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HEPATITIS

Simplified HCV Therapy in 2018

This program is supported by educational grants from AbbVie; Gilead Sciences; Janssen Therapeutics; Merck & Co., Inc; and ViiV Healthcare.

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Disclosures

Paul Y. Kwo, MD, has disclosed that he has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck, and Quest and funds for research support from AbbVie and Gilead Sciences.

Kristen Marks, MD, has disclosed that she has received funds for research support (paid to Weill Cornell) from Bristol-Myers Squibb, Gilead Sciences, and Merck.

David R. Nelson, MD, has disclosed that he has received funds for research support from AbbVie, Gilead Sciences, and Merck.

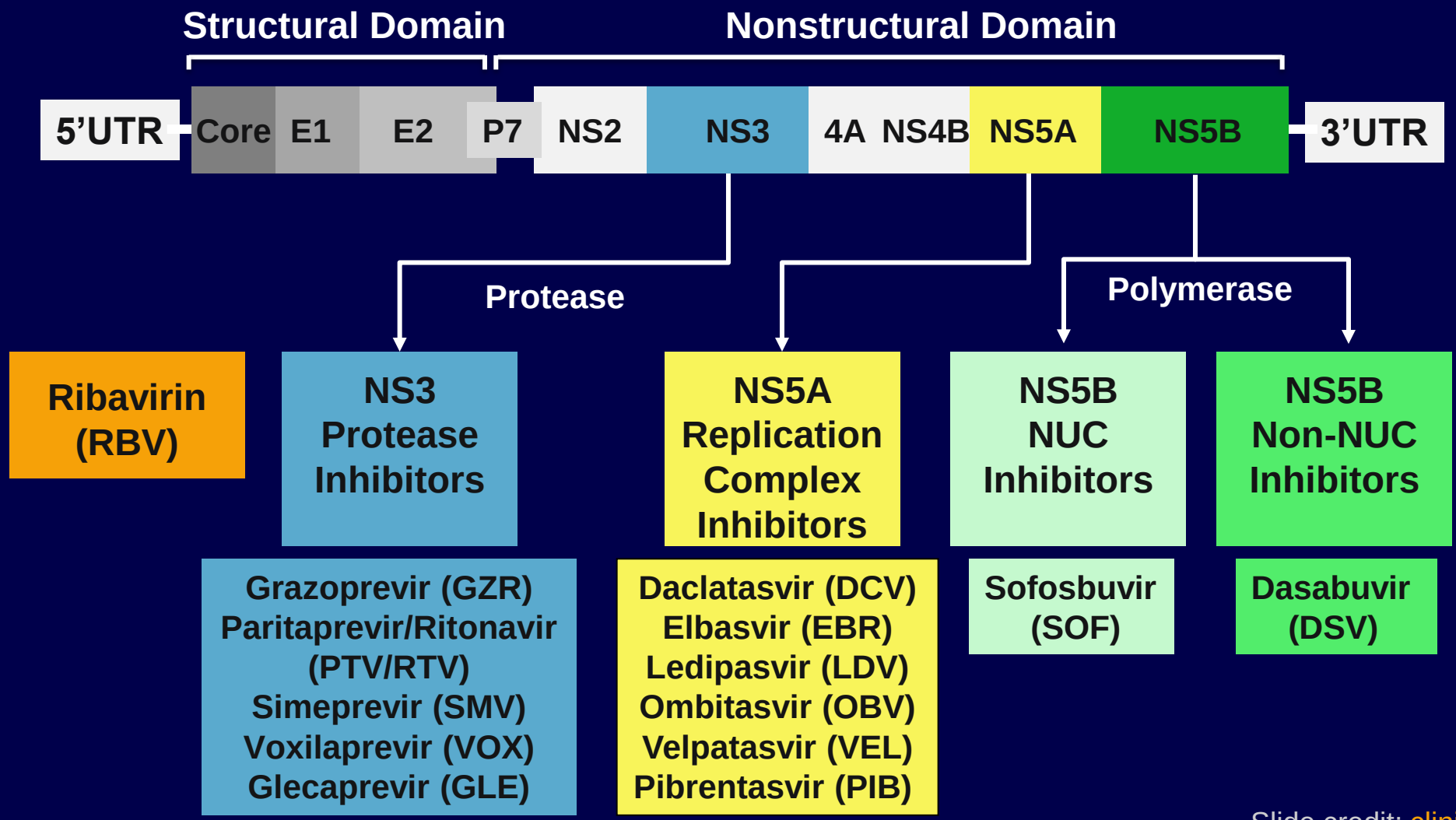
Most Patients With HCV Should Be Considered for Treatment if They Can Comply With Therapy

- AASLD/IDSA HCV guidance:
  - *Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions*
- Despite this recommendation, multiple barriers to HCV therapy persist in many regions of the United States:
  - Payer restrictions related to prescriber type, sobriety requirements, and liver disease stage
  - High costs if uninsured, in some cases high copays

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Approved DAAs From Multiple Classes: Basis of 2018 Combination HCV Regimens



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Staging of Hepatic Fibrosis is Essential Prior to HCV Treatment: Do Not Miss Cirrhosis!

Liver biopsy:
Gold standard
Rarely done

Serum Biomarkers of Fibrosis:
APRI, FIB-4: Very good negative predictive value. APRI < 0.5, FIB-4 < 1.45 rule out cirrhosis.
Commercial serum fibrosis tests also available (*FIBROSpect, FibroSURE*)

Elastography:
> 12.5 kPa = cirrhosis

CT/MRI, US
Can demonstrate cirrhotic morphology, portal hypertension

Slide credit: clinicaloptions.com

SVR Rates > 95% for All Recommended First-line HCV Regimens

AASLD/IDSA Recommendations: Initial Therapy for Genotype 1 HCV Infection

HCV GT	No Cirrhosis	Compensated Cirrhosis
1	EBR/GZR 12 wks* GLE/PIB 8 wks LDV/SOF 8-12 wks† SOF/VEL 12 wks	EBR/GZR 12 wks* GLE/PIB 12 wks LDV/SOF 12 wks SOF/VEL 12 wks

*Only if no baseline NS5A RAS for GT 1a; if NS5A RAS present for GT 1a, EBR/GZR not recommended.
†8 wks of LDV/SOF only if non-black race, HIV-uninfected, and HCV RNA < 6 million IU/mL.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA Recommendations: Initial Therapy for Genotype 2 or 3 HCV Infection

HCV GT	No Cirrhosis	Compensated Cirrhosis
2/3	GLE/PIB 8 wks SOF/VEL 12 wks	GLE/PIB 12 wks SOF/VEL 12 wks*

*Only if no baseline Y93H for GT 3. If Y93H present for GT3, add RBV or choose alternative regimen (consider SOF/VEL//VOX).

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA Recommendations: Initial Therapy for Genotype 4 HCV Infection

HCV GT	No Cirrhosis	Compensated Cirrhosis
4	EBR/GZR 12 wks GLE/PIB 8 wks LDV/SOF 12 wks SOF/VEL 12 wks	EBR/GZR 12 wks GLE/PIB 12 wks LDV/SOF 12 wks SOF/VEL 12 wks

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

AASLD/IDSA Recommendations: Initial Therapy for Genotype 5 or 6 HCV Infection

HCV GT	No Cirrhosis	Compensated Cirrhosis
5/6	GLE/PIB 8 wks LDV/SOF 12 wks SOF/VEL 12 wks	GLE/PIB 12 wks LDV/SOF 12 wks SOF/VEL 12 wks

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Baseline RAS Testing With Recommended Regimens for Treatment-Naive Patients

- **EBR/GZR:** NS5A RAS testing recommended for **GT1a**
  - If present, add RBV and increase duration to 16 wks or select different regimen
- **SOF/VEL:** NS5A RAS testing recommended for **GT3 with cirrhosis**
  - If Y93H is present, add RBV or select different regimen

Regimen	GT1a ± Cirrhosis	GT3 + Cirrhosis
LDV/SOF	No	NA
EBR/GZR	**Yes**	NA
SOF/VEL	No	**Yes**

- Resistance tests useful to determine (and justify) when a different regimen than that in the formulary is needed
- With aim of simplicity, regimens without RBV are preferred

AASLD/IDSA. HCV guidance. September 2017.

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First-line HCV Therapy: Distinguishing Among Recommended Options

EBR/GZR - QD single tablet
12 wks, GT 1 or 4
Requires RAS testing for GT1a
Contains PI: ***do not use*** if decompensated
Can be used in stage 4/5 CKD
DDI highlights: glucocorticoids, statins, PDE inhibitors, rifampin

GLE/PIB - QD 3 tablets with food
8 wks no cirrhosis, 12 wks if cirrhosis, GT 1-6
No RAS testing
Contains PI: ***do not use*** if decompensated
Can be used in stage 4/5 CKD
DDI highlights: statins, rifampin

LDV/SOF - QD single tablet
8-12 wks, GT 1, 4, 5, or 6
No RAS testing
Safe in decompensation
Not recommended for stage 4/5 CKD
DDI highlights: acid-reducing agents, statins, rifampin

SOF/VEL - QD single tablet
12 wks, GT 1-6
Requires RAS testing for some GT 3
Safe in decompensation
Not recommended for stage 4/5 CKD
DDI highlights: acid-reducing agents, rifampin

DDIs are drug specific and there are many more to consider than are listed here.
Always check! https://www.hep-druginteractions.org/

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Many Previously Challenging Clinical Scenarios Are Now Routine

Population	SVR, %	Notes
Black/Hispanic race	> 95	▪ Potential for lower efficacy of some regimens with shorter duration (8 wks)
HIV/HCV coinfection	> 95	▪ Avoid DDIs between DAAs and ART
Post orthotopic liver transplantation	> 95	▪ Clinical trial SVR rates high with: ○ LDV/SOF + RBV ○ DCV + SOF + RBV ○ GLE/PIB (off label, no RBV) ○ SOF/VEL (off label, no RBV)

AASLD/IDSA. HCV guidance. September 2017.

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Many Previously Challenging Clinical Scenarios Are Now Routine (cont.)

Population	SVR, %	Notes
Stage 4-5 chronic kidney disease (eGFR < 30 mL/min)	> 95	AASLD/IDSA recommendations for initial therapy: ▪ **GT1-6: GLE/PIB** • No cirrhosis: 8 wks • Compensated cirrhosis: 12 wks ▪ **GT1 or GT4: EBR/GZR 12 wks**

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Previous DAA Failure

AASLD/IDSA Guidance: Recommended Regimens for DAA-Exp'd Patients (SVR > 95%)

- No RAS testing recommended in this setting with recommended regimens

HCV GT	Duration, Wks	Previous DAA Experience		
		NS3/4AI Only	NS5BI (SOF w/o NS5AI)	NS5AI (± NS3/4AI, NS5BI)
1	12	LDV/SOF (no cirrhosis) SOF/VEL GLE/PIB	SOF/VEL/VOX (1a) GLE/PIB SOF/VEL (1b)	SOF/VEL/VOX
2*	12	NA	SOF/VEL GLE/PIB	NA
3	12	SOF/VEL/VOX	SOF/VEL/VOX	SOF/VEL/VOX ± RBV†
4, 5, 6	12	SOF/VEL/VOX	SOF/VEL/VOX	SOF/VEL/VOX

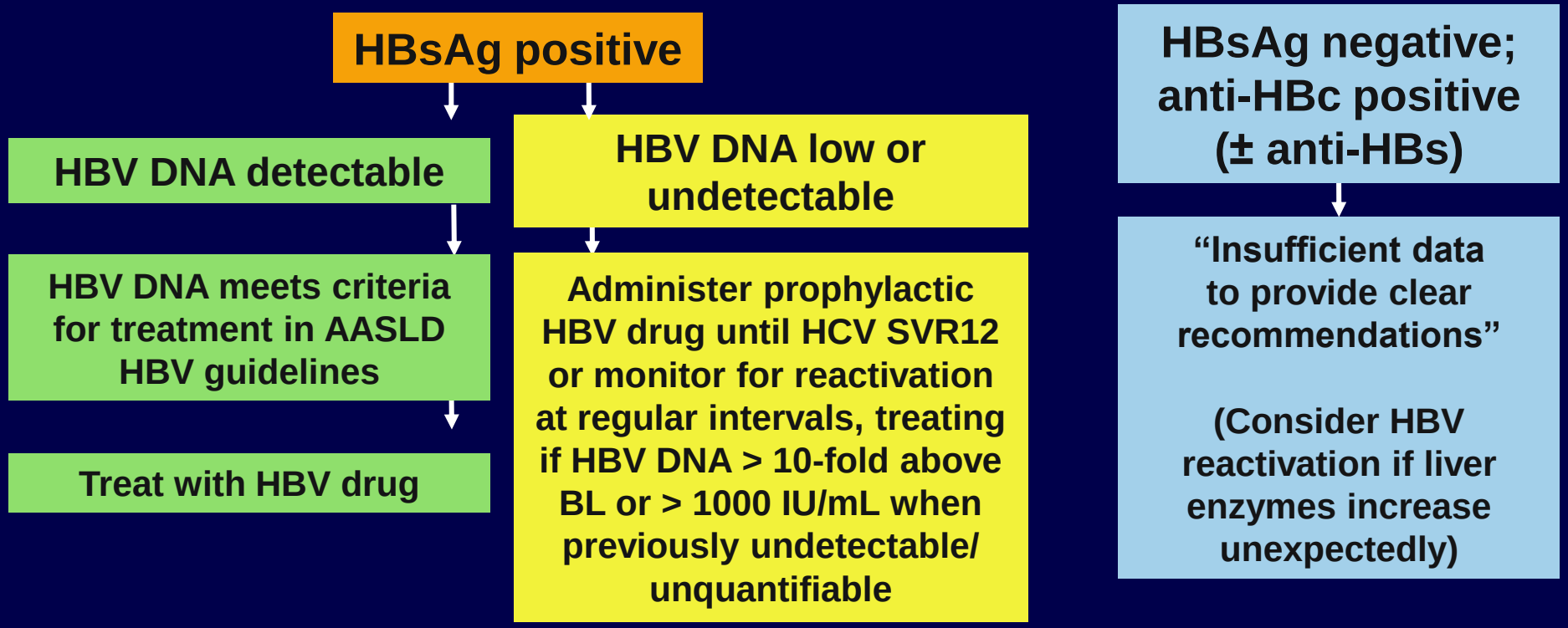
*Recommendations for any SOF + RBV experienced pt. †RBV if NS5AI failure and cirrhosis.

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
  - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



AASLD/IDSA. HCV guidance. September 2017.

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Does SVR to HCV Therapy Improve Clinical Outcomes?

The Cochrane Review: A Flawed Analysis

Authors' conclusions:

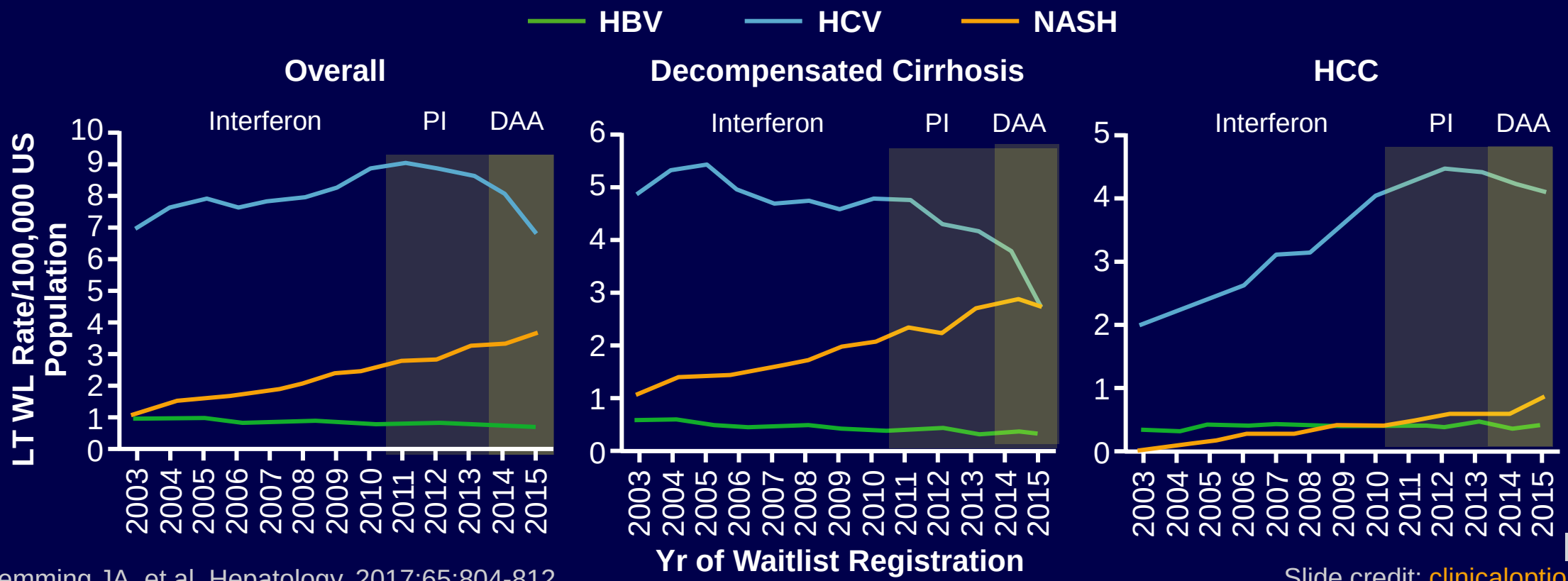
- *"Overall, DAAs on the market or under development do not seem to have any effects on risk of serious adverse events. Simeprevir may have beneficial effects on risk of serious adverse event. In all remaining analyses we could neither confirm nor reject that DAAs had any clinical effects. DAAs seemed to reduce the risk of no sustained virological response. The clinical relevance of the effects of DAAs on no sustained virological response is questionable, as it is a non-validated surrogate outcome. All trials and outcome results were at high risk of bias so our results presumably overestimate benefit and underestimate harm. The quality of the evidence was very low."*

Jakobsen JC, et al. Cochrane Database Syst Rev. 2017;9:CD012143.

Slide credit: clinicaloptions.com

Reduction in HCV-Related Liver Transplant Waitlist in the Era of HCV DAAs

- Cohort study of 47,591 adults wait-listed for liver transplant in Scientific Registry of Transplant Recipients database from 2003-2015
  - LT WL rate for HCV secondary to decompensated cirrhosis **decreased 32% in DAA vs IFN era**



Flemming JA, et al. Hepatology. 2017;65:804-812.

Slide credit: clinicaloptions.com

RESIST-HCV: Mortality Following SVR to HCV DAA Therapy

- Prospective cohort analysis of 4668 patients who started DAAs Mar 2015 - Dec 2016 (prior HCC/OLT excluded)
  - mITT analysis: N = 4468
  - CTP A: 69%; CTP B: 8.8%
  - Primary endpoint: survival since initiating HCV DAAs
  - Median follow-up: 72 wks
- SVR assoc. with reduced liver-related mortality across disease stages, but benefit lower in CTP B cirrhosis
  - Univariate HR for no SVR vs SVR in CTP B: 3.49; *P* = .036

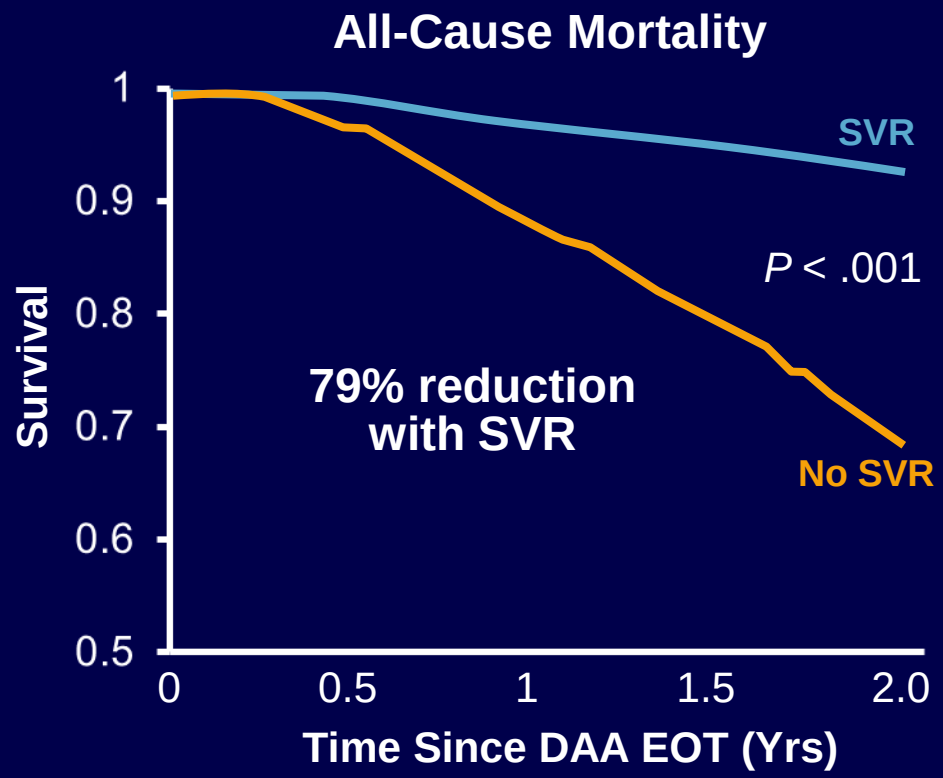
Multivariate Cox Regression	HR (95% CI)	*P* Value
Independent predictors of liver-related mortality in CTP A cirrhosis		
▪ No SVR	18.50 (6.75-50.70)	< .001
▪ Albumin < 3.5 g/dL	6.01 (2.30-15.73)	< .001
Independent predictors of cardiovascular mortality in DAA-treated patients		
▪ No SVR	10.56 (3.43-32.46)	< .001
▪ Diabetes	4.11 (1.30-12.98)	.011

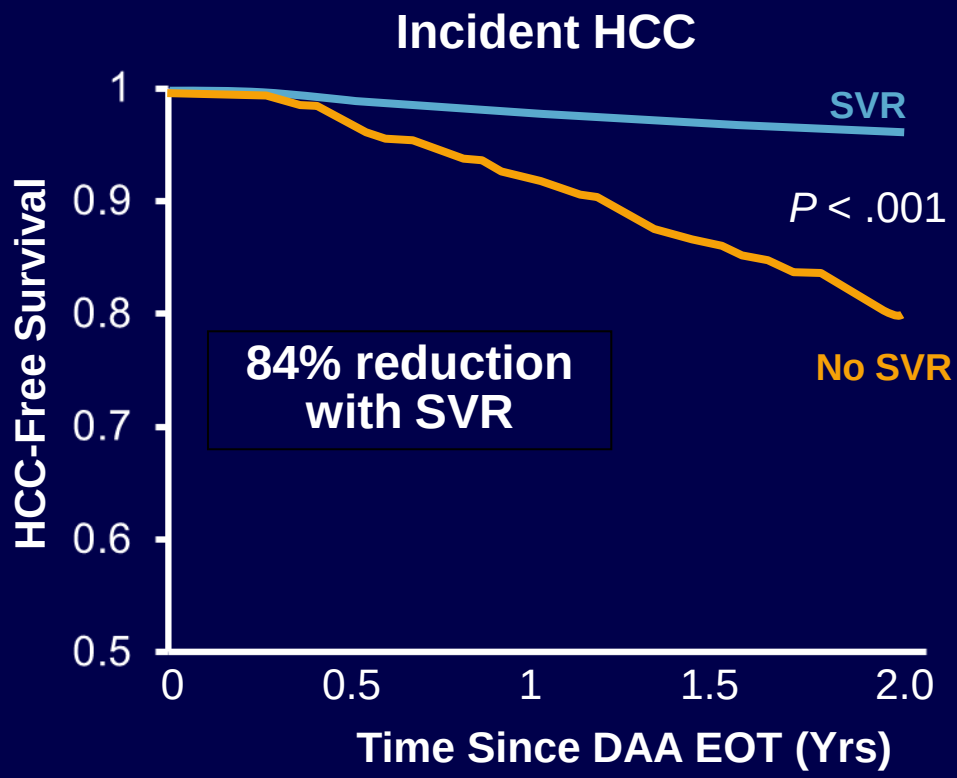
Calvaruso V, et al. EASL 2018. Abstract PS-149.

Slide credit: clinicaloptions.com

SVR With DAA Therapy: Mortality and HCC Risk

- Patients with HCV infection, FIB-4 > 3.25 in VA HCV Clinical Case Registry (N = 15,059)
  - SVR with DAA therapy significantly lowered all-cause mortality and incident HCC





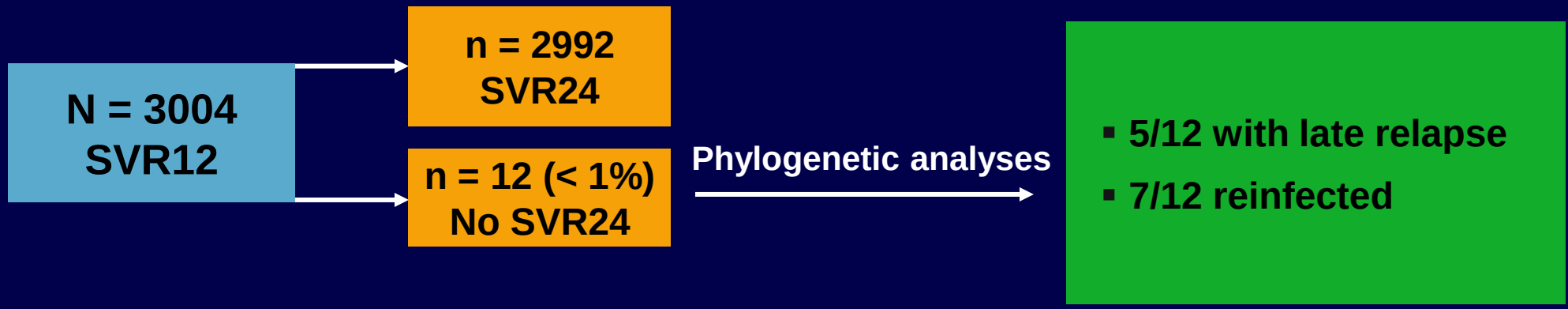
Backus LI, et al. Hepatology. 2017;[Epub ahead of print].

Slide credit: clinicaloptions.com

Post SVR Management

Low Risk of Late Relapse Beyond SVR12 With DAA Therapy

- Risk of late relapse very low, *but* can happen
- Analysis of recurrent viremia after SVR12 in 11 SOF ± LDV phase III trials



Sarrazin C, et al. Clin Infect Dis. 2017;64:44-52.

Slide credit: clinicaloptions.com

Recommendations on HCV RNA Follow-up After SVR

Organization	Recommendation
AASLD/IDSA[1]	▪ Additional testing can be considered at ≥ 24 wks post treatment for pts with ALT increases to > ULN
EASL[2]	▪ Patients with no to moderate fibrosis (F0-F2), no ongoing risk behavior, and no other comorbidities should be discharged

- Note that HCV antibody tests will remain positive for most after cure and need not be repeated
- Reinfection can occur

1. AASLD/IDSA. HCV guidance. September 2017.
2. EASL HCV Guidelines. 2018.

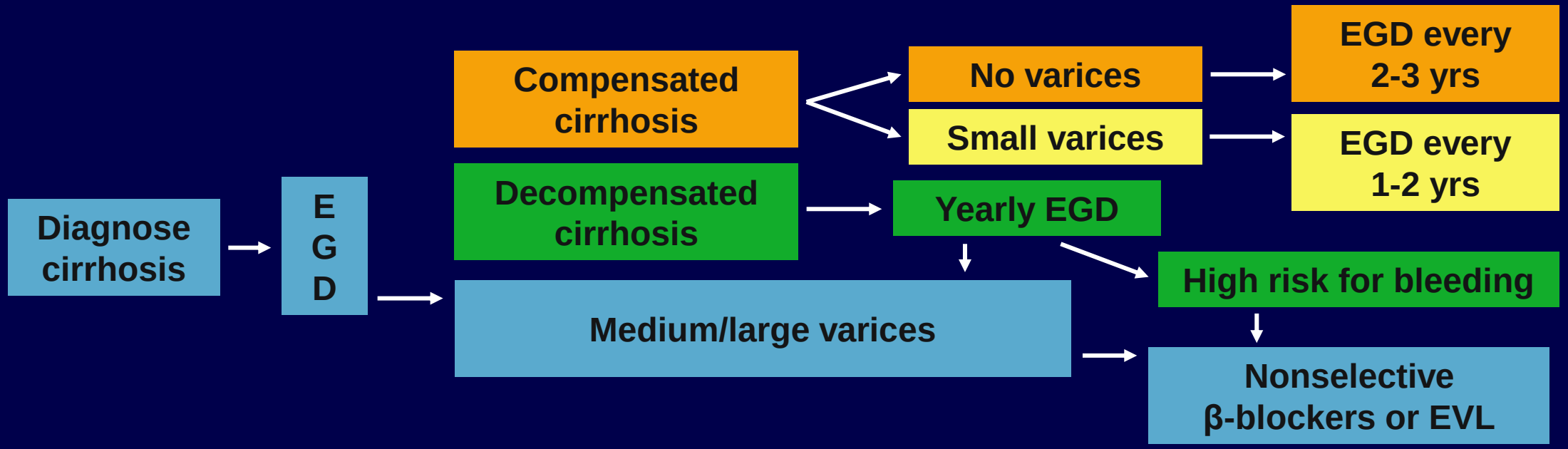
Recommendations for HCC Screening After SVR

Organization	Recommendations	
	F0-F2	F3-F4
AASLD/IDSA HCV Guidance[1]	▪ Follow-up same as for those never infected with HCV	▪ **Ultrasound surveillance every 6 mos**
EASL[2]	▪ None	▪ **Ultrasound surveillance every 6 mos**
AGA[3]	▪ None	▪ **Ultrasound surveillance with or without AFP every 6 mos**
AASLD HCC Guidance[4]	▪ None	▪ **F4: Ultrasound surveillance with or without AFP every 6 mos**

1. AASLD/IDSA. HCV guidance. September 2017.
2. EASL HCV Guidelines. 2018.
3. Jacobson IM, et al. Gastroenterology. 2017;152:1578-1587.
4. Heimbach JK, et al. Hepatology. 2018;67:358-380.

Screening for Varices: AASLD Practice Guidelines

- Patients with pretreatment LS < 20 kPa and platelet count > 150,000/mm^3 have very low probability (< 5%) of having high-risk varices, and EGD can be circumvented
- In patients who do not meet these criteria, screening endoscopy for diagnosis of GEV is recommended when the diagnosis of cirrhosis is made



Garcia-Tsao G, et al. Hepatology. 2017;65:310-335.

Slide credit: clinicaloptions.com

Conclusions

- Vast majority of HCV infections curable
- Multiple regimens highly effective and safe across HCV genotypes
  - Outcomes confirmed in “real-world” studies
  - Most historically difficult-to-treat populations are now routinely treated
- Post SVR:
  - Counsel against and monitor for reinfection
  - If advanced fibrosis (F3/F4), need long-term monitoring for HCC and decompensation -- do not dismiss them from clinic follow-up
  - If ALT is still elevated, it must be explained (NAFLD, EtOH, DILI, reinfection) – more on this in upcoming Roundtable Session!

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