, anti-HBs, and anti-HBc
- HBV vaccinate all susceptible patients
- Check HBV DNA PCR in patients who are sAg positive or cAb positive/sAb negative
- Start HBV treatment prior to HCV treatment in those who meet criteria for treatment
- Follow HBV DNA PCR regularly (monthly) in those with low detectable HBV DNA or possibly those who are cAb positive but DNA negative at treatment start

Recurrence of Hepatocellular Carcinoma (HCC)

- HCV eradication is associated with decreased incidence of HCC long-term
- Recent studies have indicated higher risk of HCC recurrence or development of new HCC in the first 4 months following DAA therapy

Recurrence of Hepatocellular Carcinoma (HCC)

Table 1: Studies, which reported naïve HCC or HCC recurrence after receiving direct agent antiviral.

Author, Year	Target Population	HCC Development or Recurrence	Whole Cohort (n)	HCC		Temporal Association Between DAA and HCC Development or Recurrence	Risk of Recurrence–HR (95%IC)*
		Primary End Point		Incidence %	Recurrence %		
Reig, Mariño, 2016 (6)	HCC treated patients with CR	Yes	58	NA	27.6	Yes	NR
Conti, 2016 (7)	HCC treated patients with CR		59		28.8		
	No HCC patients		285	3.16	NA		
Yang, 2016 (9)	Pre-LT patients		18	NA	27.8		
Kozbial, 2016 (8)	No HCC patients		NR		NA		
	HCC patients treated with CR						
Pol, 2016 (10)	HCC patients treated with CR	**No**	189		0.73/100 person-month	**NR**	1.21 (0.62-**2.34)**
	HCC patients treated with CR	Yes	79		1.11/100 person-month		0.41 (0.05-**3.08**)
	LT-patients	**No**	314		2.2	Yes	NR

*Related to patients not receiving DAA. HCC: hepatocellular carcinoma; CR: complete radiologic response; LT: liver transplantation; NR: not reported.
Bruix J. www.hepbcppa.org.

Recurrence of Hepatocellular Carcinoma (HCC)

- Consider completing HCC treatment prior to HCV treatment
- Close surveillance for HCC recurrence in those who have previously been treated
- Lifetime screening for HCC in those with cirrhosis and advanced fibrosis prior to HCV eradication

Summary

- Most DAA side effects are mild and rarely lead to discontinuation
- Sofosbuvir-containing regimens are contraindicated in patients taking amiodarone and those with GFR < 30 or on dialysis
- Protease inhibitor-containing regimens are contraindicated in cirrhotic patients with moderate to severe hepatic dysfunction
- Ribavirin is teratogenic and causes hemolytic anemia that is dose-dependent
- DAA therapy has been associated with HBV reactivation
- The risk of HCC recurrence or de novo HCC may be increased shortly after DAA therapy