INSTITUTE OF HUMAN VIROLOGY

UNIVERSITY of MARYLAND SCHOOL OF MEDICINE

Hepatitis C and Liver Cancer:

Success^of New Therapies and Treatments

And Challenges

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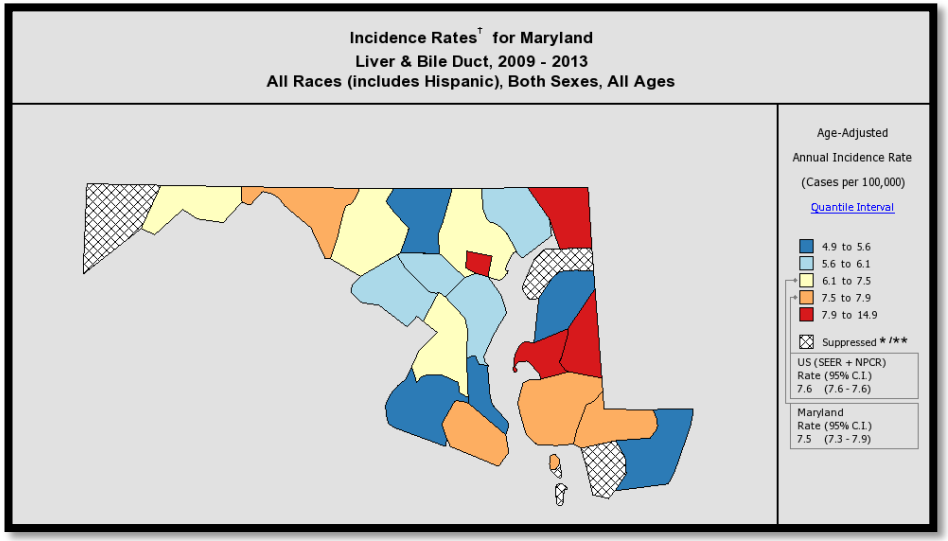
BACKGROUND

- **Hepatocellular carcinoma is rising in incidence globally and tripled in the US over the last 3 decades.**
- **Hepatocellular carcinoma is the *5th* most common cancer and *2nd* most common cause of cancer mortality worldwide**
- **Viral hepatitis is a significant risk for developing HCC**
- **Hepatitis viruses may have direct and indirect effects of hepatic carcinogenesis**

LIVER CANCER

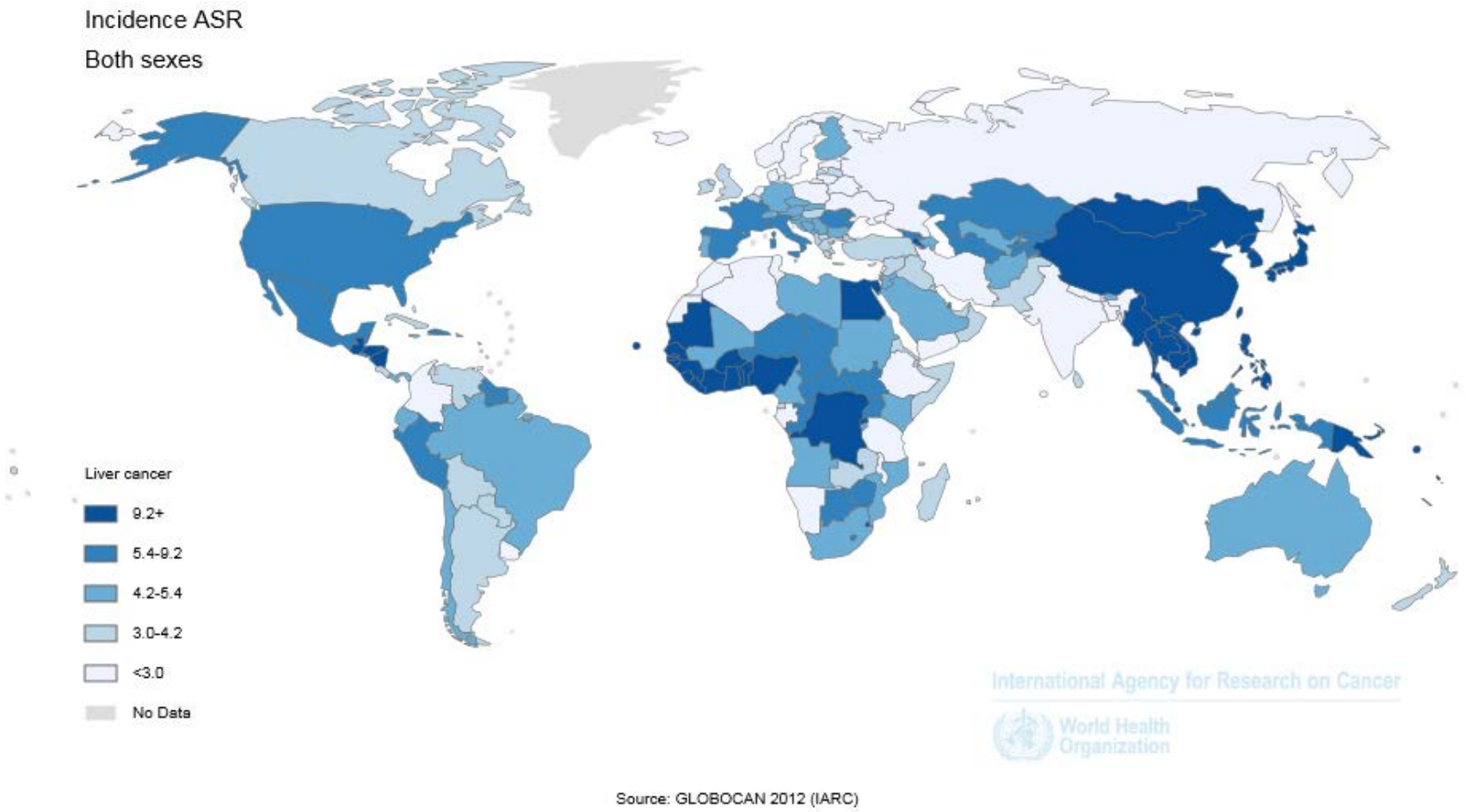
- MD Mortality Trend : Rising 4.1%/ year since 2004*
- MD Comparable to US Incidence Rate 7.9 versus 7.8/100,000 (2010-2014)*
- MD Comparable to US Mortality Rate 6.5 versus 6.3/100,000 (2014)*
- Stage distribution and 5 Year Survival
  - 43%, 31% local
  - 27%, 11% regional
  - 18%, 3% distant
- Risk factors:

  Chronic Hepatitis B and C,
  Cirrhosis, EtOH, Obesity, Diabetes
  Aflatoxin, Toxins, Anabolic steroids,
  Tobacco use, parasites ***
- Populations at risk:
  - 45+ years, males
  - Asian Americans, Pacific Islanders, Hispanics



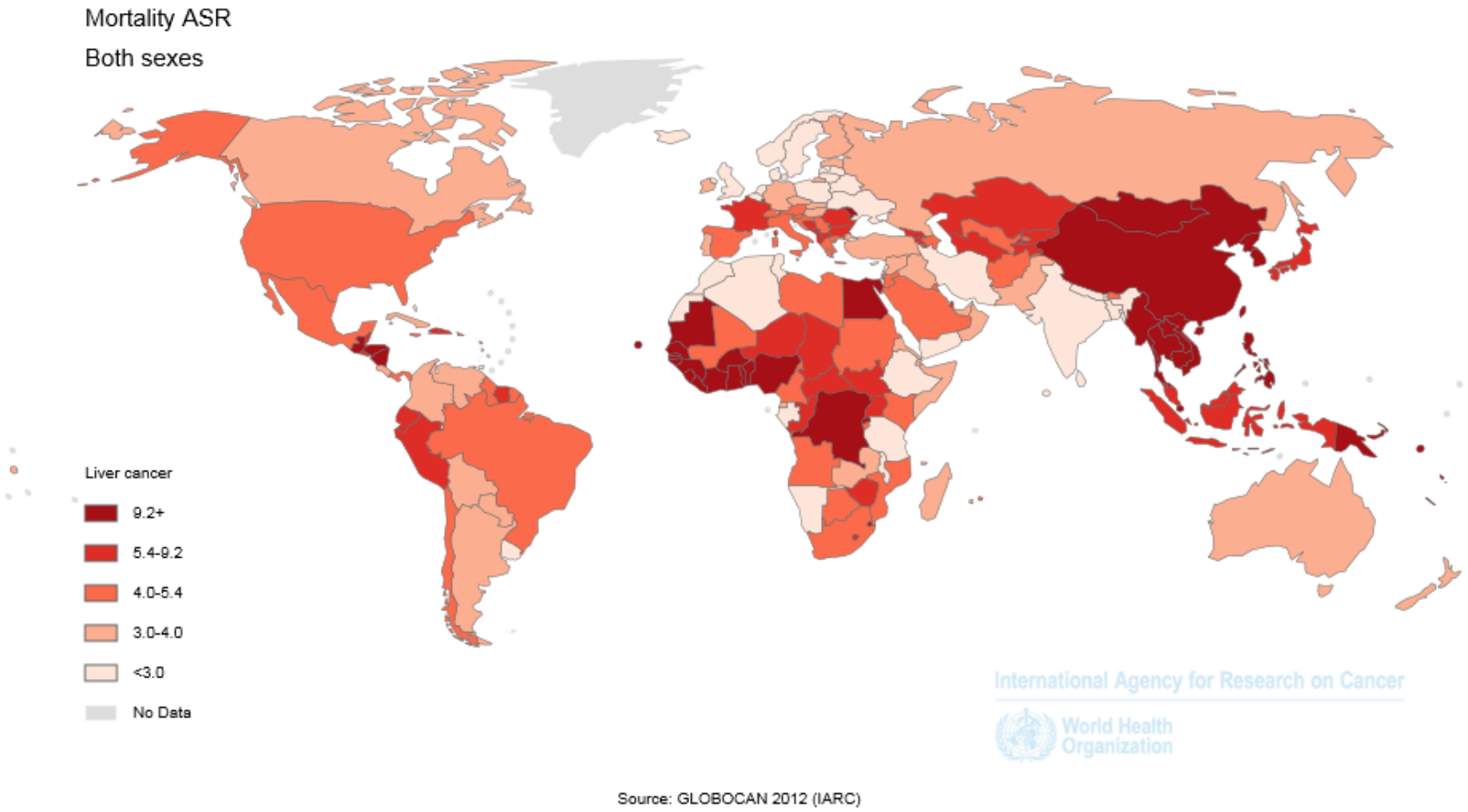
*Cancer Control P.L.A.N.E.T. ** SEER *** ACS

INCIDENCE OF LIVER CANCER



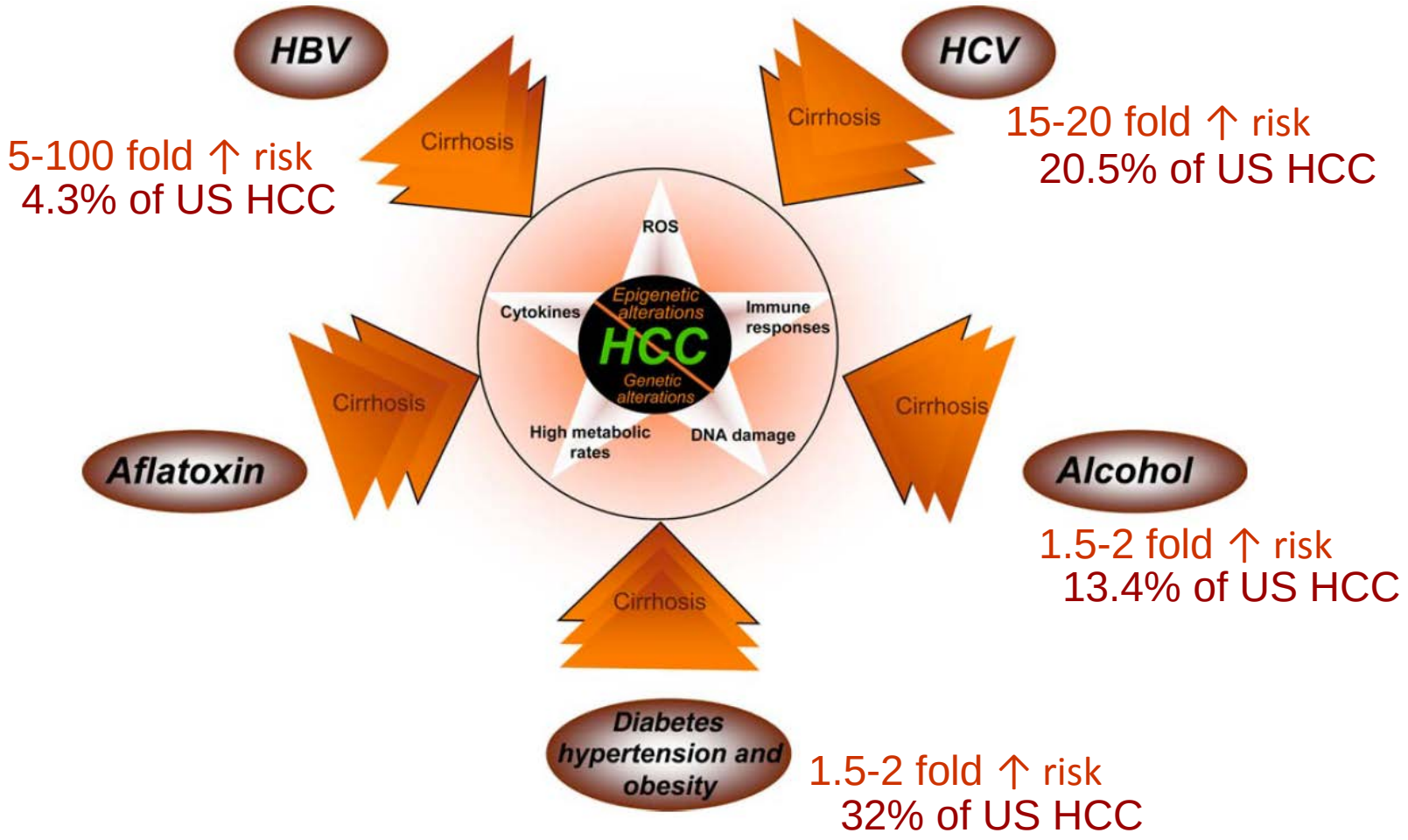
Accessed from the WHO International Agency on Research on Cancer on 11/2/2017
Available from http://globocan.iarc.fr/Pages/Map.aspx

MORTALITY OF LIVER CANCER



Accessed from the WHO International Agency on Research on Cancer on 11/2/2017
Available from http://globocan.iarc.fr/Pages/Map.aspx

RISK FACTORS FOR HCC

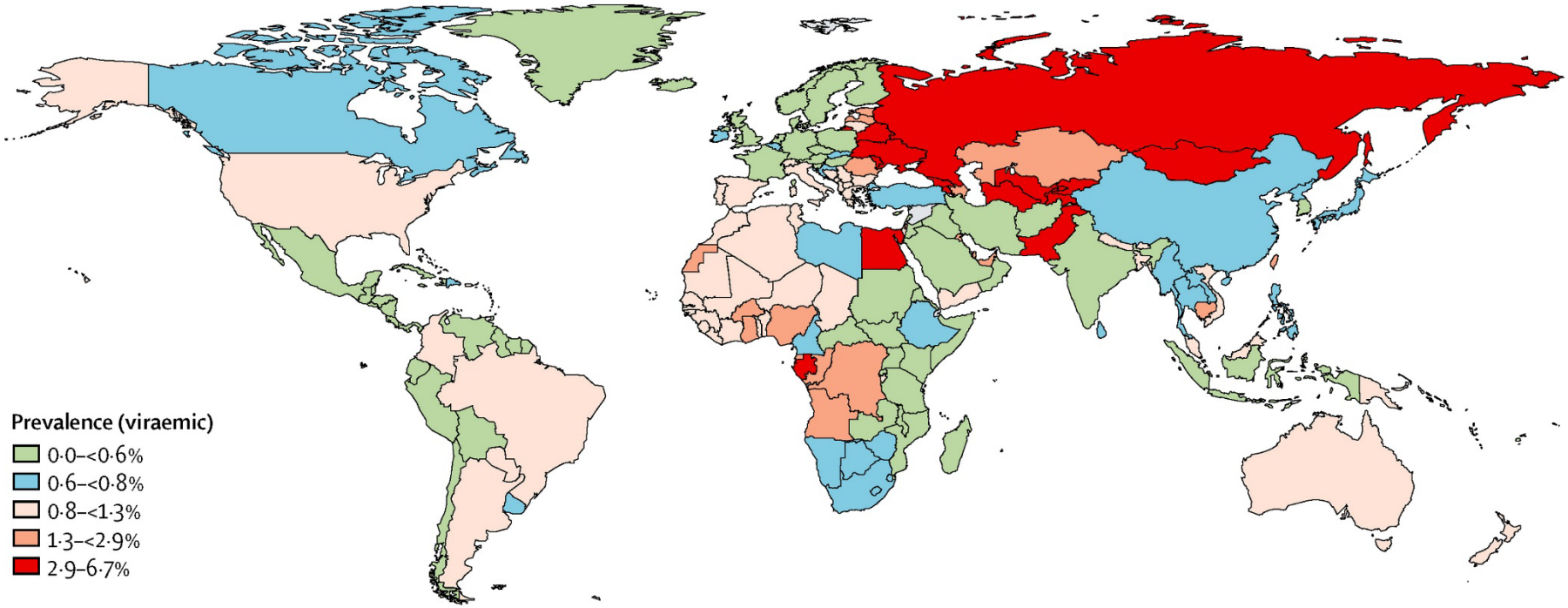


Adapted from Herceg Z and Paliwal A *Mutation Research* 2011; White *Clin Gastroenterol Hepatol* 2012; Makarova-Rusher *Cancer* 2016; Ramadori *Cancers* 2017

ALCOHOL, HEPATITIS AND HCC

Author/country	Alcohol		Hepatitis C	
	Cases/control (number)	Odds ratio (95% CI)	Cases/control (number)	Odds ratio (95% CI)
Tagger et al,[17] Italy				
Daily alcohol (*g/d*)				
<40	31/219	1.0 (reference)	47/18	26.1 (12.6–54)
40–80	27/157	1.5 (0.7–2.9)	32/7	62.6 (23.3–168)
>80	102/203	7.3 (4.0–13.1)	42/5	126 (42.8–373)
Hassan et al,[5] United States				
Daily alcohol				
No	40/136	1.0 (reference)		19.1 (4.1–89.1)
Yes	75/94	2.4 (1.3–4.4)		53.9 (7.0–415.7)
<80 g/day	33/63	1.7 (0.9–3.7)		
>80 g/day	42/31	4.5 (1.4–14.8)		
Yu et al,[3] Taiwan				
Alcohol use				
No	53/81	1.0 (reference)	8/2	6.1 (1.2–30.1)
Yes	60/44	2.1 (1.2–3.7)	6/0	Unable to calculate

ESTIMATED 71 MILLION PEOPLE WITH HCV



Polaris Observatory HCV Collaborators. *Lancet Gastroenterol Hepatol*. 2017;2:161-176.

DISCOVERY OF HEPATITIS C

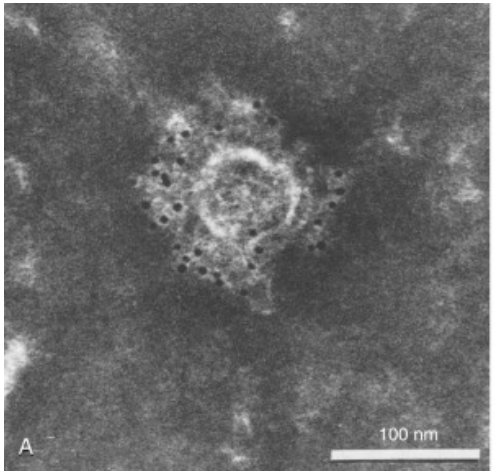
TRANSFUSION-ASSOCIATED HEPATITIS NOT DUE TO VIRAL HEPATITIS TYPE A OR B

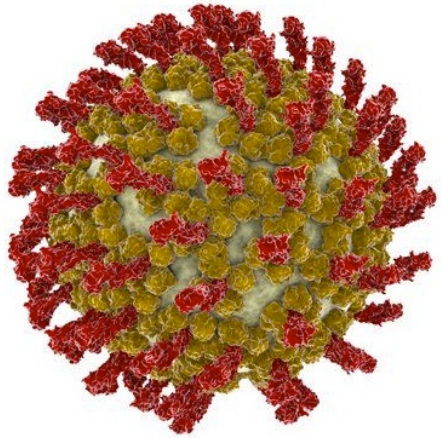
Stephen M. Feinstone, M.D., Albert Z. Kapikian, M.D., Robert H. Purcell, M.D.,
Harvey J. Alter, M.D., and Paul V. Holland, M.D.

Abstract Twenty-two patients who had an episode of transfusion-associated hepatitis not positive for hepatitis B antigen were examined for development of antibody to hepatitis A and B antigens, cytomega-lovirus and Epstein-Barr virus. Antibody response to the 27-nm virus-like hepatitis A antigen was measured by immune electron microscopy. In none of the 22 patients studied did serologic evidence of infection with hepatitis A virus develop during the study period. Nine of the 22 patients had antibody responses to cytomegalovirus, but it was difficult to relate these seroconversions to their hepatitis. In addition, all 22 patients had pre-existing antibody to the Epstein-Barr virus. It seems likely that at least a proportion of such antigen-negative transfusion-as-sociated hepatitis is caused by other infectious agents, not yet identified. (N Engl J Med 292:767-770, 1975)

Feinstone SM et al N Engl J Med (1975); 292(15):767-70

VIRAL FEATURES





- RNA virus
  - Positive single stranded
  - Family Flaviviridae
  - Genus Hepacivirus
    - Related genus Flavivirus- Dengue, Yellow Fever
  - In vivo replication: hepatocytes
  - Highly error prone, trillions of virions/day

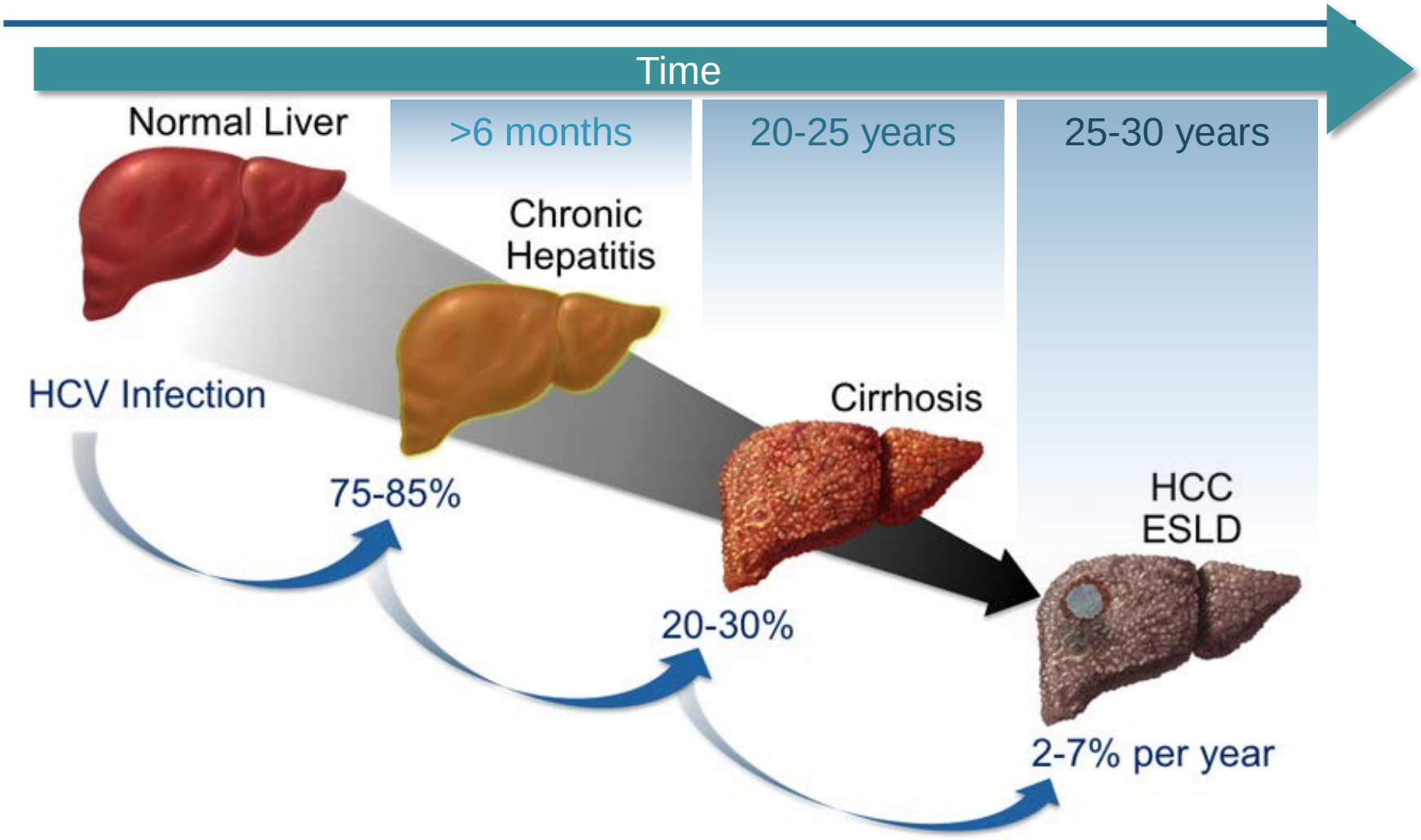
Electron microscopic image of hepatitis C virus (HCV) virions..
(From Kaito M, Watanabe S, Tsukiyama-Koham K, et al. Hepatitis C virus particle detected by immunoelectron microscopic study. J Gen Virol. 1994;75:1755-1760.)

UNLIKE HBV AND HIV, HCV CAN BE CURED

VIRUS	HIV	Hepatitis C	Hepatitis B
Population	1 million	5 million	2 million
Genome	RNA	RNA	DNA
Mutation Rates	Very high	Very high	High
Virions produced daily	10^{10}	10^{12}	10^{13}
Drug Targets	Multiple	Multiple	One
Genetic archive	Yes	NO	Yes
Ability to Cure	No (Integrated viral DNA)	YES (No DNA integration)	No (cccDNA)
Current therapeutic goal	Lifelong suppression	Cure: Clearance from plasma and liver	Lifelong suppression

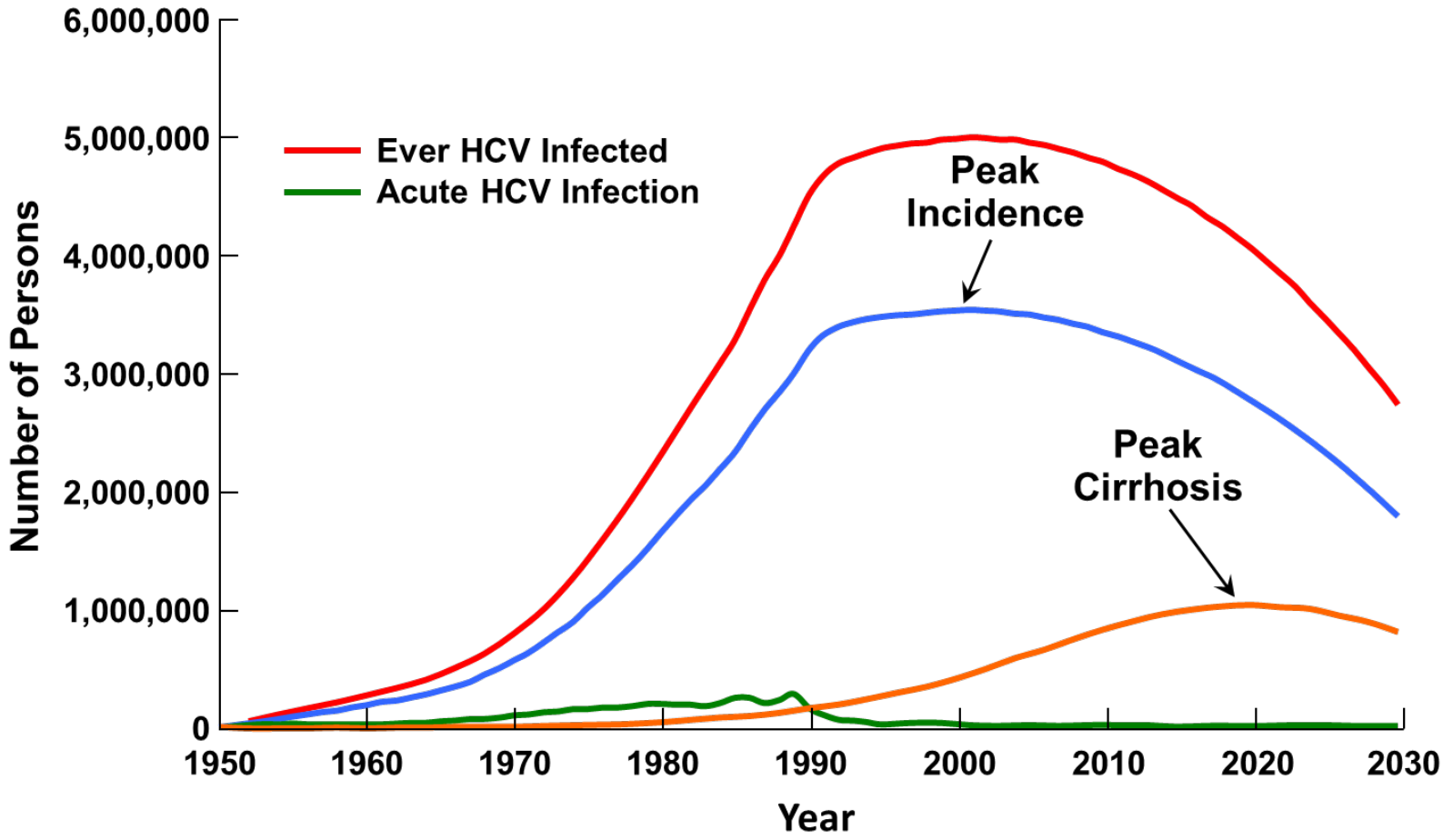
Adapted from Soriano V, JAC 2008; 62

NATURAL HISTORY OF HEPATITIS C



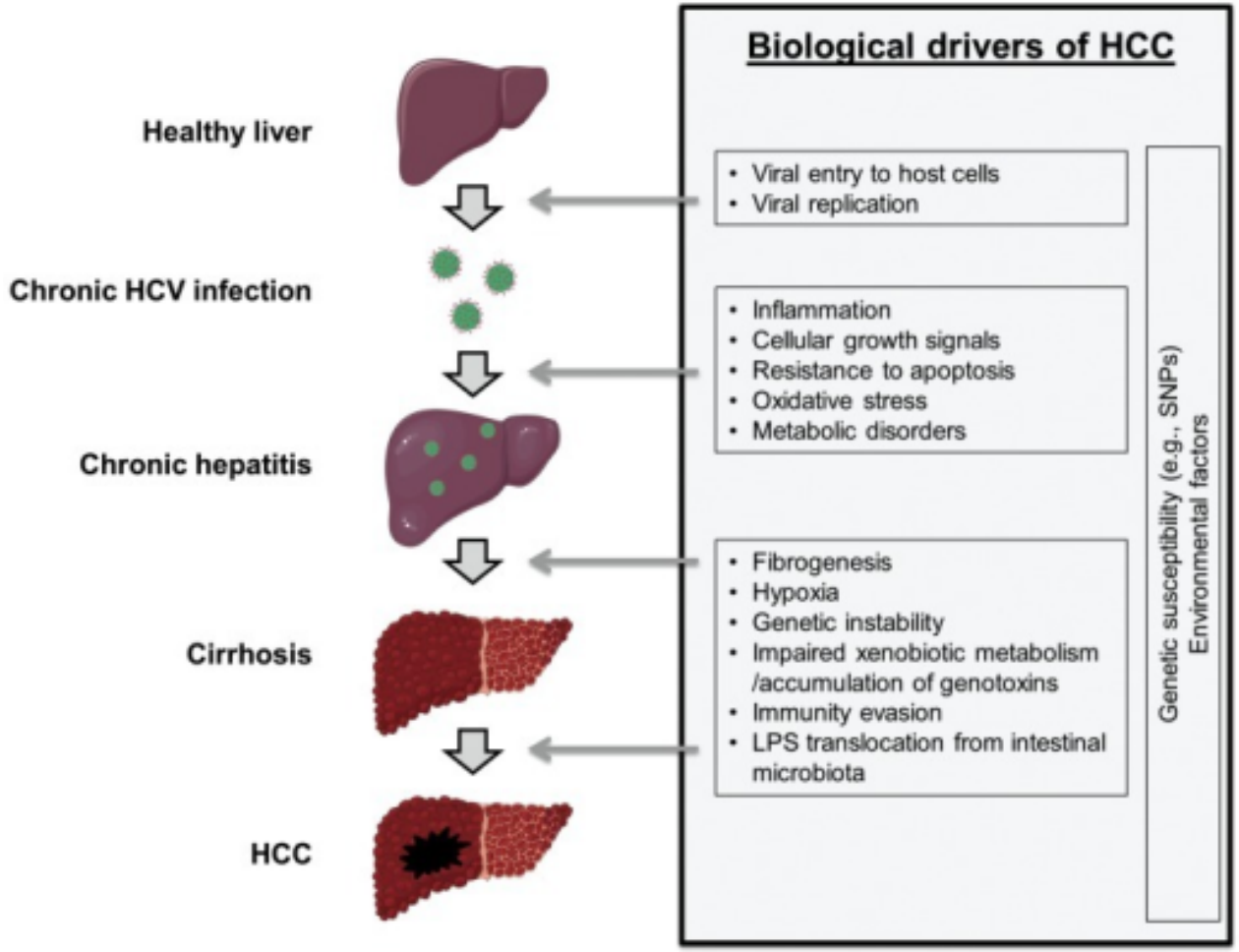
Adapted from hepatitisc.uw.edu

THE CHANGING FACE OF HCV IN US



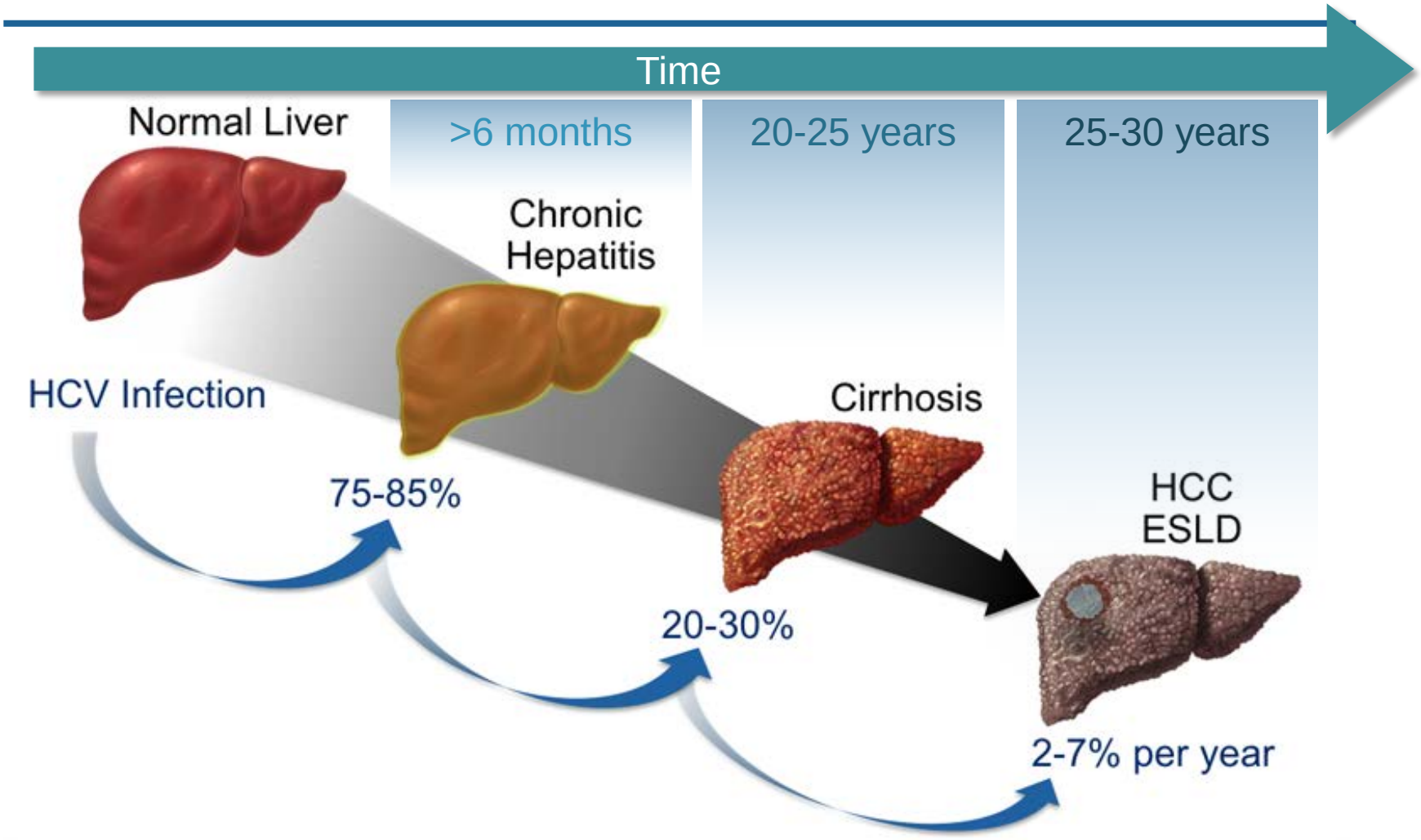
Adapted from Davis GL et al Gastroenterol 2010;138:513-521

BIOLOGICAL DRIVERS OF HCC



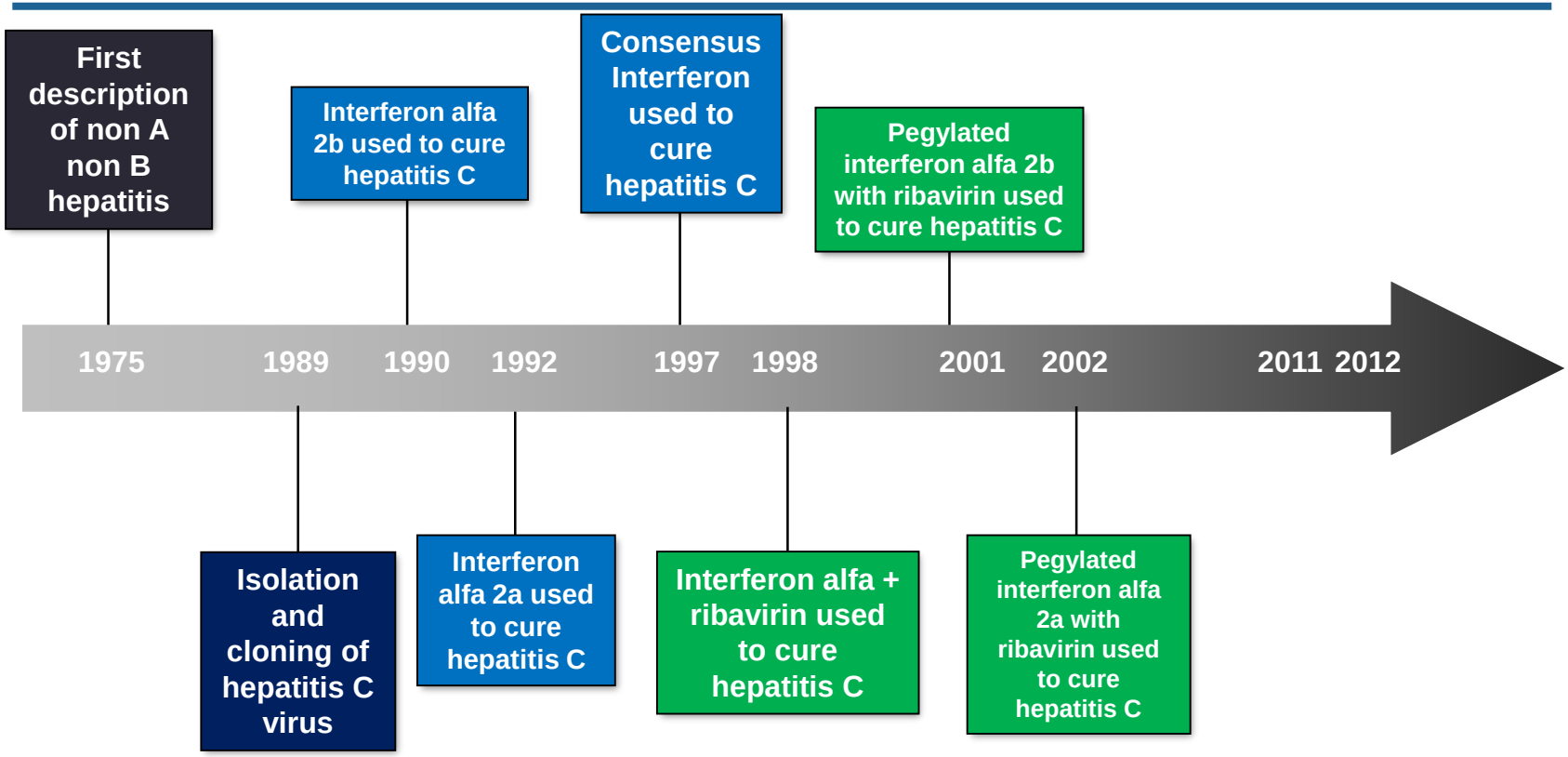
Goossens N, Hoshida Y - *Clin Mol Hepatol* (2015)

NATURAL HISTORY OF HEPATITIS C



Adapted from hepatitisc.uw.edu

EVOLUTION OF HEPATITIS C TREATMENT



Kohli A. …Kottilil S. JAMA 2014

HCV CURE IMPROVES OUTCOME

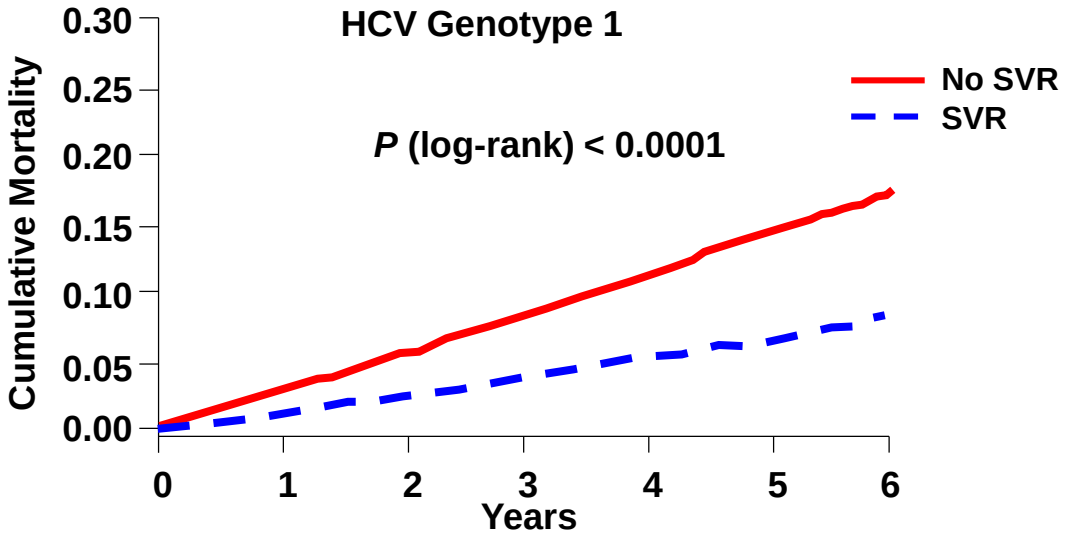
Sustained Viral Response (SVR)

- **Durable**
  - **99% stay HCV negative for > 10 years**
- **Leads to improved histology**
- **Leads to clinical benefits**
  - **Decreased decompensation**
  - **Prevents *de novo* esophageal varices**
  - **Decreased hepatocellular carcinoma**
  - **Decreased mortality**

Bruno S, et al Hepatology 2010;51:2069-2076.
Veldt BJ, et al. Ann Intern Med 2007;147:677-684.
Maylin S, et al. Gastroenterology 2008; 135:821-9.

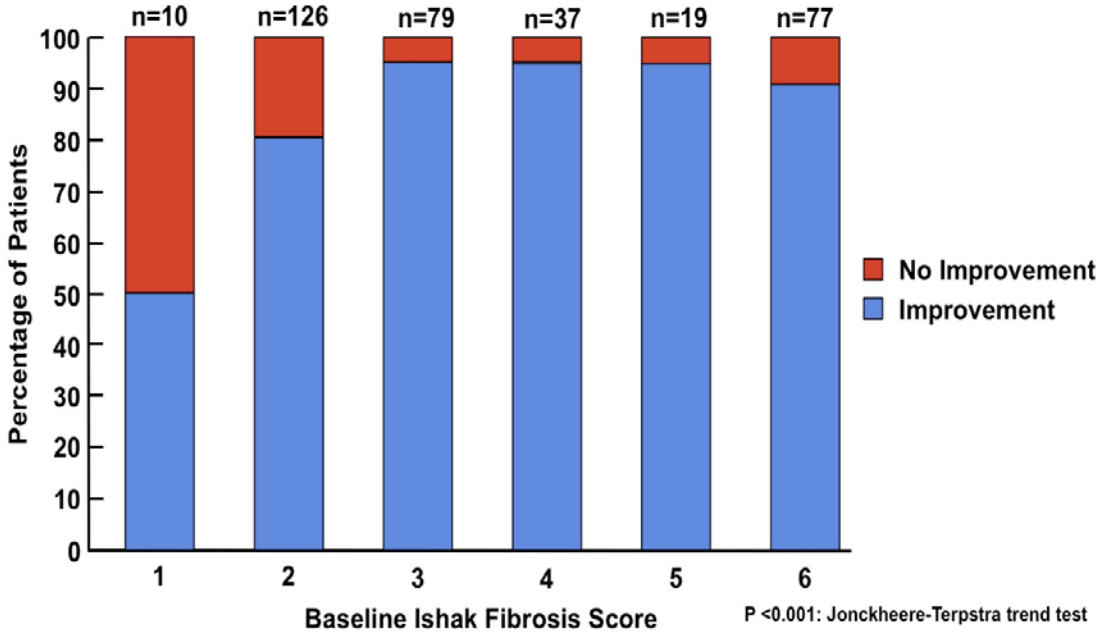
SVR REDUCES ALL-CAUSE MORTALITY

21,839 treated patients in VA Clinical Case registry; 16,864 with follow up
High rates of co-morbidities (DM, HTN, ETOH, CAD)
SVR: GT1: 35%, GT2: 72%, GT3 62%



Backus L, et al. Hepatology 2010, 52: Abstract 213

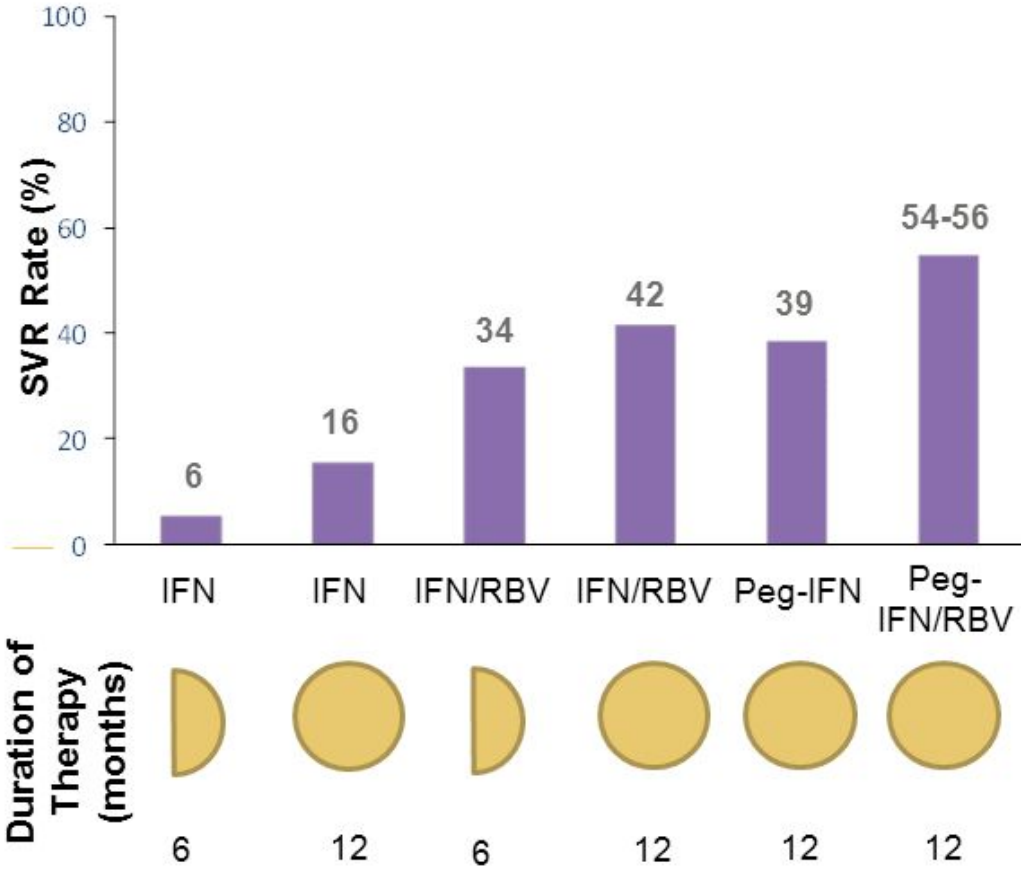
HCV TREATMENT IMPROVES FIBROSIS



74% of Patients with Cirrhosis at Baseline Were No Longer Cirrhotic at Year 5

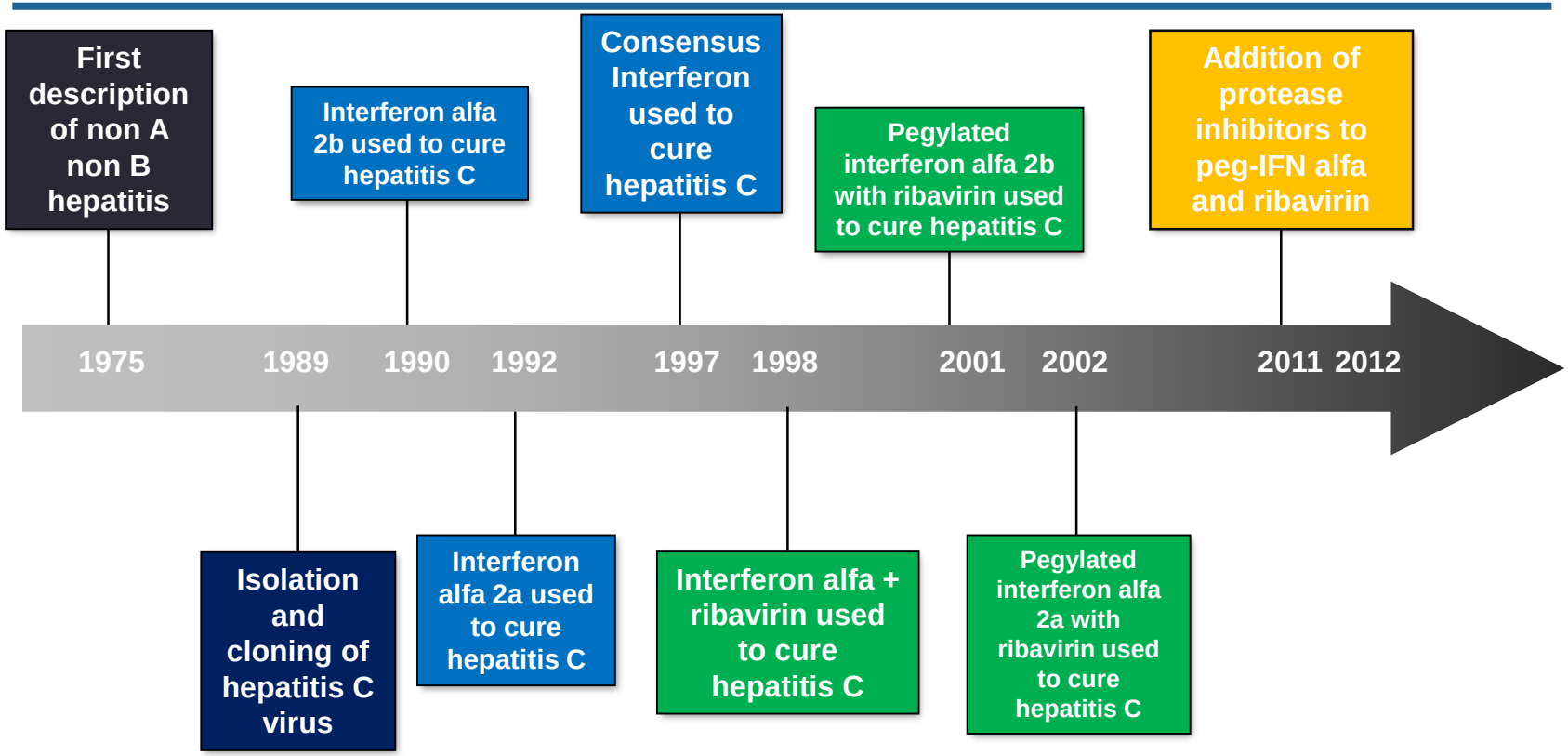
Marcellin, P et al. Lancet 2013; 381(9865):468-75

ADVANCES IN HEPATITIS C TREATMENTS



Adapted from Gilead Sciences, Inc., 2015, Manns et al *Nature Reviews Drug Discovery*, 2013, and the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting April 27-28 2011.

EVOLUTION OF HEPATITIS C TREATMENT



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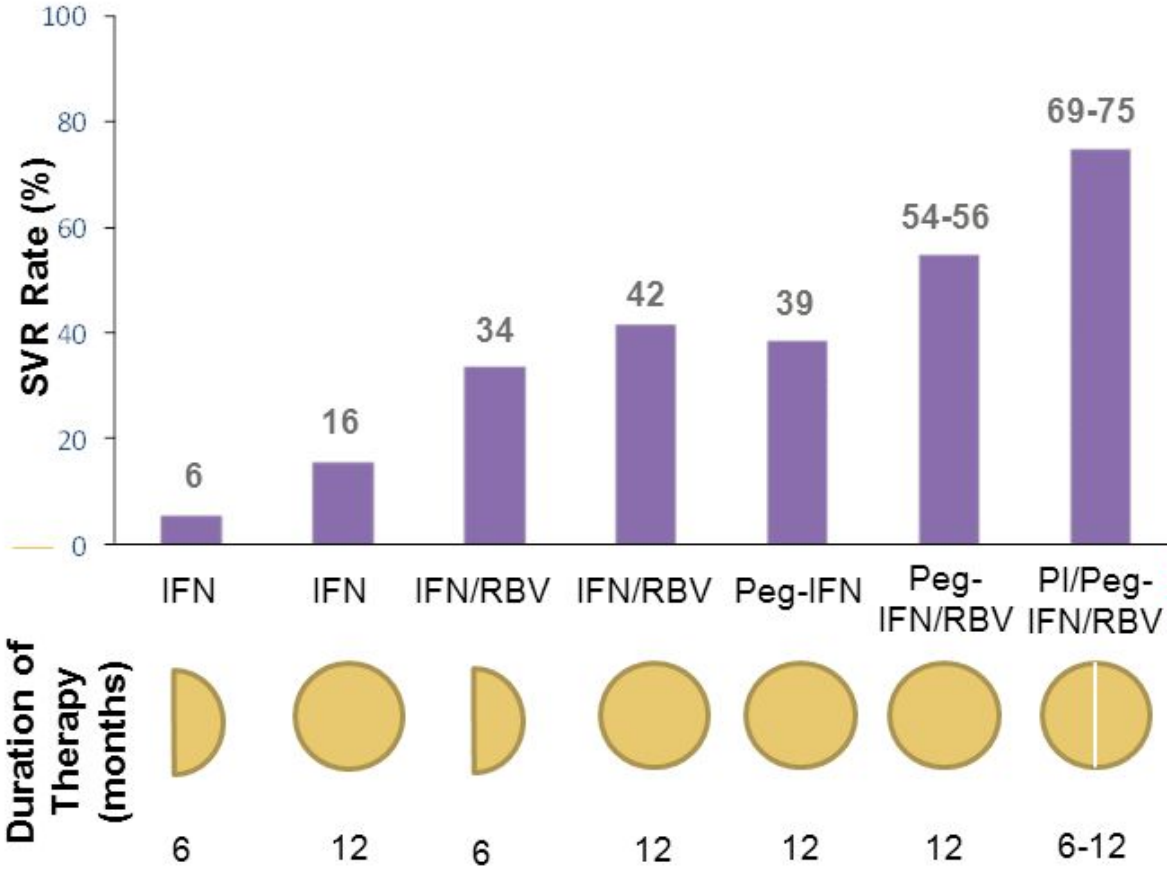
ADVANCES IN HEPATITIS C TREATMENTS



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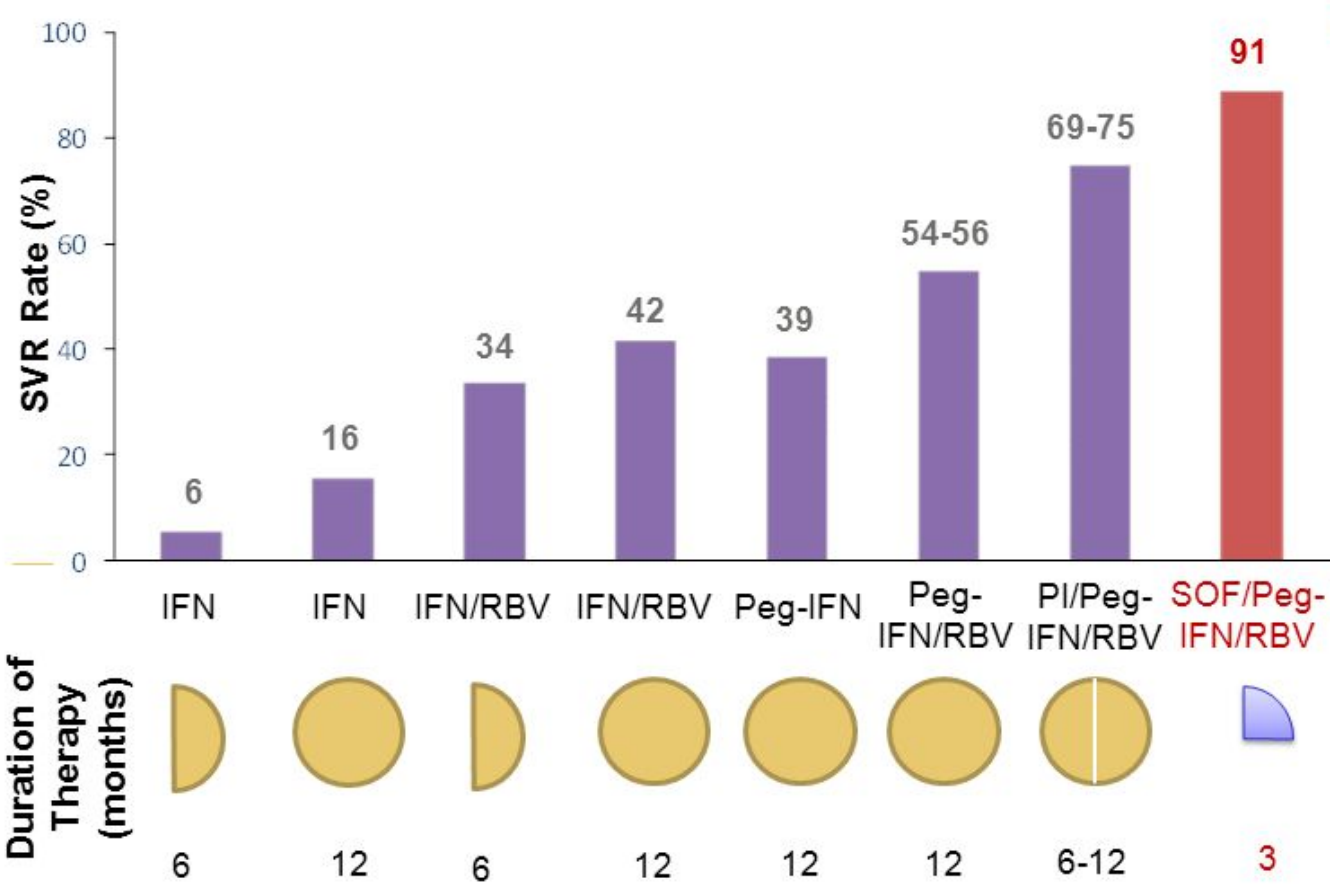

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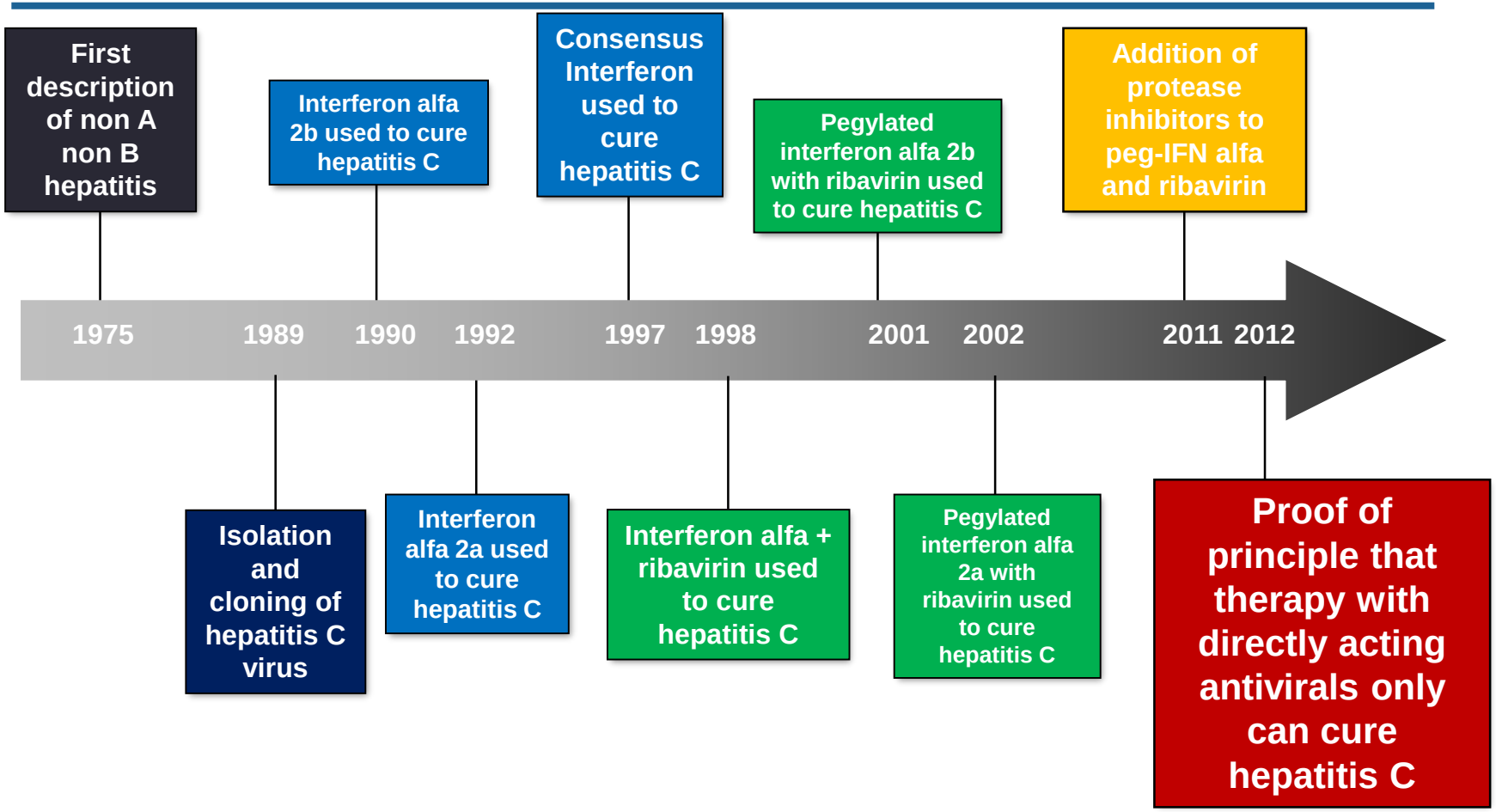

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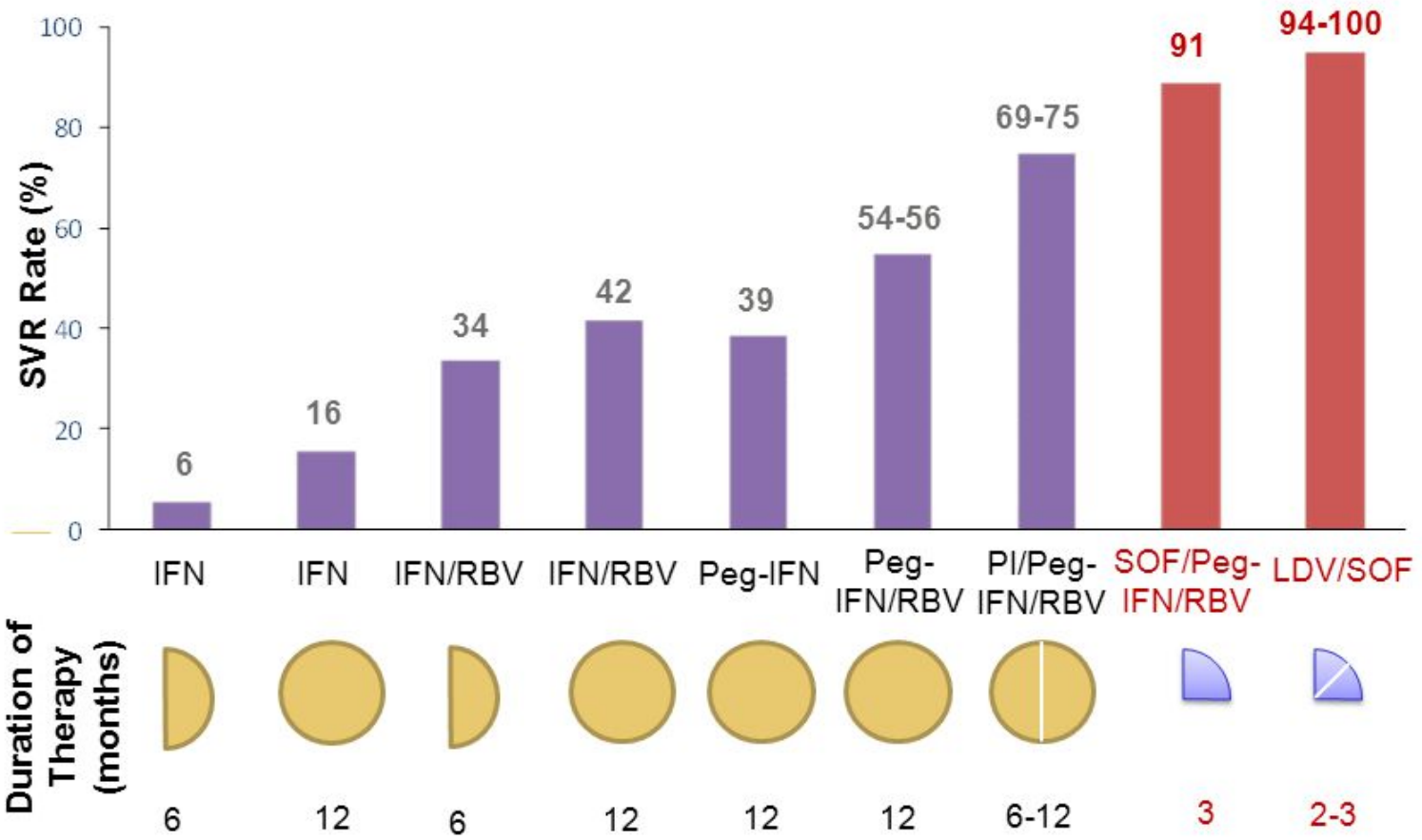
ADVANCES IN HEPATITIS C TREATMENTS

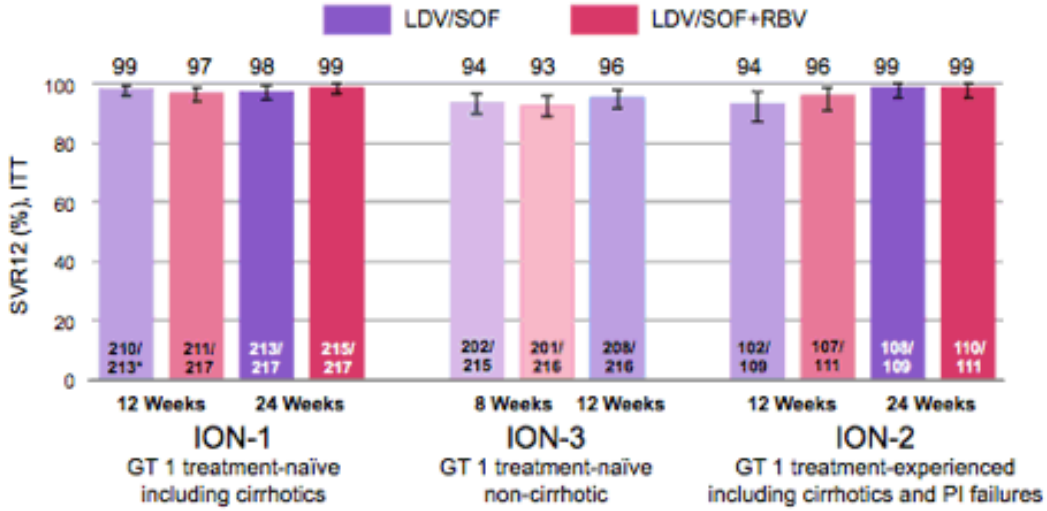


Adapted from Gilead Sciences, Inc., 2015, Manns et al *Nature Reviews Drug Discovery*, 2013, and the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting April 27-28 2011.

DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

ION Phase 3 Program (ION-1, ION-2, ION-3)

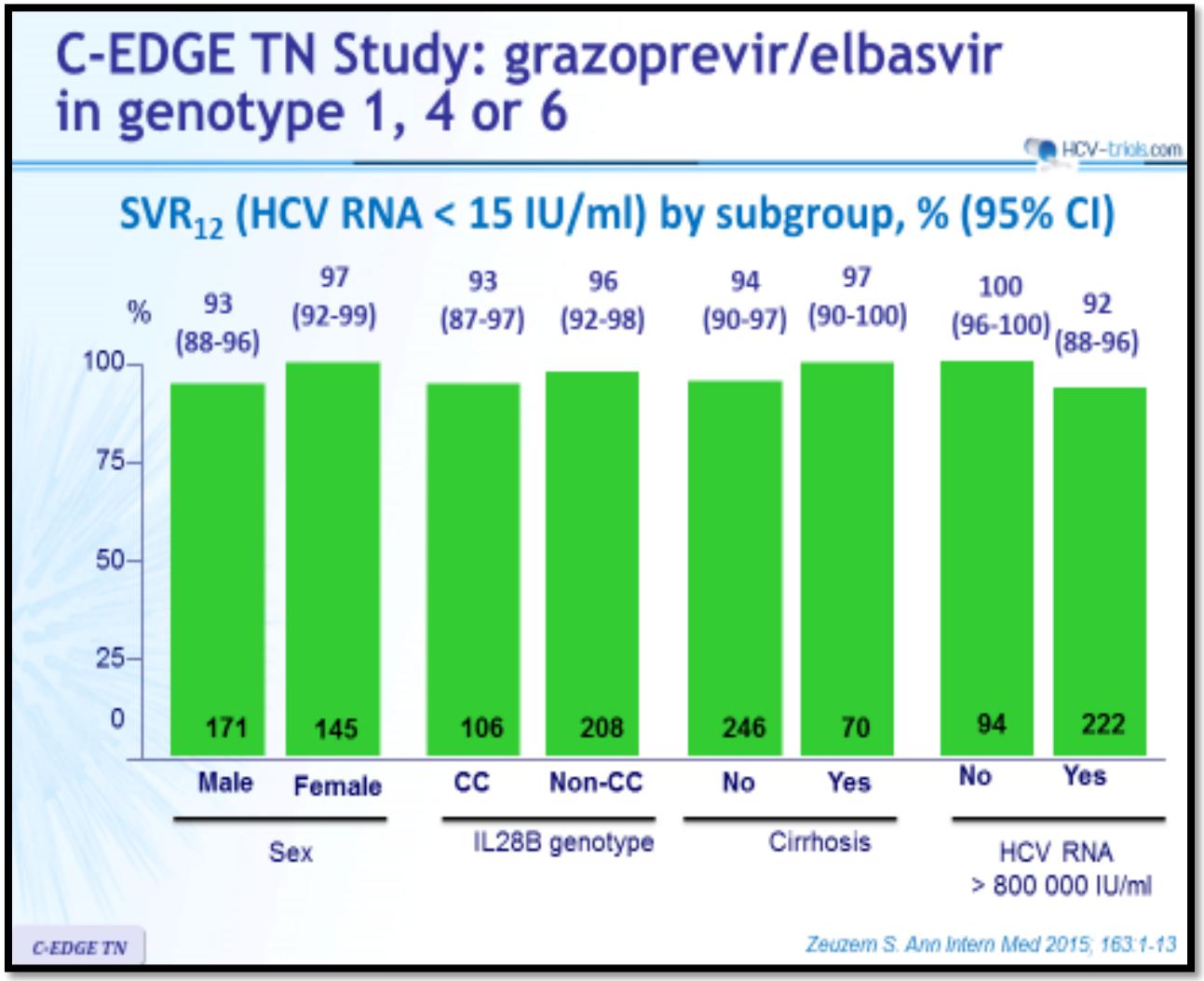
Results: Efficacy Summary (ITT)



- 97% (1887/1951) overall SVR rate
- 3% (64/1951) did not achieve SVR
  - 1.8% (36) relapsed
  - 1.3% (26) were either lost to follow up or withdrew consent
  - 0.1% (2) virologic breakthrough (both due to non-adherence)

*excluding one subject with genotype 4 infection
Error bars represent 95% confidence intervals.

DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

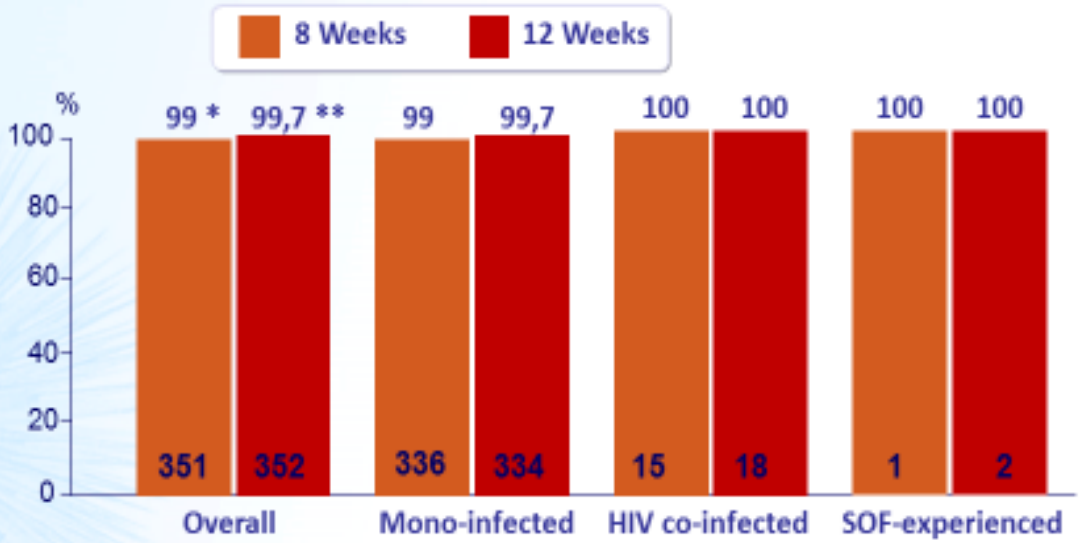


DIRECTLY ACTING ANTIVIRAL THERAPY FOR HEPATITIS C

ENDURANCE-1 Study: glecaprevir/pibrentasvir in genotype 1 without cirrhosis

HCV-trials.com

Secondary efficacy endpoints (SVR_{12}): ITT population



ITT population: all patients receiving study drug ; none excluded

* 1 patient experienced on-treatment virologic failure, 1 patient discontinued on D2 due to non-compliance, 1 patient missing SVR_{12} data

** 1 patient missing SVR_{12} data

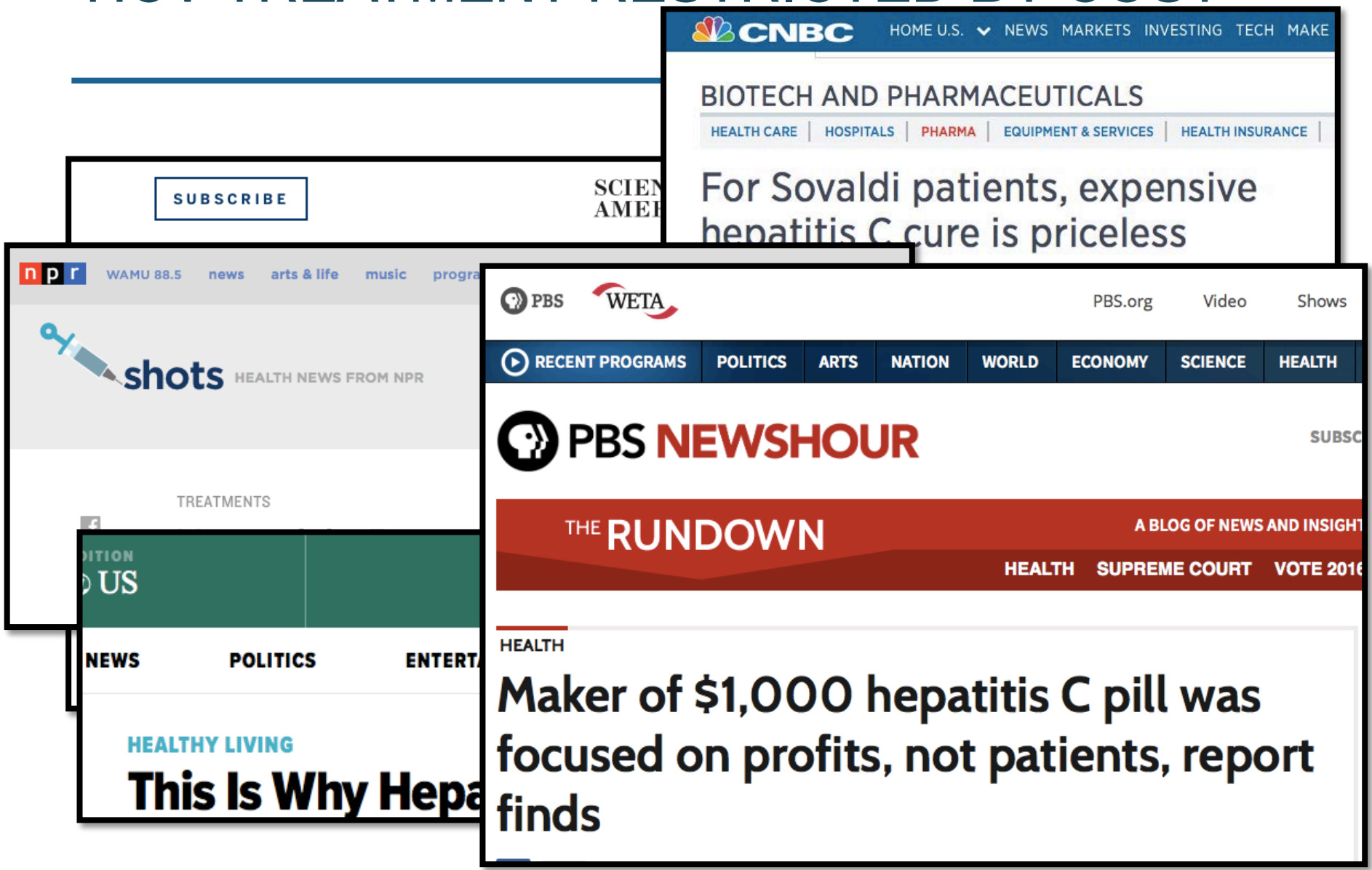
ENDURANCE-1

Zeuzem S. AASLD 2016, Abs. 253

Approved HCV Regimens in the US

	Harvoni	Viekira Pak	Zepatier	Epclusa	Mavyret
Contains	LDV/SOF	PrOD	EBR/GBR	SOF/VEL	GLE/PIB
Approved	October 2014	January 2015	January 2016	June 2016	August 2017
Duration	8-24 weeks	12-24 weeks	12-16 weeks	12-24 weeks	8-16 weeks
Efficacy	**~93-98%**	**~93-98%**	**~93-98%**	**~93-98%**	**~93-98%**

HCV TREATMENT RESTRICTED BY COST

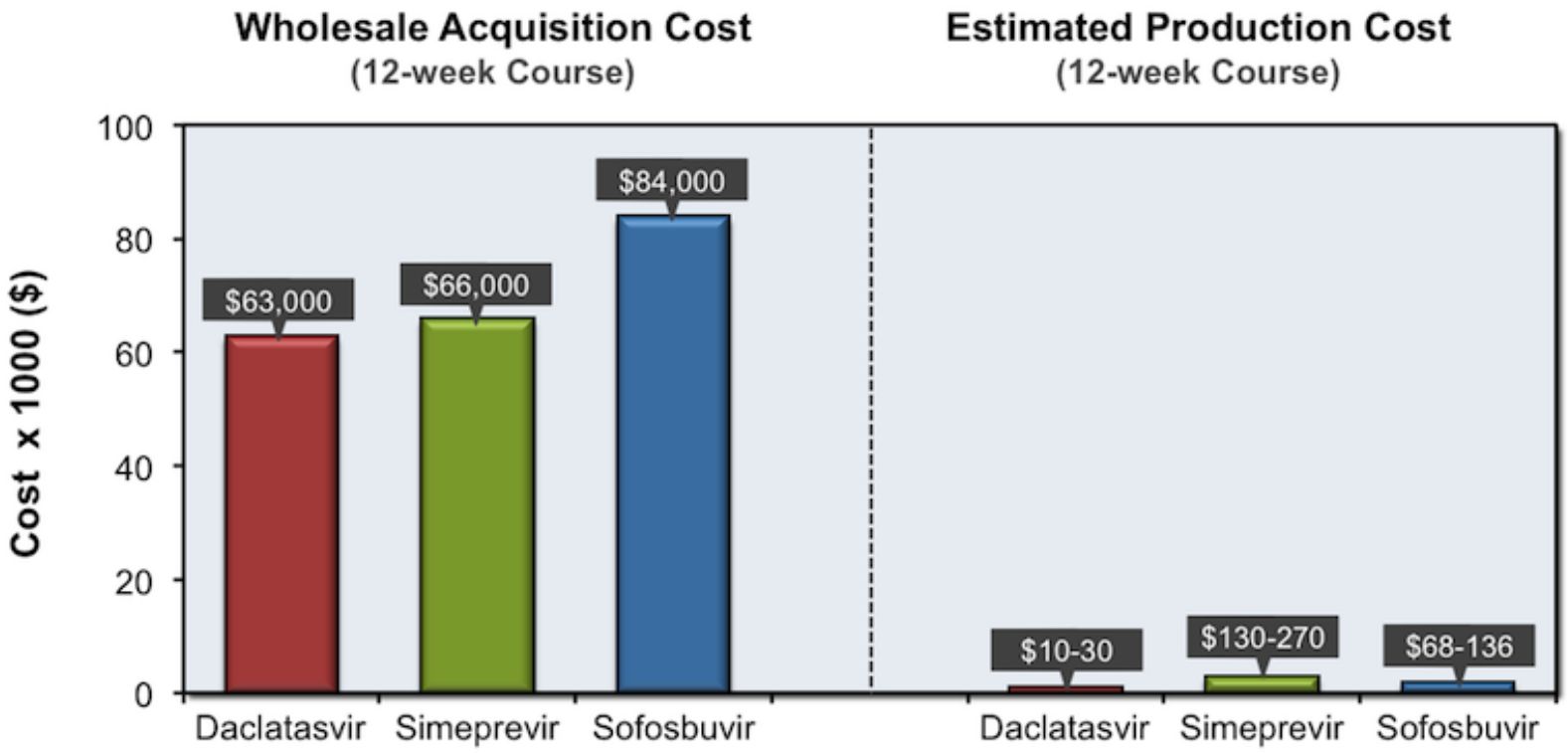


HCV TREATMENT IS RESTRICTED BY COST

Wholesale Acquisition Cost (WAC) of Direct Acting Antiviral Agents used to Treat HCV			
Medication	**Trade Name**	**Manufacturer**	**WAC for 1 Day**
Daclatasvir	*Daklinza*	Bristol-Myers Squibb	$750
Elbasvir-Grazoprevir	*Zepatier*	Merck & Co., Inc.	$650
Ledipasvir-sofosbuvir	*Harvoni*	Gilead Sciences	$1125
Ombitasvir-Paritaprevir-Ritonavir	*Technivie*	AbbVie	$912
Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir	*Viekira Pak*	AbbVie	$992
Simeprevir	*Olysio*	Janssen	$790
Sofosbuvir	*Sovaldi*	Gilead Sciences	$1000

Adapted from hepatitisc.uw.edu

HCV TREATMENT IS RESTRICTED BY COST



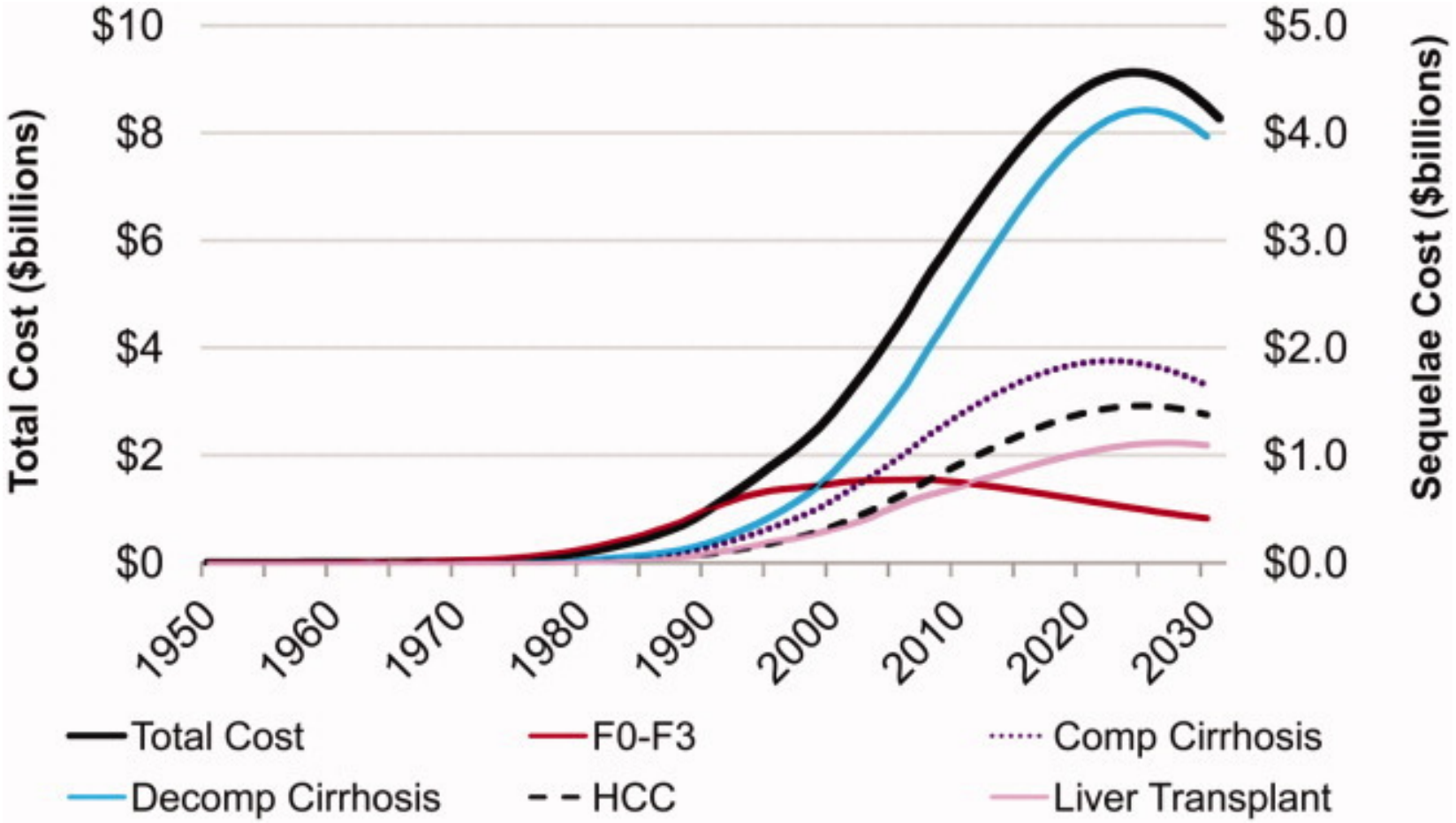
Hill A et al. Clin Infect Dis. 2014;58:928-3

PRICE PER CURE OF VARIOUS HCV REGIMENS

Regimen	SVR rates	WAC Price	Cost per SVR
Pegasys + Ribavirin x 48 weeks[1]	41%	$41,758	$101,849
Telaprevir + PegIFN + Ribavirin x 24 weeks[2]	75%	$86,843	$115,791
Sofosbuvir + PegIFN + Ribavirin x 12 weeks	90%	$94,421	$104,912
Sofosbuvir+Ledipasvir x 8 weeks	94%	$63,000	$67,021 ($36,191?)*
Sofosbuvir + Ledipasvir x 12 weeks	99%	$94,500	$95,454 ($51,545?)*

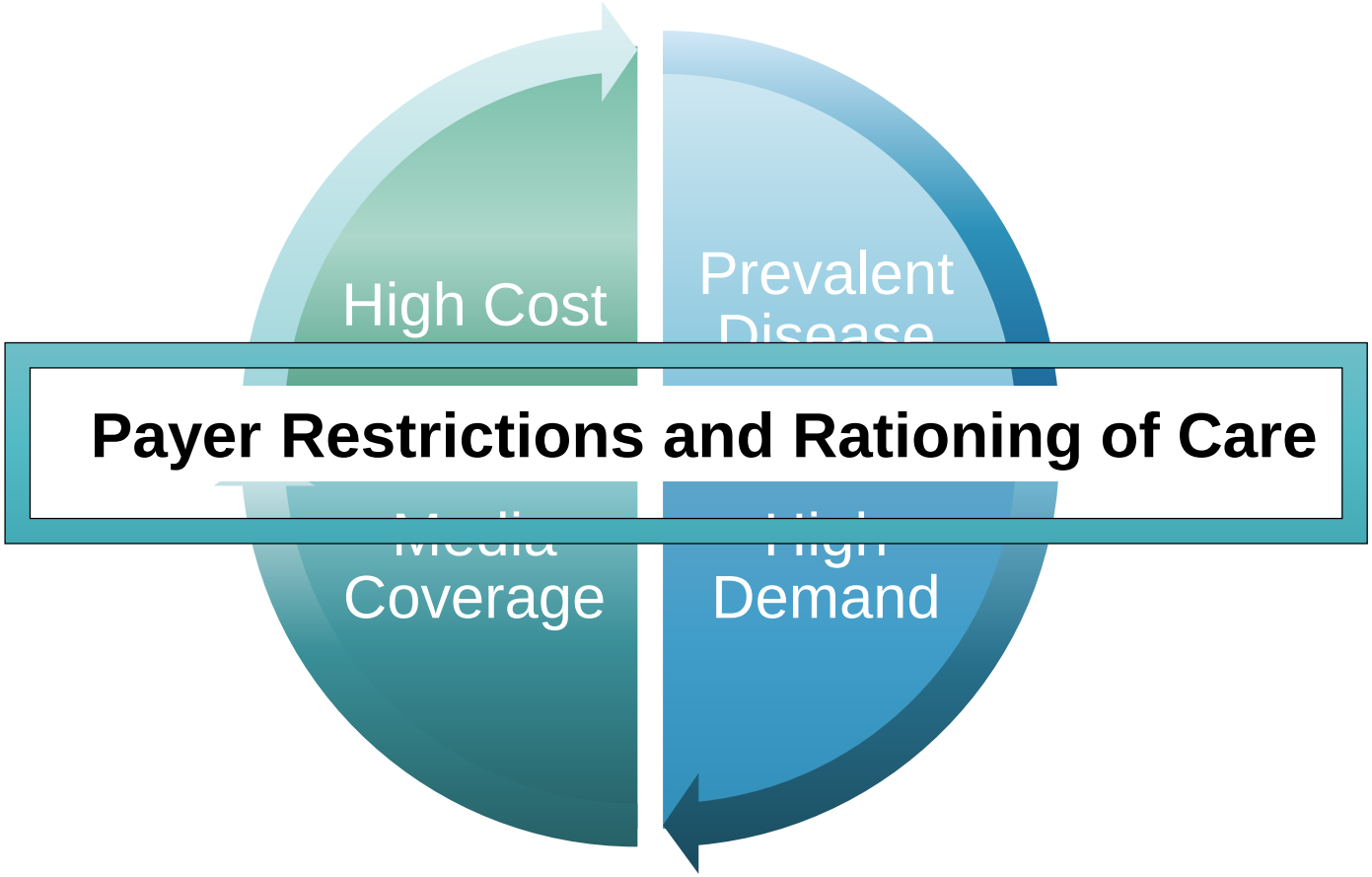
Graham and Rosenthal, Infect Agent Cancer. 2016; 11: 24.

HEALTHCARE COSTS OF UNTREATED HCV, BY SEQUELAE

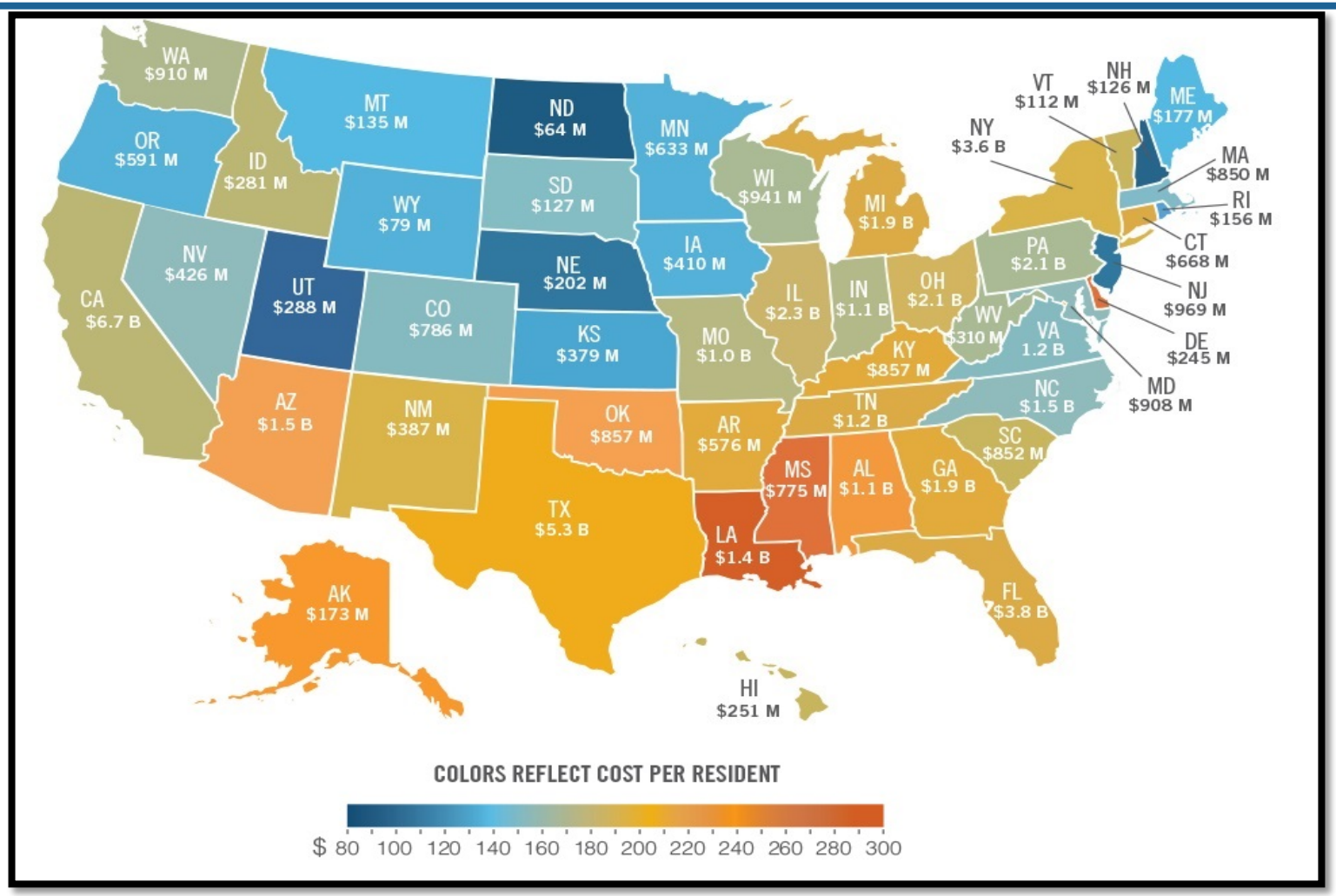


Razavi, et al, Hepatology. 2013 Jun;57(6):2164-70

HCV TREATMENT WITH DAAS IS COST EFFECTIVE, BUT NOT AFFORDABLE

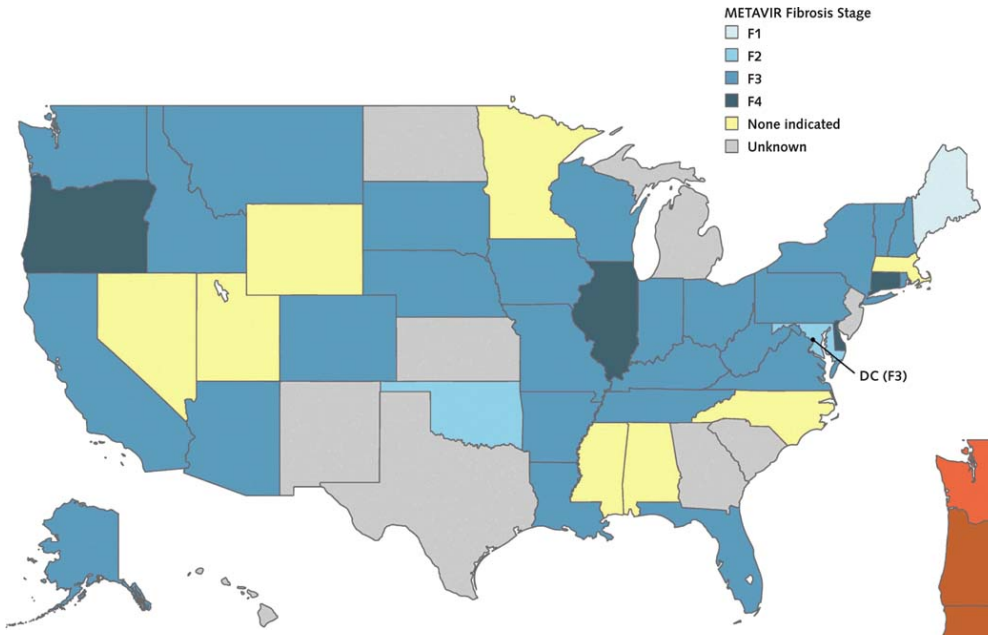


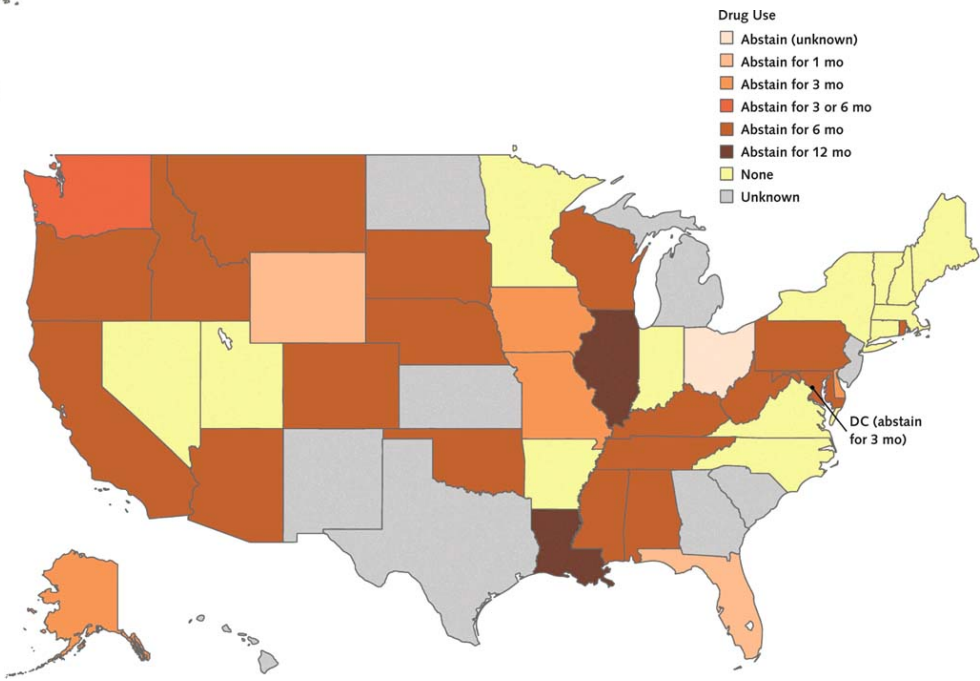
POTENTIAL COST OF STATE-FUNDED HEPATITIS C TREATMENT



Adapted from Express Scripts, 2014

MEDICAID REIMBURSEMENT CRITERIA





Baura et al *Annal Int Med* 2015

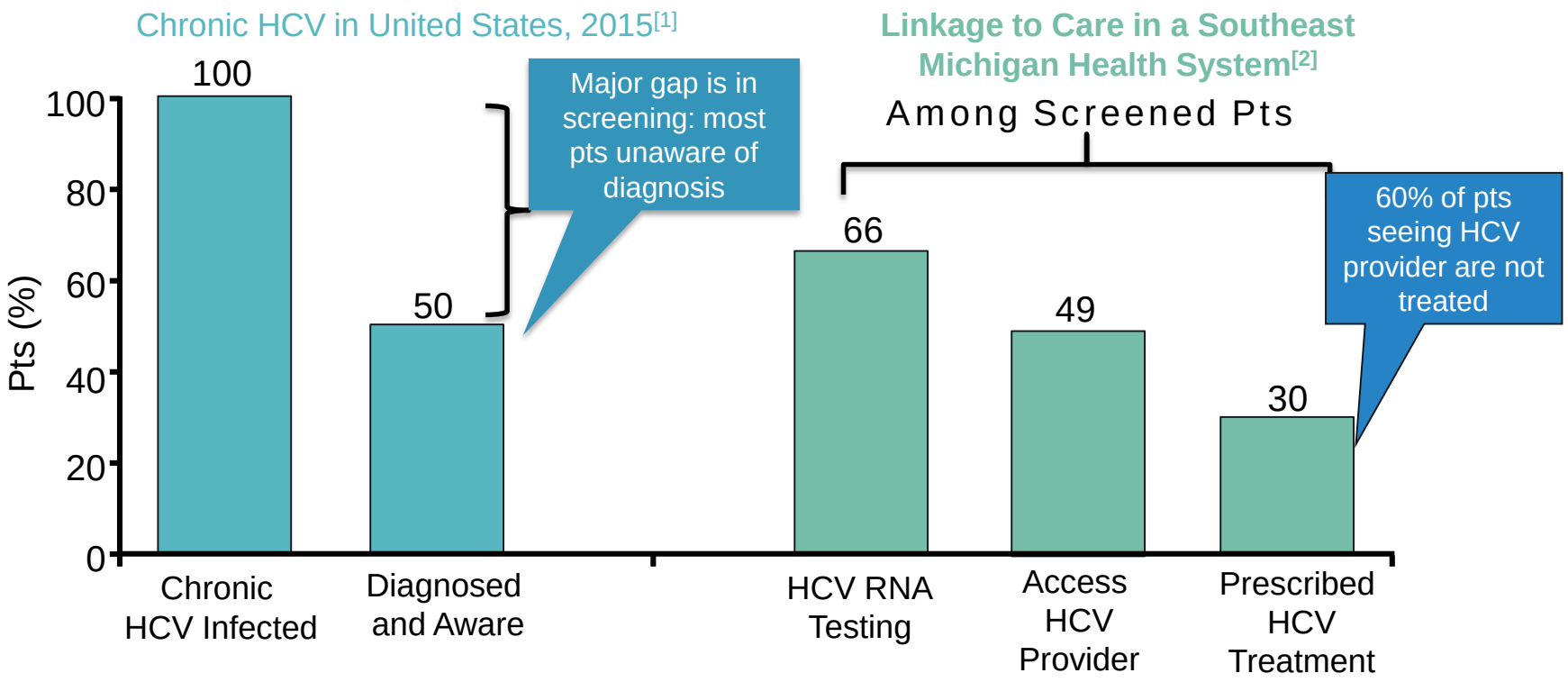
HEPATITIS C SCORECARD

Maryland : C

- ❑ Liver damage restrictions
  - ≥ F2 – Medicaid and FFS, 1 MCO ≥F3
- ❑ Sobriety restrictions
  - Screening for active alcohol/substance use
- ❑ Provider restrictions
  - Prescription written by/in consultation with a specialist
- ❑ Restrictions differ for FFS and MCOs

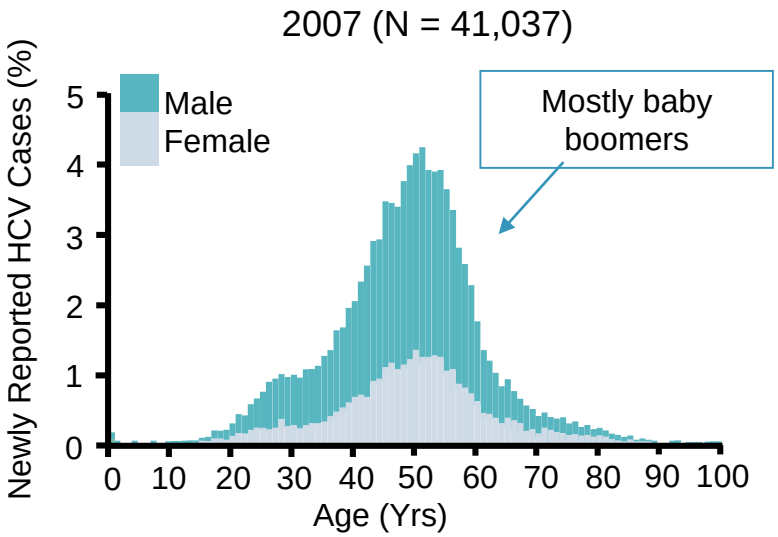
https://stateofhepc.org

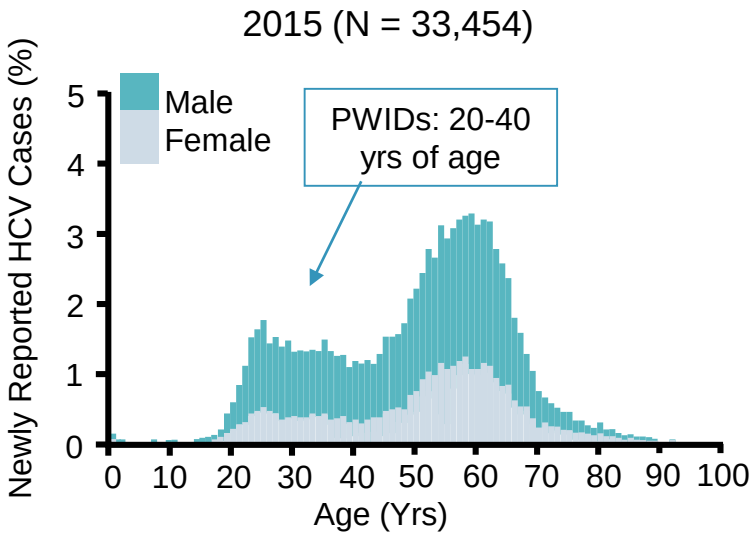
US ESTIMATES OF HCV CASCADE OF CARE



1. Bourgi K, et al. PLoS One. 2016;11:e0161241. 2. Yehia BR, et al. PLoS One. 2014;9:e101554.

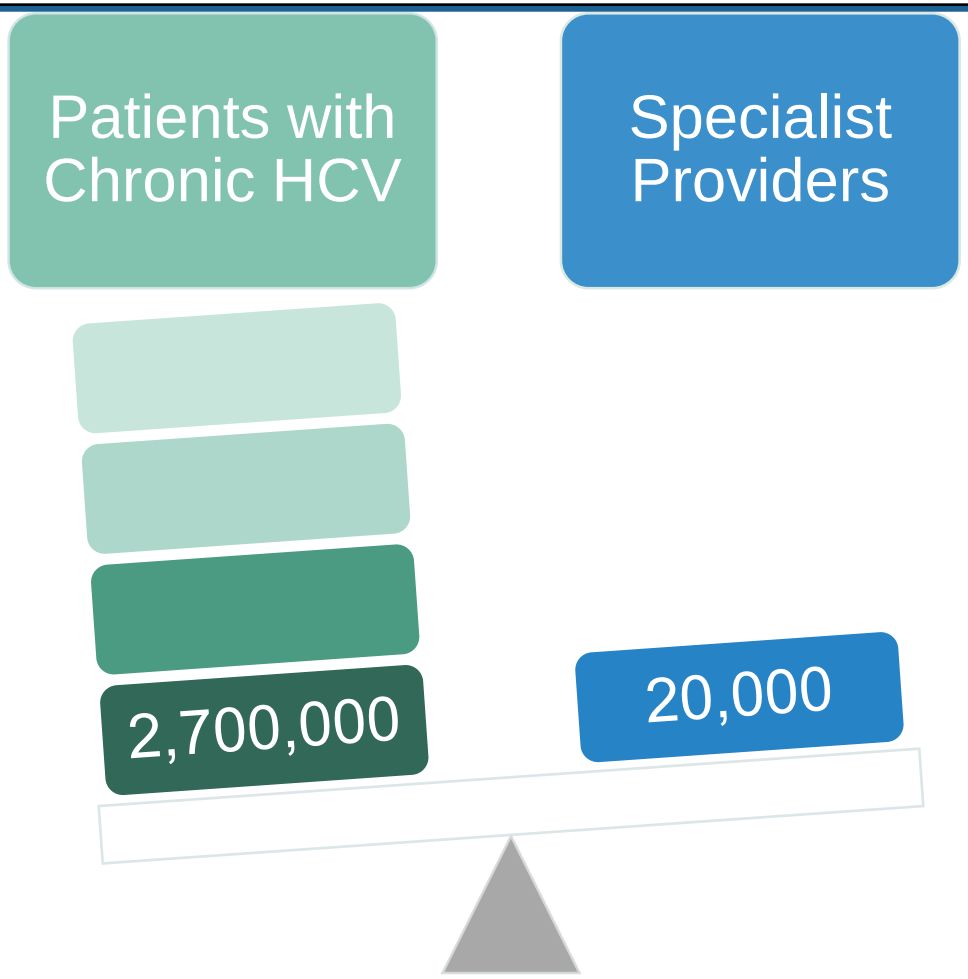
CHANGING EPIDEMIOLOGY OF HCV IN THE US



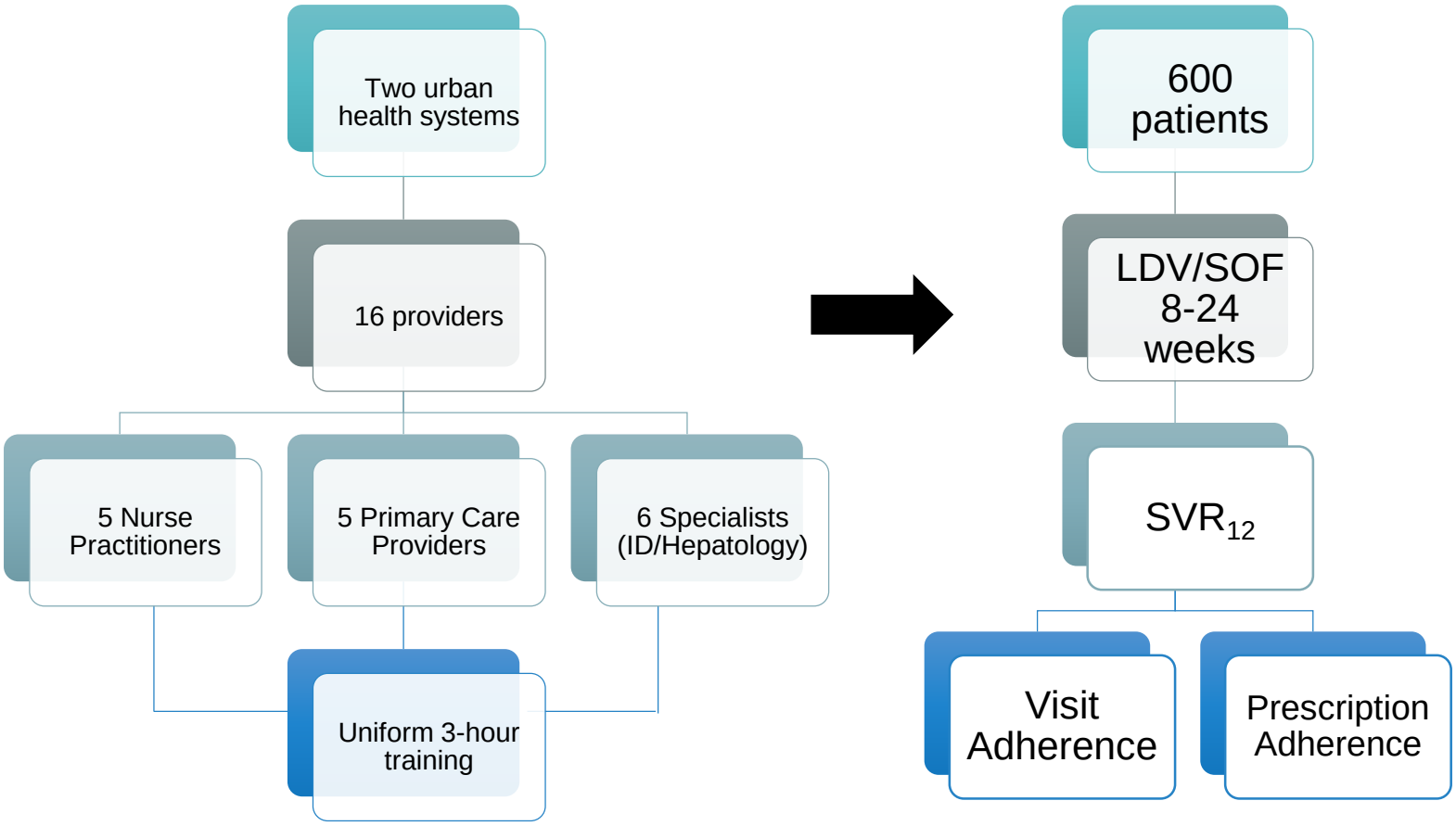


California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

LACK OF SPECIALIST AVAILABILITY LIMITS ACCESS TO HCV TREATMENT



ASCEND STUDY DESIGN



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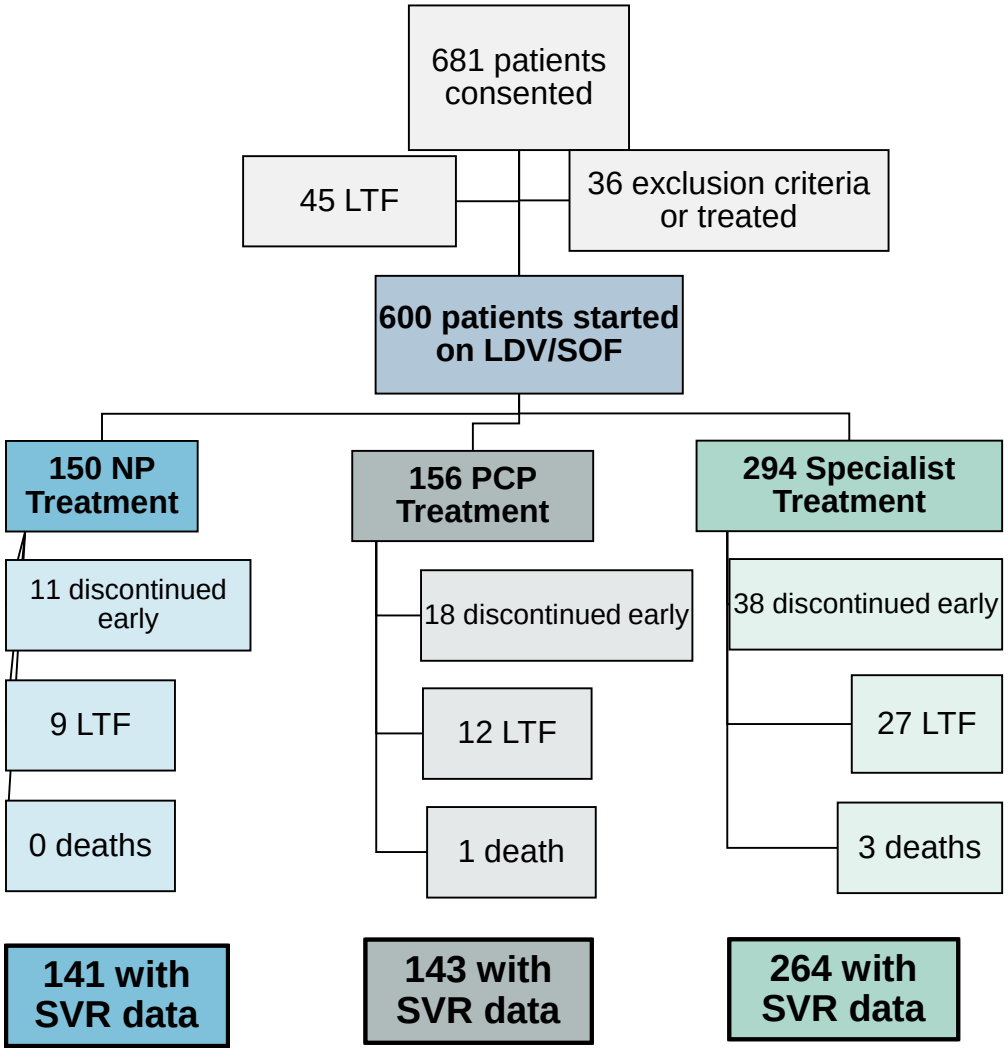
ASCEND Study Flow



Characteristic	Overall (N=600)
Age-years	58.7
Male (%)	416 (69)
Race (%)	
Black	578 (96)
White	20 (3)
Other	2 (1)
HIV-coinfected (%)	138 (23)
CD4+ cell count (cells/UL)	655
Cirrhosis (%)	121 (20)
Treatment-Naïve (%)	494 (82)
Treatment duration-12 weeks (%)	539 (90)

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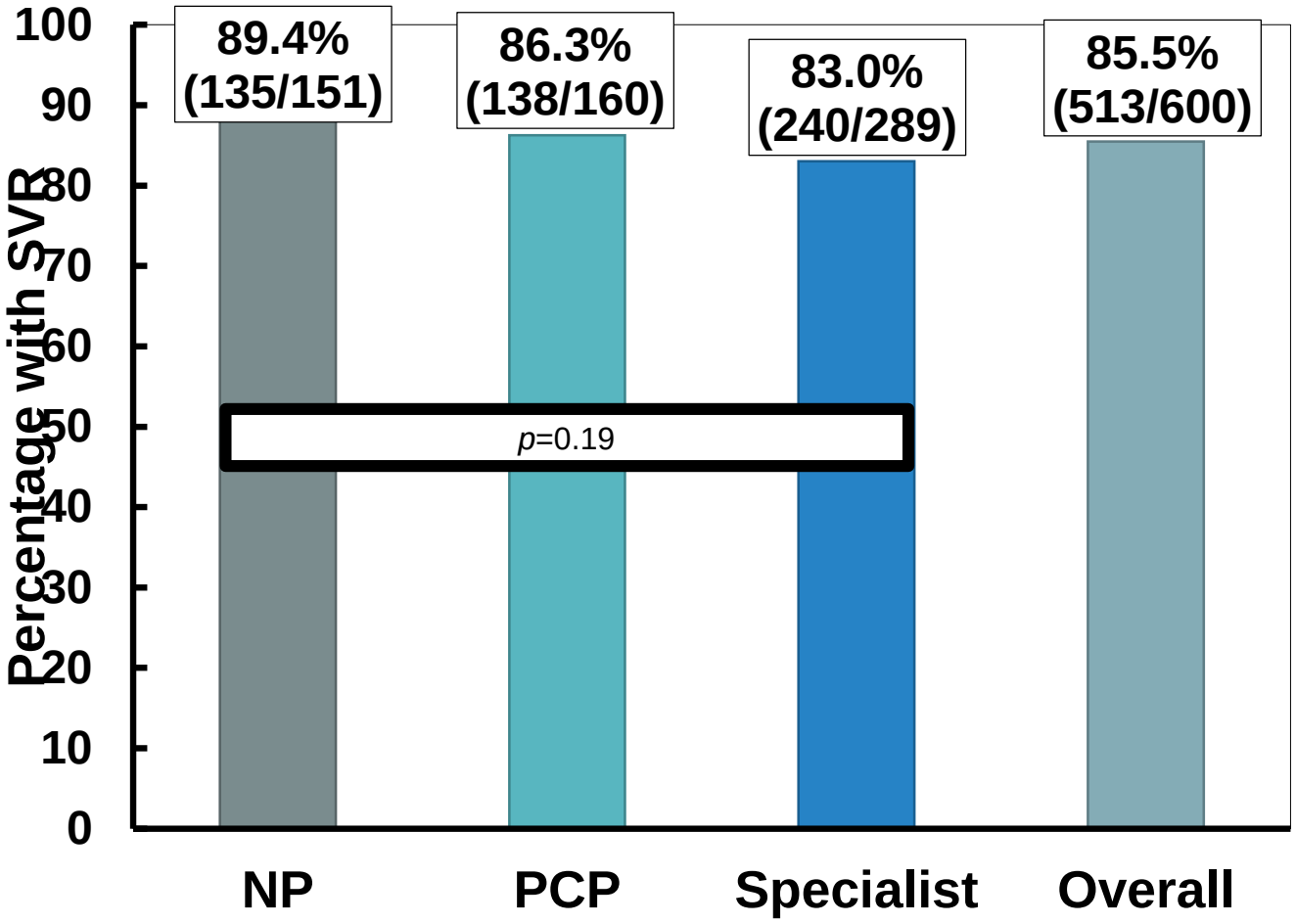
SVR (INTENTION TO TREAT)



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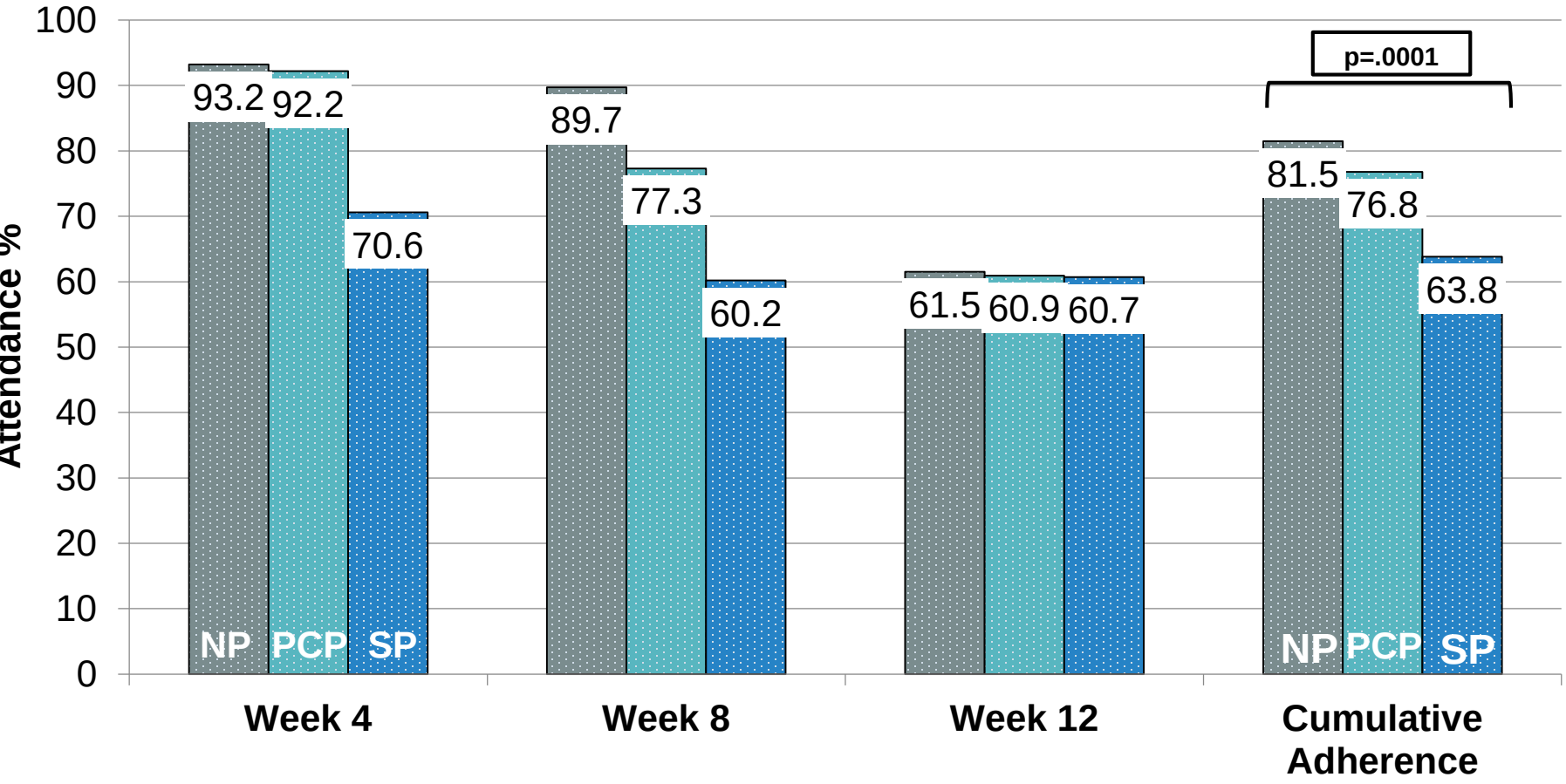
Higher Rates of Visit Adherence with Non-Specialist Providers



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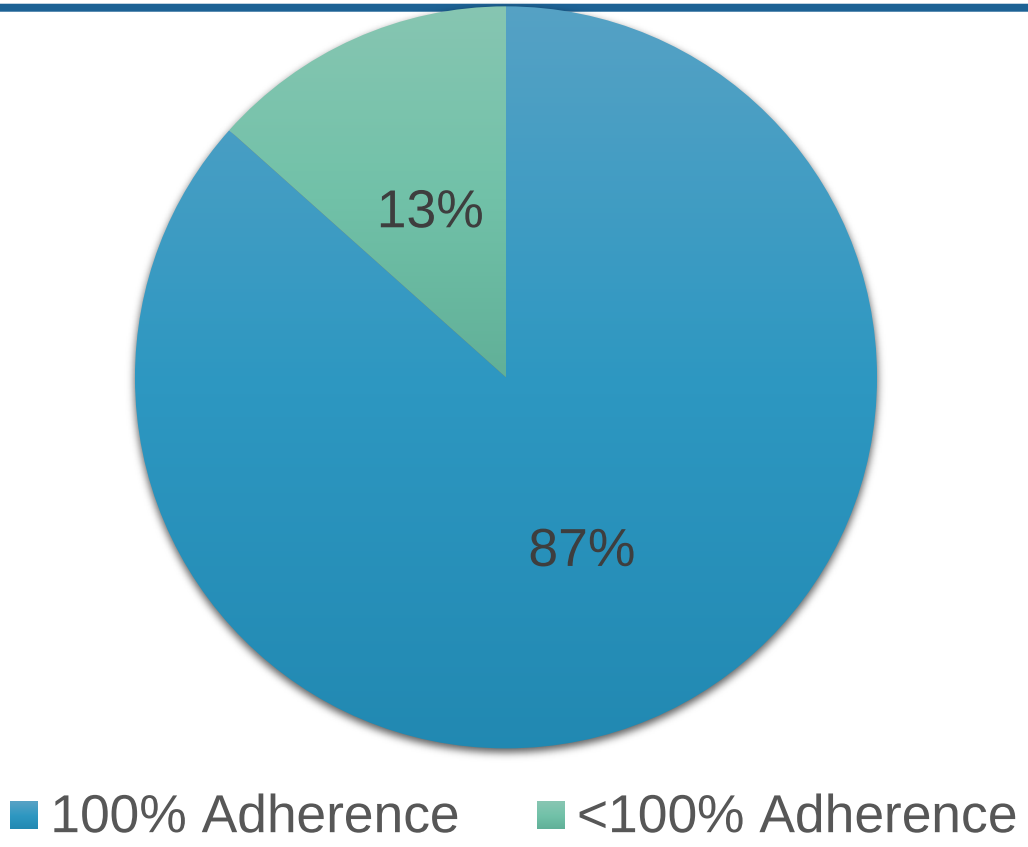
HIGH PRESCRIPTION ADHERENCE



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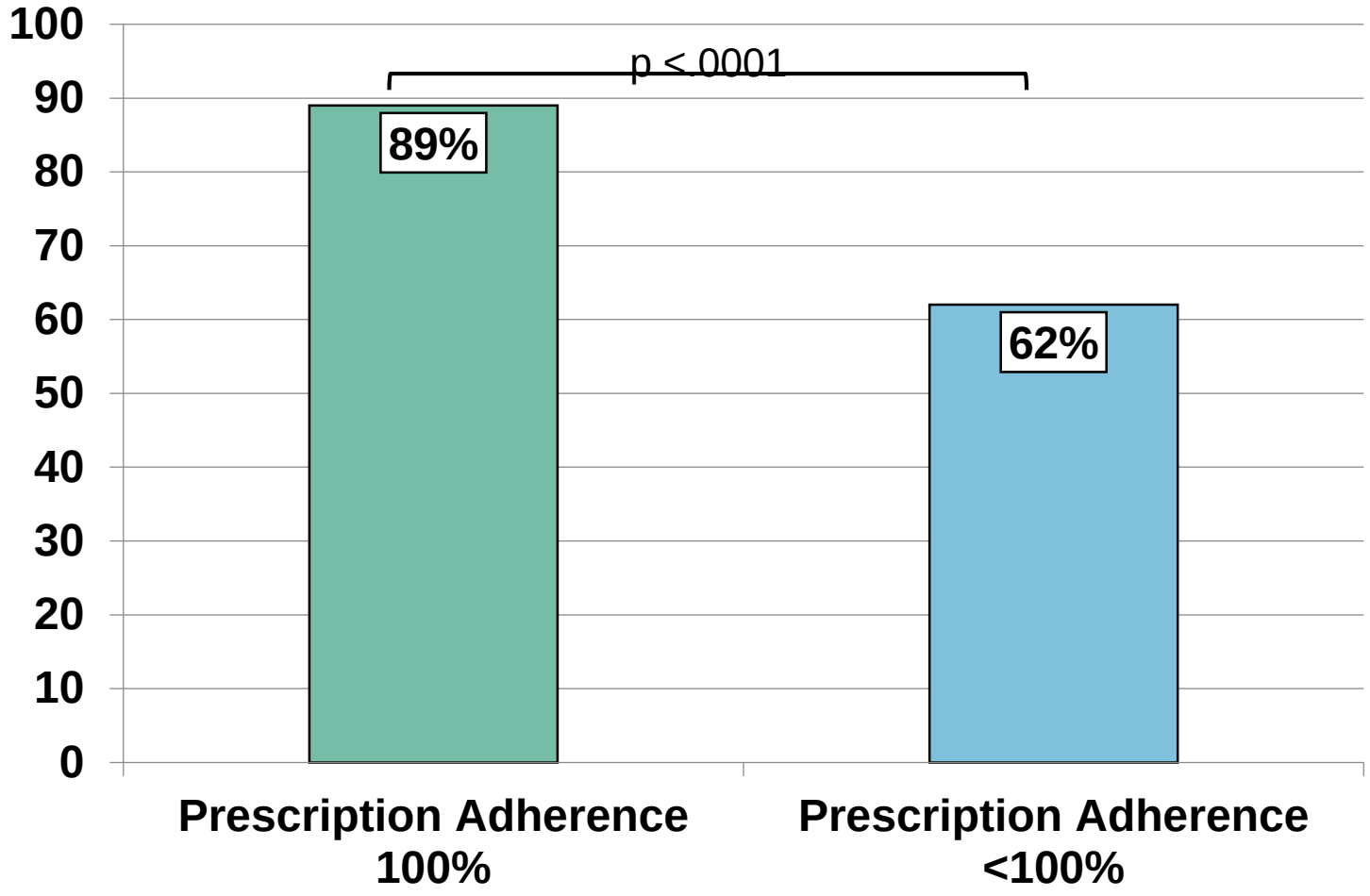
SVR (ITT) BY PRESCRIPTION ADHERENCE



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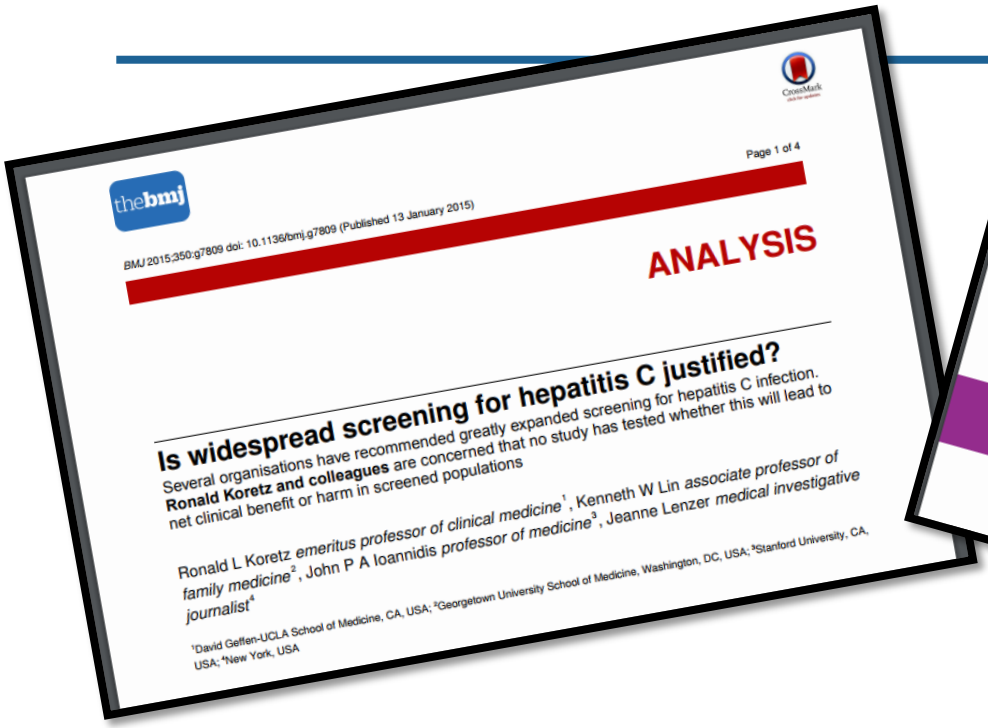
ASCEND SUMMARY

- Non-specialist providers have high rates of success with HCV treatment, comparable to specialists with appropriate training
- In the absence of insurance-based provider restrictions and prior authorization, rapid treatment uptake can be accomplished
- There is data to support elimination of provider restrictions around provision of HCV care

Kattakuzhy, S et al *Ann Int Med* 2017

MEANWHILE…



"…regulatory agencies should ensure that drugs have been evaluated by long term follow up of clinical outcomes (not just surrogate markers) in several thousands of patients…"

"The evidence for our main outcomes of interest come from short-term trials, and we are unable to determine the effect of long-term treatment with DAAs…DAAs may reduce the number of people with detectable virus in their blood, but we do not have sufficient evidence from randomized trials that enables us to understand how SVR affects long-term clinical outcomes. SVR is still an outcome that needs proper validation in randomized clinical trials."

Koretz, Lin, Ioannidis, and Lenzer, *BMJ* 2015

Jakobson, et al *Cochrane Database Syst Rev* 2017

HCC RISK PERSISTS AFTER DAA THERAPY IN PTS WITH HCV-RELATED CIRRHOSIS

- Retrospective analysis of 344 HCV-infected pts with CPT A or B cirrhosis treated with DAAs (SVR: 89%)
  - Pts followed for 12-24 wks after treatment completion
  - No HCC at baseline, but previous HCC permitted
- Overall HCC incidence after DAA therapy: 7.6%
  - **In pts without previous HCC: 3.2%**
  - **In pts with previous HCC: 29.0%**
- More advanced liver disease and previous HCC significant risk factors for HCC after DAAs

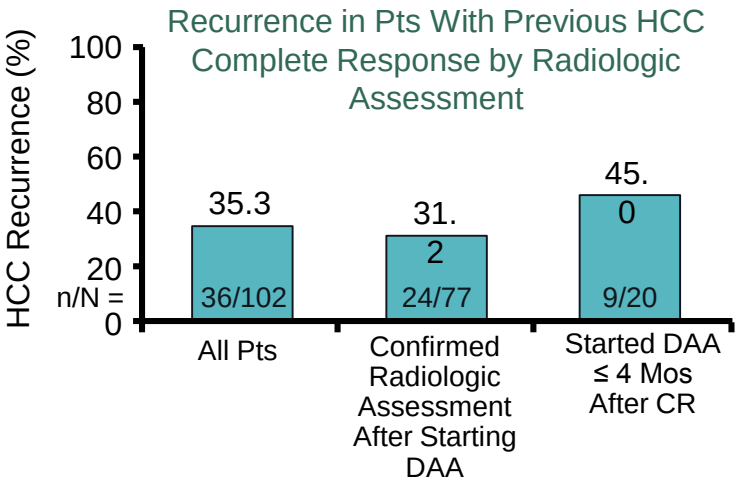
Factor	No HCC (n = 318)	HCC (n = 26)	P Value
CP class B, %	10.1	26.9	.02
Mean liver stiffness, kPa	23.2	28.1	.01
Liver stiffness, n			.005
▪ kPa < 21.3	134	5	
▪ kPa > 21.3	101	16	
Mean platelets, x 1000/mm^3	124.4	102.3	.02
Previous HCC, n			.0001
▪ Yes	42	17	
▪ No	276	9	

Buonfiglioli F, et al. EASL 2016. Abstract LBP506.

EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 2016 APRIL 13-17, BARCELONA, SPAIN

HCC RECURRENCE FOLLOWING HCV DAA THERAPY

- Retrospective study of pts with history of HCC before starting HCV DAAs (N = 105)



- ❑ Among pts starting DAAs ≤ 4 mos after CR, 4 pts (20%) died
  - Deaths occurred in Months 9, 10, 15, 16 after starting DAA

- ❑ 10 pts had HCC recurrence or progression

Endpoint	Pts With Recurrence (n = 24)*
Median time from DAA start to first recurrence, mos (IQR)	3.5 (2-7.6)
Median time from first to second recurrence/progression, mos (IQR)	6 (3.2-8.2)
▪ Within 6 mos of first recurrence, n/n (%)	6/20 (30)
▪ Death, n (%)	5 (20.8)

*Pts from cohort with confirmed radiologic assessment, no confounding factors.

Reig M, et al. EASL 2017. Abstract PS-031.

EASL The Home of Hepatology | THE INTERNATIONAL LIVER CONGRESS™ 19-23 APRIL, AMSTERDAM, THE NETHERLANDS 2017

HCC RECURRENCE EQUIVALENT WITH DAAS AND IFN

- Meta-analysis and meta-regression analysis comparing risk of HCC after SVR with DAA- vs IFN-based therapy in 41 studies (N = 13,875)

Pts With First HCC Occurrence After SVR

Characteristic	DAA	IFN
Age, yrs	60	52
Cirrhosis, %	90	87
Child-Pugh score B/C, %	34	0
Follow-up, yrs	1.0	5.5

Pts With HCC Recurrence After SVR

Characteristic	DAA	IFN
Pts with previous curative HCC treatment, %	96	100
Follow-up, yrs	1.3	5.0

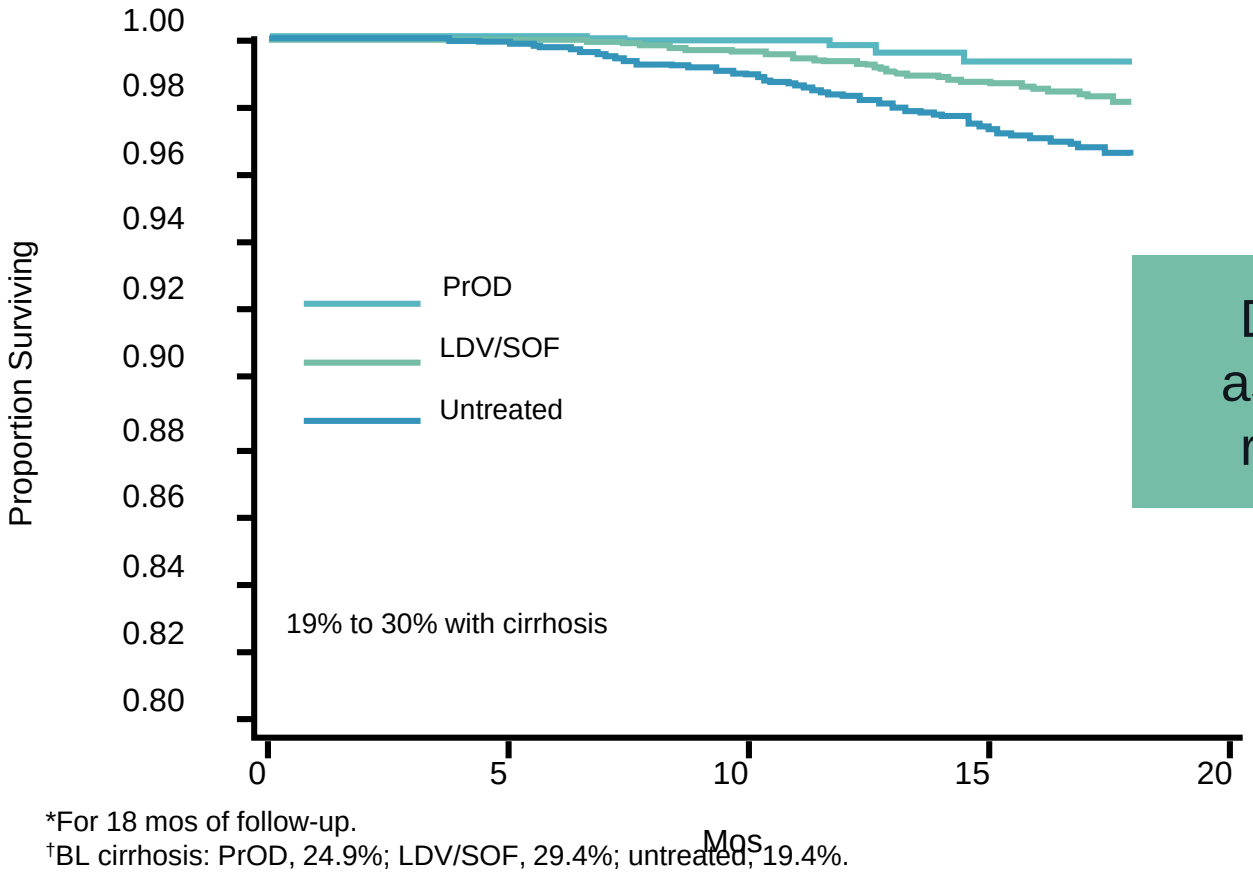
- After adjusting for these factors, no difference in risk of HCC occurrence (aRR: 0.75) or recurrence (aRR: 0.62) between DAAs and IFN

- "The more advanced cirrhosis population who can be treated by DAA compared to IFN-based therapy and the higher DAA cure rates among patients with cirrhosis mean that the impact on population-level HCC incidence should be markedly higher in the DAA-era."

Dore G, et al. EASL 2017. Abstract PS-160.
Waziry, R, et al. J Hepatol 2017, epub ahead of print

HCV CURE WITH DAAS REDUCES MORTALITY

Survival in ERCHIVES Veterans (N = 13,940*†)[1]



DAA-induced SVR is associated with a 43% reduction in mortality

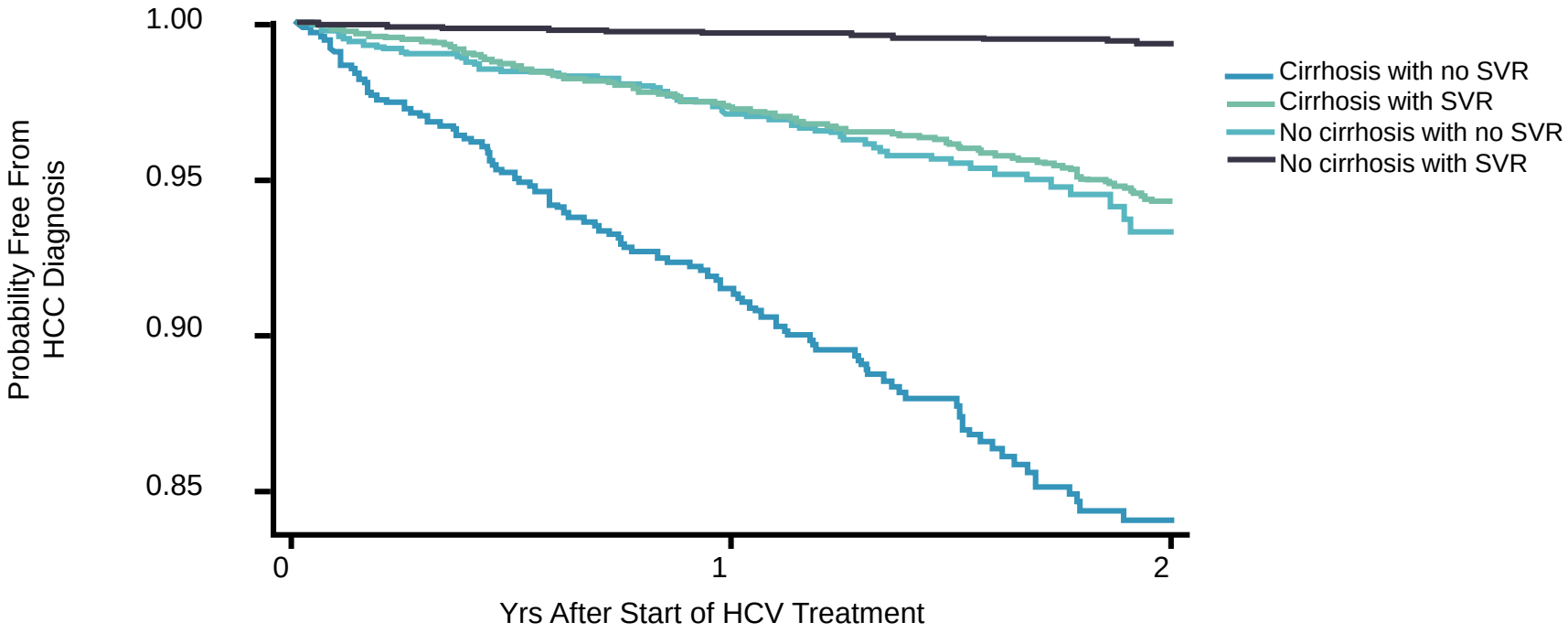
*For 18 mos of follow-up.
†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.

Butt AA, et al. Clin Infect Dis. 2017:65:1006-1011.

HCV CURE REDUCES HCC

HCC Risk in DAA-Treated Veterans (n = 25,424‡)

‡For 38,204 pt-yrs of follow-up.



DAA-induced SVR is associated with a 71% reduction in HCC risk

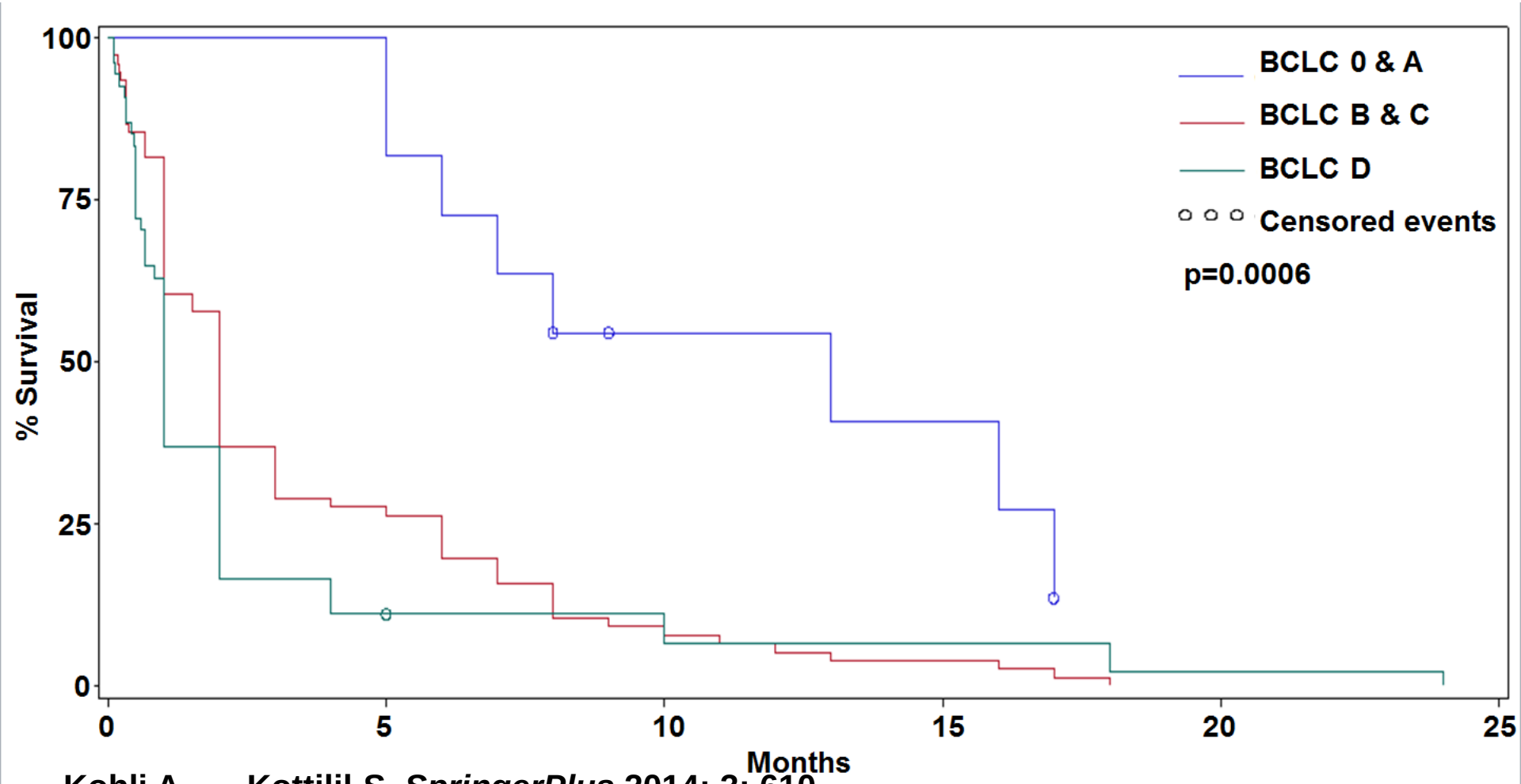
Ioannou GN, et al. J Hepatol. 2017;[Epub ahead of print].

DOES EARLY SCREENING HELP?

		Combined	Center 1	Center 2	
		n= 164	n= 36	n= 128	
Age	mean ± SD (years)	59.06 ± 9.9	58.64 ± 10.8	59.18 ± 9.74	p=0.774
AFP	mean ±SD (ng/mL)	5487.9 ± 3147.11	3188.01 ± 1697.32	6134.69 ± 4006.08	p=0.499
Size of Lesions	mean ± SD (cm)	5.27 ± 1.29	5.16 ± 3.26	5.31 ± 2.92	p=0.822
Gender	Male n (%)	137 (83.5%)	31 (86.11%)	106 (82.81%)	χ^2=0.637
Surveillance	Yes	87 (60.98%)	26 (72.22%)	74 (54.81%)	χ^2=0.117
Child-Pugh Class	A	32 (19.51%)	22 (61.11%)	10 (7.81%)	χ^2<0.0001
	B	72 (43.90%)	8 (22.22%)	64 (50%)	
	C	60 (36.59%)	6 (16.67%)	54 (42.19%)	
Etiology					
HBV		11(7%)	1 (3%)	10 (8%)	χ^2<0.0001
HBV only		10 (6%)	1 (3%)	9 (7%)	
HBV & ETOH		1 (1%)	--	1 (1%)	
HCV		73 (46%)	11 (31%)	62 (48%)	
HCV only		42 (26%)	9 (25%)	33 (26%)	
HCV & ETOH		31 (20%)	2 (6%)	29 (23%)	
HBV & HCV & ETOH		40 (25%)	13 (36%)	27 (21%)	
ETOH only		35 (22%)	9 (25%)	26 (20%)	
Unknown		5 (3%)	2 (6%)	3 (2%)	

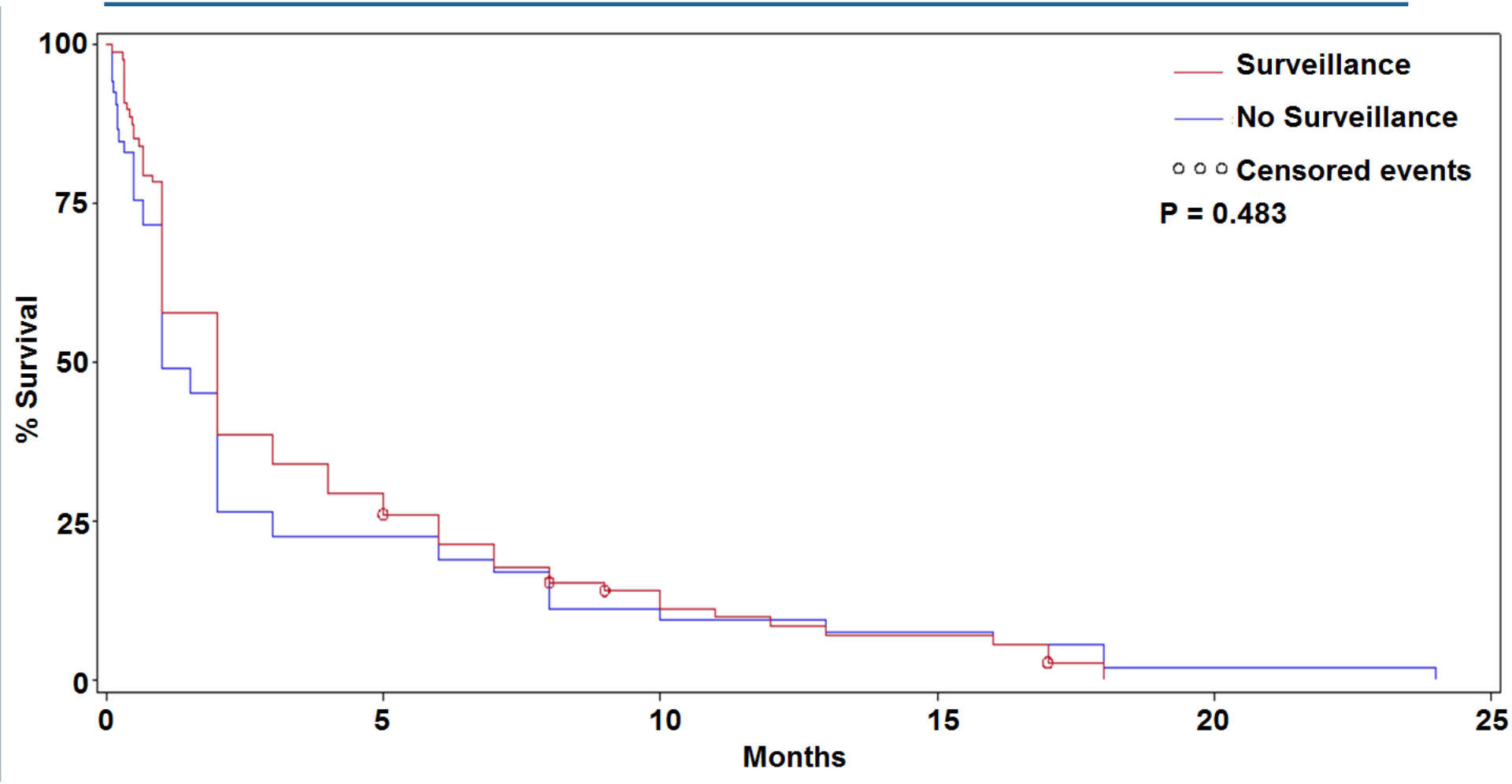
Kohli A……Kottilil S*. SpringerPlus* 2014; 3: 610

SCREENING DETECTS EARLY HCC



Kohli A……Kottilil S. *SpringerPlus* 2014; 3: 610

SURVEILLANCE WAS NOT ASSOCIATED WITH IMPROVED SURVIVAL



Kohli A……Kottilil S. *SpringerPlus* 2014; 3: 610

EVIDENCE FAVORING SURVEILLANCE

Outcomes	N of participants (studies)	Overall quality of evidence	Relative effect (95% CI)
Early tumor detection rate	10,904 (38 observational studies)	⊕⊕◯◯ LOW	OR 2.11 (1.88 to 2.33)
Early tumor detection rate (using BCLC to define early stage)	6,573 (6 observational studies)	⊕⊕◯◯ LOW	OR 1.96 (1.41 to 2.73)
Curative treatment rate	24,374 (34 observational studies)	⊕⊕⊕◯* MODERATE	OR 2.24 (1.99 to 2.52)
3-year survival rate*	10,850 (23 observational studies)	⊕⊕⊕◯* MODERATE	OR 1.90 (1.67 to 2.17)
Early detection (ultrasound only)	(5 observational studies)	⊕⊕◯◯ LOW	OR 2.04 (1.55 to 2.68)
Early detection (ultrasound +/- AFP)	(14 observational studies)	⊕⊕◯◯ LOW	OR 2.16 (1.80 to 2.60)
Receipt of curative treatment (ultrasound +/- AFP)	(24 observational studies)	⊕⊕◯◯ LOW	OR 2.19 (1.89 to 2.53)

*Upgraded because of large effect size

Adapted from Heimbach *Hepatology* 2017

EFFECTIVE SURVEILLANCE PROGRAMS PROLONG SURVIVAL

Japan: N=1174	Hong Kong: N=1675
Surveillance rate: 75%	Surveillance rate: <20%
Median survival: 52 months	Median survival: 17.8 months
Early stage at dx: 62%	Early stage at dx: 31.7%
Curative therapy: 63%	Curative therapy: 44.1%

Pros: Adjusted for lead time bias
Cons: Mixed etiologies

Johnson *Br J Cancer* 2017

CONCLUSIONS

- **Hepatitis C is an important preventable cause of HCC worldwide**
- **Prevention of HCC is possible with curative treatment for HCV, but we need to expand access**
- **Improving surveillance for and treatments for HCC remains a challenge**

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