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.

Summary Treatment Tables

Agents and Regimens Currently Used

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 and XR or PrOD or 3D)	⊙	⊙	⊙		⊙ RBV only for 1a or F3-4
Sofosbuvir + ribavirin				⊙	⊙
Daclatasvir + sofosbuvir		⊙		⊙	
Grazoprevir + Elbasvir (ZEPATIER)	⊙	⊙			
Velpatasvir + Sofosbuvir (EPCLUSA)		⊙		⊙	
Sofosbuvir + Velpatasvir + Voxilaprevir (Vosevi®)	⊙	⊙		⊙	
Glecaprevir + Pibrentasvir (Mavyret)	⊙	⊙			

Treatment of HCV in Treatment-Naïve Patients

Simplified HCV Treatment for Treatment-Naïve Patients Without Cirrhosis

ELIGIBLE FOR SIMPLIFIED HCV TREATMENT

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received Hepatitis C treatment

PRETREATMENT ASSESSMENT

Cirrhosis Assessment
- Biopsy not required
- Cutoffs suggesting cirrhosis
  - FIB-4 >3.25
  - APRI >2.0
  - Platelets <150,000/mm^3
  - FibroScan >12.5 kPa

Medication Reconciliation
- Current Rx and OTC

DDI Assessment

Education
- Tx administration, adherence, avoidance of alcohol, and reinfection

Pretreatment Lab Testing

Within 6 months
- CBC
- Hepatic function panel
- eGFR

Prior to starting antiviral therapy
- Quantitative HCV RNA (HCV viral load)
- HIV antigen/antibody test
- HBsAg

Before initiating Tx
- Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

NOT ELIGIBLE FOR SIMPLIFIED HCV TREATMENT

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Cirrhosis
- Prior liver transplant
- HIV or HBsAg positive
- Known or Suspected Hepatocellular Carcinoma
- Currently pregnant

RECOMMENDED REGIMENS

SOF/VEL for a duration of 12 weeks

GLE/PIB to be taken with food for a duration of 8 weeks

APRI, aspartate aminotransferase (AST) to platelet ratio index; CBC, complete blood count; DDI, drug–drug interaction; FIB-4, Fibrosis-4; GLE, glecaprevir; OTC, over-the-counter; PIB, pibrentasvir; RNA, ribonucleic acid.

AASLD/IDSA HCV Guidance, updated August 27, 2020
Available at: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Treatment_a.pdf

Simplified HCV Treatment for Treatment-Naïve Patients With Compensated Cirrhosis

ELIGIBLE FOR SIMPLIFIED HCV TREATMENT

Patients with chronic hepatitis C who do not have cirrhosis and have not previously received Hepatitis C treatment

PRETREATMENT ASSESSMENT

Cirrhosis Assessment
- Prior Biopsy showing Cirrhosis, or
- Cutoffs suggesting cirrhosis (Biopsy not required)
  - FIB-4 >3.25
  - APRI >2.0
  - Platelets <150,000/mm^3
  - FibroScan >12.5 kPa

Medication Reconciliation
- Current Rx and OTC

Drug-Drug Interaction Assessment

Education
- Tx administration, adherence, avoidance of alcohol, and reinfection

Pretreatment Lab Testing

Within 6 months
- CBC
- Hepatic function panel
- eGFR

Prior to starting antiviral therapy
- Quantitative HCV RNA (HCV viral load)
- HIV antigen/antibody test
- HBsAg

Before initiating Tx
- Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

NOT ELIGIBLE FOR SIMPLIFIED HCV TREATMENT

Patients who have any of the following characteristics:
- Prior hepatitis C treatment
- Current or Prior Cirrhosis Decompensation (Child-Pugh >/= 7)
- ESRD with GFR < 30 mL/min/m^2
- Prior liver transplant
- HIV or HBsAg positive
- Known or Suspected Hepatocellular Carcinoma
- Currently pregnant

RECOMMENDED REGIMENS

SOF/VEL in Genotypes 1, 2, 4, 5, 6, or in 3 without Y93H NS5A RAS, for a duration of 12 weeks	**GLE/PIB** to be taken with food for a duration of 8 weeks

APRI, aspartate aminotransferase (AST) to platelet ratio index; CBC, complete blood count; DDI, drug–drug interaction; FIB-4, Fibrosis-4; GLE, glecaprevir; OTC, over-the-counter; PIB, pibrentasvir; RNA, ribonucleic acid.

AASLD/IDSA HCV Guidance, updated August 27, 2020
Available at: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Treatment_a.pdf

Simplified HCV Treatment for Treatment-Naïve Patients

ON-TREATMENT MONITORING

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

POST-TREATMENT ASSESSMENT

- In patients with cirrhosis, may order blood tests to monitor for decompensation.
- Monitoring patients taking diabetes medication
- Monitoring INR for patients taking warfarin
- Assessment of quantitative HCV RNA and hepatic function 12 weeks after completion of therapy
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR

FOLLOW-UP AFTER SVR

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR;
- Cirrhotic patients should have U/S +/- AFP every 6 months, and surveillance with EGD for varices as per AASLD.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.

FOLLOW-UP FOR PATIENTS WHO DO NOT ACHIEVE SVR

- Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and international normalized ratio (INR) is recommended.
- Cirrhotic patients should have U/S +/- AFP every 6 months, and surveillance with EGD for varices as per AASLD.
- Patients in whom initial HCV treatment fails to achieve cure (SVR) can be retreated, often successfully. Consult the AASLD/IDSA guidance

ALT, alanine aminotransferase; CBC, compete blood count; INR, international normalized ratio; MSM, men who have sex with men; SVR, sustained virologic response.

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Available at: https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCV-Guidance_TxN-Simplified-Treatment_a.pdf

HCV: Genotype 1A and 1B

Treatment Naïve or PEG-IFN/RBV Relapser, Non-cirrhotic

Regimen	Weeks	Study	SVR12
Sofosbuvir + Ledipasvir (HCV RNA <6 M IU/mL) (HCV RNA >6 M IU/mL)	 8 12	ION-3	 119/123 (97%) 206/216 (95%)
Elbasvir/Grazoprevir (1b) (-) for NS5A RAVs (1a)	12	C-EDGE	133/135 (99%) 129/131 (99%)
Glecaprevir + Pibrentasvir	8	Endurance	333/336 (99%)
Sofosbuvir+ Velpatasvir	12	ASTRAL-1	251/257 (98)%

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 10/17/17

AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES AASLD

IDSA Infectious Diseases Society of America

HCV: Genotype 2 and 3

Treatment Naïve or PEG-IFN/RBV Relapser, Non-cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	2	12	ASTRAL-1	**99%**
Glecaprevir + Pibrentasvir	2	8	SURVEYOR-II	**99%**
Velpatasvir + Sofosbuvir	3	12	ASTRAL-3	**98%**
Glecaprevir + Pibrentasvir	3	8	Endurance 3	**95%**

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 10/17/17

HCV: Genotype 4

Treatment Naïve or PEG-IFN/RBV Relapser , Non-cirrhotic

Regimen	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	12	ASTRAL-1	100%
Sofosbuvir + Ledipasvir	12	Synergy	95%
Elbasvir + Grazoprevir	12	C-Edge	97%
Glecaprevir + Pibrentasvir	8	Endurance 4	99%

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 10/17/17

HCV: Genotype 5 and 6

Treatment Naïve or PEG-IFN/RBV Relapser, Non-cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	5	12	ASTRAL-1	**96%**
Sofosbuvir + Ledipasvir	5	12		**95%**
Glecaprevir + Pibrentasvir	5	8	Endurance 4	**100%**
Velpatasvir + Sofosbuvir	6	12	ASTRAL-1	**100%**
Sofosbuvir + Ledipasvir	6	12	Synergy	**100%**
Glecaprevir + Pibrentasvir	6	8	Endurance 4	**100%**

NOT HEAD TO HEAD TRIALS

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HCV: Genotype 1a & 1b Compensated Cirrhosis

Treatment-Naïve or PEG-IFN/RBV Relapser Genotype 1a & 1b Patients With Compensated Cirrhosis			
RECOMMENDED	DURATION	RATING	SVR12
Daily fixed-dose combination of Elbasvir (50 mg)/ Grazoprevir (100 mg) for patients with genotype 1b, or with 1a without baseline NS5A RASs[b] for Elbasvir	12 weeks	I, A	97%
Daily fixed-dose combination of Ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A	97%
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)	12 weeks	I, A	99%
Daily fixed-dose combination of Glecaprevir (300 mg)/ Pibrentasvir (120 mg)[c]	8 weeks	I, B	99%

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Updated 08/27/2020

HCV: Genotype 2 Compensated Cirrhosis

Treatment-Naive or PEG-IFN/RBV Relapser Genotype 2 Patients With Compensated Cirrhosis			
RECOMMENDED	DURATION	RATING	SVR12
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)	12 weeks	I, A	99%
Daily fixed-dose combination of Glecaprevir (300 mg)/Pibrentasvir (120 mg)[b]	8 weeks[c]	I, B	99%

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Updated 08/27/2020

HCV: Genotype 3 Compensated Cirrhosis

Treatment-Naive or PEG-IFN/RBV Relapser Genotype 3 Patients With Compensated Cirrhosis			
RECOMMENDED	DURATION	RATING	SVR12
Daily fixed-dose combination of Glecaprevir (300 mg)/Pibrentasvir (120 mg)[b]	8 weeks[c]	I, B	95%
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H for Velpatasvir	12 weeks	I, A	97%
ALTERNATIVE with **NS5A RAS Y93H for Velpatasvir**	DURATION	RATING	SVR12
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) with weight-based Ribavirin for patients with baseline NS5A RAS Y93H for Velpatasvir	12 weeks	IIa, A	96%
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)/ Voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H for Velpatasvir	12 weeks	IIa, B	96%
NOT HEAD TO HEAD TRIALS			

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org.

Updated 08/27/2020

HCV: Genotype 4 Compensated Cirrhosis

Treatment-Naive or PEG-IFN/RBV Relapser Genotype 4 Patients With Compensated Cirrhosis			
RECOMMENDED	DURATION	RATING	SVR12
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)	12 weeks	I, A	99%
Daily fixed-dose combination of Glecaprevir (300 mg)/Pibrentasvir (120 mg)[b]	8 weeks[c]	I, B	99%
Daily fixed-dose combination of Elbasvir (50 mg)/Grazoprevir (100 mg)	12 weeks	IIa, B	96%
Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg)	12 weeks	IIa, B	95%

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Updated 08/27/2020

HCV: Genotype 5 and 6 with Compensated Cirrhosis

Treatment Naïve or PEG-IFN/RBV Relapser,
Genotype 5 and 6 with Compensated Cirrhosis

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	5	12	ASTRAL-1	**96%**
Sofosbuvir + Ledipasvir	5	12		**95%**
Glecaprevir + Pibrentasvir	5	8	Endurance 4	**100%**
Velpatasvir + Sofosbuvir	6	12	ASTRAL-1	**100%**
Sofosbuvir + Ledipasvir	6	12	Synergy	**100%**
Glecaprevir + Pibrentasvir	6	8	Endurance 4	**100%**

NOT HEAD TO HEAD TRIALS

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Treatment of HCV in Peg-IFN Non-Responders

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: **SOF 400 + VEL 100**	**12**	98%
	F0-2: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism)	**12**	100%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F3-4 comp: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism)	**12**	100%
	F3-4comp: **GLE 300 + PIB 120**	**12w**	98%
	F3-4: **SOF 400 + VEL 100**	**12**	98%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** (pre-test for NS5A resistance; treat 24 weeks if > 100-fold resistance or use other regimen)	**12**	96%

NOT HEAD TO HEAD TRIALS

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

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: **SOF 400 + VEL 100**	**12**	99%
	F0-2: **GZR 100 + EBR 50**	**12**	97%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F3-4 comp: **GZR 100 + EBR 50**	**12**	97%
	F3-4: **SOF 400 + VEL 100**	**12**	99%
	F3-4c: **GLE 300 + PIB 120**	**12**	99%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** (test for NS5A resistance)	**12**	96%

NOT HEAD TO HEAD TRIALS

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

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

Genotype	Regimen	Duration (weeks)	SVR
2	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
3	F0-2: **SOF 400 + VEL 100** (without Y93H NS5A RAV)	**12**	94%
	F0-2: **GLE 300 + PIB 120 (alt)**	**16**	96%
	F0-2: **SOF 400 + VEL 100 + VOX 100 (alt)**	**12**	94-100%
	F3-4c: **SOF 400 + VEL 100 + VOX 100**	**12**	94-100%
	F3-4c: **GLE 300 + PIB 120**	**16**	96%
	F3-4: **SOF 400 + VEL 100 + RBV 1-1.2 g (alt)**	**12**	89%
	F3-4 comp: **GZR 100 + EBR 50 + SOF 400 (alt)**	**12**	100%

NOT HEAD TO HEAD TRIALS

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

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

Genotype	Regimen	Duration (weeks)	SVR
4	F0-2: **SOF/LED 400/90**	**12**	95%
	F0-2: **SOF 400 + VEL 100**	**12**	100%
	F0-2: **GZR 100 + EBR 50 + RBV**	**16**	97%
	F0-2: **GLE 300 + PIB 120**	**8**	100%
	F3-4 comp: **GZR 100 + EBR 50 + RBV**	**16**	97%
	F3-4: **SOF 400 + VEL 100**	**12**	100%
	F3-4c: **GLE 300 + PIB 120**	**12**	100%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)**	**12**	95%
5	F0-4: **SOF/LED 400/900**	**12**	95%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
	F0-4: **SOF 400 + VEL 100**	**12**	97%
6	F0-4: **SOF/LED 400/90**	**12**	96%
	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%

NOT HEAD TO HEAD TRIALS

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

Treatment of HCV in Decompensated Cirrhosis

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis

RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

HCV: Decompensated Cirrhosis

Treatment of Genotypes 1-6 with Decompensated Cirrhosis (Child-Pugh B or C)

Regimen	Genotypes	Duration	SVR12	Rating
Patients With Decompensated Cirrhosis Who Have Genotype 1-6 and are Ribavirin Eligible				
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose)	1,4,5,6	12 weeks	87%	I, A[b]
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) with weight-based Ribavirin starting with 600 mg/day; increase as tolerated)	All	12 weeks	94%	I, A[d]
Patients With Decompensated Cirrhosis Who Have Genotype 1-6 and are Ribavirin Ineligible				
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg)	1,4,5,6	24 weeks	> 81%	I, A[b]
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg)	All	24 weeks	86%	I, A[c]
Patients With Decompensated Cirrhosis and Genotype 1-6 Infection in Whom Prior Sofosbuvir- or NS5A Inhibitor-Based Treatment Failed				
Prior sofosbuvir-based treatment failure, genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of Ledipasvir (90 mg)/Sofosbuvir (400 mg) with low initial dose of ribavirin (starting with 600 mg/day; increase as tolerated)	1,4,5,6	24 weeks	98%	II, C[b]
Daily fixed-dose combination of Sofosbuvir (400 mg)/Velpatasvir (100 mg) with weight-based Ribavirin (staring with 600 mg/day; increase as tolerated)	All	24 weeks	97% G-1 78% G-3	II, C[d]

NOT HEAD TO HEAD TRIALS

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Treatment of Current-DAAs Failures

Genotype-1 NS5A DAA-Experienced
(Excluding Gle/Pib)

NS5A Inhibitor DAA-Experienced (Excluding Glecaprevir/Pibrentasvir Failures), Genotype 1 Patients, With or Without Compensated Cirrhosis		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] except NS3/4 protease inhibitor inclusive DAA combination regimens	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section

Genotype-2 NS5A DAA-Experienced
(Excluding Gle/Pib)

Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients, With or Without Compensated Cirrhosis		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIb, B
Sofosbuvir + NS5A Inhibitor-Experienced (Excluding Glecaprevir/Pibrentasvir Failures), Genotype 2 Patients, With or Without Compensated Cirrhosis[a]		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section

Genotype-3 Sofosbuvir-Experienced or NS5A DAA-Experienced (Excluding Gle/Pib)

Sofosbuvir + Ribavirin-Experienced (± Peginterferon), Genotype 3 Patients, With or Without Compensated Cirrhosis[a]		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	16 weeks	IIb, B
DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 3 Patients, With or Without Compensated Cirrhosis[a]		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A
For patients with prior NS5A inhibitor failure and **cirrhosis**, addition of weight-based **ribavirin** is recommended.	12 weeks	IIa, C

[a] For decompensated cirrhosis, please refer to the appropriate section

Genotype-4 NS5A DAA-Experienced
(Excluding Gle/Pib)

DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 4 Patients, With or Without Compensated Cirrhosis[a]		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section

Genotype-5 or 6 NS5A DAA-Experienced
(Excluding Gle/Pib)

DAA-Experienced (Including NS5A Inhibitors Except Glecaprevir/Pibrentasvir Failures), Genotype 5 or 6 Patients, With or Without Compensated Cirrhosis[a]		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section

Treatment of Glecaprevir/Pibrentasvir Failures

Glecaprevir/Pibrentasvir Treatment Failure (All Genotypes)		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIa, B
For patients with compensated cirrhosis, addition of weight-based ribavirin is recommended.	12 weeks	IIa, C

Treatment of Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure (All Genotypes)

Patients With Prior Sofosbuvir/Velpatasvir/Voxilaprevir Treatment Failure (All Genotypes), With or Without Compensated Cirrhosis		
RECOMMENDED	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] plus daily sofosbuvir (400 mg) and weight-based ribavirin	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) plus weight-based ribavirin	24 weeks	IIa, B

Treatment of HCV in HIV/HCV Co-Infection

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

RECOMMENDED	RATING
HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications	**I, B**
Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner. For HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended.	I, A
For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.	IIa, C
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) Elbasvir/grazoprevir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir.	IIa, B

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

RECOMMENDED	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a] Glecaprevir/pibrentasvir should be used with antiretroviral drugs with which it does not have clinically significant interactions: abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir. Given the increase in glecaprevir exposures and limited data on the safety of elvitegravir/cobicistat with glecaprevir/pibrentasvir, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients.	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) Sofosbuvir/velpatasvir can be used with most antiretrovirals but not efavirenz, etravirine, or nevirapine. Because tenofovir levels, when given as **tenofovir disoproxil fumarate, may increase with sofosbuvir/velpatasvir**, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Due to limited experience with this drug combination, renal monitoring is recommended in patients taking tenofovir disoproxil fumarate and cobicistat or ritonavir with sofosbuvir/velpatasvir. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during sofosbuvir/velpatasvir treatment for patients who take cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, B

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications

RECOMMENDED	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) Ledipasvir/sofosbuvir can be used with most antiretrovirals. Because this therapy **increases tenofovir levels when given as tenofovir disoproxil fumarate**, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. Absolute tenofovir levels are highest and may exceed exposures for which there are established renal safety data when tenofovir disoproxil fumarate is administered with ritonavir- or cobicistat-containing regimens. Due to lack of sufficient safety data with this drug combination, consideration should be given to changing the antiretroviral regimen. If the combination is used, renal monitoring is recommended during the dosing period. Tenofovir alafenamide may be an alternative to tenofovir disoproxil fumarate during ledipasvir/sofosbuvir treatment for patients taking cobicistat or ritonavir as part of their antiretroviral therapy.	IIa, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) Sofosbuvir/velpatasvir/voxilaprevir should be used with antiretroviral drugs with which they do not have substantial interactions: abacavir, bictegravir, dolutegravir, doravirine, emtricitabine, lamivudine, maraviroc, raltegravir, rilpivirine, and tenofovir alafenamide. Given increases in voxilaprevir AUC with darunavir/ritonavir or elvitegravir/cobicistat coadministration and lack of clinical safety data, monitoring for hepatic toxicity is recommended until additional safety data are available in HIV/HCV-coinfected patients. Because this therapy has the potential to increase tenofovir levels when given as **tenofovir disoproxil fumarate**, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. In patients concomitantly receiving sofosbuvir/velpatasvir/voxilaprevir and tenofovir disoproxil fumarate, renal monitoring is recommended during the dosing period.	IIa, B

Drug Interactions to Avoid In Treatment of HCV/HIV Coinfection

Recommendations Related to HCV Medication Interactions With HIV Antiretroviral Medications	
NOT RECOMMENDED	**RATING**
Antiretroviral treatment interruption to allow HCV therapy is **not** recommended.	III, A
Elbasvir/grazoprevir should **not** be used with cobicistat, efavirenz, etravirine, nevirapine, or any HIV protease inhibitor.	III, B
Glecaprevir/pibrentasvir should **not** be used with atazanavir, efavirenz, etravirine, nevirapine, or ritonavir-containing antiretroviral regimens.	III, B
Sofosbuvir/velpatasvir should **not** be used with efavirenz, etravirine, or nevirapine.	III, B
Sofosbuvir/velpatasvir/voxilaprevir should **not** be used with efavirenz, etravirine, nevirapine, ritonavir-boosted atazanavir, or ritonavir-boosted lopinavir.	III, B
Sofosbuvir-based regimens should **not** be used with tipranavir.	III, B
Ribavirin should **not** be used with didanosine, stavudine, or zidovudine.	III, B

Risk for HBV Reactivation

- HIV/HCV co-infected patients - Risk for HBV reactivation.
- Reactivation of HBV has been reported in patients starting DAA HCV therapy who are not on active HBV agents.
- Assess for HBV co-infection with HBsAg, anti-HBs, and anti-HBc (as in all HCV patients).
- HIV/HBV co-infection - should be on antiretroviral agents with activity against HBV, preferably TDF or TAF.

AASLD/IDSA HCV Guidance

Use of Ribavirin in HCV Therapy

Weight-Based Ribavirin Dosing

- Person >/= 75 kg = 1200 mg a day, divided in 2 doses (Decrease the dose for low GFR)
- Person < 75 kg = 1000 mg a day, divided in 2 doses (Decrease the dose for low GFR)
- Child-Pugh C = Start with 600 mg a day, divided in 2 doses (Decrease the dose for low GFR)

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

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

Treatment of HCV in ESRD

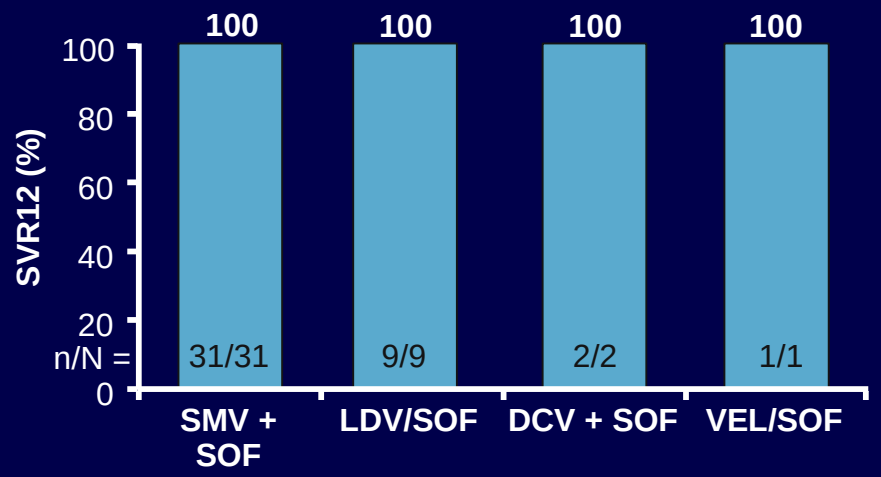
Treatment of HCV in CKD 4/5 +/- Hemodialysis (GFR < 30 mL/min)

Genotype	Regimen	Duration (weeks)	SVR
Geno 1-6 (F0-4compensated)	**GLE 300 + PIB 120**	**8** (Modify therapy as need if treatment Experienced)	98-100%
1 & 4 (F0-4compensated)	**GZR 100 + EBR 50** In genotype 1a with M28, Y93, Q30, or L31 polymorphism the 16-week extension is NOT needed	**12** (Modify therapy as need if treatment Experienced)	99% in geno-1
1 & 4	**LED 90 + SOF 400**	**12** (Modify therapy as need if treatment Experienced or Decompensated)	100%
Geno 1-6	**SOF 400 + VAL 100**	**12** (Modify therapy as need if treatment Experienced or Decompensated)	95%

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

SOF-Based, RBV-Free DAAs in Pts With HCV Infection and ESRD

- N = 43 pts mostly on dialysis (93%), treatment naive (79%), genotype 1a (65%), noncirrhotic (51%)
  - Mean baseline hemoglobin: 11.1 g/dL (range: 8.9-13.8 g/dL)
- Most pts treated for 12 wks (n = 36)



Nazario H, et al. EASL 2017. Abstract FRI-220. Reproduced with permission.

Safety

- No hepatic decompensation
- No dose adjustment of any regimen

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Treatment of HCV in Solid Organ Transplant Recipients

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

Drug-Drug Interactions of DAAs and Calcineurin Inhibitors

	Cyclosporin A	Tacrolimus
Sofosbuvir (SOF)	4.5-fold ↑ in SOF AUC, but GS-331007 metabolite unchanged; no a priori dose adjustment	No interaction observed; no a priori dose adjustment
Ledipasvir	No data; no a priori dose adjustment	No data; no a priori dose adjustment
Elbasvir / grazoprevir (EBR/GZR)	15-fold ↑ in GZR AUC and 2-fold ↑ in EBR AUC; **combination is not recommended**	43% ↑ in TAC; no a priori dose adjustment
Velpatasvir	No interaction observed; no a priori dose adjustment	No data; no a priori dose adjustment
Glecaprevir / pibrentasvir (GLE/PIB)	5-fold ↑ in GLE AUC with higher doses (400 mg) of CSA; not recommended in patients requiring stable CSA doses >100 mg/day	1.45-fold ↑ in TAC AUC; no a priori dose adjustment; monitor TAC levels and titrate TAC dose as needed
Sofosbuvir / velpatasvir / voxilaprevir (SOF/VEL/VOX)	9.4-fold ↑ in VOX AUC; **combination is not recommended**	No data; no a priori dose adjustment
AUC=area under the curve		

Treatment of Recurrent HCV After Liver Transplant

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft Without Cirrhosis		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft With Compensated Cirrhosis		
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, C

Treatment of Recurrent HCV After Liver Transplant

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft and Decompensated Cirrhosis		
RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase or decrease as tolerated)	12 to 24 weeks[c]	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ ribavirin starting at 600 mg and increase or decrease as tolerated	12 to 24 weeks[c]	I, B
DAA-Experienced Patients With Genotype 1-6 Infection in the Allograft, With or Without Compensated Cirrhosis		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) ; Consider adding Ribaviring	12 weeks	I, C

[C] 24 weeks therapy if Treatment-Experienced

Treatment of HCV in Kidney Transplant Patients

Treatment-Naive and Non-DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, C
ALTERNATIVE		
Genotype 1 or 4 only: Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg) for patients without baseline NS5A RASs[e] for elbasvir	12 weeks	I, B
DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis		
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg), with or without ribavirin[b]	12 weeks	IIa, C

Donation of HCV-RNA(+) Solid Organ to HCV-Negative Recipient

Window Time Before (+) NAT Test after Infection Acquisition

Agent	Days
HIV	HIV-RNA: 5-6
HCV	HCV-RNA: 3-6
HBV	HBV-DNA: 20-22

HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors

Recommendations When Considering Use of HCV-Viremic Donor Organs in HCV-Uninfected Recipients	
RECOMMENDED	RATING
Informed consent should include the following elements: •Risk of transmission from an HCV-viremic donor (and with a PHS-defined increased risk donor, the potential risks for other viral infections) •Risk of liver disease if HCV treatment is not available or treatment is unsuccessful •Risk of graft failure •Risk of extrahepatic complications, such as HCV-associated renal disease •Risk of HCV transmission to partner •Benefits, specifically reduced waiting time and possibly lower waiting list mortality •Other unknown long-term consequences (hepatic and extrahepatic) of HCV exposure (even if cure is attained)	I, C
Transplant programs should have a programmatic strategy to: •Document informed consent •Assure access to HCV treatment and retreatment(s), as necessary •Ensure long-term follow-up of recipients (beyond SVR12)	I, C

HCV-Negative Liver Recipients of HCV-Viremic Liver Donors

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Liver Transplant		
RECOMMENDED		RATING
Early[a] treatment with a pangenotypic DAA regimen is recommended when the patient is clinically stable.		II, B
Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C

[a] Early treatment refers to starting within the first month after liver transplant but preferably within the first week when the patient is clinically stable.
-Avoid Protease inhibitors if High Bilirubin
-Look at Drug-Drug Interactions before therapy

HCV-Negative Recipients of Non-Liver Solid Organ from HCV-Positive Donor

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Non-Liver Solid Organ Transplant		
RECOMMENDED		RATING
Prophylactic[a]/preemptive[b] treatment with a pangenotypic DAA regimen is recommended.		II, B
Treatment of HCV-Uninfected Recipients of Non-Liver Organs from HCV-Viremic Donors		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C

[a] Prior to HCV RNA results, typically immediately pre-transplant or day 0 post-transplant
[b] Day 0 to within the first week post-transplant, typically as soon as the patient is deemed clinically stable
-Avoid Protease inhibitors if High Bilirubin
-Look at Drug-Drug Interactions before therapy

Adolescents ≥12 Years Old or Weighing ≥35 kg, Without Cirrhosis or With Compensated Cirrhosis

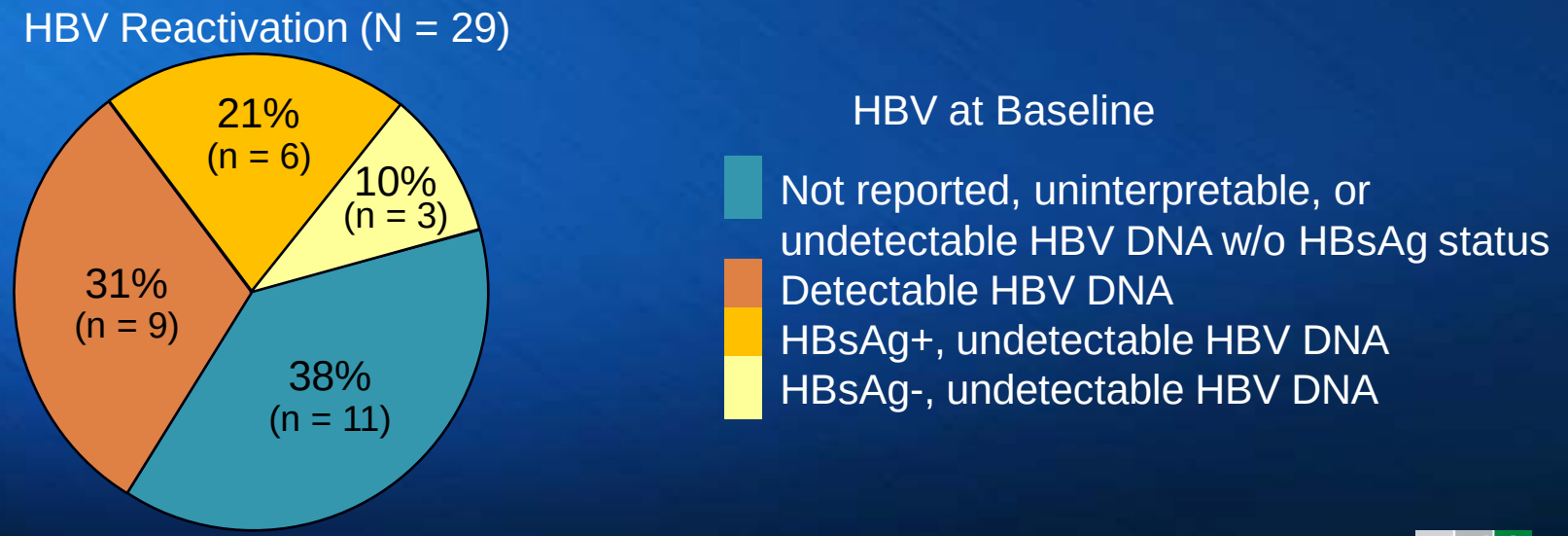
REGIMEN	Length (weeks)	SVR
ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-naive without cirrhosis or with compensated cirrhosis, or treatment-experienced without cirrhosis	12	98%
ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 1 who are treatment-experienced with compensated cirrhosis	24	98%
sofosbuvir (400 mg) plus weight-based ribavirin for patients with genotype 2 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	12	100%
sofosbuvir (400 mg) plus weight-based ribavirin for patients with genotype 3 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	24	97%
ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with genotype 4, 5, or 6 who are treatment-naive or treatment-experienced without cirrhosis or with compensated cirrhosis	12	

Dosing for Ribavirin in Combination Therapy With Sofosbuvir for Adolescents ≥12 Years Old or Weighing ≥35 kg

Body Weight (kg)	Daily Ribavirin Dosage (in 2 divided doses)
<47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
>80	1200 mg/day

HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

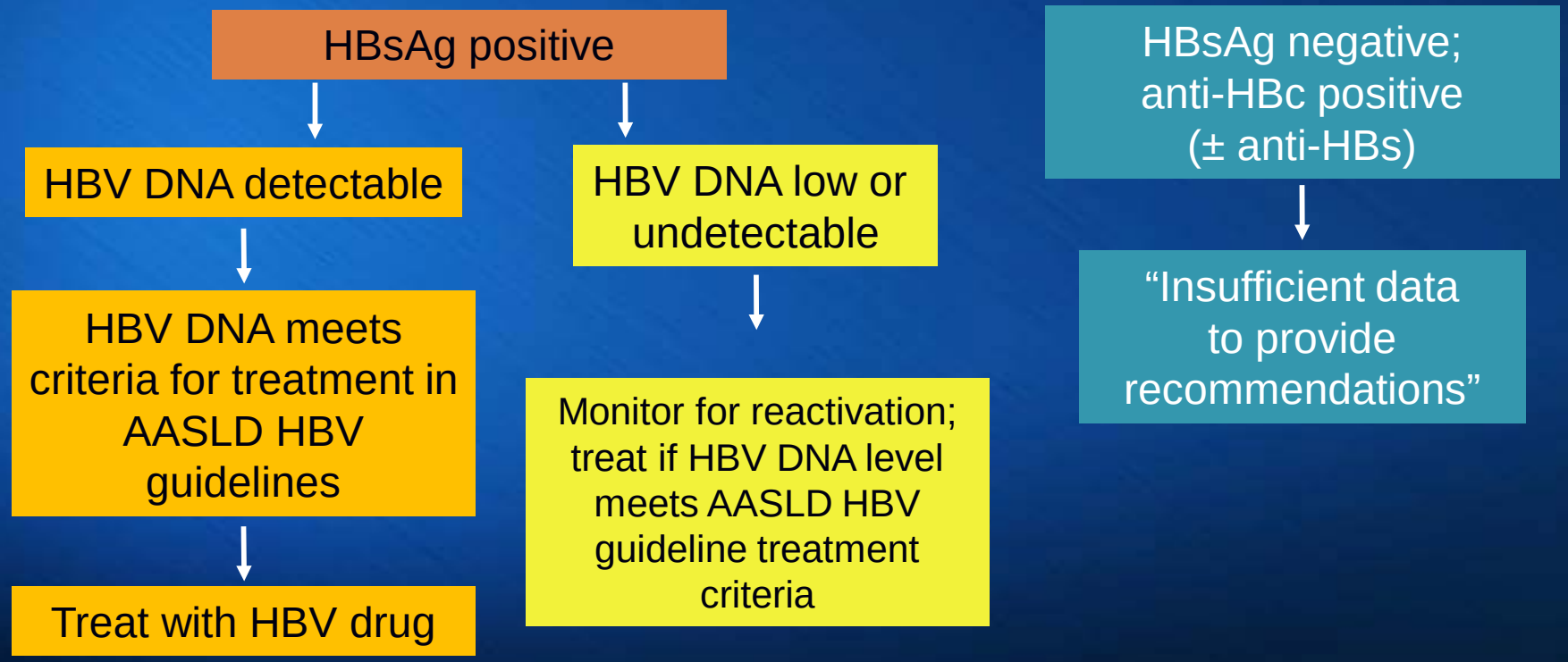


Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

Slide credit: clinicaloptions.com

HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:



AASLD/IDSA. HCV guidance. September 2016.
Graphic created by Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

My recommendations

- If HBsAg(+) with HBV-DNA of 2000 IU/mL or higher:
  - Treat for chronic HBV
- If HBsAg (+) with HBV-DNA < 2000 IU/mL, or
  If HBsAg (-) but anti-HBc (+):
  - Monitor every 4 weeks with HBsAg (if it was negative) and HBV-DNA quantitation, during therapy and up to 8-12 weeks after EOT.

Evaluation and Management of Chronic Hepatitis C

Hepatitis C Disease Burden: US

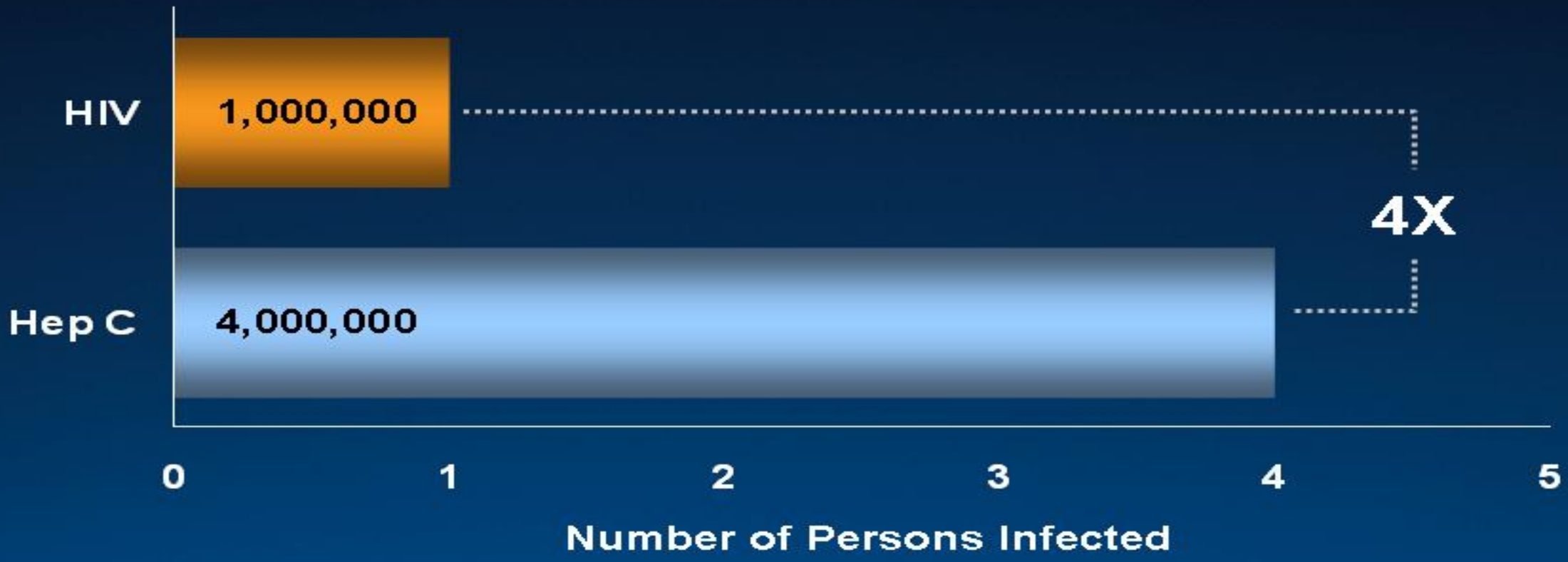
- Hepatitis C is the most common chronic blood-borne viral infection in the US[1]
  - ~ 1/2 of cirrhotic patients[2]
  - ~ 1/3 of HCC patients[3]
  - #1 reason for liver transplants[4]
  - #1 cause of death in HIV patients[5,6]

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.

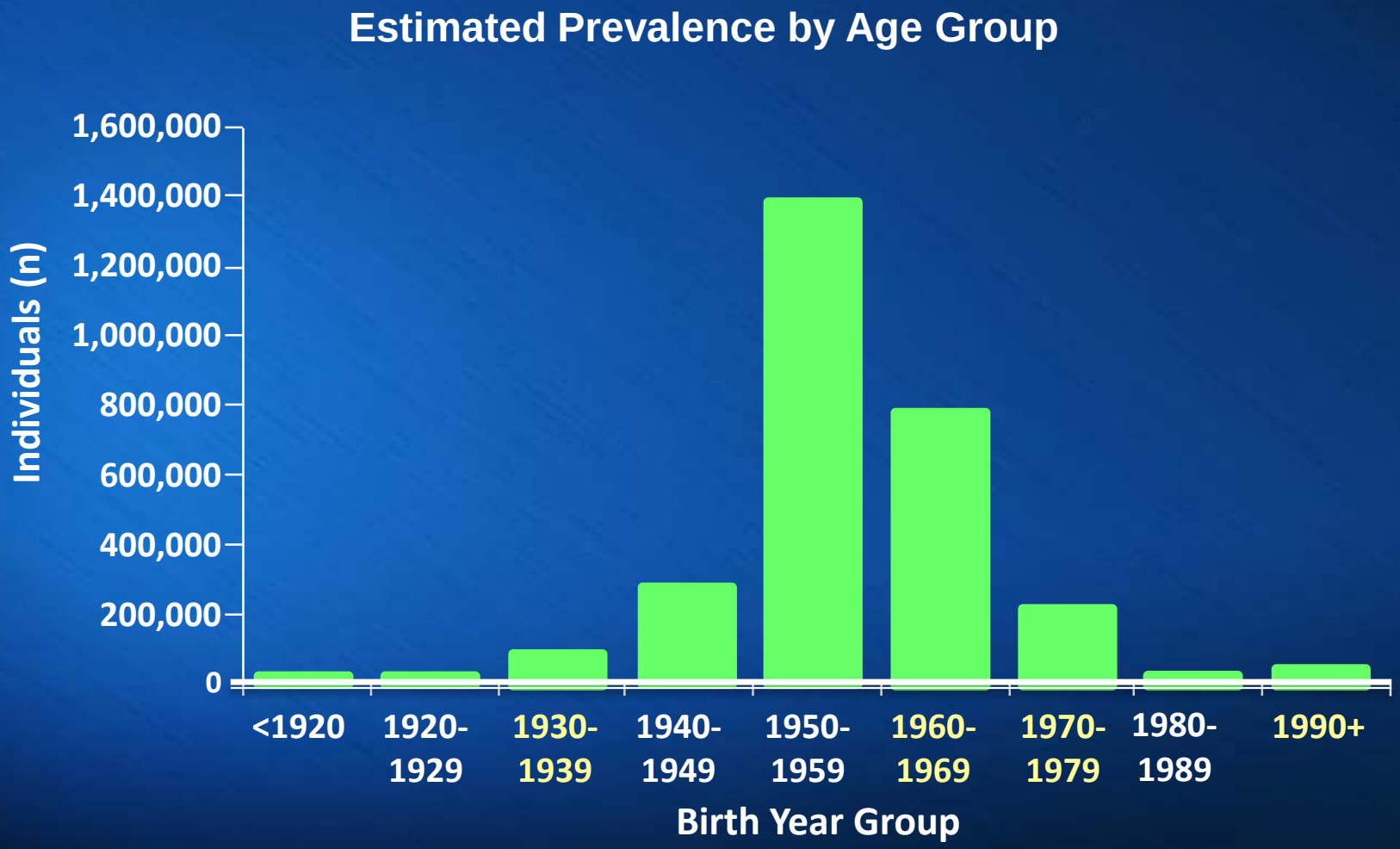
Prevalence of Hepatitis C

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



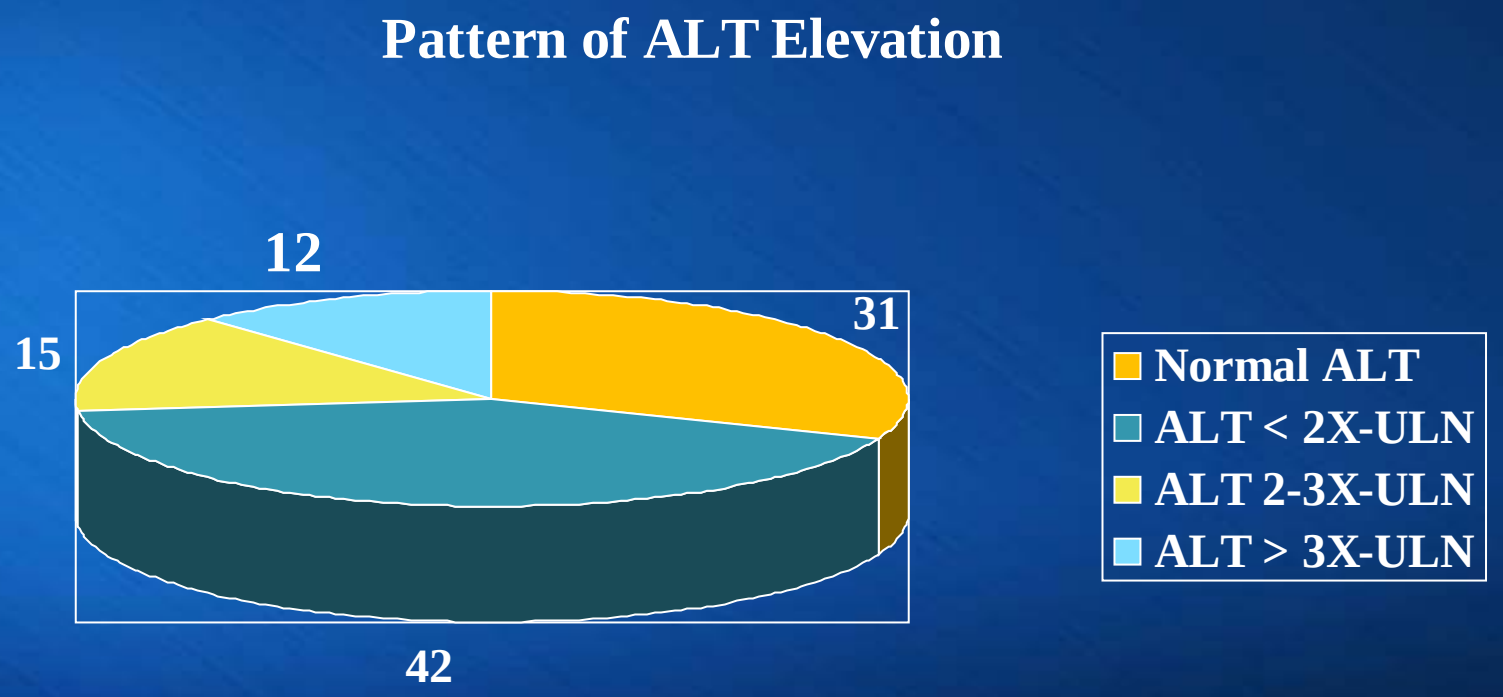
1. NIAID HIV/AIDS fact sheet. 2007. Available at: www.niaid.nih.gov/factsheets/hivinf.htm; 2. Edlin B, et al. Presented at AASLD 2005. November 11-15, 2005; San Francisco, CA. Oral Presentation #44.

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

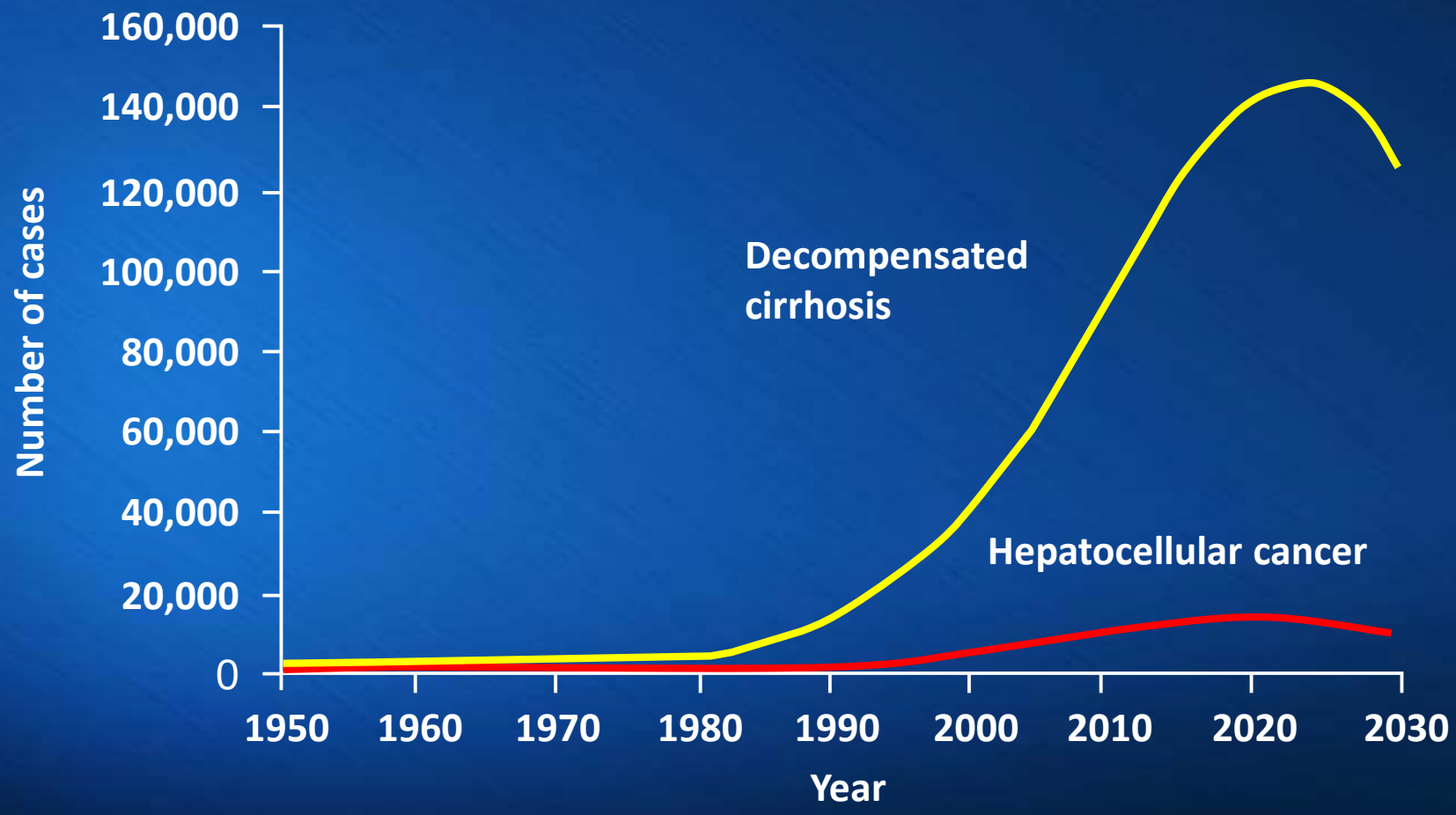
Host Factors

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

Viral Factors

- Genotype 3
- Co-infection with HBV or HIV

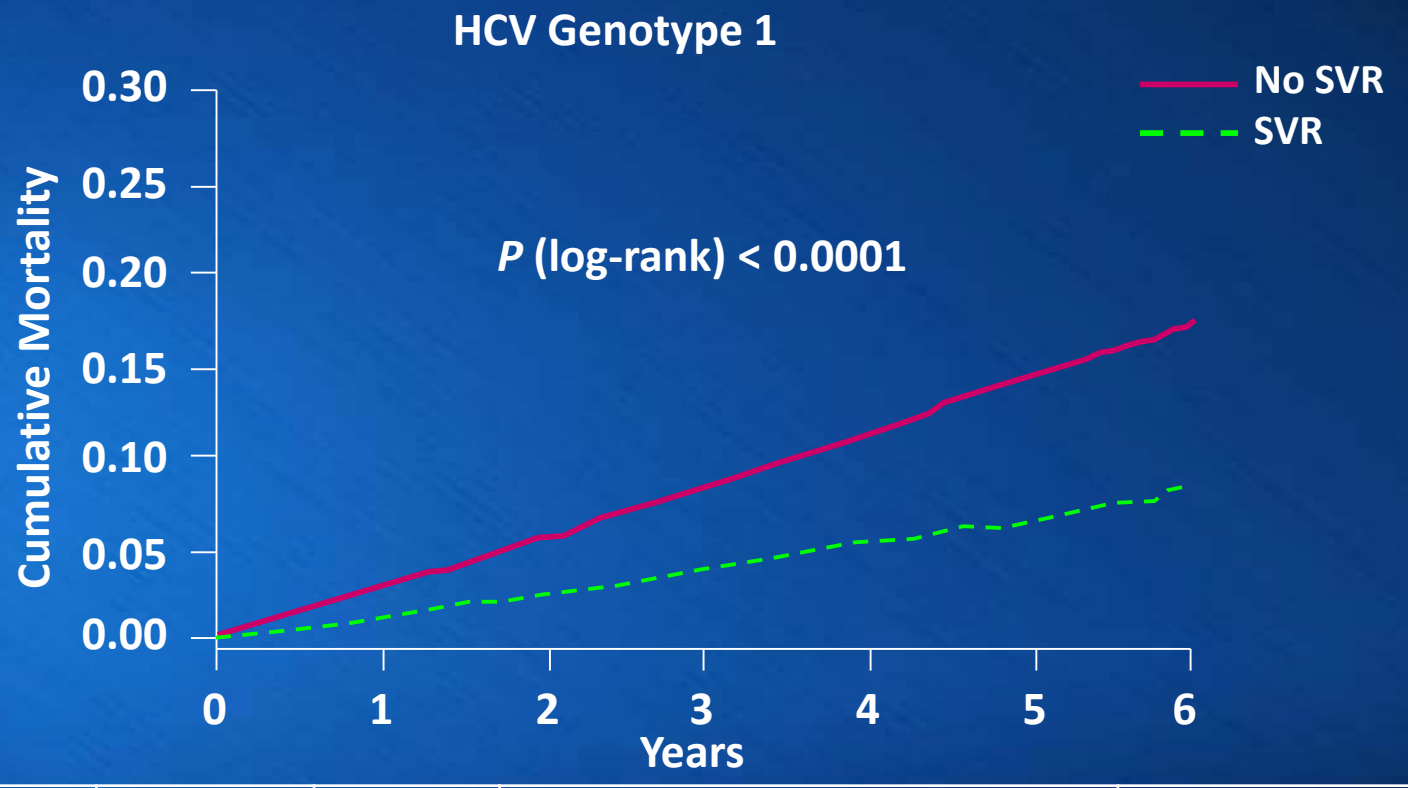
Projected Cases of Hepatocellular Carcinoma and Decompensated Cirrhosis Due to HCV



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

Recommendations for One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMENDED	RATING
One-time, routine, opt out HCV testing is recommended for **all** individuals **aged 18 years or older**.	I, B
One-time HCV testing should be performed for all **persons less than 18 years** old with activities, exposures, or conditions or circumstances associated **with an increased risk** of HCV infection (see below).	I, B
Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy.	I, B
Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an **increased risk of HCV exposure** (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP).	IIa, C

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 One-Time Hepatitis C Testing

Recommendations for Initial HCV Testing and Follow-Up	
RECOMENDED	RATING
HCV-antibody testing with reflex HCV RNA polymerase chain reaction (PCR) testing is recommended for initial HCV testing.	I, A
Among persons with a **negative HCV-antibody test who were exposed to HCV within the prior 6 months**, **HCV-RNA testing** or follow-up HCV-antibody testing 6 months or longer after exposure is recommended. HCV-RNA testing can also be considered for immunocompromised persons.	I, C
Among **persons at risk of reinfection** after previous spontaneous or treatment-related viral clearance, **HCV-RNA testing** is recommended because a positive HCV-antibody test is expected.	I, C
Quantitative HCV-RNA testing is recommended **prior to initiation of antiviral therapy** to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing may be considered for those in whom it may alter treatment recommendations.	I, A
Persons found to have a positive HCV-antibody test and **negative results for HCV RNA** by PCR should be informed that they **do not have** evidence of **current (active) HCV** infection but **are not protected from reinfection.**	I, A

Recommendations for One-Time Hepatitis C Testing

Recommendations for Counseling Persons With Active HCV Infection	
RECOMENDED	RATING
Persons with current HCV infection should receive **education** and interventions aimed at **reducing liver disease progression** and preventing HCV **transmission**.	IIa, B
Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.	IIa, B
Evaluation for other conditions that may **accelerate liver fibrosis**, including **hepatitis B and HIV infections**, is recommended for all persons with active HCV infection.	IIb, B
Evaluation for advanced fibrosis using noninvasive tests (serum panels, elastography) or liver biopsy, if required, **is recommended** for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (eg, hepatocellular carcinoma screening) (see Monitoring section).	I, A
Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.	IIa, C
Vaccination against pneumococcal infection is recommended for all patients with **cirrhosis**.	IIa, C
All persons with HCV infection should be provided **education** about **how to prevent HCV transmission to others**.	I, C

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.

Counseling Recommendations for HCV-Infected Individuals

To Prevent HCV Transmission

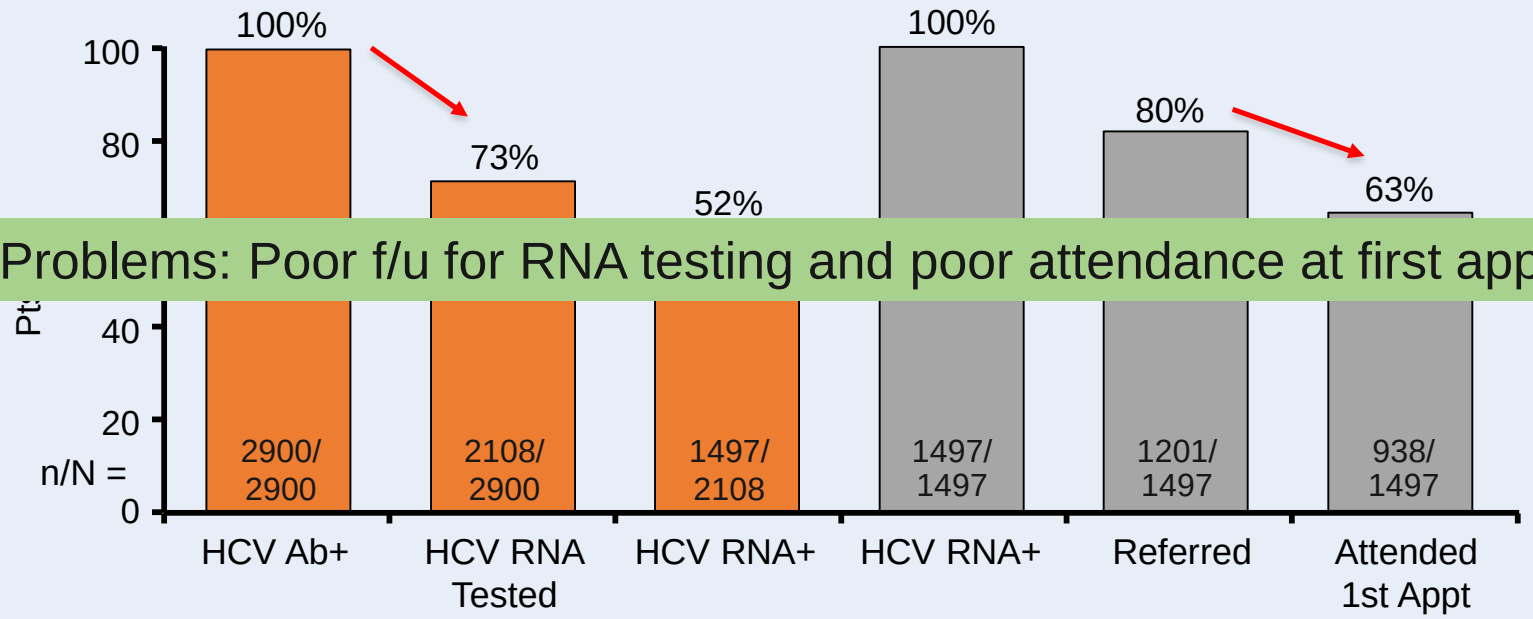
- Avoid sharing toothbrushes and dental or shaving equipment
- Prevent blood contact with others
- Stop using illicit drugs; those who continue to inject drugs should take precautions to avoid viral transmission
- Risk of sexual transmission is low, but practice "safe sex"

Additional Recommendations

- Avoid alcohol consumption
  - Excess alcohol may lead to progressive liver disease, increased HCV RNA replication, and reduced response to treatment
- Consider treatment for hepatitis C*
- Vaccinate for hepatitis A and B
- Get tested for HIV
- Encourage family members to get screened

Is Boomer Screening Working?

24,966 boomers tested in urban healthcare settings → 11.6% HCV Ab+!



Problems: Poor f/u for RNA testing and poor attendance at first appt

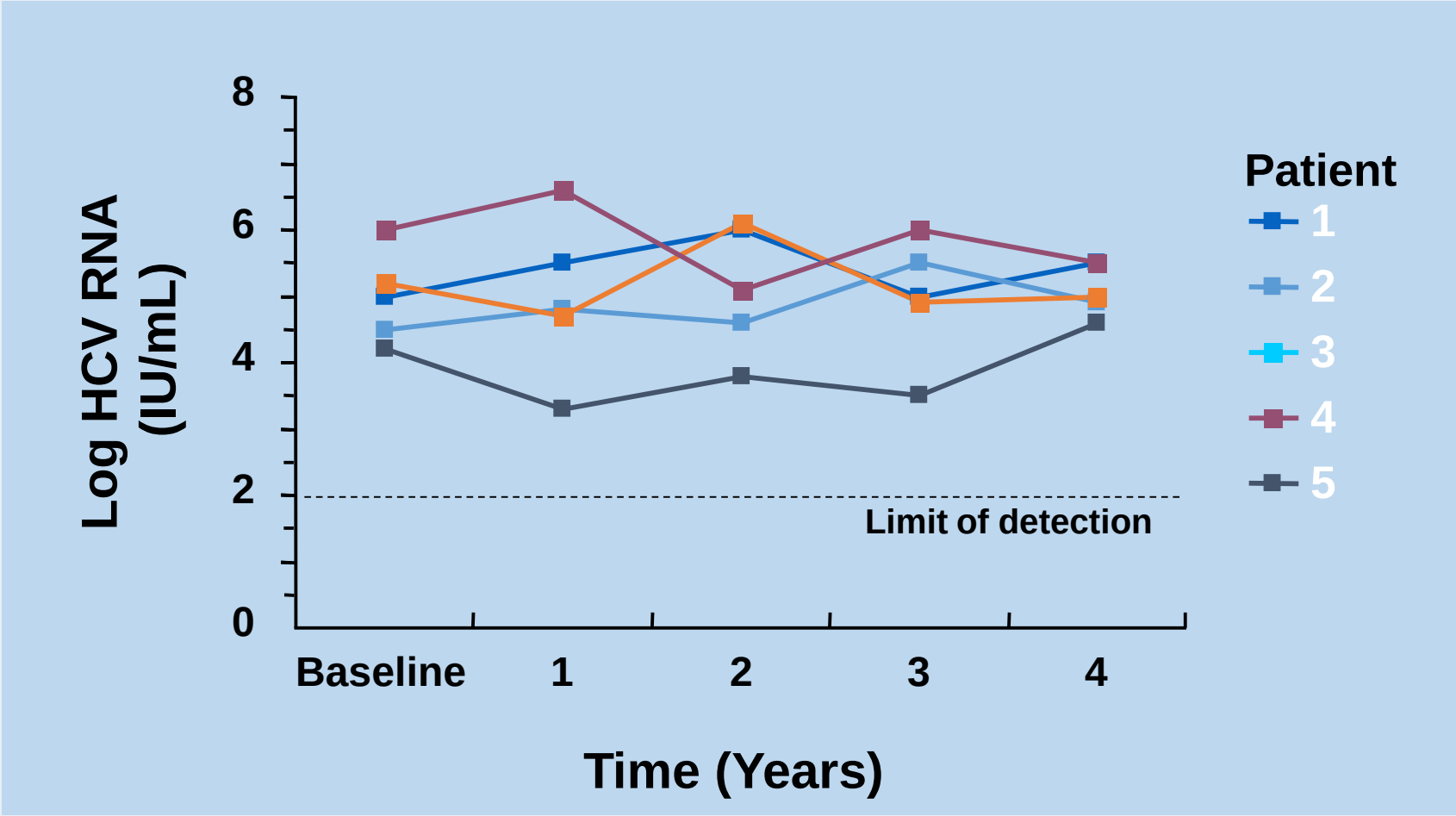
Patel RC, et al. Public Health Rep. 2016;131(suppl 2):12-19.

Slide credit clinicaloptions.com

Hepatitis C Virus Diagnostic Testing

	Diagnostic Test Type	
Specifications	**Serologic**	**Virologic**
Mode of detection	Antibodies	Virus
Sensitivity	> 95%	> 98%
Specificity	Variable	> 98%
Detection postexposure	2-6 months	2-6 weeks
Use	Screening	Confirmation

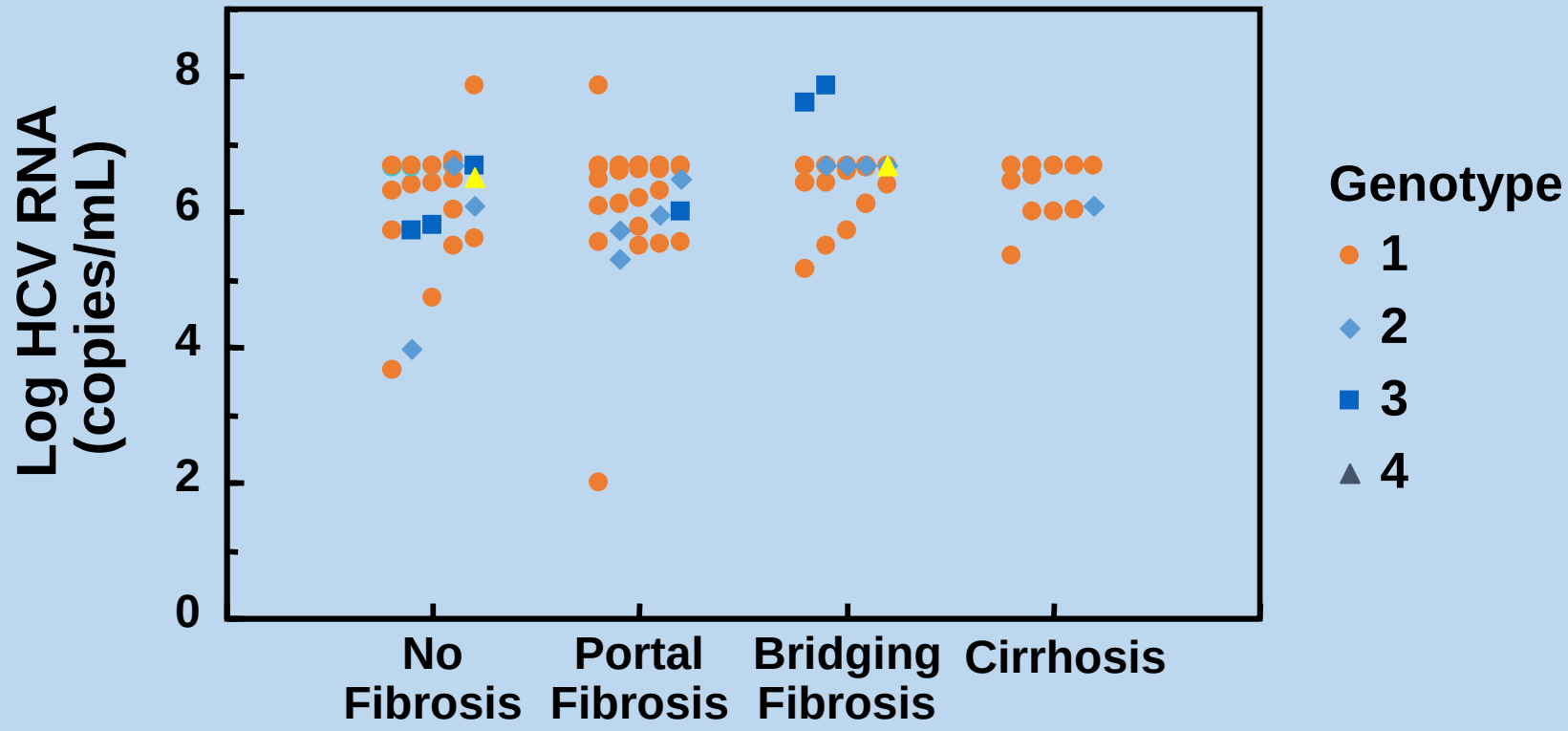
Serum HCV RNA Levels Stability Over Time



Ferreira-Gonzalez A, et al. Semin Liver Dis. 2004;24:9-18.

HCV RNA and Liver Histology Fibrosis

- Serum HCV RNA does not correlate with level of fibrosis



Ferreira-Gonzalez A, et al. Semin Liver Dis. 2004;24:9-18.

Pre-Treatment Assessment for Fibrosis is Required

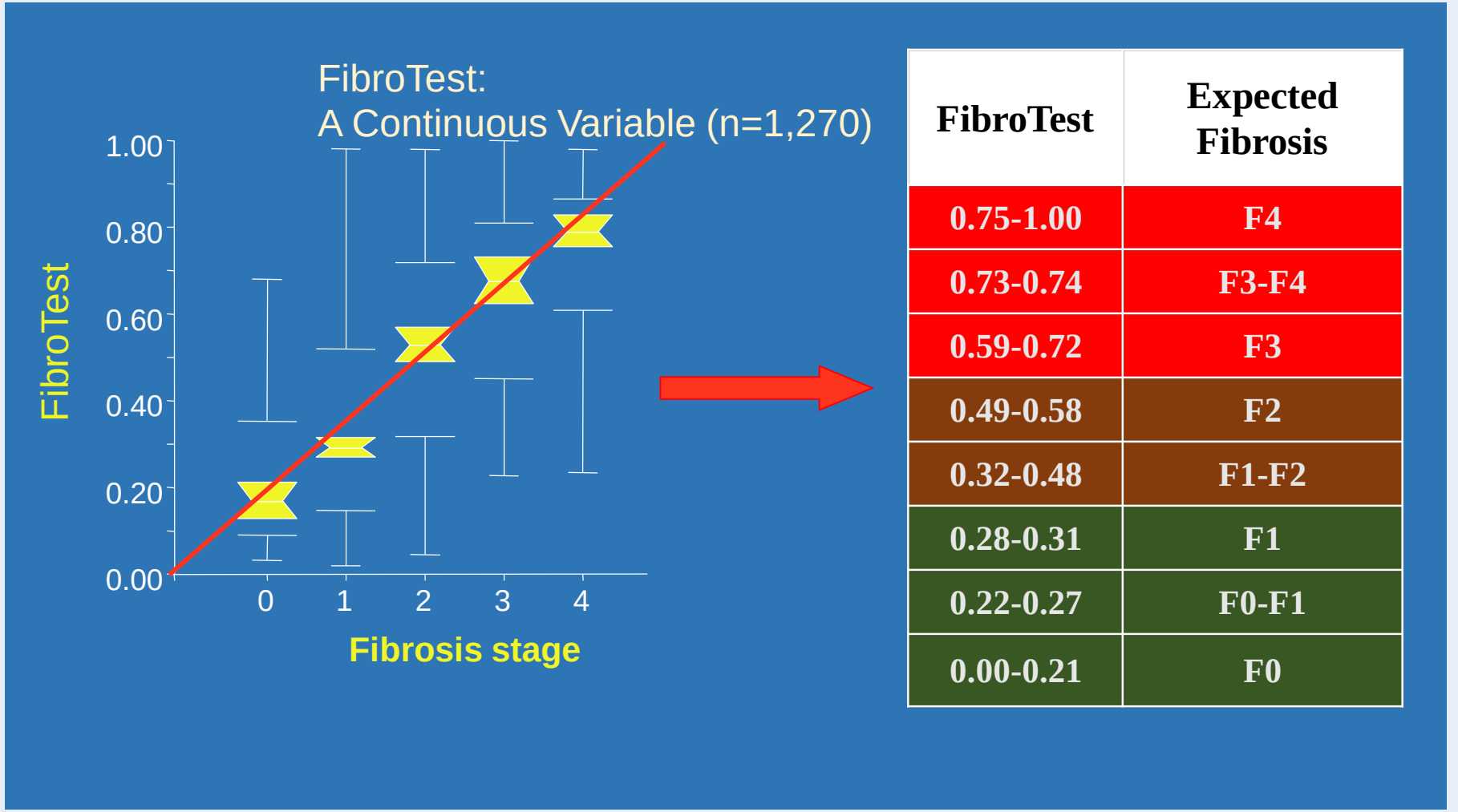
Recommendation for Pretreatment Assessment	
RECOMMENDED	RATING
Evaluation for advanced **fibrosis** using **noninvasive markers and/or elastography**, and rarely liver biopsy, is recommended for all persons with HCV infection to facilitate decision making regarding HCV treatment strategy and determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).	I, A

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

- Transient Liver Elastograpy (TLE): Cutoff Values*
  - 8.4 to 9.5 kPa correlates with Metavir F2;
  - 9.6 to 12.7 kPa with F3; and
  - 12.8 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.

*Afdhal N et al. Clin Gastroenterol Hepatol 2015;13:772-779

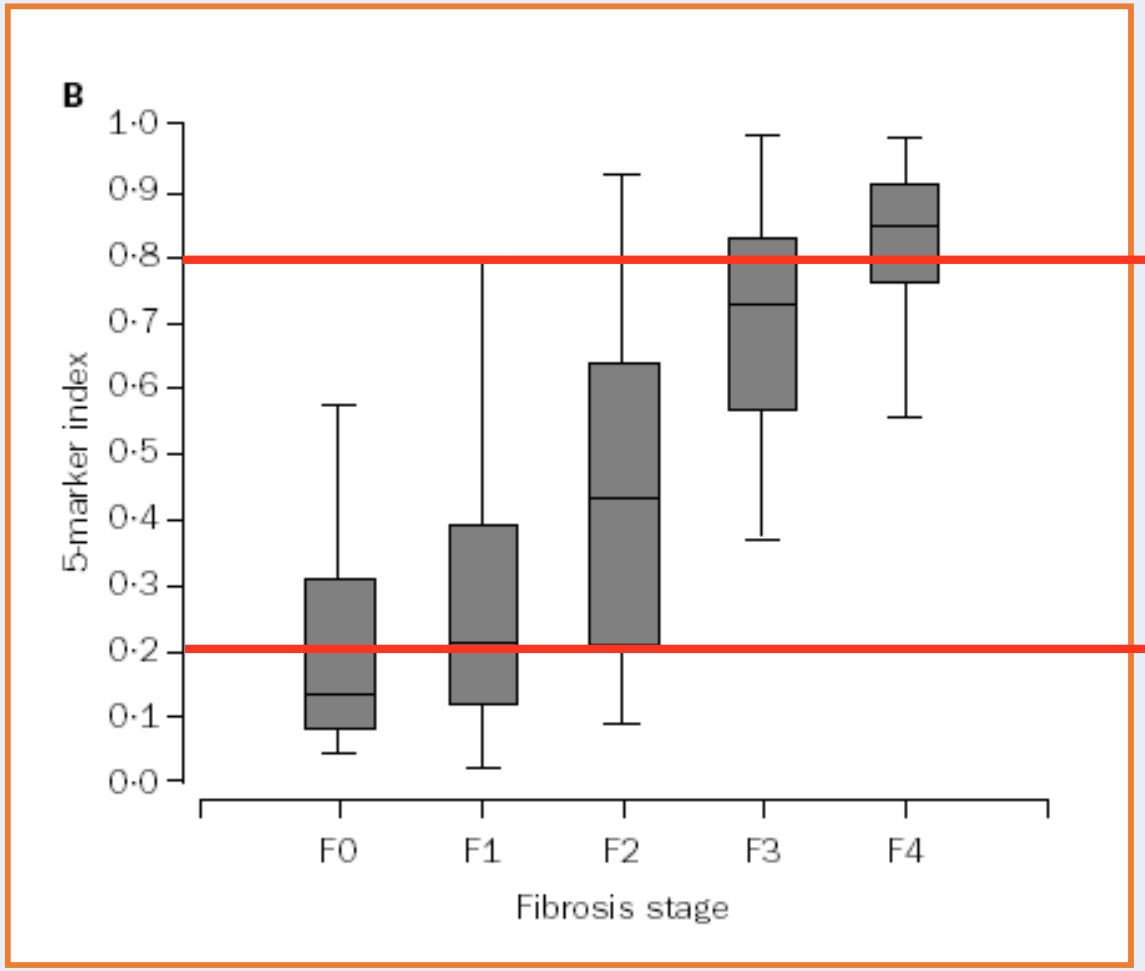
FibroTest: A Continuous Variable (n=1,270)



FibroTest	Expected Fibrosis
0.75-1.00	F4
0.73-0.74	F3-F4
0.59-0.72	F3
0.49-0.58	F2
0.32-0.48	F1-F2
0.28-0.31	F1
0.22-0.27	F0-F1
0.00-0.21	F0

Poynard, Clin Chem 2004; 50:1344-55.

» 50% of Biopsies May Be Avoidable with FibroTest



FT > 0.80
Spec 97%
PPV 92%

Indeterminate
54%

FT ≤ 0.20
Sens 92%
NPV 87%

n=134
F2-F4 fibrosis: 45%

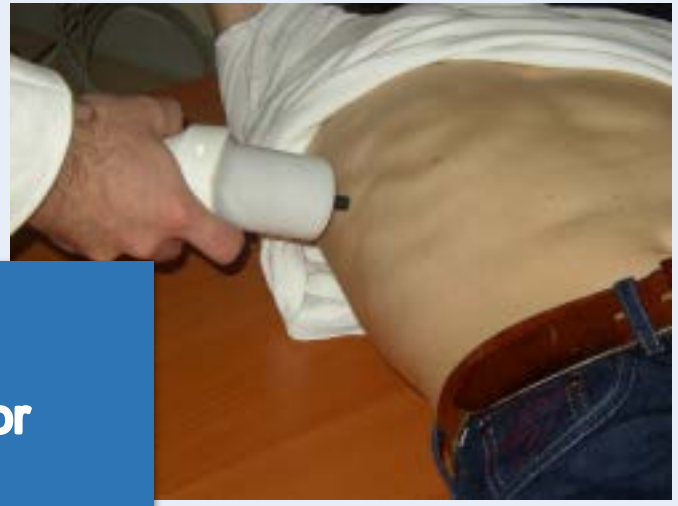
Imbert-Bismut. Lancet 2001;357:1069-75.

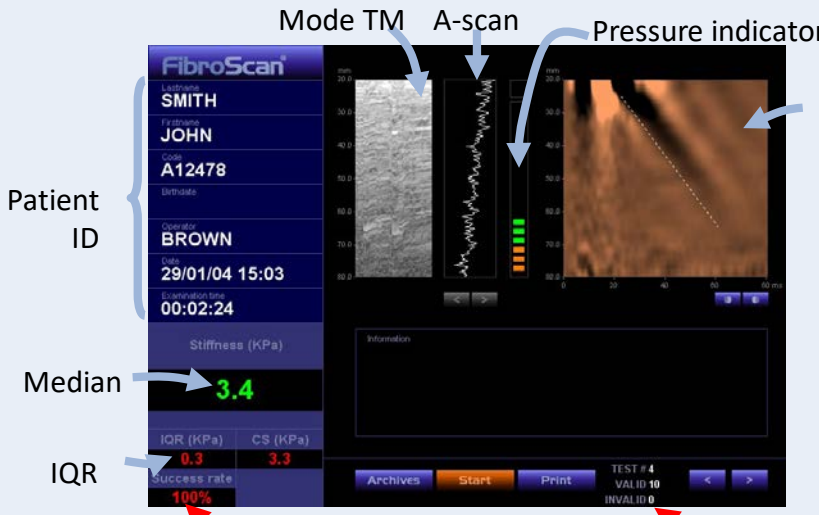
FibroScan®

Immediate results

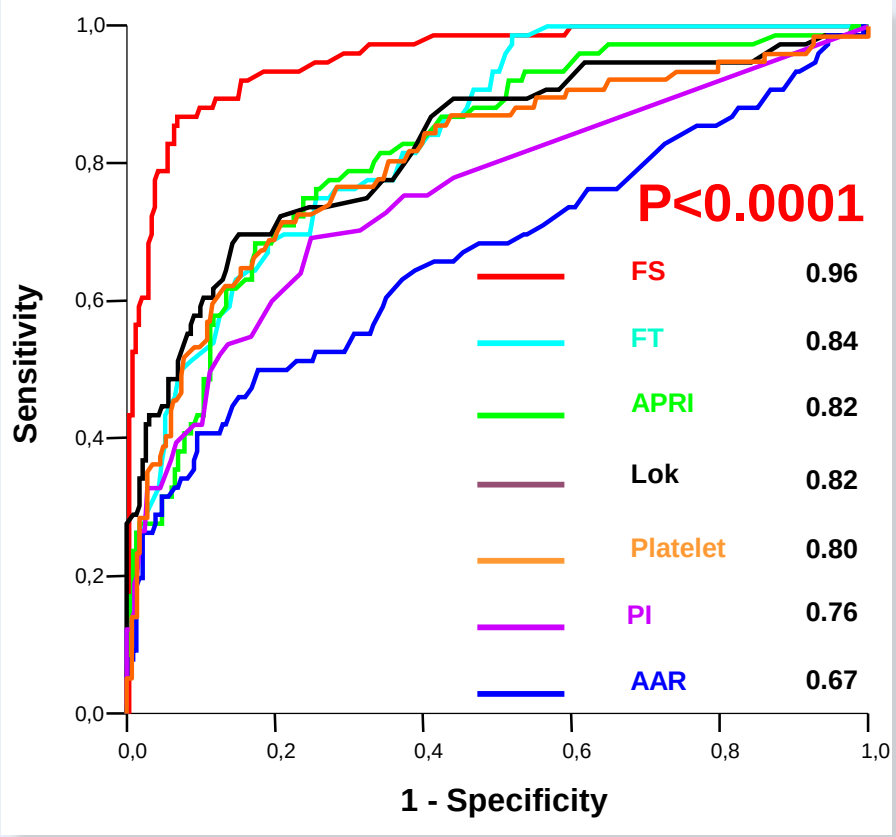
Less sampling error

Bedside procedure





Diagnosing Cirrhosis: TE vs. Biomarkers



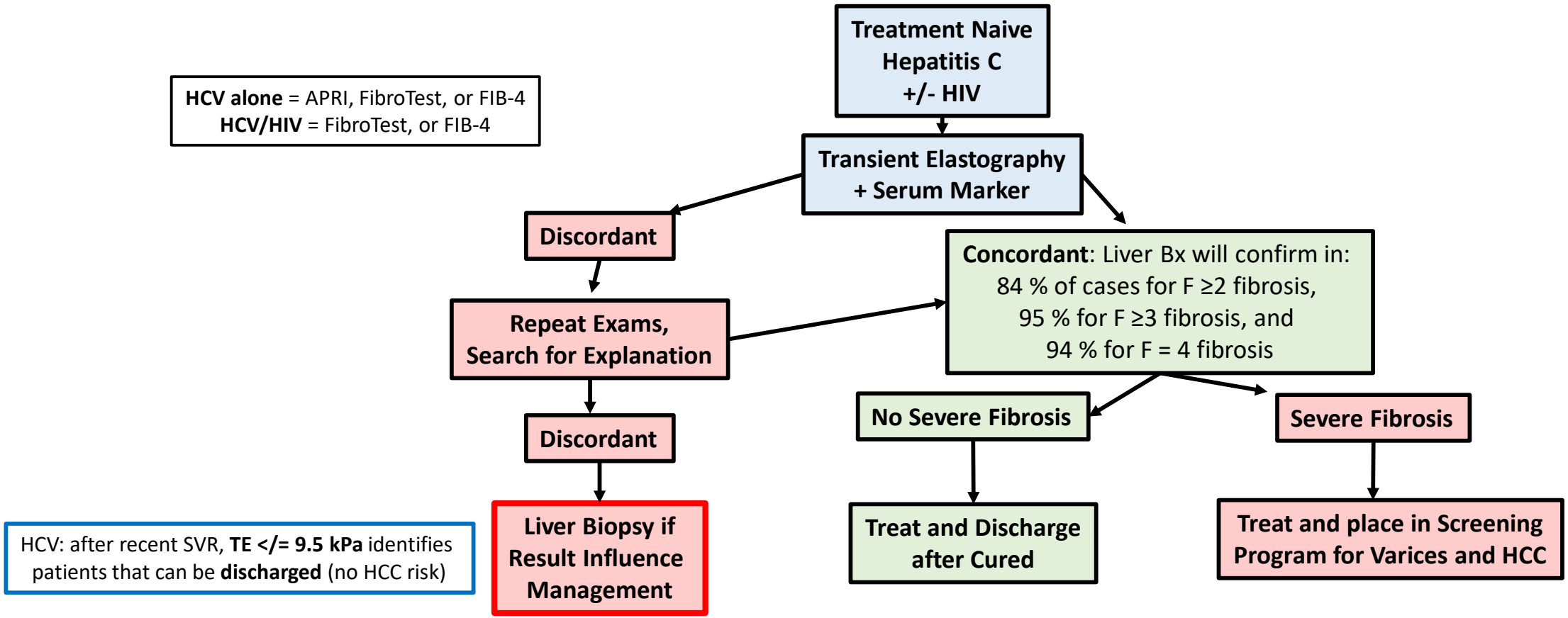
P<0.0001

Castera et al. J Hepatol 2009; 50: 59-68.

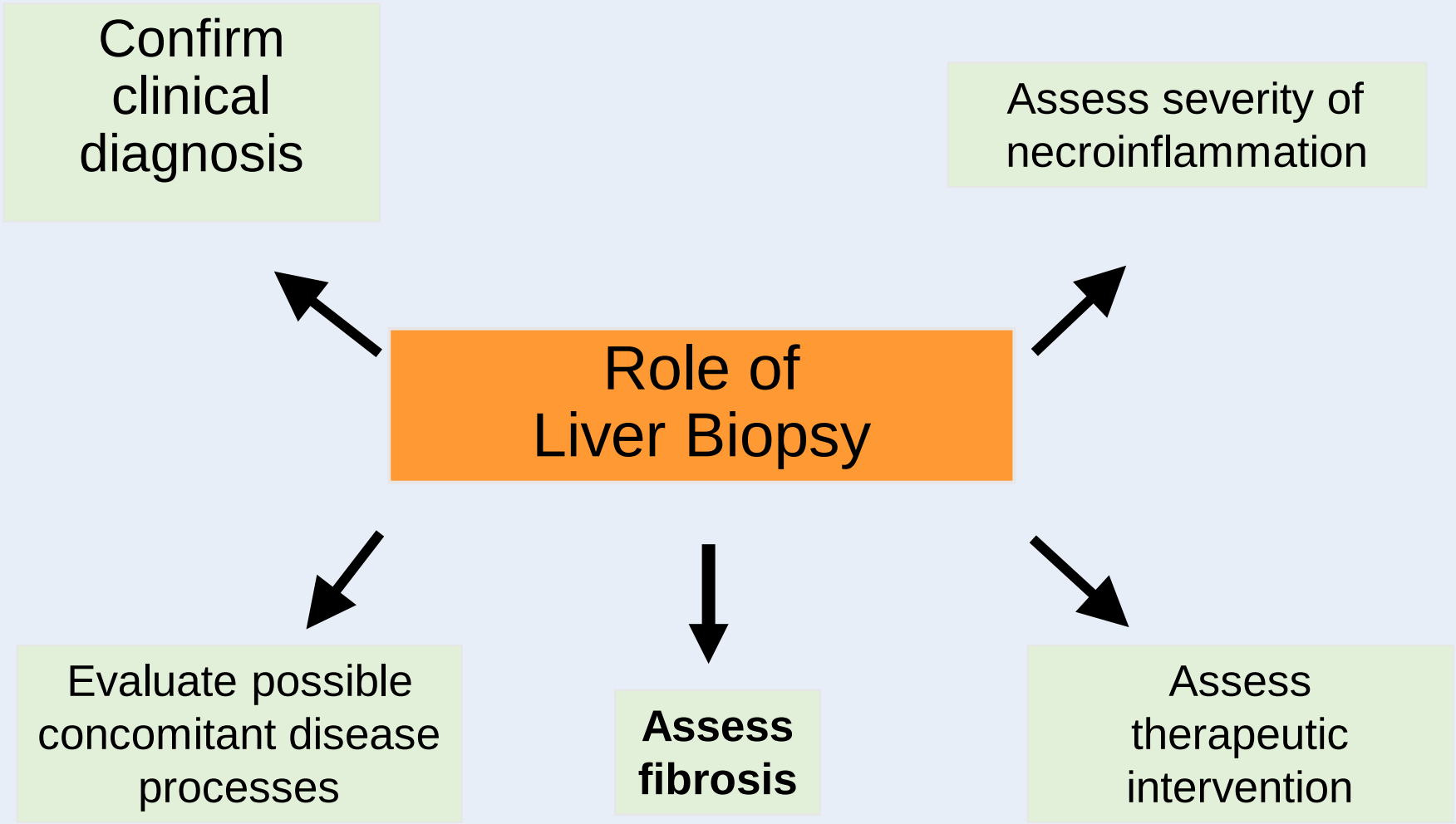
Degos et al. J Hepatol 2010; 53: 1013-21

Sequential Algorithm for Fibrosis Evaluation (SAFE) in Hepatitis C

Modified from: Journal of Hepatology 2015 vol. 63; 237–264 and Gastroenterology 2017 Vol. 152, 1536–1543



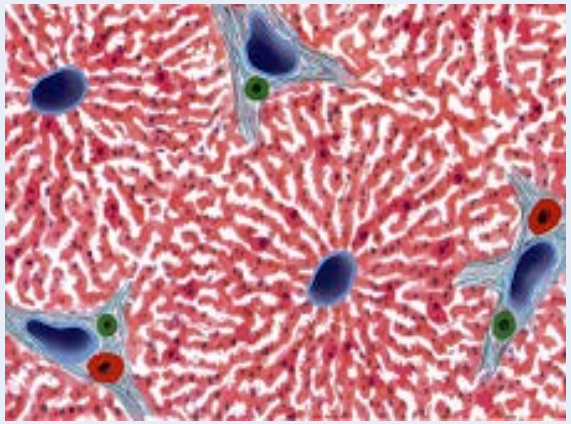
Utility of Liver Biopsy



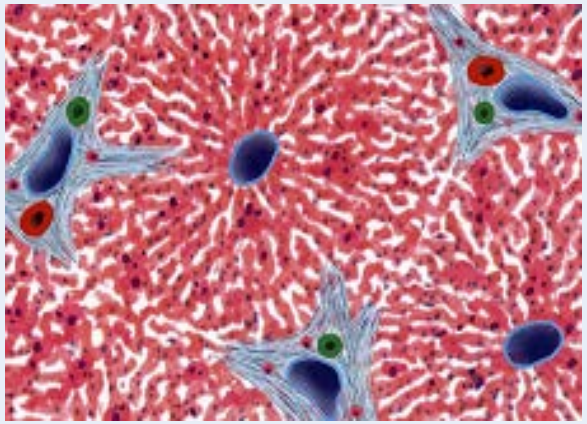
Brunt et al. *Hepatology*. 2000;31:241-246.

Histologic Staging

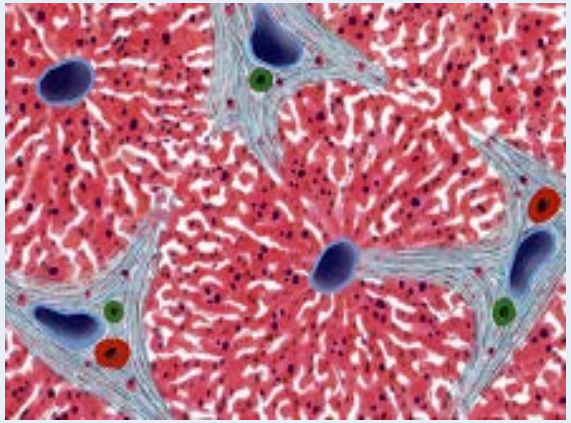
Stage 1



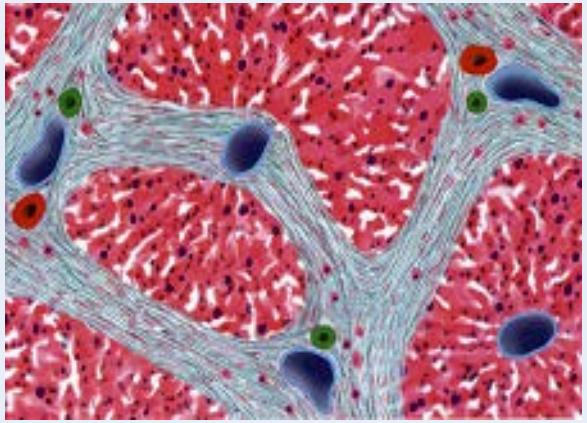
Stage 2



Stage 3



Stage 4



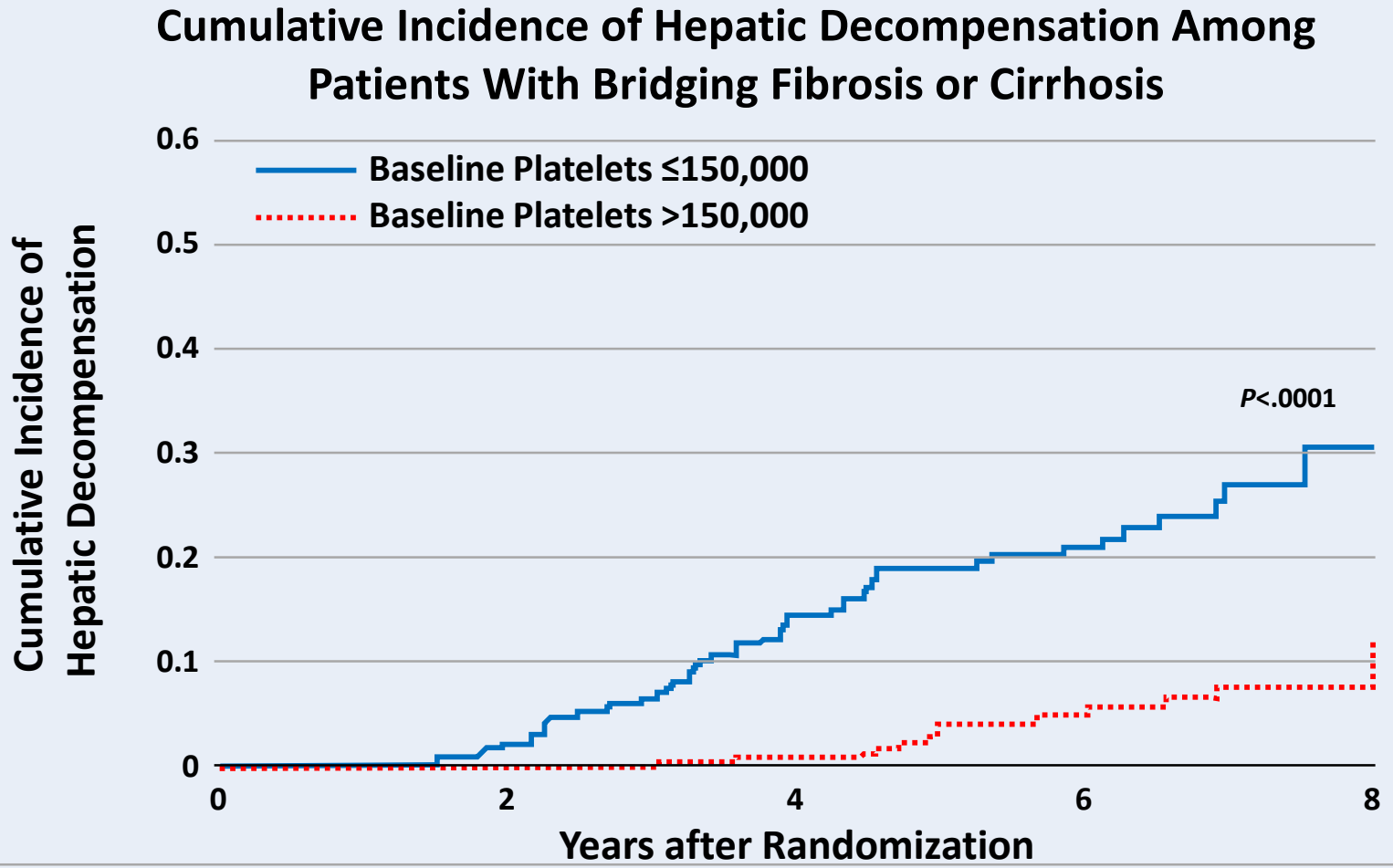
Slide courtesy of Sammy Saab, MD, MPH, AGAF

Hepatic Fibrosis Scoring Systems

	Knodell	Ishak	METAVIR
Absent	0	0	0
Portal fibrosis (some)	1	1	1
Portal fibrosis (most)	1	2	1
Bridging fibrosis (few)	3	3	2
Bridging fibrosis (many)	3	4	3
Incomplete cirrhosis	4	5	4
Cirrhosis	4	6	4

Brunt. Hepatology. 2000;31:241-246.

Platelet Counts May Serve as a Marker of Progressive Liver Disease Based on the HALT-C Trial Database



Analysis of baseline values from HALT-C trial database.
A model that included baseline platelet count and albumin as well as severe worsening of AST/ALT ratio and albumin was the best predictor of liver-related outcomes.
AST=aspartate aminotransferase.

Ghany MG, et al. Hepatology. 2011;54:1527-1537.

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, Paritaprevir (PrOD/PrO), 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.

Before Treatment

- 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)” (present in 11%) to decide length of therapy and addition of RBV (16 weeks with resistant polymorphism vs 12 weeks)
  - LEDIPASVIR, check for “NS5A Polymorphism”; with Y93 polymorphism (4%) SVR is 20% lower (96% vs 75%)
- 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.

The HCV Lifecycle Favors Resistance Development… But Not Persistence

Favors Resistance

1. High viral turnover rate
   - 10^{12} virions/day
2. Error-prone RNA polymerase
   - ~1 error per 10,000 bases
   - Involved twice in replication
3. No overlapping reading frames
4. Moderate rate of infected hepatocyte turnover

Lack of Persistence

1. No DNA intermediate
   - Contrast to integrated HIV
   - Contrast to HBV cccDNA
2. No long-lived cellular reservoir known
   - Contrast latently infected HIV + CD4 cells
   - Contrast to transfer of HBV cccDNA in dividing cells
3. There are exceptions!

Resistant variants pre-exist in all patients but are important if > 15% of virions have it

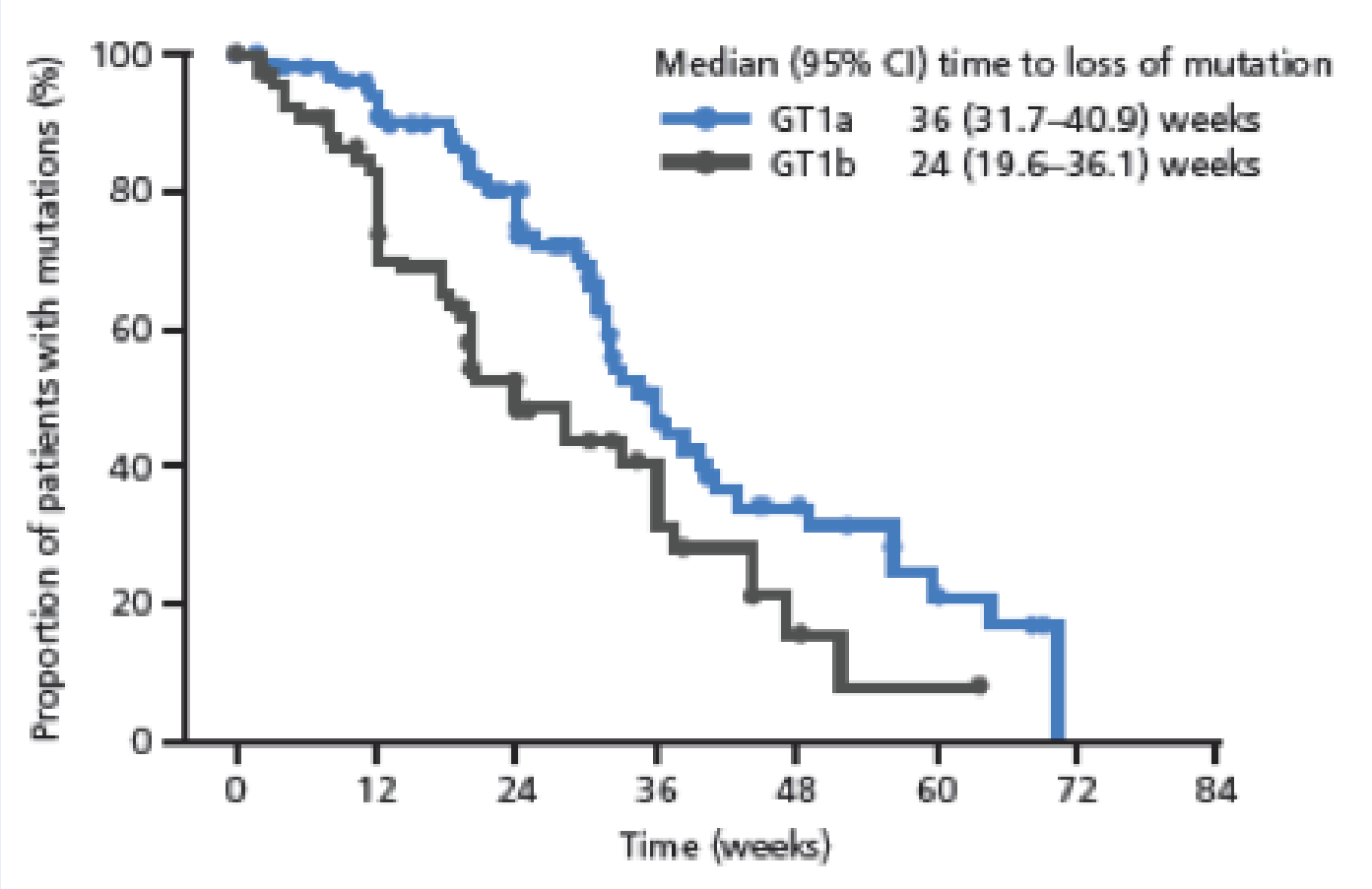
Resistant-Associated Substitutions (RASs) or Polymorphisms only in some

Available Resistance Testing (US)

- Ultra-deep (or NGS) vs population (Sanger)
  - What is available:
    1. LabCorp/Monogram Biosciences
       - NGS with 10% detection level reported
    2. Quest Diagnostics
       - RT-PCR with DNA sequencing
  - What matters in the clinic?

http://www.monogrambio.com/content/hcv-ns5a-testing
http://www.questdiagnostics.com/testcenter/testguide.action?dc=TS_HCV_NS5A_Genotype&tabview=true

The Saving Grace With PI Resistance?

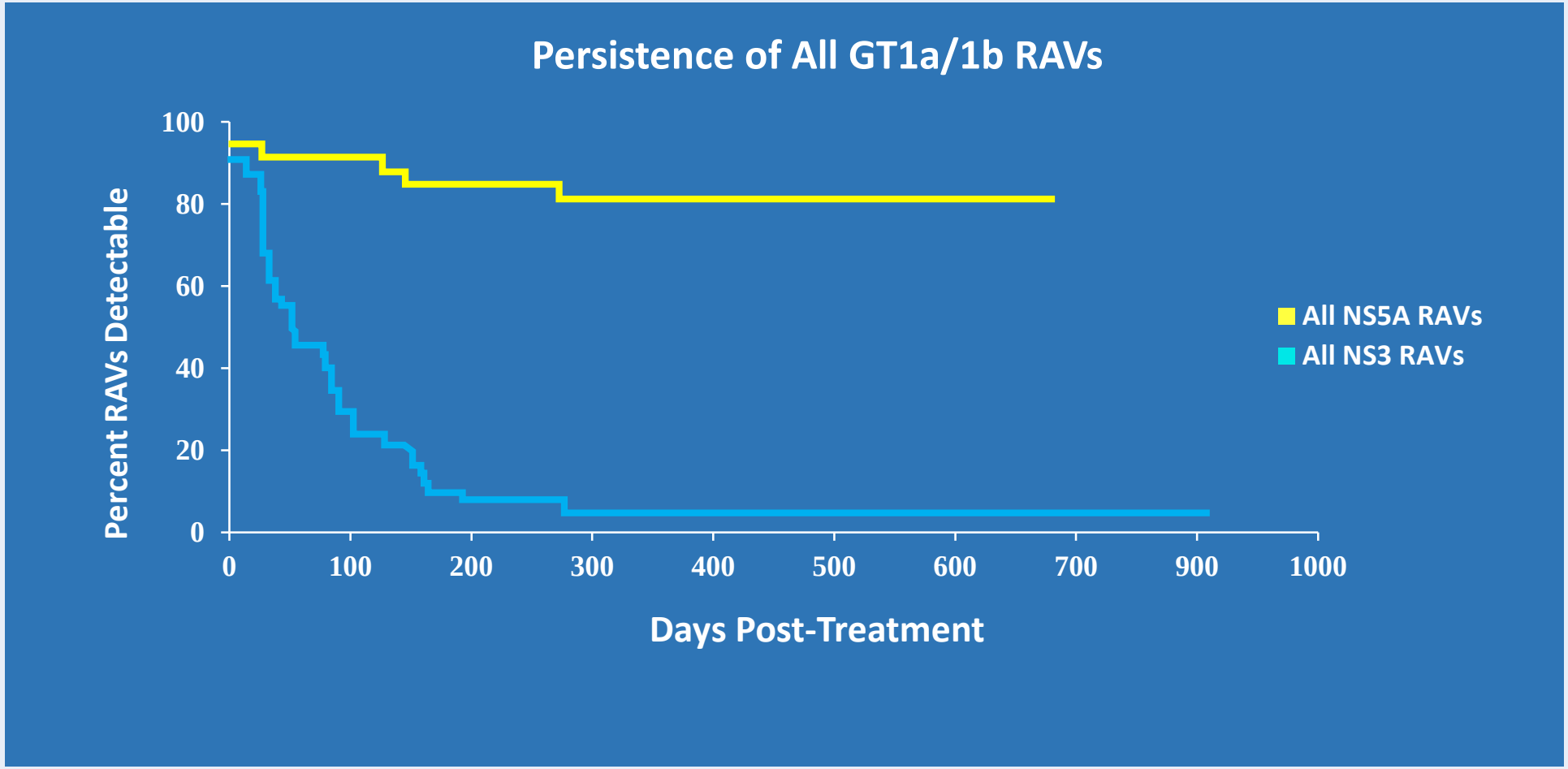


<u>91% of nonSVR with resistance</u>

1a: R155K +/- Q80K

1b: D168V

Resistance Assoc. Substitutions (RASs) After Grazoprevir + Elbasvir +/- RBV +/- PegINF/RBV



Lahser F, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 61.

NS5A Resistance-Associated Substitutions (RASs) with Potential for Clinical Significance

Wild-type Amino Acid (sensitive)	Position	Substitution Amino Acid
M	28	A/G/T
Q	30	D/E/H/G/K/L/R
L	31	F/M/V
Y	93	C/H/N/S

Genotypes 1a and 3 are the most affected

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice (NS5A only)

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice	
RECOMMENDED	RATING
Elbasvir/Grazoprevir NS5A RAS testing is recommended for **genotype 1a-infected**, **treatment-naive or -experienced** patients being considered for Elbasvir/Grazoprevir. If present M28, Q30, L31 or Y93 polymorphism, a different regimen should be considered.	I, A
Ledipasvir/Sofosbuvir NS5A RAS testing can be considered for **genotype 1a-infected**, **treatment-experienced** patients with and without cirrhosis being considered for Ledipasvir/Sofosbuvir. If clinically important[a] resistance is present, a different recommended therapy should be used.	I, A
Sofosbuvir/Velpatasvir NS5A RAS testing is recommended for **genotype 3-infected**, **treatment-naive patients with cirrhosis** and **treatment-experienced** patients (without cirrhosis) being considered for 12 weeks of Sofosbuvir/Velpatasvir. If **Y93H** is present, weight-based ribavirin should be added or another recommended regimen should be used.	I, A

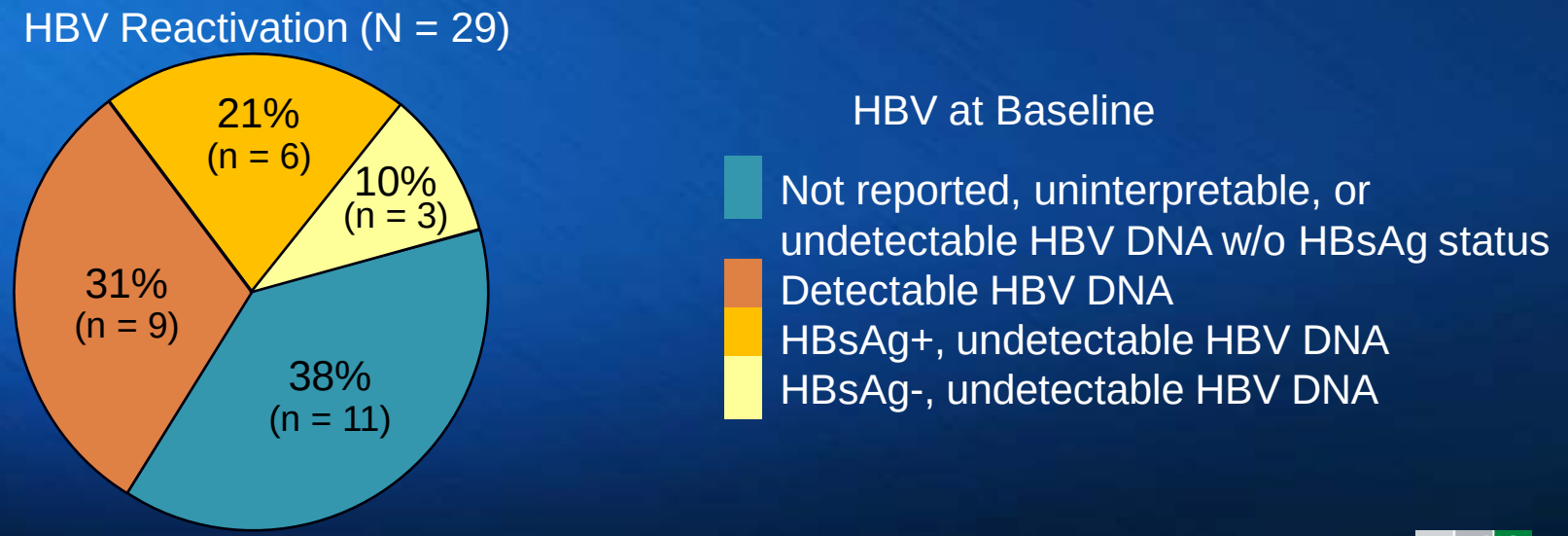
[a] Clinically important = ≥100-fold shift in the in vitro EC_{50} to Ledipasvir with Q30H/R, L31M/V, and Y93C/H/N

Before Treatment

- Patients scheduled to receive an HCV NS3 protease inhibitor (paritaprevir, simeprevir, grazoprevir) should be assessed for a history of decompensated liver disease and for severity of liver disease using CTP score. Rating: Class I, Level A
  - Patients with current or prior history of decompensated liver disease or with a current CTP score of 7 or greater should NOT receive treatment with regimens that contain NS3 protease inhibitors due to increased area under the curve (AUC) and/or lack of safety data.
  - Similarly, patients with a CTP score of 5 or 6, who cannot be closely monitored for laboratory or clinical symptoms during treatment, should not receive treatment with a regimen that contains paritaprevir/ritonavir.
- All patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg, anti-HBs, and anti-HBc. Rating: Class IIa, Level B

HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Most cases occurred within 4-8 wks of initiation
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

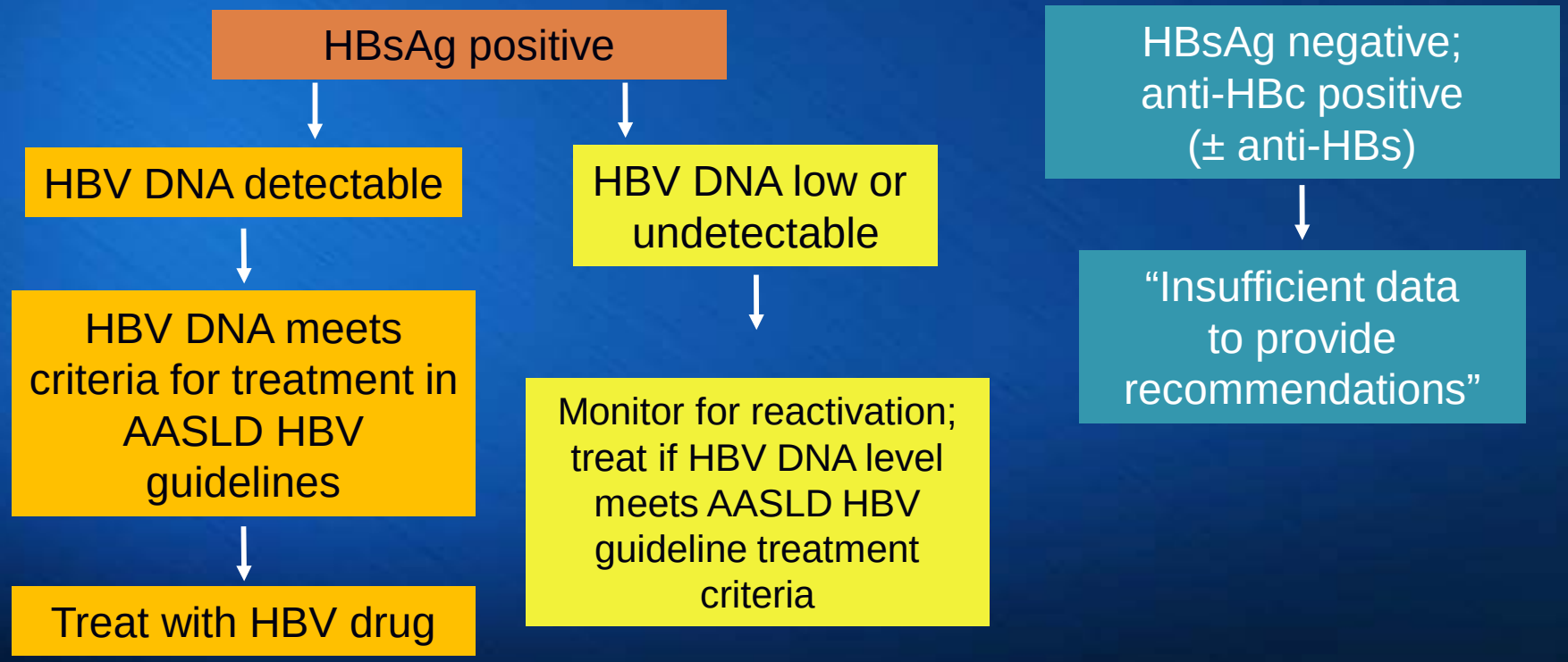


Bersoff-Matcha SJ, et al. AASLD 2016. Abstract LB17.

Slide credit: clinicaloptions.com

HBV Testing and Monitoring During HCV DAA Therapy: AASLD/IDSA Guidance

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - No HBV markers: VACCINATE (this is not new)
  - HBV markers present:



AASLD/IDSA. HCV guidance. September 2016.
Graphic created by Ira M. Jacobson, MD.

Slide credit: clinicaloptions.com

My recommendations

- If HBsAg(+) with HBV-DNA of 2000 IU/mL or higher:
  - Treat for chronic HBV
- If HBsAg (+) with HBV-DNA < 2000 IU/mL, or
  If HBsAg (-) but anti-HBc (+):
  - Monitor every 4 weeks with HBsAg (if it was negative) and HBV-DNA quantitation, during therapy and up to 8-12 weeks after EOT.

People With Hepatitis C Should Be Tested for Hepatitis B Before Starting DAAs

(**September 16, 2016**) – All patients beginning hepatitis C (HCV) treatment using direct acting antiviral (DAA) therapies should be assessed for hepatitis B (HBV) HCVguidelines.org.

Cases of HBV reactivation (an increase of the HBV virus) during or after DAA therapy for HCV have been reported in HBV/HCV co-infected patients who were not already on HBV suppressive therapy.

Recommendations Monitoring for Pregnancy-Related Issues

Pregnancy Related Issues	
RECOMMENDED	RATING
As part of **prenatal care**, all pregnant women should be **tested for HCV** infection with each pregnancy, ideally at the initial visit. (See Recommendations for Initial HCV Testing and Follow-Up.)	IIb, C
For women of reproductive age with known HCV infection, **antiviral therapy is recommended before** considering **pregnancy**, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for **HCV-antibody–positive** pregnant women to assess the risk of mother-to-child transmission (MTCT) and severity of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In **HCV-infected pregnant women with pruritus** or jaundice, there should be a high index of suspicion for **intrahepatic cholestasis of pregnancy (ICP)** with subsequent assessment of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and **serum bile acids**.	I, B
HCV-infected **women with cirrhosis** should be counseled about the **increased risk of adverse maternal and perinatal outcomes**. Antenatal and perinatal care should be coordinated with a maternal-fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B
Breastfeeding is not contraindicated in women with HCV infection, **except** when the mother has cracked, **damaged, or bleeding nipples**, **or** in the context of **HIV coinfection**.	I, B
Women with HCV infection should have their **HCV RNA reevaluated after delivery to assess for spontaneous clearance.**	I, B

Recommendations Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy that Includes Ribavirin

RECOMMENDED	RATING
Women of childbearing age should be counseled not to become pregnant while receiving a ribavirin-containing antiviral regimen, and for at least 6 months after stopping the regimen.	I, C
Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving a ribavirin-containing antiviral regimen, and for up to 6 months after stopping the regimen.	I, C
Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.	I, C
Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.	I, C
Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.	I, C

From www.HCVGuidance.org on May 24, 2018

Treatment of Chronic Hepatitis C
AASLD/IDSA Guidelines + FDA

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.

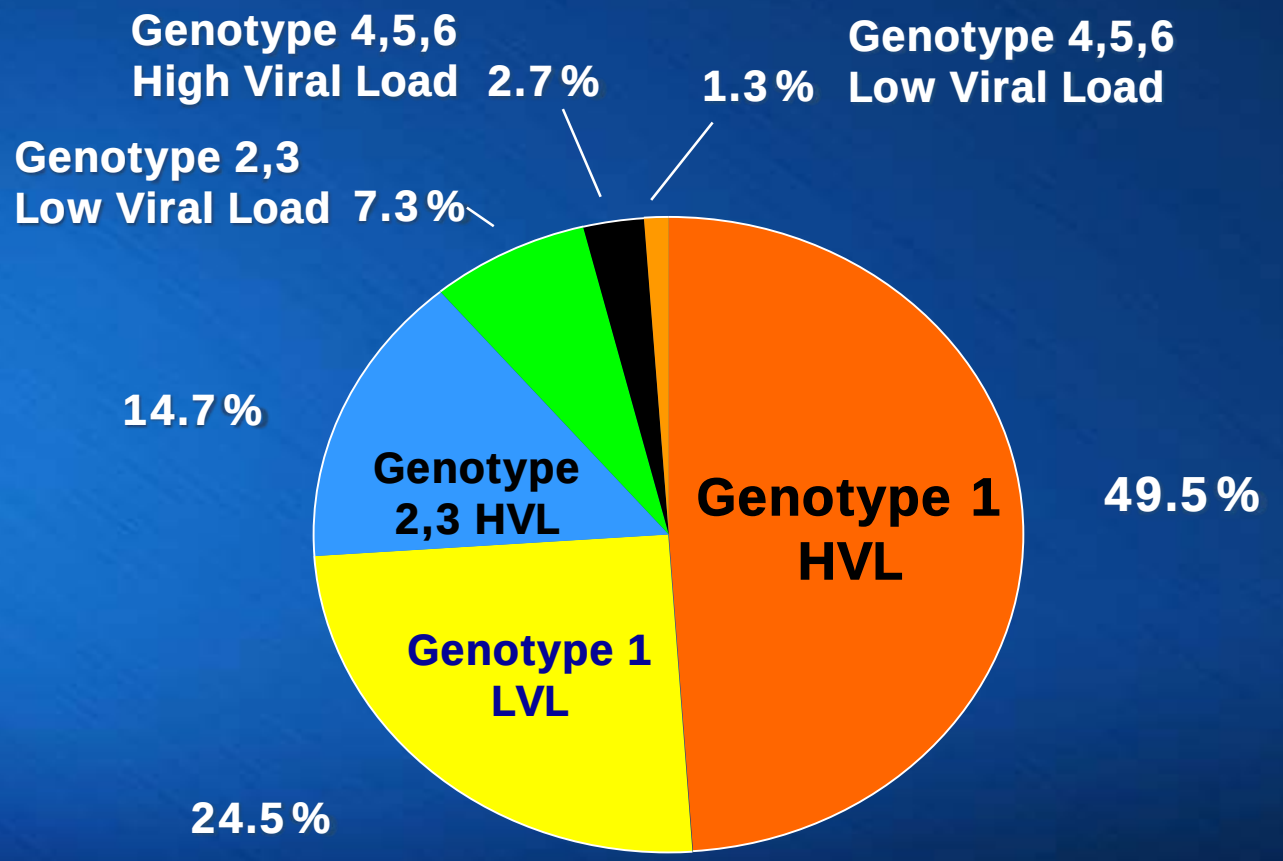
Drugs to Treat Hepatitis C

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

Agents and Regimens Currently Used

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 and XR or PrOD or 3D)	⊙	⊙	⊙		⊙ RBV only for 1a or F3-4
Sofosbuvir + ribavirin				⊙	⊙
Daclatasvir + sofosbuvir		⊙		⊙	
Grazoprevir + Elbasvir (ZEPATIER)	⊙	⊙			
Velpatasvir + Sofosbuvir (EPCLUSA)		⊙		⊙	
Sofosbuvir + Velpatasvir + Voxilaprevir (Vosevi®)	⊙	⊙		⊙	
Glecaprevir + Pibrentasvir (Mavyret)	⊙	⊙			

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.

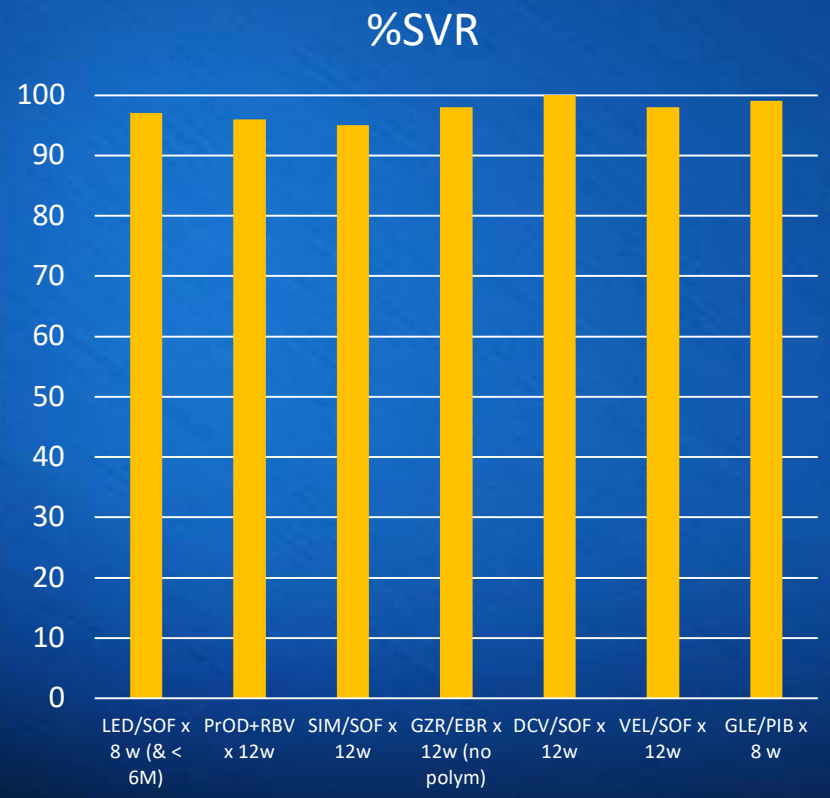
Expected SVR with First Line Regimens

- Data is NOT comparative due to different populations, inclusion and exclusion criteria.
- There are not large head-to-head studies for true comparison

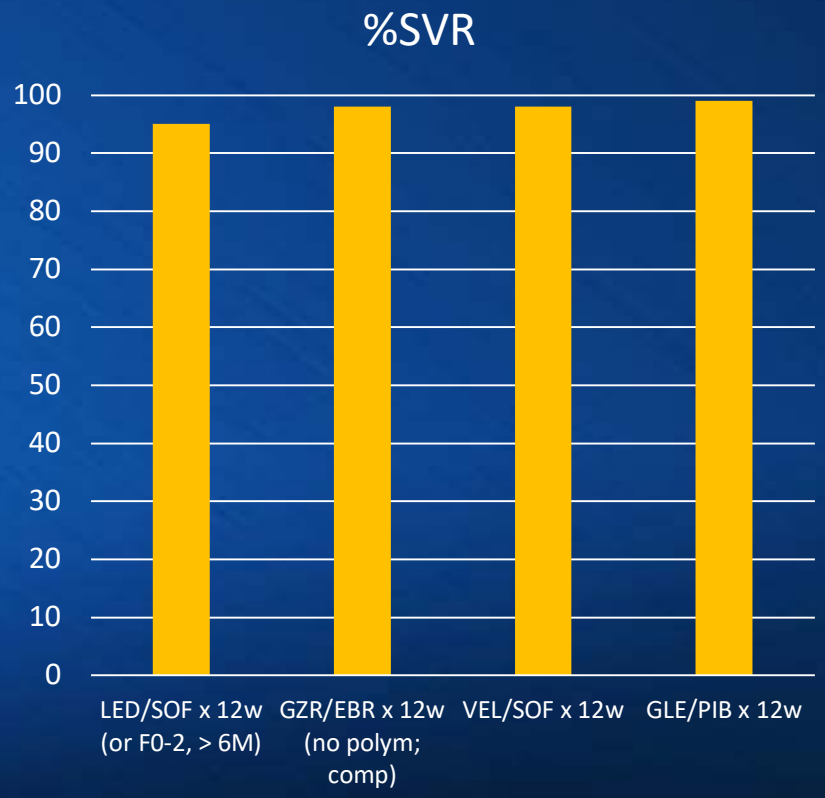
NAÏVE: Genotype 1a or Unspecified

First Line Therapy

SVR in F0-2 only



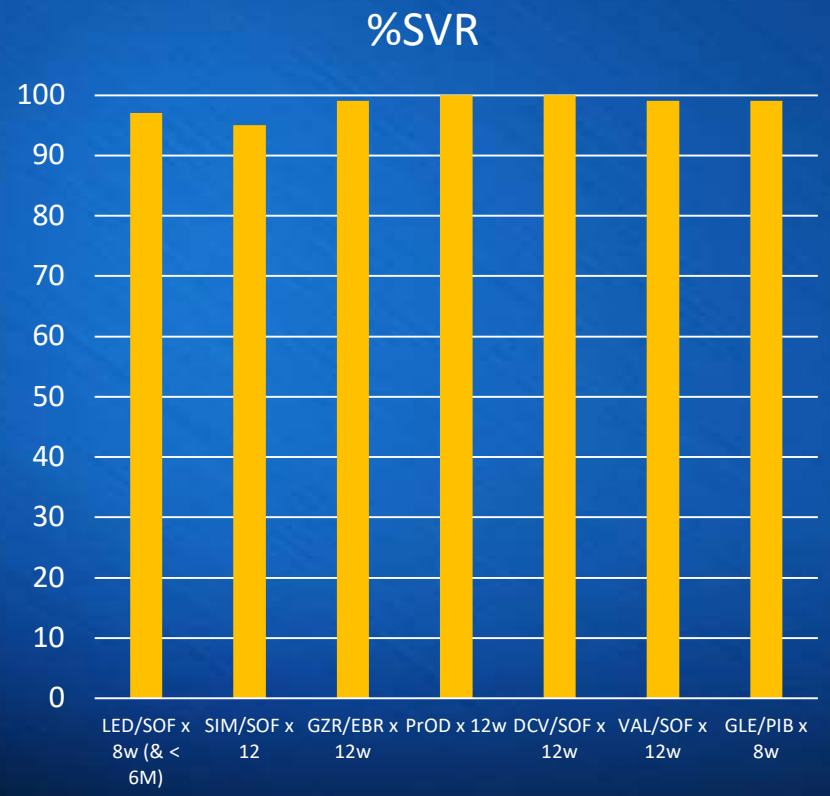
SVR in F3-4



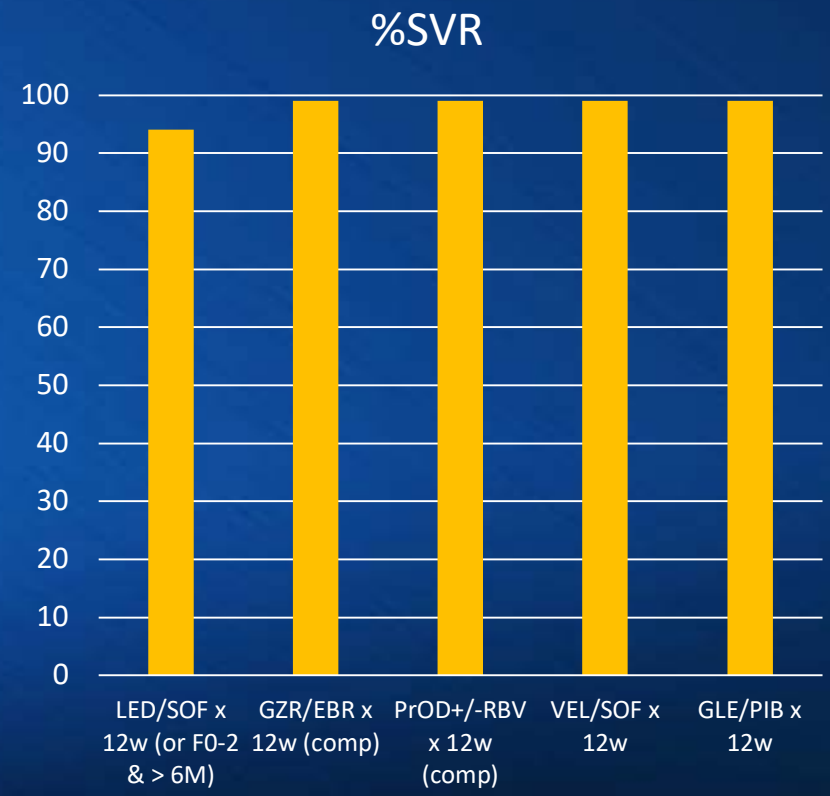
Naïve: Genotype 1b

First Line Therapy

SVR in F0-2 only



SVR in F3-4

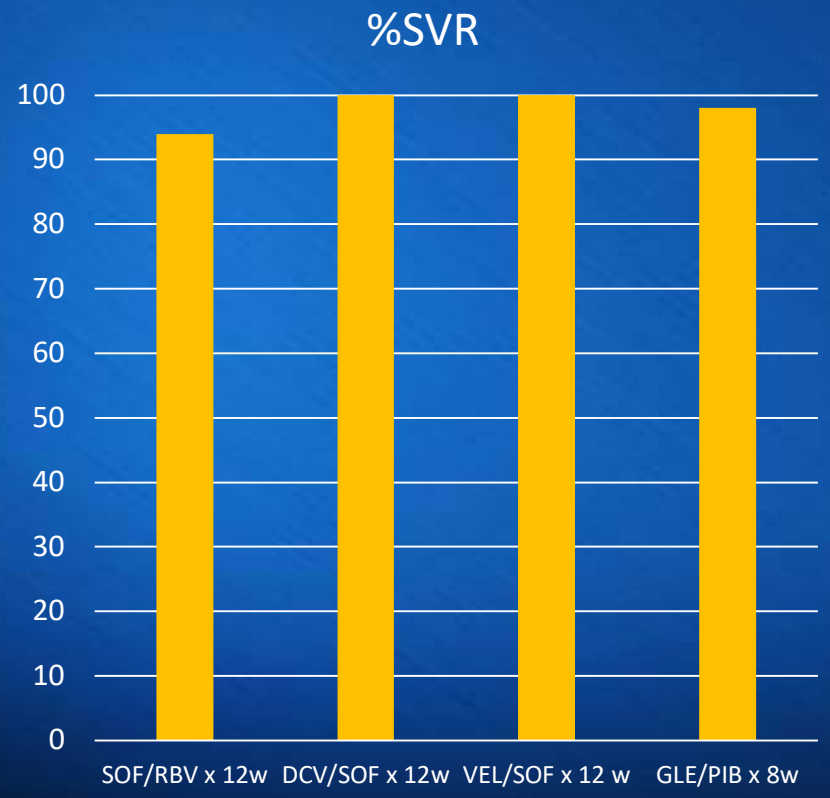


comp = compensated cirrhosis

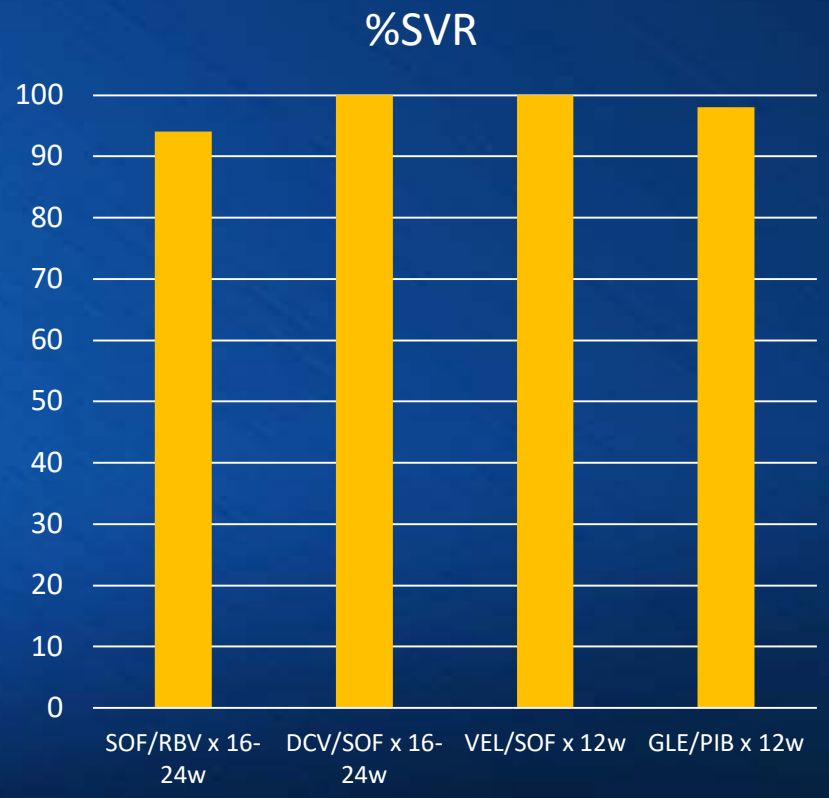
Naïve: Genotype 2

First Line Therapy

SVR in F0-2 only



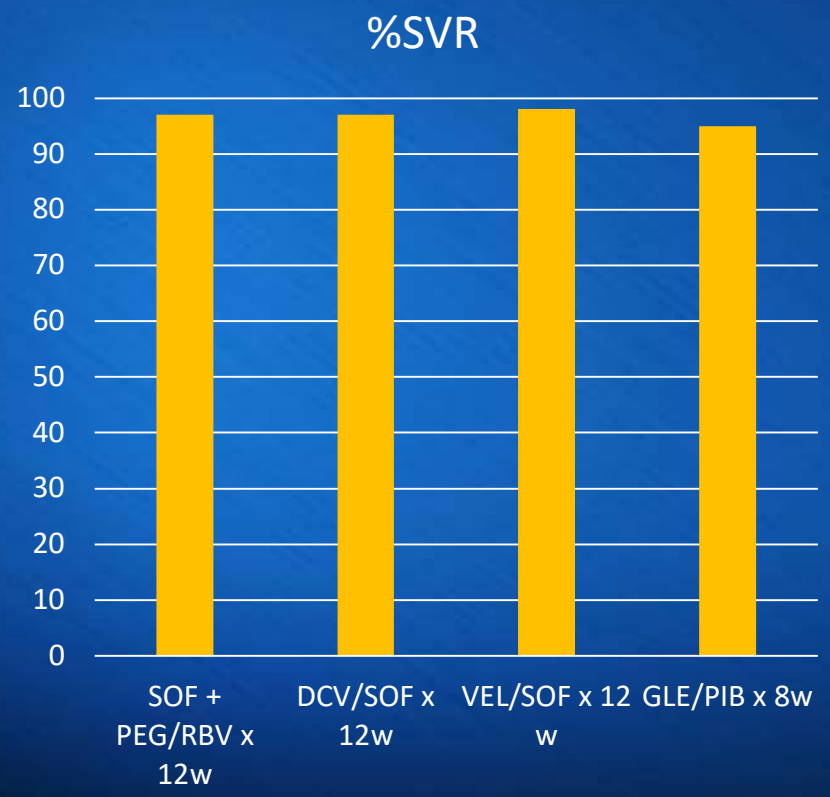
SVR in F3-4



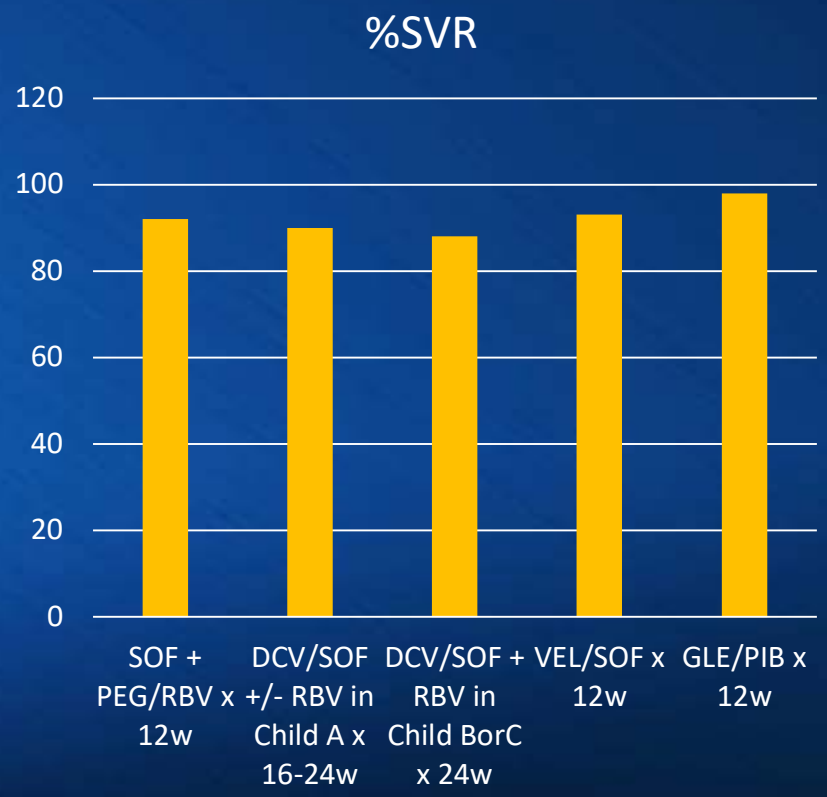
Naïve: Genotype 3

First Line Therapy

SVR in F0-2 only



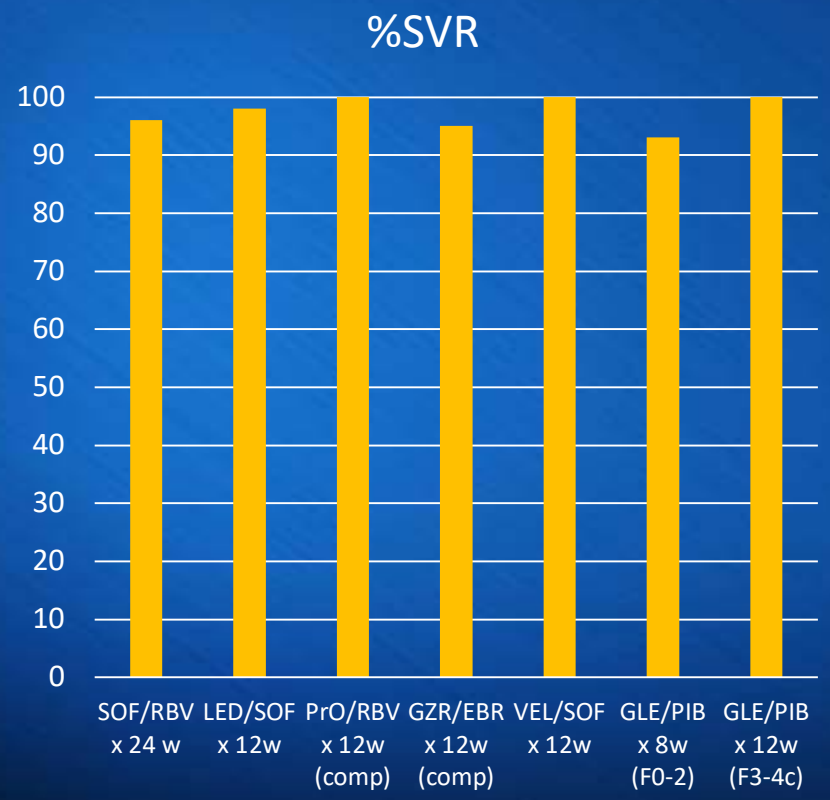
SVR in F3-4



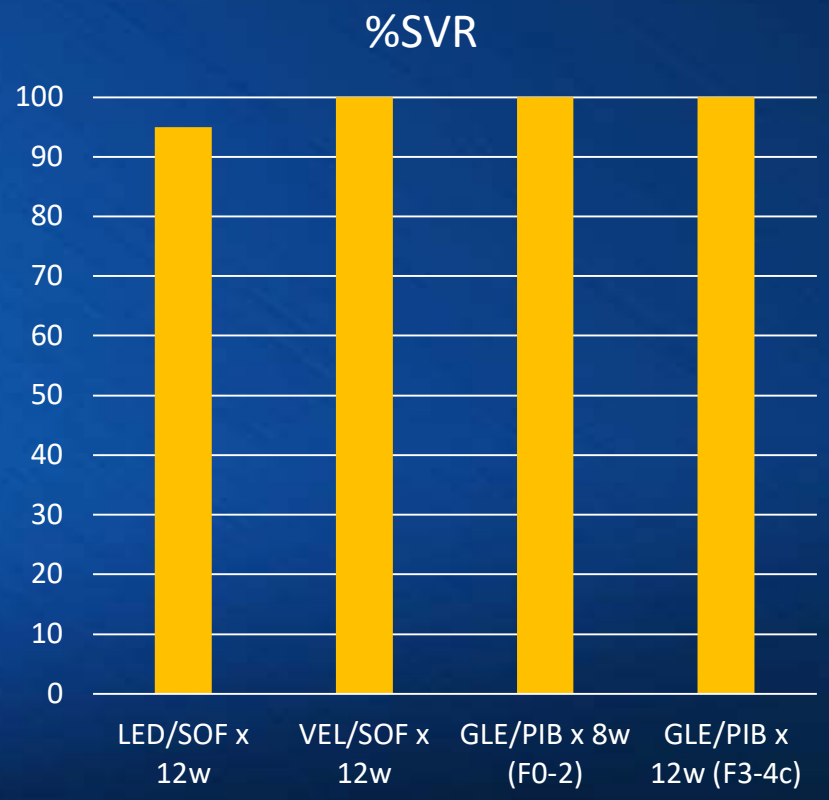
Naïve: Genotypes 4, 5, and 6

First Line Therapy

SVR in Genotype 4



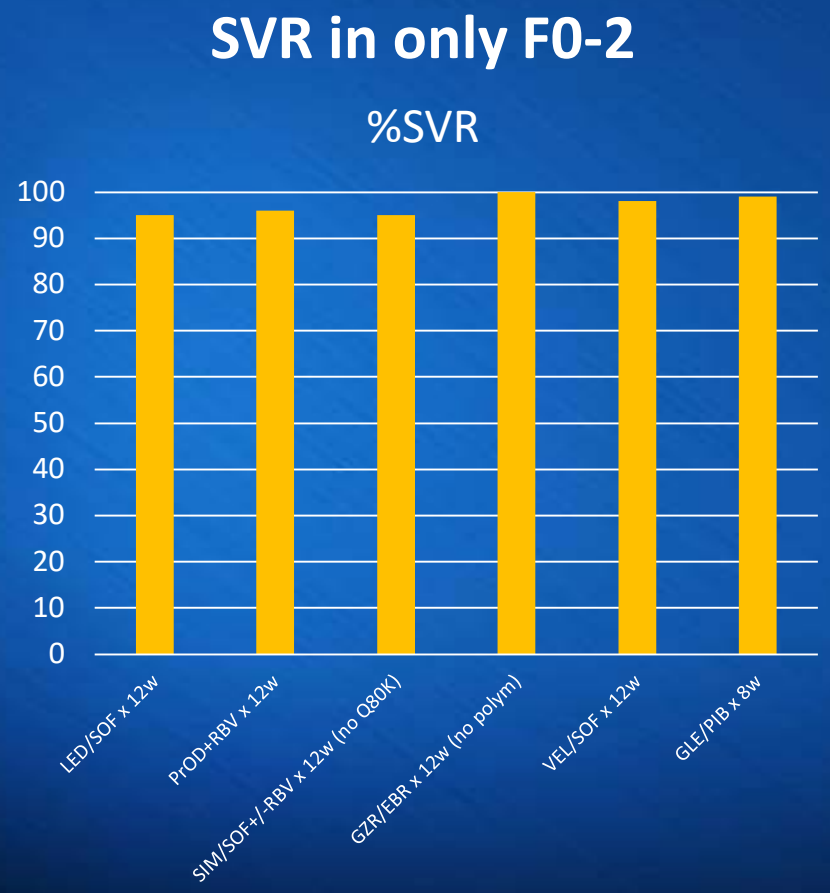
SVR in Genotypes 5 & 6

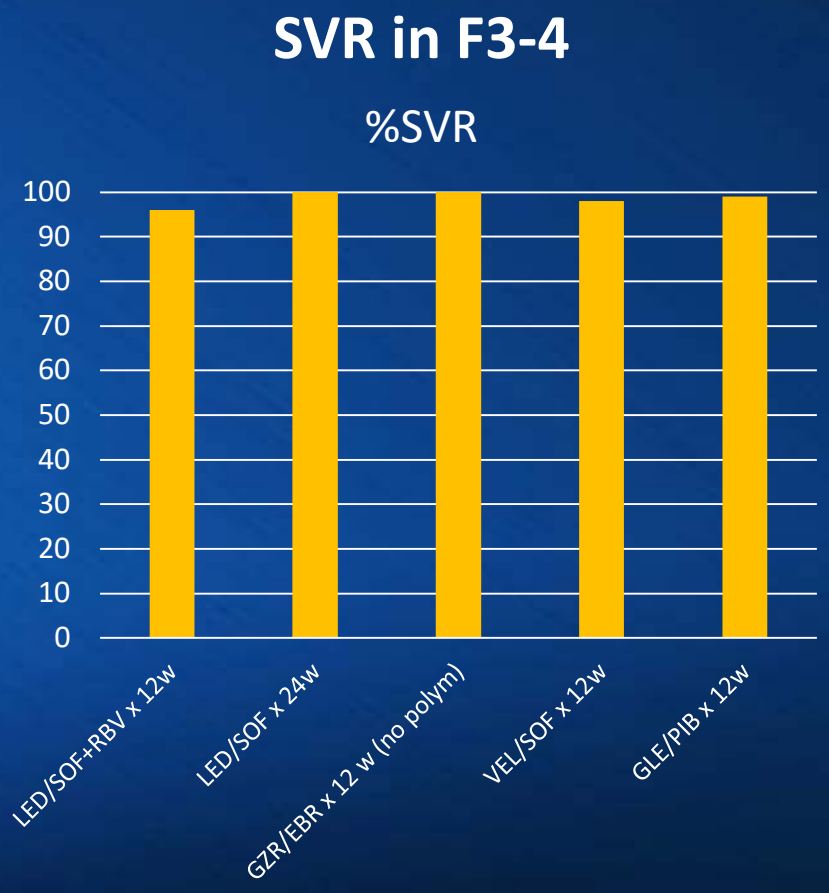


comp = compensated cirrhosis

PegIFN NR: Genotype 1a or Unspecified

First Line therapy

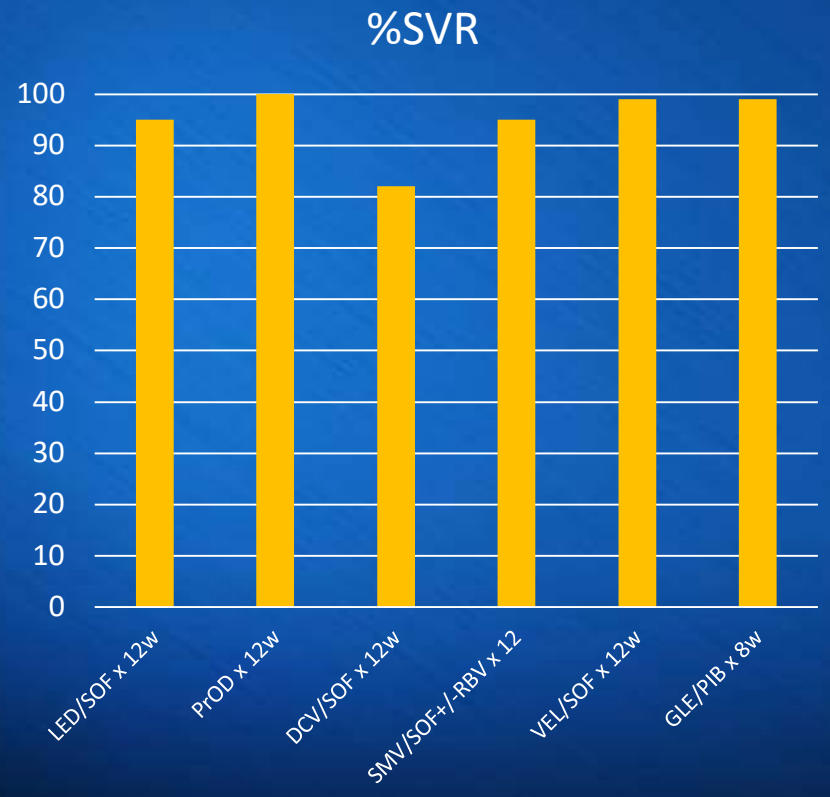




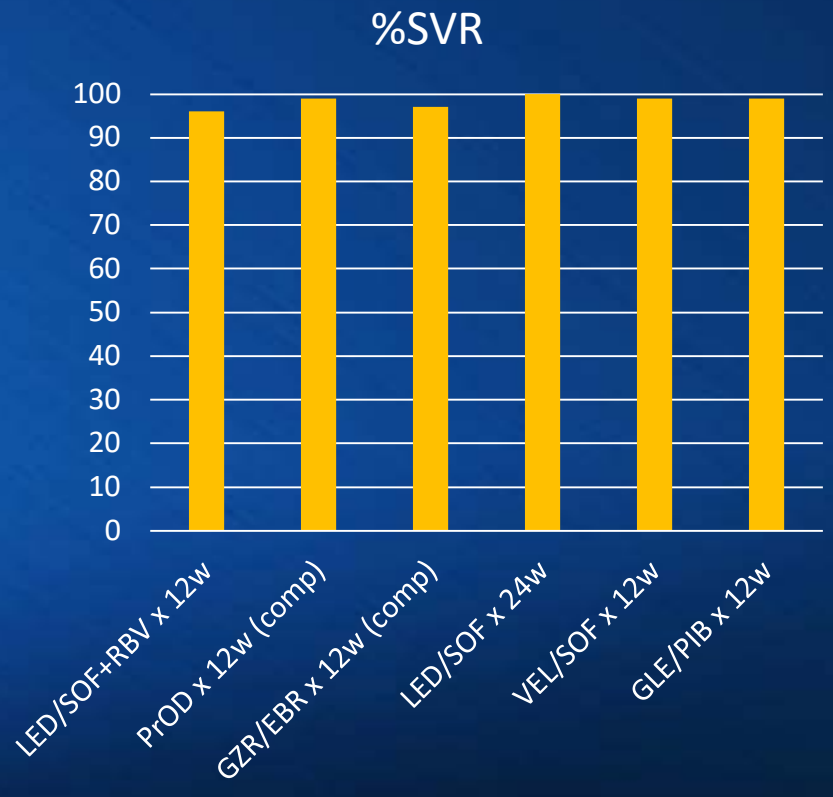
PegIFN NR: Genotype 1b

First Line Therapy

SVR in F0-2 only

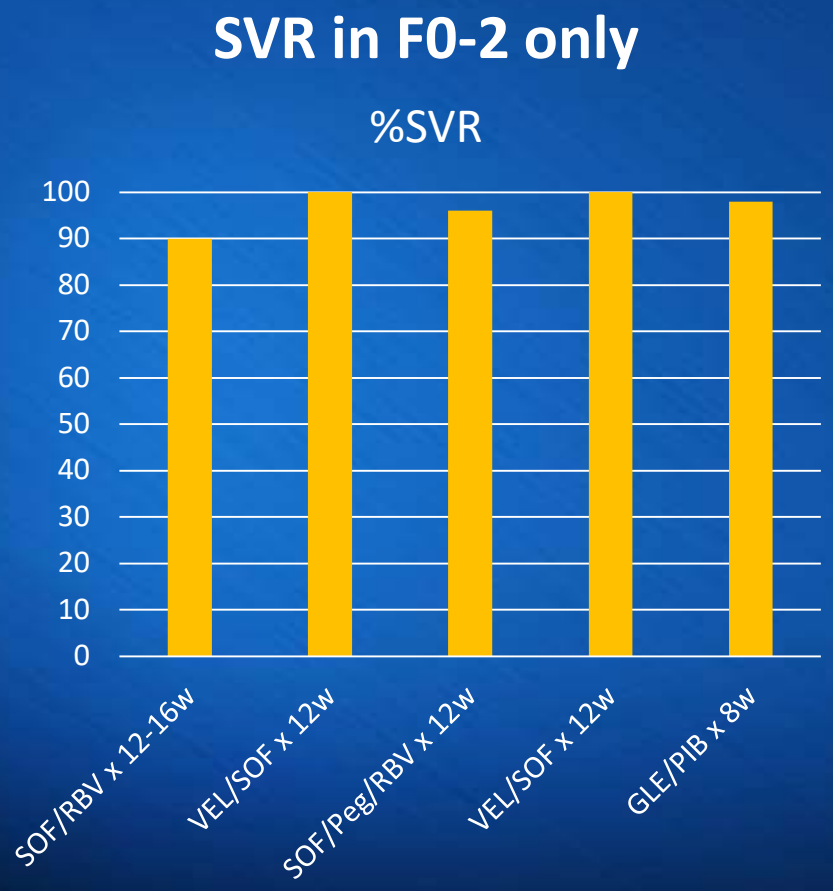


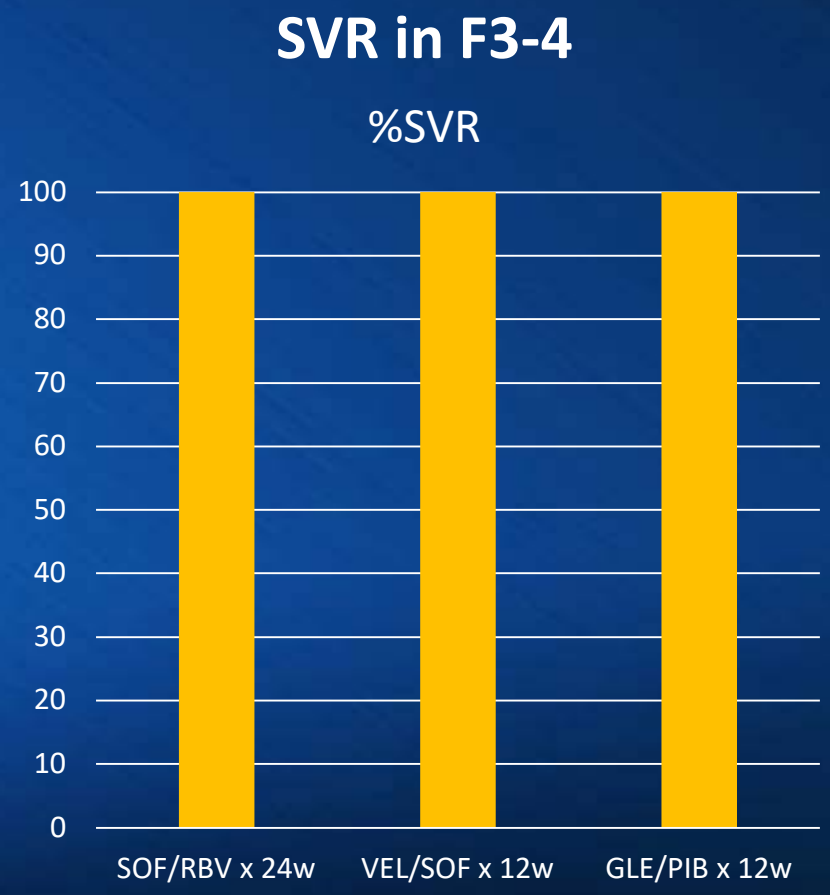
SVR in F3-4



comp = compensated cirrhosis

PegIFN NR: Genotype 2

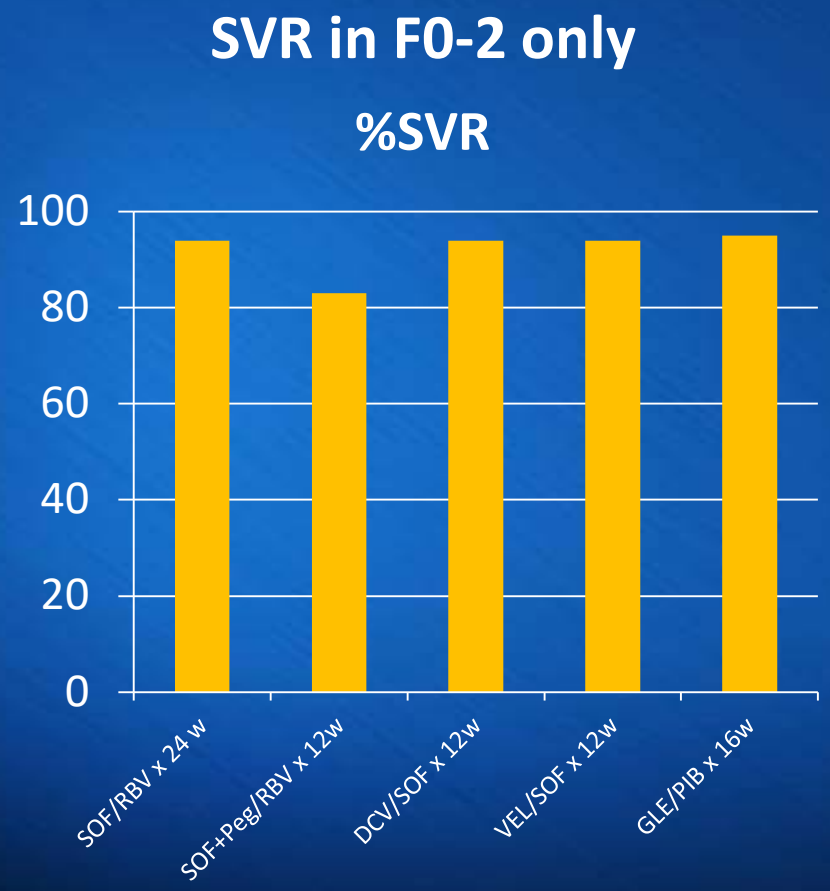


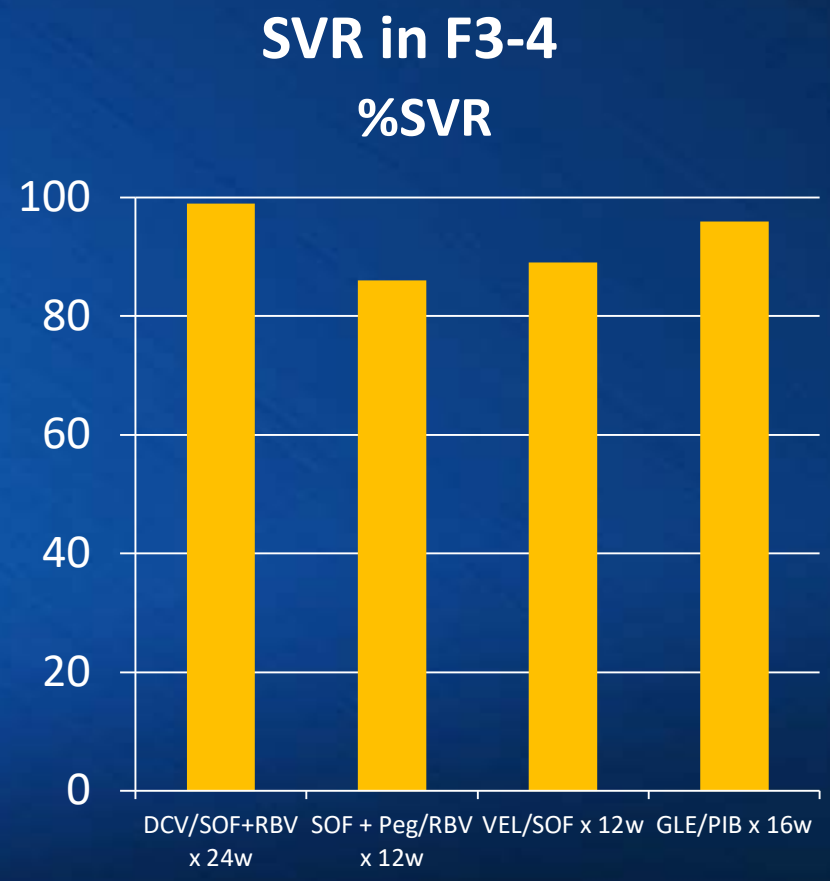


DCV/SOF +/- RBV is also recommended but there is not enough SVR data

PegIFN NR: Genotype 3

First Line Therapy

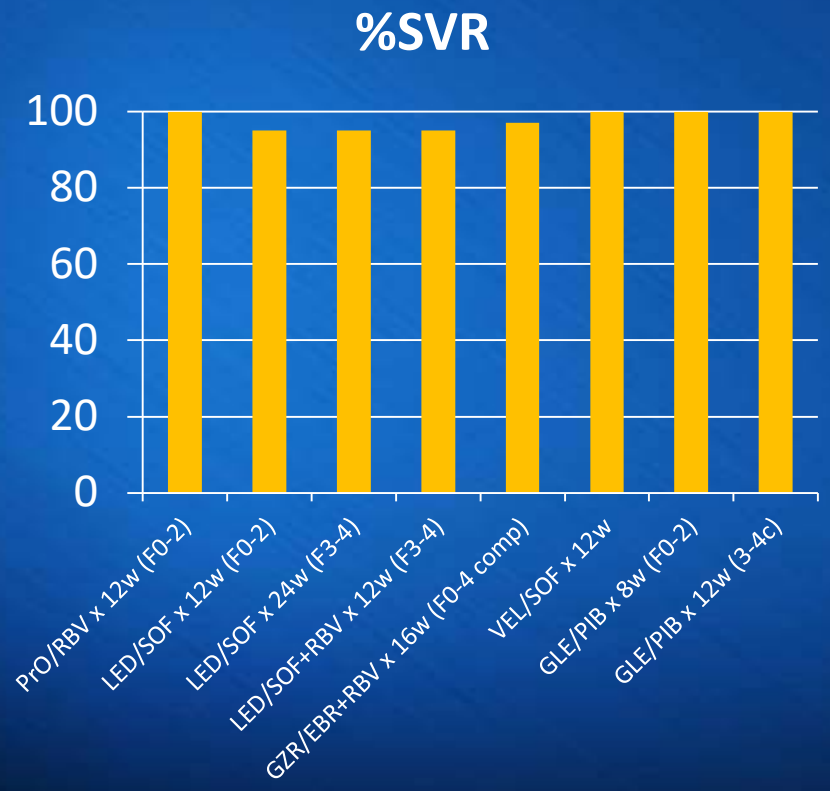




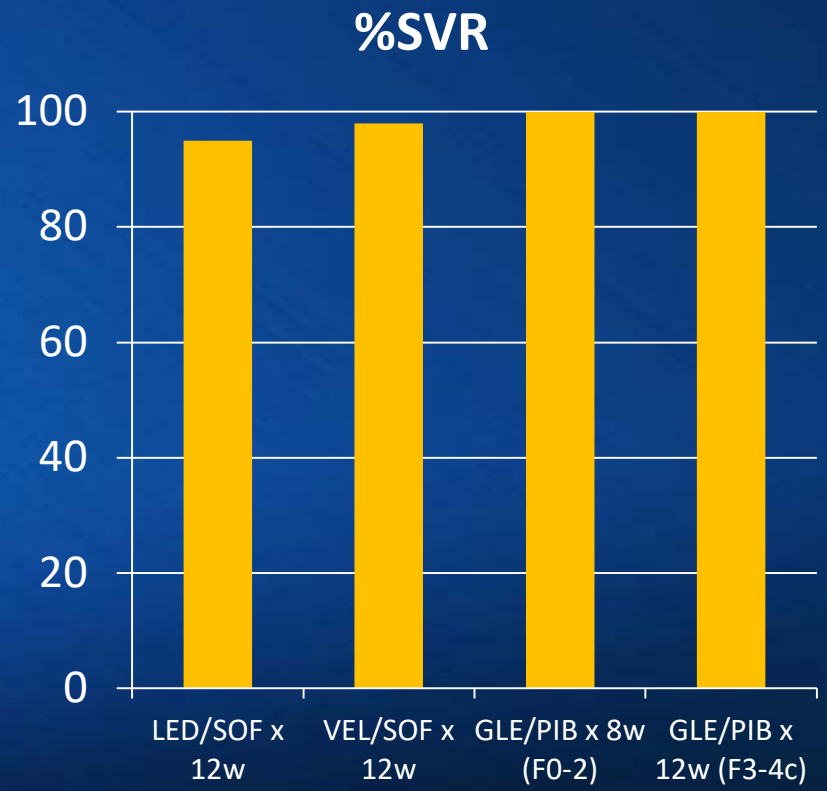
PegIFN NR: Genotypes 4, 5, & 6

First Line Therapy

SVR Genotype 4



SVR Genotypes 5 & 6



comp = compensated cirrhosis

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% ?
	F0-4c: **GLE 300 + PIB 120** (Geno 1,2,4,5,6)(Geno-3 is longer)	**F0-2: 8w; F3-4c: 12w Geno-3 (F0-4c): 16 w**	100%
	F0-4: **SOF/VEL 400/100**	**12**	100%
	F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g**	**12 (16 with RAS 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 +/- RBV 1-1.2 g**	**24**	100%
No Response to Sofosbuvir	**Regimen**	**Duration (weeks)**	**SVR**
Geno 1, 4, 5, 6 NS5A is (-) to RASs	F3-4: **SOF/LED 400/90 + RBV 1-1.2** g	**24**	100%
	F3-4: **SOF 400 + VEL 100 + RBV 1-1.2 g**	**24**	96%
	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) If in Urgent Need	**DAC 60 + SOF 400 + RBV 1-1.2**	**24**	70%?
	Geno 3 F0-4: SOF + VEL + VOX	**12**	
	SOF 400 + VEL 100 + RBV 1-1.2 g	**12**	91%(2), 76%(3)
	F0-4comp: **GZV 100 + EBR 50 + SOF 400 +/- RBV 1-1.2 g**	**12-16**	
Geno 1-6 NS5A Resistant	**F0-4: SOF + VEL + VOX**	**12**	96-100% (g4:91%; g3:95%)
Geno 1 NS5A Resistant	F0-4c: **GLE 300 + PIB 120**	**16**	100%
Geno 1, NS5A is (+) but NS3A is (-) to RASs	**SMV/SOF 150/400**	**24**	?
Failures with SOF/VEL x 12w	**SOF 400 + VEL 100 + RBV 1-1.2 g**	**24**	G-1: 98% G-2: 100% G-3: No RASs 100%; G-3 with RASs: 77%

RASs = Virus with "Resistance Associated Substitutions"

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	**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 400 + VEL 100 + RBV 1-1.2g**	**12**	100%
	SOF 400/DCV 60 + RBV 600-1000	**12** (if Naive) **24** (if previously treated)	80%
	SOF/LED 400/90 +/- RBV 600-1200 **(no FDA approved)**	**12**	?
3	**SOF 400/DCV 60 + RBV 600-1000**	**24**	88%
	SOF 400 + VEL 100 + RBV 1-1.2g	**12**	85%
5, 6	**SOF 400 + VEL 100 + RBV 1-1.2g**	**12**	N/A

Ideally treated at the Transplant Center

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

Genotype	Regimen	Duration (weeks)	SVR
Geno 1-6 (F0-4c)	**GLE 300 + PIB 120**	**F0-2: 8 w** **F3-4c: 12 w** **Geno-3 with PR or Sof Failure: 16 w** **PrOD or Zepatier Failure: 16 w**	98-100%
1a & 1 b (F0-3)	**PrOD** (+ RBV 200 TIW in 1a)	**12**	90%
1 & 4 (F0-4comp) (probably also 2, 5, y 6)	**GZR 100 + EBR 50** In genotype 1a with M28, Y93, Q30, or L31 polymorphism: GZR 100 + EBR 50 + RBV 100-200 mg	**12** **16**	99% in geno-1
2, 3, 5, 6 (F0-4comp)	**PegIFN + RBV 200** a day	**24-48 weeks**	

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

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.***
- **SOF/LED (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.
- **PrOD (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.***

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 if 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

- Patients with compensated cirrhosis‡ who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy) and for biochemical evidence of liver injury Rating: Class I, Level A
  - with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment.
  - Paritaprevir/ritonavir-based regimens should be discontinued if patients develop ascites or encephalopathy or a significant increase in direct bilirubin or ALT or AST.
- For HBsAg+ patients who are not already on HBV suppressive therapy Rating: Class IIa, Level B
  - monitoring of HBV DNA levels during and immediately after DAA therapy for HCV is recommended, and
  - antiviral treatment for HBV should be given if treatment criteria for HBV are met.

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.

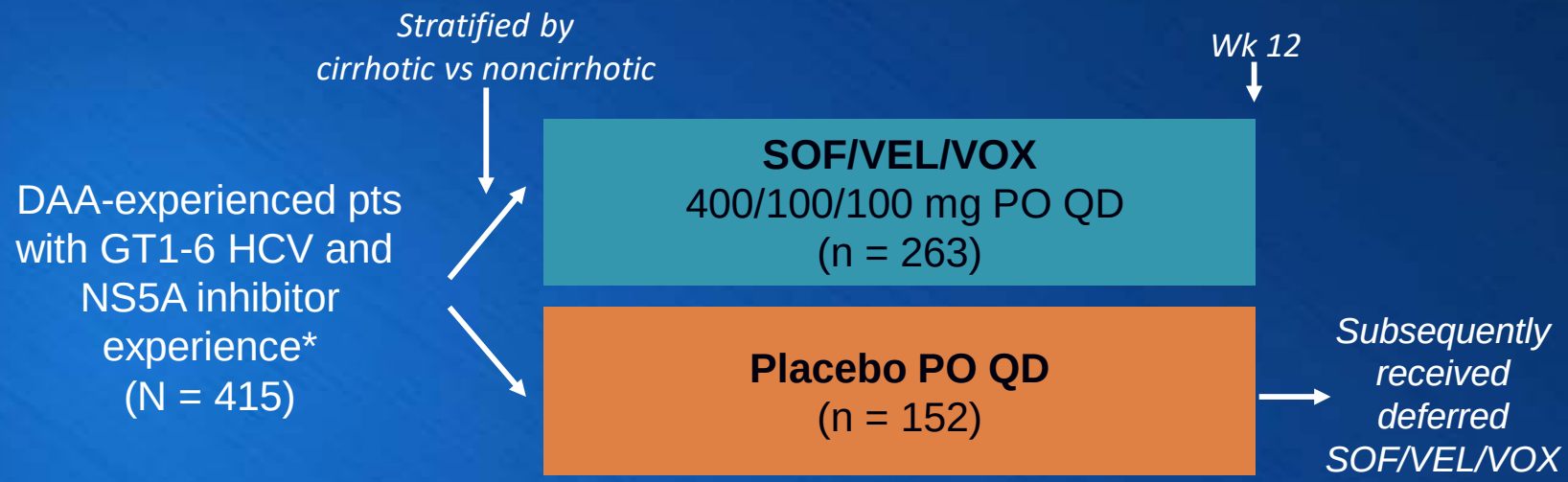
Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Glecaprevir (formerly ABT-493)	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir (formerly ABT-530)	PIB	NS5A inhibitor
Ruzasvir (formerly MK-8408)	RZR	NS5A inhibitor
MK-3682	--	NS5B polymerase nucleotide inhibitor

Slide credit: clinicaloptions.com

POLARIS-1: SOF/VEL/VOX (Vosevi®) for 12 Wks After NS5A Failure in GT1-6 HCV

- Randomized, double-blind, placebo-controlled phase III trial



*Pts with GT1 HCV at screening equally randomized between arms; pts with GT2-6 HCV assigned to active treatment arm.

- Previous NS5A treatment in SOF/VEL/VOX group (n = 263)
  - LDV, 51%; DCV, 27%; OBV, 11%; other, 13%
- Cirrhosis definition for POLARIS studies: METAVIR F4 or Ishak 5-6 on biopsy, *or FibroTest* > 0.75 + APRI > 2, *or FibroScan* > 12.5 kPa

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

POLARIS-1: SVR12 Rates With 12-Wk SOF/VEL/VOX (Vosevi®) in Previous NS5A Failure

SVR12, % (n/N)	SOF/VEL/VOX
Overall	96 (253/263)
Cirrhosis status	
▪ No cirrhosis	99 (140/142)
▪ Cirrhosis	93 (113/121)
Baseline RAVs	
▪ None	98 (42/43)
▪ Any	96 (199/208)

SVR12, % (n/N)	SOF/VEL/VOX
Genotype	
▪ 1a	96 (97/101)
▪ 1b	100 (45/45)
▪ 2	100 (5/5)
▪ 3	95 (74/78)
▪ 4	91 (20/22)
▪ 5	100 (1/1)
▪ 6	100 (6/6)

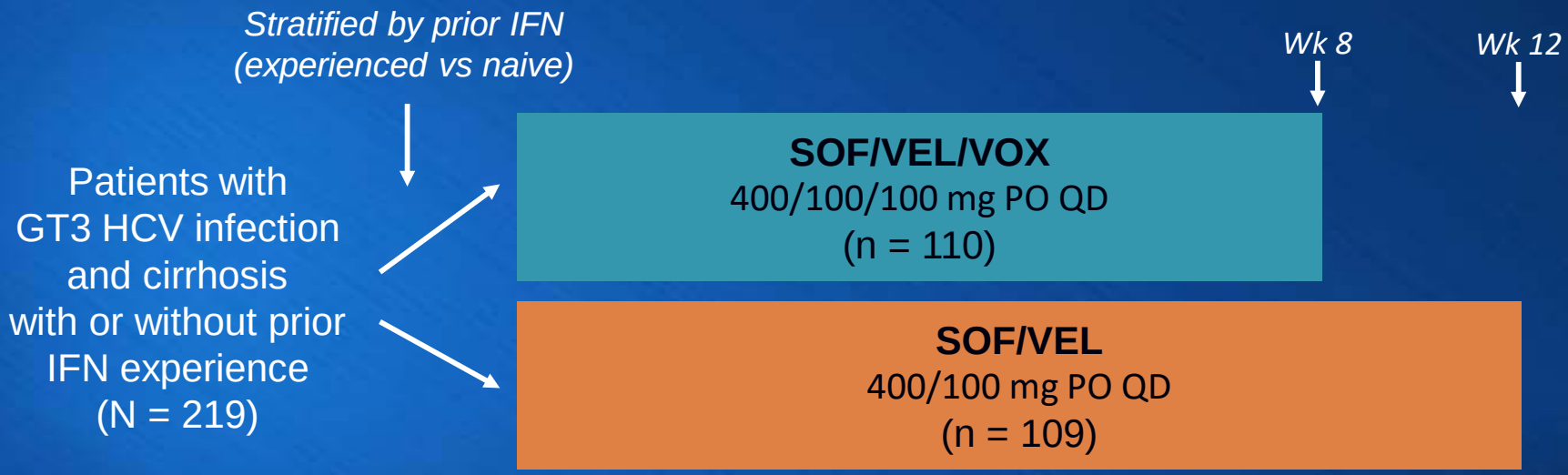
- 7 virologic failures; all cirrhotic pts (GT1a, n = 2; GT3, n = 4; GT4, n = 1)

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

POLARIS-3: 8-Wk SOF/VEL/VOX (Vosevi®) vs 12-Wk SOF/VEL for Cirrhotic, DAA Naive GT3

- Randomized, open-label, active-controlled phase III trial

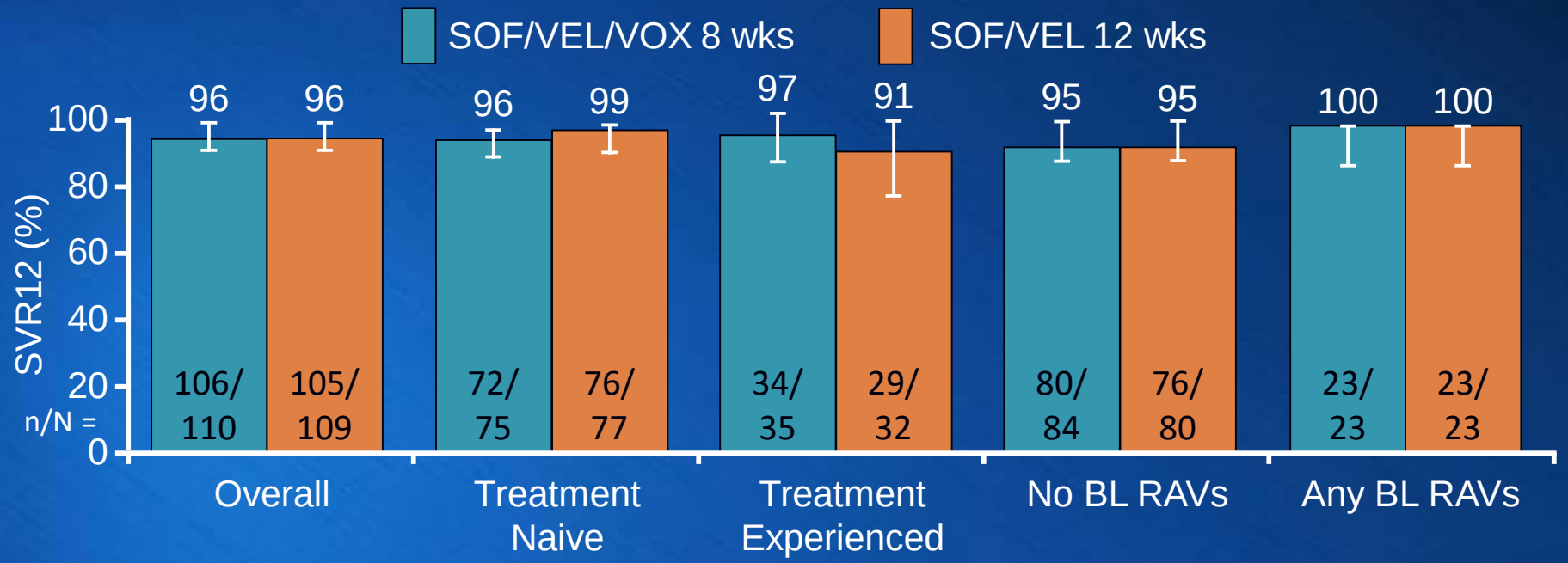


- IFN experience in 29% to 32% of pts

Foster GR, et al. AASLD 2016. Abstract 258.

Slide credit: clinicaloptions.com

POLARIS-3: SVR12 Rates With 8-Wk SOF/VEL/VOX (Vosevi®) for Cirrhotic GT3 Pts

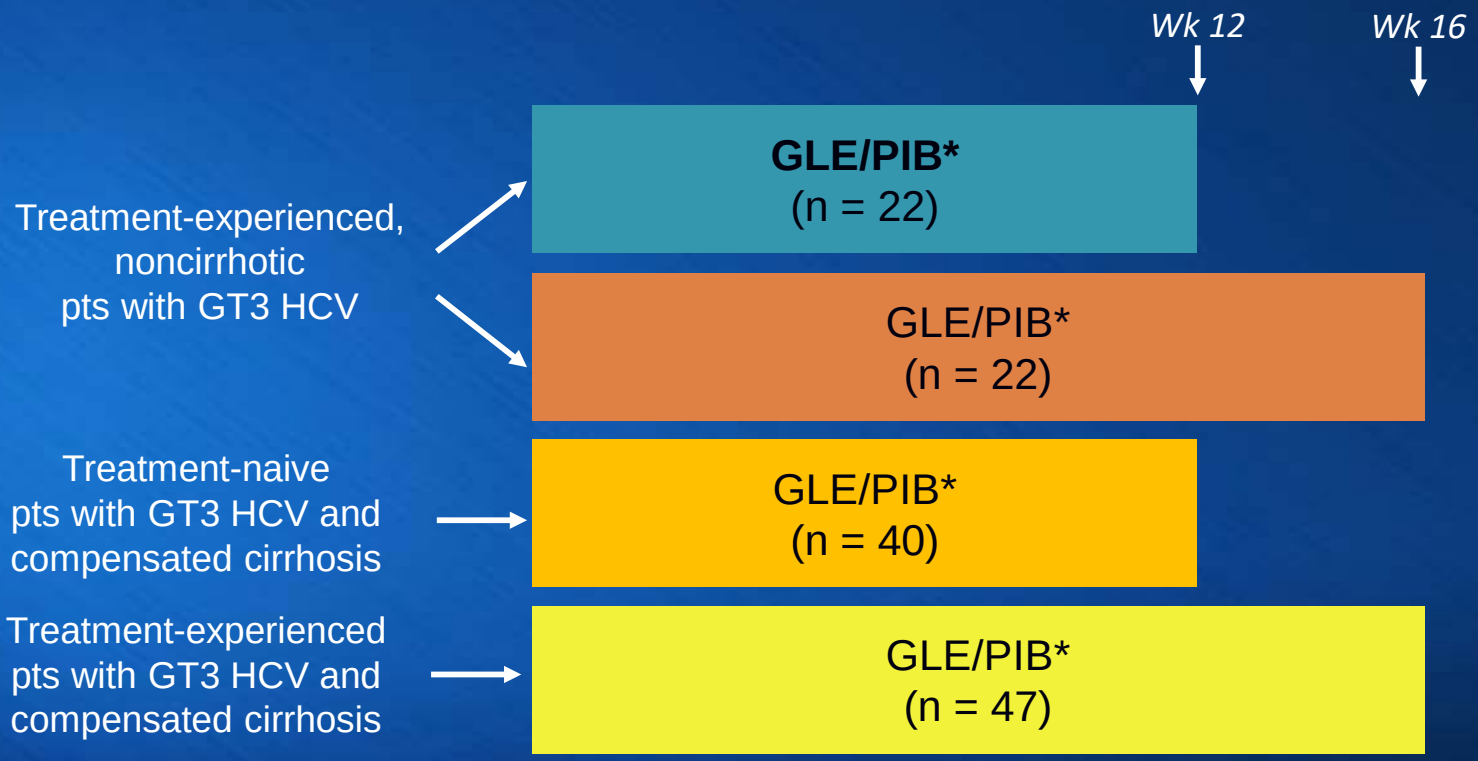


- Both regimens: *P* < .001 for superiority vs prespecified 83% goal
- Overall VF: SOF/VEL/VOX, n = 2 relapses; SOF/VEL, n = 1 each for relapse and on-treatment failure
- No treatment-emergent RAVs in SOF/VEL/VOX arm; Y93H in both virologic failures in SOF/VEL arm

Foster GR, et al. AASLD 2016. Abstract 258. Reproduced with permission. Slide credit: clinicaloptions.com

SURVEYOR-II, Part 3: GLE/PIB (Mavyret) for Pts With GT3 HCV ± Cirrhosis

- Partially randomized, open-label phase II trial (N = 131)



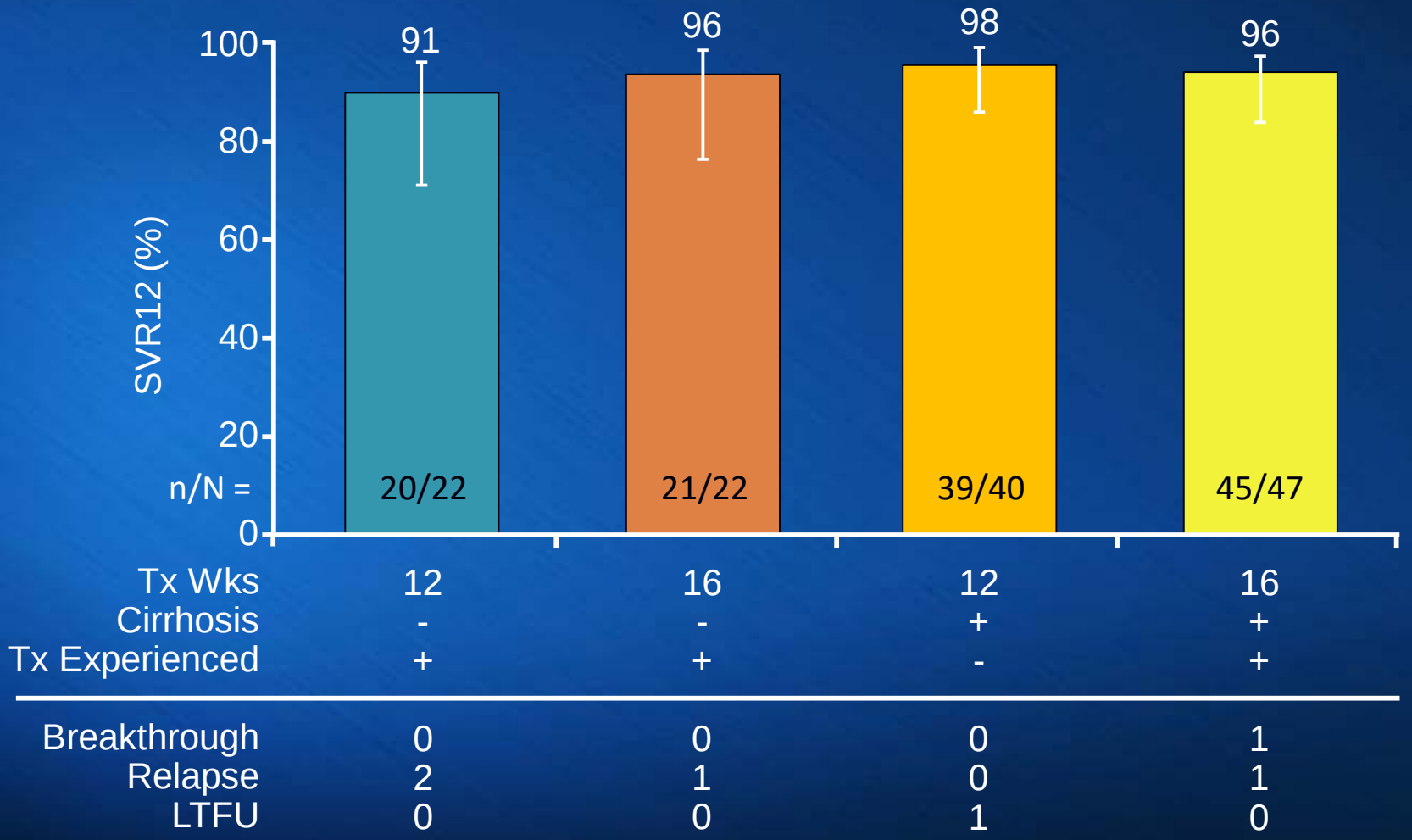
- Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

Wyles DL, et al. AASLD 2016. Abstract 113.

Slide credit: clinicaloptions.com

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB (Mavyret) for Pts With GT3 HCV ± Cirrhosis

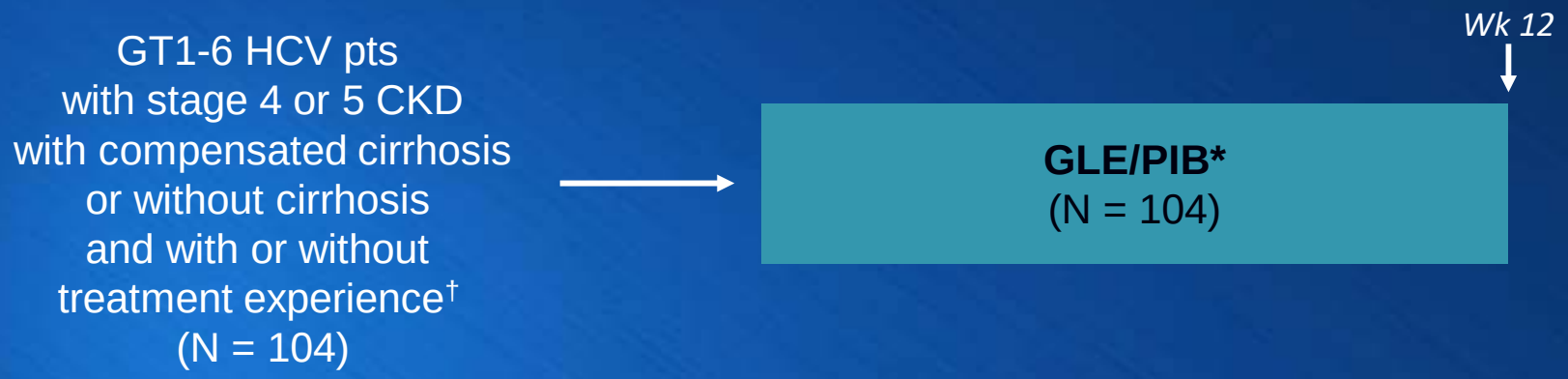


Wyles DL, et al. AASLD 2016. Abstract 113. Reproduced with permission.

Slide credit: clinicaloptions.com

EXPEDITION-IV: GLE/PIB (Mavyret) for Pts With GT1-6 HCV and Renal Impairment

- Open-label, single-arm phase III trial



- At baseline, 82% on hemodialysis; 19% cirrhotic; 42% treatment experienced
- SVR12 rate of **98%** (ITT; n/N = 102‡/104)

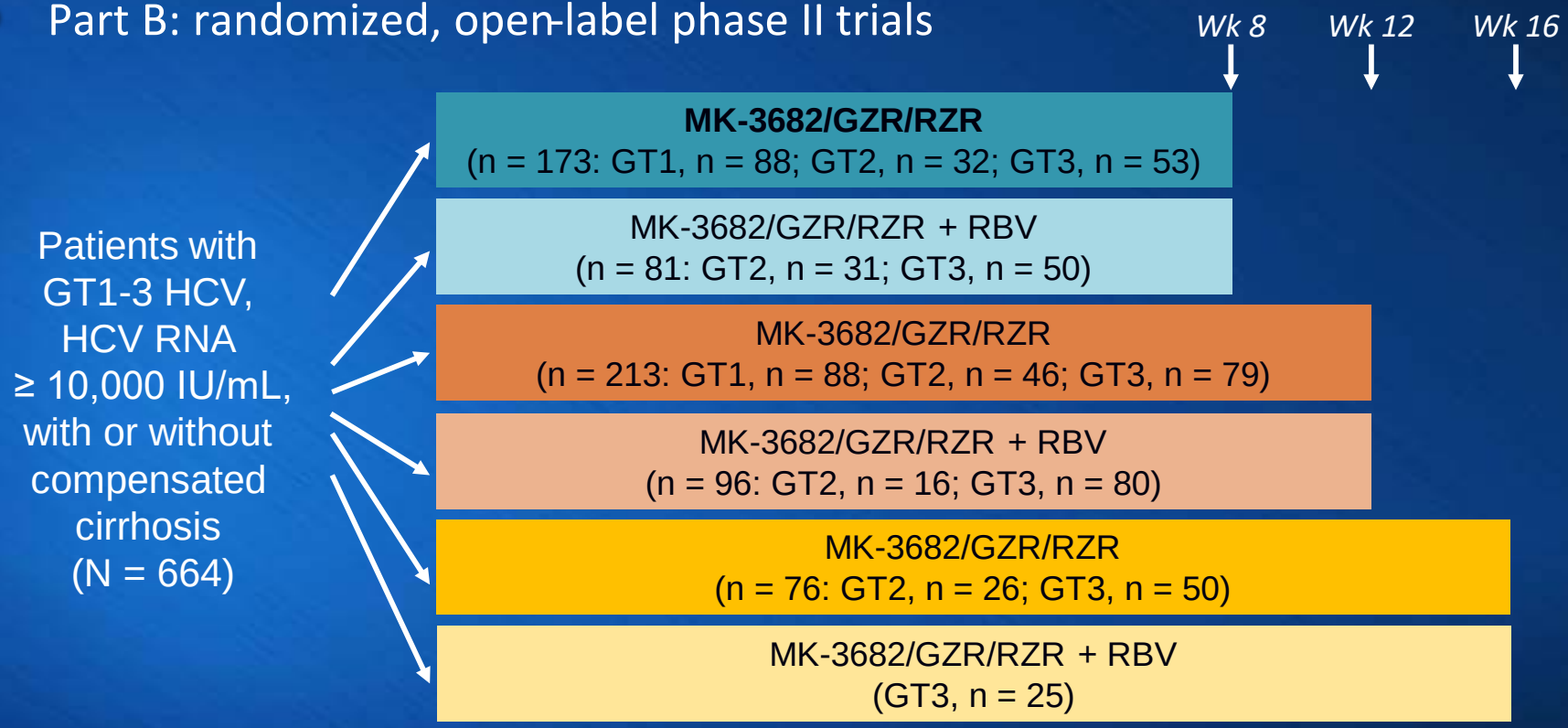
*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.
†Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.
‡1 pt d/c, 1 pt LTFU in ITT analysis of SVR12.

Gane EJ, et al. AASLD 2016. Abstract LB11.

Slide credit: clinicaloptions.com

C-CREST 1 & 2: MK-3682/GZR/RZR ± RBV for Treating Pts With GT1-3 HCV

- Part B: randomized, open-label phase II trials



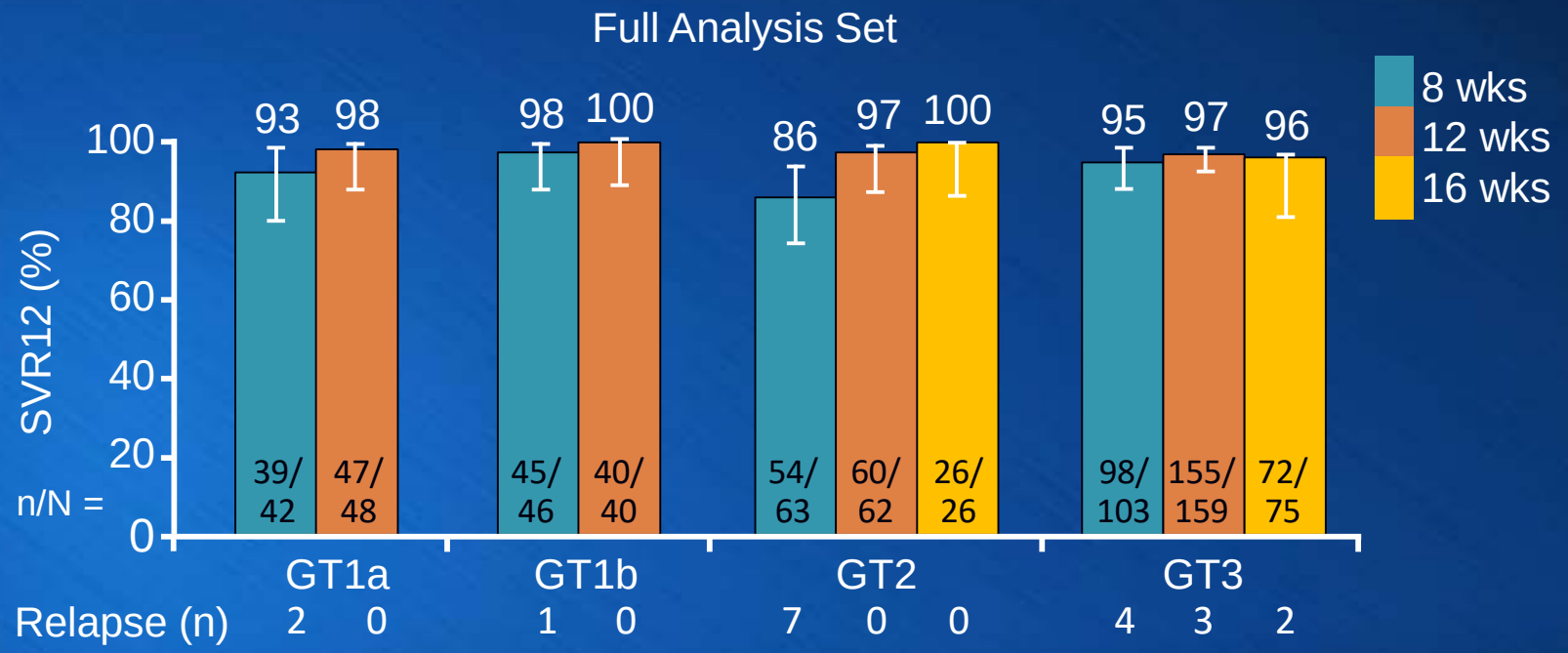
Dosing: MK-3682/GZR/RZR dosed as two 225/50/30-mg tablets QD. Pts with GT3 HCV could be treatment naive or have failed on pegIFN/RBV; all others treatment naive. Cirrhosis definition in notes.

- Baseline: 35% to 43% cirrhotic; 44% of GT3 pts had prior pegIFN/RBV

Lawitz E, et al. AASLD 2016. Abstract 110.

Slide credit: clinicaloptions.com

C-CREST 1 & 2: Efficacy of MK-3682/ GZR/RZR ± RBV for Pts With GT1-3 HCV



- Presence of cirrhosis, use of ribavirin, prior tx experience did not impact SVR12 rates

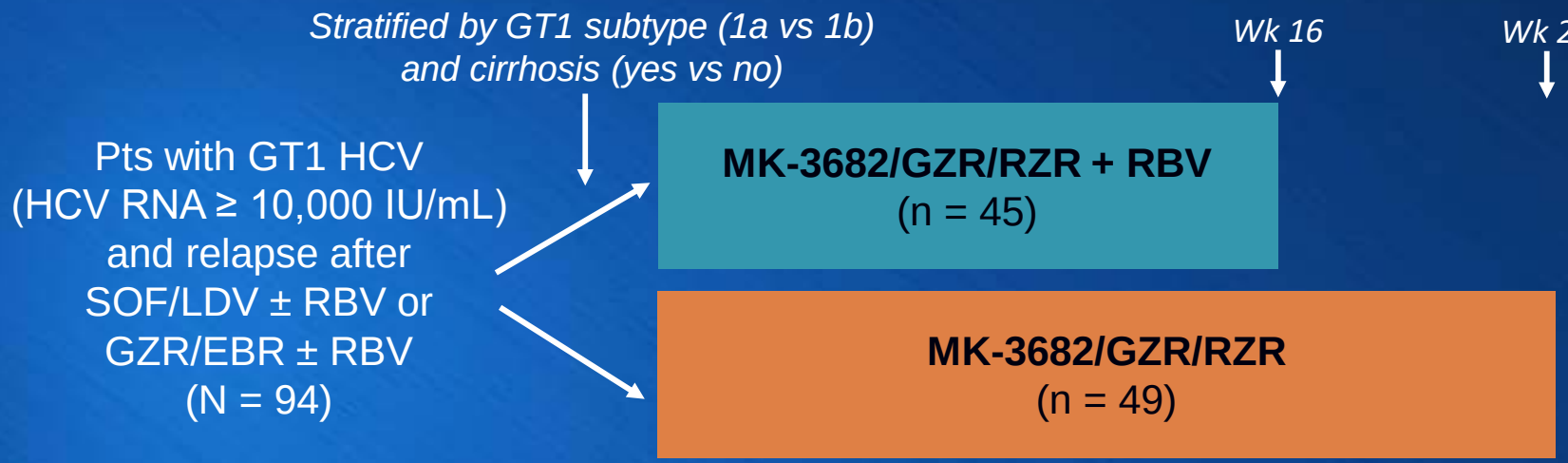
SVR12 by Baseline RAV Presence, % (n/N)	GT2 HCV		GT3 HCV	
	No L31M	L31M	No Y93H	Y93H
8 wks	94 (31/33)	80 (20/25)	98 (95/97)	50 (2/4)
12 wks	100 (23/23)	100 (28/28)	99 (147/148)	71 (5/7)

Lawitz E, et al. AASLD 2016. Abstract 110. Reproduced with permission.

Slide credit: clinicaloptions.com

C-SURGE: MK-3682/GZR/RZR for GT1 HCV Pts Who Relapsed on DAA Therapy

- Randomized, open-label phase II trial (interim analysis)



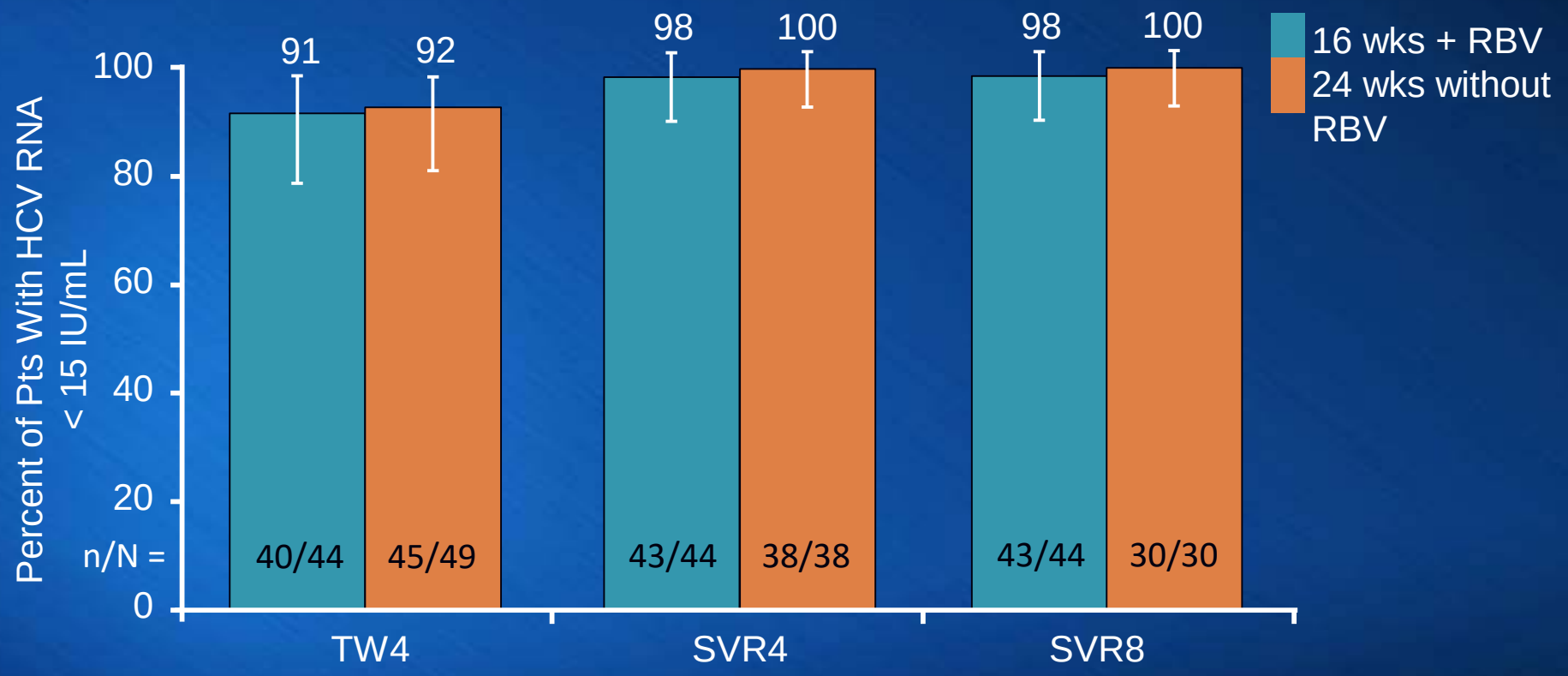
- Baseline characteristics:
  - Previous failing regimen: LDV/SOF 12-24 wks, 61%; LDV/SOF 8 wks, 15%; GZR/EBR 12 wks, 24%
  - NS5A RAVs, 84%; NS3 RAVs, 65%

Dosing: MK-3682/GZR/RZR two 225/50/30-mg tablets once daily; weight-based RBV (800-1400 mg/day).
Trial included compensated cirrhotic and noncirrhotic pts; cirrhosis definition in slidenotes.

Wyles DL, et al. AASLD 2016. Abstract 193.

Slide credit: clinicaloptions.com

C-SURGE: SVR8 Rates With MK-3682/GZR/RZR for DAA Relapses



- No impact of NS5A or NS3 RAVs on SVR4, including Y93 RAVs
  - 4% of pts had ≥ 3 NS5A RAVs; 55% had dual NS5A and NS3 RAVs

Wyles DL, et al. AASLD 2016. Abstract 193. Reproduced with permission. Slide credit: clinicaloptions.com

MK-3682/GZR/RZR Studies: Safety

Outcome, %	C-CREST 1 & 2 Part B[1] MK-3682/GZR/RZR		C-SURGE[2] MK-3682/GZR/RZR	
	No RBV (n = 462)	+ RBV (n = 202)	+ RBV, 16 Wks (n = 44)	24 Wks (n = 49)
Any AE	69	86	91	80
Drug-related AE	36	67	75	47
D/c for AE	< 1	3	0	0
Serious AE	2	2	2	8
Death	< 1*	0	0	0
AE in > 10% of pts				
▪ Fatigue	15	29	48	24
▪ Headache	19	27	14	12
▪ Nausea	11	15	NA	NA
▪ Diarrhea	NA	NA	7	10
▪ Pruritus	NA	NA	11	0
▪ Rash	NA	NA	14	4

*Deemed unrelated to study drug.

1. Lawitz E, et al. AASLD 2016. Abstract 110.
2. Wyles DL, et al. AASLD 2016. Abstract 193.

Slide credit: clinicaloptions.com

Thank you for your attention

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)

End of Supplemental Slides

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.

Multiple Direct Acting Antivirals

Protease

Polymerase

HCV PIs	NS5A Inhibitors	NS5B Nucs	NS5B Non-nucs
Viral enzyme Active site	Non-enzyme Replication complex	Viral enzyme Active site	Viral enzyme Allosteric site
Telaprevir *Boceprevir* ***Simeprevir*** Faldaprevir Asunaprevir ***Paritaprevir*** ***Grazoprevir*** Sovaprevir ACH-2684	***Daclatasvir*** ***Ledipasvir*** ***Ombitasvir*** ACH-3102 Ravidasvir GSK2336805 Samatasvir ***Elbasvir*** ***Velpatasvir***	***Sofosbuvir*** VX-135 IDX20963 ACH-3422	***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 antico-agulants	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.			

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

Genotype	Regimen	Duration (weeks)	SVR
1a or 1 unspecified	F0-2 Naïve with HCV-RNA < 6 Million& No African American: **SOF/LED 400/90**	**8**	97%
	F0-2 with HCV-RNA > 6 Million or relapse: **SOF/LED 400/90**	**12**	96%
	F0-2: **GZR 100 + EBR 50** (without M28, Q30, L31, or Y93 polymorphism)	**12**	98%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F0-2: **SOF 400 + VEL 100**	**12**	98%
	F0-2: **DAC 60 + SOF 400 (alt)**	**12**	100%
	F0-2: **PrOD + RBV 1-1.2 (alt)**	**12**	96%
	F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2 g** (No in Q80K mutation) **(alt)**	**12**	93-96%
	F3-4: **SOF/LED 400/90**	**12**	94%
	F3-4 comp: **GZR 100 + EBR 50** (without M28, Q30, L31, or Y93 polymorphism)	**12**	98%
	F3-4c: **GLE 300 + PIB 120**	**12**	99%
	F3-4: **SOF 400 + VEL 100**	**12**	98%
	F3-4: **DAC 60 + SOF 400 (not recommended anymore)**	**24** (+/- RBV 1-1.2)	100%
	F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2 g** (No in Q80K mutation) **(not recommended)**	**24**	93-96%
	F0-4 comp: **GZP 100 + EBV 50 + RBV 800-1400** (with M28, Y93, Q30, or L31 polymorphism) **(alt)**	**16**	100%
	F3-4 comp: **PrOD + RBV 1-1.2 (not recommended anymore)**	**24**	95%

F4 comp = compensated cirrhosis = Child-Pugh A (5 or 6 points)

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

Genotype	Regimen	Duration (weeks)	SVR
1b	F0-2 Naïve with HCV-RNA < 6 Million & No African American: **SOF/LED 400/90**	**8**	97%
	F0-2 with HCV-RNA > 6 Million, or F3-4: **SOF/LED 400/90**	**12**	96%
	F0-2: **GZR 100 + EBR 50**	**12**	99%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F0-2: **SOF 400 + VEL 100**	**12**	99%
	F0-2: **PrOD** (without RBV) **(alt)**	**12**	100
	F0-2: **SOF 400 + SMV 150 ± RBV 1-1.2 g (alt)**	**12**	93-96%
	F0-2: **DAC 60 + SOF 400 (alt)**	**12**	100%
	F3-4 comp: **GZR 100 + EBR 50**	**12**	99%
	F3-4c: **GLE 300 + PIB 120**	**12**	99%
	F3-4 comp: **SOF/LED 400/90**	**12**	94%
	F3-4: **SOF 400 + VEL 100**	**12**	99%
	F3-4 comp: **PrOD +/- RBV 1-1.2 (alt)**	**12**	99%
	F3-4 comp: **SOF 400 + SMV 150 ± RBV 1-1.2 g (not recommended anymore)**	**24**	93-96%
	F3-4: **DAC 60 + SOF 400 (+/- RBV 1-1.2g) (not recommended anymore)**	**24**	100%

F4 comp = compensated cirrhosis = Child-Pugh A (5 or 6 points)

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

Genotype	Regimen	Duration (weeks)	SVR
2	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w;** **F3-4c: 12w**	100%
	DAC 60 + SOF 400 (alt)	F0-2: **12** F3-4 comp: **16-24**	100%
3	**SOF 400 + VEL 100**	**12**	95% (F0-2: 98%)(F3-4c:93%)
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w;** **F3-4c: 12w**	F0-2: 95% F3-4c: 96%
	F0-2: **DCV 60 + SOF 400** (alt)	**12**	F0-2: 97%; (F3-4: 58%)
	F3-4: **DAC 60 + SOF 400 +/- RBV** (alt) (RBV helped in CP-B&C)	F4 C-P B&C (+/- RBV 1-1.2): **24** F3 & F4 CP-A (+/- RBV): **24**	88% (78% w/o RBV) 92% (88% w/o RBV)
	F3-4c: **SOF 400 + Vel 100 + Vox 100** for **Y93H RAS**	**12**	96-100%

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

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

Genotype	Regimen	Duration (weeks)	SVR
4	F0-4: **SOF/LED 400/90**	**12**	95-100%
	F0-4c: **GZR 100 + EBV 60 +/- RBV**	**12**	90-100%
	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
	F0-4c: **PrO + RBV 1-1.2 g** (alt)	**12**	100%
5	F0-4**: SOF/LED 400/90**	**12**	95%
	F0-4: **SOF 400 + VEL 100**	**12**	97%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
6	F0-4: **SOF/LED 400/90**	**12**	96%
	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%

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: **SOF 400 + VEL 100**	**12**	98%
	F0-2: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism)	**12**	100%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F0-2: **PrOD + RBV 1-1.2 g (alt)**	**12**	96%
	F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation) (alt)**	**12**	93-96%
	F0-2: **DAC 60 + SOF 400 (alt)**	**12**	> 82%
	F3-4 comp: **GZR 100 + EBR 50** *(*no M28, Y93, Q30, or L31 polymorphism)	**12**	100%
	F3-4c: **GLE 300 + PIB 120**	**12w**	98%
	F3-4: **SOF 400 + VEL 100**	**12**	98%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** (pre-test for NS5A resistance; treat 24 weeks if > 100 fold resistance or use other regimen)	**12**	96%
	F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2g (not recommended anymore)**	**24**	60% no-RBV 82% w RBV
	F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2g (No in Q80K mutation) (not recommended)**	**24**	93-96%
	F3-4: **SOF/LED 400/90 (alt)**	**24**	
	F3-4 comp: **PrOD + RBV 1-1.2 (not recommended anymore)**	**24**	95%
	F0-3: **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

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: **SOF 400 + VEL 100**	**12**	99%
	F0-2: **GZR 100 + EBR 50**	**12**	97%
	F0-2: **GLE 300 + PIB 120**	**8**	99%
	F0-2: **PrOD** (no RBV) **(alt)**	**12**	100%
	F0-2: **DAC 60 + SOF 400 (alt)**	**12**	82%
	F0-2: **SOF 400 + SMV* 150 ± RBV 1-1.2 g (alt)**	**12**	93-96%
	F3-4 comp: **GZR 100 + EBR 50**	**12**	97%
	F3-4: **SOF 400 + VEL 100**	**12**	99%
	F3-4c: **GLE 300 + PIB 120**	**12**	99%
	F3-4 comp: **PrOD (alt)**	**12**	99%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)** (test for NS5A resistance)	**12**	96%
	F3-4: **SOF/LED 400/90 (alt)**	**24**	100%
	F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (not recommended anymore)**	**24**	82%
	F3-4 comp: **SOF 400 + SMV* 150 ± RBV 1-1.2 g (not recommended anymore)**	**24**	93-96%

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

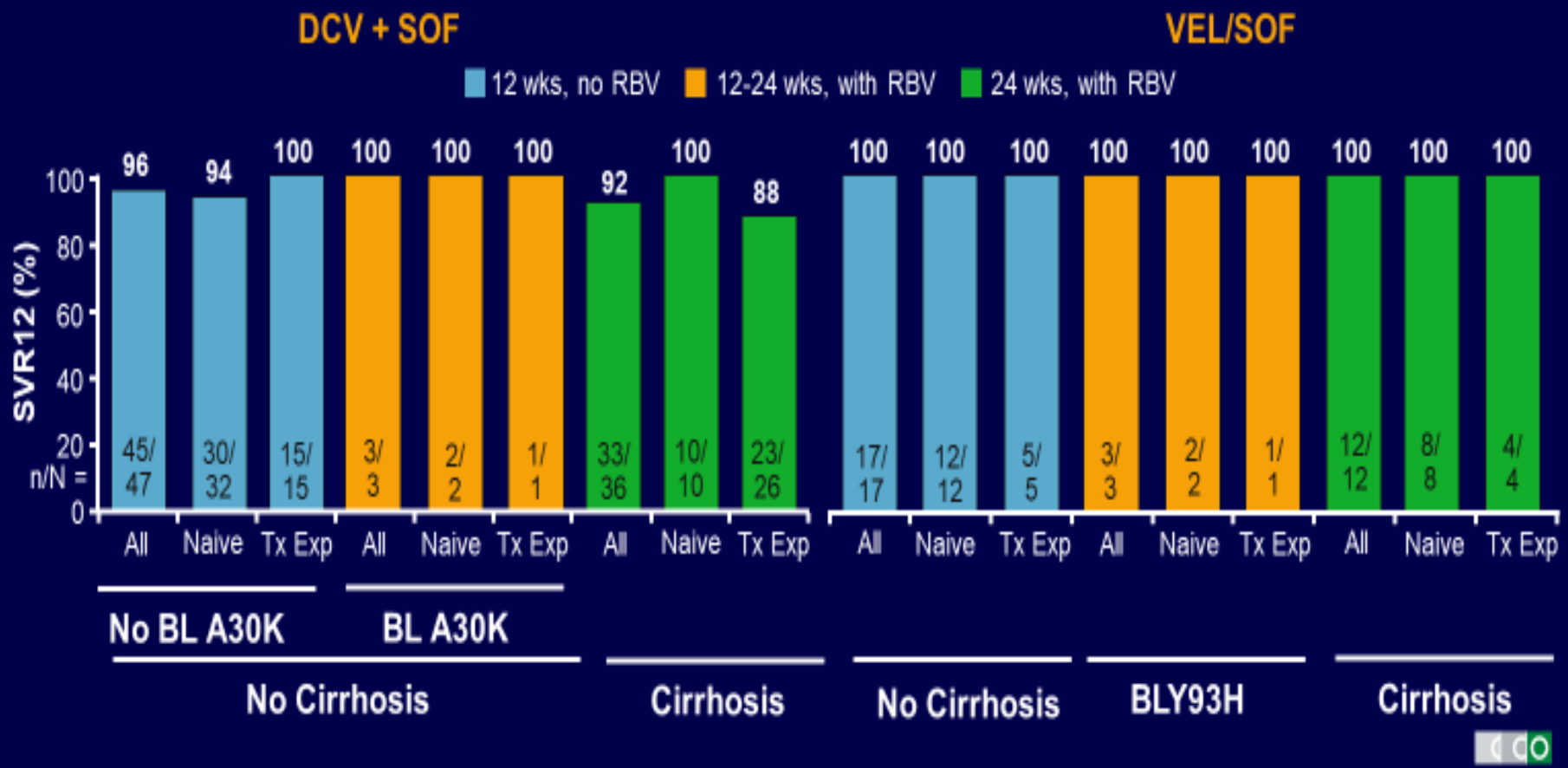
Treatment of Hepatitis C; PEG-IFN/RBV Non-Responders

Genotype	Regimen	Duration (weeks)	SVR
2	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
	F0-2: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (alt)** F3-4c: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (alt)**	**12 16-24**	?
3	F0-2: **SOF 400 + VEL 100**	**12**	94%
	F3-4c: **SOF 400 + VEL 100 + VOX 100**	**12**	94-100%
	F3-4 comp: **GZR 100 + EBR 50 + SOF 400**	**12**	100%
	F3-4: **SOF 400 + VEL 100 + RBV 1-1.2 g (alt)**	**12**	89%
	F0-2: **DCV 60 + SOF 400 (alt)**	**12**	94%
	F0-4c: **GLE 300 + PIB 120 (alt)**	**16**	96%
	F0-2: **SOF 400 + VEL 100 + VOX 100** (when Y93H is present) **(alt)**	**12**	94-100%
	F3-4: **DCV 60 + SOF 400 + RBV 1-1.2 g (not recommended)**	**24**	"Close to 100%"

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

DCV or VEL in Treatment-Experienced GT3 HCV Infection

- Real-world cohort of patients with GT3 HCV infection treated according to baseline NS5A RASs, previous treatment failure, and cirrhosis status (N = 167)



Vermehren J, et al. EASL 2017. Abstract PS-155. Reproduced with permission.

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

Genotype	Regimen	Duration (weeks)	SVR
4	F0-2: **SOF/LED 400/90**	**12**	95%
	F0-2: **SOF 400 + VEL 100**	**12**	100%
	F0-2: **GZR 100 + EBR 50 + RBV**	**16**	97%
	F0-4c: **GLE 300 + PIB 120**	**8**	100%
	F3-4 comp: **GZR 100 + EBR 50 + RBV**	**16**	97%
	F3-4: **SOF 400 + VEL 100**	**12**	100%
	F3-4c: **GLE 300 + PIB 120**	**12**	100%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g** (alt)	**12**	95%
	F0-2: **PrO + RBV 1-1.2 g** (alt)	**12**	100%
	F3-4: **SOF/LED 400/90** (alt)	**24**	95%
5	F0-4: **SOF/LED 400/900**	**12**	95%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	100%
	F0-4: **SOF 400 + VEL 100**	**12**	97%
6	F0-4: **SOF/LED 400/90**	**12**	96%
	F0-4: **SOF 400 + VEL 100**	**12**	100%
	F0-4c: **GLE 300 + PIB 120**	**F0-2: 8w; F3-4c: 12w**	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

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

Genotype or w/o RBV	Regimen	Duration (weeks)	SVR
1 o 4	**SOF/LED 400/90 + RBV 600-1200** increasing as tolerated	**12** **24 if past SOF or NS5A, or w/o RBV**	86%
	SOF 400 + VEL 100 + RBV 1000-1200 mg	**12** **24 if past SOF or NS5A, or w/o RBV**	94% in g1a; 100% g1b 100% in g4
	SOF 400/DCV 60 + RBV 600-1000 mg	**12-24** with RBV **24 if past SOF or NS5A, or w/o RBV**	12: g1:83%; g4: 100% ; 24: close to 100% in g1 Unknown (without RBV)
2	**SOF 400 + VEL 100 + RBV 1000-1200 mg**	**12** **24 if past SOF or NS5A, or w/o RBV**	100%
	SOF 400/DCV 60 + RBV 600-1000	**12** (if Naive) **24 if past SOF or NS5A, or w/o RBV**	80%
	SOF/LED 400/90 +/- RBV 600-1200 **(no FDA approved)**	**12**	?
3	**SOF 400/DCV 60 + RBV 600-1000**	**24**	88%
	SOF 400 + VEL 100 + RBV 1-1.2g	**12 (24 if past SOF or NS5A or w/o RBV)**	85%
5 or 6	**SOF 400 + VEL 100 + RBV 1000-1200 mg**	**12**	N/A
	SOF 400 + LED 90 + RBV 600-1200 mg	**12 (24 if past SOF or NS5A or w/o RBV)**	N/A
	SOF 400 + VEL 100 + RBV 600-1200 mg	**12 (24 if past SOF or NS4A or w/o RBV)**	N/A

Ideally treated at the Transplant Center

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%
	F0-4c: **GLE 300 + PIB 120** (Geno 1,2,4,5,6) (Geno-3 is longer)	**Geno 1,2,4,5,6: 12w** **Geno-3 (F0-4c): 16 w**	100%
	F0-4: **SOF/VEL 400/100**	**12**	100%
	F0-4 comp: **GZR 100 + EBR 50 + RBV .8-1.4 g (alt)**	**12 (16 with RAS mutant)**	96%
	F3-4: **SOF/LED 400/90 + RBV 1-1.2 g (alt)**	**12**	97%
	F3-4: **SOF/LED 400/90 (no longer recommended)**	**24**	97%
	F3-4: **DAC 60 + SOF 400 +/- RBV 1-1.2 g (no longer recommended)**	**24**	100%
No Response to Sofosbuvir	**Regimen**	**Duration (weeks)**	**SVR**
Never Exposed to NS5A **Geno 1, 4, 5, 6** **NS5A is (-) to RASs**	F0-4: **SOF 400 + VEL 100 + VOX 100** for **Geno 1a**	**12**	97%
	F0-4: **SOF 400 + VEL 100** for **Geno 1b**	**12**	96%
	F0-4: **GLE 300 + PIB 120**	**12**	
	F0-2: **SOF/LED 400/90 + RBV 1-1.2 g (alt)**	**12**	100%
Genotype 2 or 3 failure to SOF/RBV+/- Peg-IFN If in Urgent Need	F0-4: **Geno 2: SOF 400 + VEL 100**	**12**	97%
	F0-4c: **Geno 2: GLE 300 + PIB 120**	**12** **G3: F0-4c: 16 w (not recommended)**	98% 96%
	Geno 3 F0-4: SOF + VEL + VOX (add RBV 1-1.2 g if past NS4A failure)	**12**	96%
Geno 1-6 NS5A Resistant	**F0-4: SOF + VEL + VOX**	**12**	96-100% (g4:91%; g3:95%)
Failures with SOF/VEL x 12w	**SOF 400 + VEL 100 + RBV 1-1.2 g (not recommended)**	**24**	G-1: 98% G-2: 100% G-3: No RASs 100%; G-3 with RASs: 77%

RASs = Virus with “Resistance Associated Substitutions”

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

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

Investigational HCV Treatments

Treatment of HIV/HCV Co-infected Patients

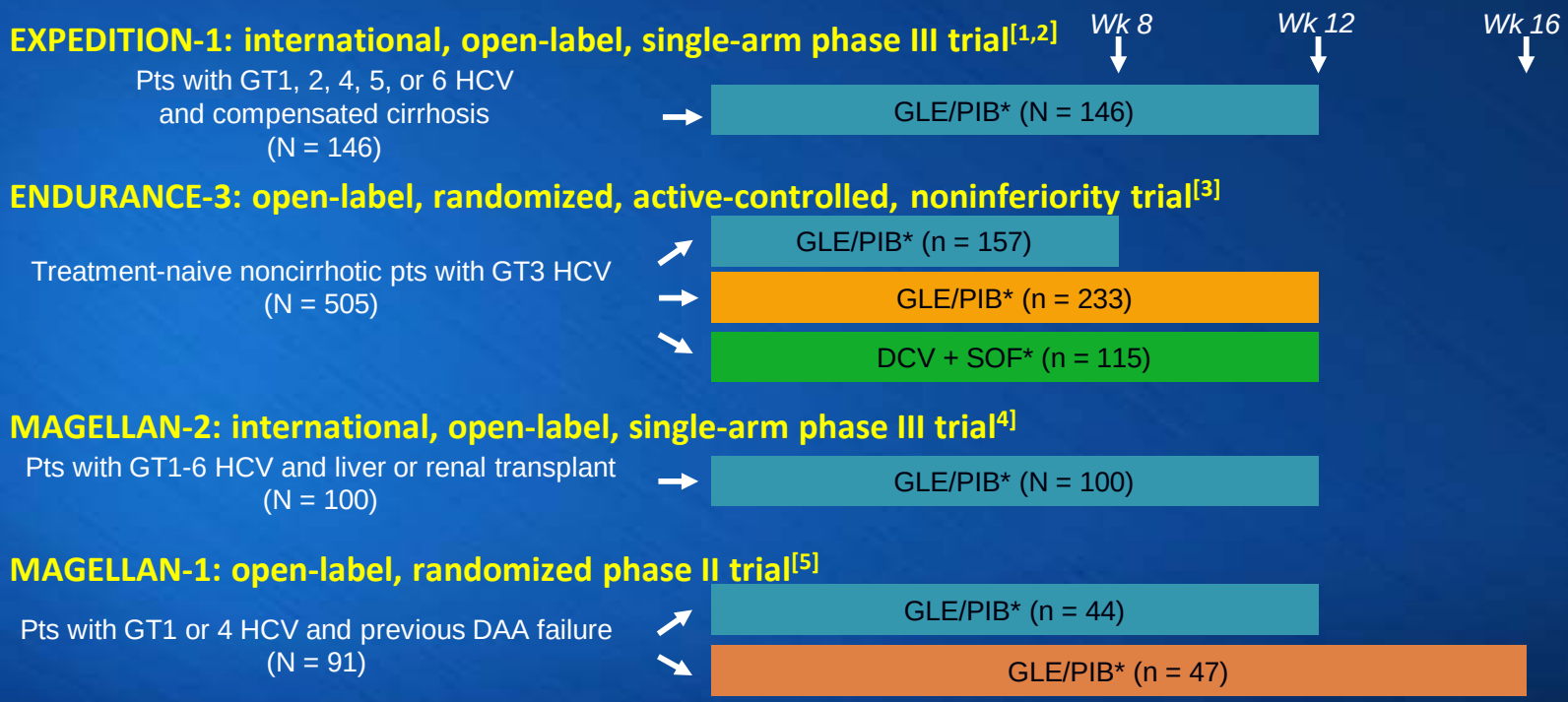
- ***Patients with HCV-HIV co-infection should be treated with the same regimen as HCV mono-infected patients.***
- **LED/SOF (HARVONI):**
  - African-American patients respond less to Harvoni.
  - The theoretical risk of Renal damage from Tenofovir in patients receiving Atripla has not been seen in 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.
  - Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide.
- **PrOD (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.***

	Medication Interactions With HIV Antiretroviral Medications
DACLATASVIR	Daclatasvir requires dose adjustment with ritonavir-boosted atazanavir (decrease to 30 mg/d), cobicistat-boosted atazanavir (decrease to 30 mg/d), elvitegravir/cobicistat (decrease to 30 mg/d), and efavirenz or etravirine (increase to 90 mg/d).
SIMEPREVIR	Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, maraviroc, raltegravir, dolutegravir, rilpivirine, and tenofovir.
ELBASVIR/ GRAZOPREVIR	Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.
GLECAPREVIR/ PIBRENTASVIR	Does not have clinically significant interactions: abacavir, emtricitabine, enfuvirtide, lamivudine, raltegravir, dolutegravir, rilpivirine, and tenofovir.
LEDIPASVIR/ SOFOSBUVIR	Can be used with most antiretrovirals. Because this therapy increases tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. With Ledipasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide.
SOFOSBUVIR/ VELPATASVIR	Can be used with most antiretrovirals, but **not efavirenz, etravirine, or nevirapine**. Velpatasvir has the potential to increase tenofovir levels when given as tenofovir disoproxil fumarate, concomitant use mandates consideration of renal function and should be avoided in those with an eGFR <60 mL/min. With Velpatasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide.
PrOD	Do not have substantial interactions: atazanavir, dolutegravir, emtricitabine, enfuvirtide, lamivudine, raltegravir, and tenofovir. The dose of ritonavir used for boosting atazanavir should be held when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. Atazanavir (300 mg) should be administered at the same time as the fixed-dose HCV combination.
SOFOSBUVIR/ VELPATASVIR/ VOXILAPREVIR	Do not have substantial interactions: dolutegravir, emtricitabine, enfuvirtide, lamivudine, rilpivirine, and raltegravir. With Velpatasvir, Tenofovir disoproxil fumarate levels are highest if administered with ritonavir- or cobicistat-containing regimens. Change to Tenofovir alafenamide.

Summary of Investigational Direct-Acting Antivirals Discussed in This Slideset

Drug	Abbreviation	Class
Glecaprevir	GLE	NS3/4A protease inhibitor
Voxilaprevir	VOX	NS3/4A protease inhibitor
Pibrentasvir	PIB	NS5A inhibitor
Ruzasvir	RZR	NS5A inhibitor
Uprifosbuvir (formerly MK-3682)	UPR	NS5B polymerase nucleotide inhibitor

Glecaprevir/Pibrentasvir for Treatment of HCV

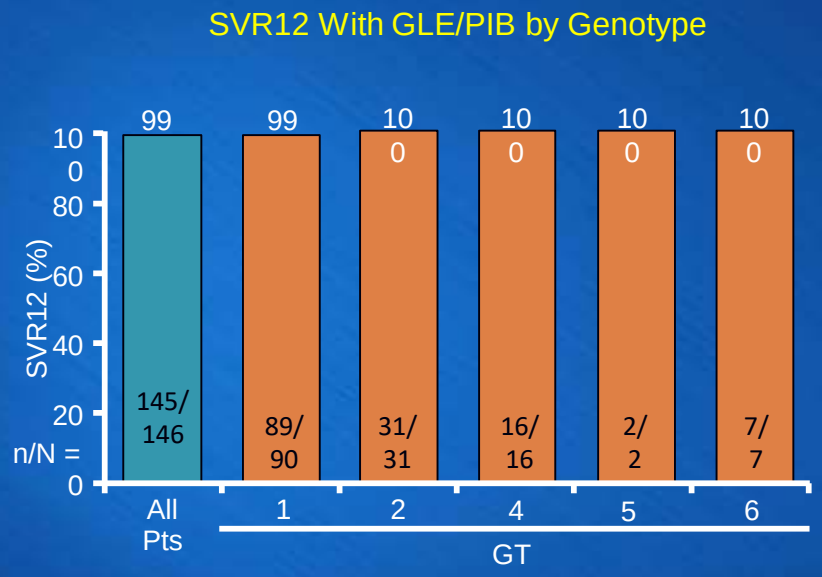


*Dosing: GLE/PIB, 300/120 mg. DCV + SOF, 60 mg + 400 mg QD.

Slide credit: clinicaloptions.com

References in slidenotes

EXPEDITION-1: GLE/PIB in GT1, 2, 4, 5, or 6 HCV and Compensated Cirrhosis



- No AE-related discontinuations or DAA-related serious AEs
  - 1 death due to cerebral hemorrhage in pt with history of hemophilia deemed unrelated to study drug

AE, n (%)	Pts (N = 146)
Any AE	101 (69)
Any serious AE	11 (8)
AEs occurring in ≥ 10% of pts	
▪ Fatigue	28 (19)
▪ Headache	20 (14)
▪ Pruritus	14 (10)
HCC	2 (1)

1 relapse in pt with GT1a HCV with new NS5Amutations (Q30R, H58D)

Slide credit: clinicaloptions.com

Forns X, et al. EASL 2017. Abstract GS-006. ClinicalTrials.gov. NCT02642432.
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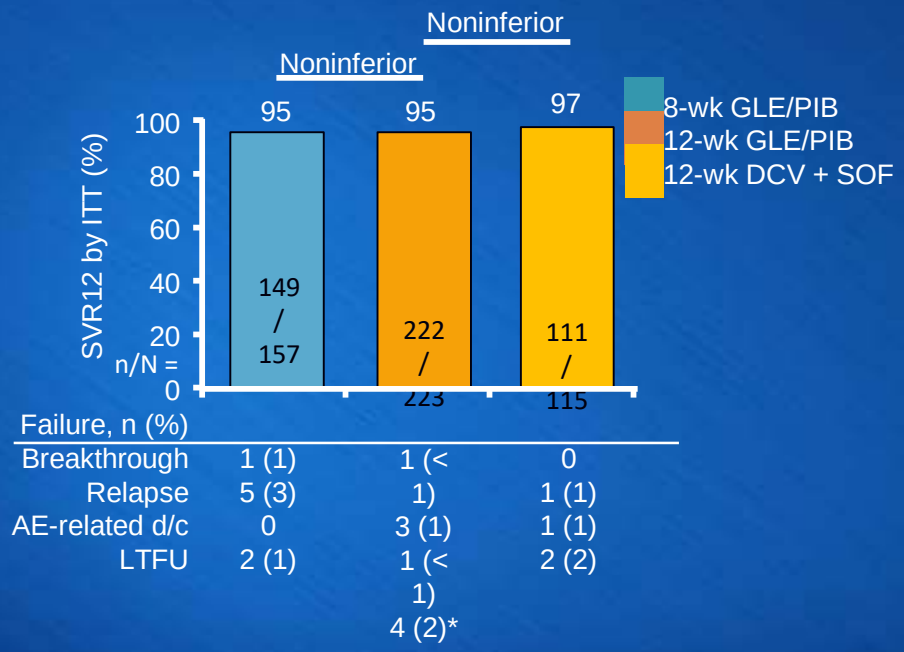
ENDURANCE-3: GLE/PIB in GT3 HCV Without Cirrhosis



- Most pts had history of IDU (63% to 66%)

*2 other failures due to consent withdrawal and noncompliance.

- No serious AEs deemed related to study drug

AE, n (%)	G/P 8 Wks (n = 157)	G/P 12 Wks (n = 233)	SOF + DCV (n = 115)
Any AE			
▪ Possibly DAA related	98 (62) 63 (40)	177 (76) 112 (48)	80 (70) 50 (43)
Serious AE	3 (2)	5 (2)	2 (2)
AEs in ≥ 10% of pts			
▪ Headache	31 (20)	60 (26)	23 (20)
▪ Fatigue	20 (13)	44 (19)	16 (14)
▪ Nausea	19 (12)	32 (14)	15 (13)

Grade ≥ 3 laboratory abnormalities: no clinically relevant ALT increases, 1 isolated bilirubin increase (G/P 8 wks), 1 isolated neutrophil count decrease (G/P 12 wks)

Foster GR, et al. EASL 2017. Abstract GS-007. Reproduced with permission

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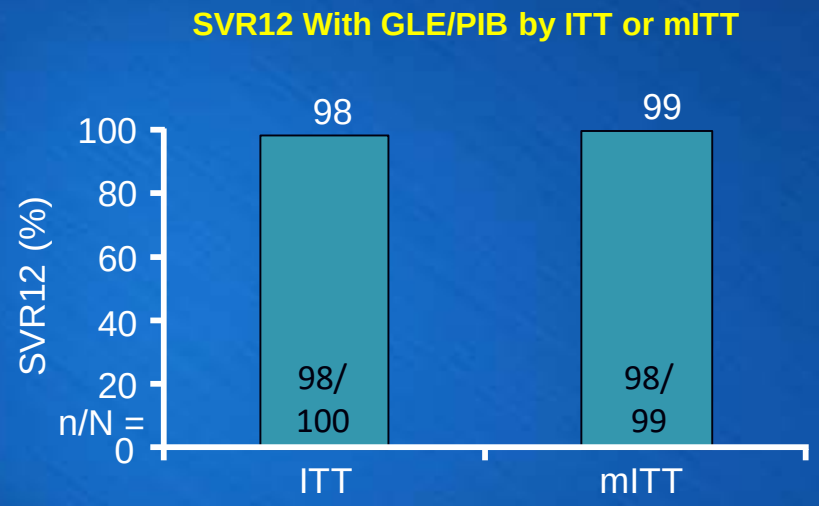
MAGELLAN-2: GLE/PIB in GT1-6 HCV With Liver or Renal Transplant



1 relapse in pt with GT3a HCV; 1 pt LTFU

- No deaths during study, 1 pt with transplant rejection (unrelated to DAA)

Safety Outcome, %	GLE/PIB (N = 100)
Any AE	85
Serious AE	8
▪ DAA related	2
AEs leading to d/c	1
▪ DAA related	0
AEs in ≥ 10% of pts	
▪ Headache	22
▪ Fatigue	22
▪ Nausea	12
▪ Pruritus	12
Grade ≥ 3 abnormality	
▪ AST	0
▪ ALT	1
▪ Total bilirubin	1
▪ CrCl	2

Reau N, et al. EASL 2017. Abstract LBO-03. Reproduced with permission

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MAGELLAN-1: GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with both NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB

SVR12, n/N (%)	GLE/PIB	
	12 Wks (n = 44)	16 Wks (n = 47)
Overall SVR12	39/44 (89)	43/47 (91)
SVR12 according to previous DAA class		
▪ PI only	14/14 (100)	13/13 (100)
▪ NS5A only	14/16 (88)	17/18 (94)
▪ PI + NS5A	11/14 (79)	13/16 (81)
SVR12 according to baseline RAS		
▪ None	13/13 (100)	13/13 (100)
▪ NS3 only	2/2 (100)	4/4 (100)
▪ NS5A only	20/24* (83)	22/23† (96)

*Virologic failure: n = 3 relapse; n = 1 on treatment. †Virologic failure: n = 1 on treatment.

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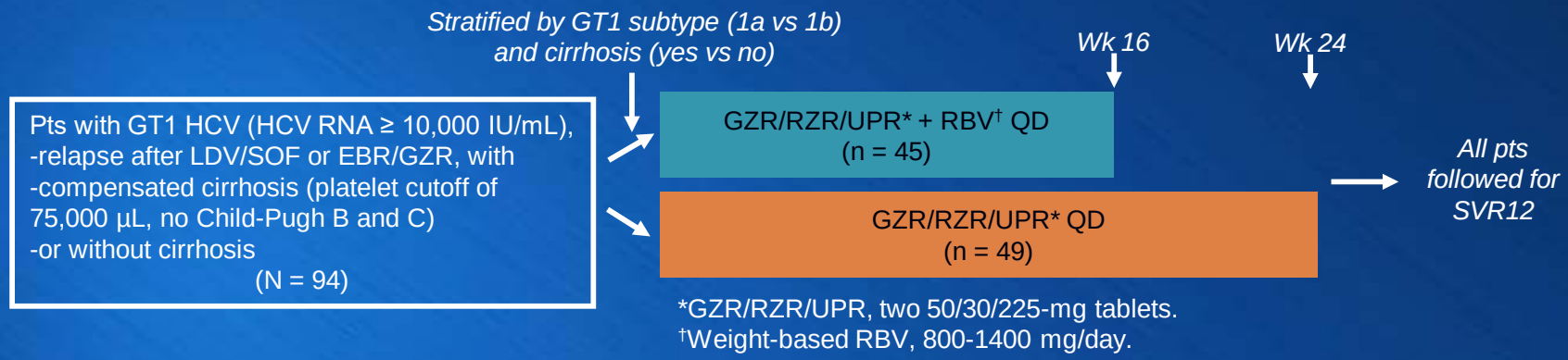
Poordad F, et al. EASL 2017. Abstract PS-156

C-SURGE: GZR/RZR/UPR for GT1 HCV Pts Who Relapsed on Previous DAA Therapy

- Randomized, open-label phase II trial



Baseline characteristics:
- Noncirrhotic, 56%; compensated cirrhosis, 43%; unknown, 1%
- NS5A RASs, 84%;
- NS3 RASs, 65%;
- dual NS5A and NS3 RASs, 55%

Primary endpoints: SVR12 (HCV RNA < 15 IU/mL), safety

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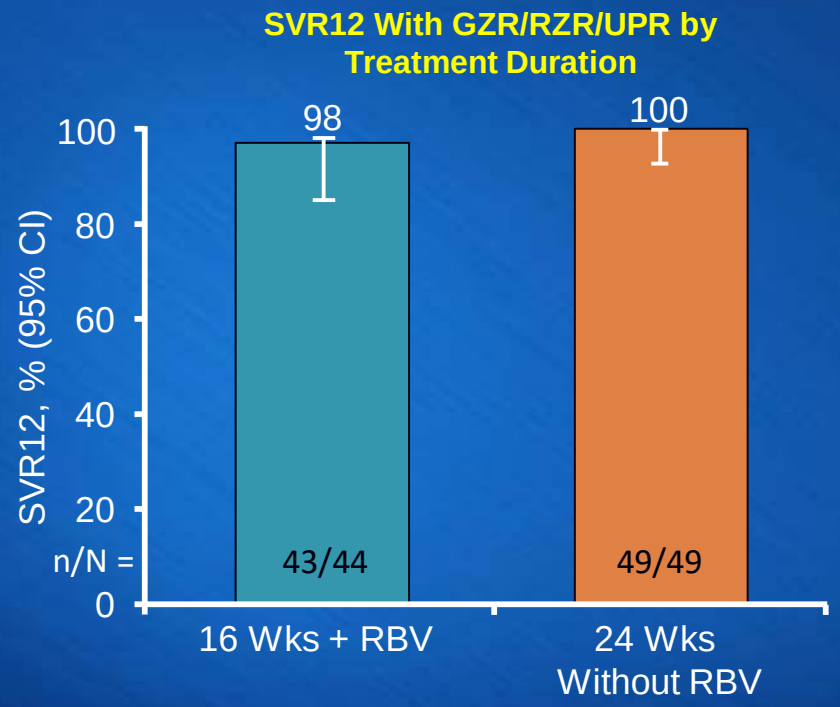
Wedemeyer H, et al. EASL 2017. Abstract PS-159

C-SURGE: Efficacy and Safety Outcomes



- SVR12 achieved independent of presence of BL NS5A/NS3 RASs (including Y93)
- GZR/RZR/UPR + RBV arm had greater frequency of fatigue, pruritus, rash, decreased hemoglobin

Safety Outcome, n (%)	16 Wks + RBV (n = 44)	24 Wks Without RBV (n = 49)
≥ 1 AE	40 (91)	39 (80)
▪ Drug-related AE	32 (73)	23 (47)
Any serious AE*	1 (2)	4 (8)
AEs occurring in ≥ 10% of pts		
▪ Fatigue	21 (48)	12 (24)
▪ Headache	6 (14)	6 (12)
▪ Diarrhea	3 (7)	5 (10)
▪ Pruritus	5 (11)	0
▪ Rash	6 (14)	2 (4)
Hemoglobin < 10 g/dL	4 (9)	0

*All serious AEs deemed unrelated to study treatment.

Wedemeyer H, et al. EASL 2017. Abstract PS-159. Reproduced with permission.

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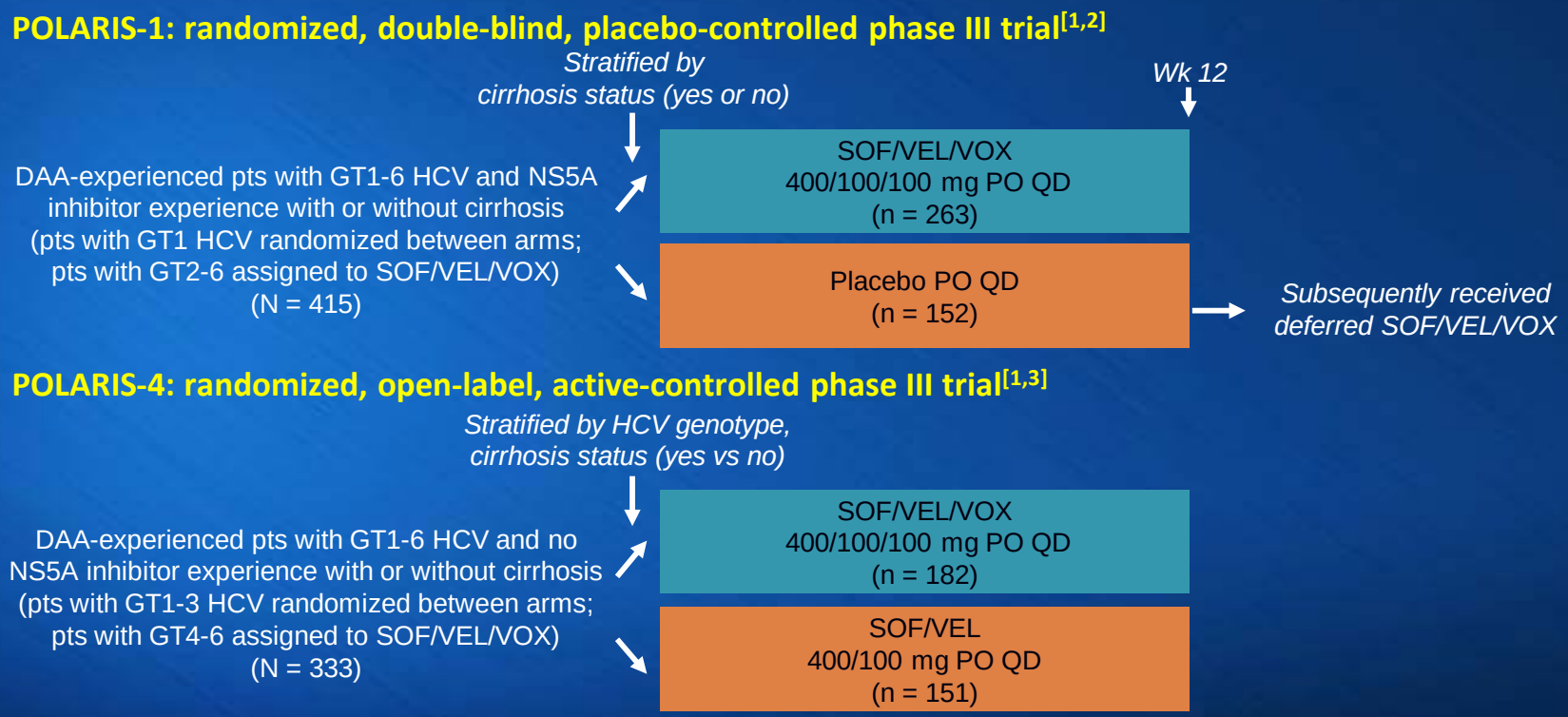
POLARIS-1 and -4: SOF/VEL/VOX in DAA-Experienced Pts



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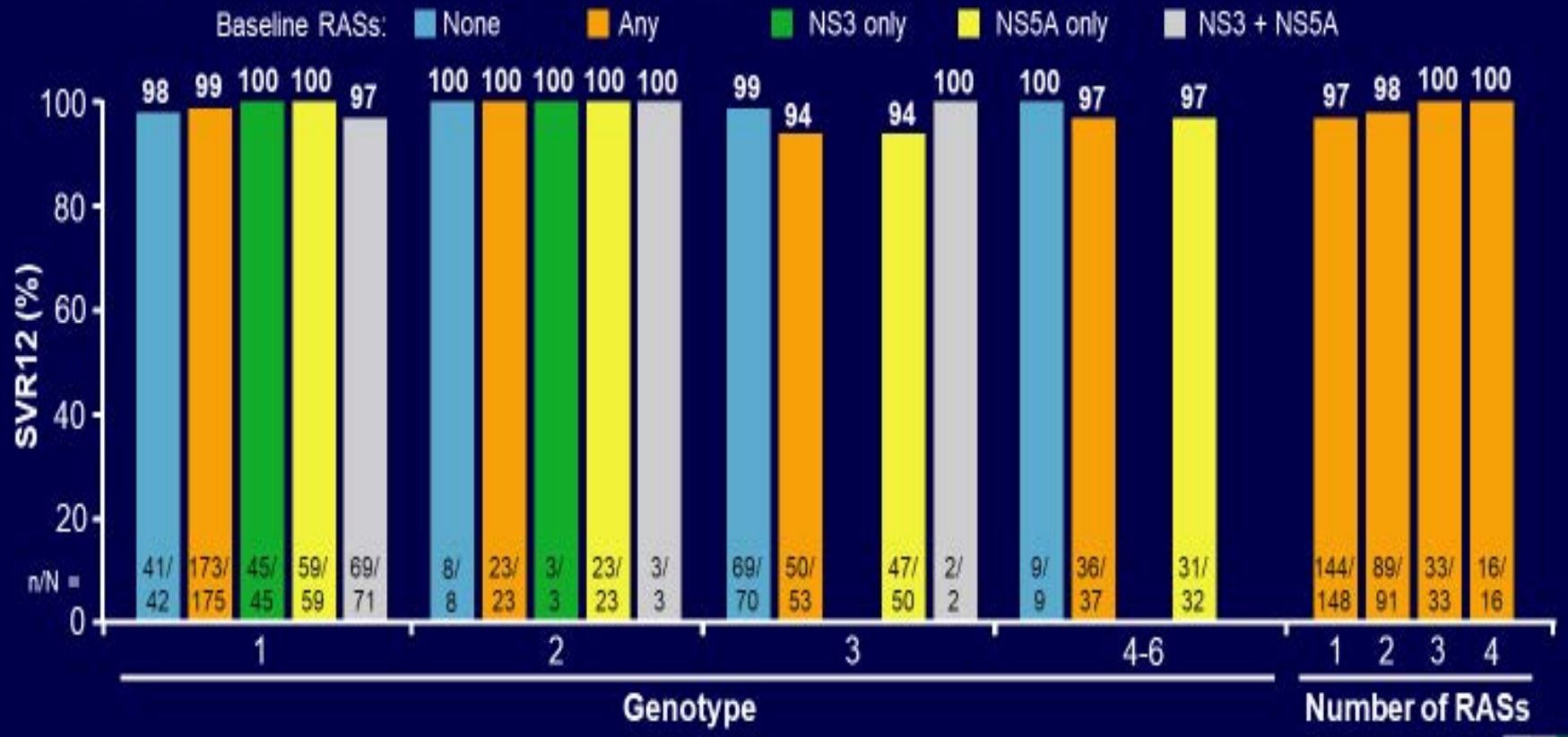
References in slidenotes

POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-experienced Pts

- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors, 46% with cirrhosis



Sarrazin C, et al. EASL 2017. Abstract THU-248. Reproduced with permission.

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