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HEPATITIS

# Hepatitis Alert: Management of Patients With HCV Who Have Achieved SVR

This program is supported by educational grants from
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# Faculty Disclosure Information

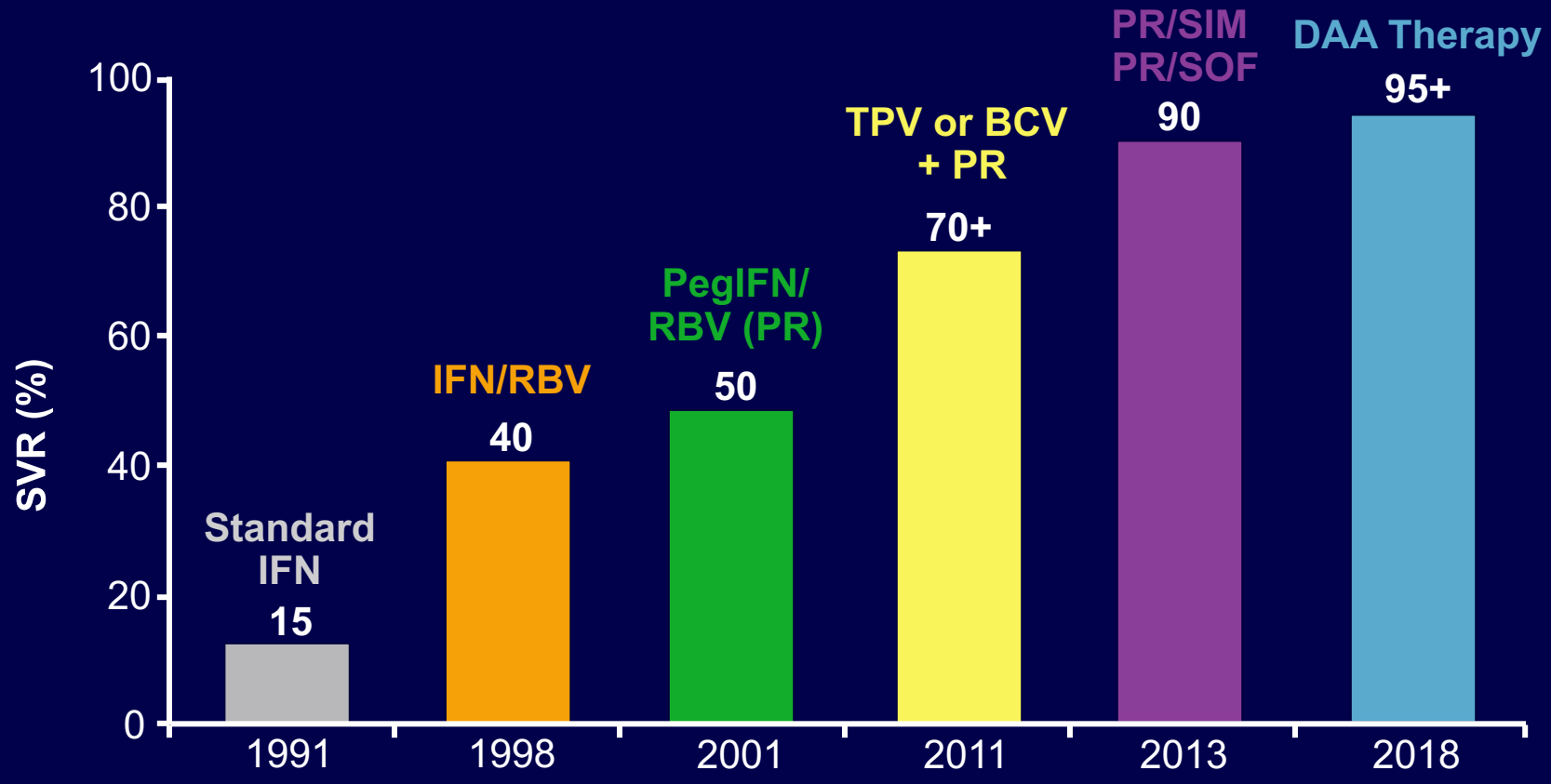
**Ira M. Jacobson, MD,** has disclosed that he has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Janssen, Merck, and Trek; fees for non-CME/CE services from Gilead Sciences, Intercept, and Merck; and funds for research support from Gilead Sciences and Merck.

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

# Program Overview

- Long-term Outcomes After SVR
- Post-SVR Monitoring of HCV RNA
- Post-SVR Monitoring for HCC
- Management of Varices
- Additional Considerations

# Current All-Oral Therapies Highly Effective




**With all the pts who will be cured, how much care do the cured need?**

References in slidenotes

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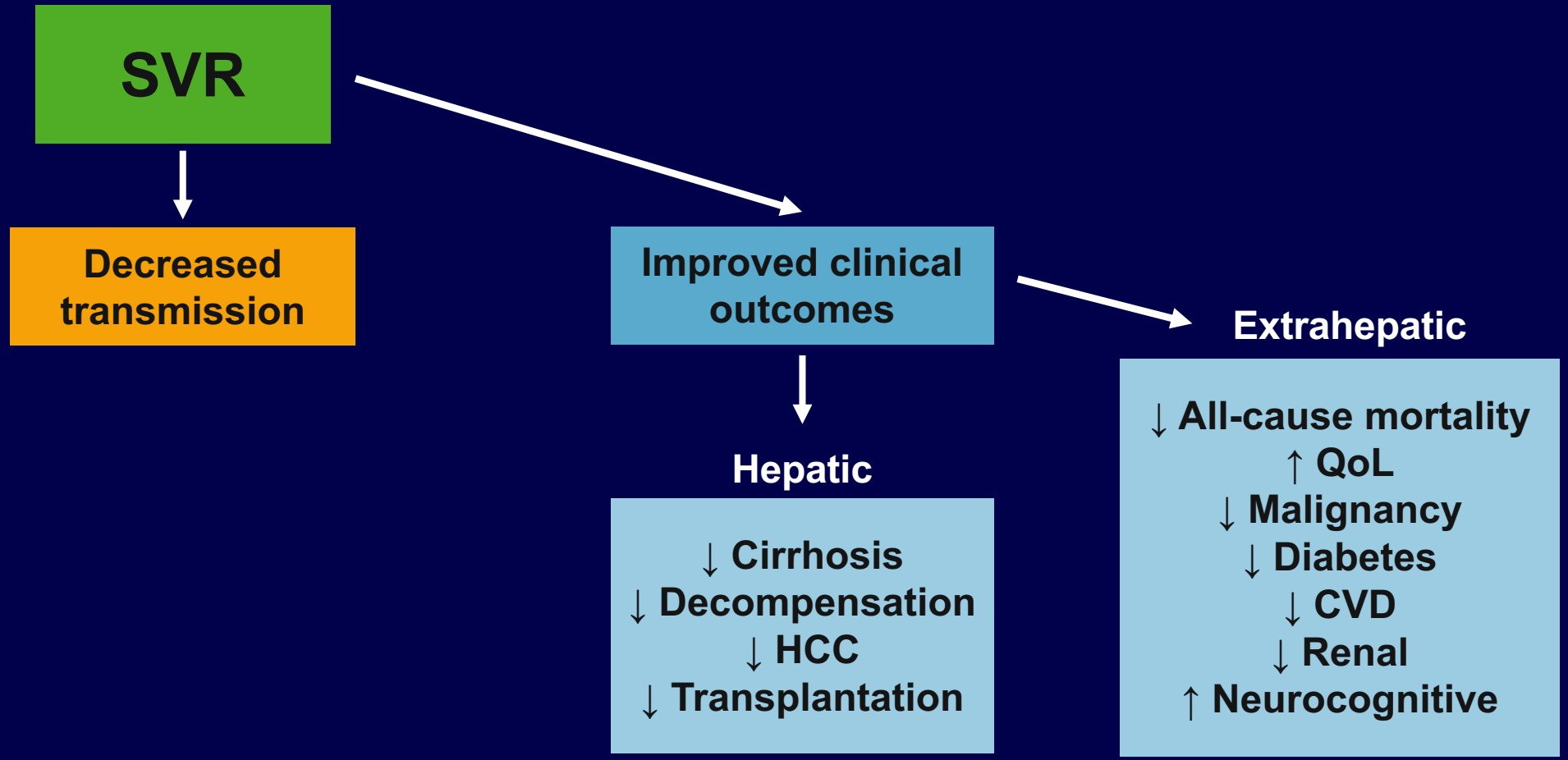
# Long-term Outcomes After SVR

# Benefits of Achieving SVR




Smith-Palmer J, et al. BMC Infect Dis. 2015;15:19. Negro F, et al. Gastroenterology. 2015;149:1345-1360.
George SL, et al. Hepatology. 2009;49:729-738.

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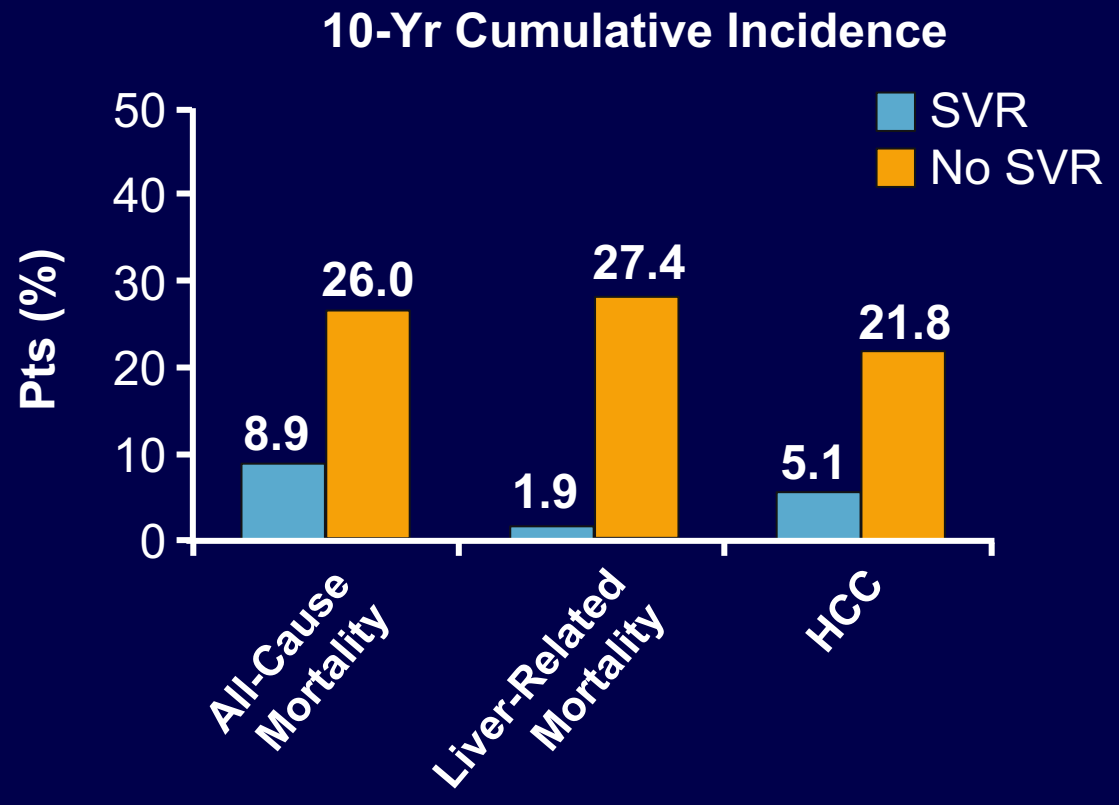
# SVR and Mortality: IFN Era

- Long-term follow-up study of pts with chronic HCV infection and advanced fibrosis or cirrhosis (N = 530 treated 1990-2003; median follow-up: 8.4 yrs)[1]



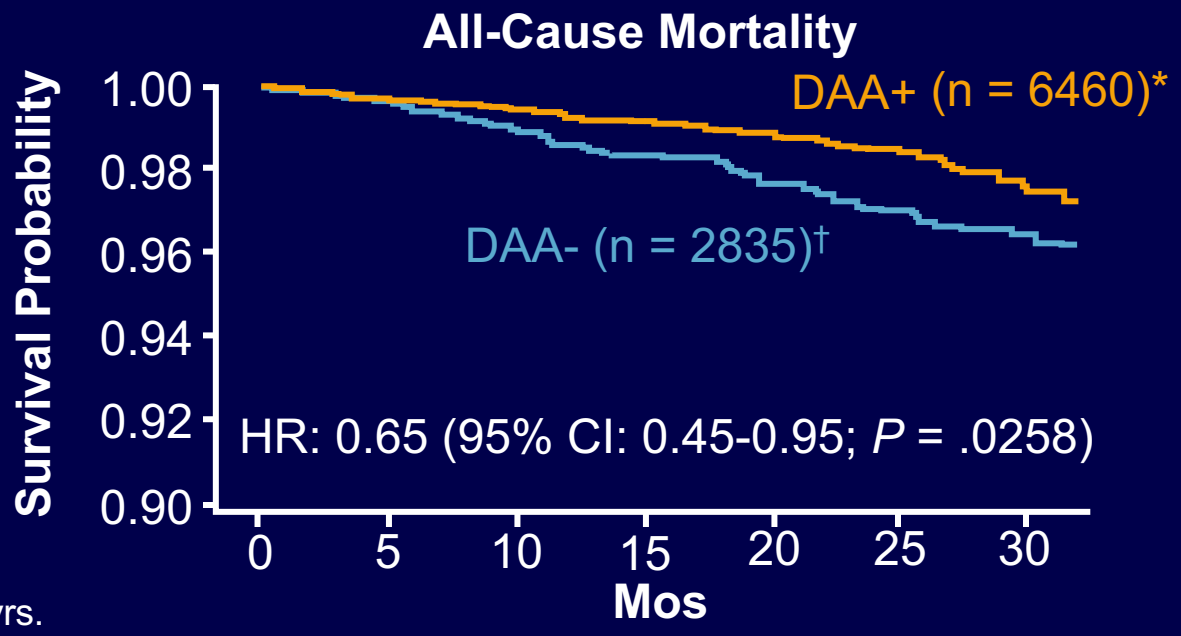

- Baseline factors significantly associated with all-cause mortality:
  - Older age
  - Genotype 3 (2-fold increase in mortality and HCC)
  - Higher Ishak fibrosis score
  - Diabetes
  - Severe alcohol use
- SVR also reduces all-cause mortality even in absence of cirrhosis[2]


1. van der Meer AJ, et al. JAMA. 2012;308:2584-2593.
2. Backus LI, et al. Clin Gastroenterol Hepatol. 2011;9:509-516.


Slide credit: clinicaloptions.com

# DAA Therapy and Risk of Mortality

- ANRS HEPATHER: multicenter observational cohort study assessing short-term effects of DAAs on mortality in pts with HCV (N = 9295)
  - Median follow-up: 24 mos
- **DAA treatment associated with decreased risk of death vs no DAA treatment**




*8482 person-yrs. †10040 person-yrs.

Carrat F, et al. AASLD 2017. Abstract LB-28.

Slide credit: clinicaloptions.com

# Post-SVR Monitoring of HCV RNA

## *When Does Virologic Victory Become Closure?*

# Recommendations on HCV RNA Follow-up After SVR

| Organization | Recommendation |
|---|---|
| AASLD/IDSA | ▪ Additional testing can be considered at ≥ 24 wks post treatment for pts with ALT increases to > ULN |
| EASL | ▪ Noncirrhotics should be tested for ALT and HCV RNA at 48 wks post treatment and discharged if ALT normal and HCV RNA negative |

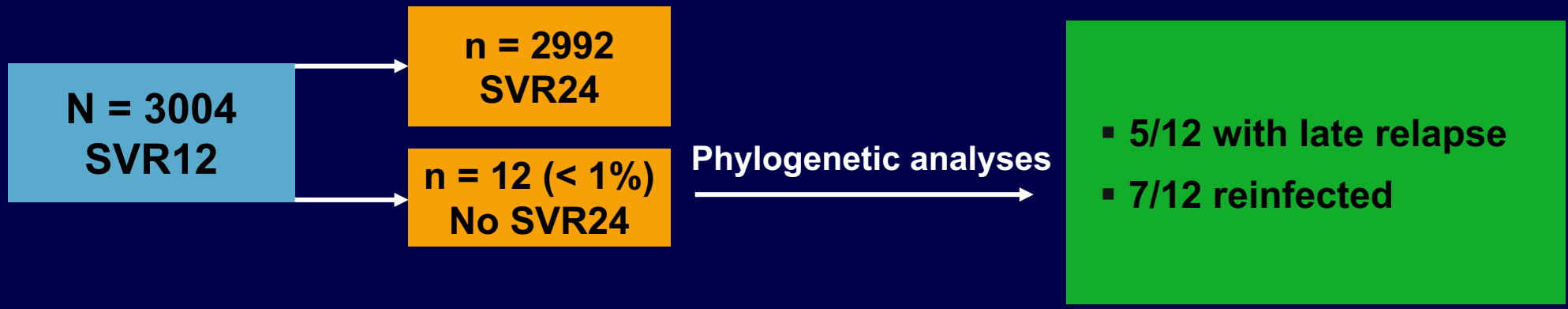
- Note that HCV antibody tests will remain positive for most after cure and need not be repeated
- Reinfection can occur

AASLD/IDSA Guidelines. September 2017. EASL Guidelines. 2016.

Slide credit: clinicaloptions.com

# 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.

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# Post-SVR Monitoring for HCC

## *Which Patients Need It?*

# SVR and HCC Risk: IFN Era

- Meta-analysis of studies assessing HCC development in HCV pts following SVR through February 2012

| Outcome | All Pts (n = 25,497) | | Pts With Advanced Fibrosis* (n = 2649) | |
|---|---|---|---|---|
| | SVR | No SVR | SVR | No SVR |
| Developed HCC, %/PY | 0.33 | 1.67 | 1.05 | 3.30 |
| Adjusted HR (95% CI) | 0.24 (0.18-0.31) | | 0.23 (0.16-0.35) | |

*METAVIR score of F3/F4 or Ishak score of 4-6.

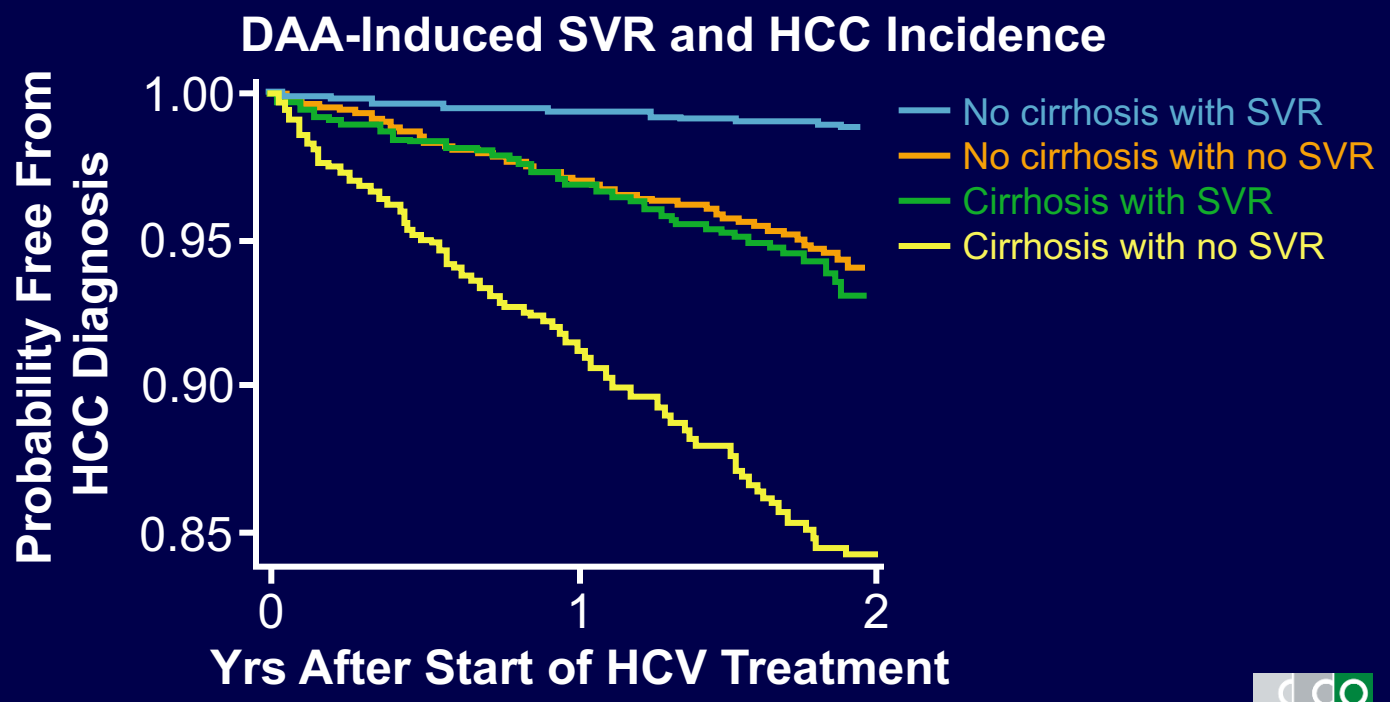
Morgan RL, et al. Ann Int Med. 2013;158:329-337.

Slide credit: clinicaloptions.com

# DAA Therapy and HCC Risk

- Retrospective cohort study assessing the relationship between SVR and de novo HCC risk in pts with HCV in the VA system receiving antiviral therapy 1999-2015 (N = 62,354)
  - Mean follow-up: 6.1 yrs
- **SVR with DAA regimen associated with 71% decrease in de novo HCC risk**

| Regimen | HCC/100 PY | aHR |
|---|---|---|
| IFN only | | |
| ▪ SVR | 0.28 | 0.32 |
| ▪ No SVR | 1.07 | |
| DAA + IFN | | |
| ▪ SVR | 0.6 | 0.48 |
| ▪ No SVR | 1.73 | |
| DAA only | | |
| ▪ SVR | 0.92 | 0.29 |
| ▪ No SVR | 5.2 | |




Ioannou G, et al. AASLD 2017. Abstract 142.

Slide credit: clinicaloptions.com

# Some Key Questions With SVR and HCC

- Pts with what stage(s) of fibrosis may be at increased risk for HCC following SVR? Are pts with < F3 fibrosis at risk?

- Is there a typical time course for when HCC develops among at-risk pts following SVR? How long should HCC surveillance continue?

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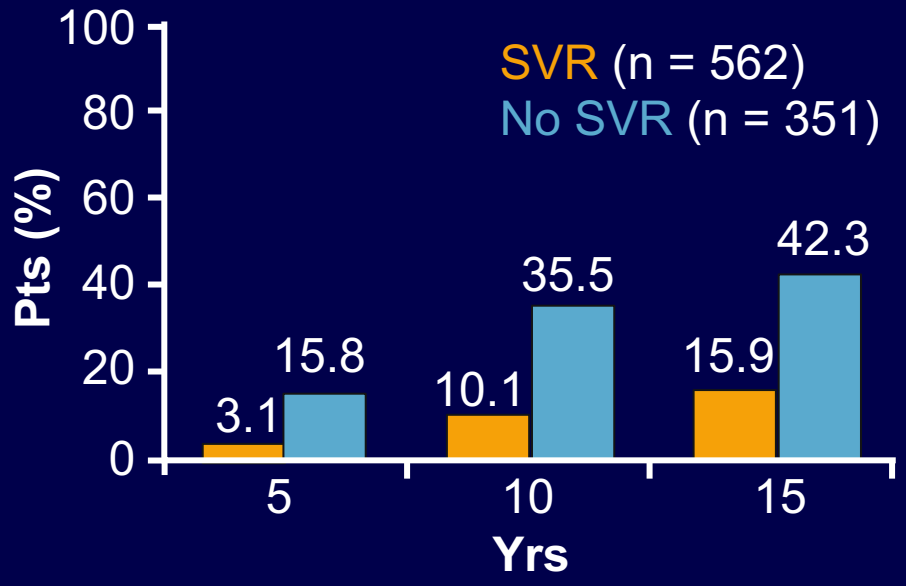
# Pretreatment Fibrosis Stage and HCC in Pts Achieving SVR: Retrospective Japanese Study

- Retrospective cohort study of de novo HCC incidence in Japanese pts achieving SVR on IFN therapy
  - Median follow-up: 4.8 yrs

**Cumulative Incidence of HCC**



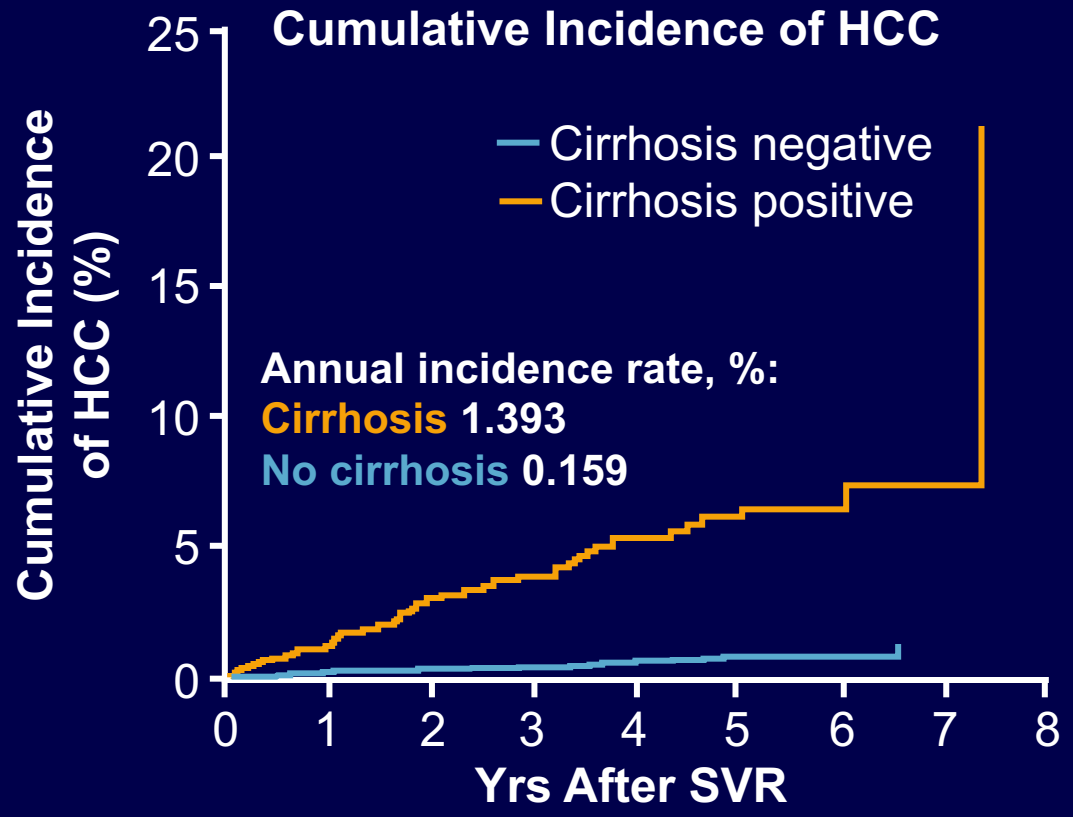

| Fibrosis Stage | n | HCC, n (%) | Cumulative HCC, % | | |
|---|---|---|---|---|---|
| | | | 5 Yrs | 10 Yrs | 15 Yrs |
| F0 | 53 | 0 (0) | 0 | 0 | 0 |
| F1 | 187 | 1 (0.5) | 0.7 | 0.7 | 0.7 |
| F2 | 193 | 13 (6.7) | 3.5 | 14.7 | 17.2 |
| F3 | 78 | 11 (14.1) | 3.7 | 12.7 | 30.5 |
| F4 | 51 | 6 (11.8) | 11.7 | 22.8 | 22.8 |
| All | 562 | 31 (5.5) | 3.1 | 10.1 | 15.9 |

Yamashita N, et al. J Gastroenterol. 2014;49:1504-1513.

Slide credit: clinicaloptions.com

# Fibrosis Stage and Incidence of HCC in Pts Achieving SVR: Retrospective US VA Study

- Retrospective cohort study of de novo HCC incidence in pts achieving SVR on IFN-based therapy in VA Healthcare System 1999-2010 (N = 10,738)




**Incidence of HCC Following SVR**

| Baseline Status | | n | HCC, n | Annual Incidence, % |
|---|---|---|---|---|
| Cirrhosis | High APRI* | | | |
| No | No | 6832 | 11 | 0.055 |
| No | Yes | 2358 | 31 | 0.476 |
| Yes | No | 584 | 9 | 0.526 |
| Yes | Yes | 964 | 49 | 1.997 |

*> 2.0.

El-Serag HB, et al. Hepatology. 2016;64:130-137.

Slide credit: clinicaloptions.com

# Recommendations for HCC Screening After SVR

| Organization | Recommendations | |
|---|---|---|
| | F0-F2 | F3-F4 |
| AASLD/IDSA | ▪ Follow-up same as for those never infected with HCV | ▪ **Ultrasound surveillance every 6 mos** |
| EASL | ▪ None | ▪ **Ultrasound surveillance every 6 mos** |

AASLD/IDSA Guidelines. September 2017. EASL Guidelines. 2016.

Slide credit: clinicaloptions.com

# Surveillance and Management of Varices After SVR

# Recommendations for Surveillance and Management of Varices After SVR

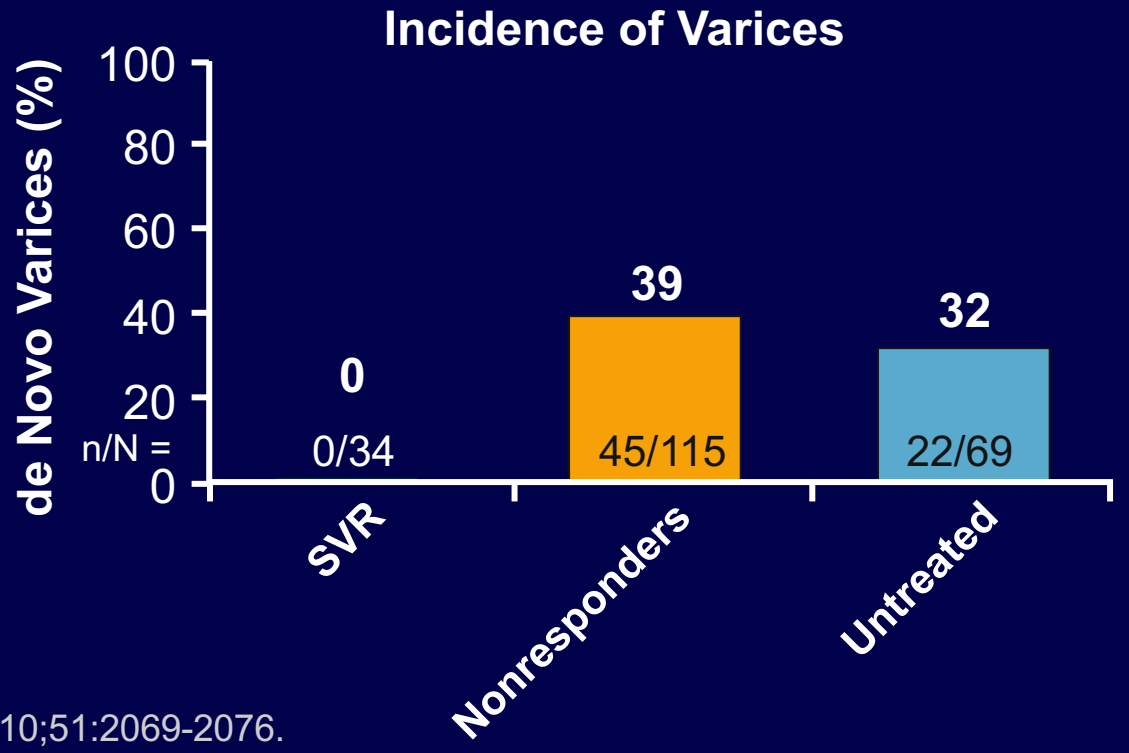
| Organization | Recommendations | |
|---|---|---|
| | Noncirrhotics | Cirrhotics |
| AASLD/IDSA and EASL | ▪ No specific recommendations | ▪ Endoscopy to screen for varices<br>▪ Pts with varices should be managed as indicated |

AASLD/IDSA Guidelines. September 2017. EASL Guidelines. 2016.

Slide credit: clinicaloptions.com

# Endoscopic Surveillance for Varices Following SVR

- Study of de novo esophageal varices in pts with HCV and compensated cirrhosis (N = 218)
  - Pts underwent endoscopic surveillance for varices every 3 yrs; median follow-up: 11.4 yrs



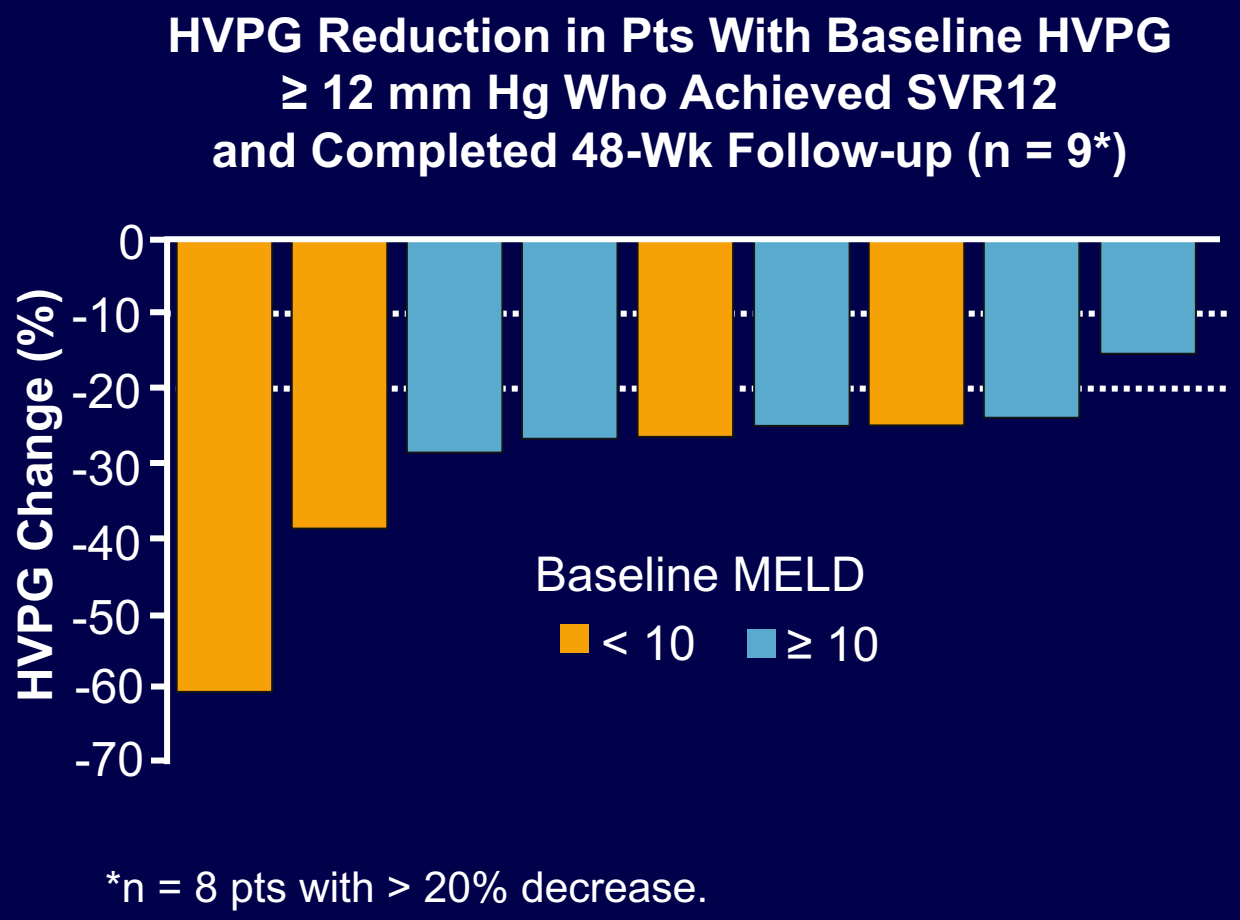

HVPG fell to < 10 mm Hg in 4/4 pts with HVPG > 10 mm Hg before treatment

Bruno S, et al. Hepatology. 2010;51:2069-2076.

Slide credit: clinicaloptions.com

# Impact of SVR on Portal Hypertension

- Study of 48 wks of SOF + RBV for cirrhotic pts with portal hypertension (N = 50)
  - SVR12: 72% (n/N = 33/46)




*n = 8 pts with > 20% decrease.

Afdhal N, et al. J Viral Hepat. 2017;24:823-831.

Slide credit: clinicaloptions.com

# Additional Considerations

# Does Regression of Cirrhosis Have an Impact on Long-term Outcomes?

- Cohort study of cirrhotic pts with HCV who underwent IFN-based treatment from 1988-2001 (N = 96; median follow-up: 118 mos; SVR12: 41%)
- n = 18 (19%) had regression from F4 to F0-2 (n = 17 had SVR)

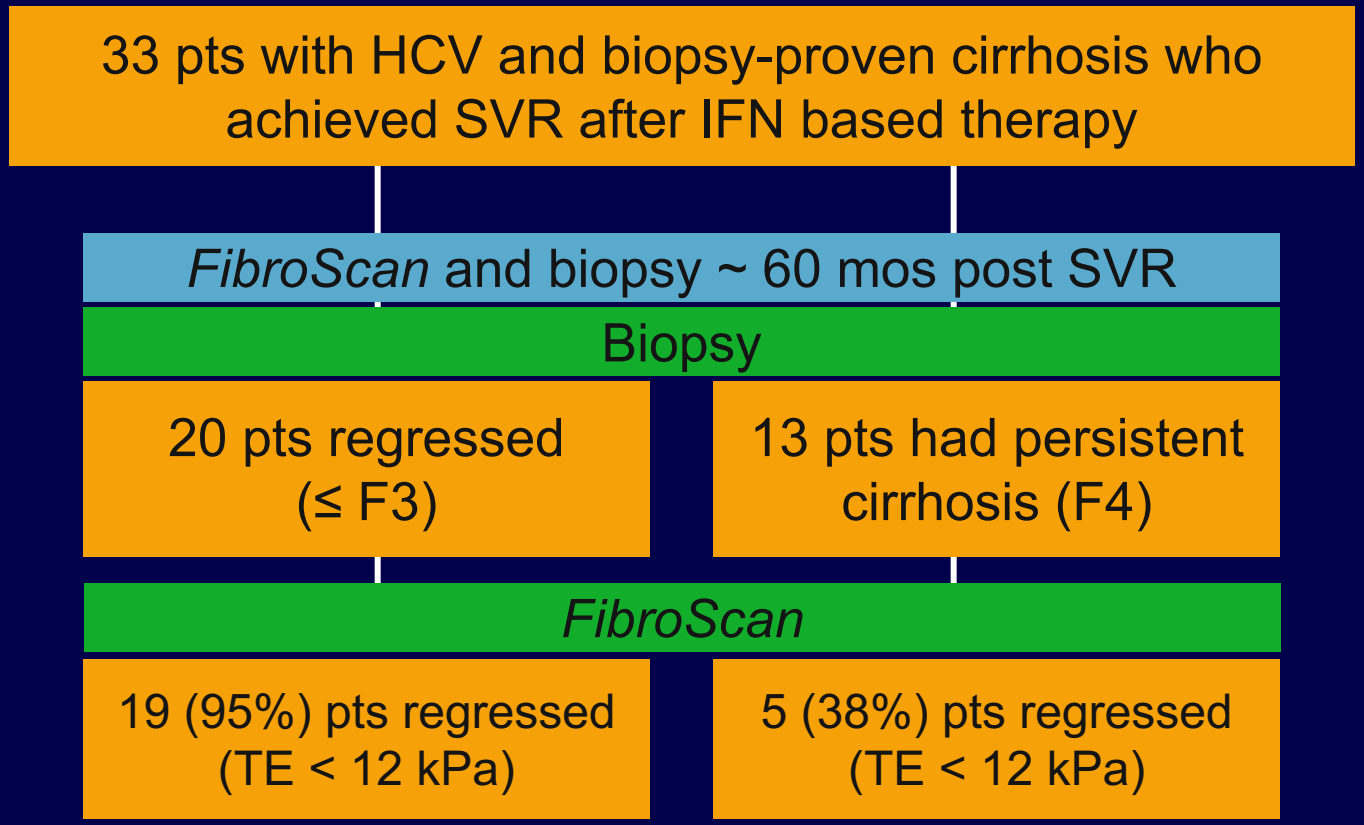
| Outcome, n (%) | SVR | | *P* Value | Cirrhosis Regression | | *P* Value |
|---|---|---|---|---|---|---|
| | No | Yes | | No | Yes | |
| Overall deaths | 17 (27.9) | 4 (11.4) | .075 | 20 (25.6) | 1 (5.6) | .110 |
| Liver-related death/transplantation | 19 (31.1) | 3 (8.6) | .012 | 22 (28.2) | 0 | .010 |
| Liver-related event | 23 (37.7) | 4 (11.4) | .009 | 27 (34.6) | 0 | .002 |
| **Hepatocellular carcinoma** | **14 (23.3)** | **3 (8.6)** | **.097** | **17 (22.1)** | **0** | **.036** |
| **Variceal bleeding** | **6 (9.8)** | **1 (2.9)** | **.42** | **7 (9)** | **0** | **.34** |
| Ascites | 10 (23.3) | 0 | .004 | 10 (16.9) | 0 | .197 |
| Spontaneous bacterial peritonitis | 2 (4.8) | 0 | .5 | 2 (3.4) | 0 | 1.0 |
| Hepatic encephalopathy | 7 (16.7) | 0 | .018 | 7 (12.1) | 0 | .33 |

- 10-yr survival: 100% with regression of cirrhosis; 74% without regression of cirrhosis

Mallet V, et al. Ann Int Med. 2008;149:399-403.

Slide credit: clinicaloptions.com

# How Accurate Is Transient Elastography to Monitor for Regression of Cirrhosis After SVR?




- Diagnostic accuracy of TE for diagnosing post-SVR cirrhosis: 61% sensitivity, 95% specificity
- Regression of *Fibroscan* scores to "sub-cirrhotic" levels does not ensure true cirrhosis regression

D'Ambrosio R, et al. J Hepatol. 2013;59:251-256.

Slide credit: clinicaloptions.com

# AASLD/IDSA Recommendations on Monitoring Fibrosis Regression in Pts Achieving SVR

- Risk of HCC in pts with advanced pretreatment fibrosis who demonstrate regression to minimal fibrosis post treatment is not known
- Such pts should continue to be monitored for HCC regularly
- No recommendations for routine assessment for regression in liver fibrosis after achieving SVR

AASLD/IDSA Guidelines. September 2017.

Slide credit: clinicaloptions.com

# Additional Considerations for Maintaining Liver Wellness After SVR

| Consideration | Key Points and Recommendations |
|---|---|
| Reinfection risk | ▪ Pts who inject drugs and those with high-risk sexual exposure at greatest HCV reinfection risk<br>▪ **Recommendations**: for pts with *ongoing risk* for HCV infection<br>– Counsel and educate on risk reduction<br>– **Test HCV RNA annually** |
| Alcohol use | ▪ Alcohol use associated with liver fibrosis progression and HCC risk with chronic HCV infection; less evidence in post-SVR setting<br>▪ **Recommendations**:<br>– Counsel avoidance of significant alcohol use in all pts and abstinence for pts with advanced liver fibrosis or cirrhosis |
| Obesity | ▪ Fatty liver disease can cause fibrosis/cirrhosis; diabetes associated with unfavorable liver-related outcomes<br>▪ **Recommendations**:<br>– Counsel lifestyle modifications, glycemic control |

AASLD/IDSA Guidelines. September 2017.
Jacobson IM, et al. Gastroenterology. 2017;152:1578-1587.

# Conclusions

- SVR associated with myriad clinical benefits
- Mandatory to continue HCC surveillance post SVR in pts with F3/F4 fibrosis; ultrasound every 6 mos
  - Consider assessing AFP levels as well for these pts
  - Less evidence to support continued screening of F0-F2 but remains a theoretical concern
- Indefinite screening for varices not warranted if varices absent at baseline: 1 more exam after SVR?
  - Surveillance of small varices if no other liver disease present requires further study but advisable
  - Large varices require ongoing management and surveillance
- Routine monitoring for fibrosis regression not the standard of care; further studies may change this
- For pts with ongoing risk for HCV infection after SVR, counsel and test HCV RNA annually

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