AETC AIDS Education & Training Center Program Northeast/Caribbean

HCV TREATMENT UPDATE 2017

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Roadmap

- Basic Epidemiology
- Basics of common HCV Regimens
  - Sofosbuvir/Ledipasvir
  - PrOD
  - Grazoprevir/Elbasvir
- Investigational
  - Abbvie, pangenotypic, dual pill
  - Gilead, Triple pill
  - Merck, Triple pill
- Basic Guidelines, resources
- Handouts?

Hepatitis C Basics: Transmission

- Injection drug use
  - IDU accounts for 60% of transmission of HCV in the US
- Receipt of donated blood, blood products and organs
- Needle-stick injuries in healthcare settings
- Can be transmitted from mother to child during delivery
  - Not transmitted through breast milk
- Sharing personal items contaminated with blood
- Can be transmitted via sexual contact

Center for Disease Control. Viral Hepatitis, located at www.cdc.gov/hepatitis. Accessed 2/12/13; Baldo V. Current Pharmaceutical Design 2008;1646-1656; Albeldawi. Cleveland Clinic Journal of Medicine 2010;616-626.

HCV – Natural Course of Disease

- **Infection with HCV less than 6 months**
  - acute hepatitis

- **For every 100 people infected with HCV**
  - 15-25% of patients spontaneously clear virus
  - 75-85% develop chronic HCV infection
  - 60-70% develop chronic liver disease
  - 5-25% develop cirrhosis after a 20-30 year period
  - 1-5% will die from liver carcinoma

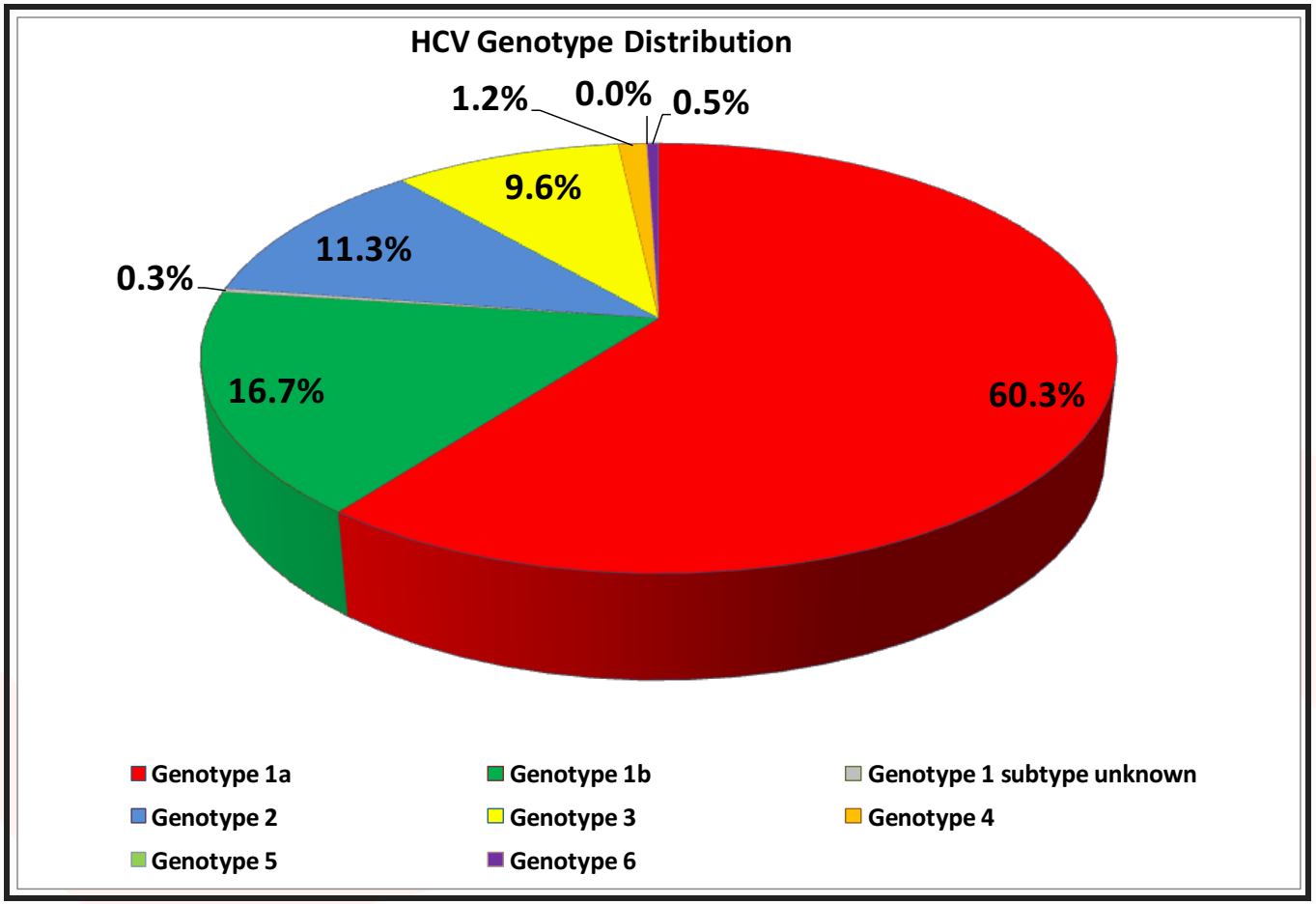
Center for Disease Control. Viral Hepatitis, located at www.cdc.gov/hepatitis. Accessed 2/12/16

HCV – United States Epidemiology

- **4 million estimated to be infected**
- **17,000 new infections annually**
- **1 of 30 baby boomers infected (those born between 1945 and 1965)**
  - 5 times greater incidence than other adults
- **HIV co-infection a problem as well**
  - Up to 90% of HIV+ IVDUs are also HCV co-infected
- **Leading cause of liver transplantation**

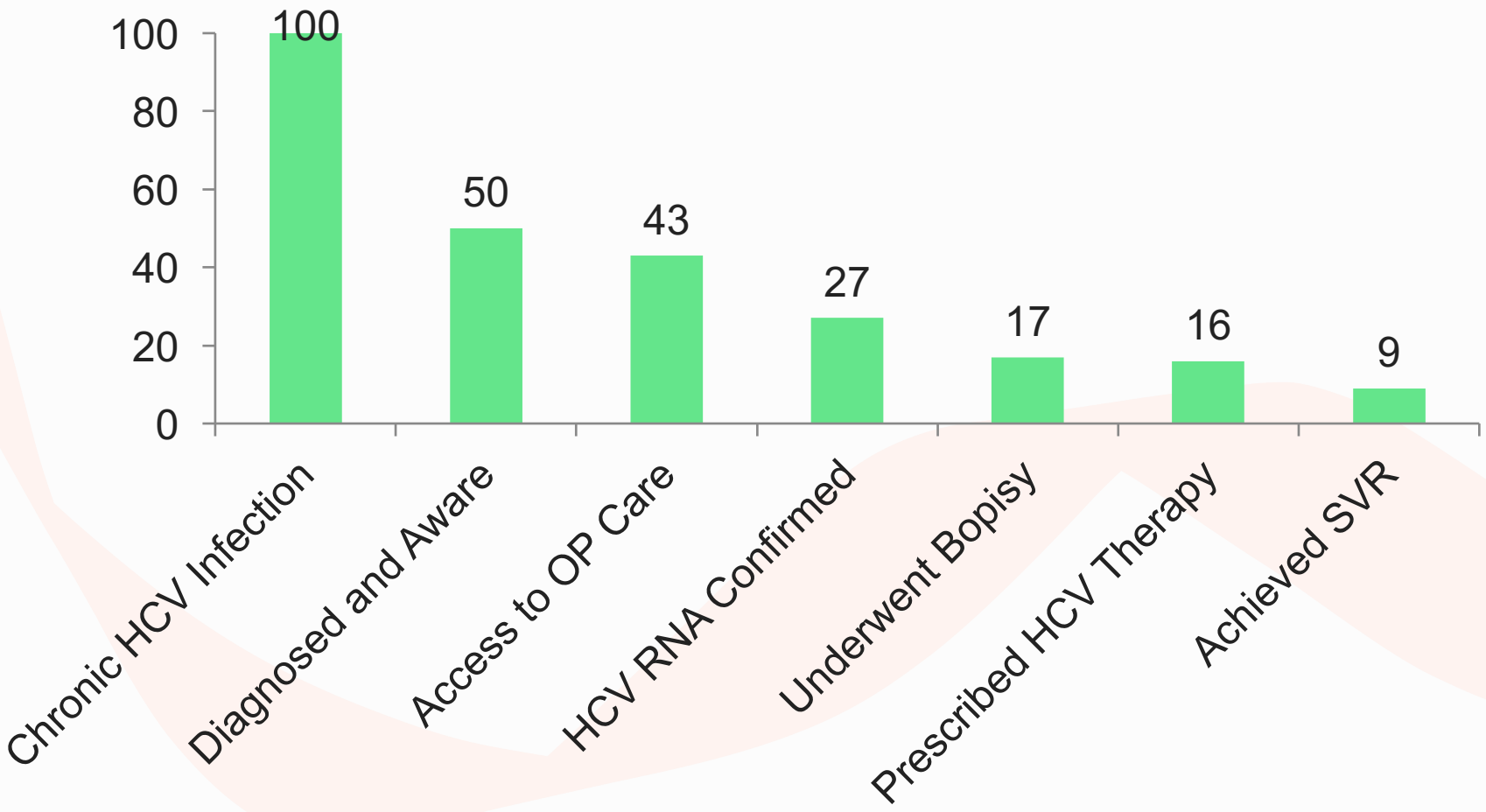
Center for Disease Control. Viral Hepatitis, located at www.cdc.gov/hepatitis. Accessed 2/12/16.

HCV Genotype Distribution in the US



Laboratory Corporation of America. Located at https://www.labcorp.com. Accessed 2/13/13. Antaki N. Liver International 2009;342-355

HCV Care Cascade – United States Data



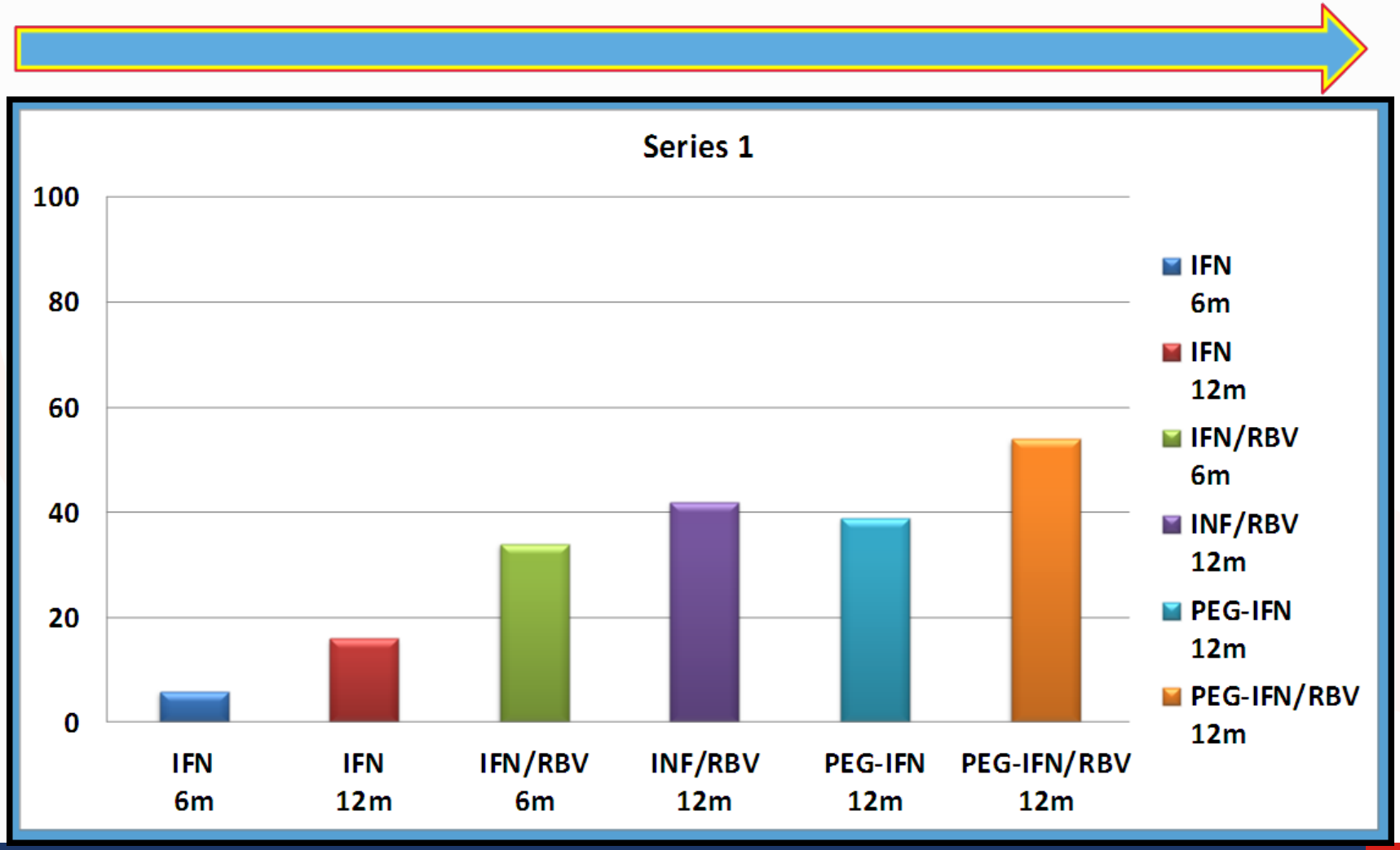
www.natap.org. Accessed 5/10/14

Goals of HCV Therapy

- Prevent complications of HCV infection through eradication of HCV infection
- HCV does not integrate into host genome, so eradication of virus is possible in many cases
- Therapy is not life long and cure is realistic in most cases
- Goal is an SVR – sustained virologic response, defined as an absence of HCV RNA in serum 12 weeks AFTER end of therapy
  - This is considered a cure of HCV

www.hcvguidelines.org. Accessed 5/4/14

Milestones in HCV Treatment



Strader BD et al. Hepatology 2004.;39(4):1147-71.

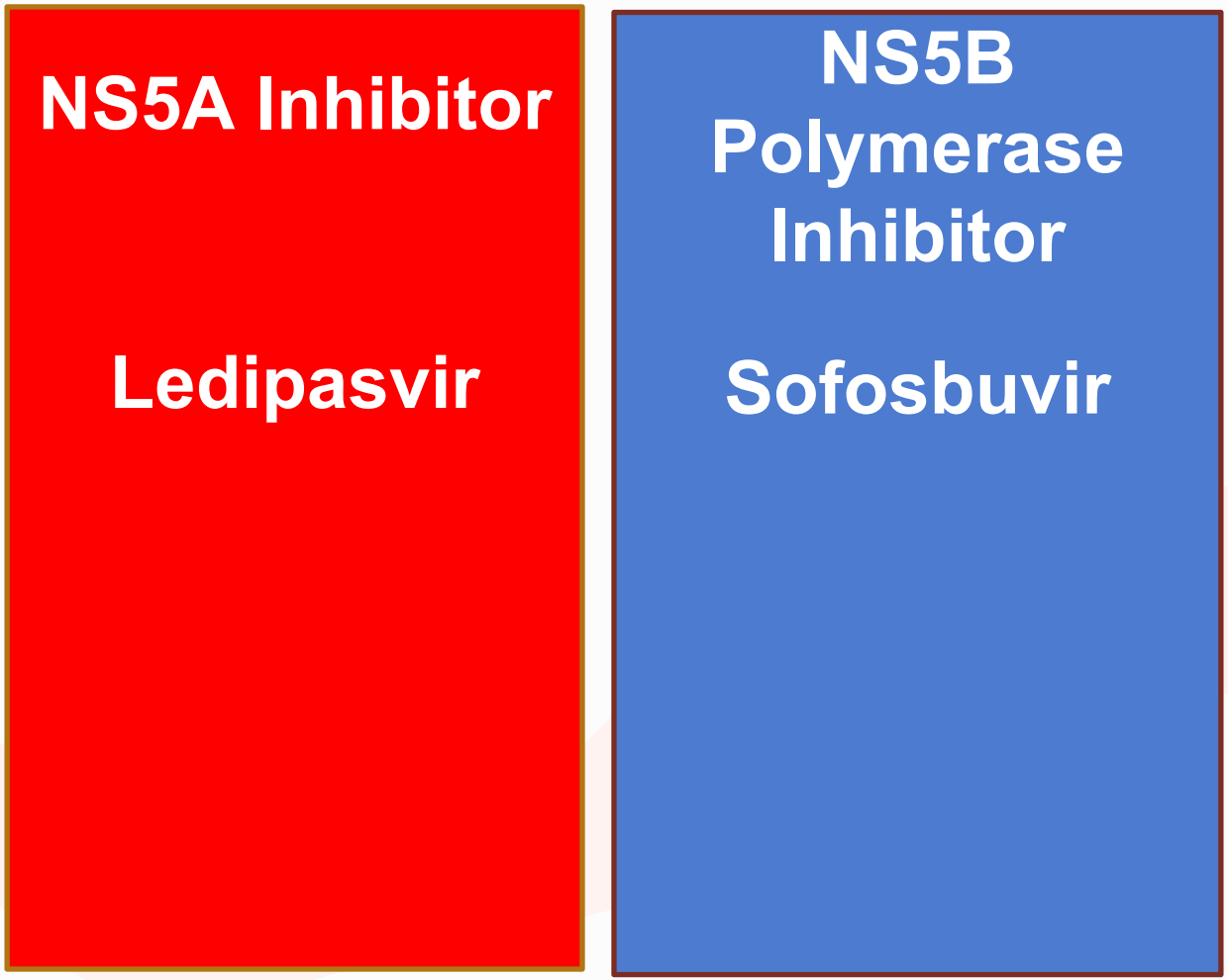
3 Classes of HCV Medications

Current Status	NS3/4a Protease Inhibitors "previr"	NS5A Inhibitors "asvir"	NS5B Polymerase Inhibitors "buvir"
FDA Approved	Simeprevir Paretaprevir/ritonavir* Grazoprevir	Ledipasvir Ombitasvir Daclatasvir Elbasvir Velpatasvir	Sofosbuvir Dasabuvir
Investigational	Glecaprevir Voxilaprevir	Pibrentasvir Ruzasvir	MK-3682
Halted development or removed from market	Boceprevir Telaprevir Faldaprevir Asunaprevir		

* Ritonavir is a pharmacokinetic booster for paretaprevir with no HCV activity

LEDIPASVIR/SOFOSBUVIR

HCV Classes and Medications



Harvoni, Ledipasvir/Sofosbuvir

Ledipasvir/Sofosbuvir, Harvoni

Genotype	Population	Regimen and Duration
1	Naïve, no cirrhosis, compensated cirrhosis	Harvoni, 12 weeks
	Experienced, no cirrhosis	Harvoni, 12 weeks
	Experienced, compensated cirrhosis (CPT A)	Harvoni, 24 weeks
	Naïve or experienced, decompensated cirrhosis, (CPT B or C)	Harvoni + RBV, 12 weeks
1 or 4	Naïve or experienced liver transplant patient, no cirrhosis OR compensated cirrhosis, (CPT A)	Harvoni + RBV, 12 weeks
4,5,6	Naïve or experienced, no cirrhosis OR compensated cirrhosis, (CPT A)	Harvoni, 12 weeks

- FDC, 90mg/400mg - One tablet daily
- FDA approval for HIV/HCV co-infection
- No dosing in CrCl<30ml/min

Relapse Rates Overall and by Baseline Viral Load, ION3

Patients, n (%)	LDV/SOF 8 weeks N=215	LDV/SOF+RBV 8 weeks N=216	LDV/SOF 12 weeks N=216
Overall SVR12	94% (202/215)	93% (201/216)	96% (208/216)
Overall Relapse Rate	5% (11/215)	4% (9/216)	1% (3/216)
SVR by baseline VL			
HCV RNA < 6M IU/mL	97% (119/123)	96% (133/138)	96% (126/131)
HCV RNA ≥ 6M IU/mL	90% (83/92)	87% (68/78)	96% (82/85)
Relapse Rates by baseline VL			
HCV RNA < 6M IU/mL	2% (2/123)	2% (3/137)	2% (2/131)
HCV RNA ≥ 6M IU/mL	10% (9/92)	8% (6/77)	1% (1/85)
SVR by baseline VL			
HCV RNA < 10M IU/mL	96% (156/163)	94% (160/171)	96% (160/166)
HCV RNA ≥ 10M IU/mL	88% (9/92)	91% (41/45)	96% (48/50)
Relapse Rates by baseline VL			
HCV RNA < 10M IU/mL	3% (5/163)	4% (7/169)	1% (2/166)
HCV RNA ≥ 10M IU/mL	12% (6/52)	4% (2/45)	2% (1/50)

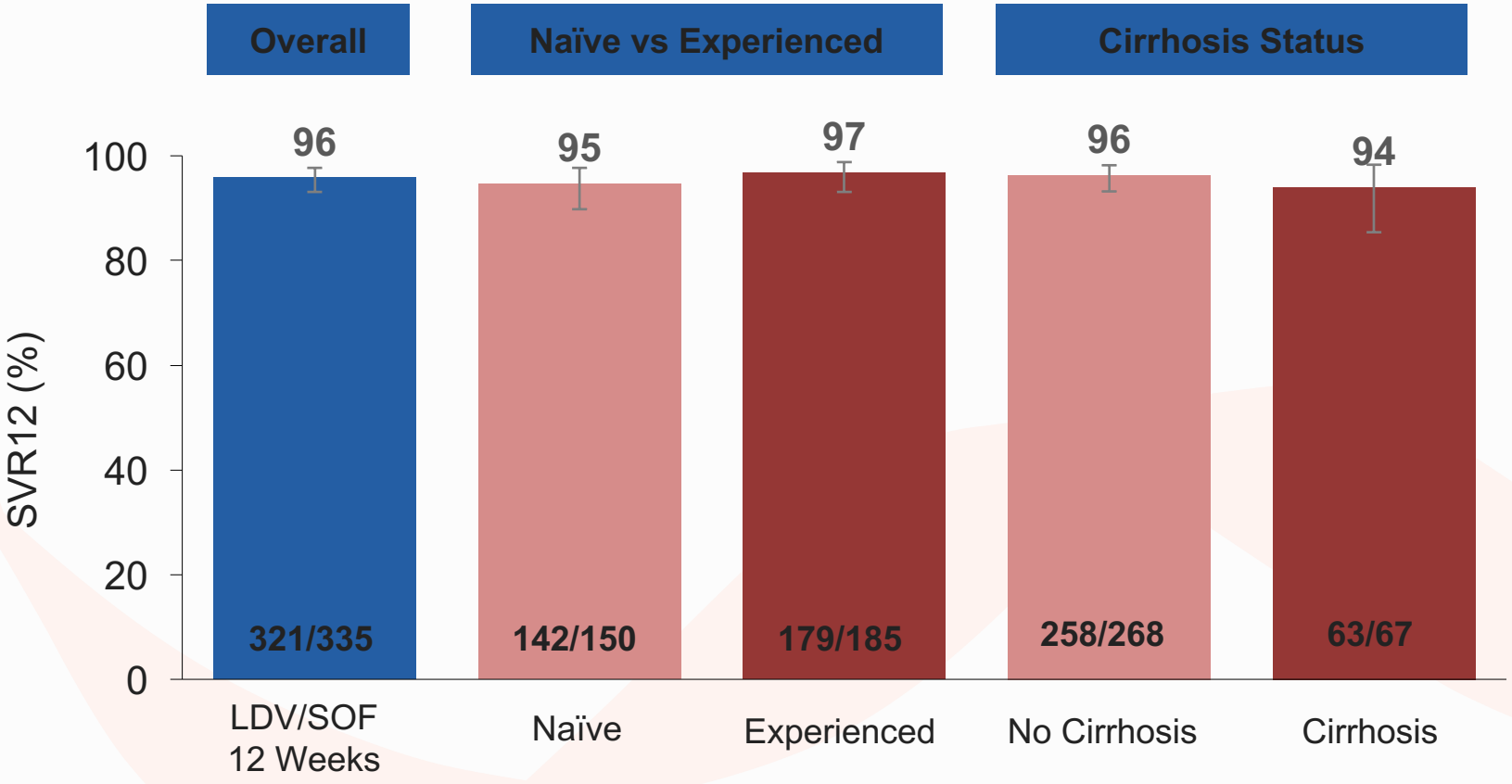
HARVONI® [PI]. Gilead Sciences, Inc. Foster City, CA 2015. Kowdley K, EASL, 2014, O56, Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888, Data on File, Gilead Sciences

ION4, Ledipasvir/Sofosbuvir in HIV/HCV co-infection

- ION 4 study evaluated the role of ledipasvir/sofosbuvir in 335 HIV/HCV co-infected patients
- Baseline characteristics
  - 82% male
  - 34% black
  - 98% genotype 1, rest were genotype 4
  - 55% treatment experienced with either PEG/RBV alone or with a PI or prior sofosbuvir use

Naggie B, et al. 2015 Conference on Retroviruses and Opportunistic Infections. Seattle, February 23-24, 2015. Abstract 152LB

Results: SVR12 by Prior Treatment Experience and Cirrhosis Status
HIV-HCV (ION-4)



Error bars represent 95% confidence intervals.

Ledipasvir/Sofosbuvir, ADR(%), All Grades, >5% patients

	8 Weeks	12 Weeks	24 Weeks
	n=215	n=539	n=326
Fatigue	16	13	18
Headache	11	14	17
Nausea	6	7	9
Diarrhea	4	3	7
Insomnia	3	5	6

Harvoni PI, 2016

Ledipasvir/Sofosbuvir – Medications to Avoid

Antiarrythmics, Anticonvulsants/Antimycobacterials	
Carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin	Coadministration not recommended.
HCV Products	
Simeprevir	Coadministration not recommended.
Herbal Supplements	
St. John's wort (Hypericum perforatum)	Coadministration not recommended.
HMG-CoA Reductase Inhibitors	
Rosuvastatin	Coadministration not recommended.

Harvoni PI, 2016, www.nynjaetc.org

Ledipasvir/Sofosbuvir – Medications with Dose Changes/Monitoring

Acid Reducing Agents	
Antacids	Separate antacids and sofosbuvir/ledipasvir administration by 4 hours.
H2-receptor antagonists	Administer simultaneously with or 12 hours apart from sofosbuvir/ledipasvir. Do not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors	Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with sofosbuvir/ledipasvir under fasted conditions.
Antiarrhythmics	
Digoxin	Coadministration of sofosbuvir/ledipasvir with digoxin may increase the concentration of digoxin. Monitor digoxin levels.

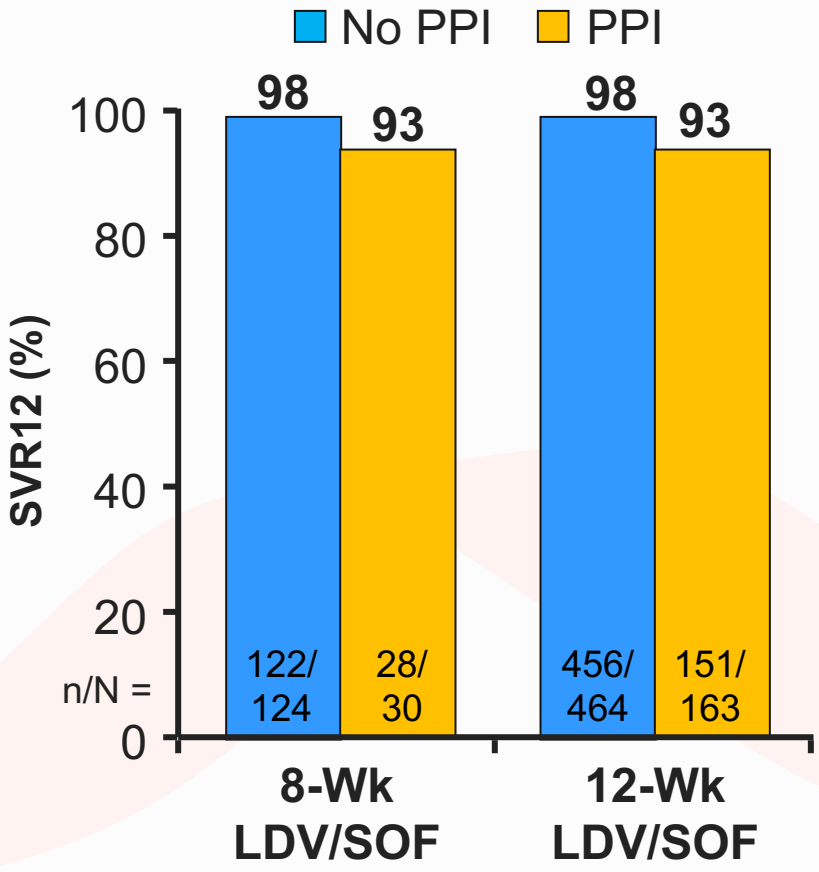
Harvoni PI, 2016

Amiodarone – Harvoni Interaction

- Post marketing reports described
- Significant bradycardia documented, key factors include
  - Patients on beta-blockers
  - Underlying cardiac abnormalities
  - Advanced liver disease
- Co-administration not recommended. If concurrent use required, cardiac monitoring is recommended, see package insert for additional information.

HCV-TARGET: SVR by PPI Use

- Antacids (e.g., aluminum and magnesium hydroxide)
  - separate by 4 hours
- H2-receptor antagonists (e.g., famotidine)
  - Simultaneously with or 12 hours apart
  - Doses comparable to famotidine 40 mg BID
- Proton-pump inhibitors (e.g., omeprazole)
  - Doses comparable to omeprazole 20 mg or lower simultaneously with HARVONI under fasted conditions.
- High doses ie: 40mg BID not recommended



Terrault N, et al. AASLD 2015. Abstract 94, Harvoni PI, 2016.

HIV Meds/Regimens with LDV/SOF – No Significant Interaction

- NRTIs
  - Abacavir/lamivudine
  - Tenofovir dioproxil/emtricitabine, tenofovir alafenamide
- NNRTIs
  - Efavirenz
  - Rilpivirine (if NOT on a proton pump inhibitor) also Complera, Odefsey
  - Others no data, probably OK
- INSTI – Based
  - Raltegravir
  - Dolutegravir
  - Genvoya
- Boosted PIs
  - OK unless with Tenofovir DF, consider changing therapy to TAF

HIV Meds/Regimens to be AVOIDED LED/SOF

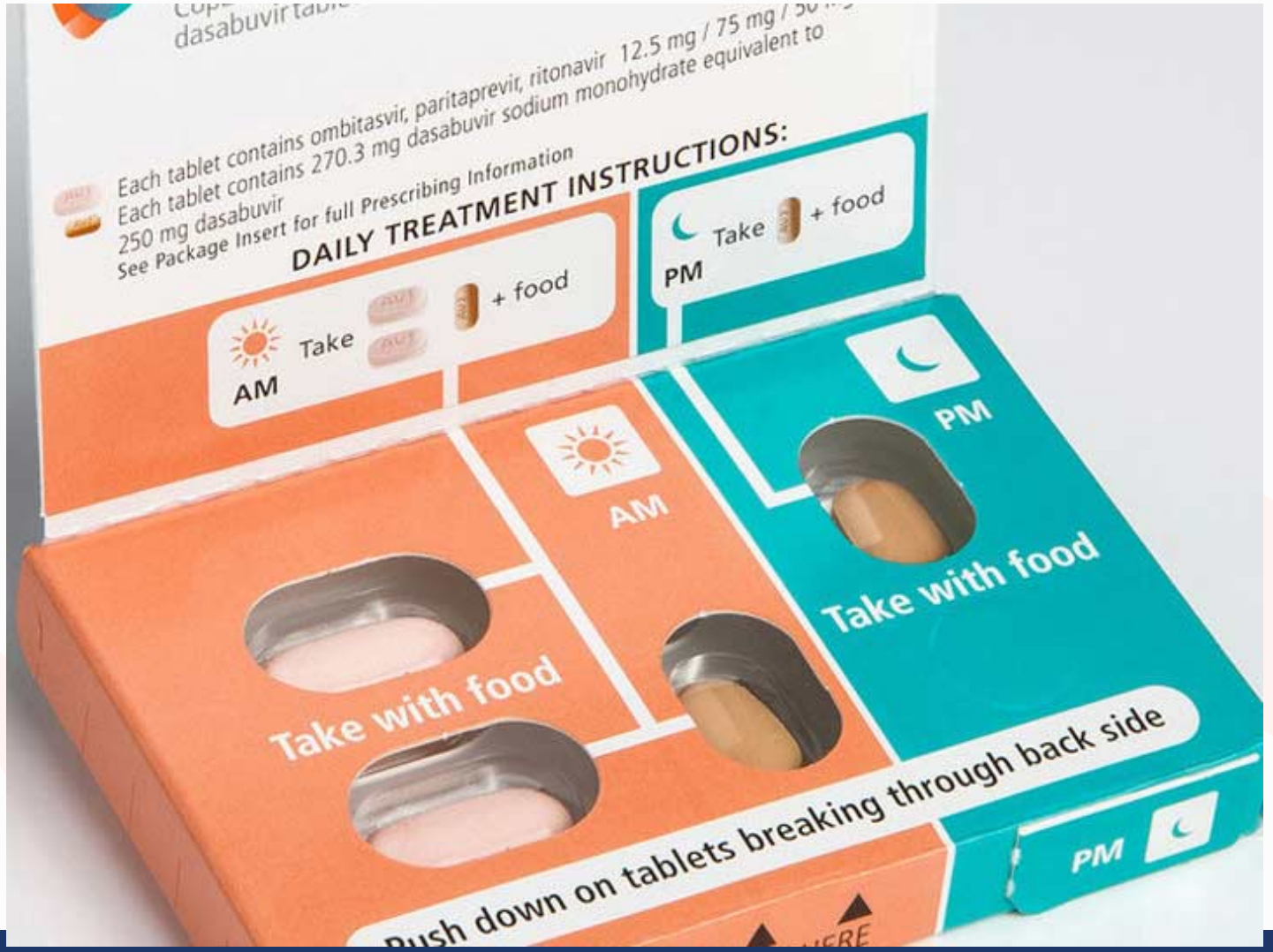
- CAN NOT OR WOULD NOT USE the following
  - Tipranavir/ritonavir
  - Stribild

PROD, VIEKERA

HCV Classes and Medications

NS3/4a Protease Inhibitor	NS5A Inhibitor	NS5B Polymerase Inhibitor
Paretaprevir with ritonavir	ombitasvir	dasabuvir

PrOD (Viekira) Packaging



Viekira XR


viekira XR™
NDC 0074-0063-28 Rx only
(dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended-release tablets
200 mg/8.33 mg/50 mg/33.33 mg
Each VIEKIRA XR tablet contains 200 mg of dasabuvir equivalent to 216.2 mg of dasabuvir sodium monohydrate, 8.33 mg of ombitasvir, 50 mg of paritaprevir, and 33.33 mg of ritonavir
Do not split, crush or chew tablets
See Package Insert for full Prescribing Information
DAILY TREATMENT INSTRUCTIONS:
Take all 3 tablets once daily at the same time with a meal
Take all 3 tablets at the same time with a meal
Push down on tablets breaking through back side
LIFT HERE

PrOD Regimen – FDA Approved

Population	Treatment	Duration
Genotype 1a, non cirrhotic	Ombitasvir/paretaprevir/ritonavir + dasabuvir + RBV	12 weeks
Genotype 1a, cirrhotic	Ombitasvir/paretaprevir/ritonavir + dasabuvir + RBV	24 weeks
Genotype 1b, non cirrhotic	Ombitasvir/paretaprevir/ritonavir + dasabuvir	12 weeks
Genotype 1b, cirrhotic	Ombitasvir/paretaprevir/ritonavir + dasabuvir	12 weeks

- **Avoid in hepatic decompensation**
- Take with food – without regard to fat or content
- No dose change in renal impairment
- Fatigue, nausea, pruritus, rash, insomnia, asthenia

Product Information, Viekera Pak. AbbVie 2016.

Viekira Results

Table 1. Response rates among patients with respect to cirrhosis and subtype

Study	Regimen	% SVR12 ATTAINMENT			
		No cirrhosis		Cirrhosis	
		1a	1b	1a	1b
▶ SAPPHIRE-I	VP + RBV x 12 weeks, naïve	95%	98%	-	-
▶ SAPPHIRE-II	VP + RBV x 12 weeks, experienced	96%	96%	-	-
▶ PEARL-III, PEARL-IV	VP + RBV x 12 weeks, naïve	97%	99%		
	VP x 12 weeks, naïve	90%	99%	-	
▶ TURQUOISE-II	VP + RBV x 12 weeks	-	-	88%	98%
	VP + RBV x 24 weeks	-	-	94%	100%

VP, Viekira Pak; RBV, ribavirin

Source: Molloy L

Viekira, Technivie - Hepatotoxicity

FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie

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[10-22-2015]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is warning that hepatitis C treatments Viekira Pak and Technivie can cause serious liver injury mostly in patients with underlying advanced liver disease. As a result, we are requiring the manufacturer to add new information about this safety risk to the drug labels.

Patients taking these medicines should contact their health care professional immediately if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools, as these may be signs of liver injury. Patients should not stop taking these medicines without first talking to their health care professionals. Stopping treatment early could result in drug resistance to other hepatitis C medicines. Health care professionals should closely monitor for signs and symptoms of worsening liver disease, such as ascites, hepatic encephalopathy, variceal hemorrhage, and/or increases in direct bilirubin in the blood.

Viekira Pak and Technivie are used to treat chronic hepatitis C, a viral infection that can last a lifetime and lead to serious liver and other health problems, including cirrhosis, liver cancer, and death. These medicines reduce the amount of hepatitis C virus in the body by preventing it from multiplying and may slow down the disease.

Our review of adverse events reported to the FDA Adverse Event Reporting System (FAERS) database and to the manufacturer of these medicines, AbbVie, identified cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis who were taking these medicines. Some of these events resulted in liver transplantation or death. These serious outcomes were reported mostly in patients taking Viekira Pak who had

New Label Change

Viekera

Technivie

Contraindicated in Childs Class B and C

Product Information, Viekera Pak. AbbVie 2016014.

Details of Events

- Cases of hepatic decompensation and liver failure in patients with underlying liver cirrhosis who were taking these medicines
- Some resulted in liver transplantation or death, mostly in patients taking Viekira Pak who had evidence of advanced cirrhosis even before starting treatment
- From December 2014 at least 26 worldwide cases submitted to FAERS were considered to be possibly or probably related to Viekira Pak or Technivie
- In most cases, liver injury occurred within 1 to 4 weeks of starting treatment. Some of the cases occurred in patients for whom these medicines were contraindicated or not recommended

Product Information, Viekera Pak. AbbVie 2016.

Viekira Pak, Contraindicated Meds

Medication and or Class
Alpha 1-antagonist (alfluzosin)
Anticonvulsants (carbamazepine, phenytoin, phenobarbital)
Antifungal (voriconazole)
Antihyperlipidemic (gemfibrozil)
Antimycobacterial (rifampin)
Beta adrenoceptor agonist (long acting salmeterol)
Corticosteroids (inhaled or nasal fluticasone)
Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)
Ethinyl estradiol containing products (Oral contraceptives)
Herbal therapy (St. Johns Wort)
HMG-CoA reductase inhibitors (lovastatin, simvastatin)
Neuroleptic (pimozide)
Phosphodiesterase-5 inhibitor (sildenafil in Pulmonary Arterial Hypertension
Sedative/hypnotics (oral midazolam, triazolam)

Product Information, Viekera Pak. AbbVie 2016014.

PrOD Medications Requiring Adjustments

Medication and or Class	Recommendation and Clinical Comment
Antiarrythmics (amiodarone, bepredil, disopyramide, flecainide, lidocaine, mexilitine, propafenone, quinidine	• Caution with concurrent use. Therapeutic concentration monitoring recommended if available when used with ombitasvir/paritaprevir/ritonavir and dasabuvir.
Antifungal (ketoconazole)	• When using ketoconazole with ombitasvir/paritaprevir/ritonavir and dasabuvir, the dose of ketoconazole should not exceed 200mg daily.
Calcium channel blocker (amlodipine)	• Consider dosage reduction for amlodipine; monitor closely for hypotension.
Diuretic (furosemide)	• Possible increase in furosemide levels; monitor closely based upon response.
HMG-CoA reductase inhibitors (atorvastatin, pravastatin and rosuvastatin)	• Increase in atorvastatin, pravastatin and rosuvastatin likely requiring dosage limitations. Do not exceed atorvastatin 20mg, pravastatin 40mg, or rosuvastatin 10mg with concurrent use of ombitasvir/paritaprevir/ritonavir and dasabuvir.
Immunosuppressants (cyclosporine, tacrolimus)	• See Label

Product Information, Viekira Pak, December 2016.

PrOD Medications Requiring Adjustments

Medication and or Class	Recommendation and Clinical Comment
Narcotic analgesics (buprenorphine/naloxone)	No dosage adjustment is required, however monitoring for sedation is appropriate.
Phosphodiesterase-5 inhibitor (when used for erectile dysfunction)	If patients receiving sildenafil for erectile dysfunction, recommended dose is 25mg maxiumum in a 48 hour period. In patients receiving tadalafil for erectile dysfunction, recommended dose is 10mg maximum in a 72 hour period. In patients receiving vardenafil for erectile dysfunction, recommended dose is 2.5mg
Proton pump inhibitor (omeprazole)	Monitor for decreased efficacy of omeprazole. Consider increasing omeprazole dose in patients not well controlled. Do not exceed omeprazole 40mg daily.
Sedative/hypnotic (alprazolam)	Monitor for excess sedation. Decrease in alprazolam dose can be considered based upon response.

Product Information, Viekira Pak, December 2016.

Viekira Pak and HIV Medications

- Dolutegravir, raltegravir – YES
- Atazanavir – YES, stop extra ritonavir
- Emtricitabine/tenofovir – YES

- Efavirenz – NO, poor tolerability, LFTs
- Darunavir – NO, lower troughs
- Lopinavir/ritonavir – NO, lower paritaprevir
- No data on other meds

Product Information, Viekera Pak. AbbVie 2016.

ELBASVIR/GRAZOPREVIR

HCV Classes and Medications

NS3/4a Protease Inhibitors

Grazoprevir

NS5A Inhibitors

Elbasvir

Zepatier – Approved late January 2016

- Elbasvir/grazopevir, NS5A and NS3/4a PI combination
- Approved for GT1a,1b and 4
- Regimens with or without ribavirin, 12 or 16 weeks depending on Tx experience, BL mutations and GT, see label
- **One daily dosing, no adjustment needed in renal impairment, dialysis**
- NS5A resistance testing required at baseline - mutations at positions 29,30,31,93 reduce response rates

Product Information, Zepatier, Merck, 2016.

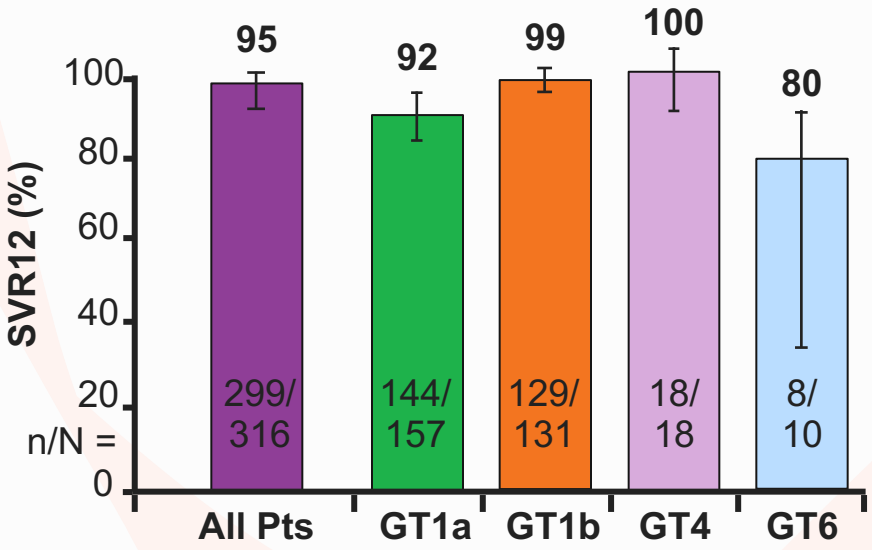
RAV Testing and ELB/GRZ

- NS5A RAVs identified at baseline in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study
  - 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RAVs
- Among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures.
- NS5A resistance testing is recommended in genotype 1a patients who are being considered for therapy with elbasvir/grazoprevir.
- If RAVs at AA positions 28, 30, 31, or 93, treatment extension to 16 weeks with the addition of weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥ 75 kg]) is recommended to decrease relapse.

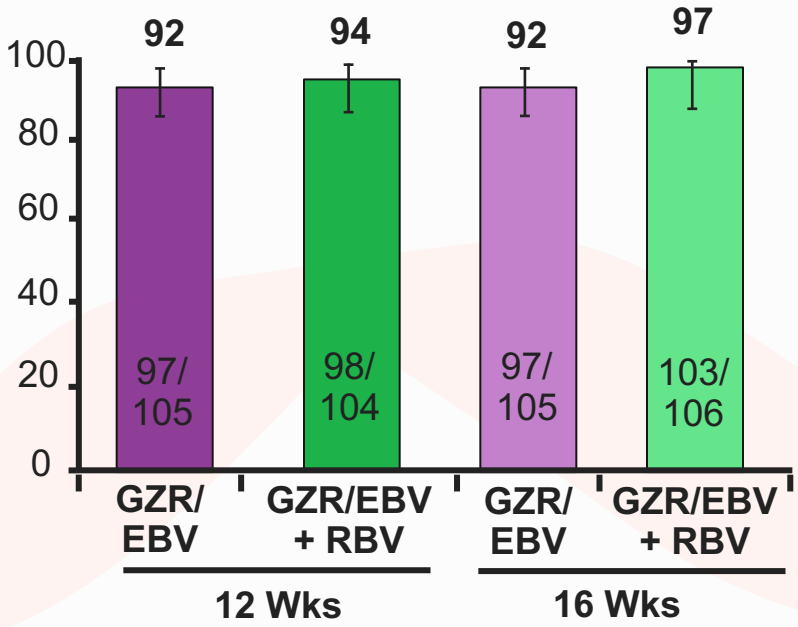
Product Information, Zepatier, Merck, 2016.

C-EDGE: Grazoprevir/Elbasvir for Tx-Naive and Tx-Experienced Pts

Tx-Naive: Grazoprevir/Elbasvir for 12 Wks in GT1, 4, or 6 HCV[1]

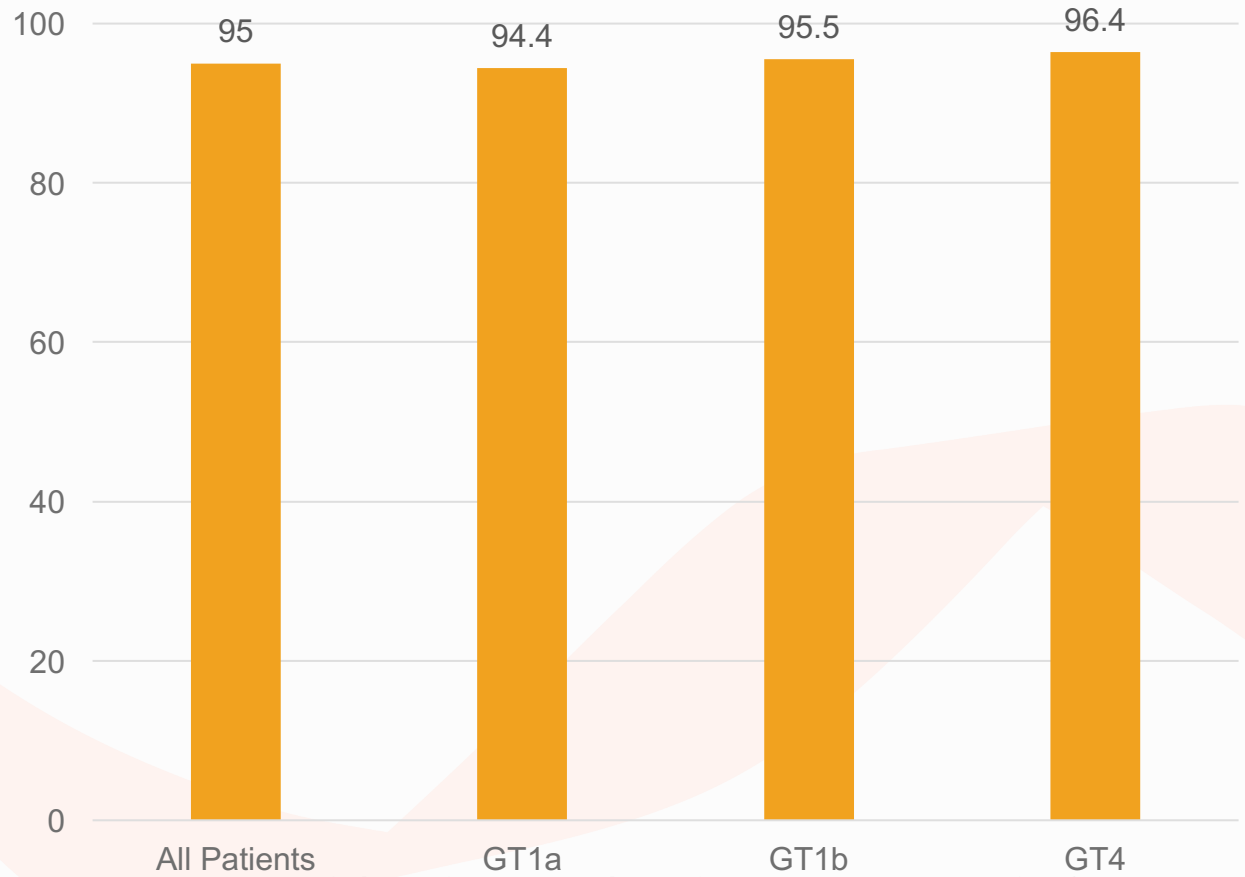


Tx-Exp'd: Grazoprevir/Elbasvir ± RBV for 12 or 16 Wks in GT1, 4, or 6 HCV[2]



1. Zeuzem Z, et al. EASL 2015. Abstract G07. 2. Kwo P, et al. EASL 2015. Abstract P0886.

HCV, GT1, ELB/GRZ for 12 Weeks, HIV/HCV, Tx Naïve, SVR12%



Compatible ARVs: ABC/3TC, TDF/FTC, + RAL, DTG OR RLP

EASL, 2015

Zepatier – Approved January 2016

- LFT monitoring (for ALT flares) - BL, 8 and 12 weeks (if using 16 weeks)
- ADRS - nausea, headache, fatigue
- NO HIV PIs allowed
- NO Efavirenz allowed, avoid etravirine as well
- NO Stribild or Genvoya
- Only HIV regimens/medications allowed are Rilpivirine, Dolutegravir, Raltegravir, TDF/FTC, ABC/3TC

Product Information, Zepatier, Merck, 2016.

GRZ/ELB Drug Interactions

Medication and or Class	Recommendation and Clinical Comments
Antibiotics – nafcillin	• Decreased concentrations of elbasvir/grazoprevir levels expected. Co-administration not recommended.
Anticonvulsants – carbamazepine, phenytoin	• Significant decrease in elbasvir/grazoprevir levels expected. Co-administration not recommended.
Antifungals – ketoconazole	• Significant increase in elbasvir/grazoprevir levels expected, increasing risk of hepatotoxicity. Co-administration not recommended.
Antimycobacterials – rifampin	• Significant decrease in elbasvir/grazoprevir levels expected. Co-administration not recommended.
Endothelin Antagonists – bosentan	• Significant decrease in elbasvir/grazoprevir levels expected. Co-administration not recommended.
Herbal products – St. John's Wort	• Significant decrease in elbasvir/grazoprevir levels expected. Co-administration not recommended.

Product Information, Zepatier, Merck, 2016.

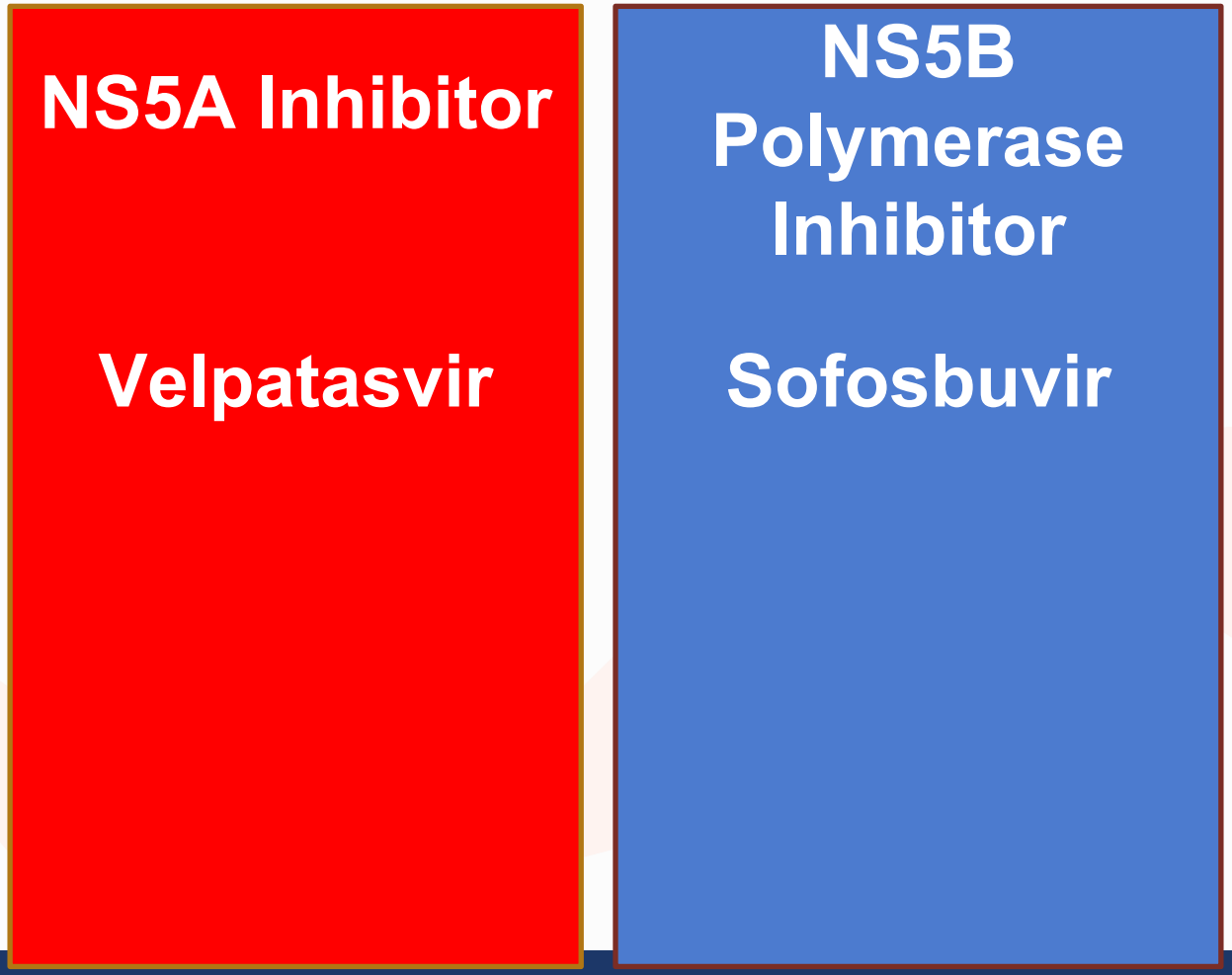
GRZ/ELB Drug Interactions

Medication and or Class	Recommendation and Clinical Comments
HMG-CoA Reductase Inhibitors – atorvastatin, rosuvastatin, fluvastatin, lovastatin, simvastatin	• Increased statin levels expected with concurrent use of elbasvir/grazoprevir. When using together: • Do not exceed atorvastatin 20mg daily • Do not exceed rosuvastatin 10mg daily • Use lowest doses and titrate with close monitoring for fluvastatin, lovastatin, simvastatin
Immunosuppressants – cyclosporine	• Significant increase in grazoprevir levels which may lead to hepatotoxicity. Co-administration not recommended.
Immunosuppressants – tacrolimus	• Significant increase in tacrolimus levels expected. Frequent monitoring for tacrolimus, changes in renal function, and tacrolimus associated adverse events recommended.
Wakefulness- Promoting Agents – modafanil	• Significant decrease in elbasvir/grazoprevir levels expected. Co-administration not recommended.

Product Information, Zepatier, Merck, 2016.

VELPATASVIR/SOFOSBUVIR

HCV Classes and Medications



Sofosbuvir 400mg/Velpatasvir 100mg (Epclusa) Indications and Dosing

- **INDICATIONS AND USAGE**
  - Indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection
  - without cirrhosis or with compensated cirrhosis
  - with decompensated cirrhosis for use in combination with ribavirin

- **DOSAGE AND ADMINISTRATION**
  - Recommended dosage: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food (2.1)

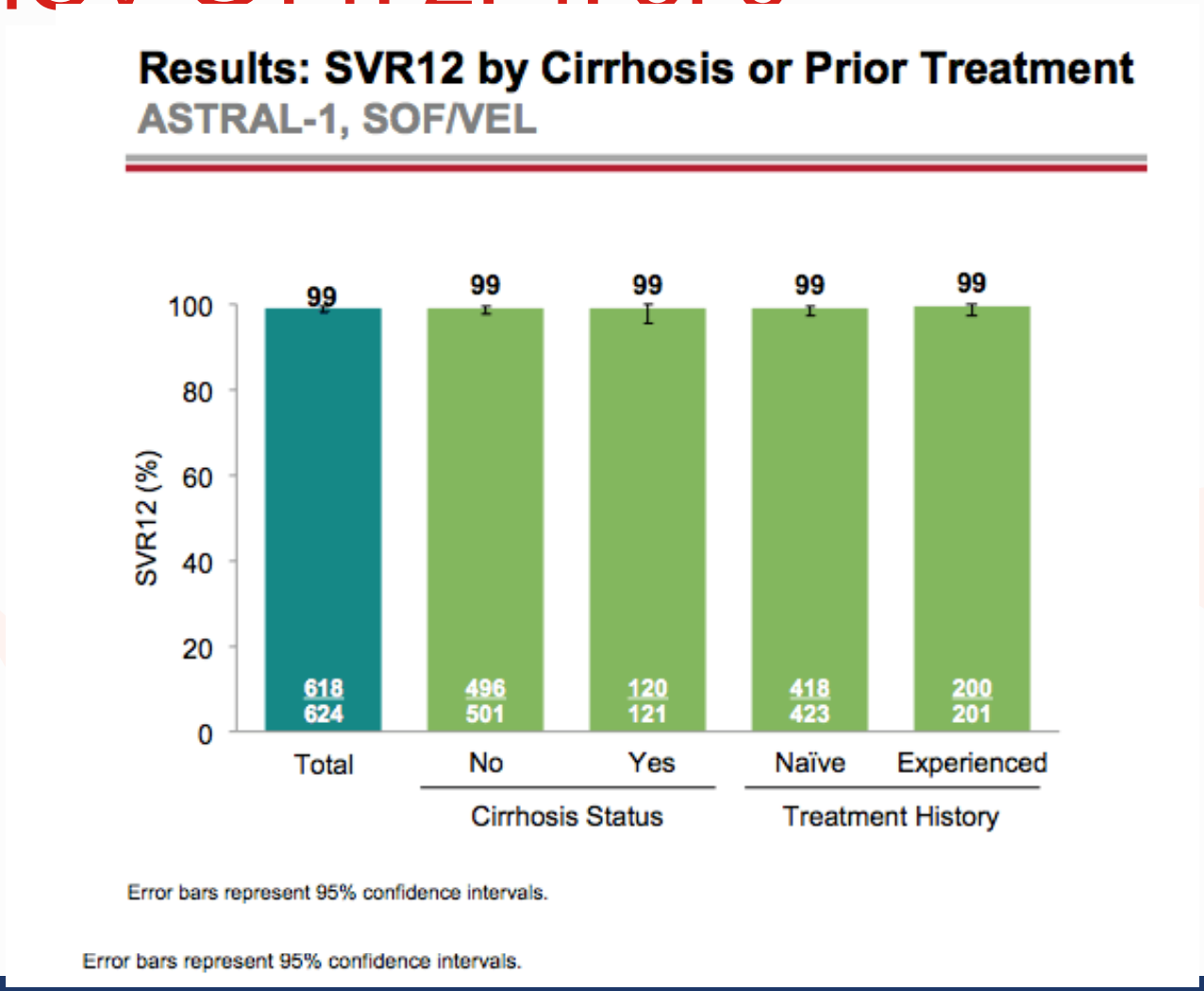
Product Information, Epclusa, Gilead, 2016

Sofosbuvir 400mg/Velpatasvir 100mg (Epclusa) Indications and Dosing

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	EPCLUSA for 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B and C)	EPCLUSA + ribavirin for 12 weeks

Product Information, Epclusa, Gilead, 2016

ASTRAL 1: Sofosbuvir/Velpatasvir, HCV GT1, 2, 4, 5, 6



Error bars represent 95% confidence intervals.

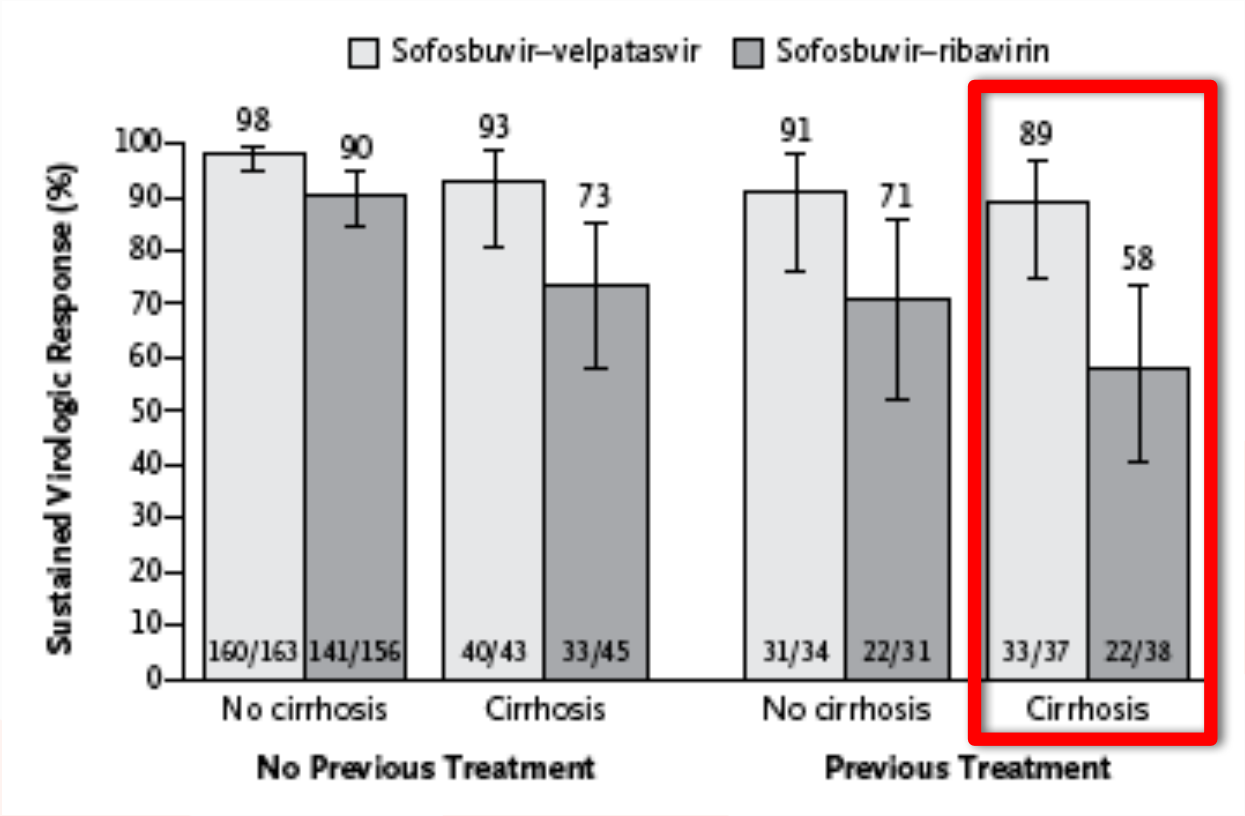
Feld JJ, Jacobson IM, Hezode C, et al. N Engl J Med 2015; 373:2599-2607.

ASTRAL-1: Safety of Sofosbuvir/ Velpatasvir in GT1, 2, 4, 5, 6 HCV

Safety Outcome, %	Placebo 12 Wks (n = 116)	Sofosbuvir/Velpatasvir 12 Wks (n = 624)
Any AE	77	78
Grade 3/4 AE	< 1	3
Serious AE	0	2
Discontinuation for AE	2	< 1
Death	0	< 1*
Laboratory abnormalities		
▪ Grade 3/4	12	7
▪ Hemoglobin < 10 g/dL	0	< 1
AEs in ≥ 10% pts		
▪ Headache	28	29
▪ Fatigue	20	20
▪ Nasopharyngitis	10	13
▪ Nausea	11	12

Feld JJ, Jacobson IM, Hezode C, et al. N Engl J Med 2015; 373:2599-2607.

ASTRAL 3: Sofosbuvir/Velpatasvir, HCV GT3 Results



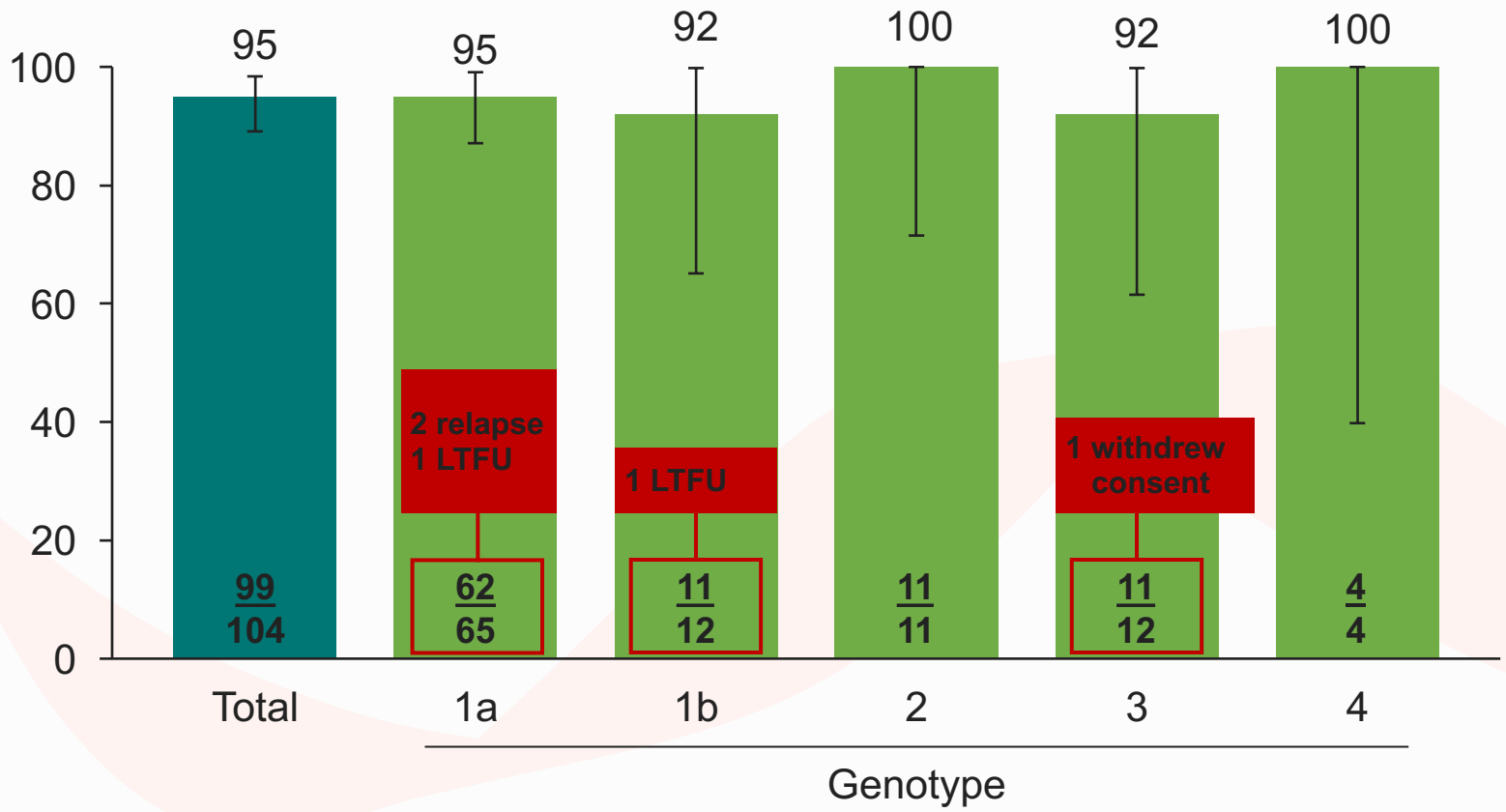
Foster GR, Afdhal N, Roberts SK, et al. N Engl J Med 2015; 373:2608-2617.

ASTRAL 5 Results: HIV Co-Infection

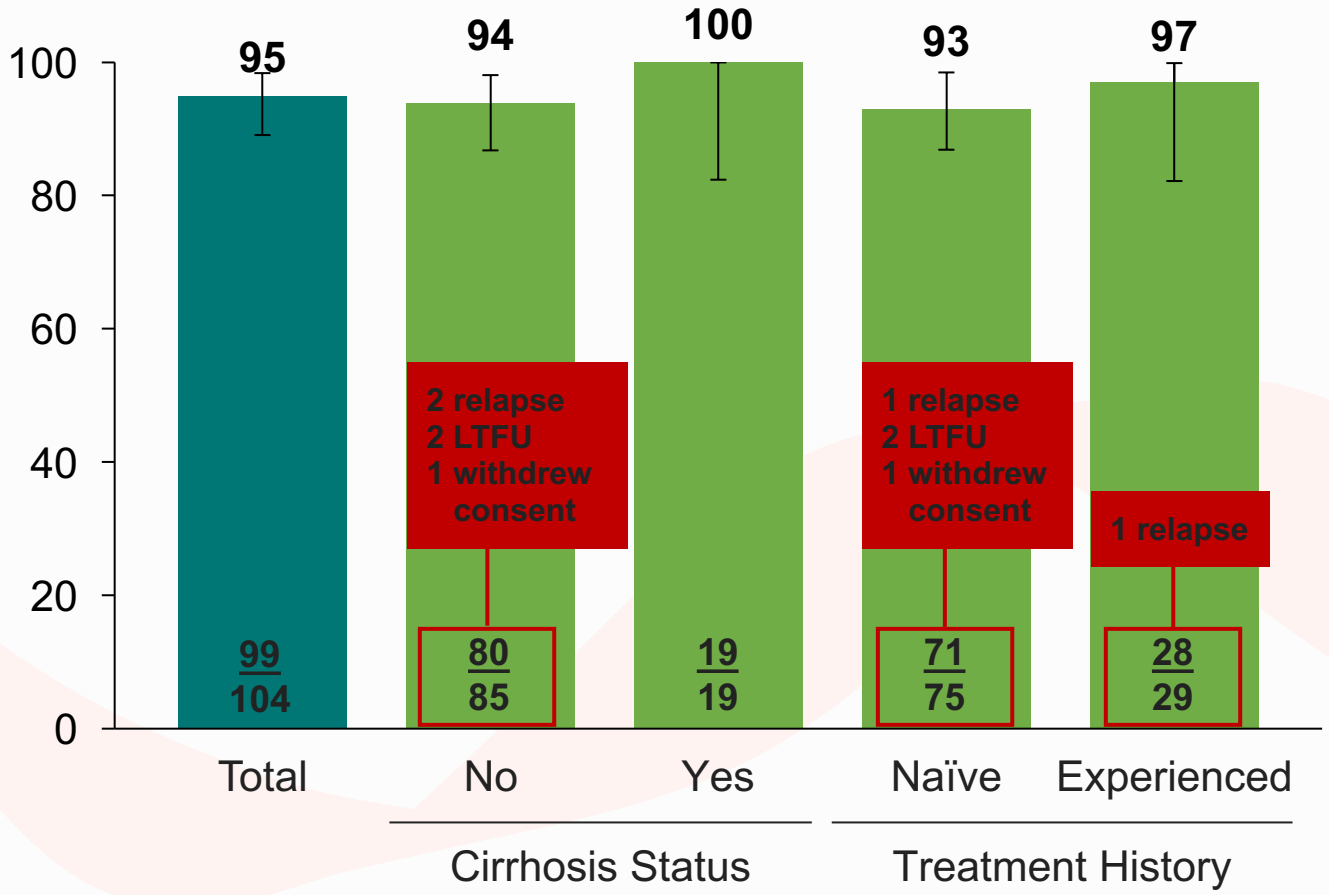
	SOF/VEL n=106
Mean CD4 count, cells/μL (range)	598 (183–1513)
NRTI backbone	
TDF-based with boosted agent (RTV or COBI)	56 (53)
TDF-based without boosted agent	35 (33)
ABC/3TC-base	15 (14)
ART use at baseline	
PI (DRV, LPV or ATV)	50 (47)
NNRTI (RPV)	13 (12)
Integrase inhibitor (RAL or EVG)	36 (34)
Other (>1 of the above classes)	7 (7)

Wyles D, et al. EASL 2016, Barcelona

ASTRAL 5 Results: SVR12 by GT



Astral 5 Results: SVR 12 by Cirrhosis or Prior Treatment



Error bars represent 95% confidence intervals.

Drug Interactions, SOF/VEL

Medication and or Class	Recommendation and Clinical Comment
Antacids	• Separate antacids and sofosbuvir/velpatasvir administration by 4 hours.
H2-receptor antagonists	• Administer simultaneously with or 12 hours apart from sofosbuvir/velpatasvir. Do not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors	• Co-administration not recommended. If required, sofosbuvir/velpatasvir should be administered with food and taken 4 hours before omeprazole 20mg. Use with other proton pump inhibitors have not been studied.
Antiarrhythmic – Amiodarone	• Significant bradycardia expected with concurrent use. Co-administration not recommended. If concurrent use required, cardiac monitoring is recommended, see package insert for additional information.
Anticonvulsants – carbamazepine, oxcarbazepine, phenobarbital, phenytoin	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.

Product Information, Epclusa, Gilead, 2016

Drug Interactions, SOF/VEL

Medication and or Class	Recommendation and Clinical Comment
Antimycobacterials – rifampin, rifabutin, rifapentine	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.
Digoxin	• Increase in digoxin levels possible. Monitor digoxin levels.
Herbal products – St. John's Wort	• Significant decrease in sofosbuvir/velpatasvir levels expected. Co-administration not recommended.
HMG Co-A Reductase Inhibitors: Atorvastatin, Rosuvastatin	• Increase in atorvastatin likely with sofosbuvir/velpatasvir; monitor for signs of myopathy and rhabdomyolysis. • Significant increase in rosuvastatin levels when used with sofosbuvir/velpatasvir leading to increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be used at a dose that does not exceed 10mg.

Product Information, Epclusa, Gilead, 2016

Drug Interactions, SOF/VEL and HIV Medications

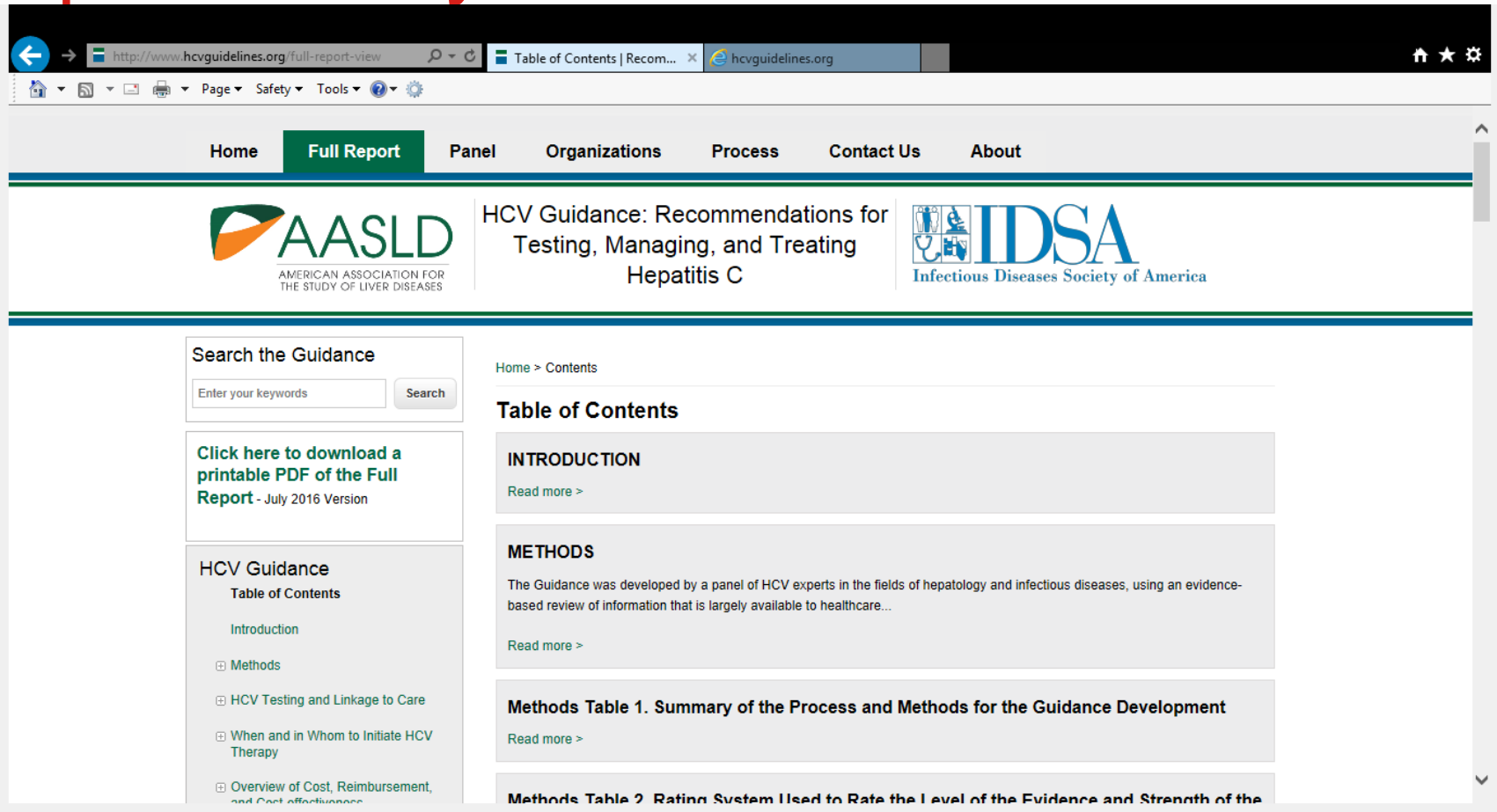
Medication	Recommendation
Efavirenz	• Do not coadminister
Tipranavir	• Do not coadminister
Tenofovir disoproxil fumarate	• Potential increase in tenofovir levels when given as tenofovir disoproxil fumarate; monitor for renal adverse events.

Product Information, Epclusa, Gilead, 2016

AASLD GUIDELINES

www.hcvguidelines.org

AASLD HCV Guidelines, Recently Updated, July 2016



What's in the Guidelines?

- HCV Testing and Linkage to Care
- When and in Whom to Initiate HCV Therapy
- Overview of Cost, Reimbursement, and Cost-effectiveness Considerations for Hepatitis C Treatment Regimens
- Initial Treatment of HCV Infection
- Initial Treatment Box. Summary of Recommendations for Patients Who are Initiating Therapy for HCV Infection by HCV Genotype
- Retreatment of Persons in Whom Prior Therapy has Failed
- Monitoring Patients who are Starting Hepatitis C Treatment, are on Treatment, or have Completed Therapy
- Unique Patient Populations: Patients with HIV/HCV Coinfection
- Unique Patient Populations: Patients with Decompensated Cirrhosis
- Unique Patient Populations: Patients who Develop Recurrent HCV Infection Post-liver Transplantation
- Unique Patient Populations: Patients with Renal Impairment
- Management of Acute HCV Infection

Genotype 1a Treatment-Naïve Patients Without Cirrhosis – Recommended, by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12, no baseline NS5A RAVs**
  Rating: Class I, Level A
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks**
  Rating: Class I, Level A
- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin for 12 weeks**
  Rating: Class I, Level A
- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks**
  Rating: Class I, Level A
- **Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks**
  Rating: Class I, Level

INVESTIGATIONAL MEDICATIONS

HCV Classes and Medications

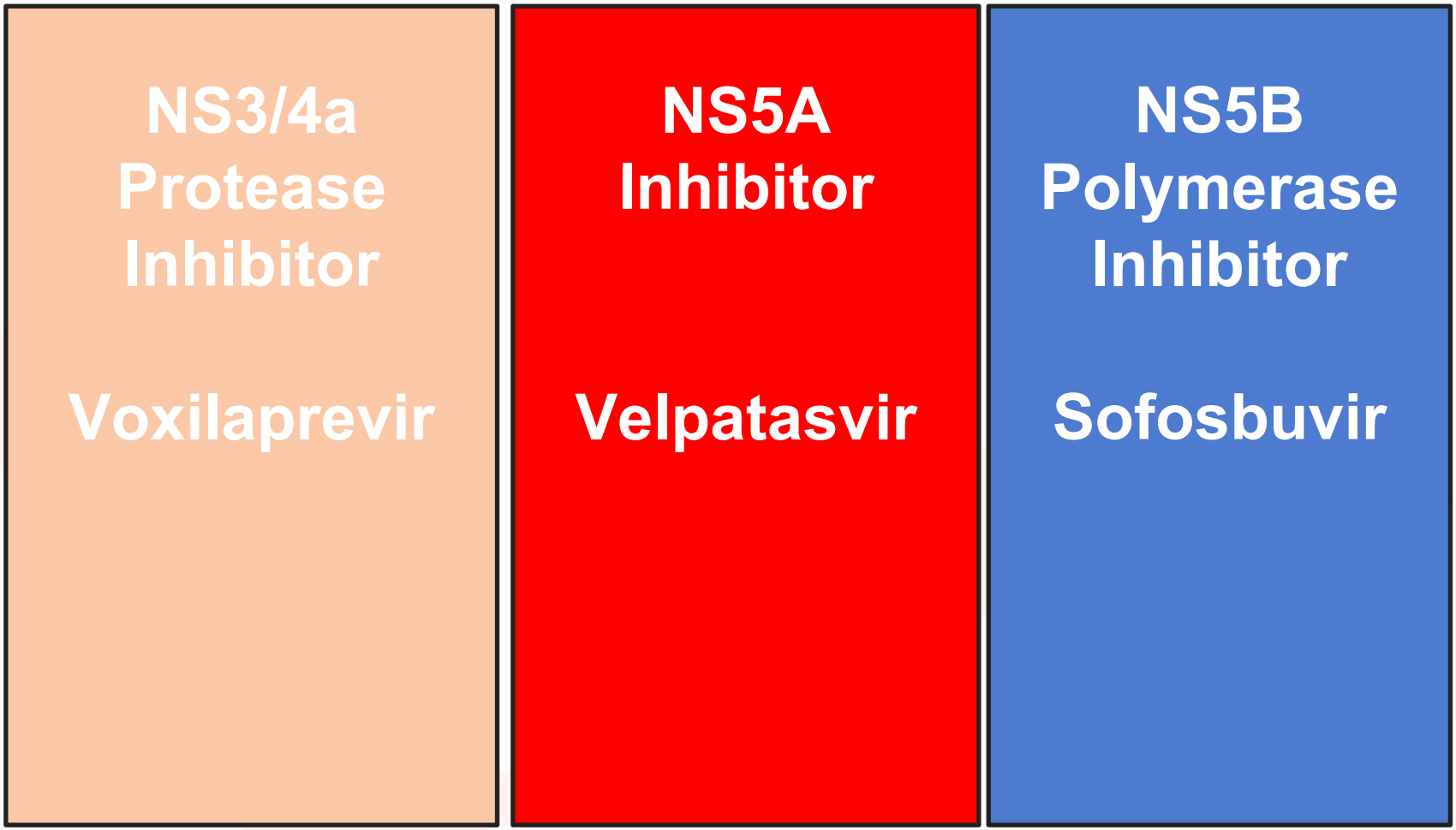
AbbVie, PanGenotypic Regimen

- Glecaprevir 300mg/ Pibrentasvir 120mg
- - 97.5 percent of chronic HCV infected patients without cirrhosis and new to treatment across all major genotypes (GT1-6) achieved SVR12 with 8 weeks of G/P
- - Across the 8-week arms of three registrational studies, no patients discontinued treatment due to adverse events
- - G/P is an investigational, pan-genotypic, once-daily, ribavirin-free regimen for the treatment of chronic HCV

Study Designs

Study Name	Patient Population	Treatment Duration	Treatment Regimen	SVR_{12} Rate
ENDURANCE-1	GT1 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN) , and patients co-infected with HIV-1	8 week	G/P	99% (n=348/351)
ENDURANCE-3	GT3 without cirrhosis, new to treatment	8 week	G/P	95% (n=149/157)
SURVEYOR-2 (Part 4)	GT2, 4, 5, 6 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN, SOF/RBV or pegIFN/SOF)	8 week	G/P	97% (n=196/203)

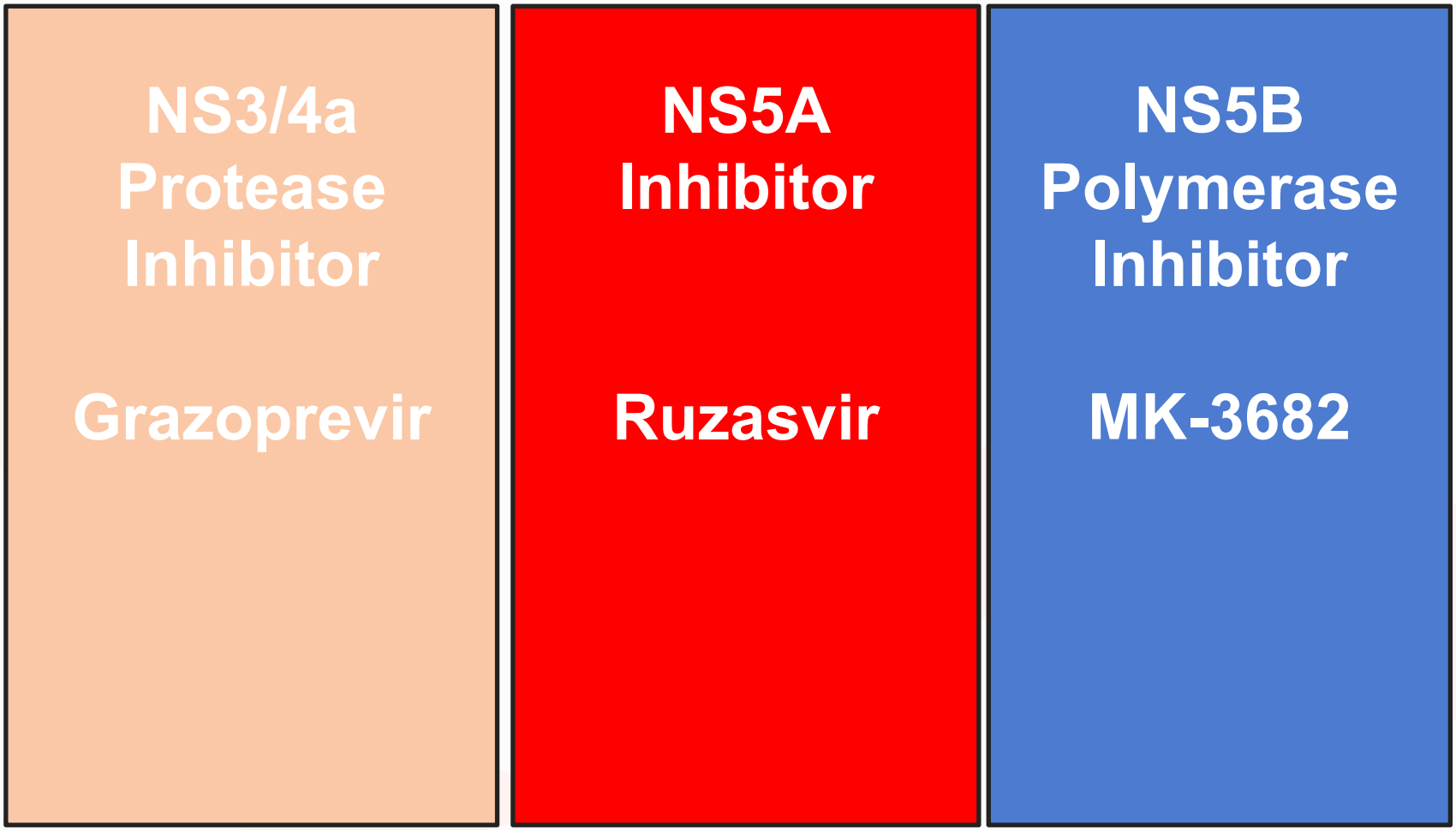
HCV Classes and Medications



POLARIS 1-4

- POLARIS-1 study was a double-blind, placebo-controlled study in 415 genotype 1-6 NS5A inhibitor-experienced patients.
  - The most common prior NS5A inhibitors were ledipasvir (55 percent) and daclatasvir (23 percent).
- POLARIS-4 study evaluated the use of SOF/VEL/VOX or SOF/VEL for 12 weeks in 333 genotype 1-4 HCV-infected patients with prior DAA experience that did not include an NS5A inhibitor.
  - Most patients (85 percent) had prior DAA experience with sofosbuvir.
- POLARIS-2 study evaluated the use of SOF/VEL/VOX for eight weeks or SOF/VEL for 12 weeks in 941 genotype 1-6 DAA-naïve HCV-infected patients, including 18 percent with cirrhosis and 23 percent who had previously failed treatment with an interferon-based regimen.
- POLARIS-3 study randomized patients with genotype 3 HCV infection and cirrhosis to receive SOF/VEL/VOX daily for eight weeks or SOF/VEL for 12 weeks.
  - Of the 219 patients treated, 31 percent had previously failed treatment with an interferon-based regimen.
- The POLARIS-1, POLARIS-3 and POLARIS-4 studies met their respective pre-specified primary endpoints for the patients receiving SOF/VEL/VOX. The POLARIS-2 study did not meet its primary endpoint; with a pre-specified 5 percent margin, the SVR12 rate for patients receiving treatment with SOF/VEL/VOX for eight weeks was not statistically non-inferior to the SVR12 rate for patients receiving SOF/VEL for 12 weeks.

HCV Classes and Medications



Summary of SVR12 Findings

Population	N	MK-3682B +/- RBV 8 weeks	MK-3682B +/- RBV 12 weeks	MK-3682B +/- RBV 16 weeks
GT1a	90	93% (39/42)	98% (47/48)	-
GT1b	86	98% (45/46)	100% (40/40)	-
GT2	151	86% (54/63)	97% (60/62)	100% (26/26)
GT3*	337	95% (98/103)	97% (155/159)	96% (72/75)

*28 percent (29/103), 36 percent (58/159) and 81 percent (61/75) of patients with GT3 infection receiving eight, 12 or 16 weeks of therapy, respectively, were previously treated with peginterferon/RBV

RESOURCES

DHHS Guidelines, 2016

Select ARV Drugs by Drug Class	HCV Drugs						
	HCV Direct-Acting Antiviral Agents					HCV Non-Direct-Acting Antiviral Agents	
	NS5B Inhibitor	Co-Formulated NS5A/NS5B Inhibitor	HCV Protease Inhibitors				
	Sofosbuvir	Ledipasvir/ Sofosbuvir	Simeprevir	*No Longer Recommended by HCV Guidelines*		Ribavirin	Pegylated interferon alpha
				Boceprevir	Telaprevir (Discontinued from U.S. market in October 2014)		
Integrase Strand Transfer Inhibitors							
DTG	✓	✓	✓	✓	✓	✓	✓
EVG/cobi/ TDF/FTC	✓	✘	✘	✘	✓	✓	✓
EVG + (PI/r without cobi)	Refer to recommendations for specific ritonavir-boosted PI						
RAL	✓	✓	✓	✓	✓	✓	✓
RPV	✓	✓	✓	✓	✓	✓	✓

NY NJ AETC AIDS EDUCATION & TRAINING CENTER

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions
A Quick Guide for Clinicians – March 2016

John J Faragon, PharmD, BCPS, AAHIVP, Kristen Marks, MD, Marshall Glesby, MD, PhD, Douglas Fish, MD

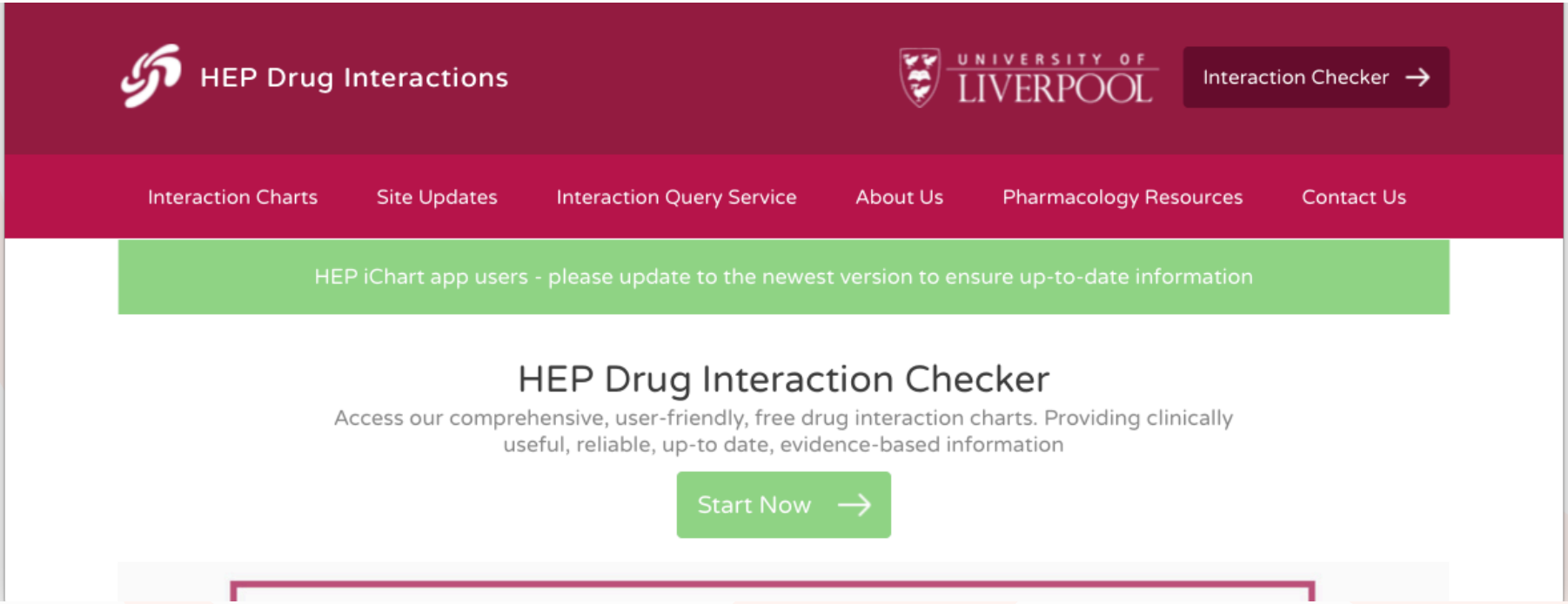
Mechanism of Action and Route of Metabolism for Ledipasvir/Sofosbuvir (Harvoni®)

Medication	HCV Mechanism of Action	Route of Metabolism and Drug Interaction Potential
Ledipasvir/Sofosbuvir (Harvoni®)	NS5a inhibitor and NS5b polymerase inhibitor	• Ledipasvir is an inhibitor of P-glycoprotein (P-gp) and brea cancer resistance protein (BCRP). Unknown metabolism v slow oxidative metabolism has been observed. • Sofosbuvir is a substrate for P-glycoprotein (P-gp) and bre cancer resistance protein (BCRP). The intracellular metabo

Ledipasvir/Sofosbuvir (Harvoni®) Drug Interactions with HIV Medications

Concurrent Medication	Recommendation and Clinical Comments
HIV Protease Inhibitors	
Atazanavir (Reyataz®) + ritonavir (Norvir®) Darunavir (Prezista®) + ritonavir (Norvir®) Lopinavir/ritonavir (Kaletra®) In addition, likely to occur with: Fosamprenavir (Lexiva®) + ritonavir (Norvir ®) Saquinavir (Invirase®) + ritonavir (Norvir®)	• HIV/HCV co-infection studies to date have not included patients rece boosted HIV PIs • Increase in tenofovir levels when used with ledipasvir. Ritonavir boos inhibitors used for HIV have also been shown to increase tenofovir le a ritonavir boosted HIV protease inhibitor with tenofovir and ledipas there may be increased risk of tenofovir induced renal toxicity. ○ Use alternative HCV therapy or change HIV antiretroviral ther that does not include tenofovir ○ If unable to change therapy and co-administration required, n for tenofovir-associated renal adverse events.
Tipranavir (Aptivus®) + ritonavir (Norvir®)	• Co-administration of ledipasvir/sofosbuvir with tipranavir + ritonavir decrease the concentration of ledipasvir and sofosbuvir, leading to re Co-administration not recommended.

www.hep-druginteractions.org



Questions/Contact

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Please contact me with questions