

# Managing After the Cure:

Hepatocellular Carcinoma, Fatty Liver Disease,  
and More

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# General Outcomes with AASLD-IDSA Recommended HCV Regimens for Genotype 1 Patients

	<b>SVR12 Rate (%)</b>	<b>Relapse Rate (%)</b>	<b>Discontinuations Due to Adverse Events (%)</b>
<b>Treatment-naïve</b>			
No cirrhosis	97-99	0-3	0-1
Compensated cirrhosis	88-100	<1-6	0-3
<b>PegIFN/RBV-experienced</b>			
No cirrhosis	95-100	0-5	0-3
Compensated cirrhosis	79-99	<1-19	0-3
<b>Decompensated cirrhosis</b>	81-92	8	3-17

AASLD-IDSA recommended regimens:

Treatment-naïve: sofosbuvir/velpatasvir, ledipasvir/sofosbuvir, elbasvir/grazoprevir, ombitasvir/paritaprevir/r + dasabuvir ± RBV, simeprevir + sofosbuvir, and daclatasvir + sofosbuvir.

PegIFN/RBV-experienced: sofosbuvir/velpatasvir, ledipasvir/sofosbuvir ± RBV, elbasvir/grazoprevir, ombitasvir/paritaprevir/r + dasabuvir ± RBV, simeprevir + sofosbuvir, and daclatasvir + sofosbuvir.

Decompensated cirrhosis (pre-liver transplantation): sofosbuvir/velpatasvir; ledipasvir/sofosbuvir ± RBV, daclatasvir + sofosbuvir ± RBV).

# SVR Is Great!

- SVR12 = Durable virologic cure. Long-term risk of relapse: ~0.1%
- Improves long-term clinical outcomes
  - **Stabilizes/improves liver fibrosis/cirrhosis**
  - **Lower liver-related and all-cause mortality**
  - **Decreased HCC**
- Improves quality of life
- Decreases infectivity/risk of spread in high-risk populations

BUT....

# SVR Does Not Do Everything

- Does not prevent reinfection—No immunity
- Does not eliminate HCC risk in advanced fibrosis/cirrhosis
- Does not prevent other liver diseases from progressing—Alcoholic and nonalcoholic fatty liver, others
- So all patients need post-SVR care and monitoring

# Long-Term Follow-up of HCV Patients Treated with DAA Regimens

- Prospective, observational cohorts

- **SVR registry: SVR12 achievers (n = 5433)**

Median follow-up: 71 weeks

- **Sequence registry: virologic failure patients (n = 536)**

Median follow-up: 44 weeks

- Maintained SVR: 99.7% (5,414/5,433)

- **Late virologic relapse: 0.1%**

- **HCV reinfection: 0.2%**

- Low rates of clinical disease progression

- Incidence of HCC

- **SVR registry: 0.3% (16/5433)**

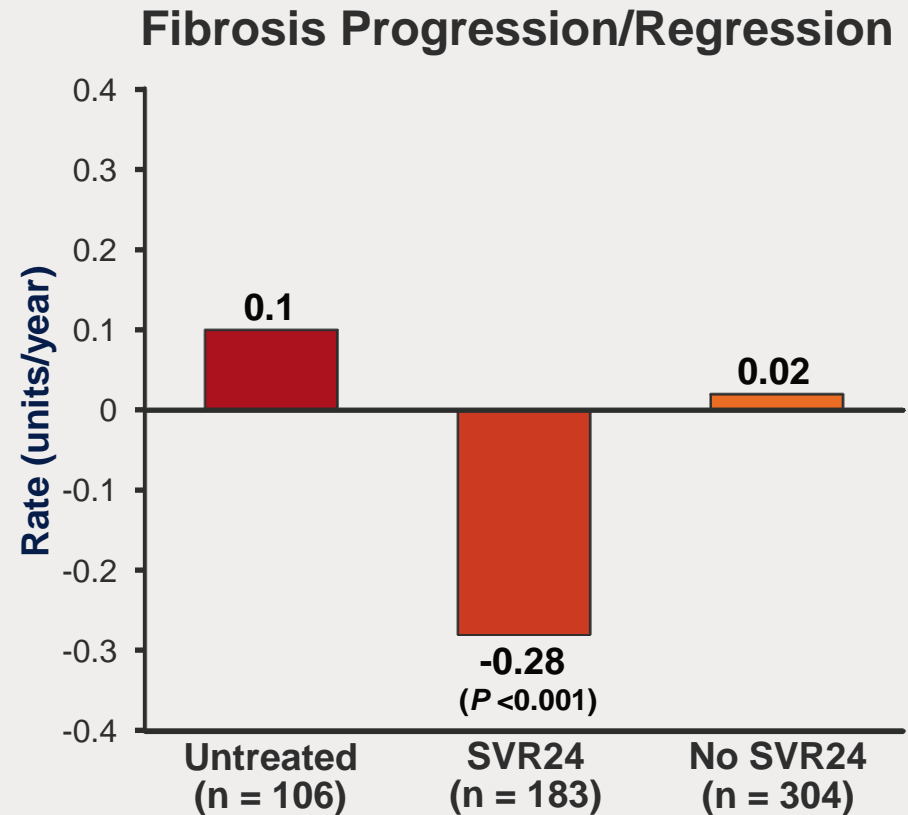
- **Sequence registry: 0.9% (5/536)**

## Registry Characteristics

	SVR (n = 5433)	Sequence (n = 563)
Median age (years)	54	54
Male (%)	63	78
White (%)	85	84
Cirrhotics (%)	20	22
HCV genotype (%)		
1	67	62
2	10	5
3	20	32
4	3	<1
5	<1	<1
6	<1	0

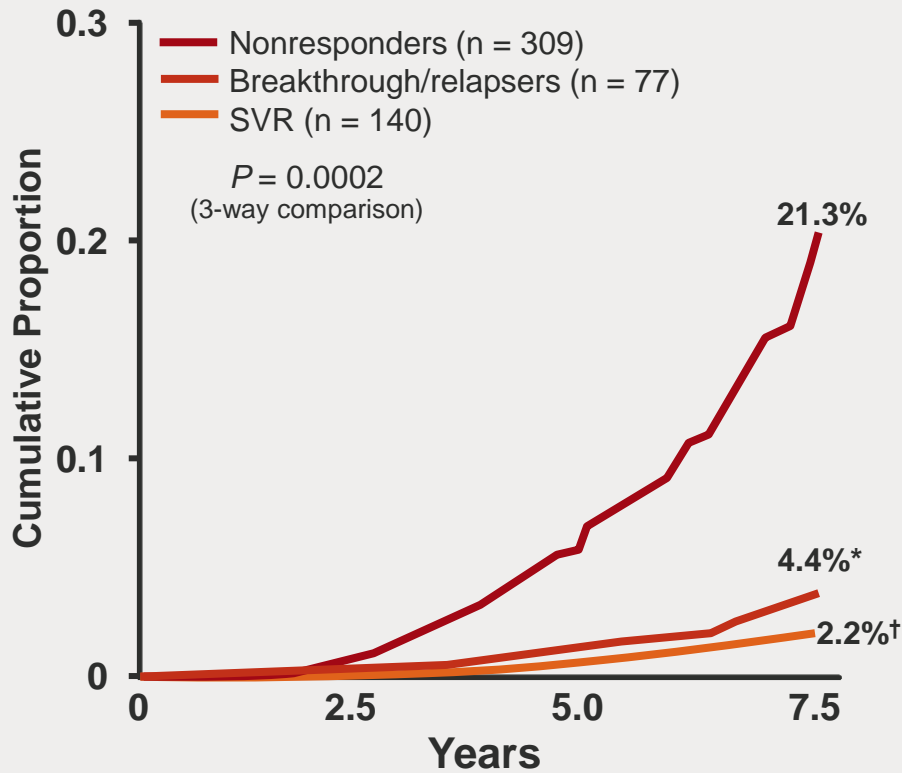
# Histologic Improvement of Fibrosis in HCV Patients with SVR24 to INF Therapy

- Retrospective cohort study (n=593)
  - **Paired biopsy (1987-1997)**  
Median 3.7 years apart
  - **IFN started within 6 months of initial biopsy**
- Baseline fibrosis
  - **F0-F1: 33%**
  - **F2-F3: 57%**
  - **F4: 10%**
- Fibrosis score may remain the same over several years even though gradual regression is demonstrated in liver tissue specimens

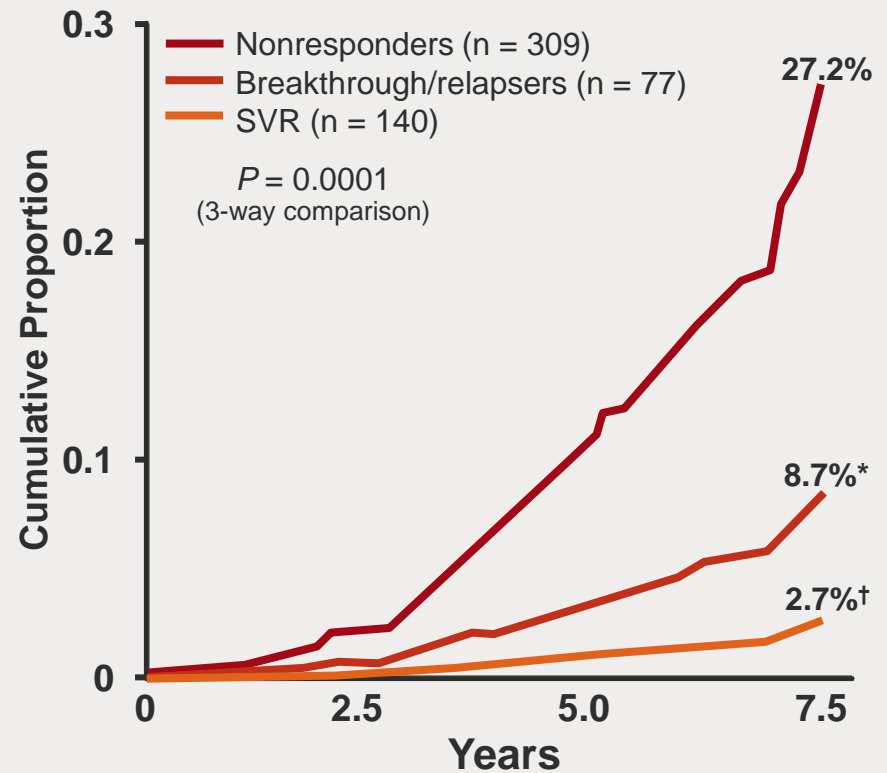


# HALT-C: Impact of Achieving SVR on Mortality and Liver-Related Outcomes

## All-cause Death or Transplantation



## Liver-related Outcomes

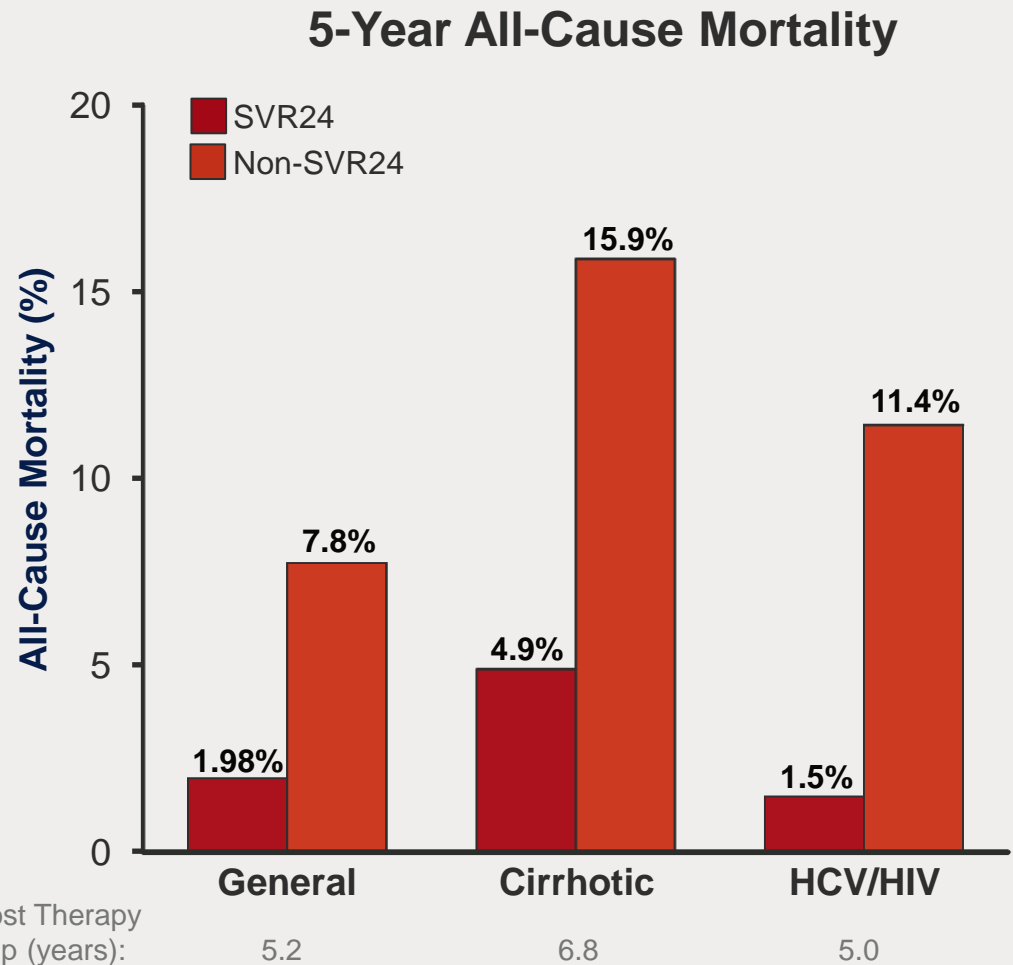


Prospective, randomized trial of previous IFN-based treatment failures with advanced bridging fibrosis (Ishak fibrosis stages 3-4) or cirrhosis (stages 5-6) via biopsy.

\* $P \leq 0.05$  and † $P < 0.001$  vs nonresponders.

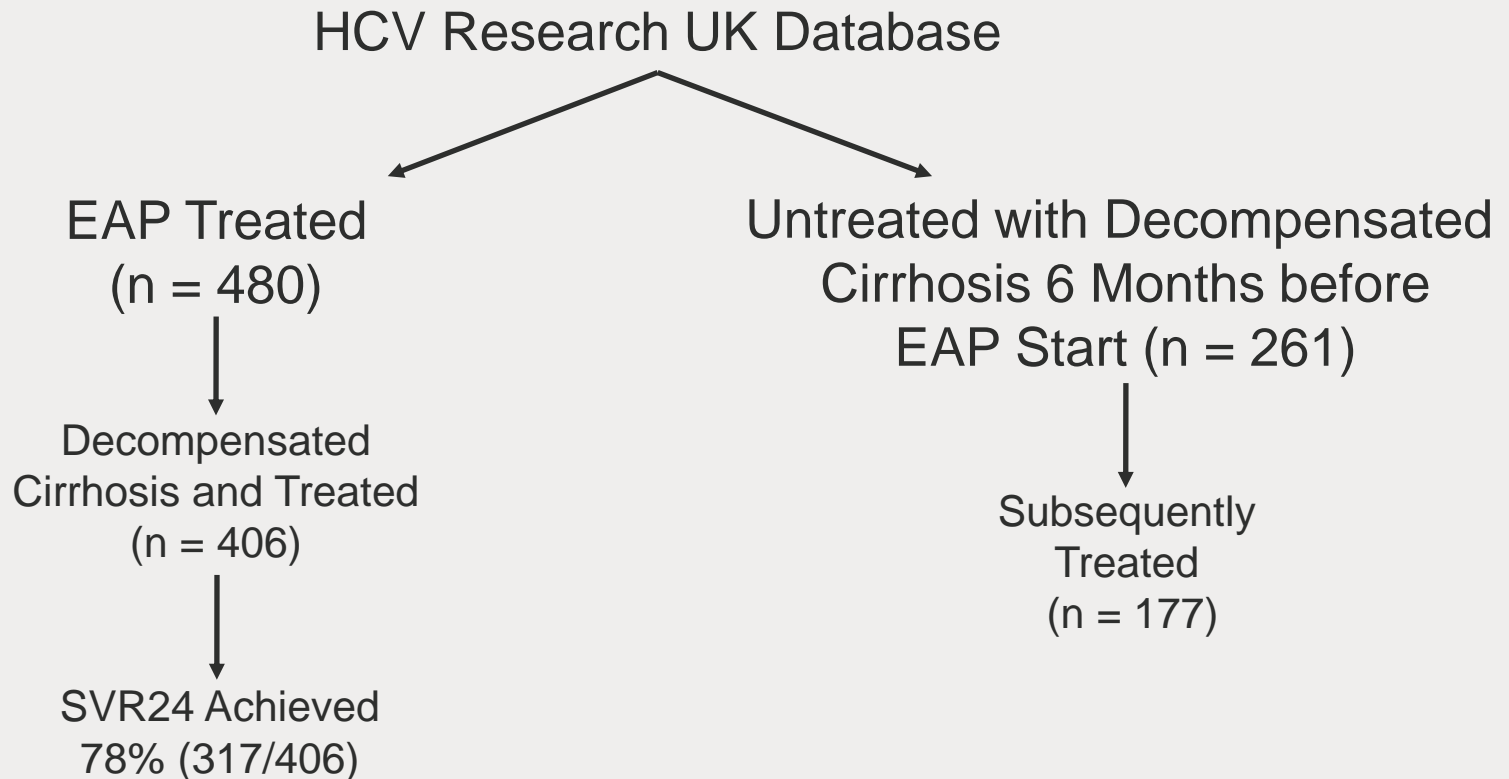
# 5-Year Risk of All-Cause Mortality: SVR24 vs Non-SVR24

- Significant survival benefit with achieving SVR24
  - **Adjusted hazard ratios for mortality: SVR vs non-SVR (95% CI)**
    - General: 0.33 (0.23-0.46)
    - Cirrhotic: 0.26 (0.18-0.37)
    - HCV/HIV: 0.21 (0.10-0.45)
- Research need
  - **Prospective data with all-oral, IFN-free DAA regimens**





# UK Expanded Access Program: Treatment of HCV Patients with Advanced Cirrhosis



EAP: expanded access program.

Baseline demographics were similar among those initially treated and not treated for HCV.

Treatments: ledipasvir/sofosbuvir  $\pm$  RBV or daclatasvir  $\pm$  sofosbuvir + RBV for 12 weeks.

Outcomes: clinical events during and after treatment.

Short term: months 0-6 (SVR [3 months during and 3 months post-treatment] vs untreated patients).

Longer term: months 6-15.

# UK Expanded Access Program: Treatment of Decompensated HCV Patients

- Benefits seen in the treated group during the first 6 months
  - **Significant reduction of liver-related events ( $P < 0.05$ )**
- Over 15-month follow-up, adverse events decreased in SVR24 patients
- Predicting long-term benefits
  - **Early MELD change was not predictive of long-term outcome**
  - **Achieving SVR24 in Child-Pugh B patients led to improvement in adverse events for the majority**
  - **Only a minority of Child-Pugh C patients derived long-term benefits**

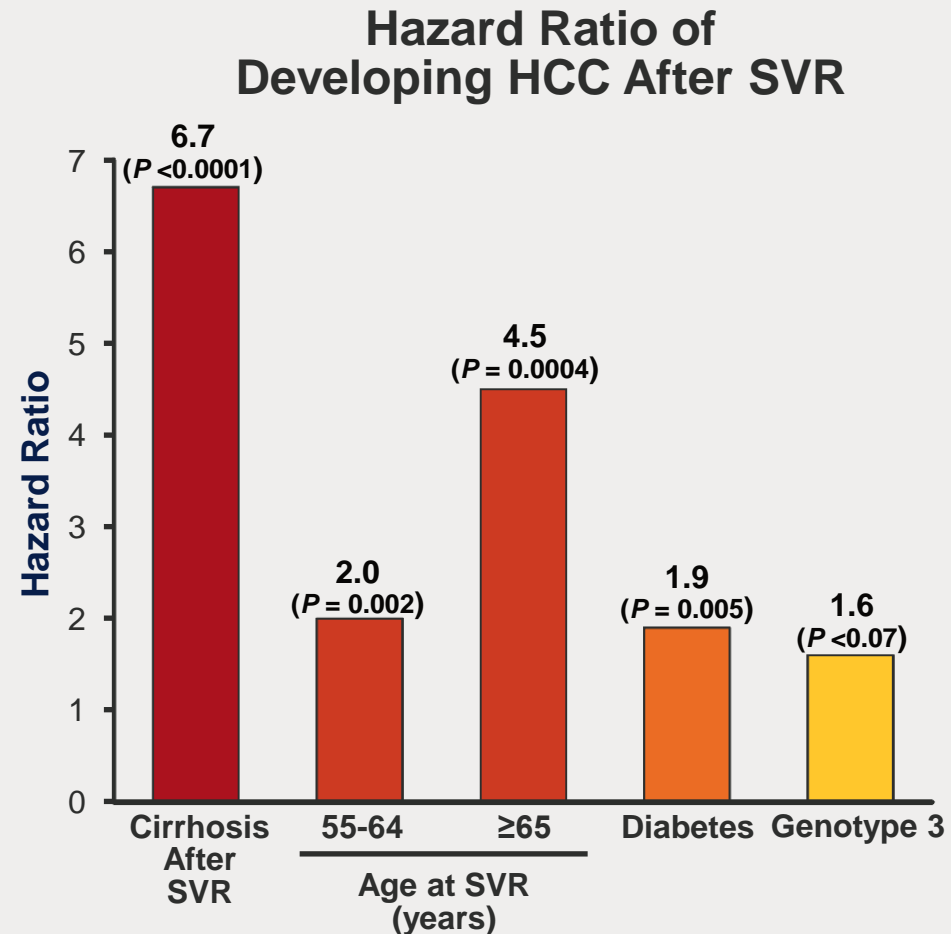
## Adverse Events

	First 6 Months		Over 15 Months
	All Treated (n=406)	Untreated (n=261)	Treated With SVR24 (n=317)
Deaths (%)	3	5	3
Decompensation (%)	18*	28	5
HCC (%)	4	4	2
Liver transplant (%)	7	4	4

\* $P < 0.05$ .

# VA HCV Clinical Case Registry (1999-2009): Incidence and Predictors of HCC after SVR

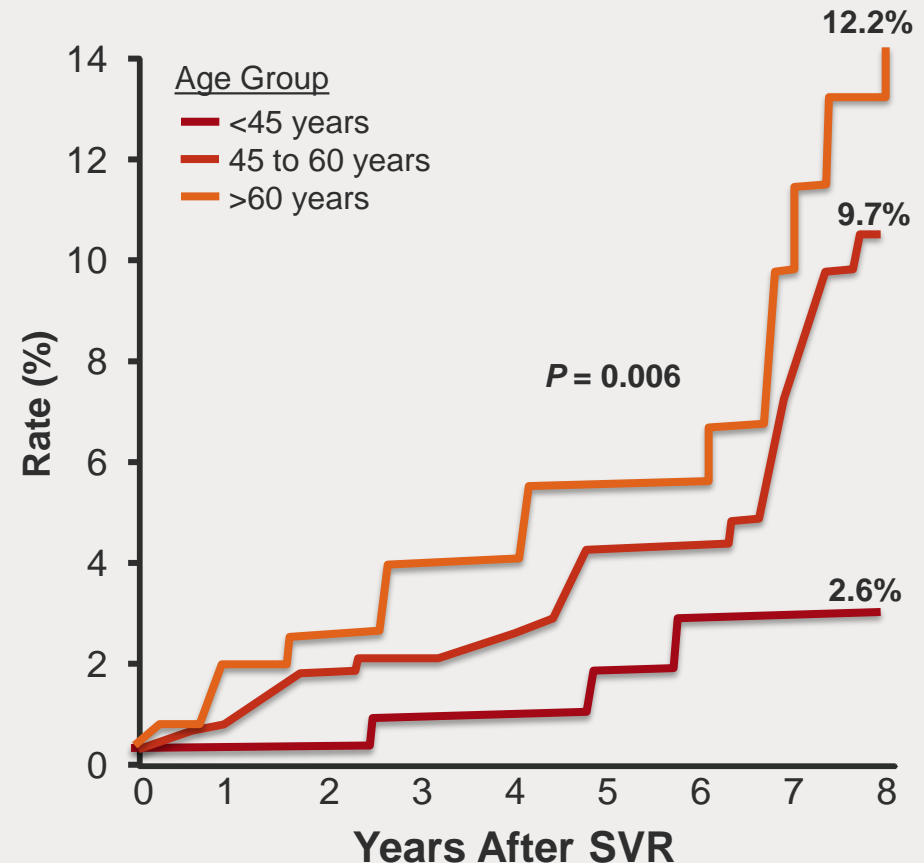
- Retrospective cohort study (n = 10,738)
- Incidence of HCC (per 1,000 patient-years)
  - **With SVR: 3.27 (0.327%/year)**
  - **No SVR: 13.2 (1.32%/year)**
- SVR cohort (no HCC, pegIFN + RBV)
  - **Mean age (53 years; 12% >60 years of age), male (95%), black (13%), non-Hispanic white (64%), Hispanic (3%)**
  - **New HCC cases post SVR (n = 100 during 30,562 person-years, median 2.8 years after SVR)**
- Significant predictors of HCC after SVR
  - **Cirrhosis after SVR, older age (>55 years), diabetes, HCV genotype 3 (vs 1)**



# Risk of HCC Remains after SVR in HCV Patients with Advanced Hepatic Fibrosis

- Meta-analysis (n = 1000)
  - 10 cohorts, individual patient data
  - SVR with IFN-based therapy
  - Bridging fibrosis or cirrhosis
  - No HIV or HBV coinfection
- 51 events of HCC over 5.1 years of follow-up
- Patients with HCV-induced cirrhosis who achieve SVR remain at risk for HCC
- Risk increased with age, severity of liver disease, and presence of diabetes mellitus

## Cumulative HCC by Age Group



# Liver-Related Morbidity and Mortality in Patients Who Achieved SVR

- Many studies show there is a nonzero risk of hepatocarcinogenesis after achieving SVR
  - **Cumulative incidence after SVR**
    - 5 years: 2.3% to 8.8%
    - 10 years: 3.1% and 11.1%
  - **Risk in noncirrhotic patients requires further long-term follow-up, including patients in Western countries**
- Risk remains long after HCV is cleared
  - **One study found 50% of HCC cases developed  $\geq 7$  years after SVR**
- HCC risk may be multifactorial
  - **Long-standing exposure to this potentially carcinogenic virus may be a primary factor for liver cancer during chronic HCV infection**

Li DK, et al. *Cancer*. 2015;121:2874-2882.

D'Amrosio R, et al. *Int J Mol Sci*. 2015;16:19698-19712.

# Pre-SVR Risk Factors Associated with Development of HCC in SVR Patients

- The most well-established risk factor is advanced fibrosis or cirrhosis
- Other risk factors identified
  - **Diabetes mellitus**
  - **Older age**
  - **Male gender**
  - **Alcohol use**
- Management of comorbidities once HCV is cured
  - **May play an important role in minimizing risk of HCC development**
  - **Need to work up and manage abnormal LFTs, NAFLD, ETOH**

# 2011 AASLD Guidelines for HCC Surveillance in Patients with Chronic HCV

- Surveillance is deemed cost-effective if the expected HCC risk exceeds 1.5% per year
- AFP determination lacks adequate sensitivity and specificity for effective surveillance (and for diagnosis)
- HCC surveillance has to be based on ultrasound examination
- Recommended screening interval is 6 months
  - **Diagnosis of HCC should be based on imaging techniques and/or biopsy**

# Challenges for HCC Surveillance in HCV Patients after Achieving SVR

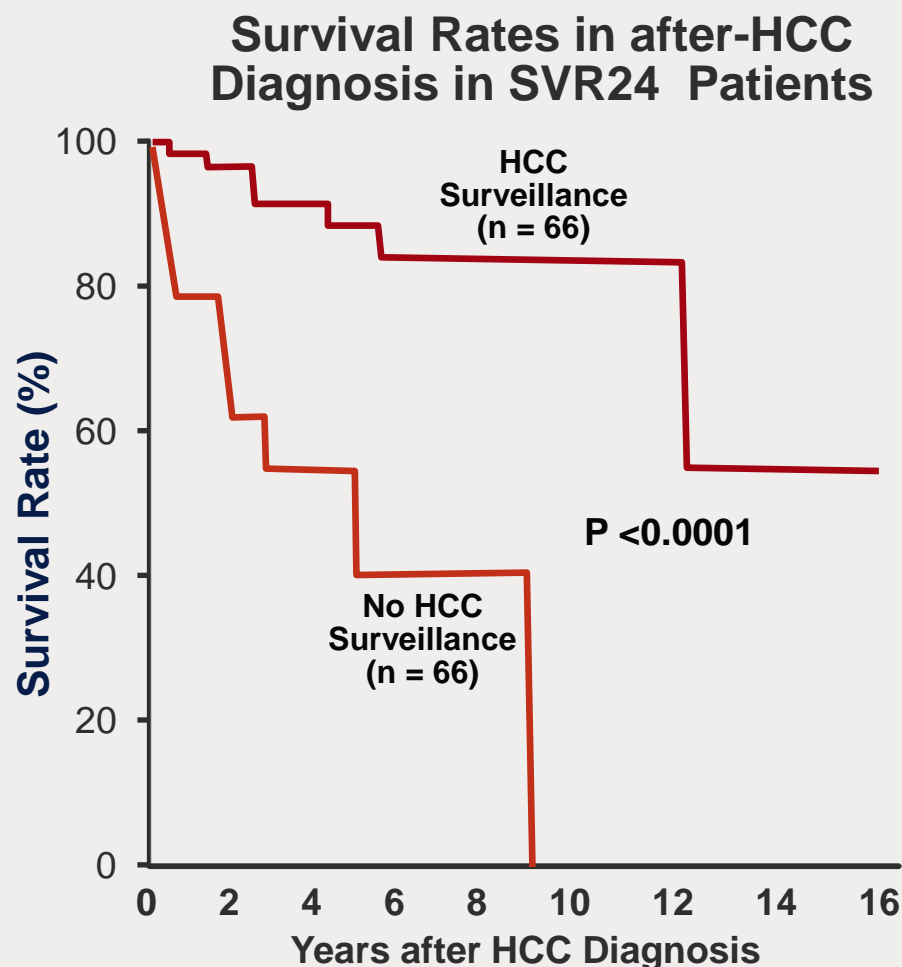
- Surveillance is deemed cost-effective if the expected HCC risk exceeds 1.5% per year
  - **A rate higher than most estimates for SVR patients**
  - **Population of SVR patients will expand with all-oral, IFN-free, DAA therapy**
  - **12% of new HCV-related HCC cases are diagnosed via screening in the US**
  - **<20% of patients with cirrhosis who develop HCC have undergone regular surveillance**
- Unclear whether or not to continue screening patients who achieve SVR
  - **Risk of disease progression is reduced but not eliminated**
  - **No direct prospective comparison of regular post-SVR screening and usual care**



# Prognosis of HCC Based on Surveillance Status in HCV Patients Achieving SVR24

- Retrospective, multi-center study (n = 2152; 1998-2014)
  - **HCC patients after SVR24 with IFN-based therapy (3.9%, 83/2152)**  
Mean time between SVR24 and HCC diagnosis: 6.7 years
- No HCC surveillance
  - **Lower survival rates**
  - **More advanced disease at detection**  
Larger tumors  
Multiple HCC and portal vein invasion  
BCLC class C or D (40%)  
TNM stage III or IV (60%)

HCC surveillance: every 3 or 6 months  
(no difference in survival based on surveillance interval).



# Achieving SVR Does Not Protect Against HCV Reinfection/Recurrence

- Given the lack of protective immunity
  - **Ongoing risk behaviors can lead to reinfection after successful treatment**
  - **Immunocompromised patients may be at risk of HCV recurrence**
- Reinfection may compromise long-term benefits of treatment for patients with ongoing risk behaviors

# Risk of HCV Recurrence with HCV after Achieving SVR

- Meta-analysis of HCV recurrence after SVR (n = 9049; 1990-2015)
  - **Adults with SVR12 or SVR24 with IFN-based therapy**
  - **≥6 months follow-up post-SVR**
  - **Not included: recurrence after spontaneous clearance, liver transplant recipients**
- HCV recurrence
  - **Overall and due to late relapse or reinfection**
- HCV monoinfection
  - **Low-risk population (n = 43 studies, 7,969 patients)**
  - **High-risk population (n = 14 studies, 771 patients)**
- HCV/HIV (n = 4 studies, 309 patients)

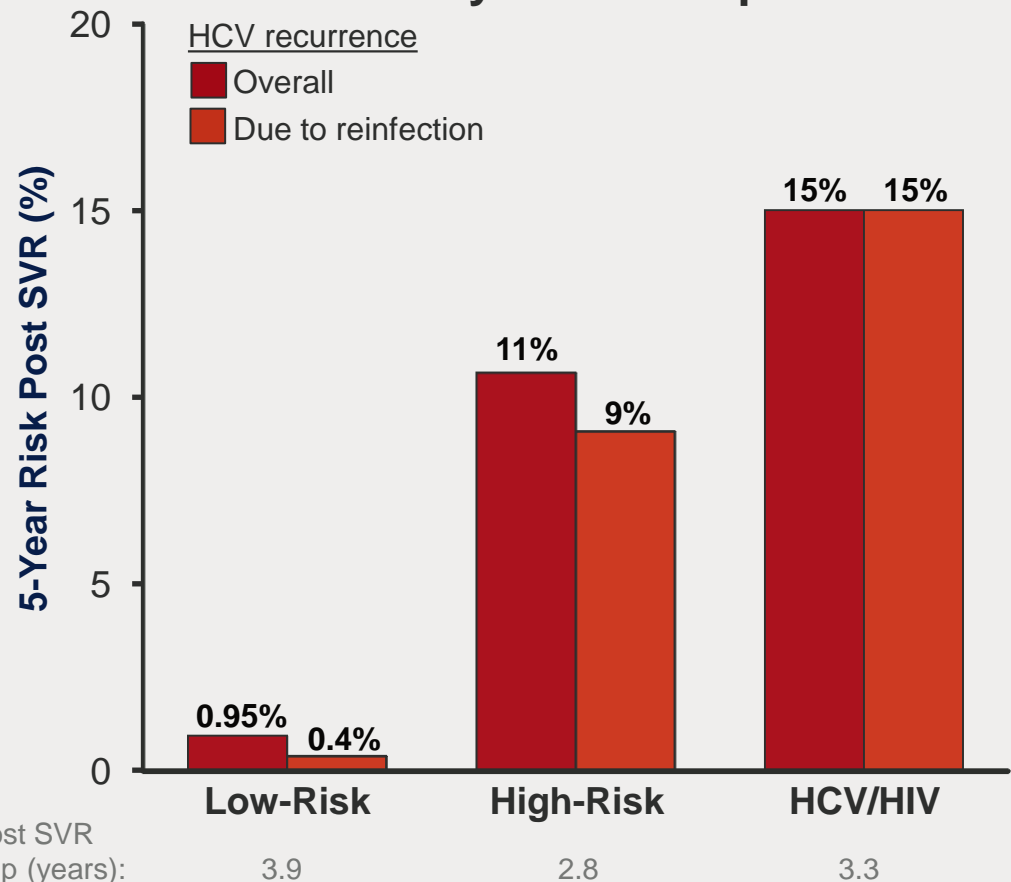
Risk factors for reinfection: current or former PWID, imprisonment, MSM.

# 5-Year Risk of HCV

## Reinfection/Recurrence Post SVR

- HCV recurrence in high-risk and HCV/HIV groups was driven by reinfection in those with high-risk behaviors
- HCV reinfection rates (events/1,000 person-years)
  - **Low-risk population: 0**
  - **High-risk population**  
19.1 (95% CI 11.4-28.2)
  - **HCV/HIV population**  
32.0 (95% CI 0-123.5)
- Research need
  - **Prospective data with all-oral, IFN-free DAA regimens**

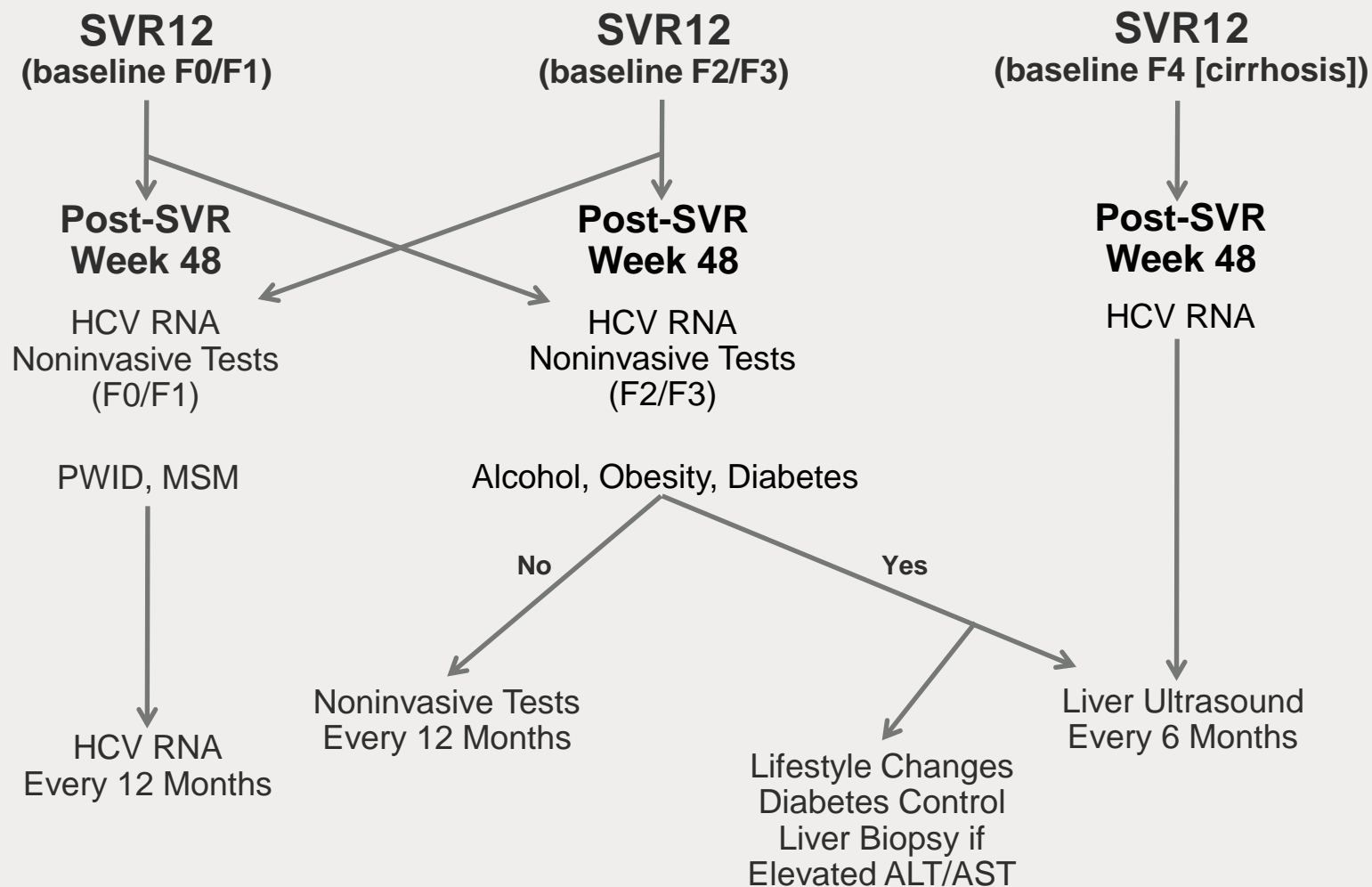
### 5-Year Risk of HCV Recurrence by Risk Group



# Post SVR Monitoring

- All patients
  - **Monitor LFTs at least annually**
  - **HCV RNA at least once, more if risk factors. No HCV antibodies (positive forever)**
  - **Work-up/treat abnormal LFTs**
- Mild fibrosis (F0-2)
  - **No HCC screening due to very low risk**
  - **No liver-related restrictions on lifestyle if LFTs normal**
- Advanced fibrosis/cirrhosis
  - **HCC screening q 6 months**
  - **Alcohol avoidance/restriction**

# Considerations for Follow-Up of SVR Patients



# WHO: Global HCV Strategy (2016-2030)

- By 2020
  - **50% reduction in HCV incidence**
  - **10% reduction in HCV-related mortality**
- By 2030
  - **70% reduction in HCV incidence**
  - **60% reduction in HCV-related mortality**
- The strategy calls for a major increase in diagnosis of chronic infection, and for treatment coverage of eligible persons by 2030

Lanini S, et al. *Clin Microbiol Infect.* 2016;22:833-838.  
World Health Organization. May 2016.

# Eradication of HCV in the US: Nationwide Epidemiologic and Surveillance Considerations

- Assess and monitor HCV incidence in high-risk populations
  - **Emerging epidemics in young people who use prescription opioids, sexually active HIV-infected MSM, and PWID**
- Identify new outbreaks and emerging epidemics
  - **Quickly assess the magnitude of new transmission patterns as they emerge**
- Assess and monitor HCV prevalence in high-risk populations
  - **Homeless, the incarcerated, PWID**



# Beyond the Cure: Conclusions

- HCV patients with SVR
  - **Improved survival and liver-related morbidity compared with non-SVR patients**
- Long-term follow-up studies in SVR patients
  - **Regression of fibrosis varies and risk of liver-related complications remains, even in the absence of cirrhosis**
- Patients with cirrhosis are still at risk of HCC
  - **Comorbidities (eg, diabetes, obesity, or alcohol consumption) may play a major role in the outcome of liver disease in SVR patients without cirrhosis**
- Monitoring after a cure of HCV infection remains a major challenge
- Risk of reinfection is high in PWID and MSM
- The elimination of HCV in the US is technically feasible
  - **Will require a sustained national commitment to reach, test, treat, cure, and prevent every case of HCV**

HIV Management  
Hepatitis Management

# THE NEW YORK COURSE

