Viral Hepatitis Update

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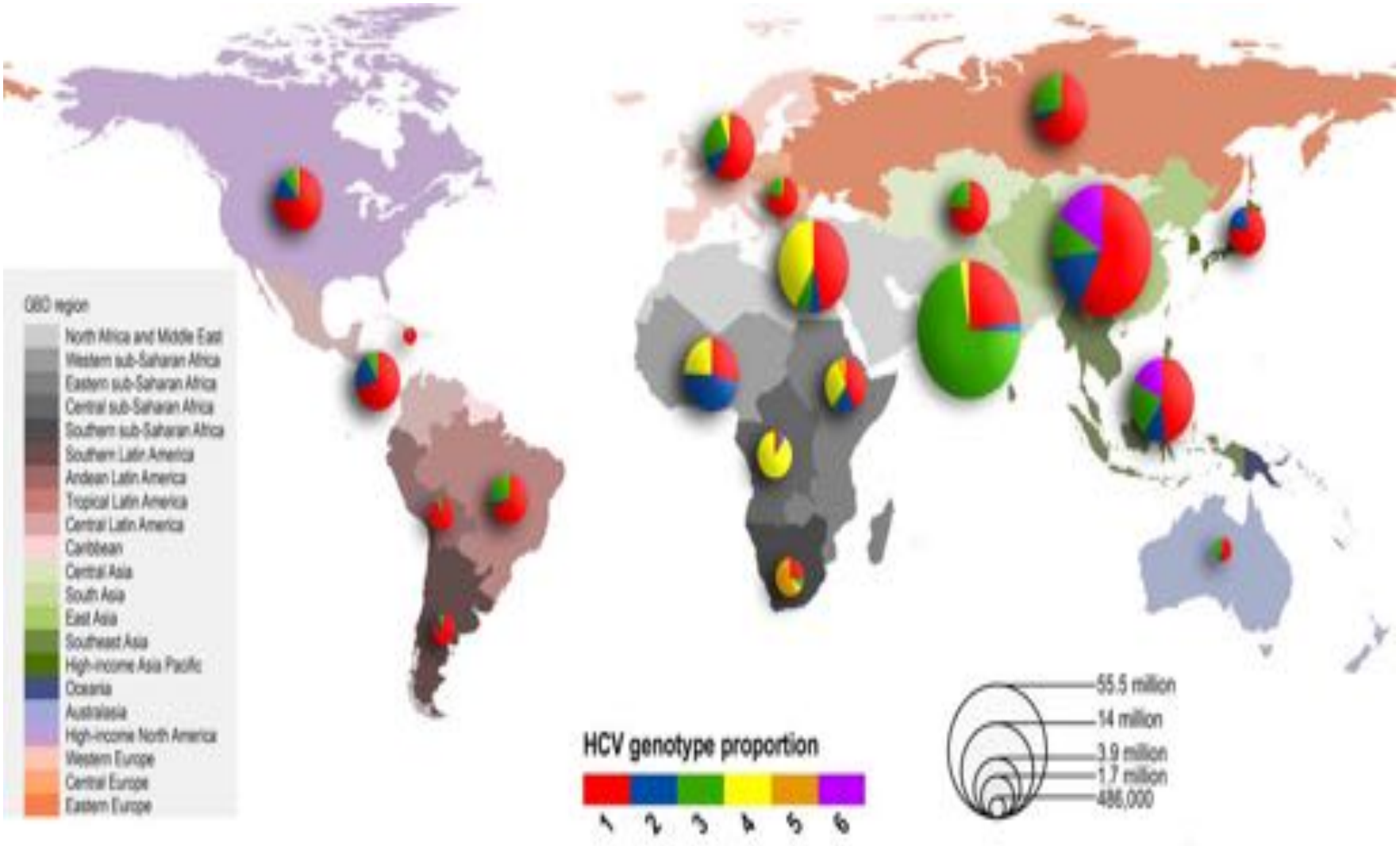
Disclosures

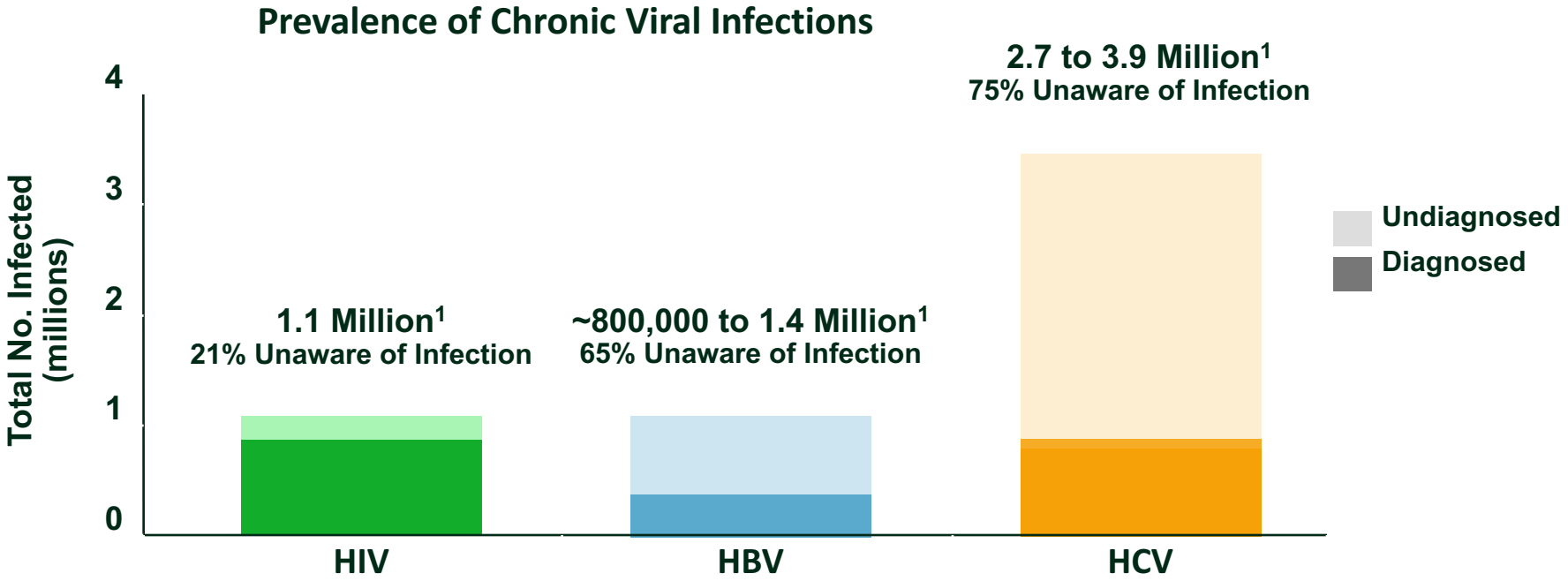
- *Advisory Board Member – Abbott, Abbvie, BMS, Conatus, Gilead, Merck, Intercept*
- *Shareholder – Durect*
- *Grant Recipient – Abbvie, BMS, Gilead, Merck, Conatus*

Global Distribution and Prevalence of HCV Genotypes



•**Messina JP et al, *Hepatology*, 2015; 61: 77-87.**

HCV is Nearly 4 Times as Prevalent as HIV and HBV

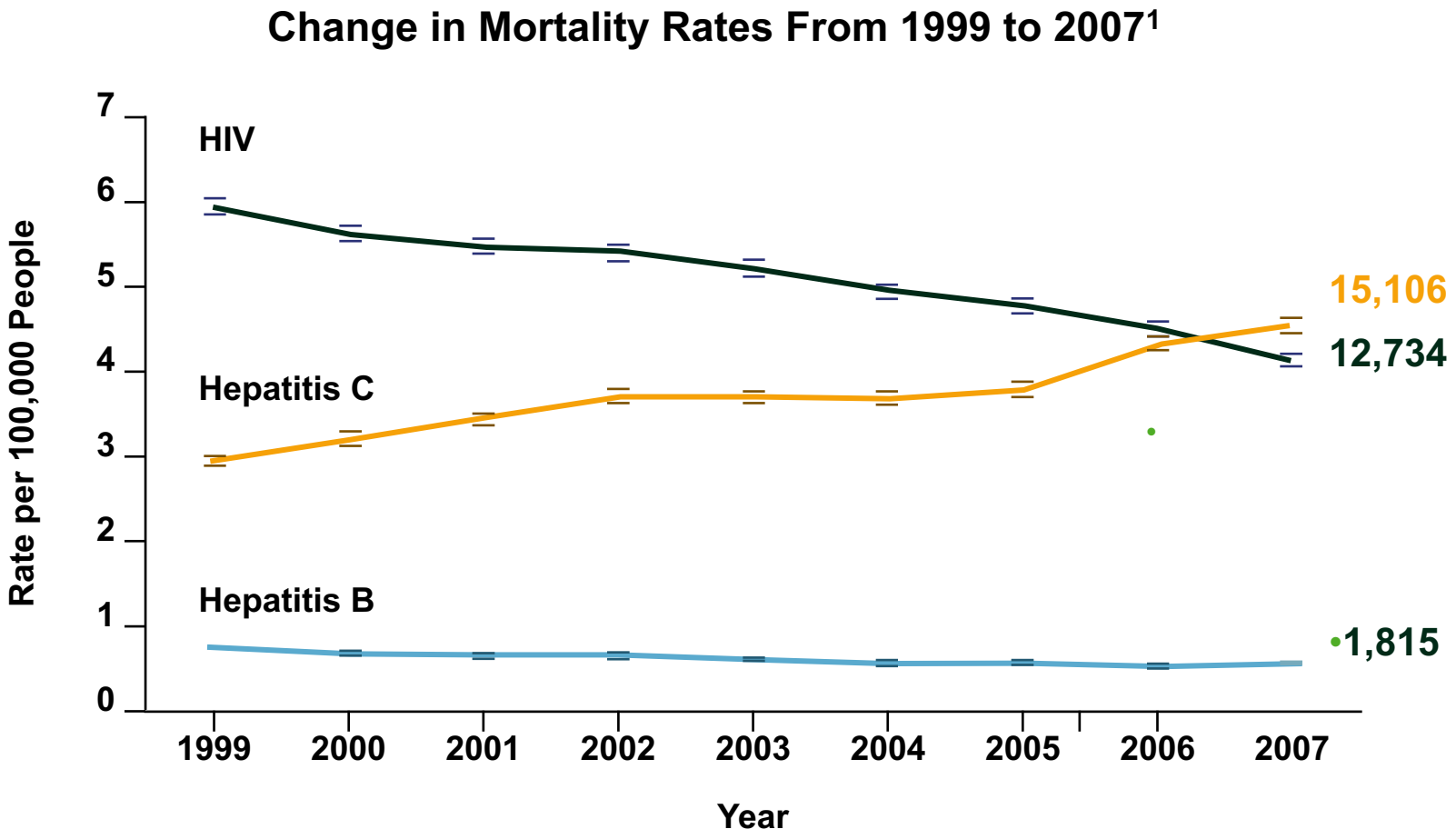


- A 2011 study estimated that as many as 5.2 million persons are living with HCV in the United States[2, 3]
- Based on a 2015 literature search that takes into account populations excluded from NHANEs, the number of US residents who have been infected with HCV is ~4.6 million (range 3.4 million-6.0 million)[4]

HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.

1. Institute of Medicine. Washington, DC: The National Academies Press; 2010; 2. Chak E, et al. *Liver Int*. 2011;31(8):1090-1101; Gish R et al., *Hepatology*. 2016: DOI 10.1002/hep.28026; 4. Edlin BR et al. *Hepatology*. 2015;62(5):1353-63.

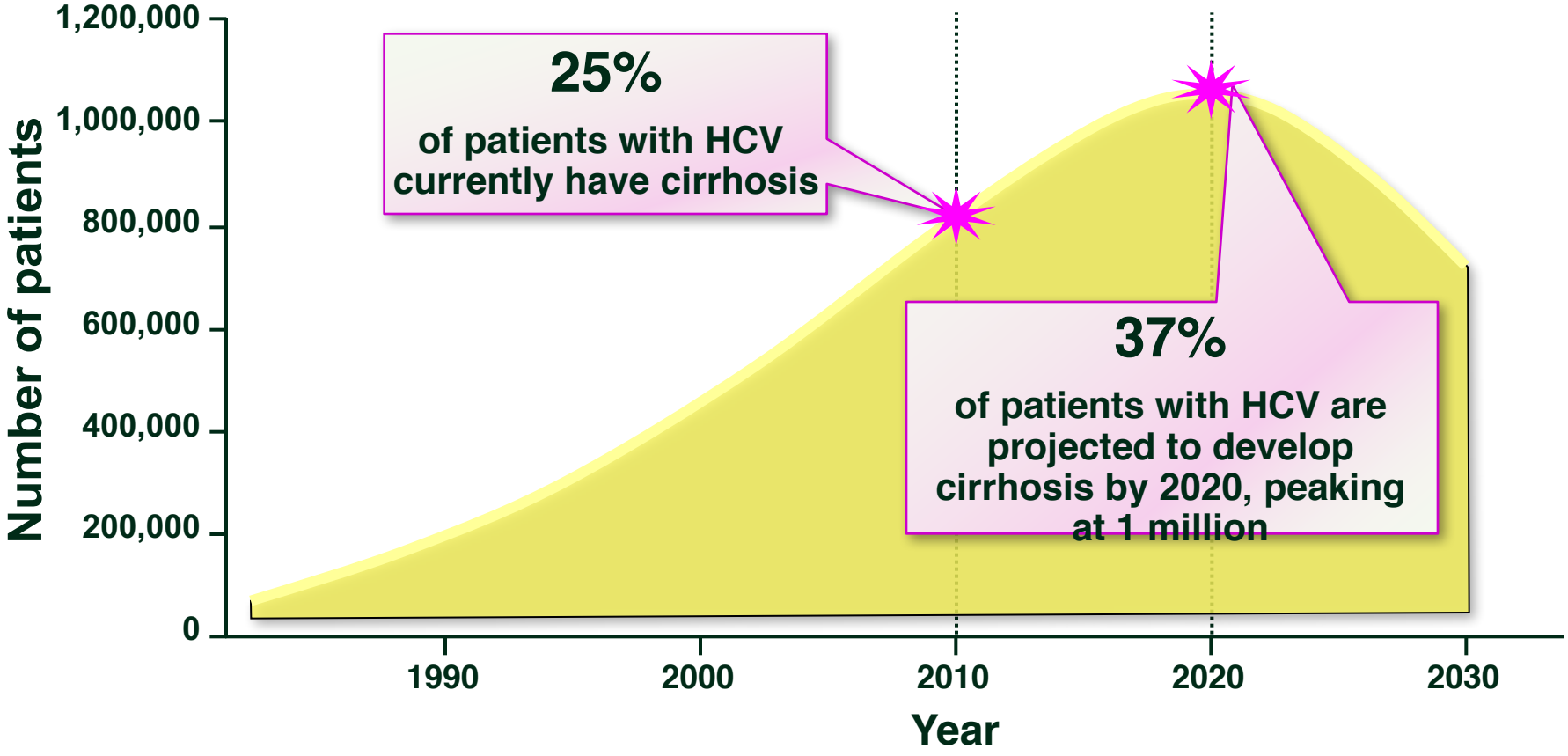
Deaths From HCV Surpassed Those From HIV



1. Ly KN, et al. *Ann Intern Med*. 2012;156(4):271-278.

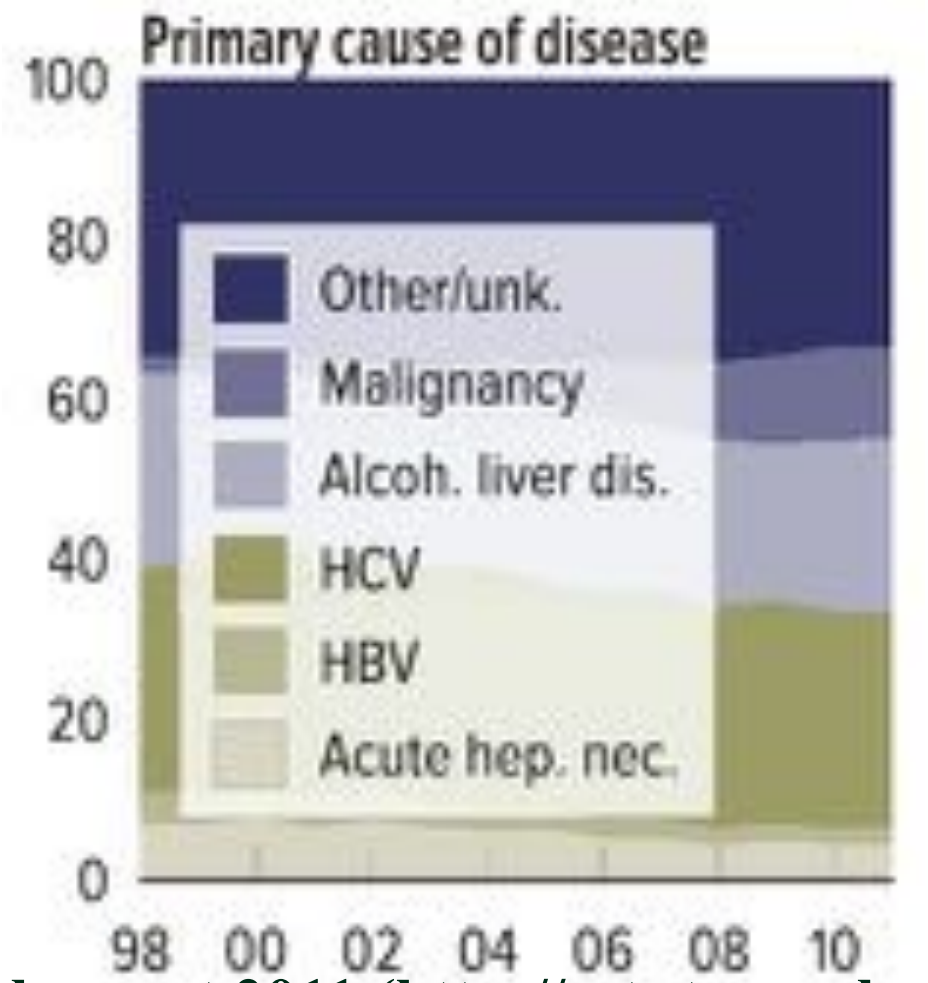
2. Available at : http://www.cdc.gov/hepatitis/statistics/2014surveillance/commentary.htm. Accessed May 10, 2016.

Hepatitis C-Related Cirrhosis Is Projected to Peak Over Next 10 Years



•Davis GL, et al. *Gastroenterology.* 2010;138:513-521.

Indications for OLT over 12 years: HCV still most common indication for OLT, that will change soon

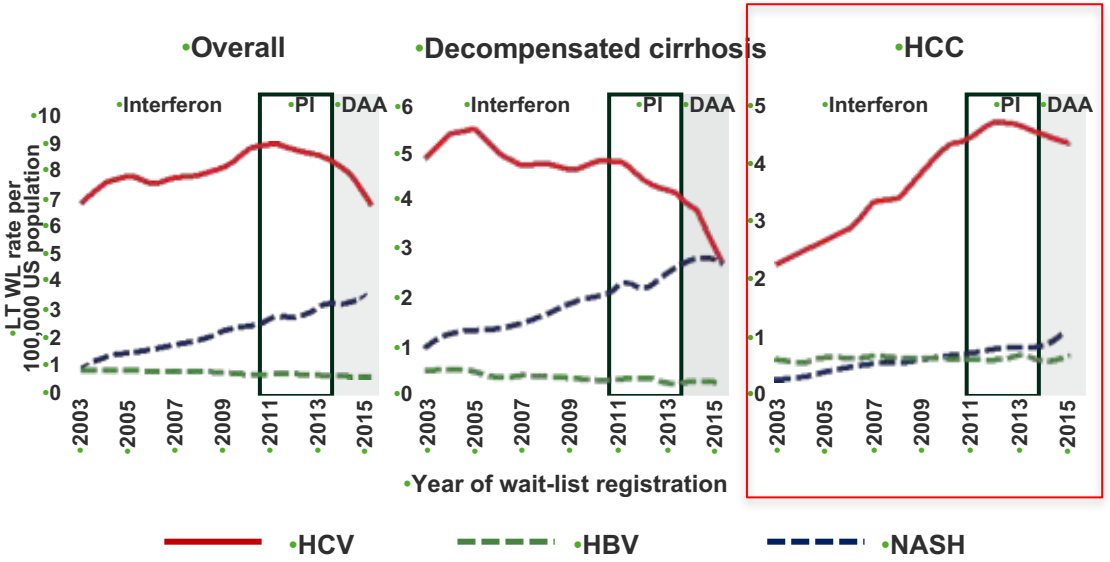


SRTR Annual report 2011 (http://srtr.transplant.hrsa.gov)

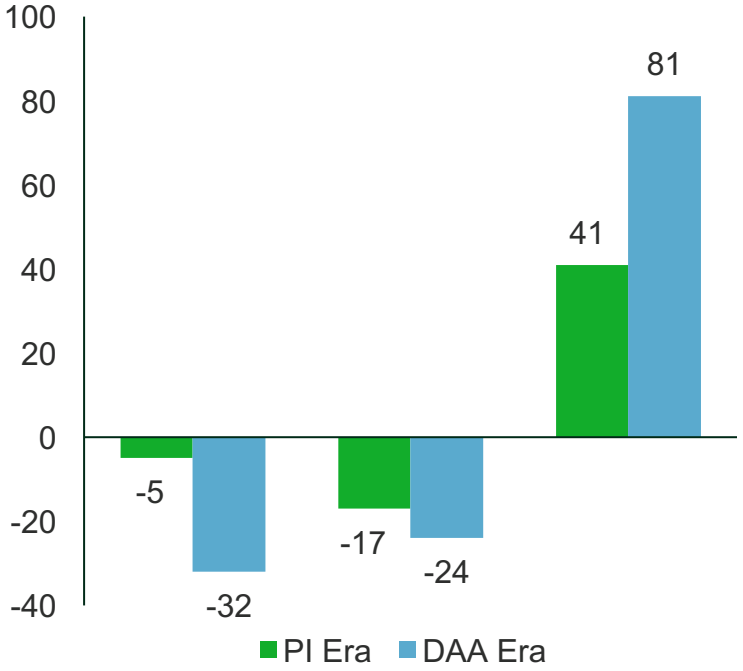
Reduction in Liver Transplant Waitlist in the Era of HCV DAAs

Cohort study of 47,591 adults wait-listed for liver transplant (LT WL) using the Scientific Registry of Transplant Recipients database from 2003–2015

- **Annual Standardized Incidence Rates (ASIR) of LT Wait-Listing per 100,000 US Population**



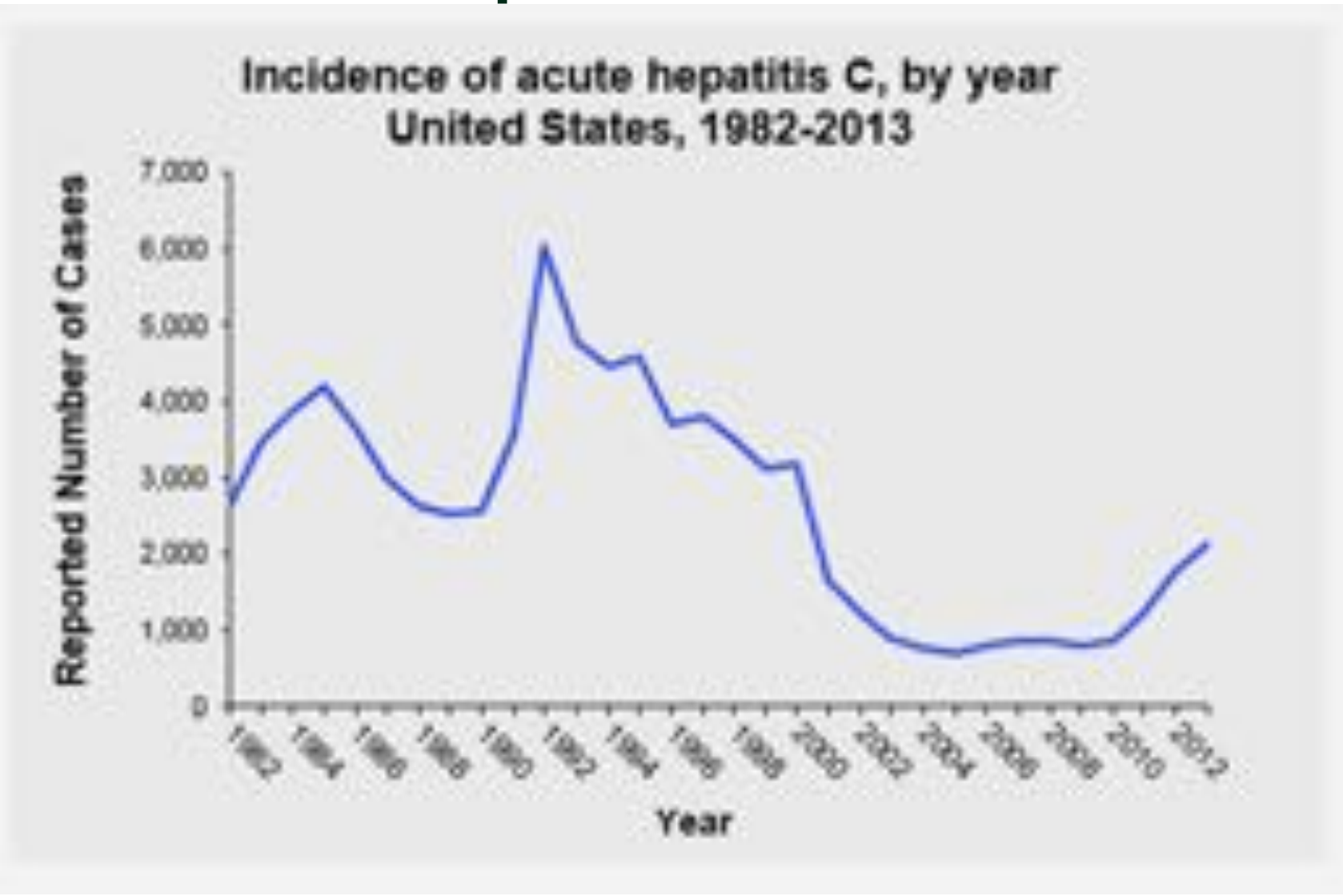
Incidence of Liver Transplant Wait-Listing for Decompensated Cirrhosis Compared to IFN Era



- **The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% in the era of DAA therapy as compared to the IFN era**

Flemming JA, AASLD 2016, Poster LB-23

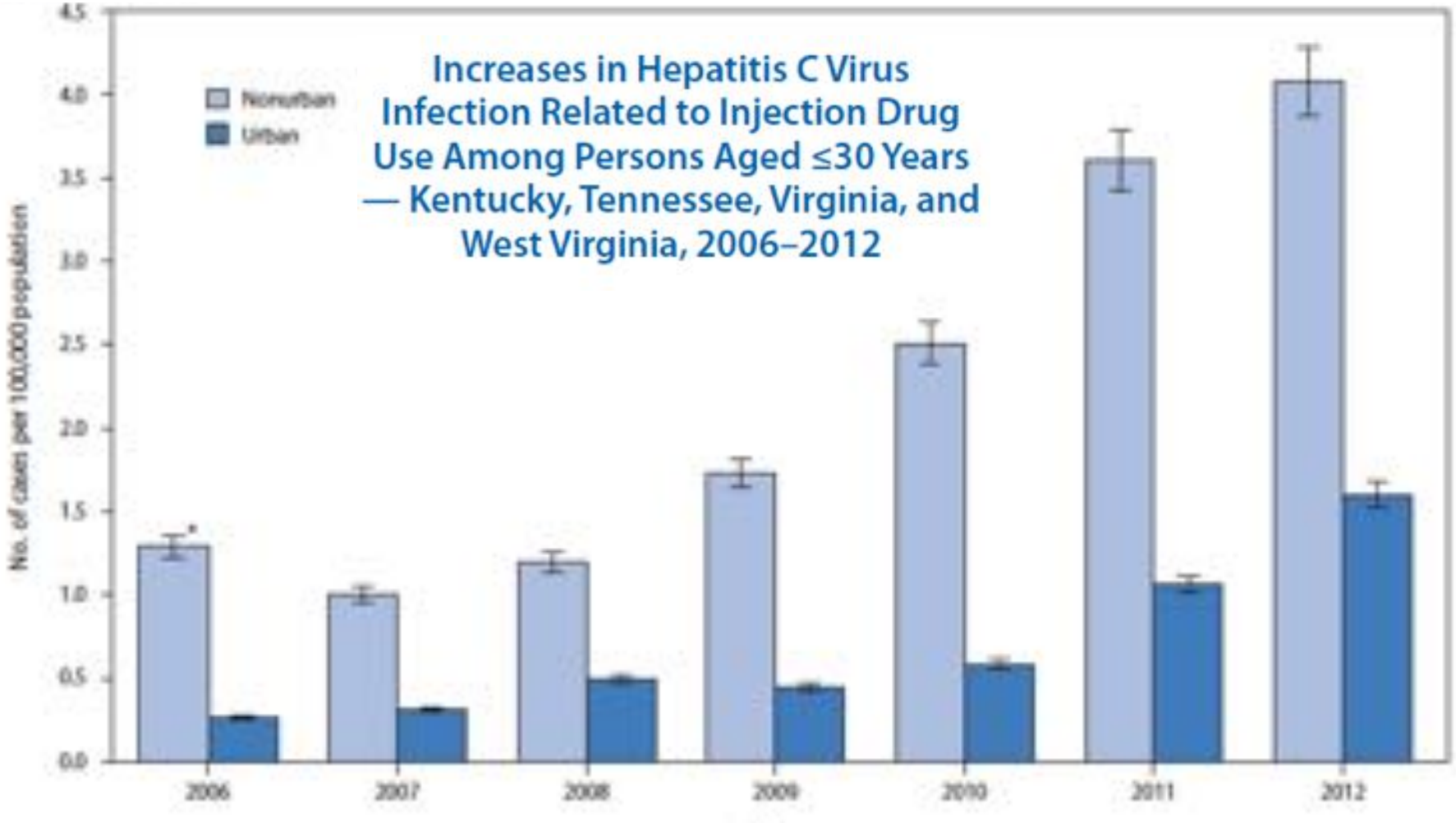
Estimated 29,700 estimated cases of acute hepatitis C: 2013



http://www.cdc.gov/hepatitis/Statistics/index.htm

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 64 / No. 17
May 8, 2015

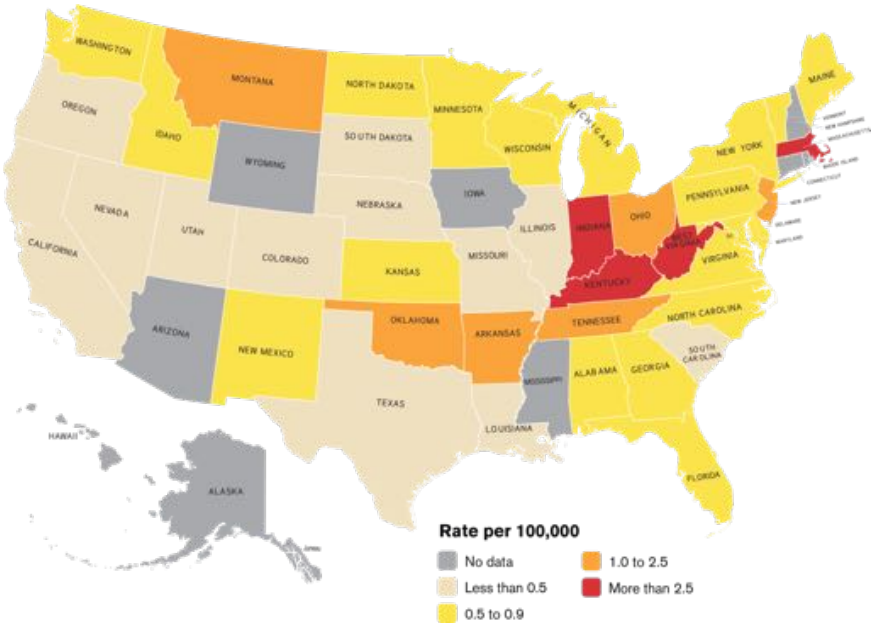
Increases in Hepatitis C Virus Infection Related to Injection Drug Use Among Persons Aged ≤30 Years — Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012



Acute HCV vs. Death from Heroin Overdose

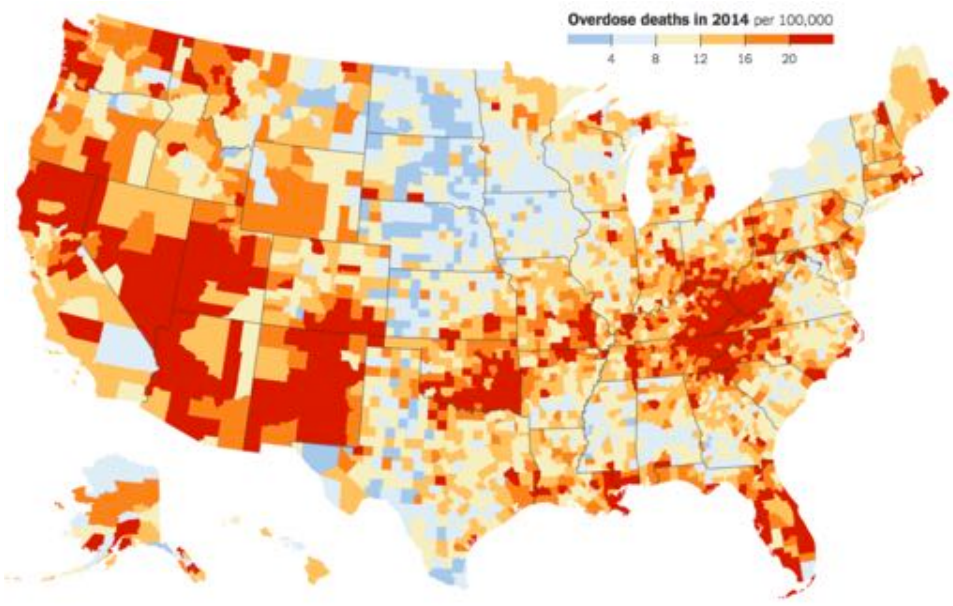
Acute HCV, 2013

By State



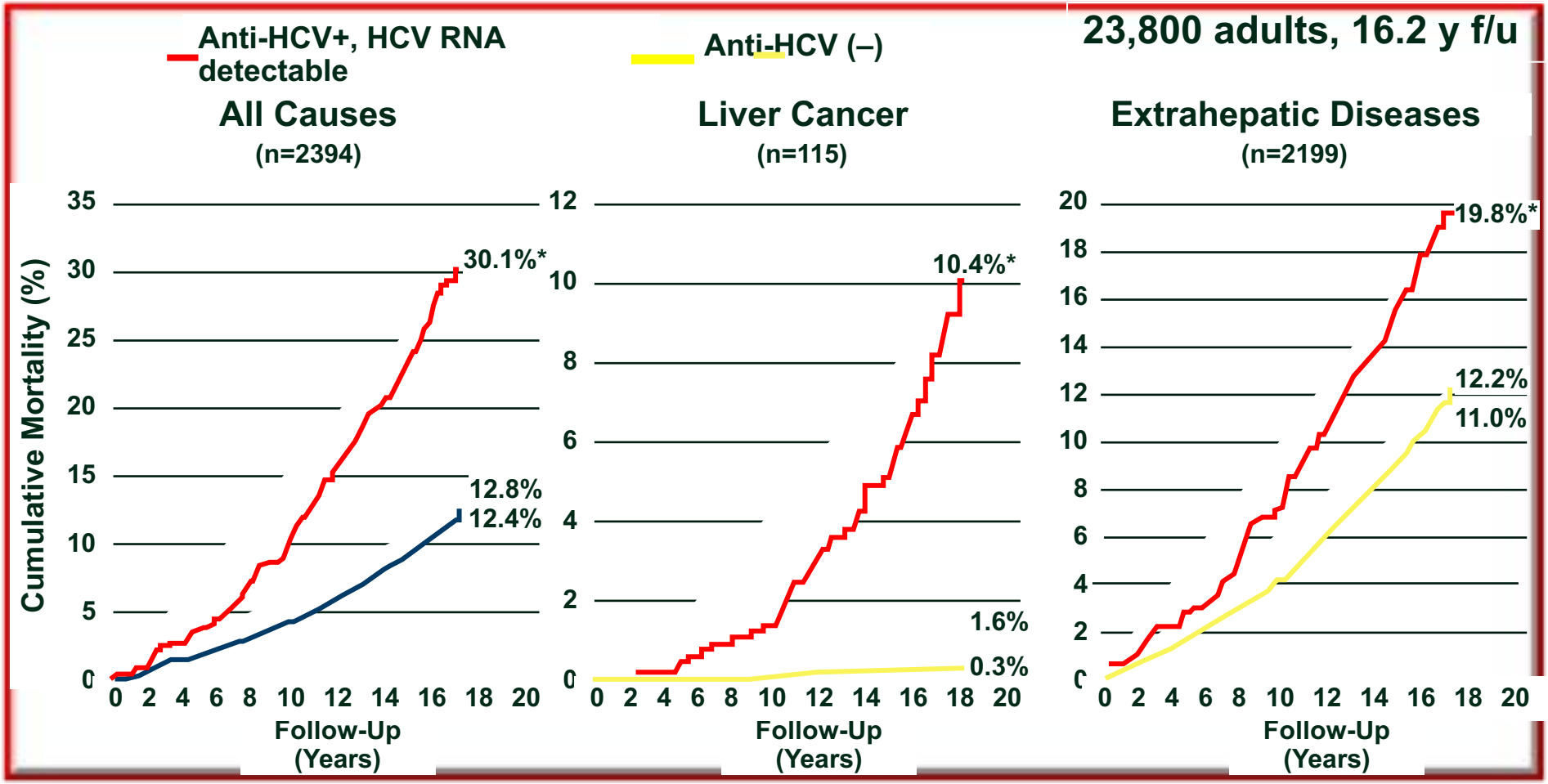
Deaths from Heroin Overdose, 2014

By County



Centers for Disease Control and Prevention. Drug Poisoning Mortality: United States, 1999-2014. http://blogs.cdc.gov/nchs-data-visualization/drug-poisoning-mortality/. Accessed 5/19/16.

REVEAL C: Hepatitis C is a systemic disease

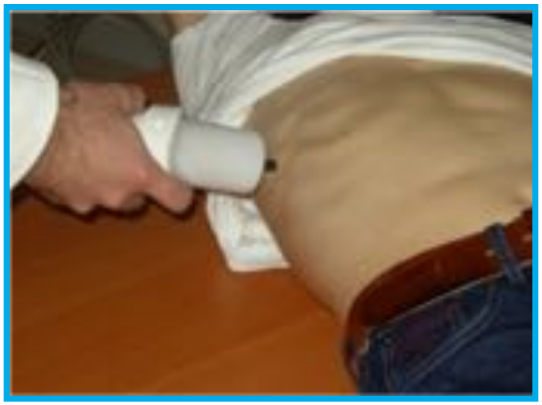


Lee M-H, et al. *J Infect Dis*. 2012;206:469-477

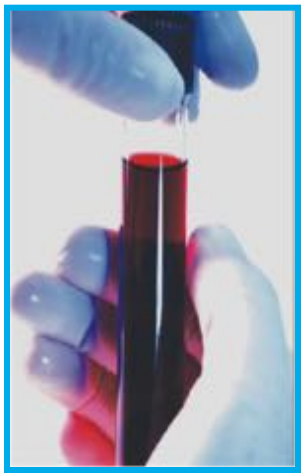
Options for Liver Fibrosis Assessment: Liver biopsy rarely done now

No single test is accurate enough, make sure non-invasive tests align

Liver biopsy: Gold standard

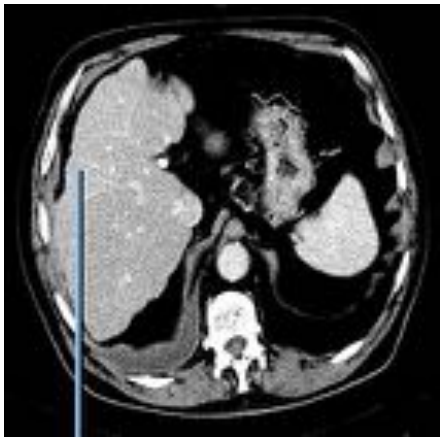


Elastography: Approved in US



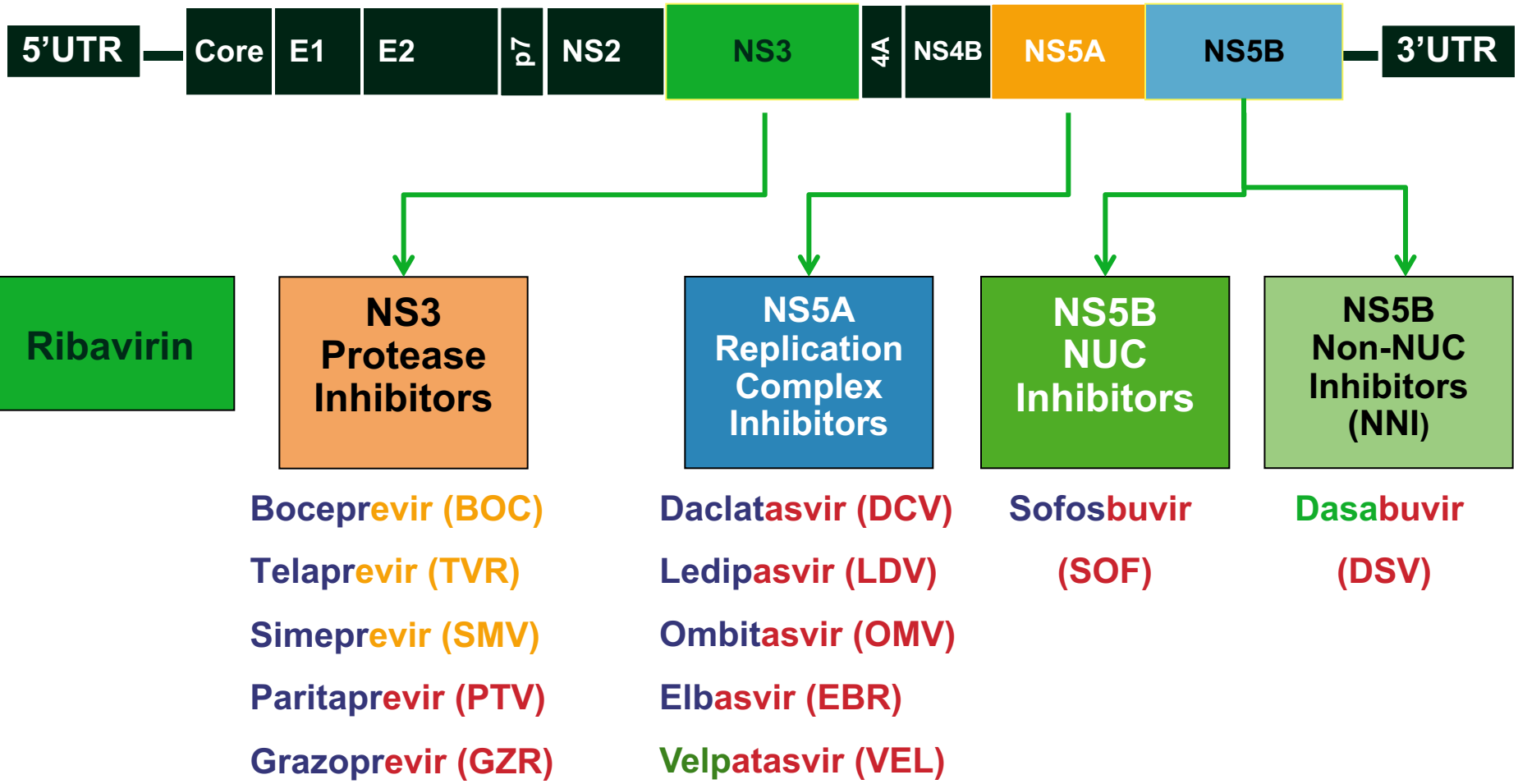
Serum Biomarkers

Serum Markers of Fibrosis: FIBROSpect®, FibroSURE®, APRI, FIB-4



Axial CT/MRI, US can demonstrate cirrhotic morphology, portal hypertension

Approved Direct-Acting Antiviral Agents (DAAs) from Multiple Classes



HCV: Genotype 1A and 1B

Treatment Naïve, 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%)
Elbasivr/grazoprevir (1b) (-) -NS5A RAVs (1a)	12	C-EDGE	133/135 (99%) 129/131 (99%)
PrOD (1b)	12	PEARL III	207/209 (99.5%)
PrOD +/- ribavirin (1a)	12	PEARL IV SAPPHIRE-I	97/100 (97%) 307/322 (95%)
Simeprevir + Sofosbuvir	12	COSMOS OPTIMIST-1	20/21 (95%) 112/115 (97%)
Daclatasvir + Sofosbuvir	12	ALLY-2 (HIV CoInfected)	70/72 (97%)
Sofosbuvir+ velpatasvir	12	ASTRAL-1	251/257 (98)%

•AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 4/

HCV: Genotypes 2 and 3
Treatment Naïve, Non-cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	2	12	ASTRAL-1	**99%**
Velpatasvir + Sofosbuvir	3	12	ASTRAL-3	**98%**
Daclatasvir + Sofosbuvir	3	12	ALLY-3	**97%**

NOT HEAD TO HEAD TRIALS

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org. Accessed 4/ 26/2016

HCV: Genotypes 4
Treatment Naïve, Non-cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	4	12	ASTRAL-1	100%
Sofosbuvir + ledipasvir	4	12	Synergy	95%
Elbasvir/grazoprevir	4	12	C-Edge	97%
Paritaprevir/Ombitasvir/RBV	4	12	PEARL-1	100%

- NOT HEAD TO HEAD TRIALS

HCV: Genotypes 5 and 6

Treatment Naïve, Non-cirrhotic

Regimen	Geno-type	Weeks	Study	SVR12
Velpatasvir + Sofosbuvir	5	12	ASTRAL-1	**96%**
Sofosbuvir + ledipasvir	5	12		**95%**
Velpatasvir + Sofosbuvir	6	12	ASTRAL-1	**100%**
Sofosbuvir + ledipasvir	6	12	Synergy	**100%**

NOT HEAD TO HEAD TRIALS

Elbasvir/Grazoprevir experience in the VA healthcare system

- 2,436 patients (evaluable population) starting EBR/GZR between 2/2016 and 8/2016
- SVR 95.6% (EP) and 97% (PP)

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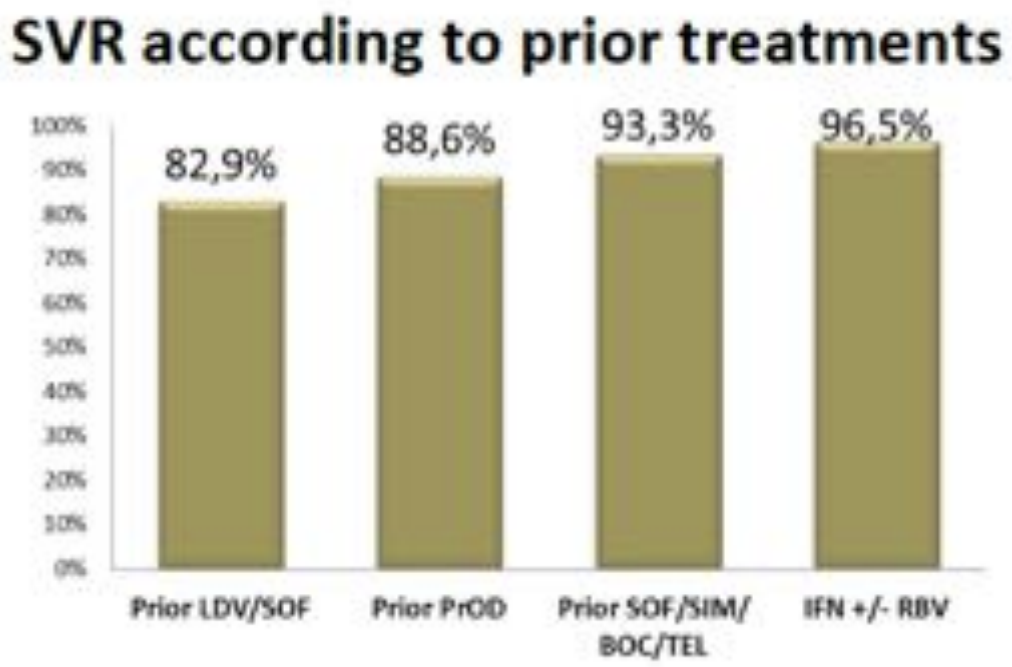
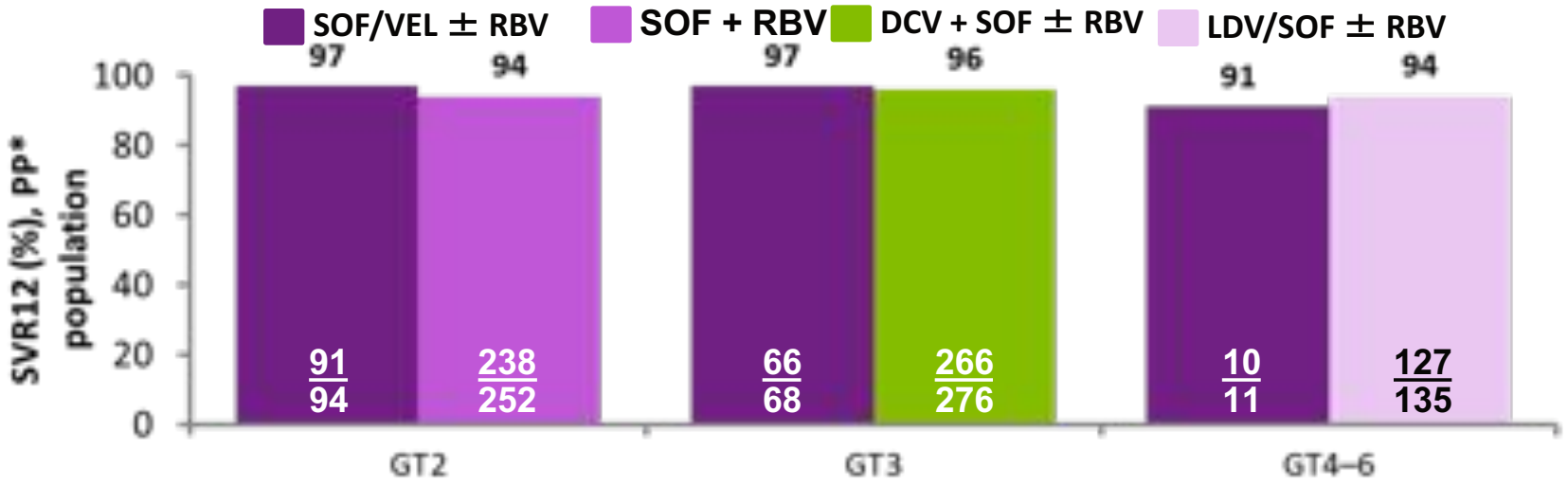
- Similar high SVR rates in
  - pts. with history of acohol abuse
  - pts. with history of drug abuse
  - cirrhosis (n=808)
  - CKD stage 4-5 (n=407)
  - HIV infection (n=74)
  - GT4 (n=64)
  - Afr. Americ (n=1400)
  - Hispanics (n=81)



Kramer, Puenpatom et al., PS-095 EASL 2017:

Sofosbuvir/velpatasvir compared to existing Standards of Care in GT2-6 HCV

Real-world study of 1827 patients in the US HCV TRIO Network to evaluate treatment utilization and compare outcomes between SOV/VEL ± RBV and existing DAA therapies in patients with GT2–6 chronic HCV



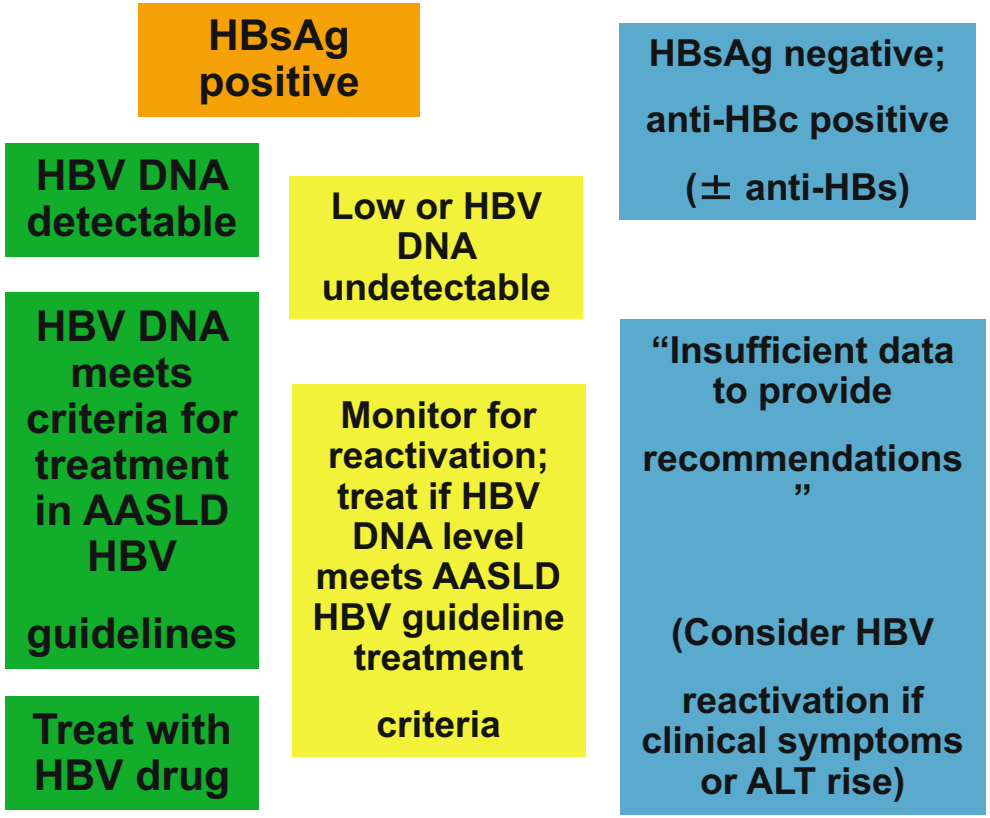
SOF/VEL ± RBV SVR12, % (n/N)	GT2	GT3
Treatment-naive	97 (70/72)	98 (55/56)
Treatment-experienced	95 (21/22)	92 (11/12)
F0–3	97 (70/72)	100 (52/52)
F4	95 (21/22)	93 (14/15)

*Includes patients who completed treatment and excluded patients with non-virologic failure.

Curry M, et al. EASL 2017; oral #PS-102.

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



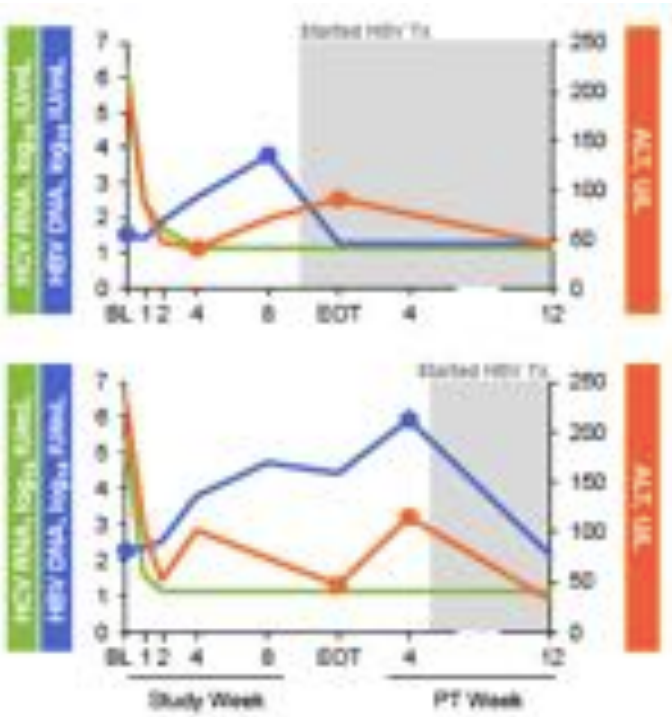
AASLD/IDSA. HCV Guidelines 2017. Graphic adapted from Ira M. Jacobson, MD.

LDV/SOF for 12 Wks in Pts With GT1 or 2 HCV and HBV Coinfection

- Open-label study of HBsAg-positive pts not receiving HBV treatment, mostly HBeA negative (99%), HCV treatment naive (67%)
- 18/111 with cirrhosis
- HCV SVR12 was 100% (111/111)
- HBV DNA reactivated in 63% of pts (70/111)

HBV Increase, n (%)	Overall (N = 111)	BL HBV DNA	
		< LLOQ (n = 37)	≥ LLOQ (n = 74)
≥ LLOQ ▪ALT > 2x ULN	31 (28) 0	31 (84) 0	-- --
> 1 to < 2 log_{10} IU/mL ▪ALT > 2x ULN	37 (33) 1 (< 1)	11 (30) 0	26 (35) 1 (1)
≥ 2 log_{10} IU/mL (any visit) ▪ALT > 2x ULN	24 (22) 4 (4)	11 (30) 0	13 (18) 4 (5)

BL Factor, Mean (Range)	HBV Reactivation		*P* Value
	No (n = 106)	Yes (n = 5)	
BL ALT, U/L	64 (17-281)	149 (40-228)	.0032
HBV DNA, log_{10} IU/mL	2.05 (1.28-5.83)	2.97 (1.54-5.46)	.0188



Liu CJ, et al. EASL 2017. Abstract PS-098.

Dose Adjustments of DAAs in Cirrhosis

Protease inhibitors should not be used in Childs B/C

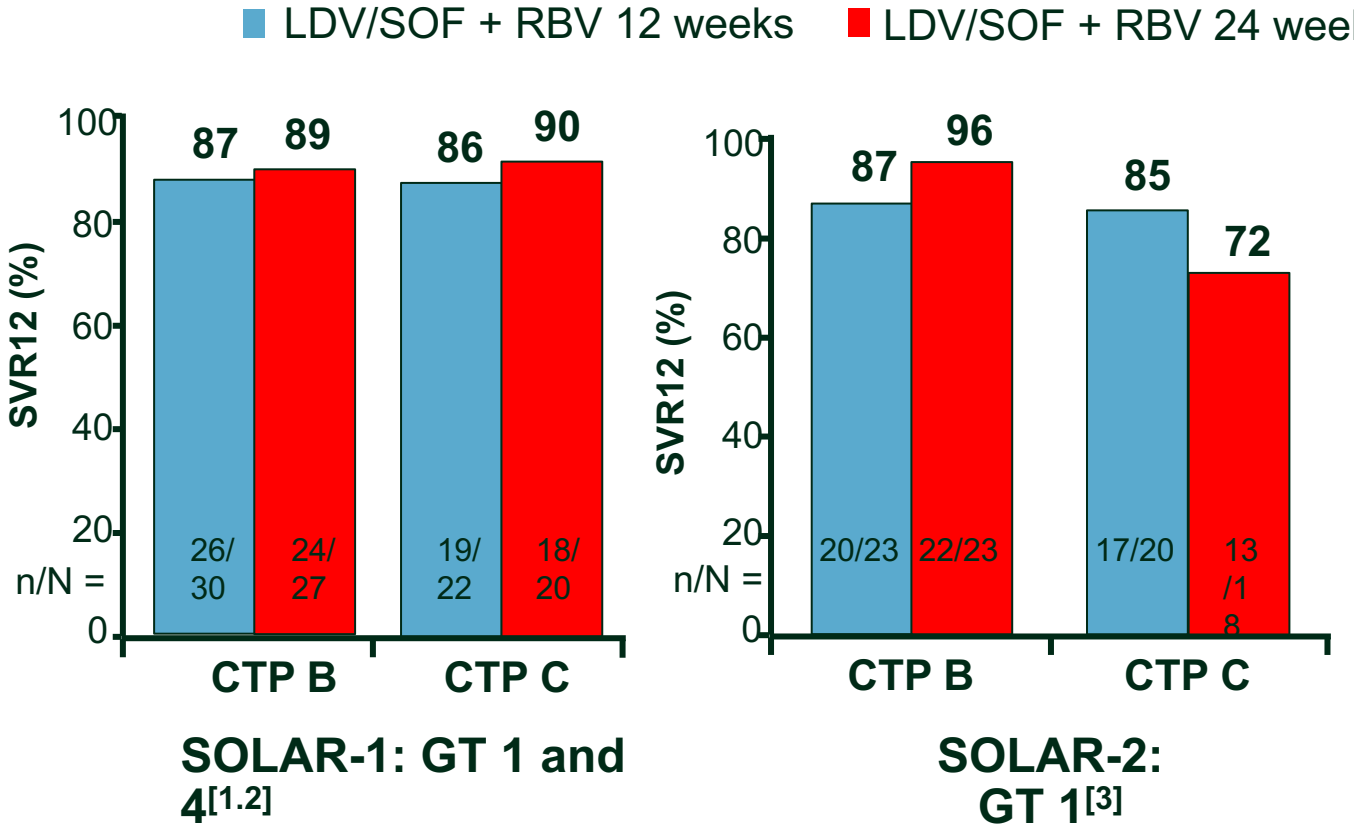
Childs Class	Sofosbuvir	Simeprevir	Ribavirin Daily
A	400 mg	150 mg	1000-1200 mg/day
B	400 mg	No	600 mg
C	400 mg	No	600 mg

Childs Class	Ledipasvir/ sofosbuvir	PTV/OMB/DSB	Daclatasvir	Grazoprevir/ Elbasvir	Sofosbuvir/ velpatasvir
A	90mg/400mg	75/50/12.5 mg + 250 mg	60 mg	100/50	400mg/100mg
B	90mg/400mg	No	60 mg	No	400mg/100mg
C	90mg/400mg	No	60 mg	No	400mg/100mg

Bifano M, et al. AASLD 2011. Abstract 1362. Garimella K, et al. Clinical Pharm 2014. Abstract P43. Sofosbuvir [package insert]. Simeprevir [package insert]. Khatri A, et al. AASLD 2012. Abstract 758. German, et al. AASLD 2013. Abstract 467. Kirby R, et al. Clinical Pharm 2013. Abstract PO20.

LDV/SOF + RBV: SVR12 in Genotype 1 or 4 with Decompensated Cirrhosis

Comparable efficacy between SOLAR-1 and SOLAR-2 studies

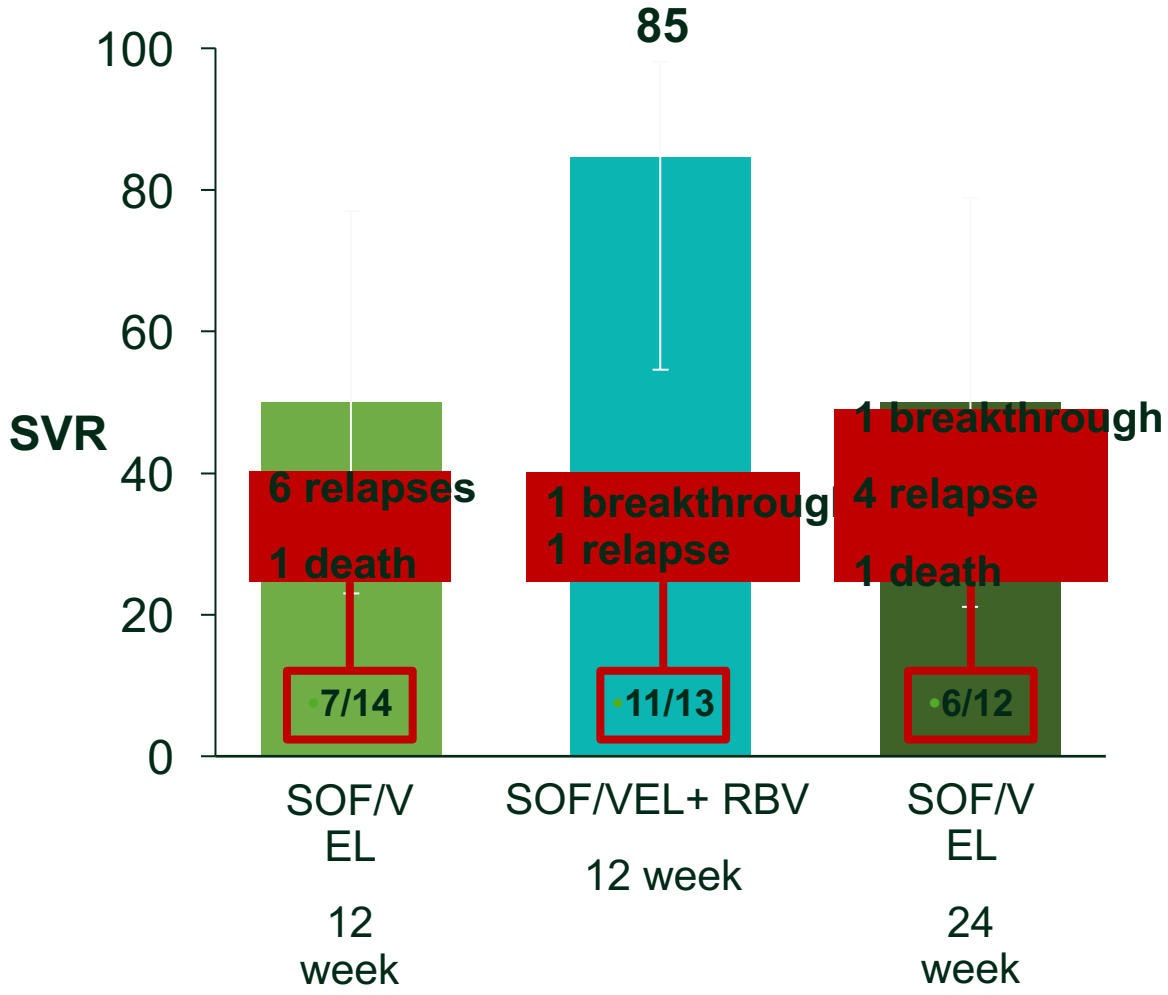


AE, adverse event; CTP, Child-Turcotte-Pugh; LDV, ledipasvir; RBV, ribavirin; SAE, serious adverse event; SOF, sofosbuvir.

- 1. Charlton M, et al. *Gastroenterology*, 2015 [epub ahead of print]
- 2. Flamm SL, et al. Presented at: AASLD; November 7-11, 2014; Boston, MA. Abstract 239.

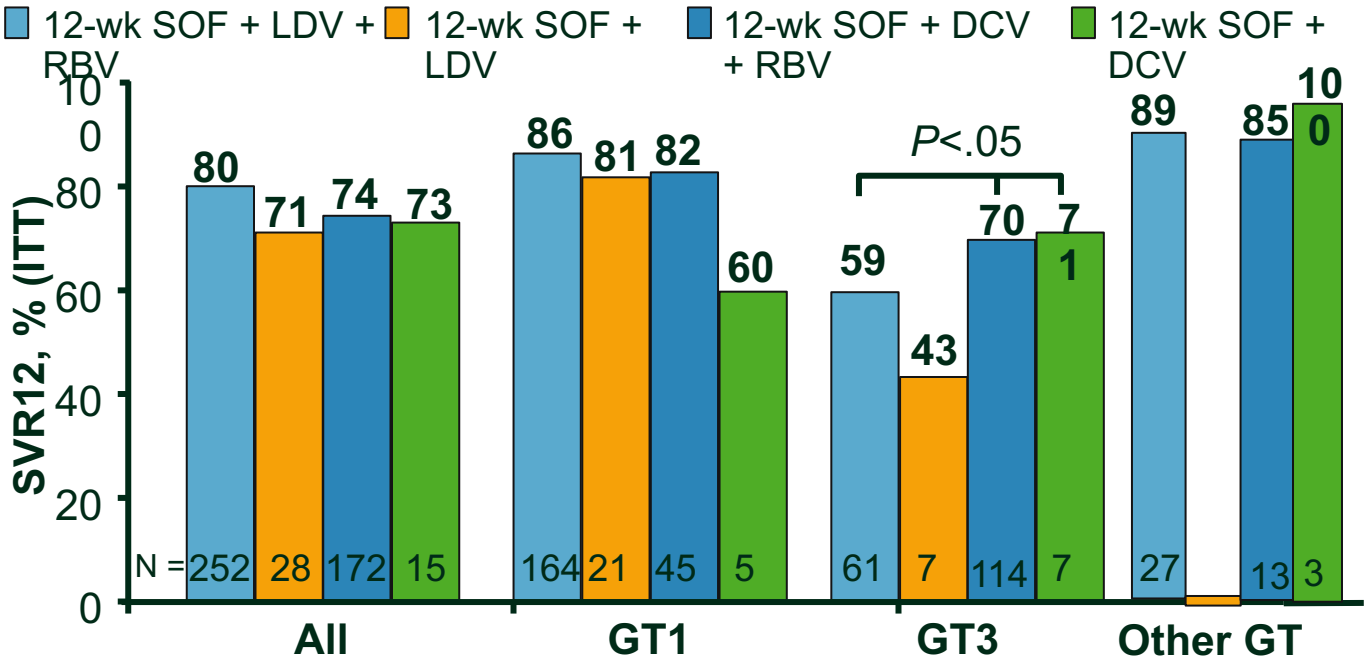
3. Manns M, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract G02.

ASTRAL-4 Childs B Cirrhosis SOF/VEL± RBV: SVR12 in GT 3 Patients



Treatment of Decompensated HCV Cirrhosis in Patients with Diverse Genotypes: 12 weeks Sofosbuvir and NS5A inhibitors With/Without Ribavirin

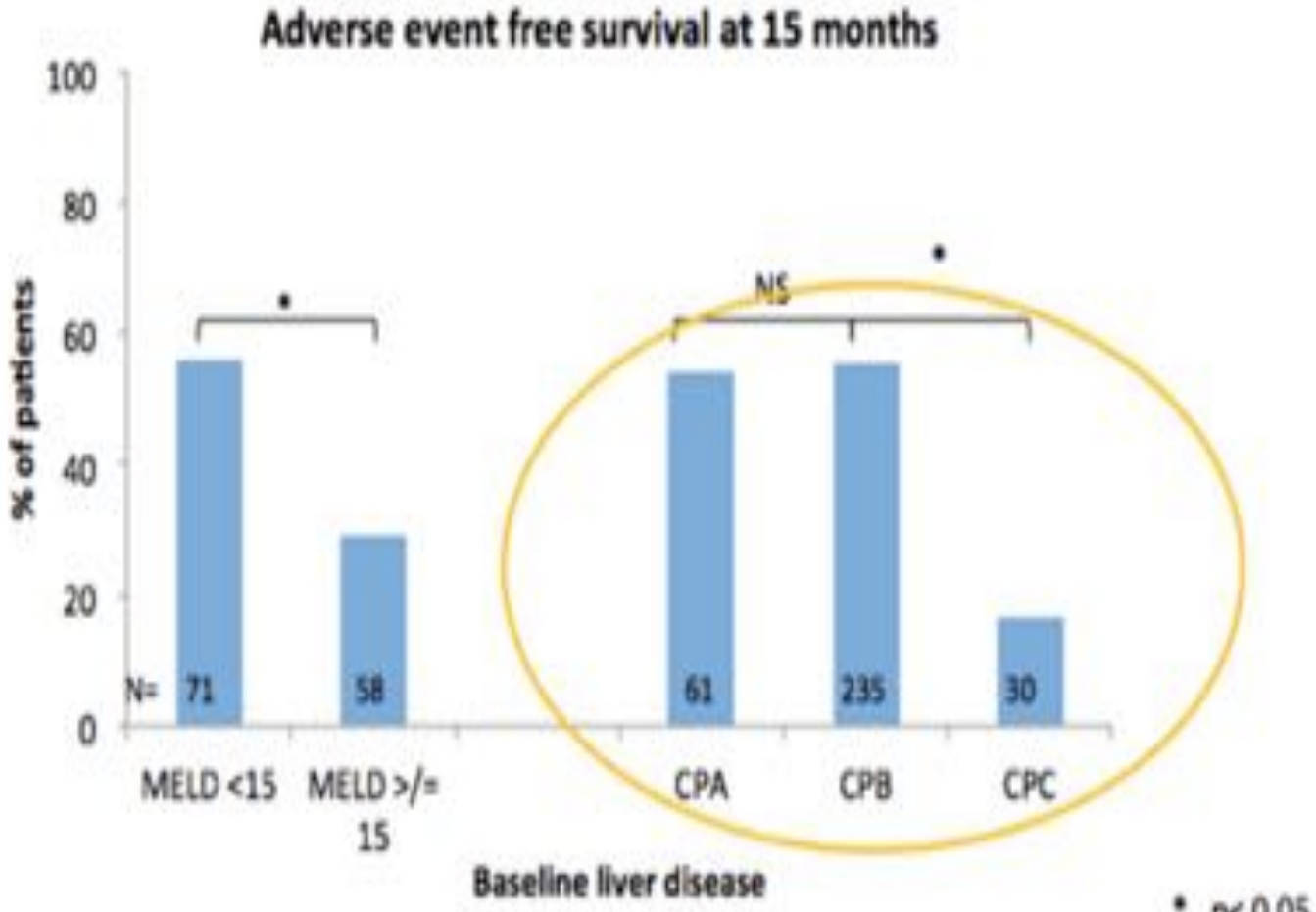
- Non-randomized observational cohort study of National Health Service of England (N = 467)
- Patients received 12 weeks SOF + LDV or DCV ± RBV at treating MD discretion (non-randomized)



DCV, daclatasvir; GT, genotype; HCV, hepatitis C virus; ITT, intent to treat.

- **Foster GR, et al. Presented at: EASL; April 22-26, 2015; Vienna, Austria. Abstract O002.**

Which Patients Benefit from Viral Clearance?

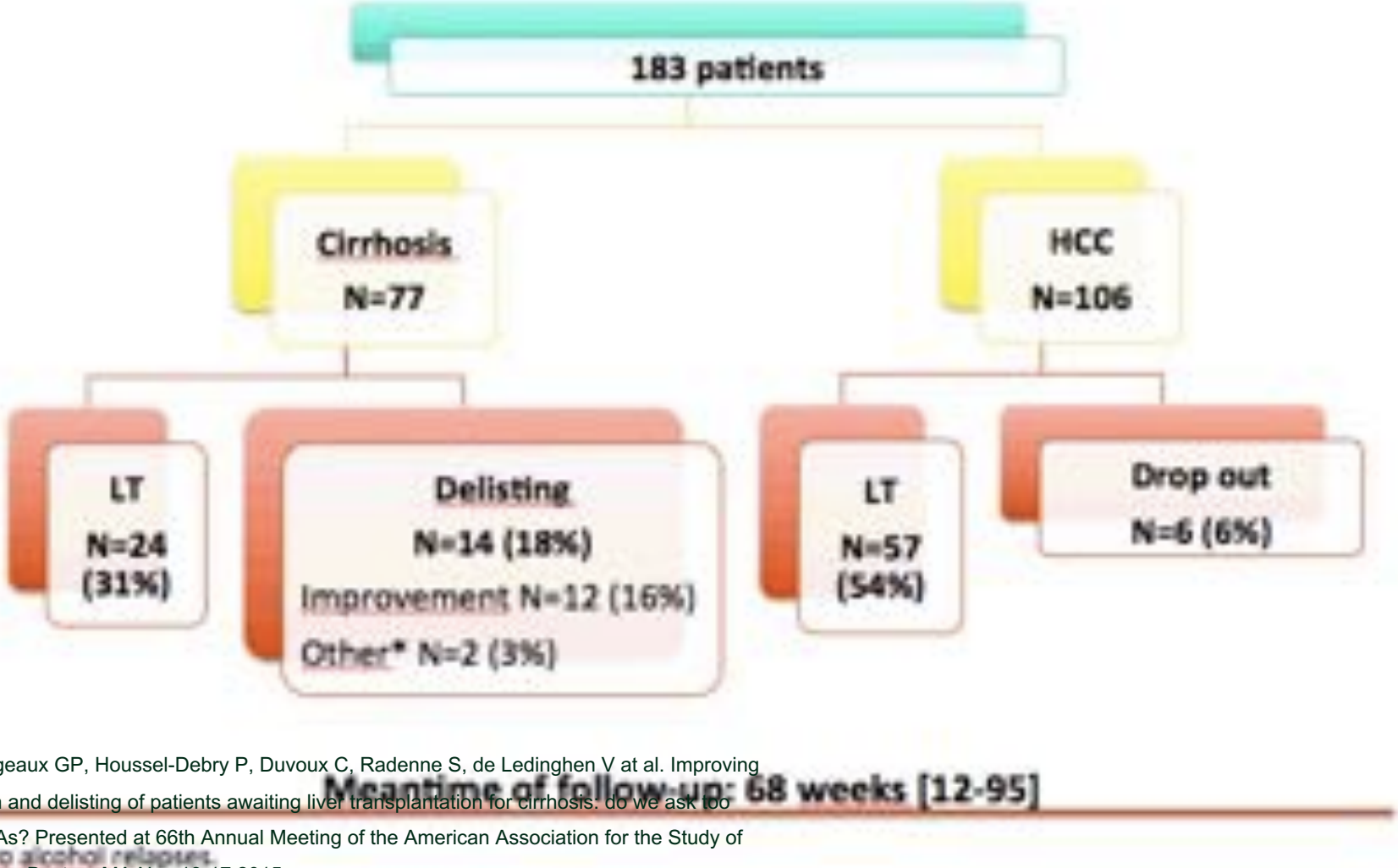


Only 20% of CPC patients are free of adverse events despite clearing virus

For CPB – 60% are virus free and free of significant problems, and did just as well as CPA

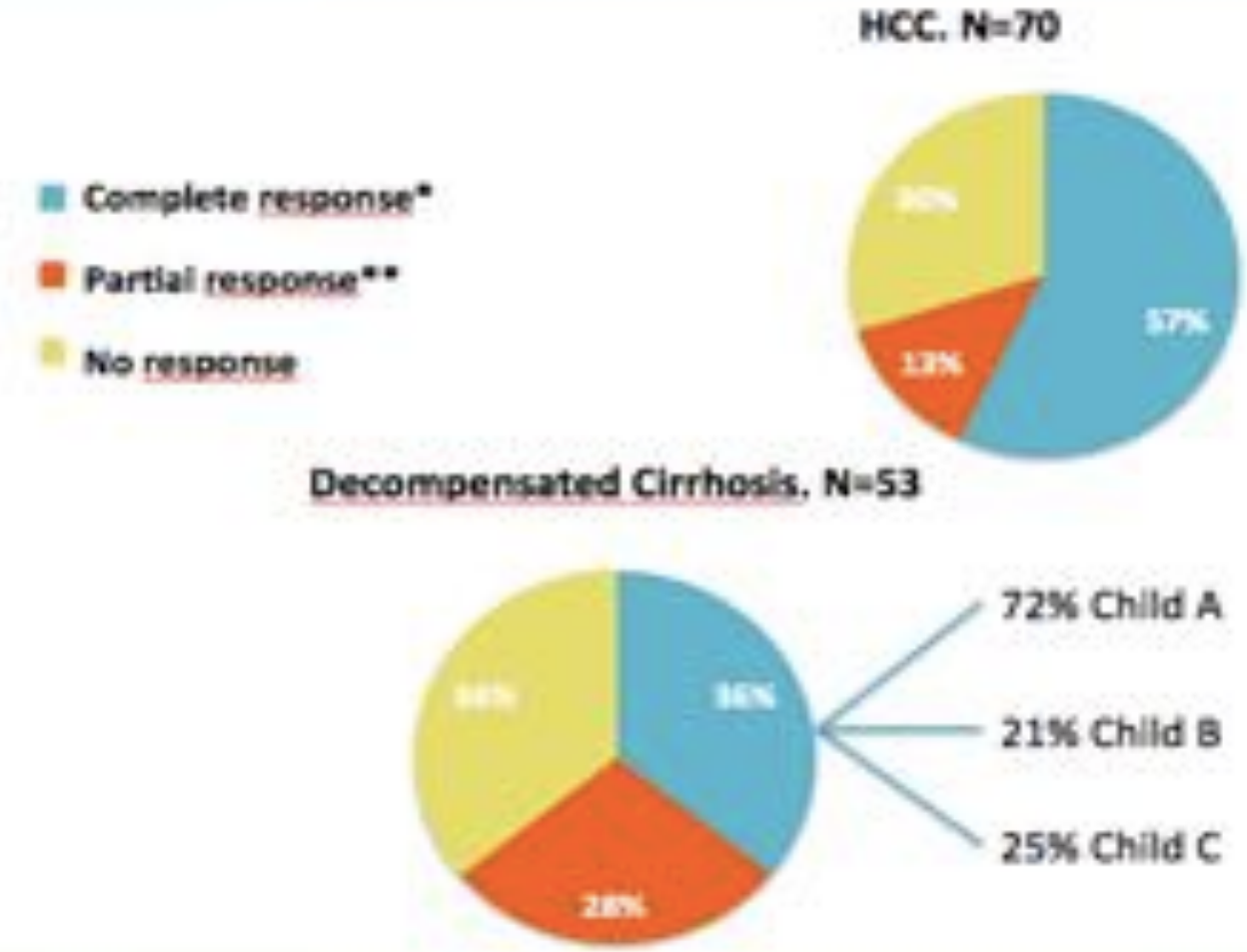
Delisting patients who receive DAAs

- 183 individuals with decompensated cirrhosis and/or HCC treated with SOF based regimens



Coilly A, Pageaux GP, Houssel-Debry P, Duvoux C, Radenne S, de Ledinghen V at al. Improving liver function and delisting of patients awaiting liver transplantation for cirrhosis: do we ask too much to DAAs? Presented at 66th Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA Nov 13-17 2015

Clinical and Biochemical responses post DAA therapy

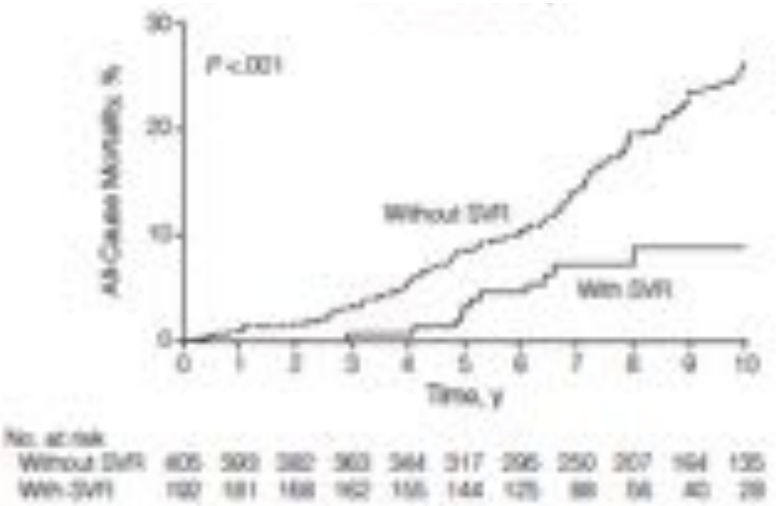


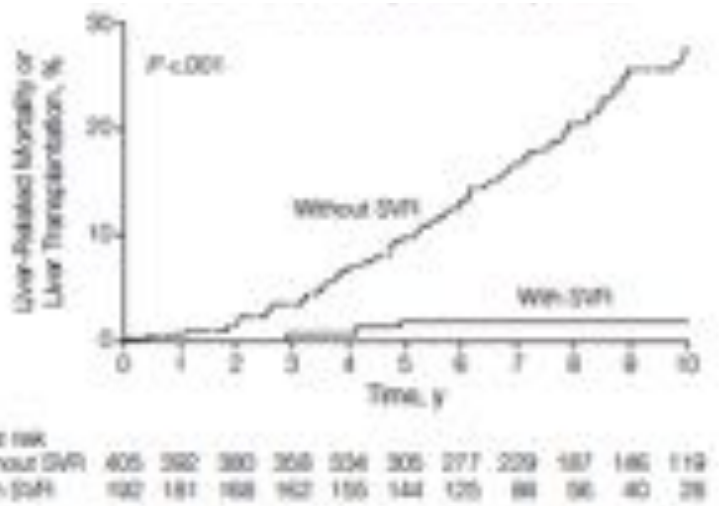
* Total bilirubin < 35μmol/l + PT>50% + albumin>35g/l + no ascites + no hepatic encephalopathy
** Child Class Change

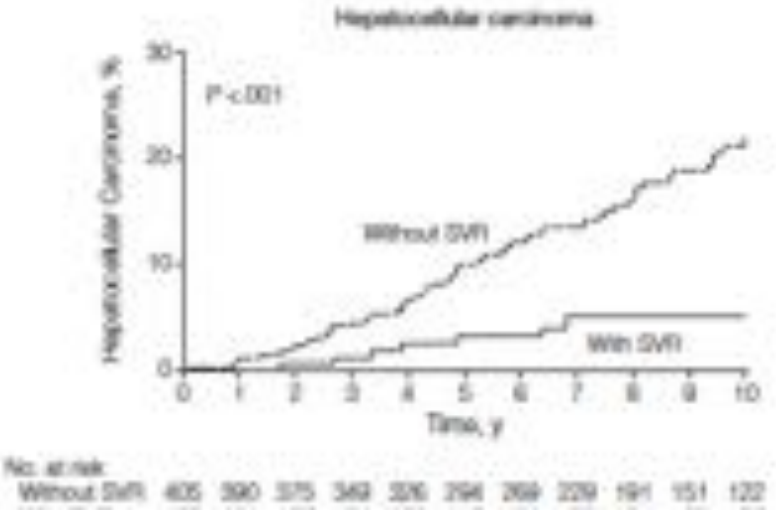
Which patients can you treat to achieve SVR and potentially not transplant?

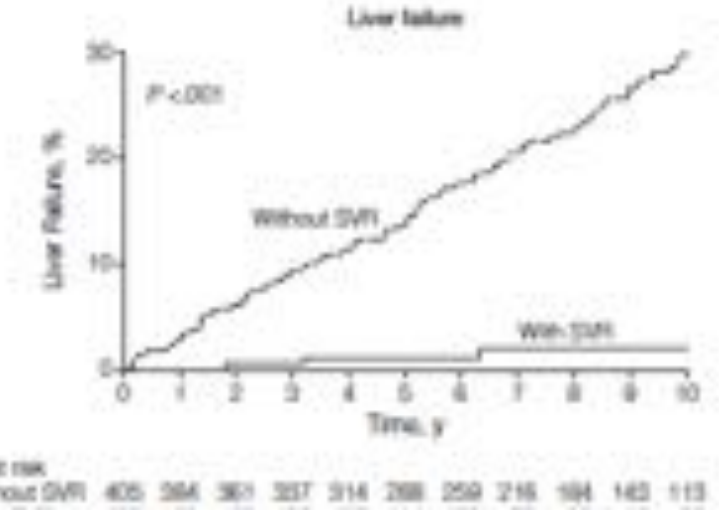
- Achieving SVR with DAAs will reduce inflammation in the liver
- Reversal of fibrosis is required to reduce portal hypertension, may take years
- About 20% of those with MELD <20 may improve and be delisted with DAA therapy and these individuals should be considered for treatment
  - Pay close attention to those with severe portal hypertension
- Those with MELD scores above 20 require careful assessment on individual basis
  - More data required in this population
  - Ribavirin free regimens are ideal, none yet available that give optimal SVR

Cure of Hepatitis C Reduces Liver Related Complications in those with hepatitis C





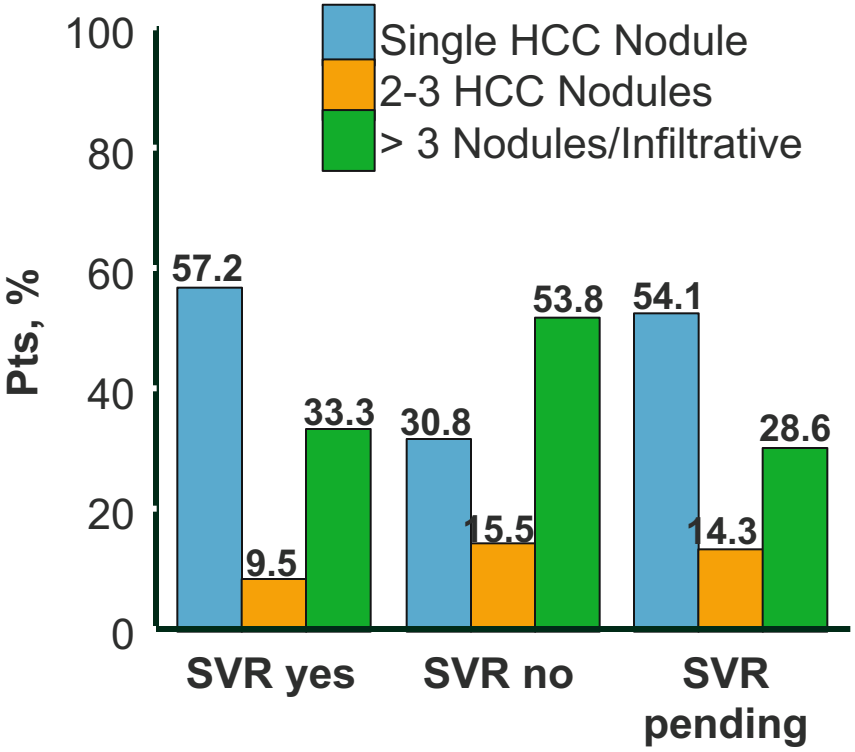


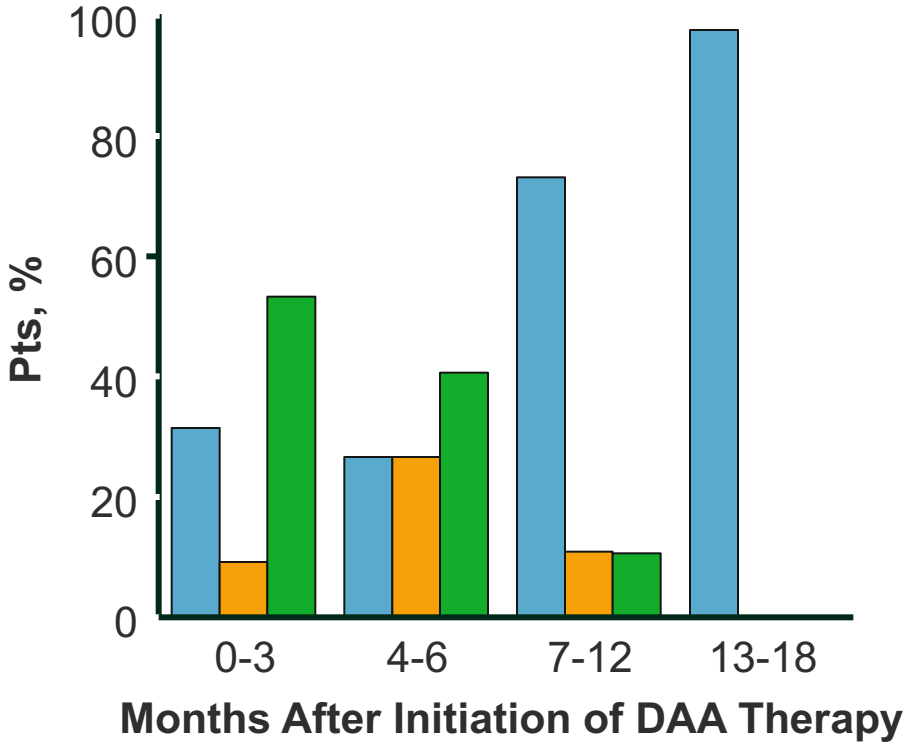


Van der Meer, et al. *JAMA* 2012:308:2584-2593.

De Novo HCC After DAA Treatment; Jury is still out

- Italian registry study of HCV-infected pts with no current or prior HCC, treated with DAAs
  - Mean follow-up after starting DAA therapy: 300.8 ± 100 days

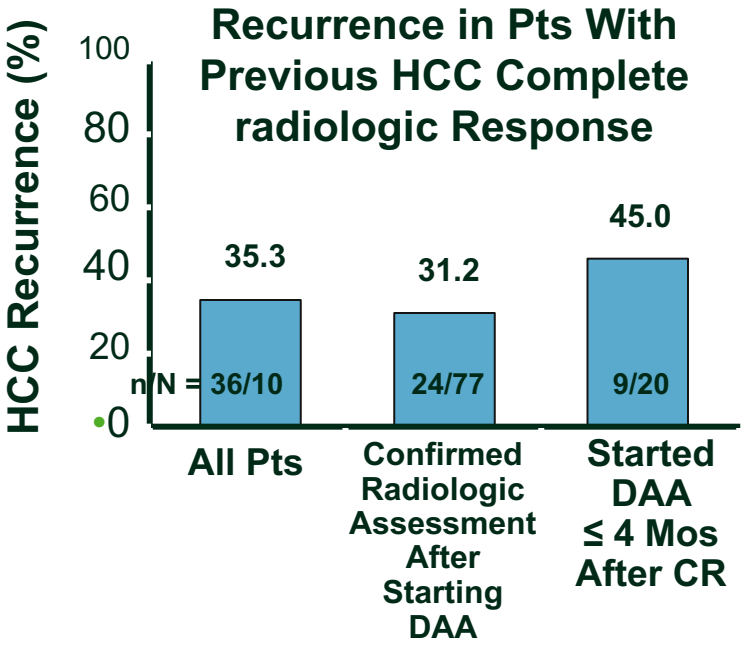




Romano A, et al. AASLD 2016. Abstract 19.

HCC Recurrence Following HCV DAA Therapy

- Retrospective study of pts with history of HCC before starting HCV DAAs (N = 105)
- AFP levels ranged from 1-369 ng/ml in those who had response



10 pts had second 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)

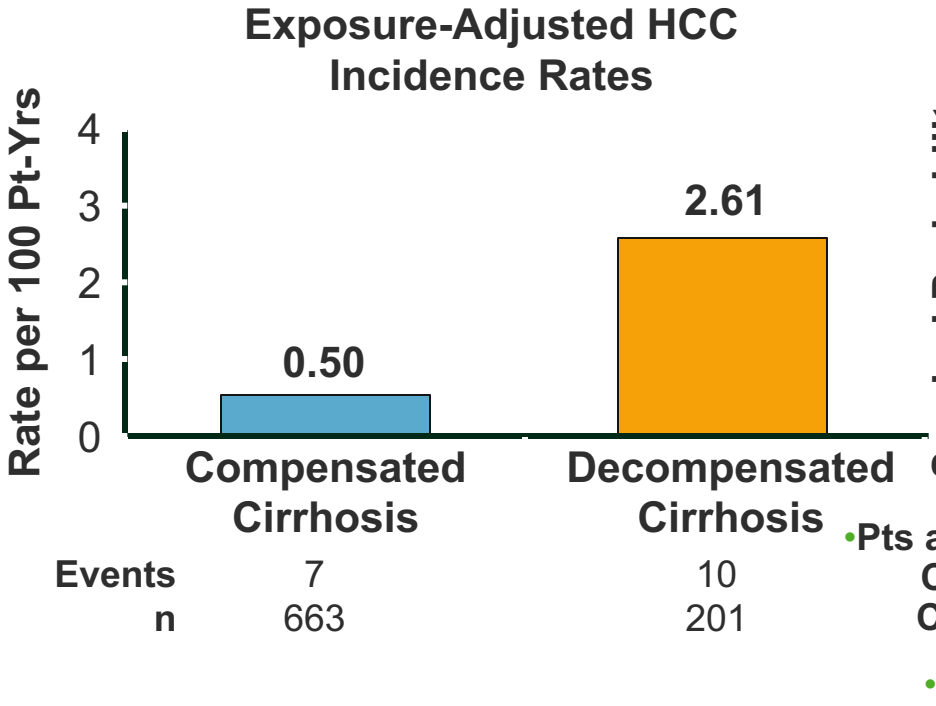
- Among pts starting DAAs ≤ 4 mos after CR, 4 pts (20%) died
  - Deaths occurred in Months 9, 10, 15, 16 after starting DAA

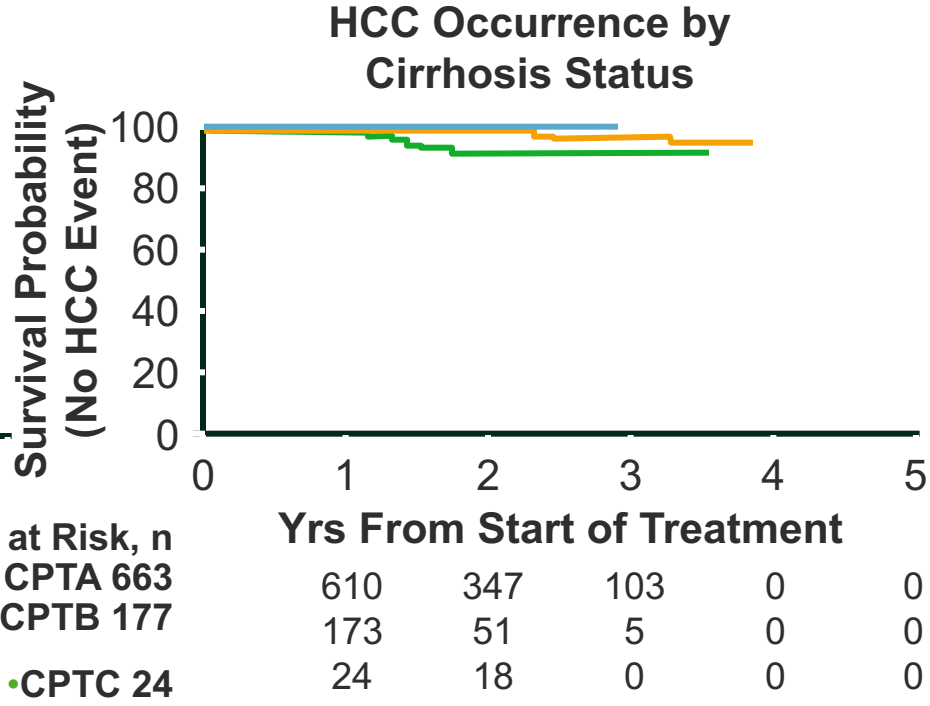
•Reig M, et al. EASL 2017. Abstract PS-031. Reproduced with permission.

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

De Novo HCC After DAA Treatment in Pts With Cirrhosis

- Pts with compensated or decompensated cirrhosis and SVR after SOF-based HCV treatment
  - At baseline, 9/845 (1%) had HCC
  - Median follow-up after end of DAA therapy: 85 wks (range: 8-187)





Muir A, et al. AASLD 2016. Abstract 880.

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 Class B/C, %	34	0
Follow-up, yrs	1.0	5.5

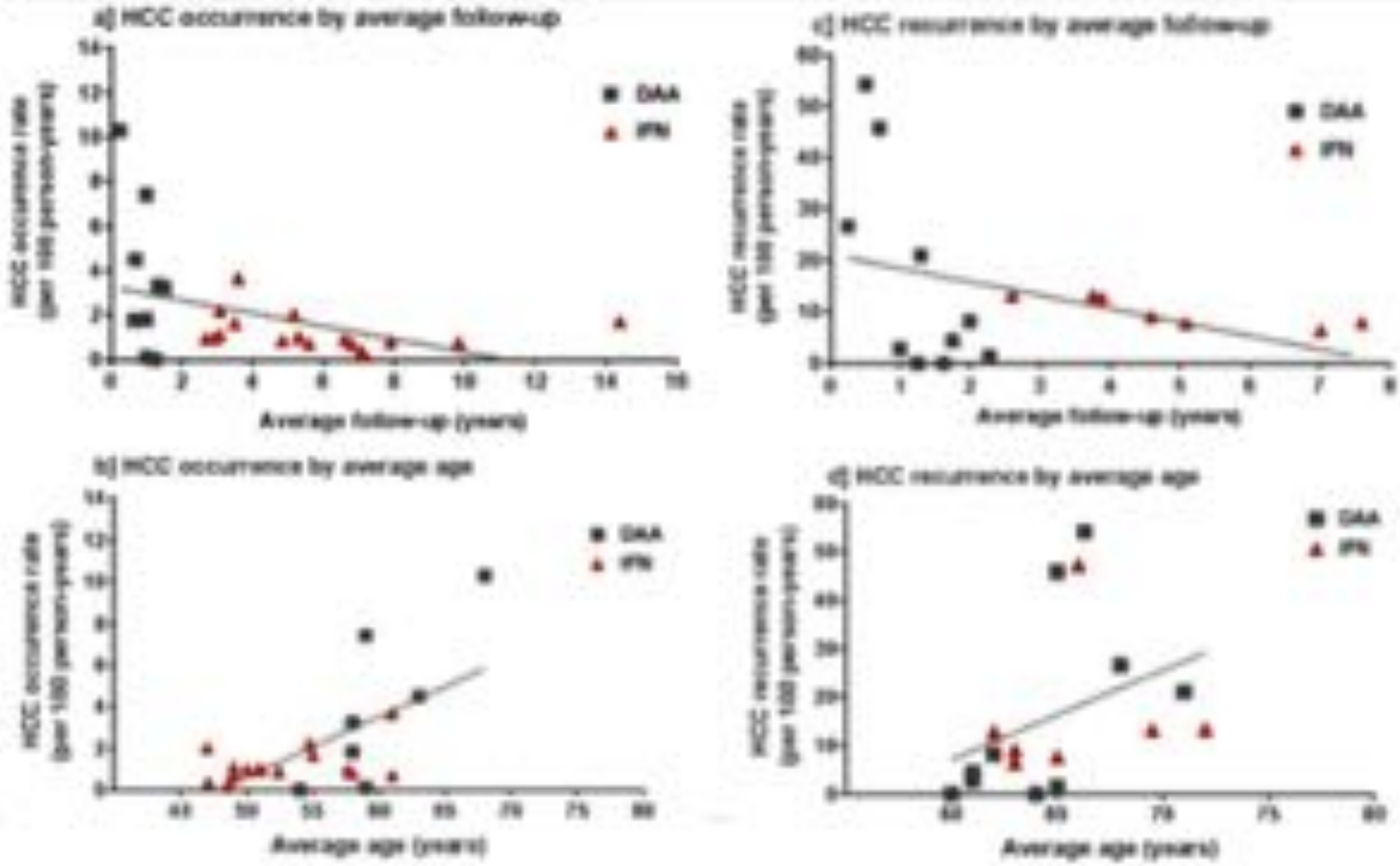
Pts With HCC Recurrence After SVR

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

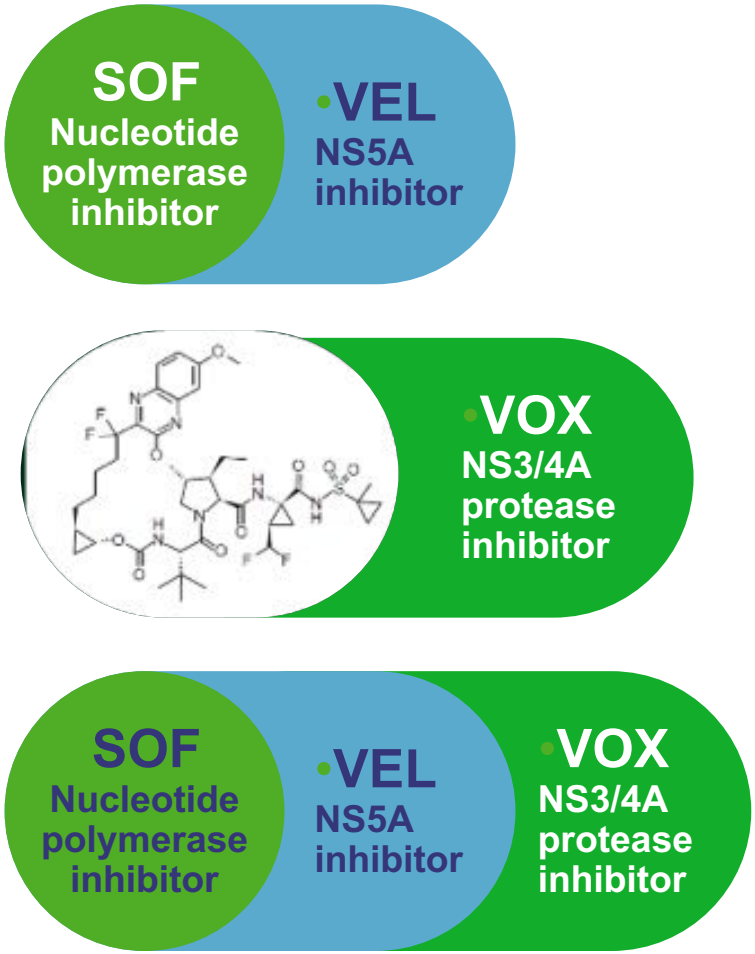
Dore G, et al. EASL 2017. Abstract PS-160.

Impact of age and follow on HCC



More pan-genotypic and salvage strategies coming

Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)
POLYMERASE/PROTEASE/NS5A



Sofosbuvir (SOF)/Velpatasvir (VEL)

- **SOF:** Nucleoside polymerase inhibitor with activity against HCV GT 1-6
- **VEL:** Potent pangenotypic NS5A inhibitor

Voxilaprevir (VOX)

- HCV NS3/4A PI with potent antiviral activity against GT 1-6, including most RASs

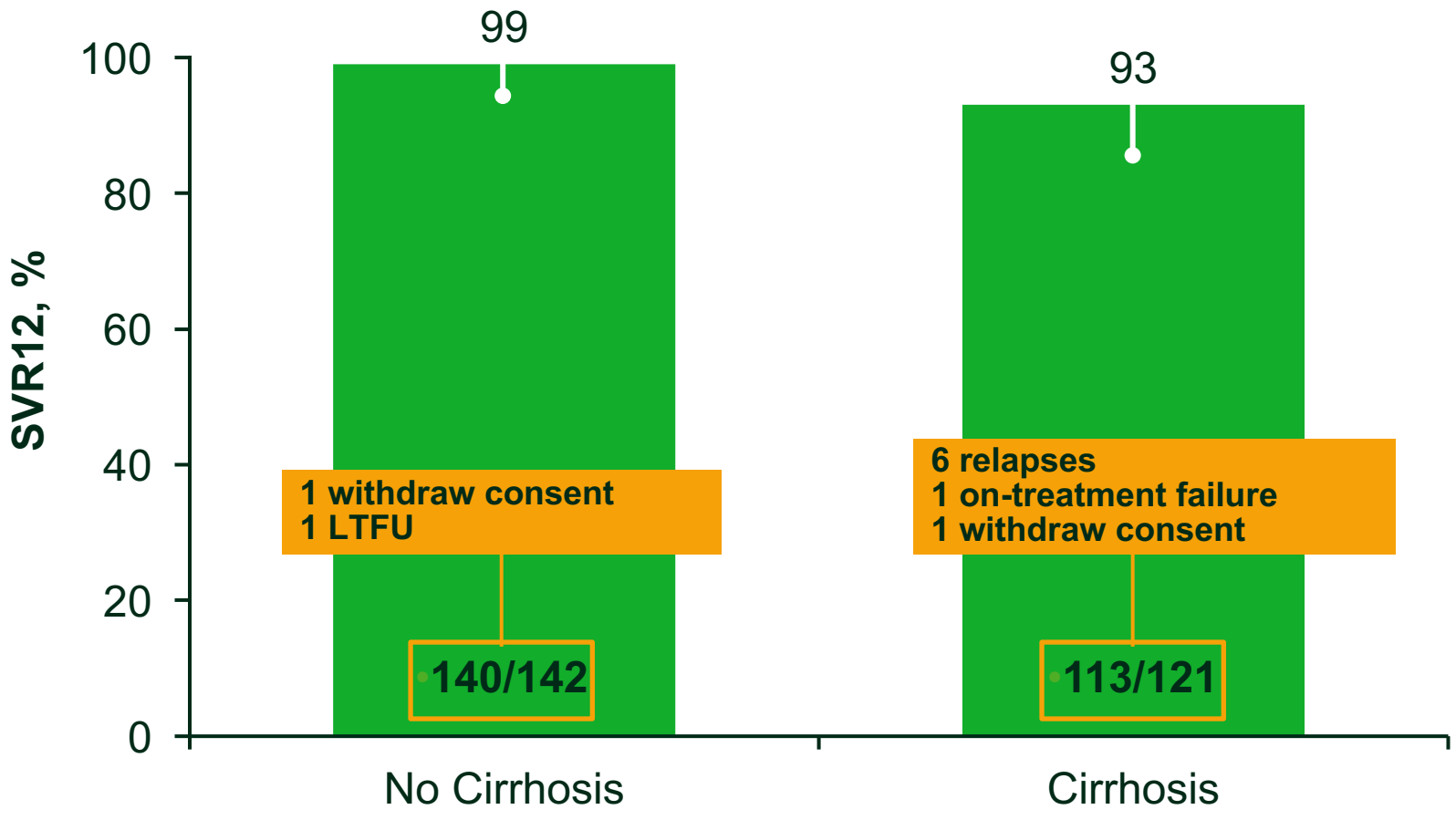
SOF/VEL/VOX

- Once daily, oral, fixed-dose combination (400/100/100 mg) for GT 1-6

•Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

POLARIS-1 Study: SOF/VEL/VOX 12 Weeks (n=263) for NS5a exposed individuals

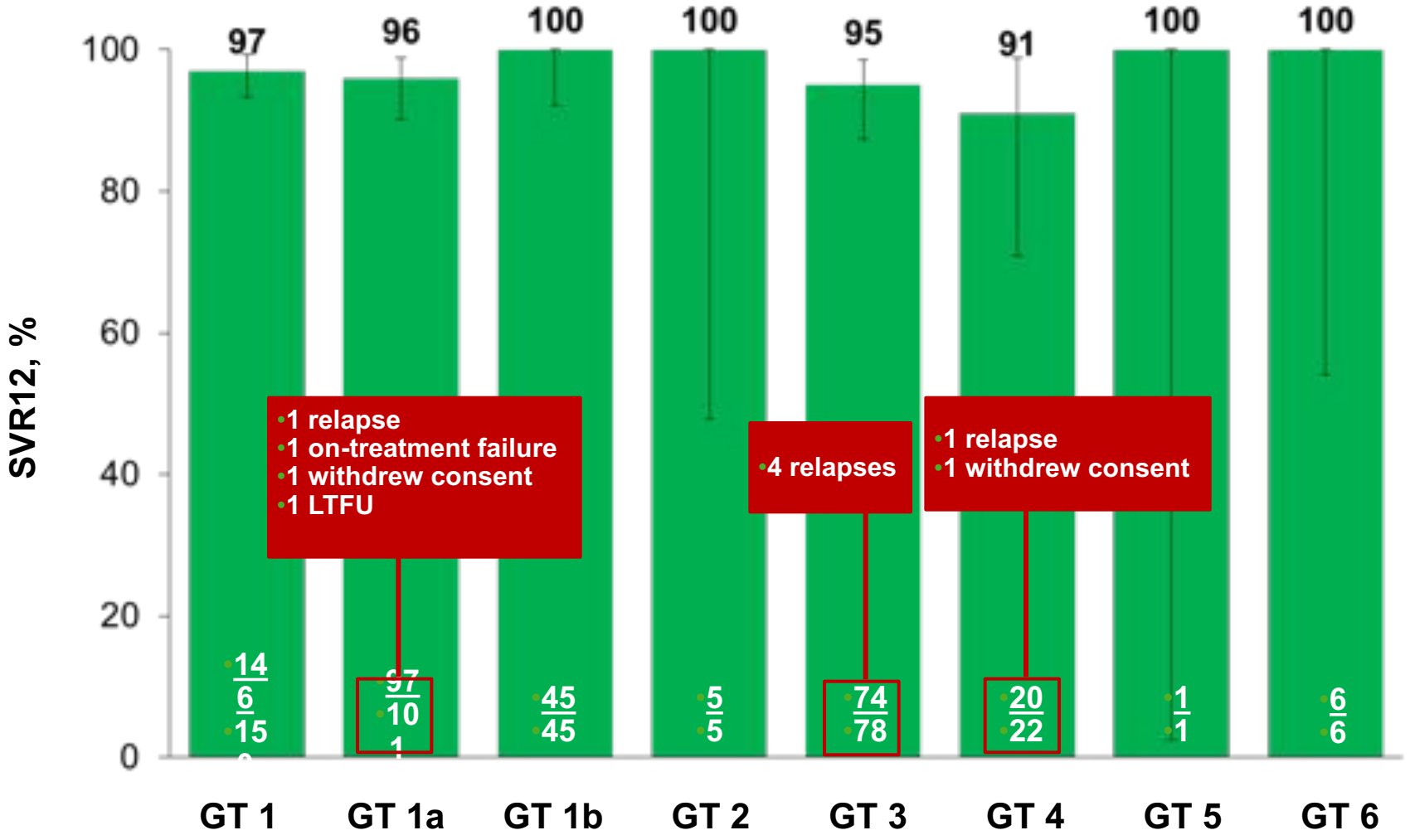
Results (SVR12) by Cirrhosis Status



Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

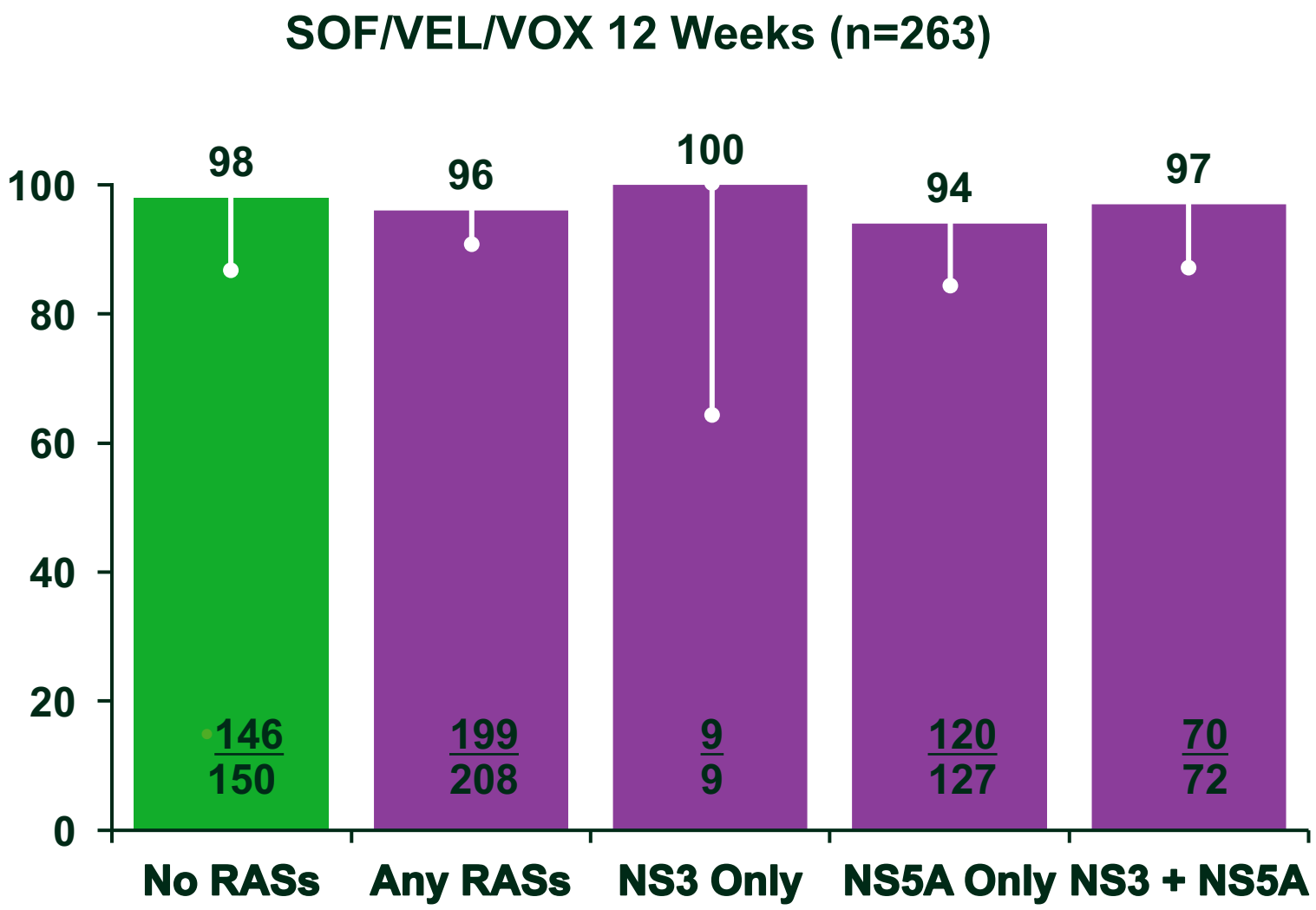
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor–Experienced HCV GT 1-6

One of the 6 patients who relapsed had treatment-emergent RASs



•Bourliere M. AASLD 2016. Oral 194.

POLARIS-1 Study: Results (SVR12)



Bourlière M, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 194.

POLARIS-4: Phase 3 RCT Of SOF/VEL/VOX or SOF/VEL for 12 Weeks in DAA-experienced Patients (Other Than NS5As)

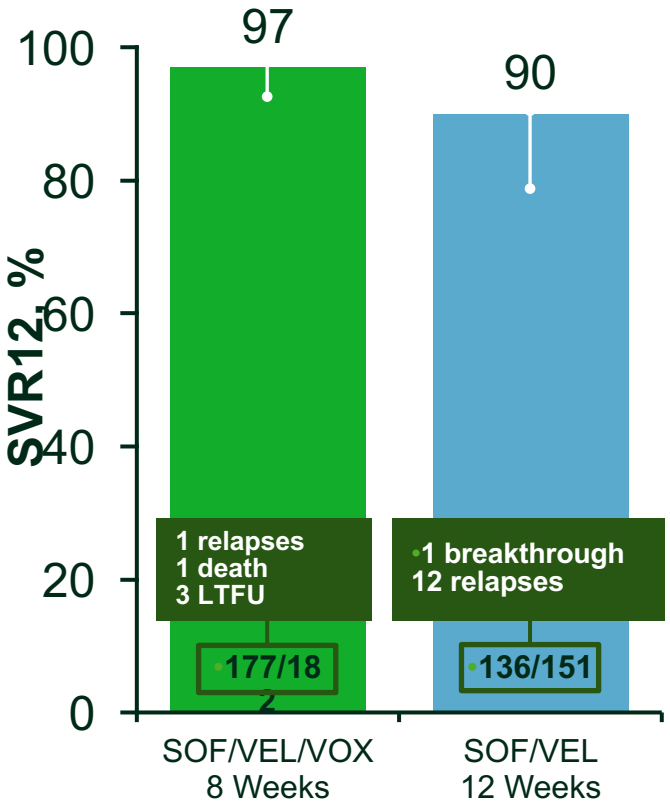
- Randomized controlled trial of persons who failed non-NS5A containing DAA regimens (SOF 73% or SOF+RBV/IFN)
  - SOF/VEL/VOX for 12 weeks (n=182) versus SOF/VEL for 12 weeks (n=151)

		SOF/VEL/VOX 12 Weeks n=182	SOF/VEL 12 Weeks n=151
Mean age, y (range)		57 (25-85)	57 (24-80)
Male, n (%)		143 (79)	114 (75)
White, n (%)		160 (88)	131 (87)
Mean BMI, kg/m^2 (range)		29 (18-45)	29 (18-53)
Cirrhosis, n (%)		84 (46)	69 (46)
Genotype, n (%)	1a / 1b	54 (30) / 24 (13)	44 (29) / 22 (14)
	2	31 (71)	33 (22)
	3	54 (30)	52 (34)
	4	19 (10)	-
IL28B CC, n (%)		33 (18)	29 (19)
Mean HCV RNA, $\log_{10}$ IU/mL (range)		6.3 (5.0 – 7.5)	6.3 (3.6 - 7.3)

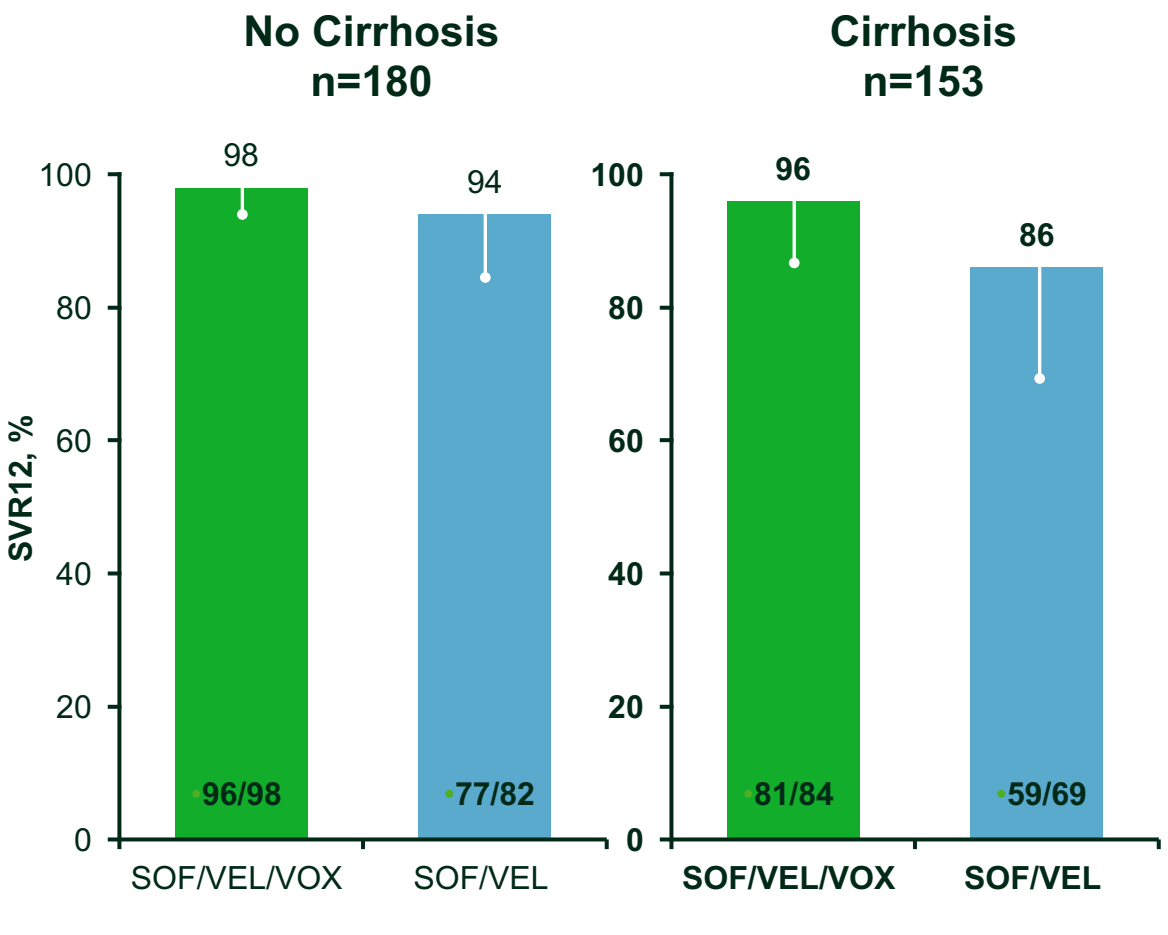
Zeuzem S, et al. 67th AASLD, Boston, MA, November 11-15, 2016; Abst. 169.

POLARIS-4: Phase 3 RCT Of SOF/VEL/VOX or SOF/VEL for 12 Weeks in DAA-experienced Patients (Other Than NS5As)

Overall SVR Rate

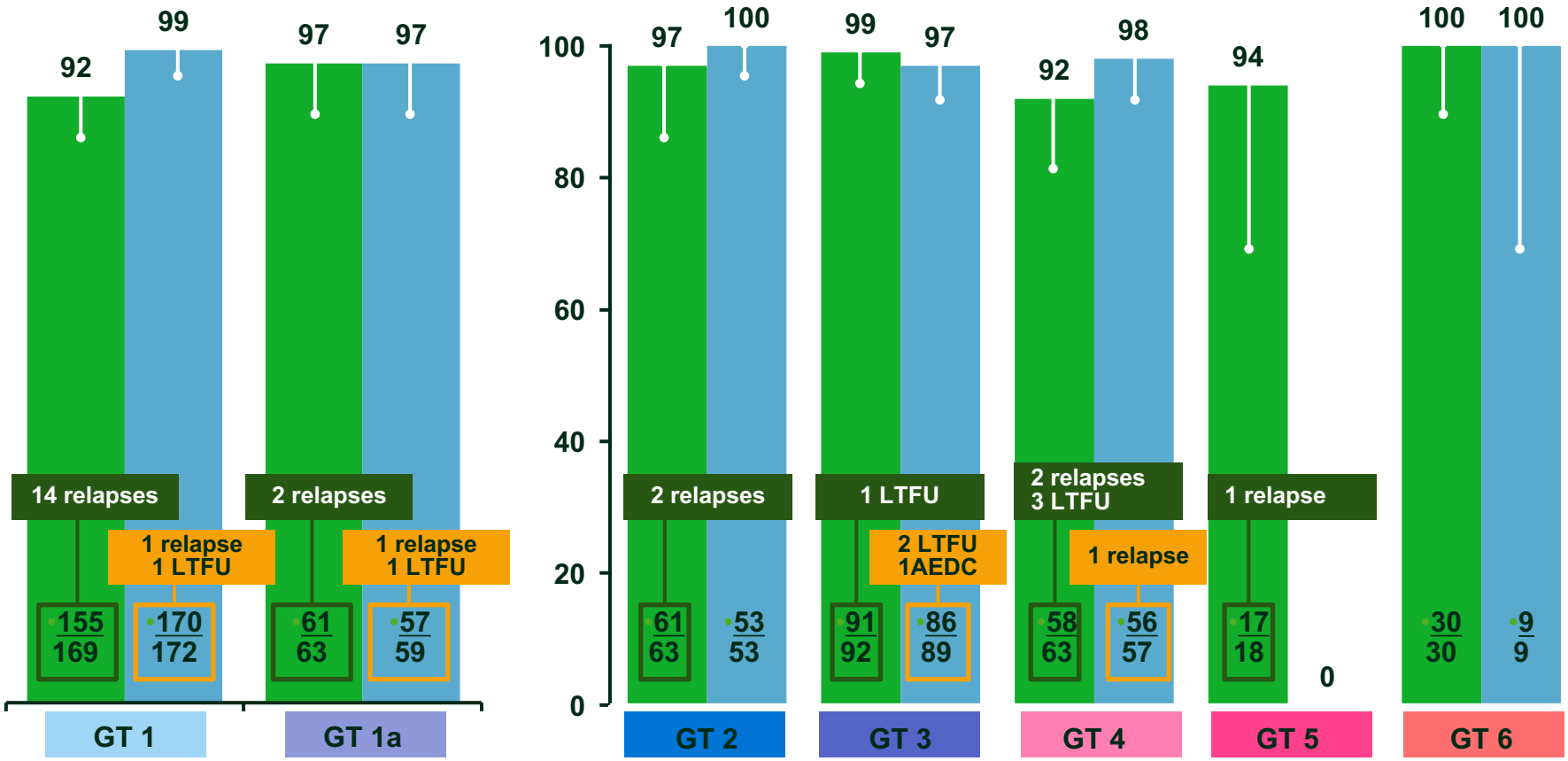


SVR Rate by Cirrhosis Status



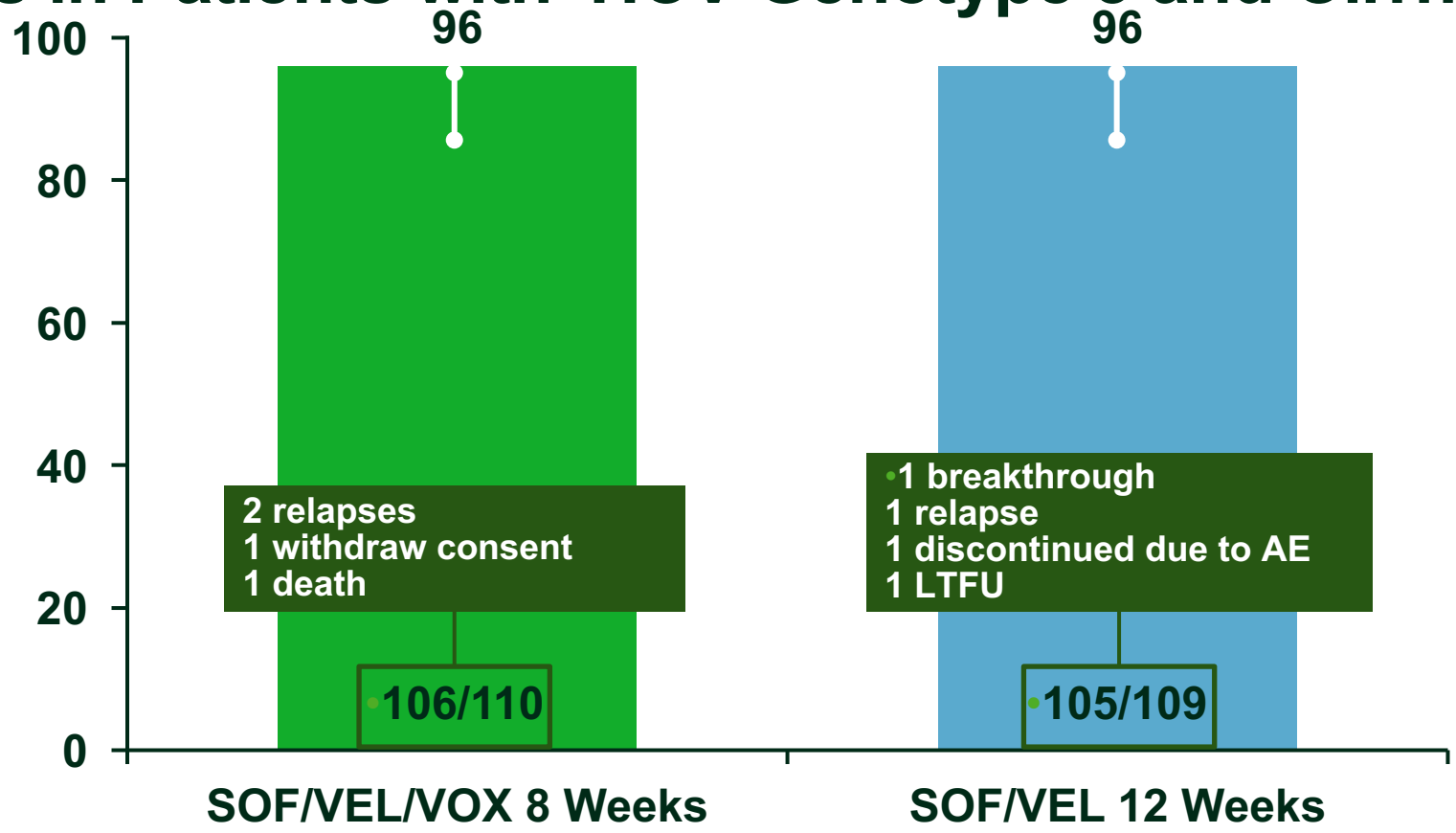
Zeuzum S, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 109.

POLARIS-2: Randomized Controlled Trial of SOF/VEL/VOX for 8 Weeks versus SOF/VEL for 12 Weeks



Jacobson I, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-12.

POLARIS-3: Randomized Controlled Trial of SOF/VEL/VOX for 8 Weeks Versus SOF/VEL for 12 Weeks in Patients with HCV Genotype 3 and Cirrhosis



- There were 6 patients with Y93H in the SOF/VEL/VOX group and 4 in the SOF/VEL group; all achieved SVR12
- No treatment emergent RASs in the SOF/VEL/VOX group. In the SOF/VEL group, both virologic failures had Y93H

Foster G, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 258.

Glecaprevir/Pibrentasvir

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

- **Collectively: G/P**

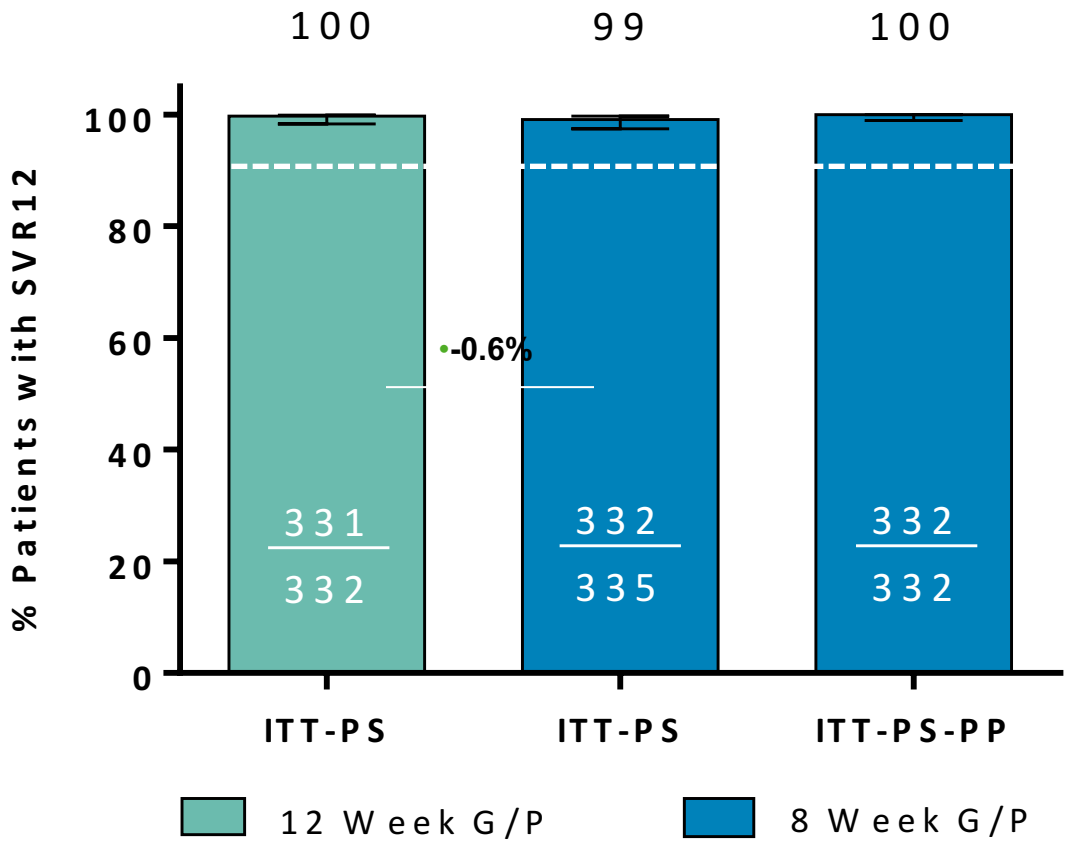
In vitro:[1,2]
- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31 and 93)

Clinical PK & metabolism:
- Additive/synergistic antiviral activity
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%); no dose adjustment for CKD[3]

- G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
- Glecaprevir was identified by AbbVie and Enanta

1. Ng TI, et al. Abstract 636. CROI, 2014.
2. Ng TI, et al. Abstract 639. CROI, 2014.
3. Kosloski M, et al. Abstract THU-230. EASL 2016.

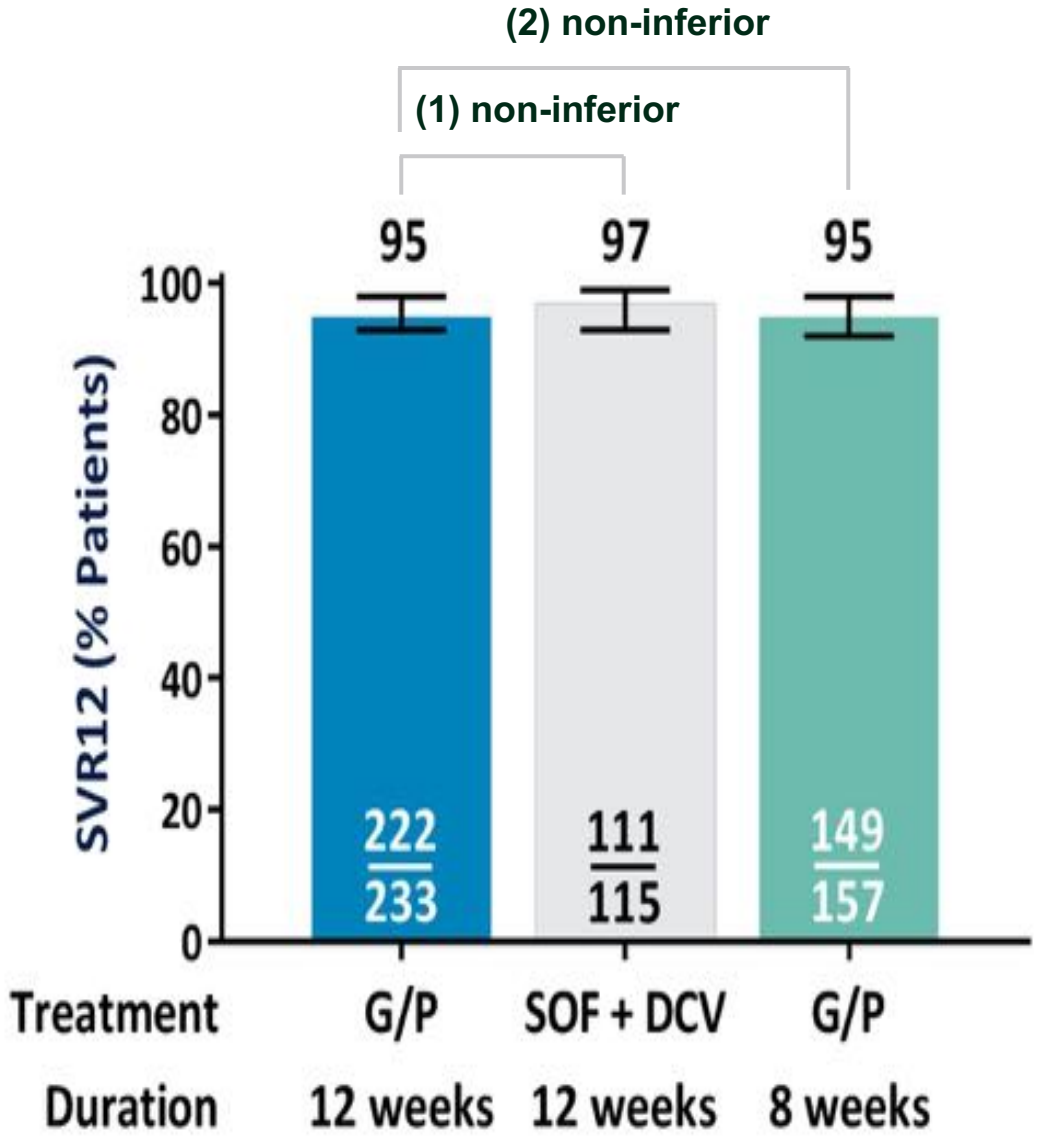
ENDURANCE-1: GLE/PIB x 8 Weeks or 12 Weeks in GT1 Noncirrhotics



- **Primary endpoint threshold: 91%**
- **ITT-PS: ITT population, excluding HIV co-infected *and* SOF-experienced patients**
- **ITT-PS-PP: ITT-PS population excluding patients with premature D/C or virologic failure prior to week 8, and missing data in the SVR12 window**

- Zeuzem S, et al. Abstract #253, AASLD 2016.

ENDURANCE-3: SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR COMPARED TO SOFOSBUVIR PLUS DACLATASVIR IN TREATMENT-NAÏVE HCV GENOTYPE 3-INFECTED PATIENTS WITHOUT CIRRHOSIS



Non-inferiority:

Lower bound of the confidence interval (CI) of the difference in SVR12 must be above -6%*

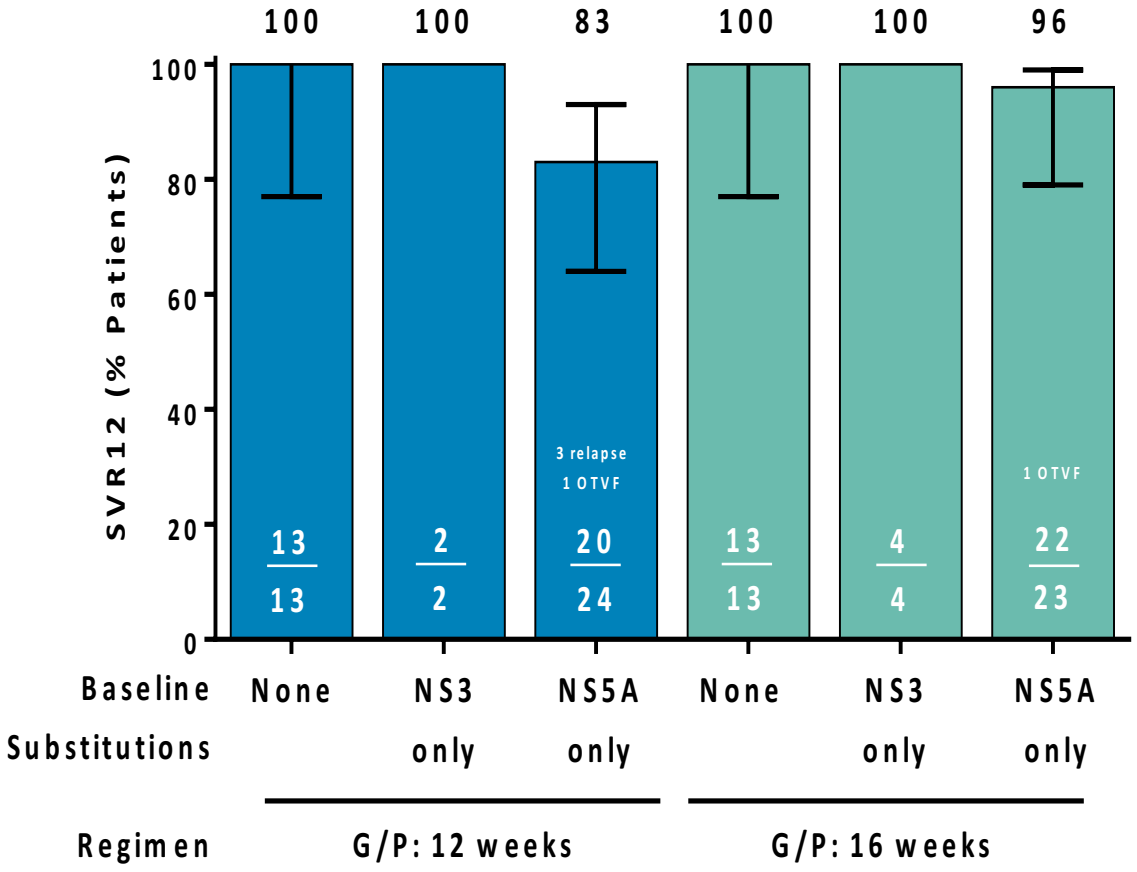
(1) -1.2% (95% CI -5.6 – 3.1)

(2) -0.4% (97.5% CI -5.4 – 4.6)

Both G/P treatments met non-inferiority criteria for the primary endpoint

*Conventional statistical methods were used in multiplicity comparison for determining non-inferiority

MAGELLAN-1, PART 2: GLECAPREVIR/PIBRENTASVIR FOR 12 OR 16 WEEKS IN PATIENTS WITH CHRONIC HCV GENOTYPE 1 OR 4 AND PRIOR DIRECT-ACTING ANTIVIRAL TREATMENT FAILURE



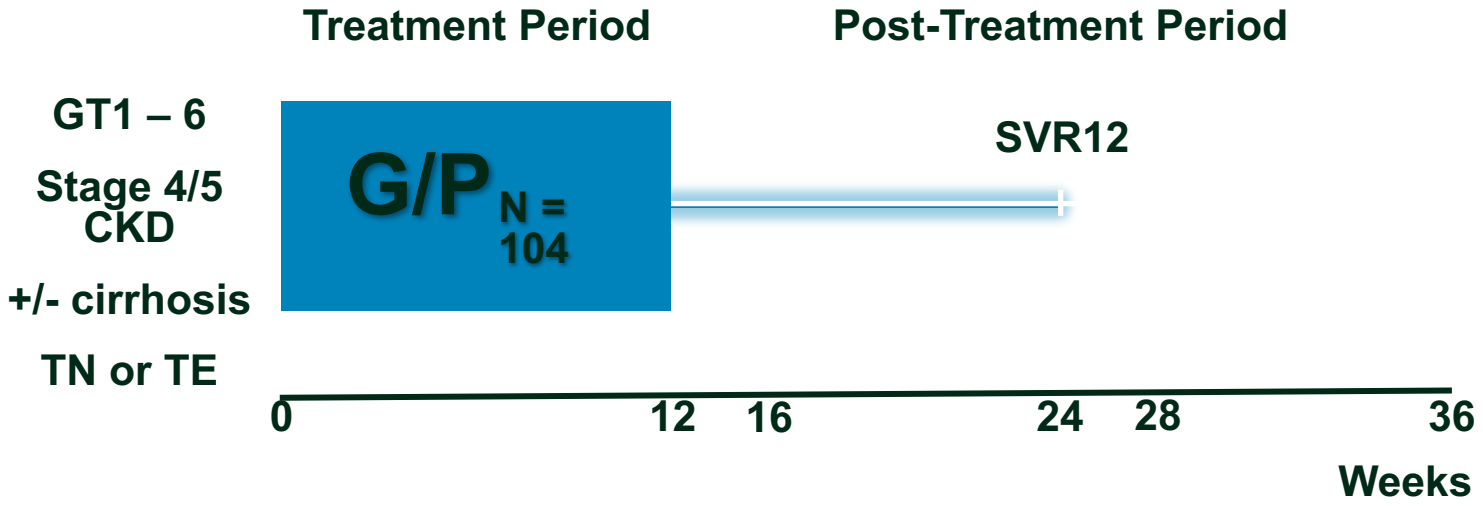
Key baseline NS3 and NS5A substitutions were only present in patients with prior failure to both PI and NS5A inhibitors

5/9 of these patients achieved SVR12

Key NS3 positions: 155, 156, 168
Key NS5A positions: 24, 28, 30, 31, 58, 92, 93
OTVF: on-treatment virologic failure

Y93H/N at baseline: 100% (13/13) SVR12 in patients with NS5A inhibitor experience (PI-naïve)

EXPEDITION-4: G/P for 12 weeks in patients with HCV GT1-6 and stage 4 or 5 chronic kidney disease (CKD)



G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg

Objective

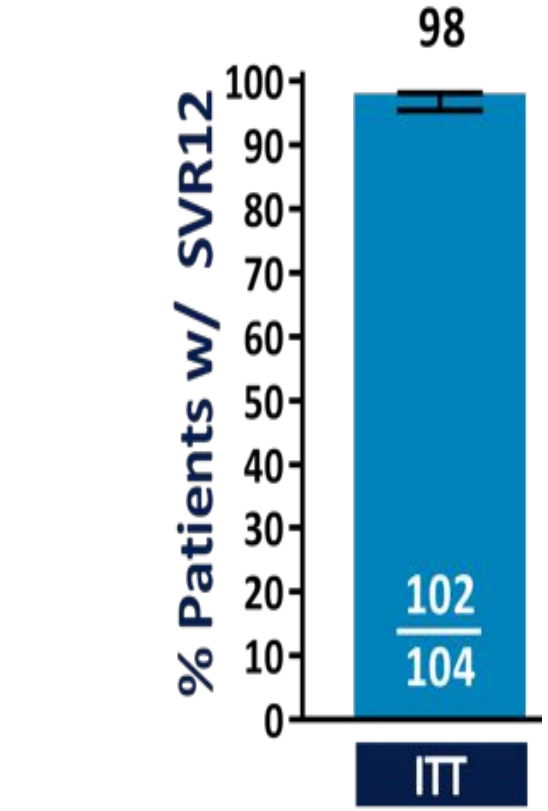
Determine the efficacy and safety of pangenotypic

Endpoints

Efficacy: SVR12 defined as HCV RNA below the lower limit of quantification (LLOQ; 15 IU/mL)

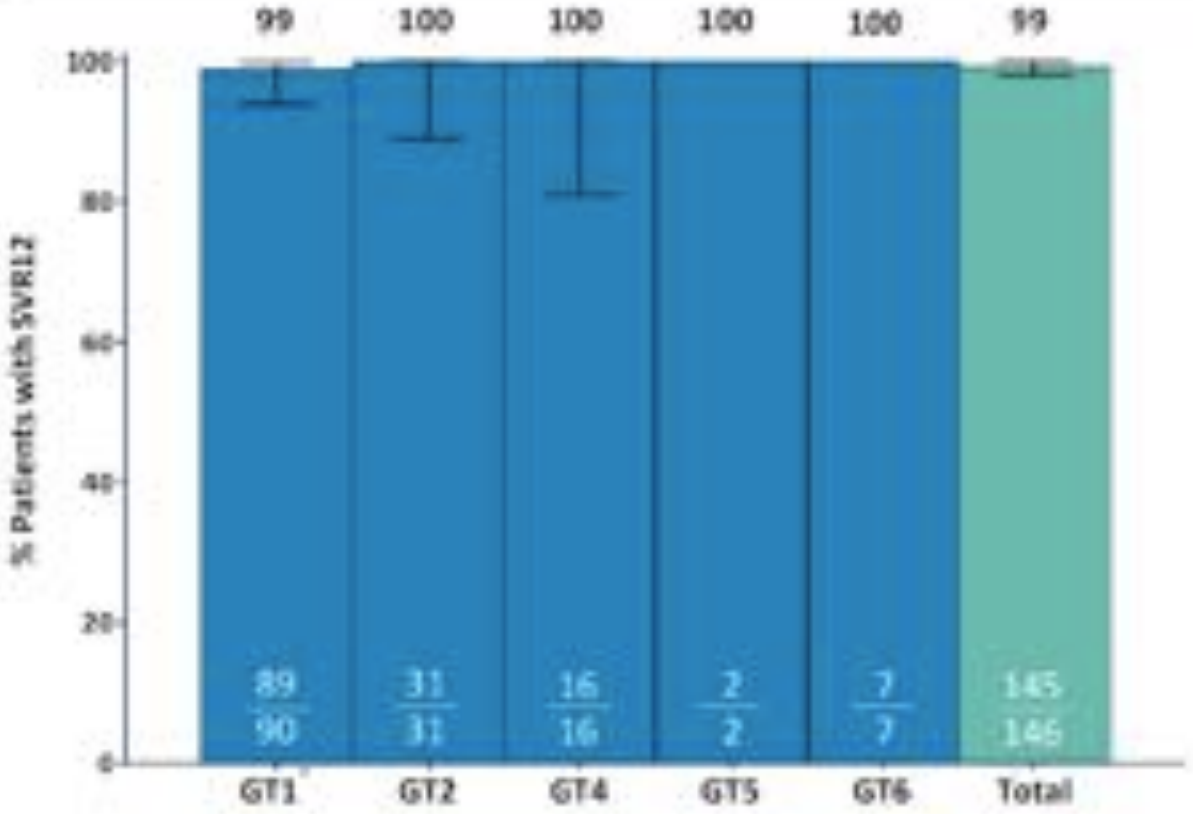
Safety: adverse events (AEs) and laboratory abnormalities

EXPEDITION-4: G/P for 12 weeks in patients with HCV GT1-6 and stage 4 or 5 chronic kidney disease (CKD)



Breakthrough	0
Relapse	0
Discontinuation	1
LTFU	1

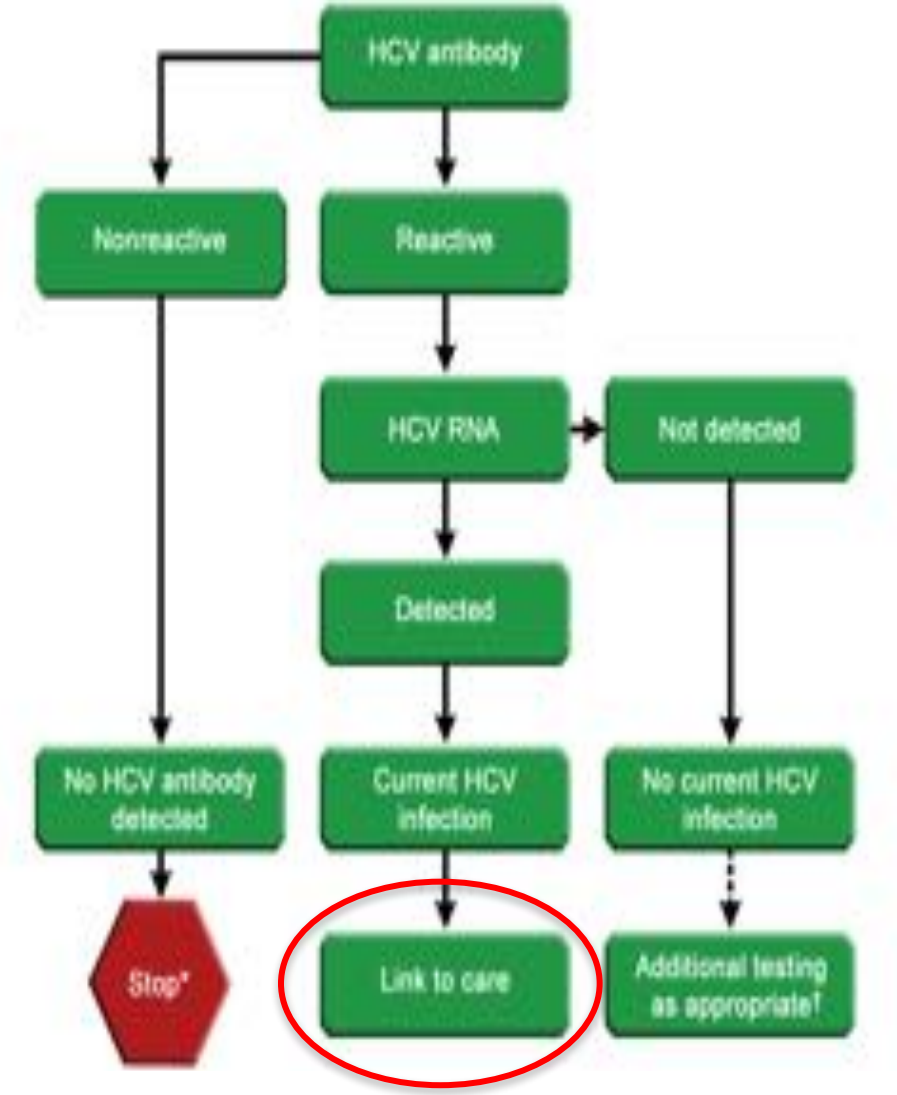
EXPEDITION-I: Efficacy and Safety of Glecaprevir/Pibrentasvir for Treatment of Chronic Hepatitis C Virus Genotype 1, 2, 4, 5 or 6 Infection in Adults with Compensated Cirrhosis; SVR-12



*Patient with HCV GT1a infection relapsed at PTW8
- No treatment-emergent substitutions were present in NS3
- In NS5A, Y93N was present at baseline; Y93N, Q30R and H58D were present at the time of failure

Forns et al EASL 2017

CDC Recommended Testing Sequence for Identifying Current HCV Infection



www.hcvguidelines.org **Adapted from Centers for Disease Control and Prevention (CDC), 2013.**

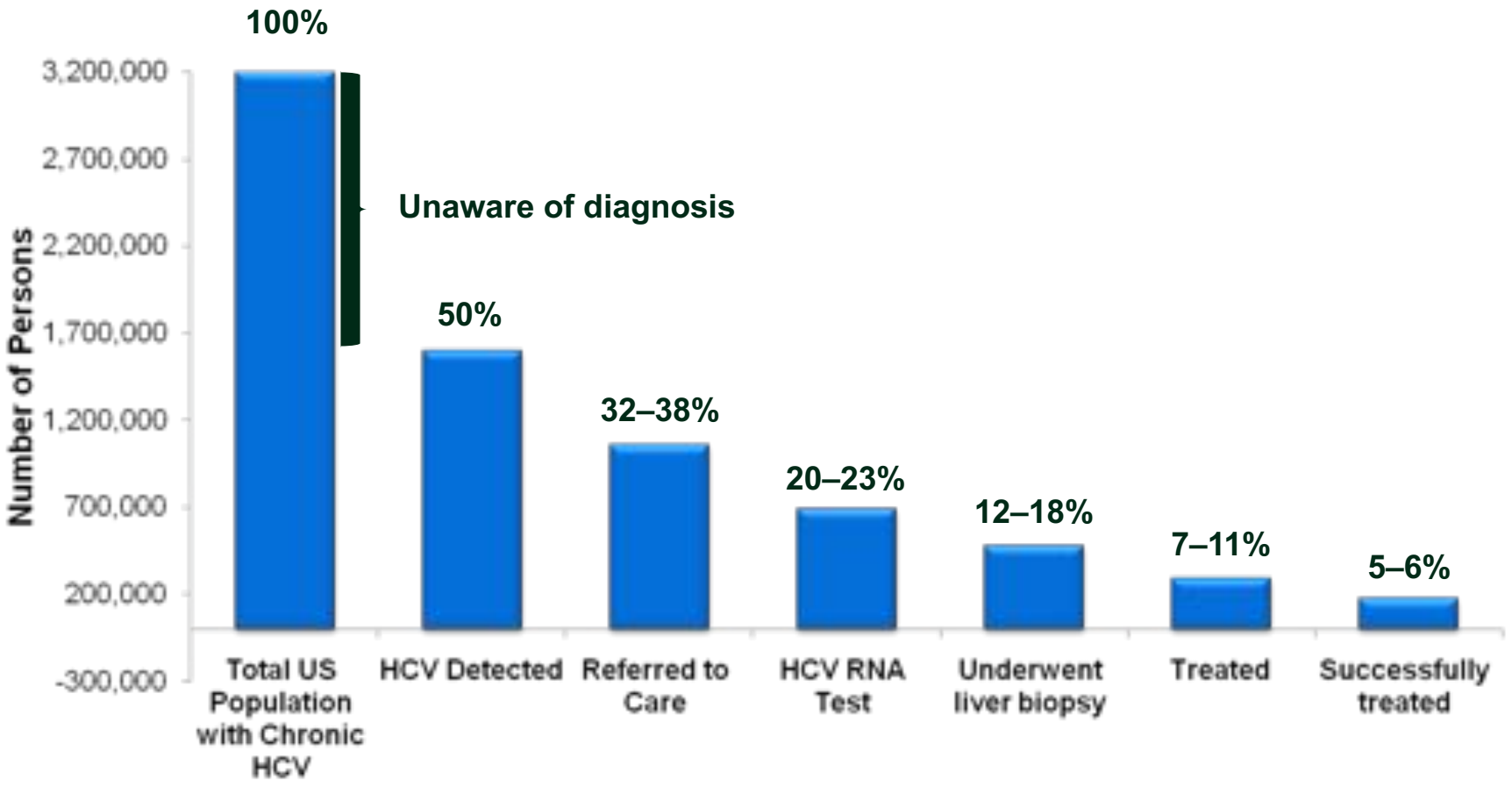
The AASLD/IDSA Recommendation for Linkage to Care

All persons with current active HCV infection should be linked to a practitioner who is prepared to provide comprehensive management

: www.hcvguidelines.org.

Identifying Priorities to Improve Outcomes

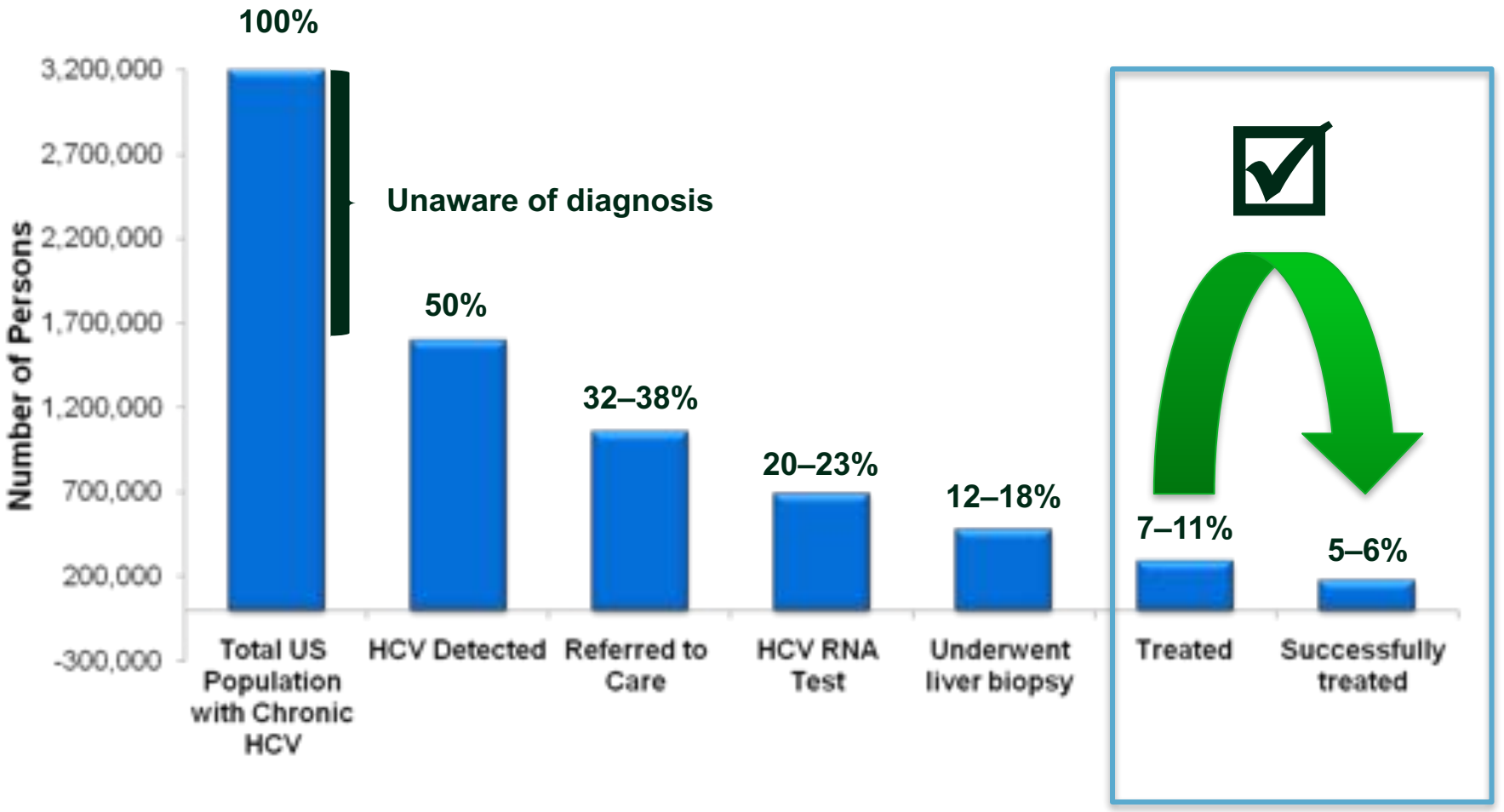
HCV Care Cascade



Holmberg SD, et al. *N Engl J Med*. 2013:368(20):1859-1861.

Identifying Priorities to Improve Outcomes

HCV Care Cascade

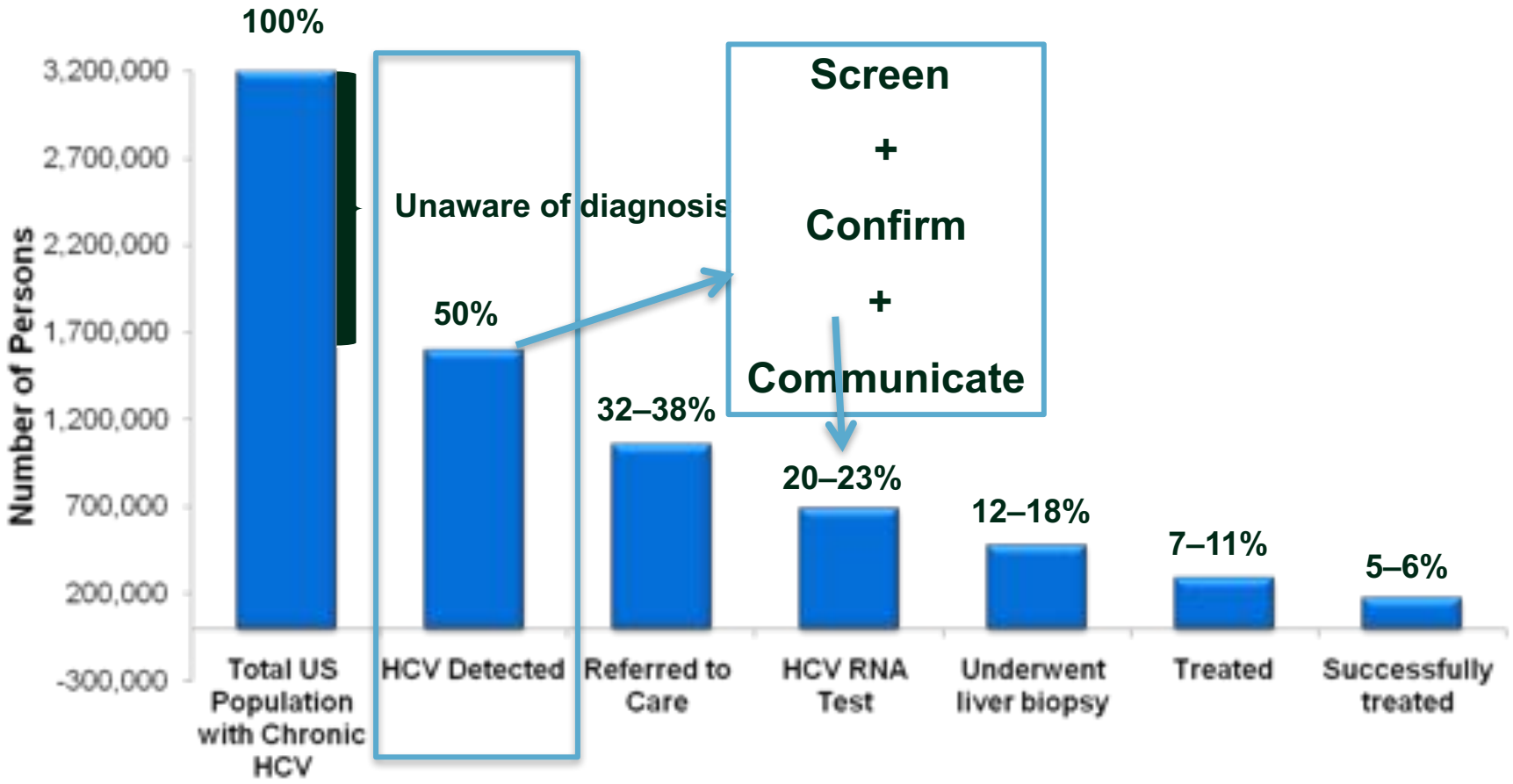


Holmberg SD, et al. *N Engl J Med*. 2013:368(20):1859-1861.

Identifying Priorities to Improve Outcomes

#1

HCV Care Cascade



Holmberg SD, et al. *N Engl J Med*. 2013:368(20):1859-1861.

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

AASLD/IDSA Treatment Guidelines

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions

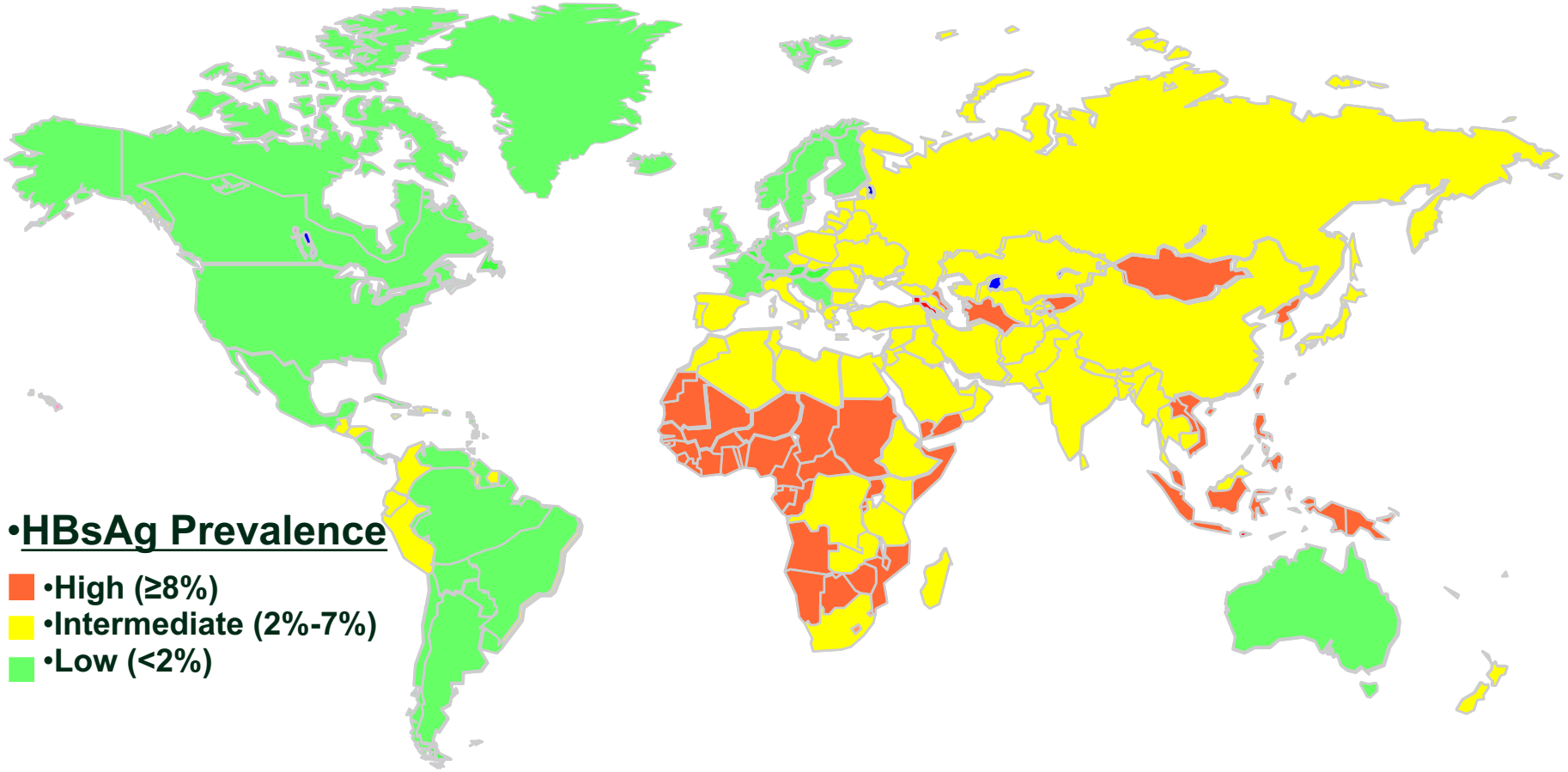
AASLD/IDSA. www.hcvguidelines.org/full-report-view. Updated July 6, 2016.

AASLD/IDSA HCV Treatment Guidelines: PWID

- "Recent and active IDU should not be seen as an absolute contraindication to HCV therapy"
- "Scale up of HCV treatment in PWID is necessary to positively impact the HCV epidemic in the United States and globally"

•AASLD/IDSA HCV Guidelines.

Prevalence of Chronic HBV Infection: Global Estimates: 250 Million world wide



•Schweitzer A, et al. *Lancet.* 2015;386:1546-1555.
•MacLachlan JH, et al. *Lancet.* 2015;386:1515-1517.
•Ott JJ, et al. *J Hepatol.* 2017;66:48-54.

Hepatitis B: Natural History

- If it is not treated, in 1/3 of patients, hepatitis B can cause liver damage leading to cirrhosis and liver cancer[1]

- Hepatitis B is responsible for 80% of primary liver cancer globally, which is almost always fatal[2]
  - Liver cancer is the 2nd highest cause of death by cancer [3]
  - Without appropriate treatment or monitoring, 1 in 4 persons with chronic hepatitis B will die of liver cancer or liver disease

Hepatitis B Serology

- HBsAg (hepatitis B surface antigen)
  - A protein on the surface of HBV
  - Can be detected during acute or chronic HBV infection
  - Presence indicates an individual is INFECTED OR INFECTIOUS
- Anti-HBs (hepatitis B surface antibody)
  - Presence indicates recovery and IMMUNITY from HBV infection
  - Also develops following vaccination against hepatitis B
- Anti-HBc (total hepatitis B core antibody)
  - Appears at the onset of symptoms in acute hepatitis and persists for life
  - Presence indicates EXPOSURE (previous or ongoing infection with HBV)

- Adapted from http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#general. .

Hepatitis B Serology

- IgM anti-HBc
  - (IgM antibody to hepatitis B core antigen)
    - Positivity indicates recent infection with HBV (≤6 mos)

- Occasionally occurs in the presence of a severe flare of CHRONIC HBV disease
  - 2-3% of patients with CHB are IgM anti-HBc +

•Adapted from http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm#general.

Hepatitis B Serology (cont.)

- HBeAg (hepatitis B e antigen)
  - A secreted co-product of the nucleocapsid gene of HBV that is found in serum during acute and chronic HBV
    - Not a breakdown product of the core protein
  - Presence indicates that the virus is replicating and the infected person has high levels of HBV (HBV DNA) and transmit the virus more easily (Wild type virus)
- Anti-HBe (hepatitis B e antibody)
  - Produced by the immune system temporarily during acute HBV infection or consistently during or after a burst in viral replication in the setting of wild type infection clearance
  - Conversion from e antigen to e antibody (a change known as seroconversion) is a predictor of
    - Emergence of precore or core promoter mutant infection and the transition to CHB HBeAg negative disease in persons not on treatment
      - *…or…*
    - Long-term clearance of HBV in patients undergoing antiviral therapy and indicates lower levels of HBV DNA levels

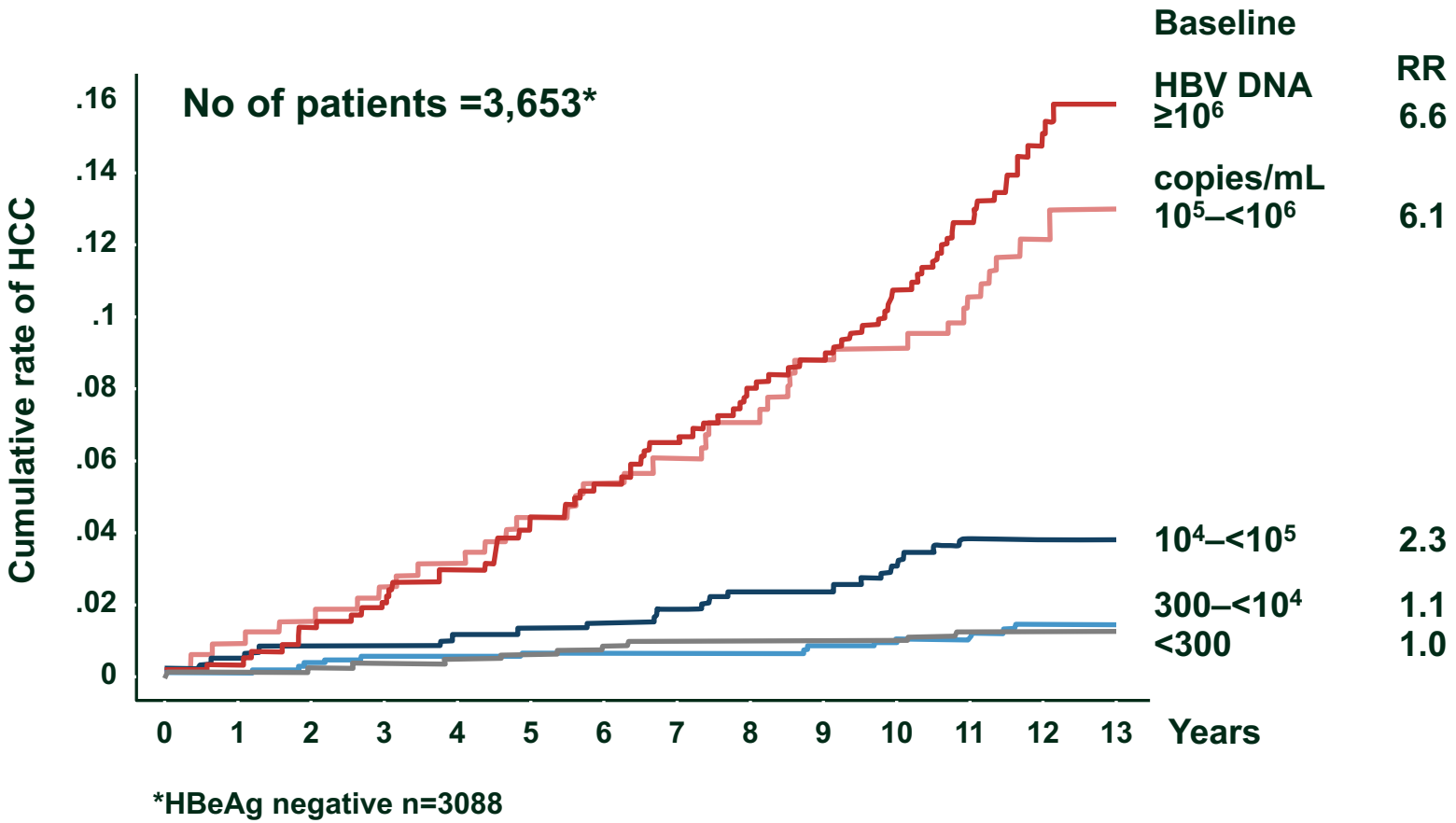
Quantitative HBsAg assay now approved
Potential Applications

Table 5. Potential Applications of HBsAg Level Monitoring

	Potential Application	Benefit
During natural history	Identification of true inactive carriers	Reassurance that treatment is not required
	Identification of patients who need therapy now or whose disease is likely to be reactivated in the near future	Identification of patients who need closer monitoring and possible identification of patients who need treatment
During therapy	Early identification of patients who are unlikely to respond to PEG-IFN	Early stopping rule for avoiding unnecessary and ineffective therapy
	Early identification of patients who are responding to PEG-IFN	Motivation for patients to continue therapy
	Early identification of patients who experience a rapid decline in HBsAg levels during NA therapy (LdT or TDF)	Identification of patients who have a high chance of HBsAg clearance and development of a stopping rule that enables patients with a low chance of relapse to stop NA therapy

•Liaw, Y.-F. (2011), Clinical utility of hepatitis B surface antigen quantitation in patients with chronic hepatitis B: A review. Hepatology, 54: E1–E9. doi:10.1002/hep.24473

HBV DNA vs. HCC : REVEAL Data



*HBeAg negative n=3088

Chen CJ, et al. JAMA 2006;295:65-73.

US FDA dates of Approved Therapies for CHB

Nucleosides/Nucleotides			
Tenofovir alafenamide	Vemlidy®	Gilead Sciences	2016
Tenofovir disoproxil *	VIREAD®	Gilead Sciences	2008
Telbivudine	TYZEKA™	Idenix / Novartis	2006
Entecavir*	BARACLUDE™	Bristol-Myers Squibb	2005
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998
Interferons			
Peginterferon alfa-2a*	PEGASYS®	Roche Laboratories	2005
Interferon alfa-2b, recombinant	INTRON® A	Schering / Merck	1992

Preferred therapies – AASLD Guidelines

Candidates for HBV Treatment

	APASL (2008)	EASL (2012)	Martin et al (2015)	AASLD (2016)
HBV DNA threshold (IU/L) HBeAg positive HBeAg negative	 20,000 2000	 2000 2000	 20,000 2000	 20,000 2000
ALT: Normal range	-	-	(M: 30 U/L; F: 19 U/L)	2X ULN (M: 30 U/L; F: 19 U/L)
When to treat: key factors	HBV DNA and ALT	HBV DNA and ALT	HBV DNA and ALT	HBV DNA and ALT
Biopsy	Consider in certain groups	Consider in certain groups	Consider in certain groups	Consider in certain groups

- Lok AS, et al. *Hepatology* 63.1 (2016): 284-306.
- Martin P, et al. Clinical Gastroenterology and Hepatology 2015;13:2071–2087.

EASL. *J Hepatol.* 2012 vol. 57 j 167–185.

- Liaw Y-F, et al. *Hepatol Int.* 2008;2:263-283.
- Terrault, Norah A., et al. *Hepatology* 63.1 (2016): 261-283.

Other Caveats From Recent AASLD Guideline Update

- The decision to treat persons with ALT above the ULNs, but <2 ULN, requires consideration of severity of liver disease (defined by biopsy or noninvasive testing).
- Therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level
- The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy showing significant necroinflammation or fibrosis.

Terrault, Norah A., et al. *Hepatology* 63.1 (2016): 261-283.

Treatment Guidelines: Recommendations for First-Line Therapy in Patients Without Cirrhosis

HBeAg Positive or Negative Chronic HBV

Preferred	Alternative	Not Preferred
Tenofovir DF	Adefovir	Lamivudine
Entecavir	Telbivudine*	
Peg-IFN alfa-2a		

- *HBV DNA must be undetectable at 24 weeks to continue (Keeffe).
- AASLD guidelines: lamivudine and telbivudine not preferred due to relatively high rate of resistance. Adefovir not preferred due to weak antiviral activity and relatively high rate of resistance in HBeAg-negative studies.

- Lok AS, et al. *Hepatology* 63.1 (2016): 284-306.
- Martin P, et al. Clinical Gastroenterology and Hepatology 2015;13:2071–2087.

EASL. *J Hepatol.* 2012 vol. 57 j 167–185.

- Liaw Y-F, et al. *Hepatol Int.* 2008;2:263-283.
- Terrault, Norah A., et al. *Hepatology* 63.1 (2016): 261-283.

Treatment Guidelines: Recommendations for Patients With Cirrhosis

Compensated Cirrhosis

Preferred	Potential	Not Preferred
Tenofovir DF	Peg-IFN alfa-2a*	Lamivudine
Entecavir		Telbivudin

Decompensated Cirrhosis

Preferred	Not Preferred
Tenofovir DF	
Entecavir	

- Note: therapies are approved for monotherapy only.
- *Early cirrhosis only.
- †Contraindicated.

(Tenfovir AF can be likely substituted)

- Lok AS, et al. *Hepatology* 63.1 (2016): 284-306.
- Martin P, et al. Clinical Gastroenterology and Hepatology 2015;13:2071–2087.

EASL. *J Hepatol.* 2012 vol. 57 j 167–185.

- Liaw Y-F, et al. *Hepatol Int.* 2008;2:263-283.
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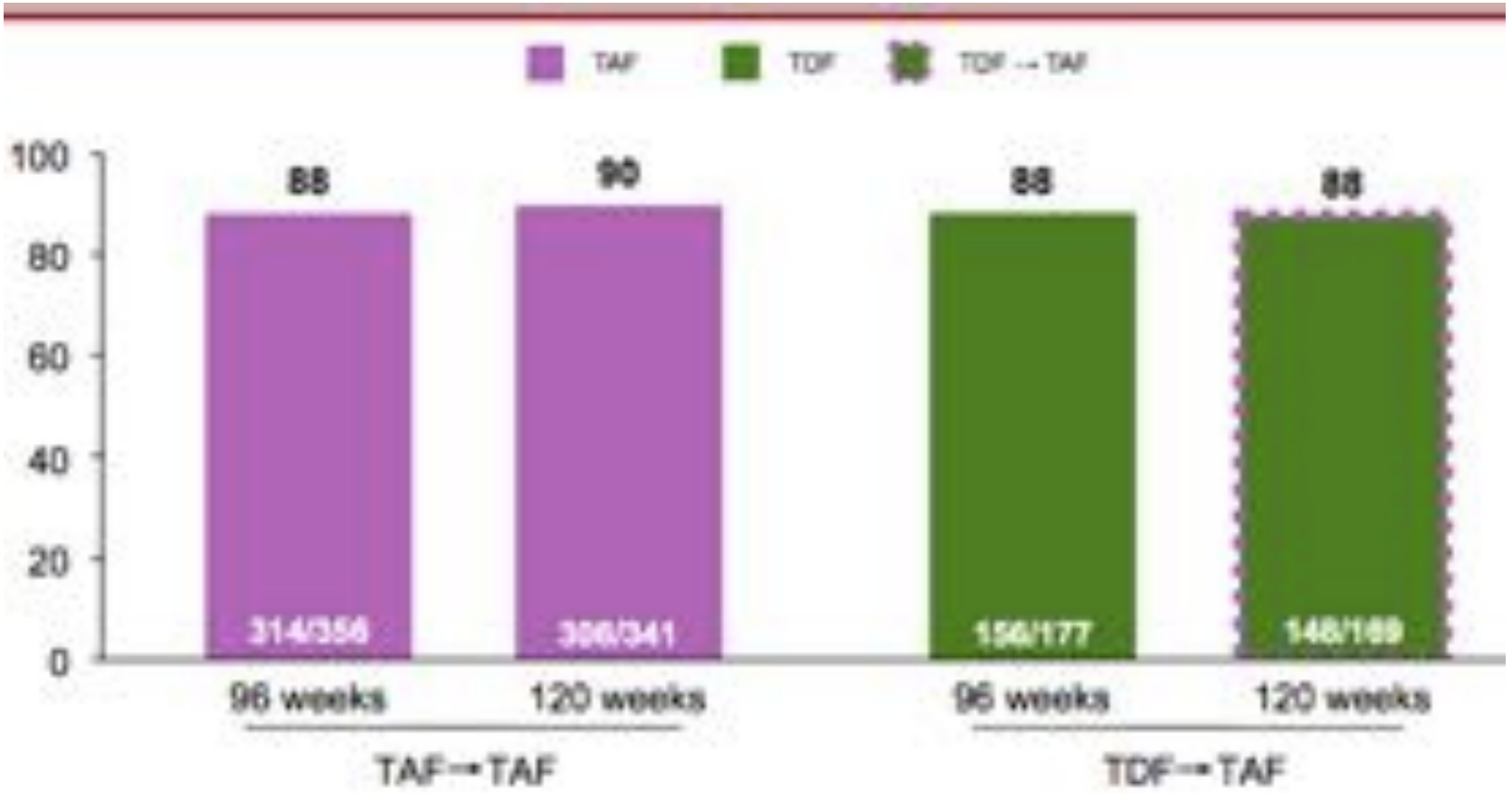
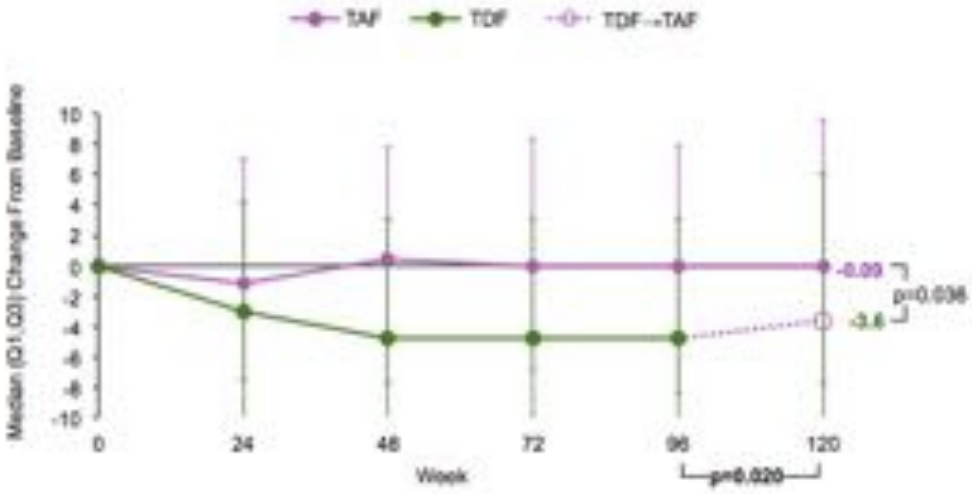
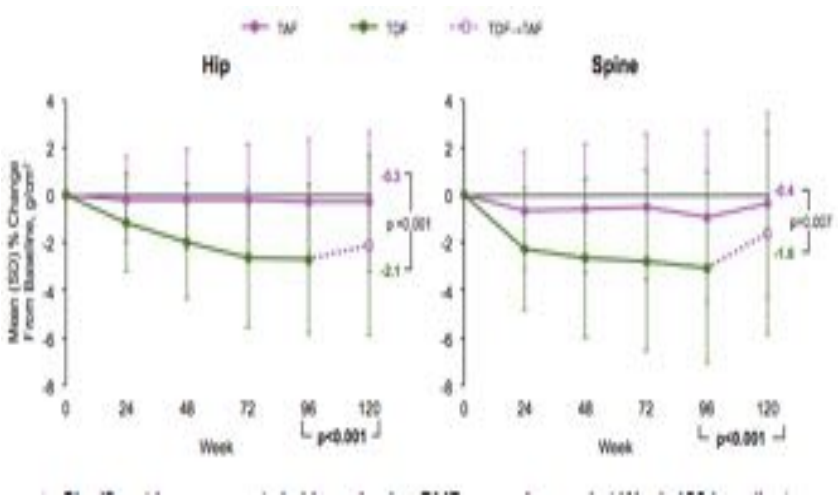
Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF)



Chan et al EASL 2017

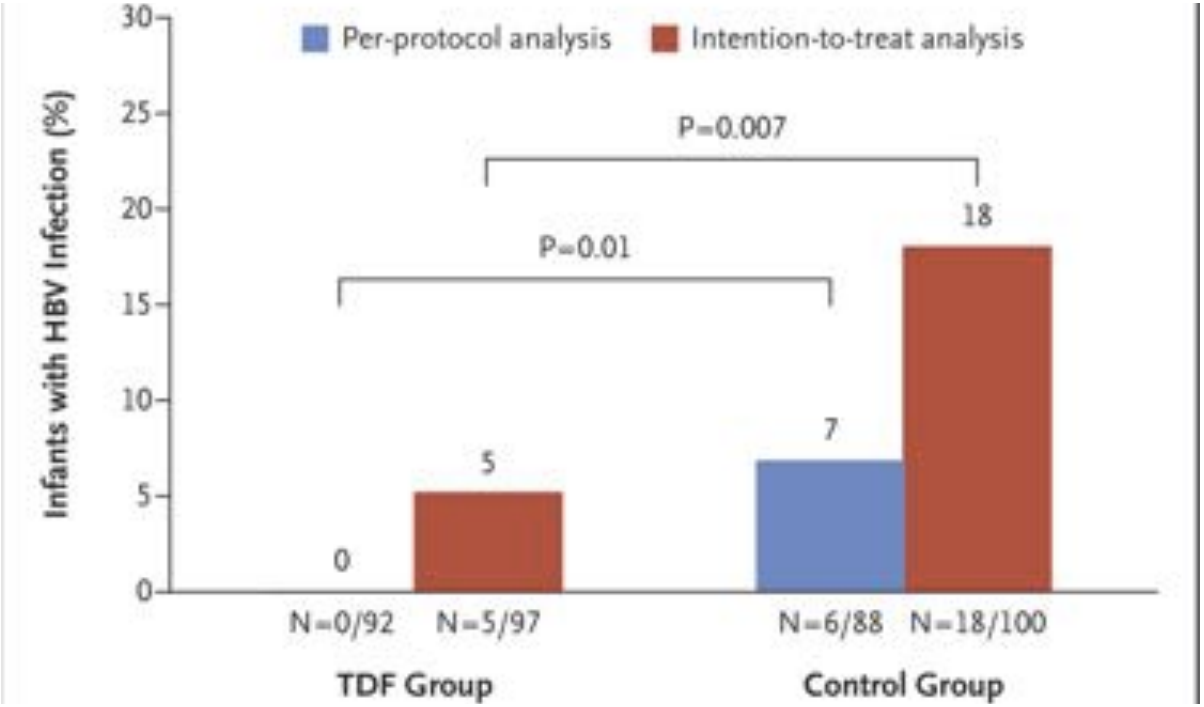
Renal and Bone Parameters improve on tenofovir alafenamide at week 120





Chan et al EASL 2017

Treatment during pregnancy



- Lamivudine, telbivudine, and tenofovir may be used, started at 28-32 weeks of gestation (>200,000 IU/ml)
- Antiviral therapy was discontinued at birth to 3 months postpartum, monitor for flares
- Breastfeeding is not contraindicated.

Terrault, Norah A., et al. *Hepatology* 63.1 (2016): 261-283.

Pan et al **N Engl J Med 2016; 374:2324-2334**

When can treatment be stopped?

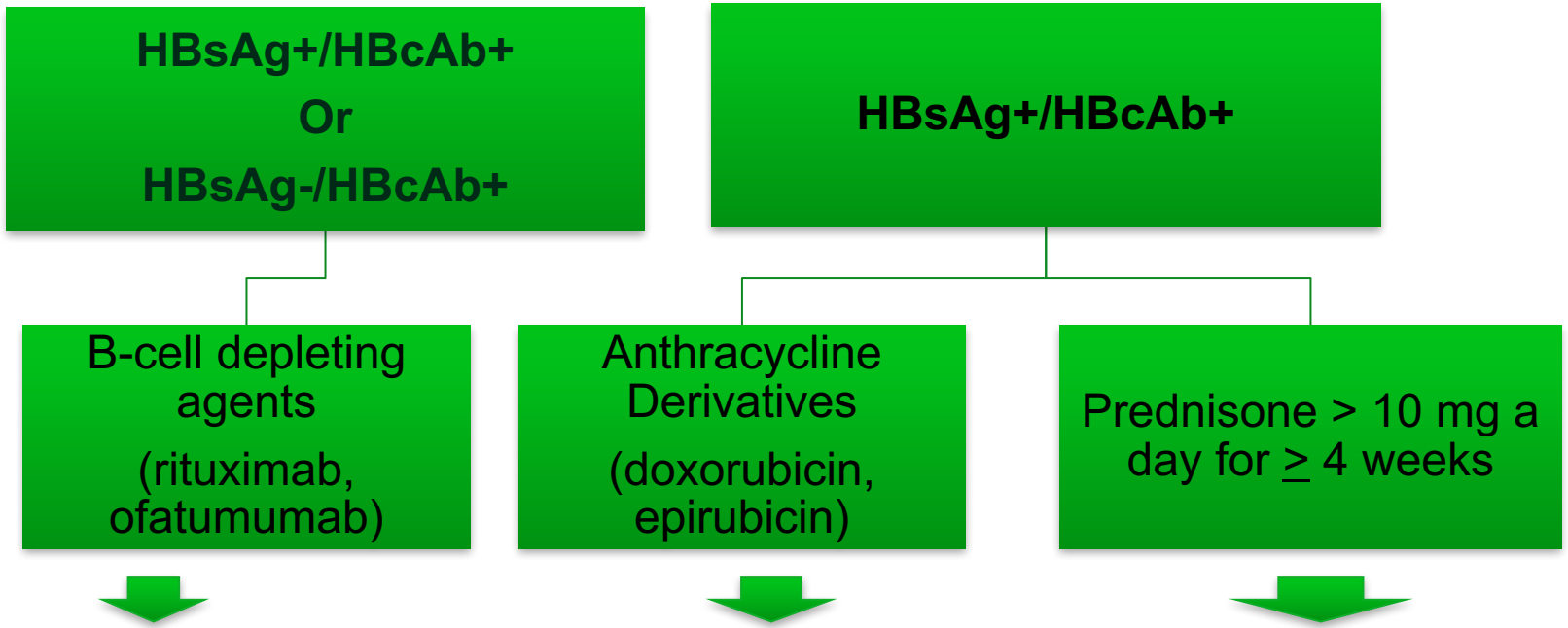
PEG IFN → defined duration, 12 months for both HBeAg+ and HBeAg- patients

Nucleos(t)ide analogues → until treatment endpoint

- HBeAg+ patients → HBeAg seroconversion + ≥12 mos consolidation Rx, ~50% after 5 yr Rx
  - An alternative approach is to treat until HBsAg loss.
- HBeAg- patients → Indefinite therapy
  - HBsAg loss ~5% after 5 yr Rx
- Cirrhotics → life-long Rx

•Terrault, Norah A., et al. *Hepatology* 63.1 (2016): 261-283

AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: High Risk Groups TDF/ETV preferred

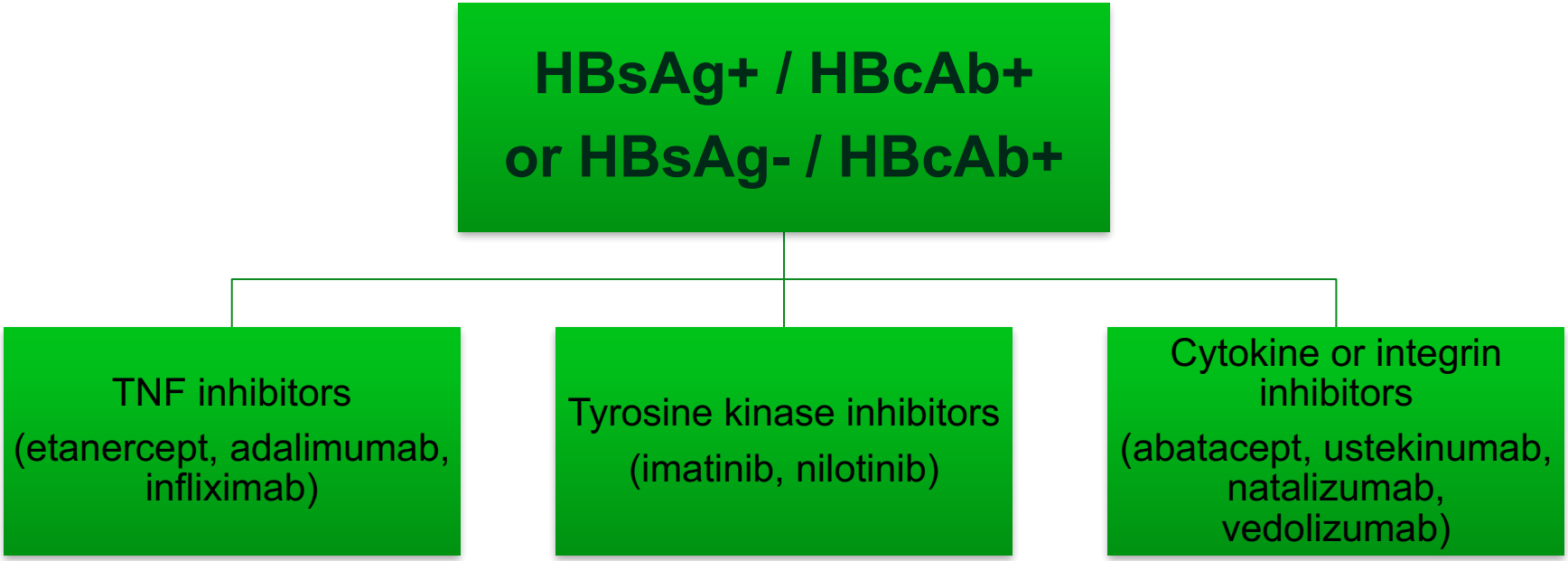


Suggest anti-viral prophylaxis for at least 12 months after discontinuation of immunosuppressive therapy

Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

Reddy et al. Gastro 2015; 148:215-9

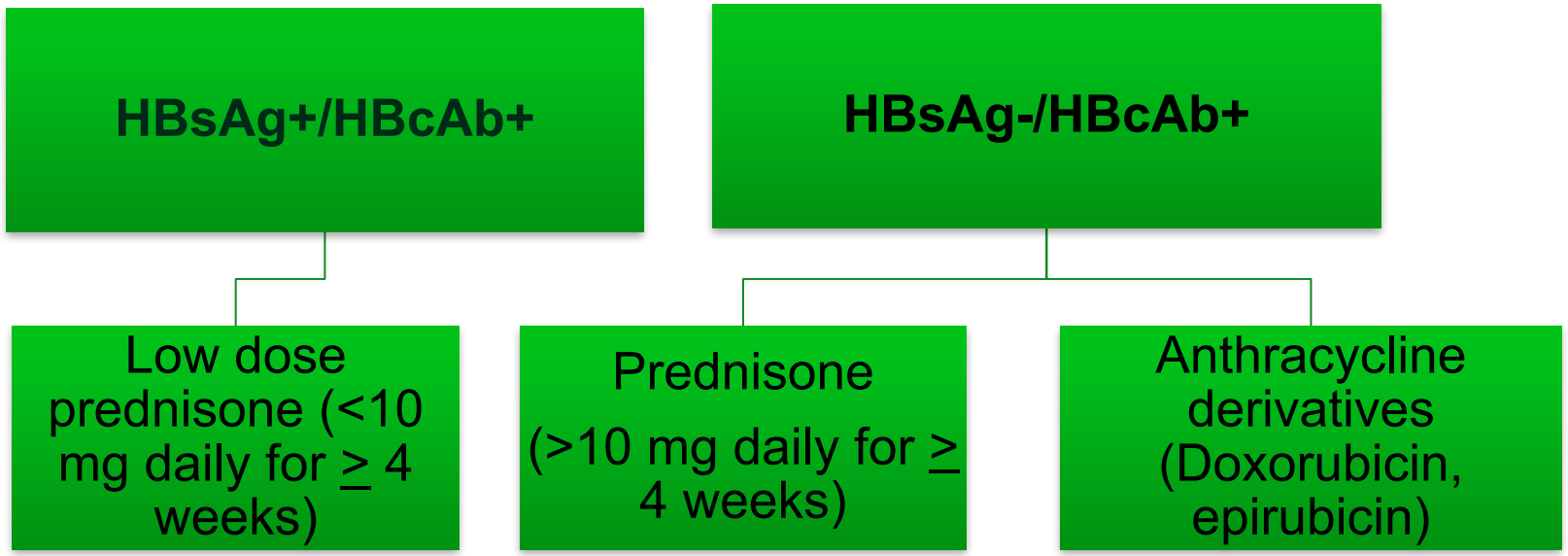
AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: Moderate Risk Groups



Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy: TDF/ETV preferred

Reddy et al. Gastro 2015; 148:215-9

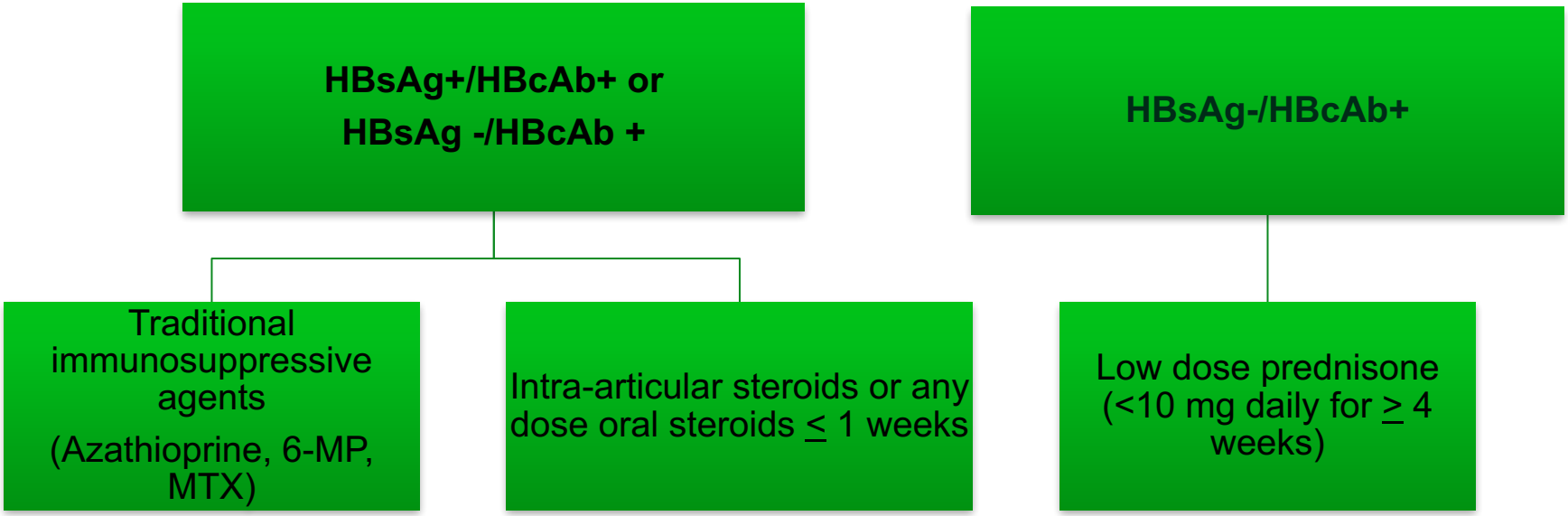
AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: Moderate Risk Groups



Suggest anti-viral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy: TDF/ETV preferred

Reddy et al. Gastro 2015; 148:215-9

AGA Recommendations for Prevention and Treatment of HBV Reactivation during Immunosuppressive Drug Therapy: Low Risk Groups



- **No use of anti-viral prophylaxis**

Reddy et al. Gastro 2015; 148:215-9

Who Should Be Screened Prior to Chemotherapy?

- AASLD recommends screening high-risk individuals[1]
  - Immigrants
    - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
  - Children of immigrants
  - Men who have sex with men
  - HIV/HCV positive
  - History of IDU, incarceration
  - Hemodialysis patients

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  - History of IDU, incarceration
  - Hemodialysis patients

- CDC[2,3] & EASL[4] recommend screening ALL patients prior to starting chemotherapy

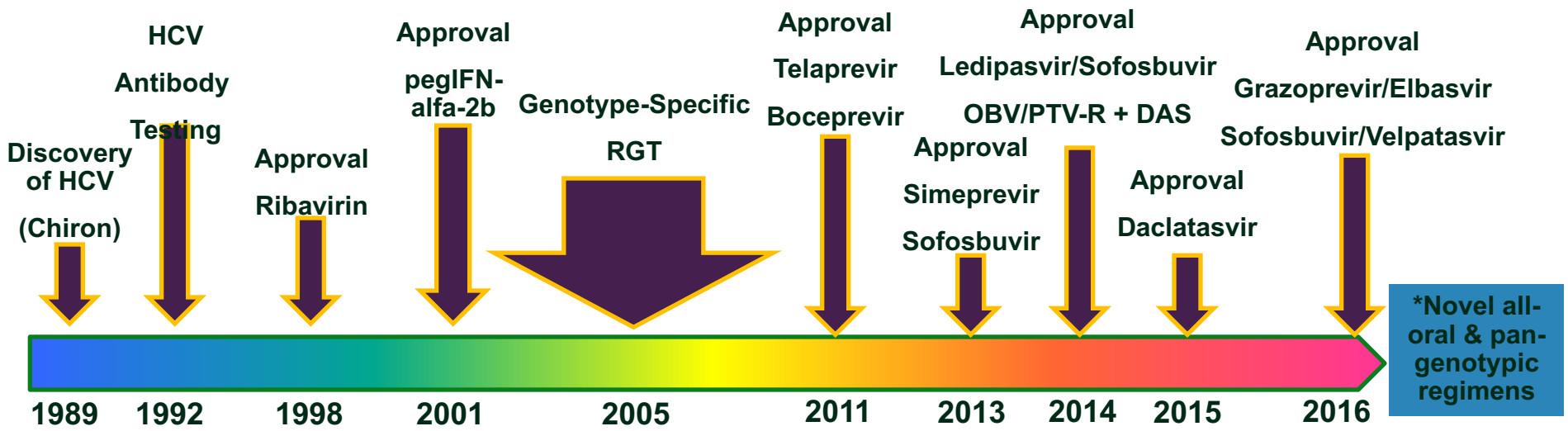
AASLD Guidelines: HBV

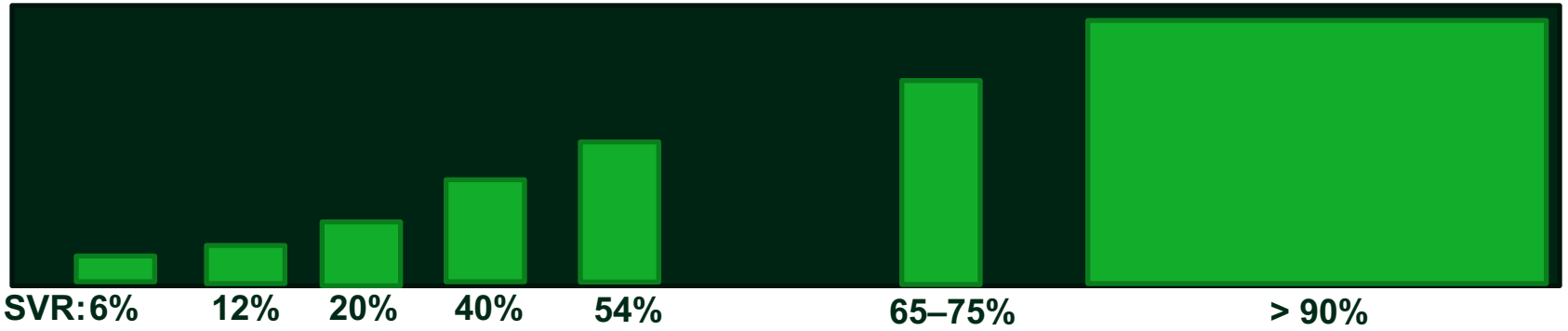
- Surveillance recommended in at-risk groups
  - Specific hepatitis B carriers
    - Asian males >40 years
    - Asian females >50 years
    - Africans >20 years
    - All HBV cirrhotic pts
    - Family history of hepatoma
- Patients should be screened at 6-month intervals
  - US and AFP level

Summary

- We can cure most people with hepatitis C we encounter if they comply with therapy
- Optimal management of decompensated patients still not yet defined
- Rigorously survey Cirrhosis patients/HCC patients in whom you treat HCV with DAAs
- Post SVR, risks of progressive liver disease/HCC remain, though are reduced
- HCV elimination can only be achieved with screening **and** linkage to care strategies **that lead to treatment**
- Elimination of HCV prior to 2030 in the US is achievable with only modest increases in treatment
- We will need to treat populations that have not been historically treated

History and Evolving Landscape of HCV Therapy





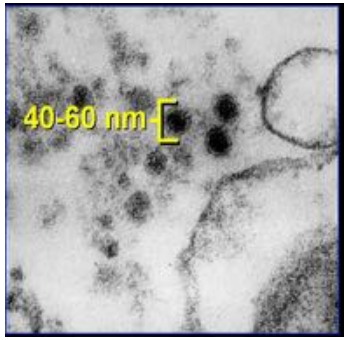
pegIFN-alfa 2b = peg-interferon alfa-2b; RGT = response-guided therapy; OBV/PTV-R + DAS = ombitasvir/paritaprevir and ritonavir + dasabuvir (or 3D).

Houghton M. *Liver Int*. 2009;29(Suppl 1):82-88; Carithers RL, et al. *Hepatology*. 1997;26(3 Suppl 1):S83-S88; Zeuzem S, et al. *N Engl J Med*. 2000;343(23): 1666-1672; Poynard T, et al. *Lancet*. 1998;352(9138):1426-1432; McHutchison JG, et al. *N Engl J Med*. 1998;339(21):1485-1492; Lindsay KL, et al. *Hepatology*. 2001;34(2):395-403; Fried MW, et al. *N Engl J Med*. 2002;347(13):975-982; Manns MP, et al. *Lancet*. 2001;58(9286):958-965; Poordad F, et al. *N Engl J Med*. 2011;364(13):1195-1206; Jacobson IM, et al. *N Engl J Med*. 2011;364(25):2405-2416; Lawitz E, et al. *N Engl J Med*. 2013;368(20):1878-1887; Jacobson IM, et al. *Lancet*. 2014;384(9941):403-413; Afdhal N, et al. *N Engl J Med*. 2014;370(20):1889-1898; Nelson DR, et al. *Hepatology*. 2015;61(4):1127-1135; Zeusem S, et al. *Ann Intern Med*. 2015;163(1):1-13; Feld JJ, et al. *N Engl J Med*. 2015;373(27):2599-2607.; Foster GR, et al. *N Engl J Med*. 2015;373(27):2608-2617.

Hepatitis C Therapy Has Paralleled *Helicobacter pylori* Therapy

H pylori

HCV



Selected Long-Duration Regimens for *Helicobacter pylori*

Treatment regimen	Duration	Eradication rate (%)
Omeprazole (Prilosec), 20 mg twice daily, *plus* amoxicillin, 1 g twice daily, *plus* clarithromycin (Biaxin), 500 mg twice daily	14 days	80 to 86
Lansoprazole (Prevacid), 30 mg twice daily, *plus* amoxicillin, 1 g twice daily, *plus* clarithromycin, 500 mg twice daily	10 to 14 days	86
Bismuth subsalicylate (Pepto-Bismol), 525 mg four times daily, *plus* metronidazole (Flagyl), 250 mg four times daily, *plus* tetracycline, 500 mg four times daily, *plus* histamine H_2 blocker	14 days (H_2 blocker alone for an additional 14 days taken once or twice daily)	80

All Oral Therapy

Duration 8-24 weeks

Polymerase Inhibitor

±

Protease Inhibitor

±

NS5a

±

Non-nucleoside Inhibitor

±

ribavirin

All Oral Therapy,

single tablet