Treatment of Chronic Hepatitis C

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Disclaimer

- No conflict of interest to report.
- Several of the treatment protocols described are not within FDA label but they are inside the “Practice Guidelines Recommendations” from the AASLD and IDSA.
- One of the drugs mentioned is not yet FDA approved but is under “Rapid/Breakthrough Review” and expected to be approved by the FDA within the next few months. The data presented is the one sent to FDA for approval. The drug is
  - *Velpatasvir*

Hepatitis C Disease Burden: US

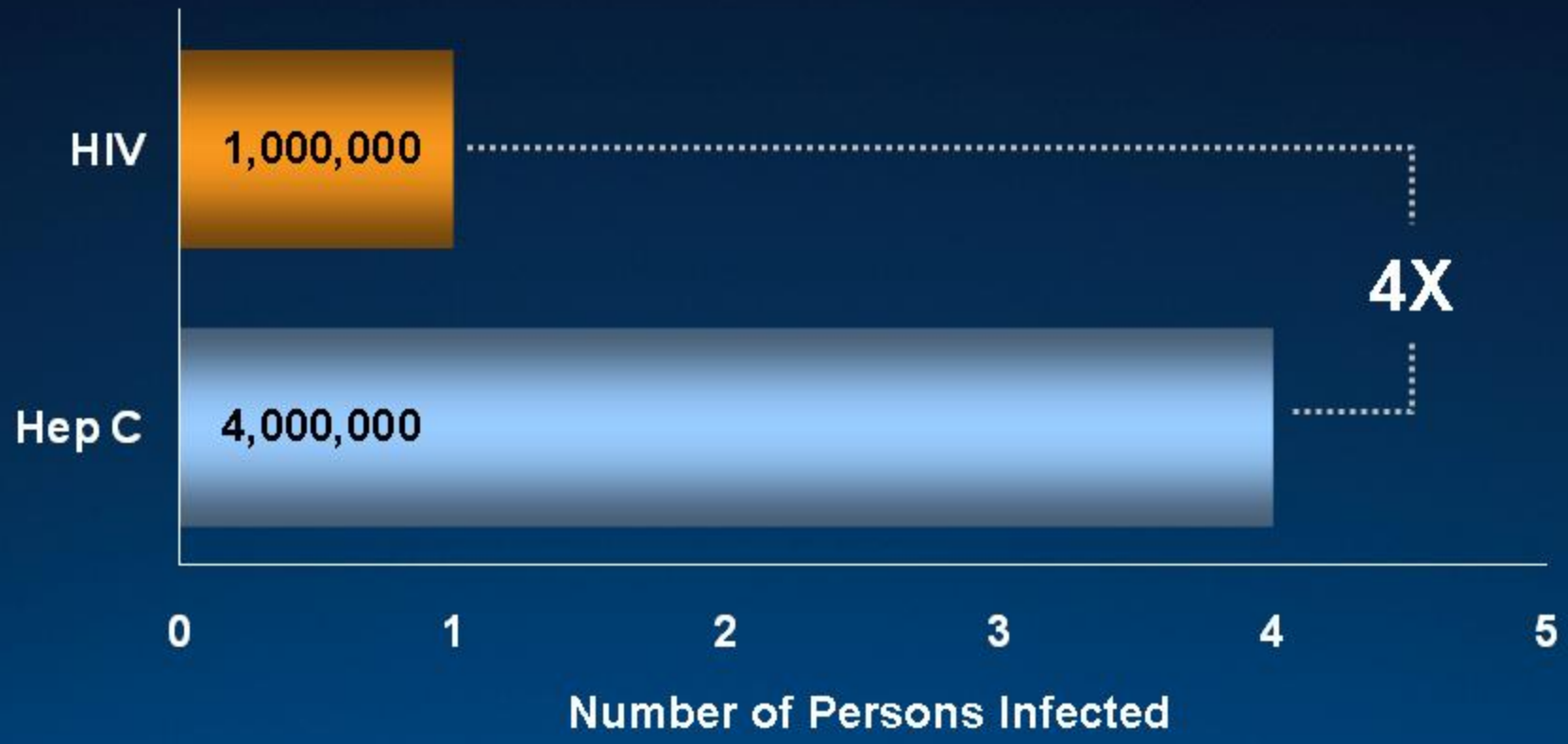
- Hepatitis C is the most common chronic blood-borne viral infection in the US[1]
  - ~ 1/2 of cirrhotic patients[2]
  - ~ 1/3 of HCC patients[3]
  - #1 reason for liver transplants[4]
  - #1 cause of death in HIV patients[5,6]

It is estimated that 4 million Americans are infected with HCV[7]

1. Alter M, et al. *N Engl J Med*. 1999;341:556-562; 2. NDDIC, 2006. Available at http://digestive.niddk.nih.gov/ddiseases/pubs/chronichepc; 3. NIH. *NIH Consens State Sci Statements*. 2002;19:1-46; 4. CDC Hepatitis Fact Sheet. http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm. Updated December 8, 2006; 5. Bica I et al. *Clin Infect Dis*. 2001;32:492-497; 6. Salmon-Ceron D et al. J Hepatol 2005;42:700-805; 7. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

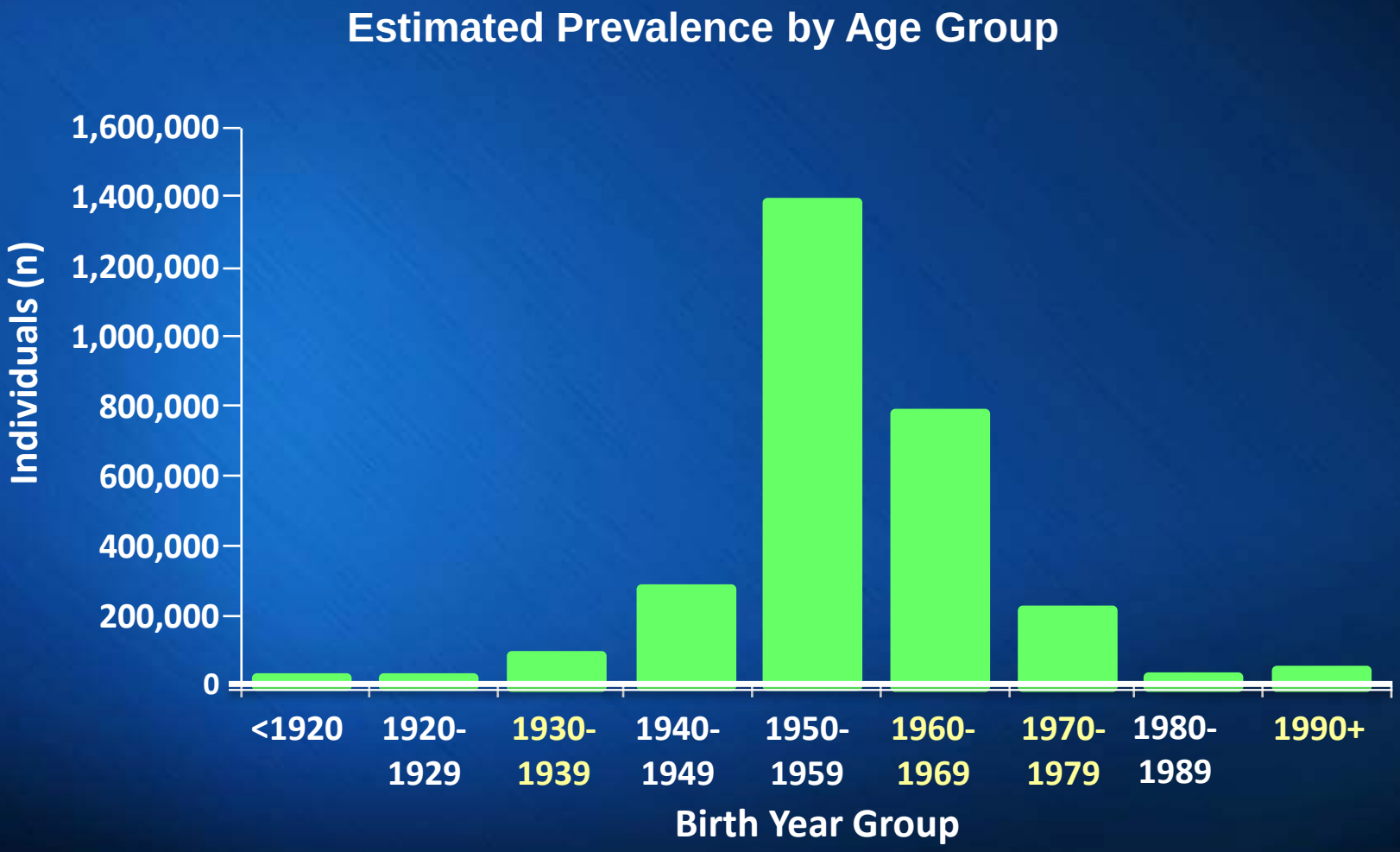
Prevalence of Hepatitis C

- Hepatitis C is 4 times more prevalent than HIV[1,2]



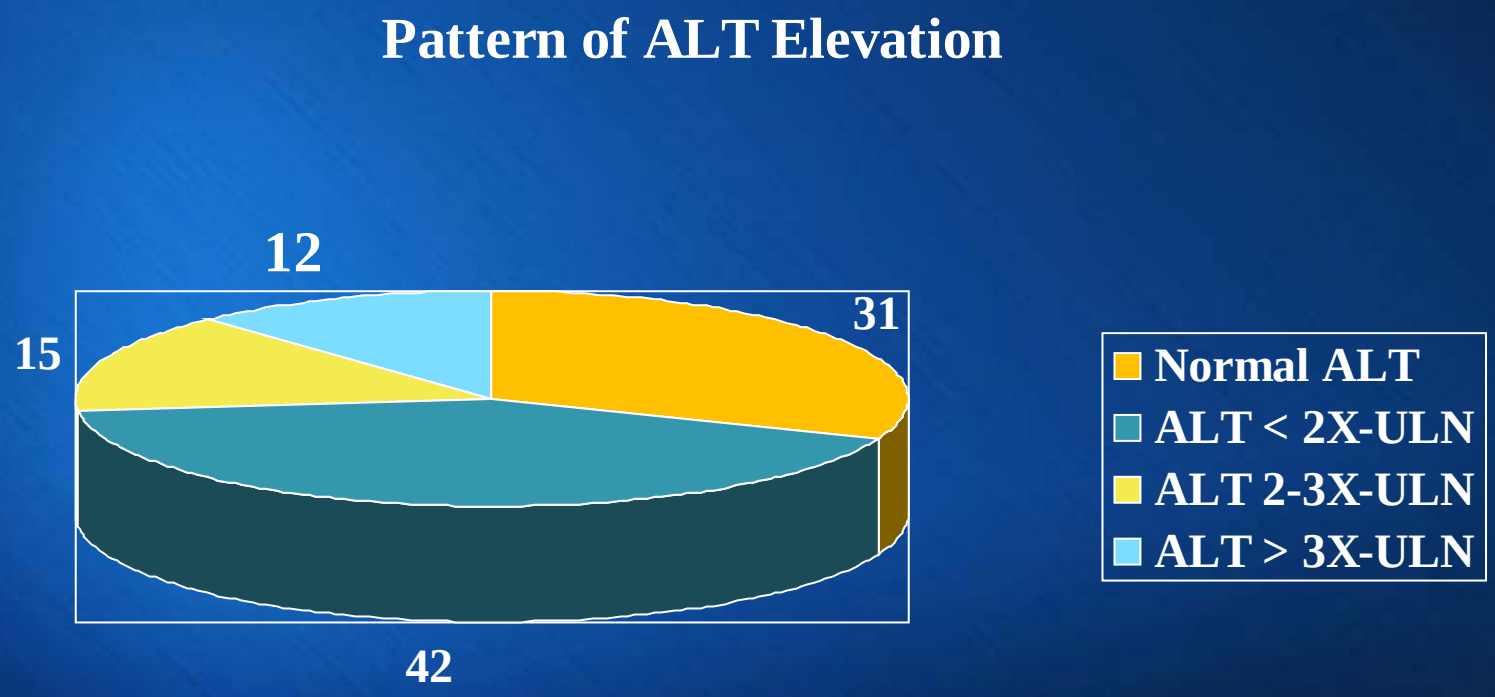
1. NIAID HIV/AIDS fact sheet. 2007. Available at: www.niaid.nih.gov/factsheets/hivinf.htm; 2. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

Two-Thirds of Those With Chronic HCV in the US Were Born Between 1946 and 1964



Pyenson B, et al. *Consequences of Hepatitis C Virus (HCV): Costs of a Baby Boomer Epidemic of Liver Disease.* New York, NY: Milliman, Inc; 2009.

Pattern of ALT Elevation Chronic HCV



Factors Associated with Accelerated Fibrosis in HCV

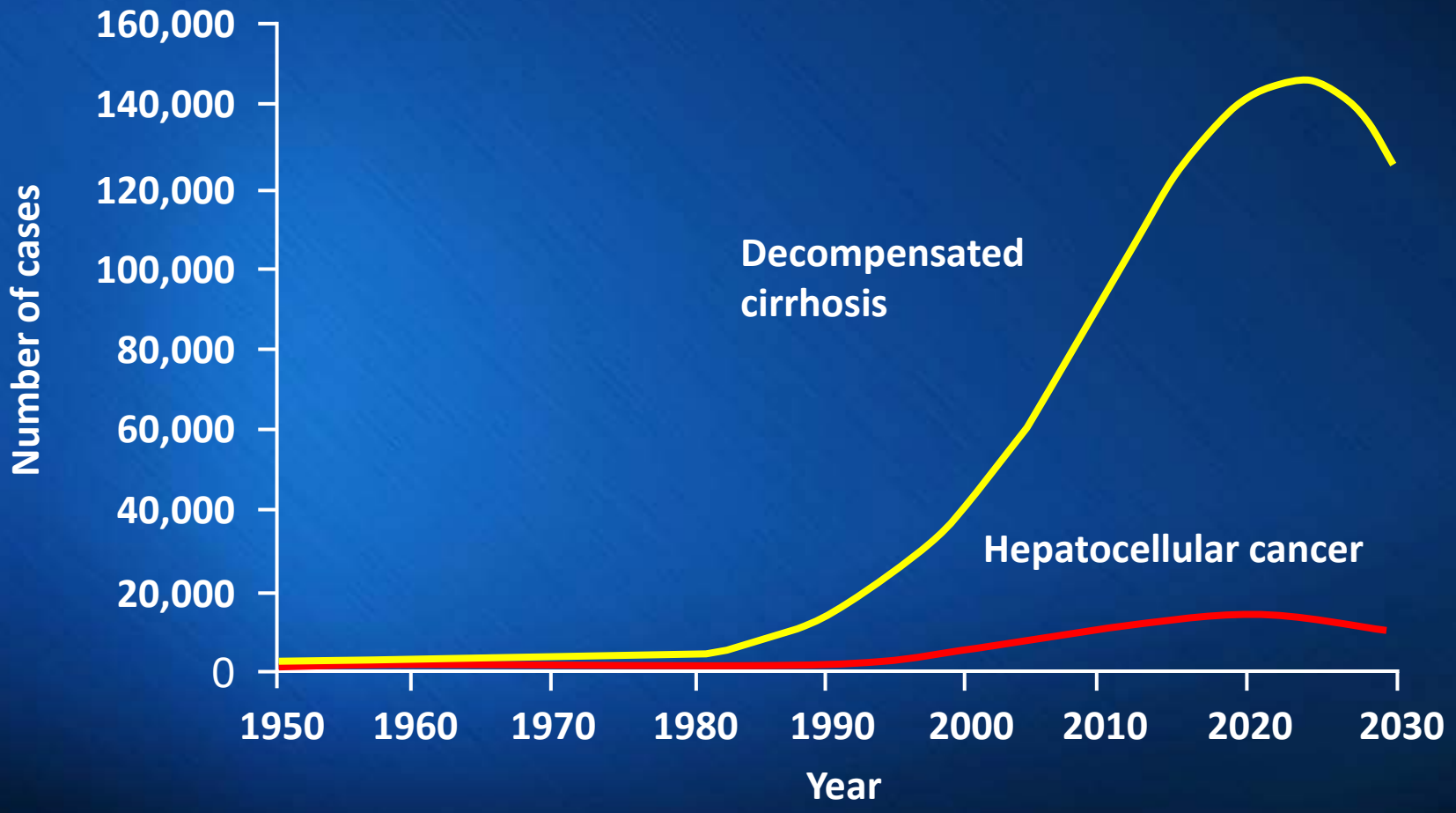
Host Factors

- **Non-Modifiable**
  - Fibrosis stage
  - Inflammation grade
  - Older age at time of infection
  - Male sex
  - Organ transplant
- **Modifiable**
  - Alcohol consumption
  - Nonalcoholic fatty liver disease
  - Obesity
  - Insulin resistance

Viral Factors

- Genotype 3
- Co-infection with HBV or HIV

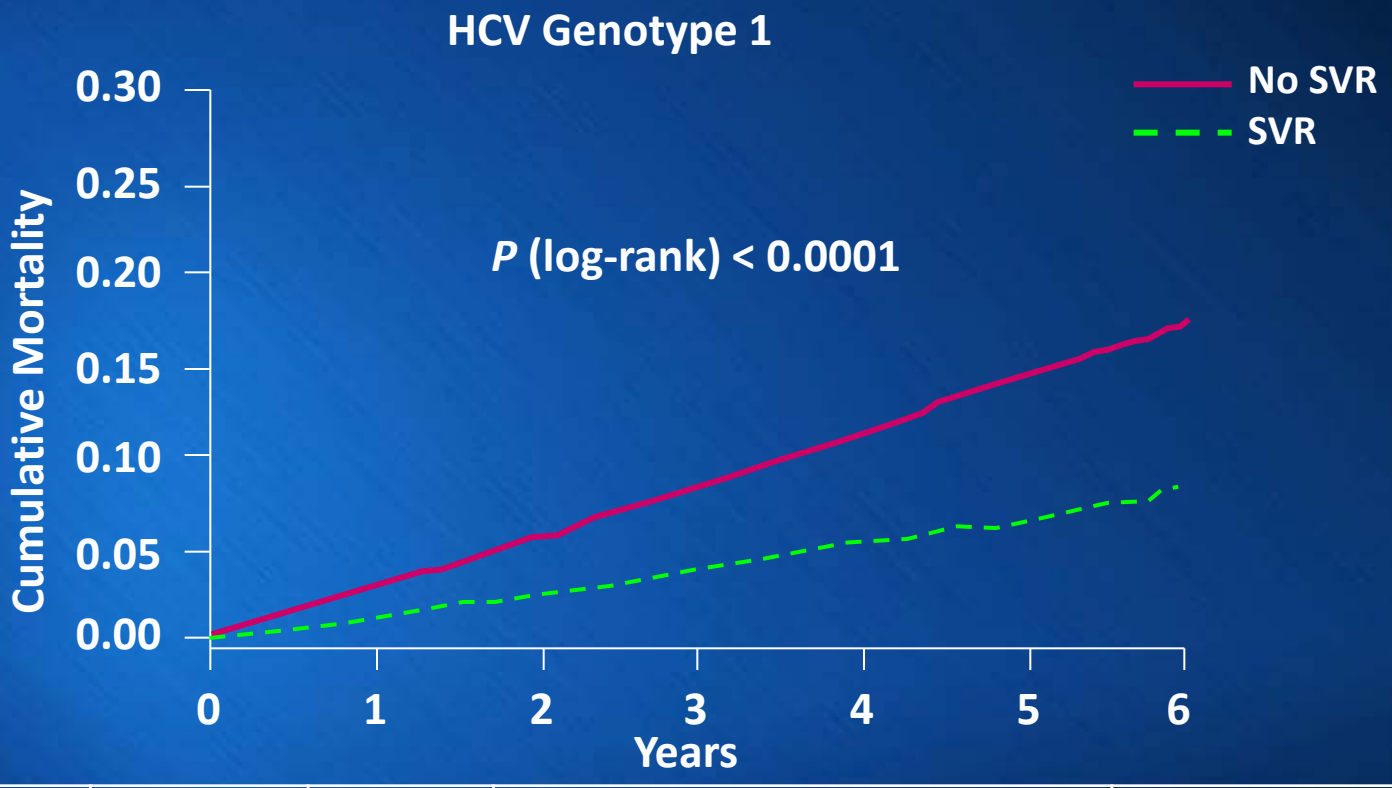
Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV



Davis GL, et al. *Gastroenterology*. 2010;138(2):513-521

SVR and Reduced Risk of All-Cause Mortality

US VA Study: Treatment with Pegylated Interferon/Ribavirin



Genotype	N	SVR	Hazard Ratio for Death with SVR	*P*-value
1	12,166	35%	0.70	< 0.0001
2	2904	72%	0.64	0.006
3	1794	62%	0.51	0.0002

Backus L, et al. *Clin Gastroenterol Hepatol*. 2011;9:509-516.

Who should be Tested for HCV?

- **HCV testing is recommended at least once for persons born between 1945 and 1965. Rating:** Class I, Level B

- **Other persons should be screened for risk factors for HCV infection, and**
  - **one-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection. Rating:** Class I, Level B

Who should be Tested for HCV?

Behaviors, Exposures and Conditions with High HCV Risk

- ***Risk behaviors***
  - **Injection-drug use (current or ever, including those who injected once)**
  - **Intranasal illicit drug use**

- ***Other medical conditions***
  - **HIV infection**
  - **Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase (ALT) levels**

Who should be Tested for HCV?

Behaviors, Exposures and Conditions with High HCV Risk

- ***Risk exposures***
  - Long-term hemodialysis (ever)
  - Getting a tattoo in an unregulated setting
  - Healthcare, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior recipients of transfusions or organ transplants, including persons who:
    - were notified that they received blood from a donor who later tested positive for HCV infection
    - received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
    - received clotting factor concentrates produced before 1987
    - were ever incarcerated

Recommendations for patients with HCV

- Avoid sharing toothbrushes and dental or shaving equipment.
- Cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
- Stop using illicit drugs and enter substance abuse treatment.
- If continue to inject drugs should:
  - avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment;
  - use new sterile syringes and filters and disinfected cookers; clean the injection site with a new alcohol swab; and dispose of syringes and needles after one use in a safe, puncture-proof container.

Recommendations for patients with HCV

- Do not donate blood
- Discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
- MSM with HIV infection and those with multiple sexual partners or sexually transmitted infections should use barrier precautions to prevent sexual transmission.
  - Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Treatment of Chronic Hepatitis C AASLD/IDSA Guidelines

(drugs to be approved soon have been added)

http://www.hcvguidelines.org/

Who should be treated for HCV

- ***Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.***
  - A 15-year follow-up study of patients with early (F0-1) chronic hepatitis C showed a survival of:
    - 92% in patients who were cured (SVR),
    - 87% in non-treated patients, and
    - 82% in those patient who did not respond to therapy.
- Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority.

Hepatitis C shortens the life expectancy of all infected patients and its eradication improves survival.

Who should be treated for HCV

Highest Priority (Highest Risk for Severe Complications)

- Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
- Organ transplant recipients
- Type 2 or Type 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
- Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Who should be treated for HCV
High Priority

Owing to High Risk for Complications

- Fibrosis (Metavir F2)
- HIV-1 coinfection
- HBV coinfection
- Other coexistent liver disease (eg, NASH)
- Debilitating fatigue
- Type 2 Diabetes mellitus (insulin resistant)
- Porphyria Cutanea Tarda

Owing to Transmission Risk

- MSM with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- HCV-infected women of child-bearing potential wishing to get pregnant
- Persons on long-term hemodialysis

All Patients should be counseled on ways to decrease transmission and minimize the risk of reinfection.

Evaluation of Liver Fibrosis: Serum Fibrosis Tests + TLE and Liver Biopsy

- Transient Liver Elastograpy (TLE): Cutoff Values
  - 8.7 to 9.4 kPa correlates with Metavir F2;
  - 9.5 to 14.4 kPa with F3; and
  - 14.5 or higher kPa with F4 or cirrhosis.
- The measurement range overlap between stages.
- When the elastography and FibroTest (e.g.: Fibro Sure, Fibro Test-ActiTest) results agreed, liver biopsy examination confirmed the stage of fibrosis in:
  - 84 percent of cases for F ≥2 fibrosis,
  - 95 percent for F ≥3 fibrosis, and
  - 94 percent for F = 4 fibrosis
- If serum fibrosis markers are discordant with TLE, do liver biopsy.

Drugs to Treat Hepatitis C

- Interferon
- PEGylated-Interferon (Peg-IFN)
- Ribavirin
- **Direct Antiviral Agents**

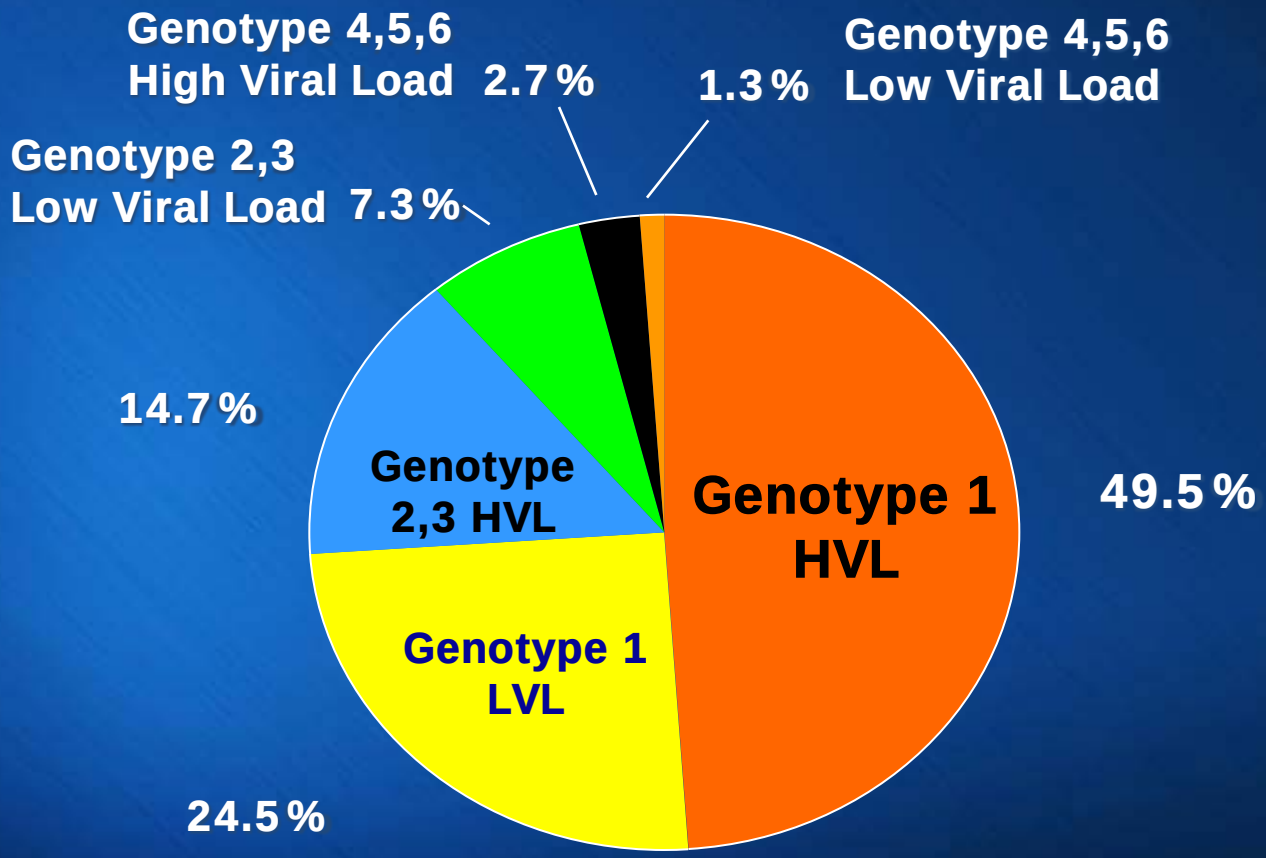
Agents and Regimens
Approved and Soon to be Approved

Combinations	Type of Antiviral				
	NS3	NS5A	Non-Nuc NS5B	Nuc NS5B	RBV
	"previr"	"asvir"	"buvir"	"buvir"	
Simeprevir + sofosbuvir	⊙			⊙	
Ledipasvir/sofosbuvir FDC (HARVONI)		⊙		⊙	
Paritaprevir/r/Ombitasvir FDC (TECHNIVIE or PrO) + Dasabuvir (VIEKIRA Pak or PrOD or 3D)	⊙	⊙	⊙		⊙ RBV only for 1a or F3-4
Sofosbuvir + ribavirin				⊙	⊙
Daclatasvir + sofosbuvir		⊙		⊙	
Grazoprevir + Elbasvir (ZEPATIER)	⊙	⊙			
Velpatasvir + Sofosbuvir		⊙		⊙	

Before Treatment

- Check for Co-Infection (HBV, HIV)
  - Vaccinate for HAV, HBV, Pneumonia, as appropriate.
- Evaluate the Fibrosis Stage of the Disease, previous therapies, and the Viral Load and Genotype.
  - In “decompensated cirrhosis” (Child-Pugh B or C), DO NOT USE “NS3 containing regimens”like Simeprevir, PrOD, nor Grazoprevir (Zepatier); liver failure risk.
- Evaluate Potential Interactions of the Antiviral Regimen with all the drugs that the patient is taking (prescription, OTC, or Complementary/Alternative).
  - Eliminate what is not indispensable.
- Genotype 1a; if planning to use:
  - SIMEPREVIR, check “NS3 Resistance Panel” for Q80K mutation. Do not use if Q80K mutation is present.
  - ELBASVIR, check for “NS5A Polymorphism (M28, Y93, Q30, L31)” to decide length of therapy (16 weeks with resistant polymorphism vs 12 weeks)
- Plan for anti-conceptive therapy, especially if Ribavirin will be used.
- Inform the patient that he/she must not start nor discontinue any medication without previous discussion with you or with another Physician or Pharmacist who will evaluate the effects of this change on the hepatitis C treatment.

Genotype and Viral Load in US Patients



Alter et al. *N Engl J Med.* 1999;341;556-562.
Blatt et al. *J Viral Hepatitis.* 2000;7:196-202.

Drug-Drug Interactions
(Including “Herbals” and “Natural”)

DAAs and Illicit Recreational Drugs

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

Concomitant Medications	Daclatasvir	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir	Elbasvir/ Grazoprevir
Acid-reducing agents*		X	X			
Alfuzosin/ tamsulosin			X			
Amiodarone	X	X	X	X	X	X
Anticonvulsants	X	X	X	X	X	X
Antiretrovirals*	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section	See HIV section
Azole antifungals*	X**		X	X		X
Buprenorphine/ naloxone			X			
Calcineurin inhibitors*			X	X		X
Calcium channel blockers*	X		X	X		X
Cisapride			X	X		X
Digoxin	X	X		X		X
Ergot derivatives			X			
Ethinyl estradiol–containing products			X			

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

Concomitant Medications	Daclatasvir	Ledipasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir	Elbasvir/ Grazoprevir
Furosemide			X			
Gemfibrozil			X			
Glucocorticoids*	X		X (inhaled, intranasal)	X		X
Herbals St. John's wort Milk thistle	X	X	X	X X	X	X X
Macrolide antimicrobials*	X**			X		X
Other antiarrythmics*			X	X		X
Phosphodiesterase type 5 inhibitors*			X	X		X
Pimozide			X			
Rifamycin antimicrobials*	X	X	X	X	X	X
Salmeterol			X			
Sedatives*			X	X		X
Statins*	X	X	X	X		X

*Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
**Requires a daclatasvir dose modification.

Anti-HIV DRUG	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)	Grazoprevir/ Elbasvir
Ritonavir-boosted atazanavir	**No data**	No data	Ledipasvir ↑; atazanavir ↑[a] (okay with TAF not TDF)	Daclatasvir ↑[b]	Paritaprevir ↑; atazanavir ↑	**Paritaprevir ↑; atazanavir ↔**	**Grazoprevir ↑; elbasvir ↑; atazanavir ↑**
Ritonavir-boosted darunavir	**Simeprevir ↑ ; darunavir ↔**	Sofosbuvir ↑ ; darunavir ↔	Ledipasvir ↑, darunavir ↔[a] (okay with TAF not TDF)	Daclatasvir ↑; darunavir ↔	**Paritaprevir ↓/↑; darunavir ↓**	Paritaprevir ↑; darunavir ↔	**Grazoprevir ↑; elbasvir ↑; darunavir ↔**
Ritonavir-boosted lopinavir	**No data**	No data	No data[a]	Daclatasvir ↑ ; lopinavir ↔	**Paritaprevir ↑; lopinavir ↔**	**Paritaprevir ↑; lopinavir ↔**	**Grazoprevir ↑ ; elbasvir ↑; lopinavir ↔**
Ritonavir-boosted tipranavir	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**	**No data**
Efavirenz	**Simeprevir ↓ ; efavirenz ↔**	Sofosbuvir ; efavirenz ↔	Ledipasvir ↓ ; efavirenz ↓[a]	Daclatasvir ↓[b]	**No pharmacokinetic data[c]**	**No data**	**Grazoprevir ↓ ; elbasvir ↓ ; efavirenz ↓**
Rilpivirine	Simeprevir ↔ rilpivirine ↔	Sofosbuvir ↔; rilpivirine ↔	Ledipasvir ↔; rilpivirine ↔	No data	**Paritaprevir ↑; rilpivirine ↑**	**No data**	Grazoprevir ↔ ; elbasvir ↔ ; rilpivirine ↔

[a]Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.
[b]Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.
[c]PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

Anti-HIV DRUG	Simeprevir	Sofosbuvir	Ledipasvir	Daclatasvir	Paritaprevir, ritonavir, ombitasvir plus dasabuvir (PrOD)	Paritaprevir, ritonavir, ombitasvir (PrO)	Grazoprevir/ Elbasvir
Etravirine	No data	No data	No data	Daclatasvir ↓[b]	No data	**No data**	**No data**
Raltegravir	Simeprevir ↔; raltegravir ↔	Sofosbuvir ↔; raltegravir ↔	Ledipasvir ↔; raltegravir ↔	No data	PrOD ↔; ↑ raltegravir	PrO ↔; raltegravir ↑	Grazoprevir ↔; elbasvir ↔; raltegravir ↑
Cobicistat-boosted elvitegravir	**No data**	Cobicistat ↑[a]; sofosbuvir ↑ (okay with TAF not TDF)	Cobicistat ↑[a]; ledipasvir ↑ (okay with TAF not TDF)	No data	No data	**No data**	**No data**
Dolutegravir	No data	No data	Ledipasvir ↔; dolutegravir ↔	Daclatasvir ↔; dolutegravir ↑	Paritaprevir ↓; dolutegravir ↑	No data	Grazoprevir ↔; elbasvir ↔; dolutegravir ↑
Maraviroc	No data	No data	No data	No data	No data	No data	No data
Tenofovir disoproxil fumarate	Simeprevir ↔; tenofovir ↔	Sofosbuvir ↔; tenofovir ↔	Ledipasvir ↔; tenofovir ↑	Daclatasvir ↔; tenofovir ↔	PrOD ↔; tenofovir ↔	Pro ↔; tenofovir ↔	Grazoprevir ↔; elbasvir ↔; tenofovir ↑

[a]Only problematic when administered with tenofovir disoproxil fumarate; tenofovir levels are increased.
[b]Decrease daclatasvir dose to 30 mg once daily with atazanavir; increase daclatasvir dose to 90 mg once daily with efavirenz or etravirine.
[c]PrOD administered with efavirenz led to premature study discontinuation owing to toxic effects.

HIV-HCV Genotype 1 Cheat Sheet

(Dr. Matt Cave)

	HIV Backbone	HIV Brand Name	HIV Generic Names	Compatible HCV regimen
Recommended HIV Regimens DHHS - 2015	Integrase	**Triumeq**	dtg/abc/3tc	Harvoni, dcv/sof, sim/sof, GRZ + EBR, Viekira Pak probably OK (AASLD/IDSA)
		Tivicay/Truvada	dtg/tdf/ftc	Harvoni, dcv/sof, sim/sof., GRZ + EBR, Viekira Pak probably OK (AASLD/IDSA)
		Stribild	evg/cobi/tdf/ftc	NO DATA; ? dcv (30 mg) / sof
		Isentress/Truvada	ral/tdf/ftc	Harvoni, Viekira Pak, dcv/sof, sim/sof, GRZ + EBR
	PI	**Prezista/r/Truvada**	drv/r/ftc/tdf	Harvoni, dcv/sof (dcv 30 mg given in Ally-2 but dose reduction not recommended in prescribing information).
Alternate HIV Regimens DHHS - 2015	NNRTI	**Atripla**	efv/tdf/ftc	dcv (90 mg) / sof, Harvoni
		Complera	rpv/tdv/ftc	Harvoni, dcv/sof, sim/sof, GRZ + EBR
	PI	**Reyataz/r/Truvada**	atv/r+tdv/ftc	Viekira Pak (hold r), dcv (30mg) / sof
		Prezista/r/Ziagen/Epivir	drv/r/abc/3tc	Harvoni, dcv/sof (dcv 30 mg given in Ally-2 but dose reduction not recommended in prescribing information).

DAAs and Immunosuppressants

	SIM	DCV	SOF	SOF/ LDV	3D
Azathioprine	•	•	•	•	•
Cyclosporine	•	•	•	•	•
Etanercept	•	•	•	•	•
Everolimus	•	•	•	•	•
Mycophenolate	•	•	•	•	•
Sirolimus	•	•	•	•	•
Tacrolimus	•	•	•	•	•

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

Dose Modifications with Cyclosporine and Tacrolimus

	Cyclosporine	Tacrolimus
Sofosbuvir	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Ledipasvir	No data; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No data; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Daclatasvir	No interaction observed; no a priori dose adjustment, but monitor CSA levels and titrate CSA dose as needed	No interaction observed; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
Simeprevir	5.81-fold ↑ in SIM AUC; **combination is not recommended**	85% ↑ in SIM AUC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed
PrOD	5.8-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrOD treatment, monitor CSA levels and titrate CSA dose as needed	57-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrOD treatment, monitor TAC levels and titrate TAC dose as needed
PrO	4.3-fold ↑ in CSA AUC; modeling suggest using 1/5 of CSA dose during PrO treatment, monitor CSA levels and titrate CSA dose as needed	86-fold ↑ in TAC AUC; modeling suggests TAC 0.5 mg every 7 days during PrO treatment, monitor TAC levels and titrate TAC dose as needed
Elbasvir/Grazoprevir	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; **combination is not recommended**	43% ↑ in TAC; no a priori dose adjustment, but monitor TAC levels and titrate TAC dose as needed

Interferon Ineligible

Definition

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- History of depression
- Clinical features consistent with depression
- A baseline neutrophil count below 1500/µL
- A baseline platelet count below 90,000/µL
- A baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

MOST PATIENTS REFUSE TO BE TREATED WITH IFN

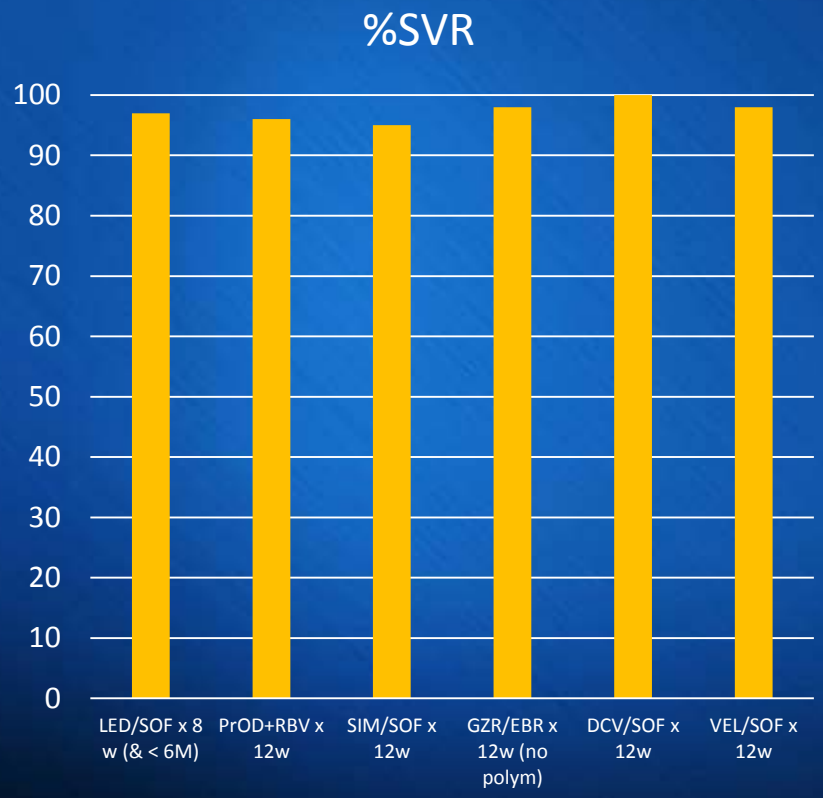
Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

Genotype	Regimen	Duration (weeks)	SVR
1a or 1 unspecified	Naïve F0-2 with HCV-RNA < 6 Million: **SOF/LED 400/90**	**8**	97%
	F0-2 with HCV-RNA > 6 Million, or F3-4: **SOF/LED 400/90**	**12**	F0-2: 96%; F3-4: 94%
	GZR 100 + EBR 50 (without M28, Q30, L31, or Y93 polymorphism) (F0-4 comp)	**12**	98%
	F0-2: **VIEKIRA + RBV 1-1.2**	**12**	96%
	SOF 400 + VEL 100	**12**	98%
	DAC 60 + SOF 400	F0-2**: 12** F3-4: **24** (+/- RBV 1-1.2) (alt)	100% 100%
	SOF 400 + SMV* 150 ± RBV 1-1.2 g (No in Q80K mutation)	F0-2: **12** F3-4: **24** (alt)	93-96%
	GZP 100 + EBV 50 + RBV 800-1400 (with M28, Y93, Q30, or L31 polymorphism) (F0-4 comp) (alt)	**16**	100%
	F3-4: **VIEKIRA + RBV 1-1.2** (alt)	**24**	95%

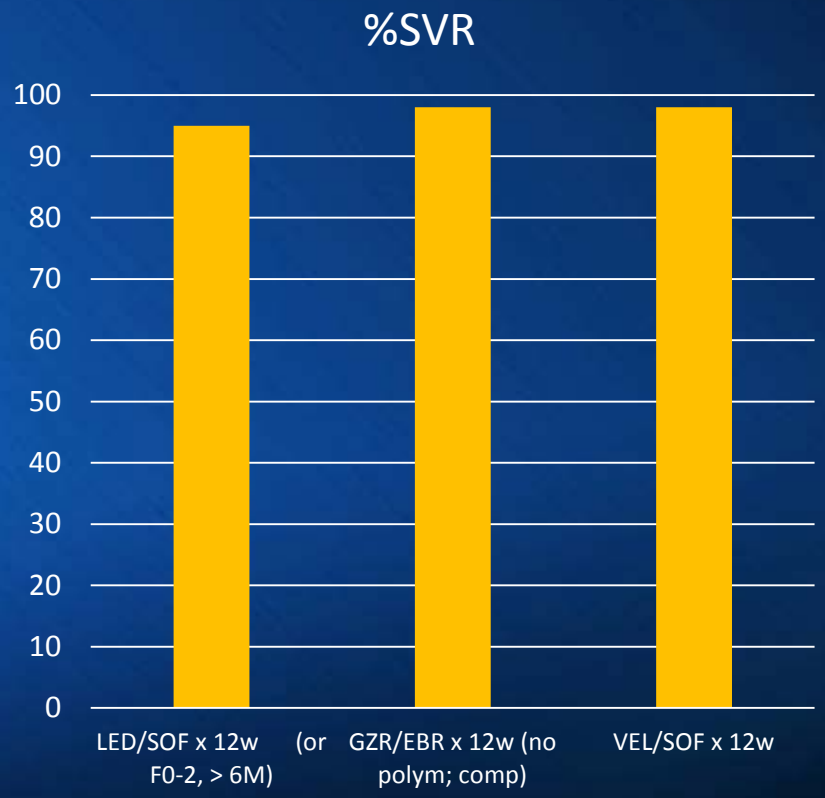
NAÏVE: Genotype 1a or Unspecified

First Line Therapy

SVR in F0-2 only



SVR in F3-4



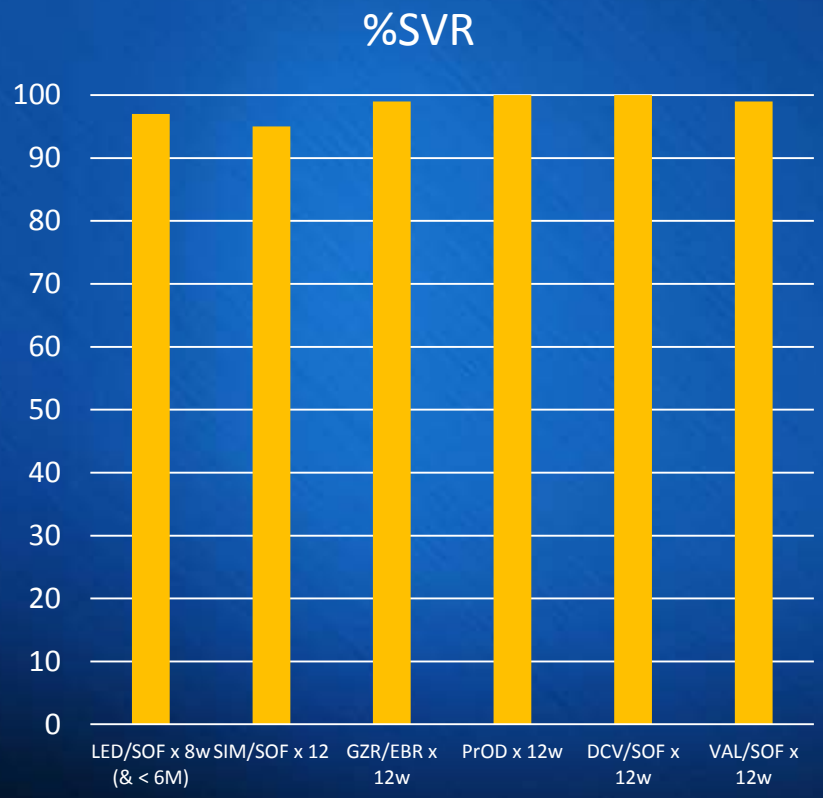
Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

Genotype	Regimen	Duration (weeks)	SVR
1b	Naive F0-2 with HCV-RNA < 6 Million: **SOF/LED 400/90**	**8**	97%
	F0-2 with HCV-RNA > 6 Million, or F3-4: **SOF/LED 400/90**	**12**	F0-2: 96%; F3-4: 94%
	GZR 100 + EBR 50 (F0-4 comp)	**12**	99%
	F0-2: **Viekira** (without RBV)	**12**	100
	F3-4: **Viekira +/- RBV 1-1.2**	**12**	99
	SOF 400 + VEL 100	**12**	99%
	SOF 400 + SMV 150 ± RBV 1-1.2 g	F0-2: **12** F3-4: **24 (alt)**	93-96%
	DAC 60 + SOF 400	F0-2**: 12** F3-4: **24** (+/- RBV 1-1.2) (alt)	100% 100%-100%

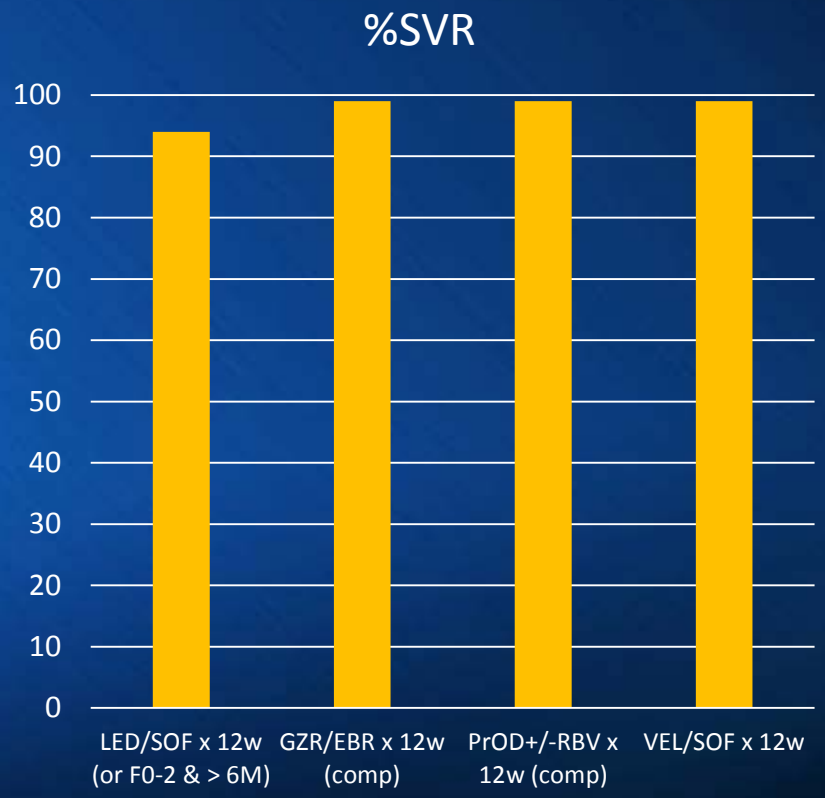
Naïve: Genotype 1b

First Line Therapy

SVR in F0-2 only



SVR in F3-4



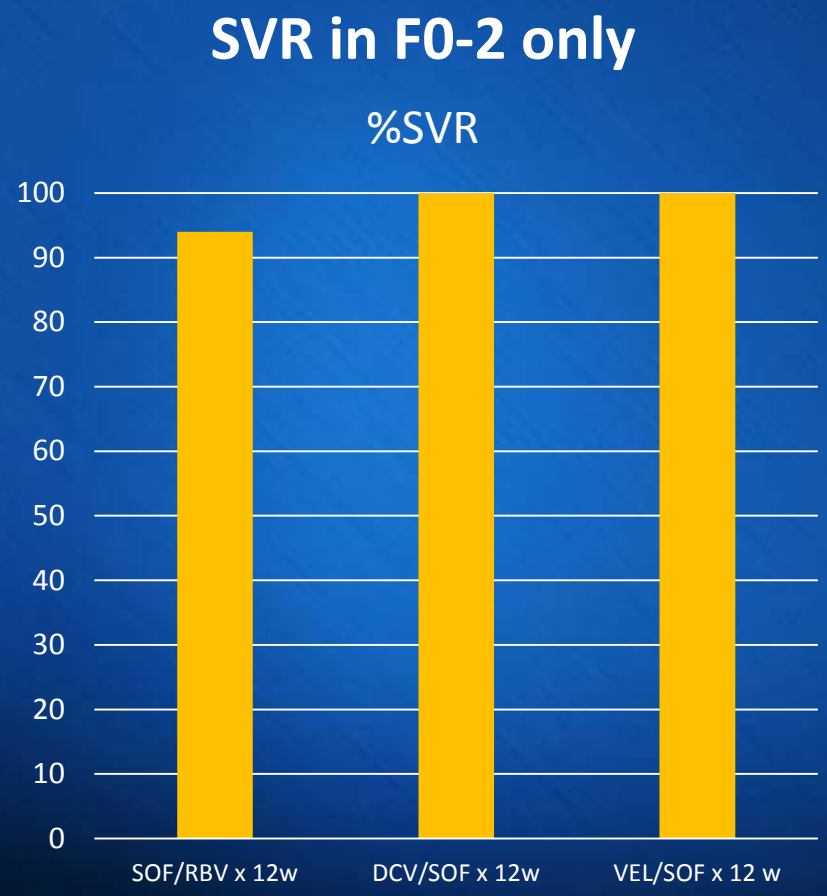
Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

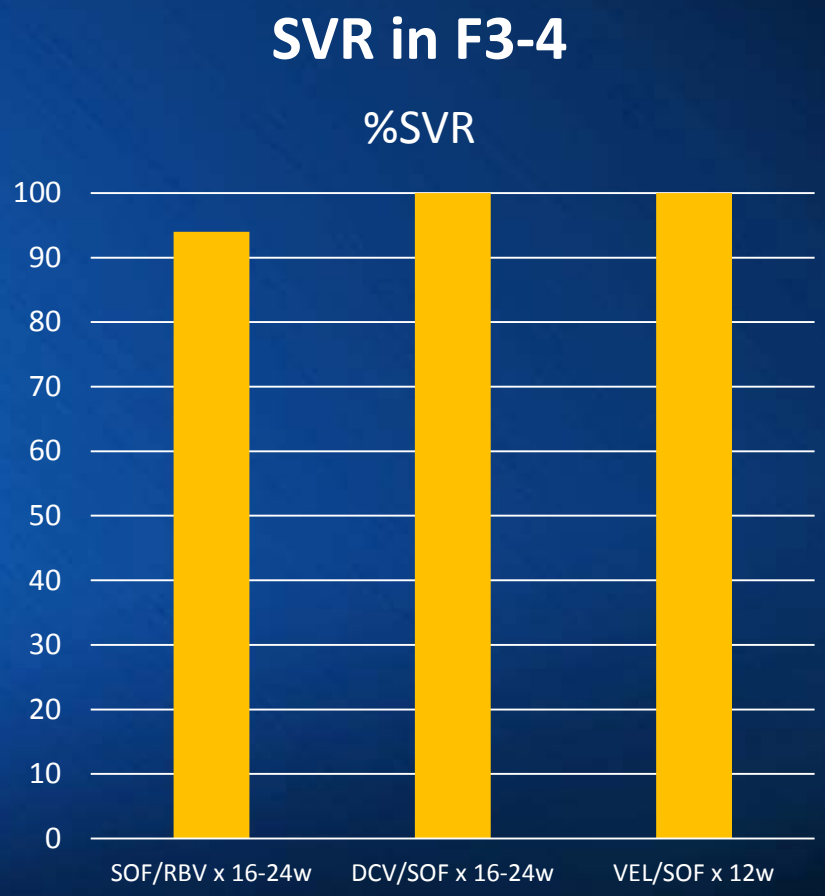
Genotype	Regimen	Duration (weeks)	SVR
2	**SOF 400 + RBV 1-1.2 g**	F0-2: **12** F3-4: **16-24**	94%
	DAC 60 + SOF 400	F0-2: **12** F3-4 comp: **16-24**	100%
	SOF 400 + VEL 100	**12**	100%
	SOF/LED 400/90 (no FDA approved)	**12**	96%
3	**SOF 400 + PEG/RBV 1-1.2 g**	**12**	97%; (F3-4 Compensated: 92%)
	DCV 60 + SOF 400	F0-2: **12**	F0-2: 97%; F3-4: 58%
	DAC 60 + SOF 400 +/- RBV (RBV helped in CP-B&C)	F4 C-P B&C (+/- RBV 1-1.2): **24** F3 & F4 CP-A (+/- RBV): **16-24**	88% (78% w/o RBV) 92% (88% w/o RBV)
	SOF 400 + VEL 100	**12**	95% (F0-2: 98%)(F3-4c:93%)
	SOF 400 + RBV 1-1.2 g (alt)	**24**	93% (77% in Relapse) (F3-4: 82-92%)
	GZP + EBV + SOF (no FDA approved)	**12**	91% in comp. cirrhosis

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

Naïve: Genotype 2

First Line Therapy

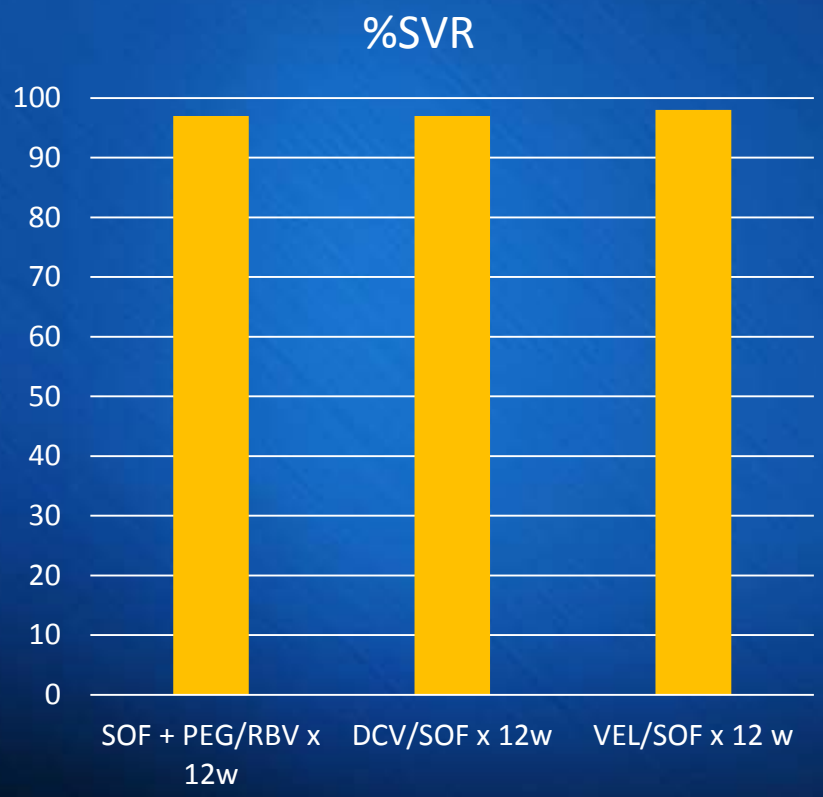




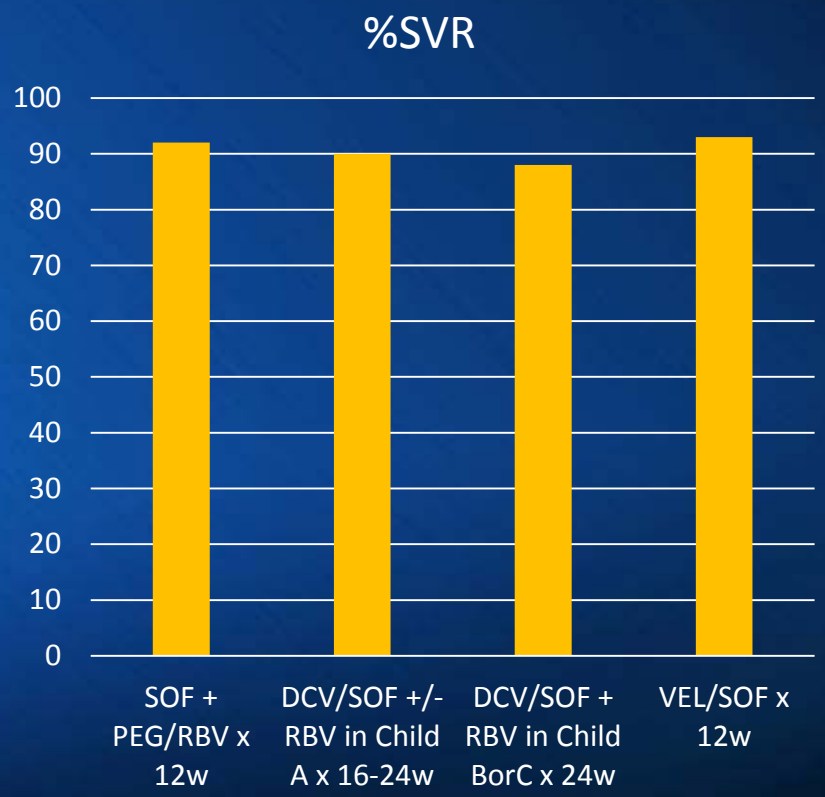
Naïve: Genotype 3

First Line Therapy

SVR in F0-2 only



SVR in F3-4



Treatment of Hepatitis C ; Treatment Naïve or Relapse to PEG/RBV

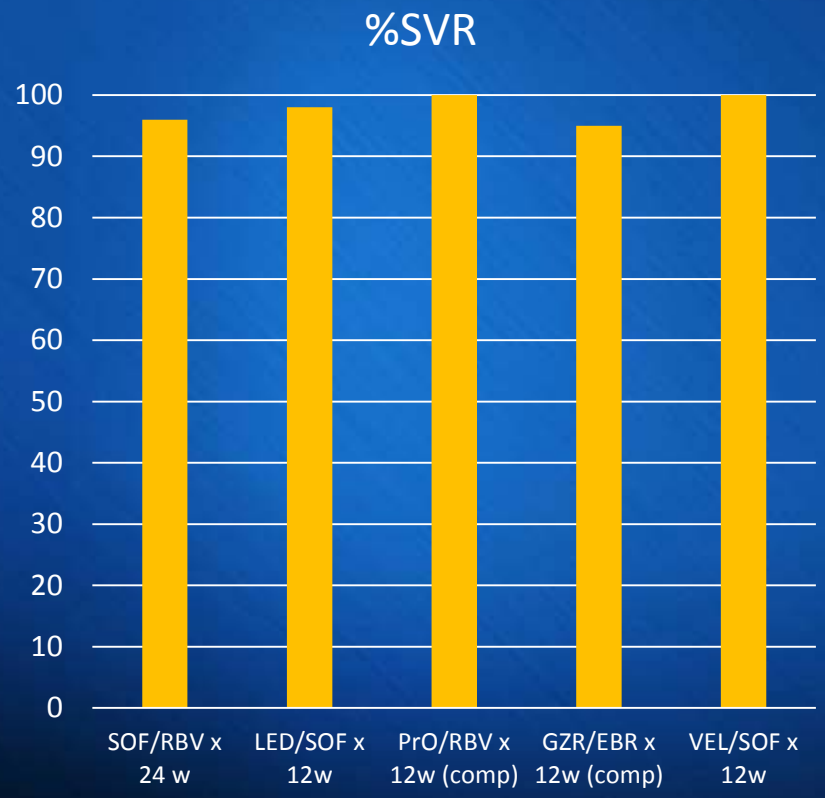
Genotype	Regimen	Duration (weeks)	SVR
4	**SOF 400 + RBV 1-1.2 g**	**24**	92-100%
	SOF/LED 400/90 (F0-4)	**12**	95-100%
	TECHNIVIE (PrO) + RBV 1-1.2 g (F0-4 comp)	**12**	100%
	GZR 100 + EBV 60 +/- RBV (F0-4 comp)	**12**	90-100%
	SOF 400 + VEL 100	**12**	100%
	SOF 400 + PEG/RBV 1-1.2 g (alt)	**12**	96%
	SOF/SMV 400/150 +/- RBV (no FDA approved)	**12**	100%
5	**SOF/LED 400/90** (F0-4)	**12**	95%
	SOF 400 + VEL 100	**12**	97%
	SOF 400 + PEG/RBV 1-1.2 g (alt)	**12**	?
	GZR 100 + EBV 60 + RBV (no FDA approved)	**12**	100%
	PEG/RBV 1-1.2 g (not recommended)	**48**	55-60%
6	**SOF/LED 400/90**	**12**	96%
	SOF 400 + VEL 100	**12**	100%
	SOF 400 + PEG/RBV 1-1.2 g (alt)	**12**	100%
	GZR 100 + EBV 60 (no FDA approved)	**12**	80%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

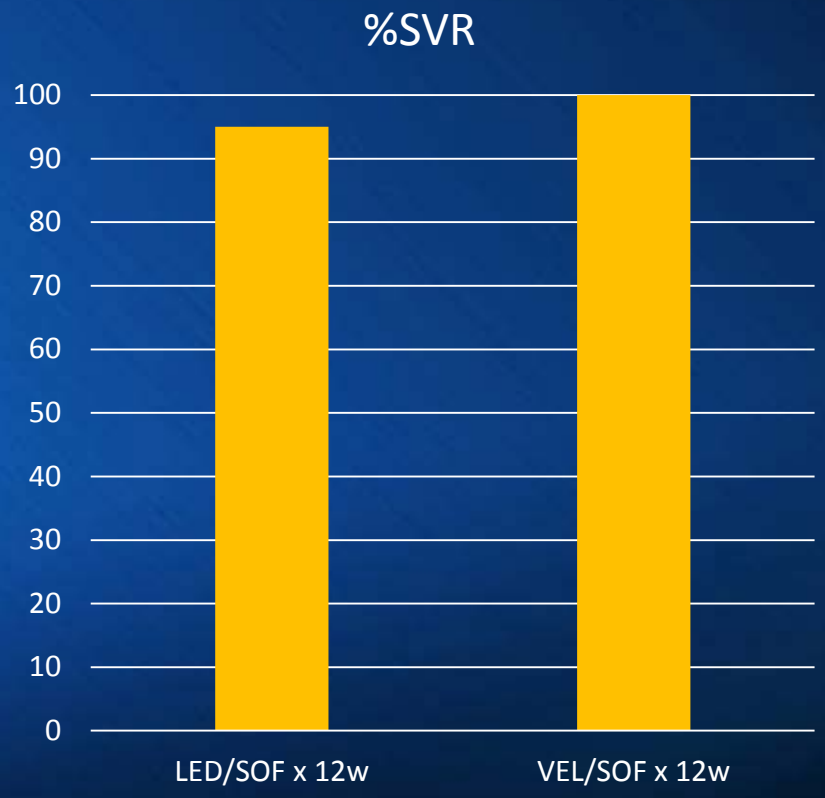
Naïve: Genotypes 4, 5, and 6

First Line Therapy

SVR in Genotype 4



SVR in Genotypes 5 & 6



Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

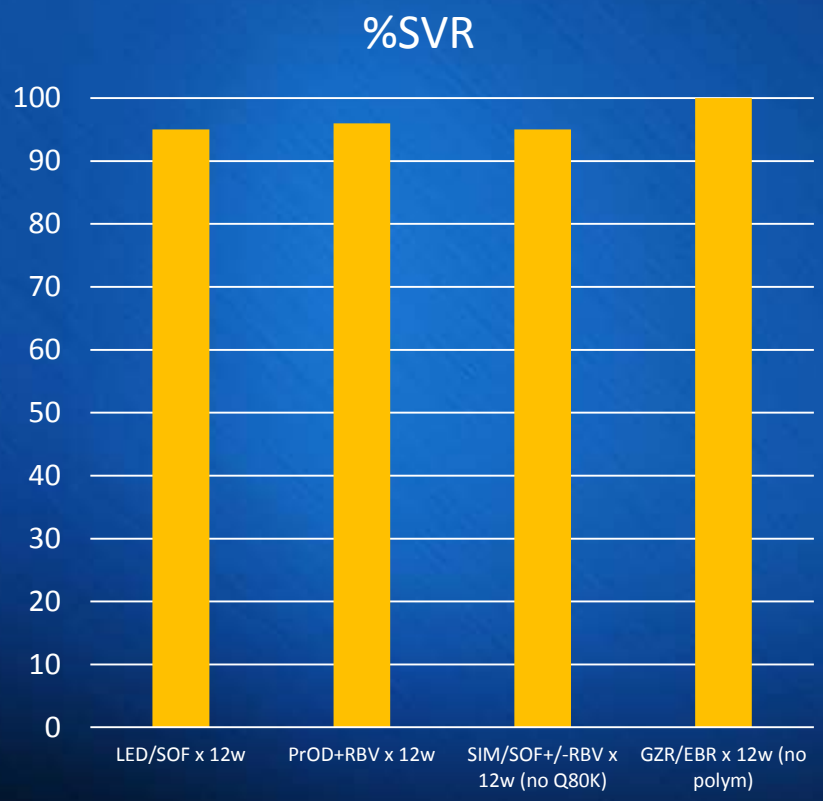
Genotype	Regimen	Duration (weeks)	SVR
1a or 1 unspecified	F0-2: **SOF/LED 400/90**	**12**	95%
	F0-2: **VIEKIRA + RBV 1-1.2 g**	**12**	96%
	F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation)**	**12**	93-96%
	F0-2: **DAC 60 + SOF 400**	**12**	> 82%
	F0-4 comp: **GZR 100 + EBR 50** (no M28, Y93, Q30, or L31 polymorphism)	**12**	100%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g**	**12**	96%
	F3-4: **SOF/LED 400/90**	**24**	100%
	F3-4: **DAC 60 + SOF 400 (alt)**	**24** (+/- RBV 1-1.2)	+/- 60% no-RBV 82% w RBV
	F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation) (alt)**	**24**	93-96%
	F3-4 comp: **VIEKIRA + RBV 1-1.2 (alt)**	**24**	95%
	F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g** (with M28, Y93, Q30, or L31 polymorphism) (alt)	**16**	97%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

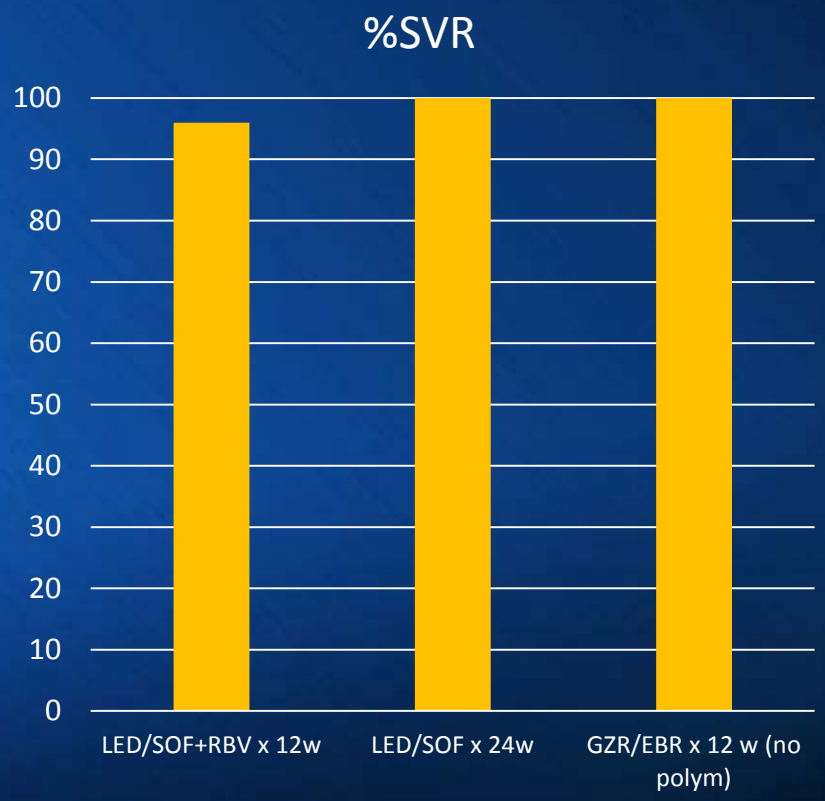
PegIFN NR: Genotype 1a or Unspecified

First Line therapy

SVR in only F0-2



SVR in F3-4



Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

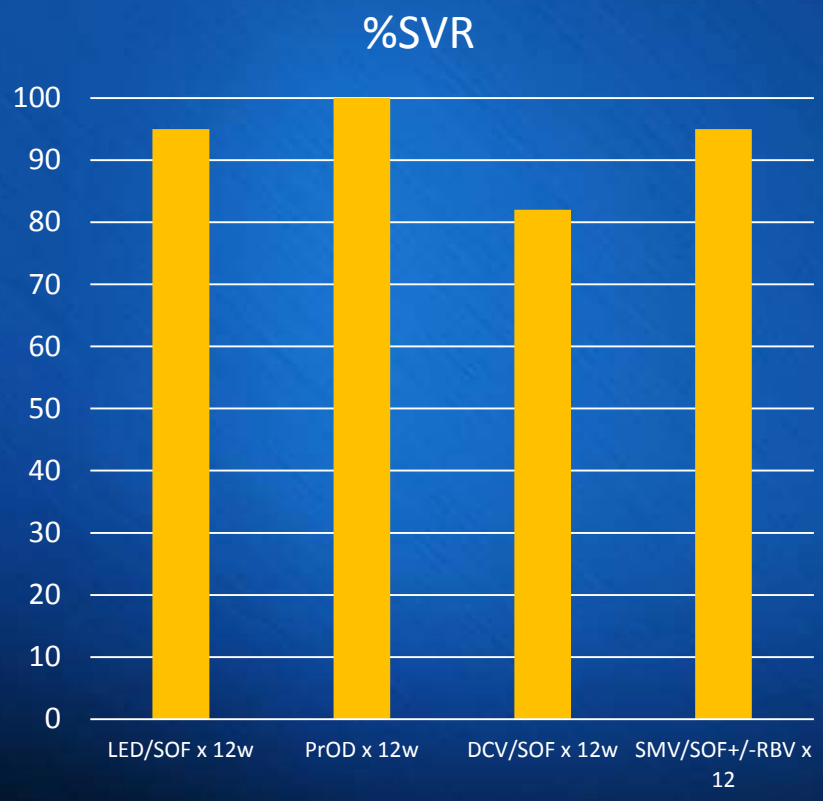
Genotype	Regimen	Duration (weeks)	SVR
1b	F0-2: **SOF/LED 400/90**	**12**	95%
	F0-2: **VIEKIRA** (no RBV)	**12**	100%
	F0-2: **DAC 60 + SOF 400**	**12**	82%
	F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2 g**	**12**	93-96%
	F0-4 comp: **GZR 100 + EBR 50**	**12**	97%
	F3-4 comp: **VIEKIRA**	**12**	99%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g**	**12**	96%
	F3-4: **SOF/LED 400/90**	**24**	100%
	F3-4: **DAC 60 + SOF 400**	**24** (+/- RBV 1-1.2) (alt)	82%
	F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2 g**	**24** (alt)	93-96%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

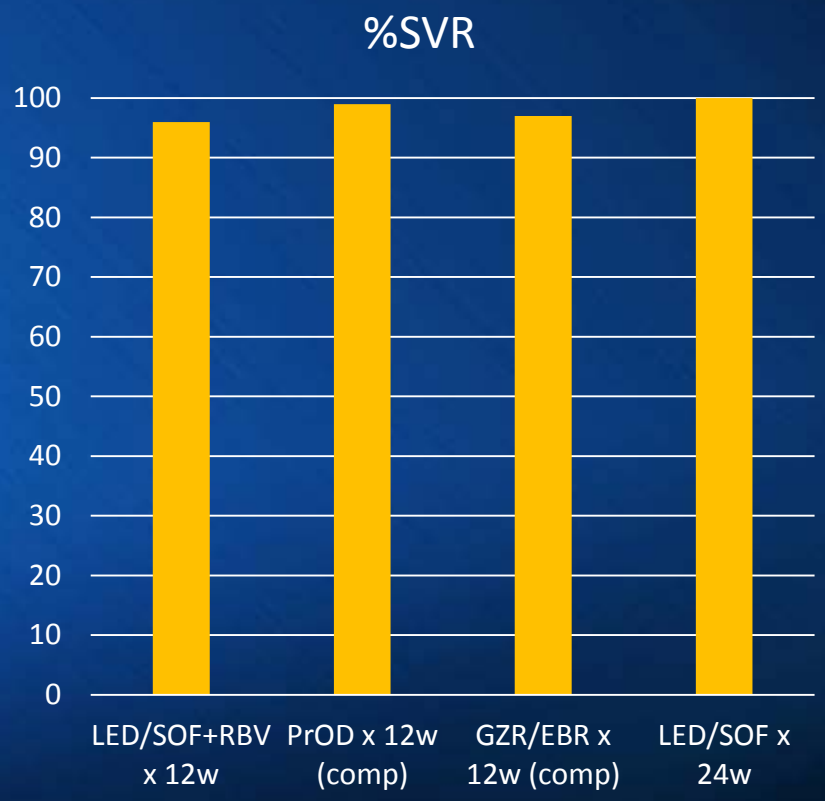
PegIFN NR: Genotype 1b

First Line Therapy

SVR in F0-2 only



SVR in F3-4

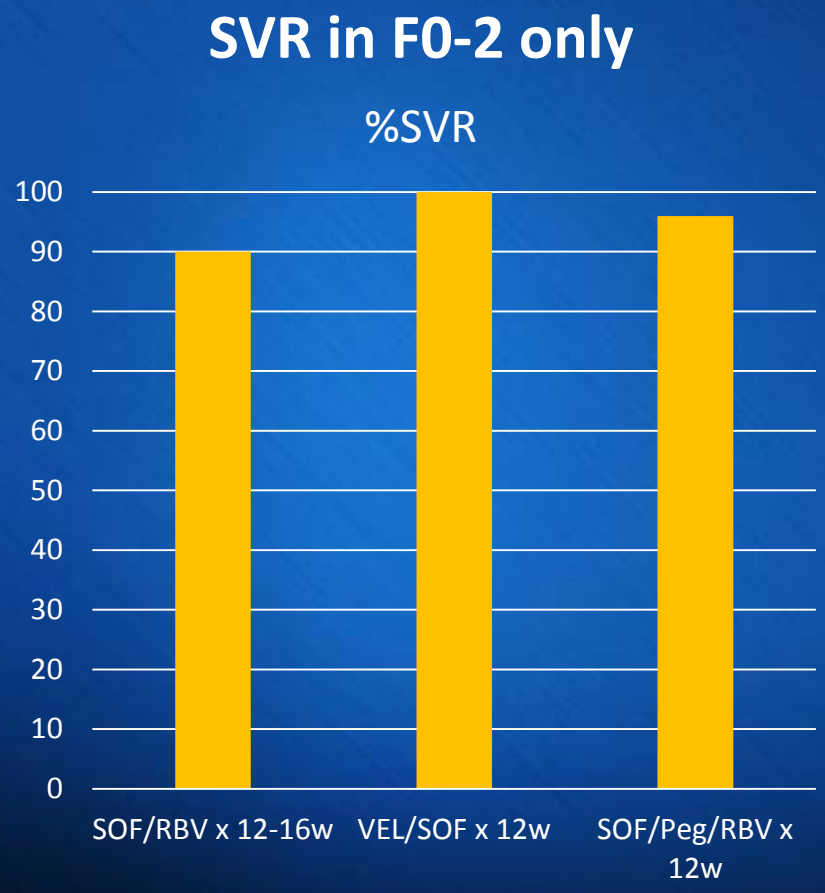


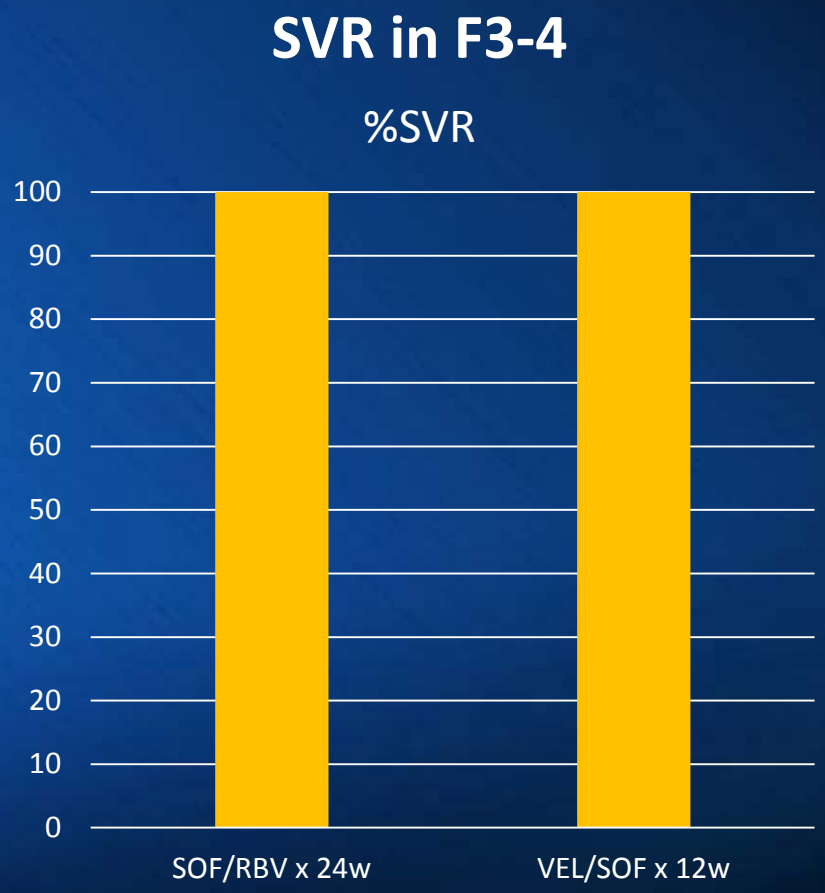
Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

Genotype	Regimen	Duration (weeks)	SVR
2	**SOF 400 + RBV 1-1.2 g**	F0-2: **12-16** F3-4: **24**	88-91% 100%
	DAC 60 + SOF 400 +/- RBV 1-1.2 b	F0-2: **12** F3-4: **16-24**	?
	SOF 400 + VEL 100	**12**	100%
	SOF 400 + PEG/RBV 1-1.2 g (alt)	**12**	96%
3	F0-2: **SOF 400 + RBV 1-1.2g**	**24**	94%
	F0-2: **SOF 400 + PEG/RBV**	**12**	83%
	F0-2: **DCV 60 + SOF 400**	**12**	94%; (F3-4: 58-69)
	F0-2: ***SOF 400 + VEL 100***	**12**	91%
	F3-4: **DCV 60 + SOF 400 + RBV 1-1.2 g**	**24**	"Close to 100%"
	F3-4: **SOF 400 + Peg/RBV 1-1.2 g**	**12**	86%
	F3-4: ***SOF 400 + VEL 100***	**12**	89%
	F3-4: **SOF 400 + RBV 1-1.2 g** (alt)	**24**	60%
	F0-2: **SOF/LED 400/90 + RBV 1-1.2 g** (no FDA approved)	**12**	F0-2: 89% F3-4: 73%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

PegIFN NR: Genotype 2

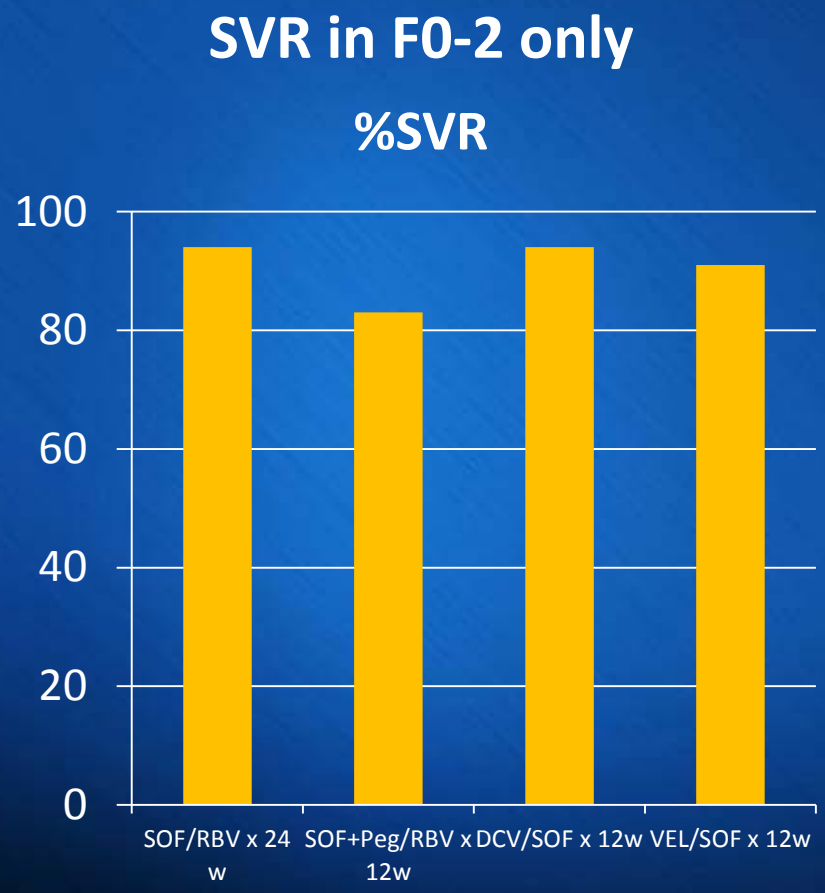


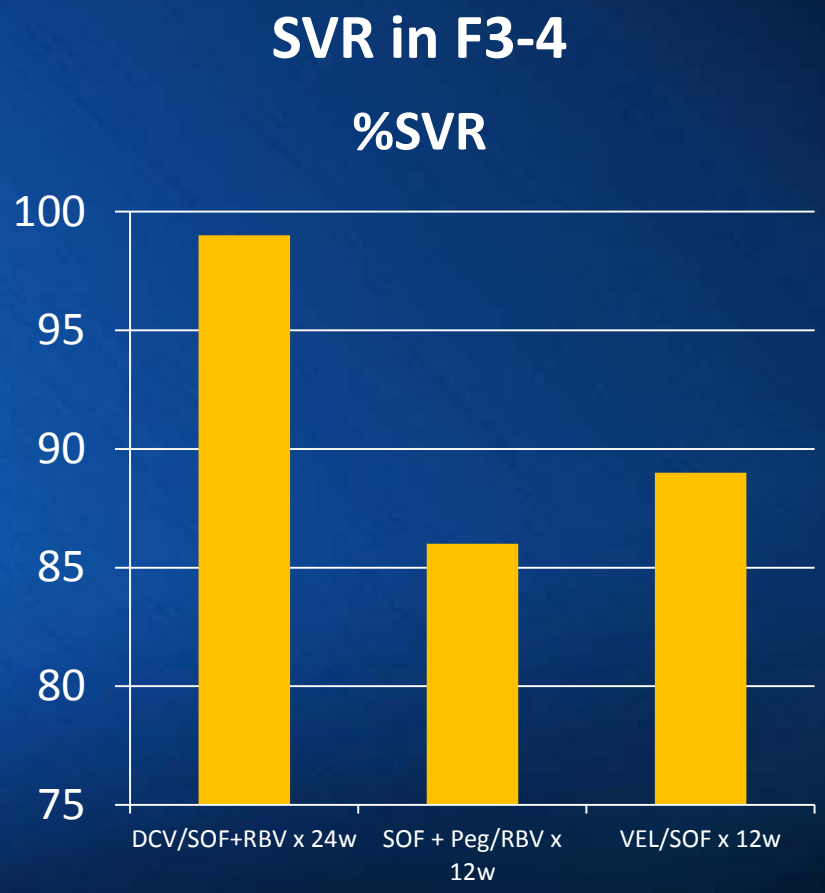


DCV/SOF +/- RBV is also recommended but there is not enough SVR data

PegIFN NR: Genotype 3

First Line Therapy





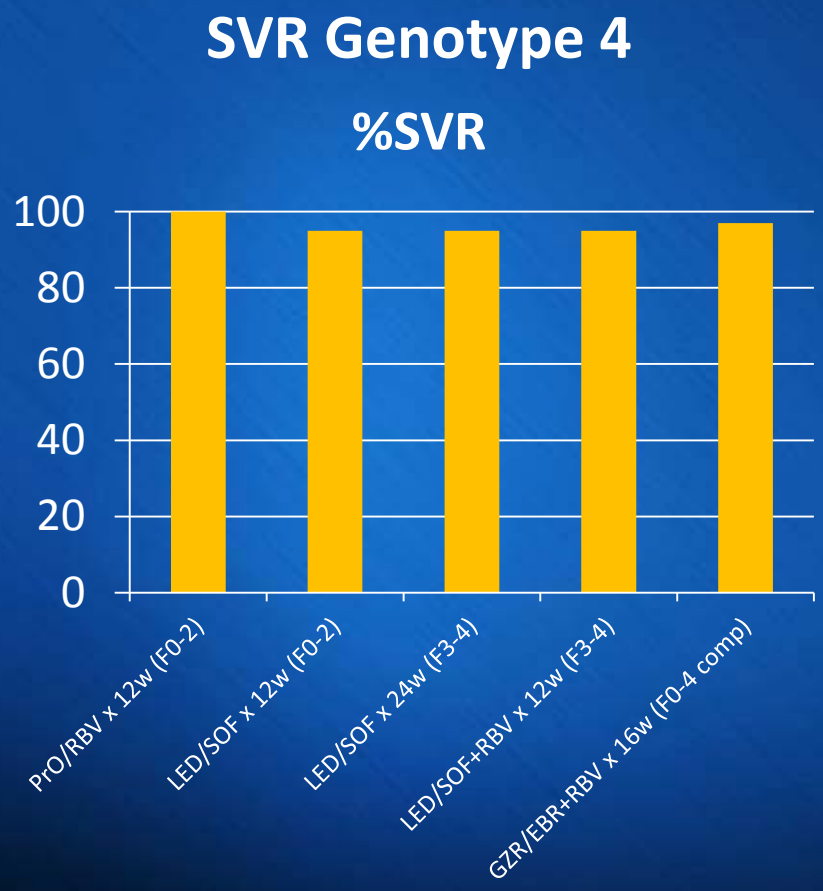
Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

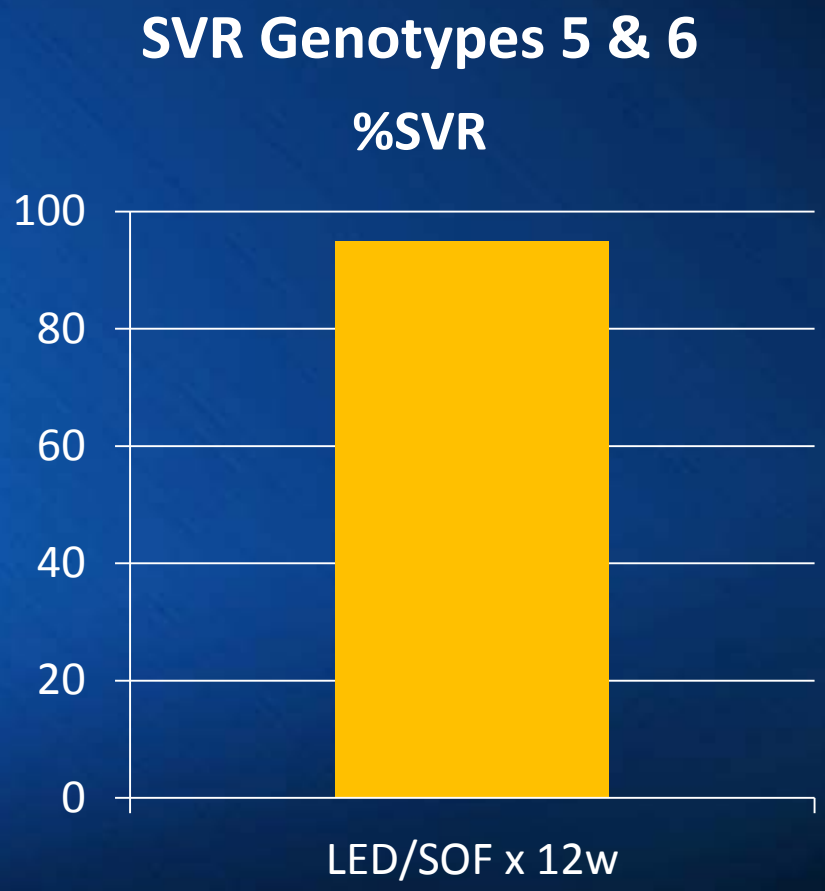
Genotype	Regimen	Duration (weeks)	SVR
4	F0-2: **TECHNIVIE (PrO) + RBV 1-1.2 g**	**12**	100%
	F0-2: **SOF/LED 400/90**	**12**	95%
	F0-4 comp: **GZR 100 + EBR 50 + RBV**	**16**	97%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g**	**12**	95%
	F3-4: **SOF/LED 400/90**	**24**	95%
	F0-4: **SOF 400 + RBV 1-1.2 g (alt)**	**24**	89%
	F0-4: **SOF 400 + PEG/RBV 1-1.2 g (alt)**	**12**	96%
5	**SOF/LED 400/900**	**12**	95%
	SOF 400 + PEG/RBV 1-1.2 g (alt)	**12**	?
6	**SOF/LED 400/90**	**12**	96%
	SOF + Peg/RBV 1-1.2 g (alt)	**12**	100%
	GZR 100 + EBR 50 + RBV 1-1.2 g (no FDA approved)	**16**	97%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

PegIFN NR: Genotypes 4, 5, & 6

First Line Therapy





Treatment in Resistance to Direct Antiviral Agents

No Response to Telaprevir or Boceprevir or Simeprivir	Regimen	Duration (weeks)	SVR
	F0-2: **SOF/LED 400/90**	**12**	96%
	F0-2: **DAC 60 + SOF 400**	**12**	95% ?
	F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g**	**12 (16 with RAV mutant)**	96%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g**	**12**	97%
	F3-4: **SOF/LED 400/90**	**24**	97%
	F3-4: **DAC 60 + SOF 400**	F3-4: **24** (+/- RBV 1-1.2)	100%
No Response to Sofosbuvir	**Regimen**	**Duration (weeks)**	**SVR**
NS5A is (-) to RAVs	F3-4: **SOF/LED 400/90 + RBV 1-1.2** g	**24**	100%
	F0-2 with urgent need for therapy: **SOF/LED 400/90 + RBV 1-1.2 g**	**12**	100%
(Genotype 2 or 3 failure to SOF/RBV)	**DAC 60 + SOF 400 + RBV 1-1.2**	**24**	70%?
	SOF 400 + PEG/RBV	**12**	70%?
NS5A is (+) but NS3A is (-) to RAVs	**SMV/SOF 150/400**	**24**	?

RAVs = Virus with “Resistance Associated Variants”

Treatment of Decompensated Cirrhosis
(Child-Pugh class B or C)

Genotype	Regimen	Duration (weeks)	SVR
1 o 4	**SOF/LED 400/90 + RBV 600-1200** increasing as tolerated	**12** **24** if SOF failure, or without RBV	86%
	SOF 400 + VEL 100 + RBV 1-1.2g (C-P B)	**12**	94% in g1a; 100% g1b 100% in g4
	SOF 400/DCV 60 + RBV 600-1000	**12-24** with RBV **24** without RBV	12: g1:83%; g4: 100% - 24: close to 100% in g1 Unknown (without RBV)
	GZR 50 + EBR 50 (C-P B, geno-1) **(no FDA approved)**	**12**	95%
2	**SOF/LED 400/90 +/- RBV 600-1200** **(no FDA approved)**	**12**	?
2 o 3	**SOF 400/DCV 60 + RBV 600-1000**	**12** (g2 if Naive) **24** (g3, or g2 if previously treated)	80% 88% in g3
	SOF 400 + VEL 100 + RBV 1-1.2g (C-P B)	**12**	100% in g2 85% in g3

Ideally treated at the Transplant Center

Treatment After Transplant

Genotype	Regimen	Duration (weeks)	SVR
1	F0-4: **SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day)	**12**	96%
	F0-4: **SOF/LED 400/90**	**24**	?
	F0-4: **SOF 400 + DCV 60 +/- RBV 600-1000**	**12** (with RBV) **24** (without RBV)	1a: 97% 1b: 90%
	Only in F0-2: **VIEKIRA + RBV 1-1.2 (alt)** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day) [CSA :1/5 of usual dose when starting Viekira and follow daily levels; TAC do not give on 1st day of Viekira; monitor levels and then give 0.5 mg/week as determined by levels]	**24**	1a: 97% 1b: 100%
	F0-4 comp: **SOF 400 + SIM 150 +/- RBV 1-1.2 g (alt)** (not in genotype 1a with Q80K mutation)	**12**	92%
4	**SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day)	**12**	96%
	SOF/LED 400/90	**24**	?
	SOF 400 + DCV 60 + RBV 600-1000	**12** (with RBV) **24** (without RBV)	91%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

Treatment After Transplant

Genotype	Regimen	Duration (weeks)	SVR
2	**Sofosbuvir (400 mg) and RBV 1-1.2 g** (RBV: if decompensated, start with 600 mg/day, and increase weekly as tolerated up to 1000 mg/day [<75 kg] or 1200 mg/ day [≥75 kg] 1200 mg depending on Clcr and hemoglobin).	**24**	?
	DAC 60 + SOF 400 +/- RBV 600-1200 (F0-4 comp)	**12** (with RBV) **24** (without RBV)	?
	SOF/LED 400/90 if intolerant to RBV (no FDA approved)	**12**	?
3	**Sofosbuvir (400 mg) and RBV 1-1.2 g** (RBV: if decompensated, start with 600 mg/day, and increase weekly as tolerated up to 1000 mg/day [<75 kg] or 1200 mg/ day [≥75 kg] 1200 mg depending on Clcr and hemoglobin).	**24**	?
	SOF 400 + DCV 60 + RBV 600-1200 mg	**12** **24** without RBV **24** with RBV for fibrosing cholestatic hepatitis	91%
	SOF/LED + RBV (?) no enough data (no FDA approved)		?

Treatment of HIV/HCV Co-infected Patients

- ***Patients with HCV-HIV co-infection should be treated with the same regimen as HCV mono-infected patients.***
- **HARVONI:**
  - African-American patients respond less to Harvoni.
  - The theoretical risk of Renal damage from Tenofovir in patients receiving Atripla has not been seen in the clinical trials.
  - Treatments of only 8 weeks with Harvoni or with DAC + SOF are probably insufficient for co-infection; treat for 12 weeks.
  - Harvoni should not be given with Tenofovir if the GFR is < 60 mL/min, and should not be co-administer with Protease Inhibitors boosted with Ritonavir.
- **Viekira Pak:** should not be given to co-infected patients who are not receiving anti-HIV therapy.
- **DAC + SOF:** Patients receiving darunavir/r could have inferior response.
- **RIBAVIRIN:** Do not give to patients taking didanosine, stavudine, or zidovudine.
- ***DO NOT INTERRUPT ANTI-HIV THERAPY.***

Dose Adjustment for Renal Impairment

Renal Impairment	eGFR / CrCl level (mL/min)	PEG-IFN	RBV	Sofosbuvir	Ledipasvir	Daclatasvir	Ombitasvir	Dasabuvir	Paritaprevir	Simeprevir
Mild	50-80	**PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1.5 µg/kg**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**
Moderate	30-50	**PEG-IFN (2a) 180 µg; PEG-IFN (2b) 1 µg/kg (25% reduction)**	**Alternating doses 200 mg and 400 mg every other day**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**	**Standard**
Severe	<30	**PEG-IFN (2a) 135 µg; PEG-IFN (2b) 1 µg/kg (50% reduction)**	**200 mg/d**	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	**Standard**
ESRD with HD		**PEG-IFN (2a) 135 µg/wk or PEG-IFN (2b) 1 µg/kg/wk or standard IFN 3 mU 3x/wk**	**200 mg/d**	Limited data available	Data not available	Limited data available	Limited data available	Limited data available	Limited data available	Limited data available

Treatment of HCV in CKD 4/5 +/- Hemodialysis
(GFR < 30 mL/min)

Genotype	Regimen	Duration (weeks)	SVR
1a & 1 b (F0-3)	Viekira (+ RBV 200 TIW in 1a)	**12**	90%
1 & 4 (probably also 2, 5, y 6)	GZR 100 + EBR 50	**12**	99% in geno-1
2, 3, 5, 6	PegIFN + RBV 200 a day	**24-48 weeks**	

Patients with GFR > 30 mL/min can be treated with standard doses of other regimens

Suggested RBV dose by Creatinine Clearance

Kamar N et al. Am J Kidney Dis. 2004;43:140-146 &
Bruchfeld A et al. Drug Monit. 2002;24:701-708

Creatinine Clearance (Cockcroft-Gault)	>/= 100 mL/min	80 mL/min	60 mL/min	40 mL/min	20 mL/min	< 20 mL/min
RBV (mg/day)	1200	1000	800	600	400	200

SLAM-C: Sofosbuvir + Ledipasvir or Simeprevir for Acute HCV Infection

- Randomized, open-label, prospective pilot study
  - N = 29 pts with acute HCV infection at 6 drug rehabilitation centers (NYC)
- Group A (n = 14)
  - LDV/SOF 90/400 mg QD for 4 wks
- Group B (n = 15)
  - SOF 400 mg + SMV 150 mg QD for 8 wks

Outcome, % (n/N)	LDV/SOF for 4 Wks (n = 14)	SOF + SMV for 8 Wks (n = 15)
SVR12		
▪ All pts	100 (14/14)	87 (13/15)
▪ Per protocol*	100 (14/14)	100 (13/13)
Retention through 20 wks	93 (13/14)	87 (13/15)

*Excludes pts lost to follow-up or who discontinued for nonvirologic reasons.

Basu P, et al. AASLD 2015. Abstract 1074.

Ribavirin and Teratogenicity

- Patients should be informed that Ribavirin is teratogenic.
- Ribavirin should not be started unless a pre-treatment pregnancy test has been negative.
- Women of childbearing potential and all males should use 2 methods of contraception during treatment and for 6 months after therapy.
- If pregnancy occurs, they should be advised of the significant teratogenic risk to the fetus.
- Physicians are strongly encouraged to report any pregnancy in a patient or partner, during treatment or 6 months after treatment to: Ribavirin Pregnancy Registry @ 1-800-593-2214

Follow up During Therapy

- Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (GFR), and hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated.
  - More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated.
- Thyroid-stimulating hormone (TSH) is recommended every 12 weeks for patients receiving IFN.

Follow up During Therapy

- Any 10-fold increase in alanine aminotransferase (ALT) activity at week 4 should prompt discontinuation of therapy.
- Any increase in ALT of less than 10-fold at week 4 and accompanied by any weakness, nausea, vomiting, jaundice, or increased bilirubin, alkaline phosphatase, or international normalized ratio should also prompt discontinuation of therapy.
- Asymptomatic increases in ALT of less than 10-fold elevated at week 4 should be closely monitored and repeated at week 6 and week 8. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.

Follow up During Therapy

- If quantitative HCV viral load is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6).
  - If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), then discontinuation of HCV treatment is recommended.
- The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week 6 or week 8 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.

Management after Treatment

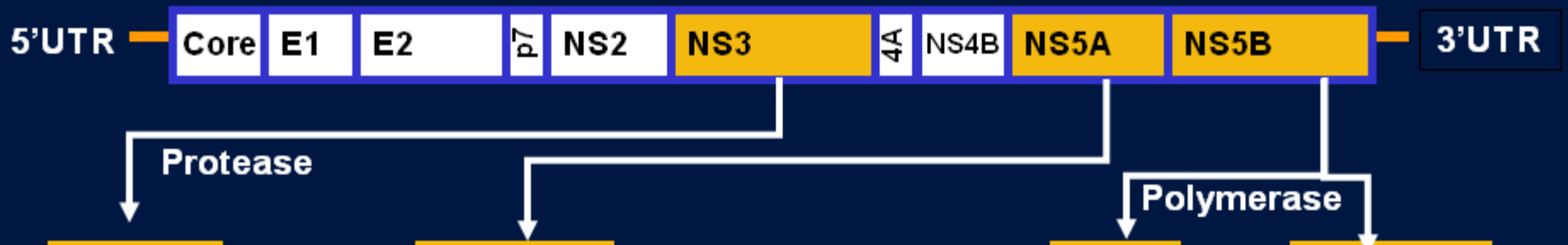
- Patients are considered “cured from hepatitis C” if the HCV-RNA is negative 12 weeks after the end of therapy.
  - Is reasonable to confirm cure 18 months after the end of therapy.
- Patients with “early disease” (F0-2) can be discharged if cured.
- Patients with “advanced disease” (F3-4) need long-term follow-up with:
  - Liver Ultrasound every 6 months to R/O HCC;
  - Clinical and Laboratory follow up for early detection of complications from cirrhosis or portal hypertension,
  - Patients with cirrhosis should be evaluated for gastro-esophageal varices with EGD.
- Non-Responder patients:
  - Need to be considered for re-treatment, under the care of a Hepatologist or other expert.
  - Should be evaluated for disease progression every 6-12 months with CBC, Hepatic Panel, and PT/INR.

Cost Effectiveness for IFN-Free Regimens
(Dollars/QUALY) (Good value = $ 50,000 – 100,000)

- Genotype 1:
  - Naive: $ 0 - 31,452 (depending on cirrhosis).
  - IFN-Experienced: $ 84,744 – 178,295
- Genotype 2:
  - $35,500 - $238,000 (depending on cirrhosis)
- Genotype 3:
  - Up to $410,548
  - PEG-IFN + SOF + RBV is most cost effective
- Genotype 4:
  - $34,349 - $80,793 (depending on cirrhosis)

Thank you for your attention

Multiple Direct Acting Antivirals



Protease

Polymerase

HCV PIs

NS5A Inhibitors

NS5B Nucs

NS5B Non-nucs

Viral enzyme
Active site

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir
Paritaprevir
Grazoprevir
Sovaprevir
ACH-2684

Non-enzyme
Replication complex

Daclatasvir
Ledipasvir
Ombitasvir
ACH-3102
Ravidasvir
GSK2336805
Samatasvir
Elbasvir
Velpatasvir

Viral enzyme
Active site

Sofosbuvir
VX-135
IDX20963
ACH-3422

Viral enzyme
Allosteric site

Dasabuvir
Deleobuvir
BMS-791325
PPI-383
GS-9669
TMC647055

Direct-Acting Antiviral Profiles

	Direct-Acting Antiviral					
	NS3[1]	NS3[2]	NS5A[1]	NS5A[2]	Non Nuc NS5B	Nuc NS5B
Resistance profile	🔴	🟡	🟡	🟢🟡	🔴	🟢
Pan-genotypic efficacy	🔴	🟢🟡	🟡	🟢🟡	🟡	🟢
Efficacy	🟡	🟢	🟢	🟢	🟡	🟢
Adverse events	🔴	🟢	🟡	🟢	🟡	🟡
Drug-drug interactions	🔴	🟡	🟡	🟡	🟡	🟢

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

[1] 1st generation.
[2] 2nd generation.

DAAs and HIV anti-Retrovirals

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

DAAs and Lipid Lowering Drugs

	SIM	DCV	SOF	SOF/ LDV	3D
Atorvastatin	•	•	•	•	•
Bezafibrate	•	•	•	•	•
Ezetimibe	•	•	•	•	•
Fenofibrate	•	•	•	•	•
Fluvastatin	•	•	•	•	•
Gemfibrozil	•	•	•	•	•
Lovastatin	•	•	•	•	•
Pitavastatin	•	•	•	•	•
Pravastatin	•	•	•	•	•
Rosuvastatin	•	•	•	•	•
Simvastatin	•	•	•	•	•

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

DAAs and CNS Drugs

		SIM	DCV	SOF	SOF/ LDV	3D
Anti-depressants	Amitriptyline	•	•	•	•	•
	Citalopram	•	•	•	•	•
	Duloxetine	•	•	•	•	•
	Escitalopram	•	•	•	•	•
	Fluoxetine	•	•	•	•	•
	Paroxetine	•	•	•	•	•
	Sertraline	•	•	•	•	•
	Trazodone	•	•	•	•	•
	Trimipramine	•	•	•	•	•
	Venlafaxine	•	•	•	•	•
Anti-psychotics	Amisulpiride	•	•	•	•	•
	Aripiprazole	•	•	•	•	•
	Chlorpromazine	•	•	•	•	•
	Clozapine	•	•	•	•	•
	Flupentixol	•	•	•	•	•
	Haloperidol	•	•	•	•	•
	Olanzapine	•	•	•	•	•
	Quetiapine	•	•	•	•	•
	Risperidone	•	•	•	•	•

DAAs and Cardiovascular Drugs

		SIM	DCV	SOF	SOF/ LDV	3D
Antiarrythmics	Amiodarone	•	•	•	•	•
	Digoxin	•	•	•	•	•
	Flecainide	•	•	•	•	•
	Vernakalant	•	•	•	•	•
Antiplatelet and anticoagulants	Clopidogrel	•	•	•	•	•
	Dabigatran	•	•	•	•	•
	Warfarin	•	•	•	•	•
Beta blockers	Atenolol	•	•	•	•	•
	Bisoprolol	•	•	•	•	•
	Propranolol	•	•	•	•	•
Calcium channel blockers	Amlodipine	•	•	•	•	•
	Diltiazem	•	•	•	•	•
	Nifedipine	•	•	•	•	•
Hypertension and heart failure agents	Aliskiren	•	•	•	•	•
	Candesartan	•	•	•	•	•
	Doxazosin	•	•	•	•	•
	Enalapril	•	•	•	•	•

GREEN: NO INTERACTION; AMBER: DOSE ADJUSTMENT; RED: DO NOT CO-ADMINISTER

Concomitant Medications	Ledipasvir	Daclatasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Acid-reducing agents*	-Decrease Omeprazole not to exceed 20 mg a day.		-Increase Omeprazole but do not exceed 40 mg a day ; decreases effect of Omeprazole.		
Alfuzosin/tamsulosin			-Do not take with Viekira; can cause hypotension.		
Anticonvulsants	-AVOID: Carbamazepine, Phenytoin; decrease Ledispavir	-CONTRAINDICATED: Phenytoin, Carbamazepine	-Do not take with Carbamazepine, phenytoin, Phenobarbital. Loss of effectiveness of Viekira.	-DO NOT USE; DECREASES SIMEPREVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin.	-DO NOT USE; DECREASES SOFASBUVIR EFFECT: Carbamazepine, Oxcarbazepine, Phenobarbital, Phenytoin
Antiretrovirals*	-with tenofovir only if CrCl >/= 60; -DO NOT USE with cobicistat, elvitegravir nor tipranavir	-Monitor for DAC adverse events: Atazanavir, fosanprenavir, darunavir/ritonavir. -Increase dose to 90 mg/d: Efavirenz, Etravirine	-Atazanavir without Ritonavir: give only 300 mg and only in am. Likely to elevate bilirubin. -Do not give Darunavir/Ritonavir -Do not give Lopinavir/Ritonavir -Do not give Rilpivirine (QT prolongation) -Do not give with Efavirenz (liver enzyme elevation).	-DO NOT USE; INCREASES SIMEPREVIR LEVELS: Cobicistat-containing product (elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate), Darunavir, Ritonavir -DO NOT USE; DECREASES SIMEPREVIR EFFECT: Efavirenz -DO NOT USE; VARIABLE EFFECT ON SIMEPREVIR: Atazanavir, Fosamprenavir, Lopinavir, Indinavir, Nelfinavir, Saquinavir, Tipranavir, Delavirdine, Etravirine, Nevirapine	-DO NOT USE; DECREASES SOFOSBIVIR EFFECT: tipranavir / ritonavir only.
Azole antifungals*		-Monitor for DAC adverse events: Fluconazole. -Decrease DAC to 30/day: Itraconazole, Ketoconazole, Posaconazole, Voriconazole.	-Do not exceed Fluconazole 200 mg a day. -Avoid using Voriconazole.	-DO NOT USE; INCREASES SIMEPREVIR LEVELS: Itraconazole, Ketoconazole, Posaconazole, Fluconazole , Voriconazole.	
Buprenorphine/ naloxone			-No dose modification, BUT monitor closely for sedation and cognitive effects.		

Concomitant Medications	Ledipasvir	Daclatasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Calcineurin inhibitors*			-Reduce CSA to 1/5th of original dose and monitor levels; readjust by blood levels at EOT. Monitor renal function. -Tacrolimus: do not give in day 1 of Viekira; start day 2 with 0.5 mg a week adjusting dose and frequency by blood levels. Monitor renal function.	-MODEST EFFECT AND REQUIRES MONITORING: Cyclosporine, Tacrolimus, Sirolimus	
Calcium channel blockers*		-Monitor for DAC adverse events: Diltiazem, Verapamil	- Dose reduce Amlodipine and monitor BP.	-USE WITH CAUTION AND MONITORING: Amlodipine, Diltiazem , Felodipine, Nicardipine, Nifedipine, Nisoldipine, Verapamil	
Cisapride			X	-Increases Cisapride level	
Digoxin	-AVOID: increases Digoxin levels.	-Measure Digoxin level and decrease dose by 30-50%, and monitor level. -Start Digoxin at lowest possible dose and monitor levels.		-Increases Digoxin levels; reduce dose and monitor levels.	
Ergot derivatives			-Do not give with Ergotamine, dihydroergotamine, methylergonovine.; can cause ergot toxicity (vasospasm + ischemia).		
Ethinyl estradiol–containing products			-Do not give with BCPs or patches (Lo Estrin, FE, Norinyl, Ortho Tri-Cyclen Lo, Ortho Evra), or Rings (NuvaRing), or hormone replacement (FEM HRT); Causes ALT elevation.		
Furosemide			-Increases effect of furosemide; reduce dose or monitor.		

Concomitant Medications	Ledipasvir	Daclatasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Gemfibrozil			-Do not take with Gemfibrozil (Lopid); causes QT prolongation.		
Glucocorticoids		-Increase DAC to 90 mg/d: Dexamethasone	-Inhaled, or Intranasal Fluticasone is absolved in excess and causes decreased cortisol levels.	-Decreases Simeprivir effect: Dexamethasone.	
Herbals **St. John's wort** **Milk thistle**		-CONTRAINDICATED with St John's wort.	-Causes loss of activity of Viekira: St. John's wort	-DO NOT USE; DECREASES SIMEPREVIR LEVEL: St John's wort. -DO NOT USE; INCREASE SIMEPREVIR LEVEL: Milk Thistle	-DO NOT USE; DECREASES SOFOSBUVIR EFFECT: St. John's wort
Macrolide antimicrobials*		-Decrease DAC to 30 mg/d: Clarithromycin, Telithromycin. -Increase DAC to 90 mg/d: Nafcillin, Rifapentine. -Monitor for DAC adverse events: Ciprofloxacine, Erythromycin.		-DO NOT USE: Erythromycin, Clarithromycin, Telithromycin; increases Simeprivir levels. -Simeprevir also increases antibiotic level.	
Other antiarrythmics*		-CONTRINDICATED: Amiodarone + SOF/DAC	-USE WITH CAUTION AND MONITORING: Amiodarone, Bepridil, Disipyramide, Flecainidine, Lidocaine (systemic), Mexiletine, Propafenone, Quinidine; increases antiarrhythmic effect; follow drug levels.	-USE WITH CAUTION AND MONITORING: Digoxin, Amiodarone, Disopyramide, Flecainide, Mexiletine, Propafenone, Quinidine	
Phosphodiesterase type 5 inhibitors*			-Revatio CONTRAINDICATED because effect is increased; risk of visual disturbance, hypotension, priapism, and syncope.	-USE WITH CAUTION AND MONITORING: Sildenafil , Tadalafil , Vardenafil all need dose adjustment when treating pulmonary hypertension.	

Concomitant Medications	Ledipasvir	Daclatasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Pimozide			-Do not give Pimozide with Viekira; risk of cardiac arrhythmias.		
Rifamycin antimicrobials	-AVOID; Decreases Ledipasvir level.	-CONTRAINDICATED: Rifampin	-Rifampin causes loss of effect of Viekira.	-DO NOT USE; Decrease Simeprivir level: Rifampin, Rifabutin, Rifapentine	-DO NOT USE; DECREASES SOFOSBUVIR EFFECT: Rifampin, Rifabutin, Rifapentine
Salmeterol			-Not recommended due to increased risk of QT prolongation and sinus tachycardia.		
Sedatives			- Do not give with Oral Midazolam nor Triazolam; prolonged sedation and respiratory depression. -Alprazolam : consider dose reduction; effect is increased.	-USE WITH CAUTION AND MONITORING: Oral Midazolam and Triazolam	
Simeprevir	-AVOID: Increases levels of both drugs.				
Statins	-Rosuvastatin: AVOID; Increases rosuvastatin level and risk of myopathy and rhabdomyolysis.	-Monitor for Myopathy and other side effects: Atorvastatin, Fluvastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin.	-CONTRAINDICATED with Lovastatin and Simvastatin ; risk of myopathy and rhabdomyolysis. -Limit Rosuvastatin to 10 mg/d . -Limit Pravastatin to 40 mg/d.	-Rosuvastatin max 10 mg, -Atorvastatin max 40 mg, -Simvastatin lowest possible dose, -Pitavastatin lowest possible dose, -Pravastatin lowest possible dose, -Lovastatin lowest possible dose	

Concomitant Medications	Ledipasvir	Daclatasvir	Paritaprevir / Ritonavir / Ombitasvir + Dasabuvir	Simeprevir	Sofosbuvir
Anticoagulants		-Do not use in Renal Impairment: Dabigatran etexilate mesylate	-		
Antidepressants		-Decrease DAC to 30 mg/d: Nefazodone			
Eugeroics		-Increase DAC to 90 mg/d: Modafinil			
Antihypertensives		-Increase DAC to 90 mg/d: Bosentran.			