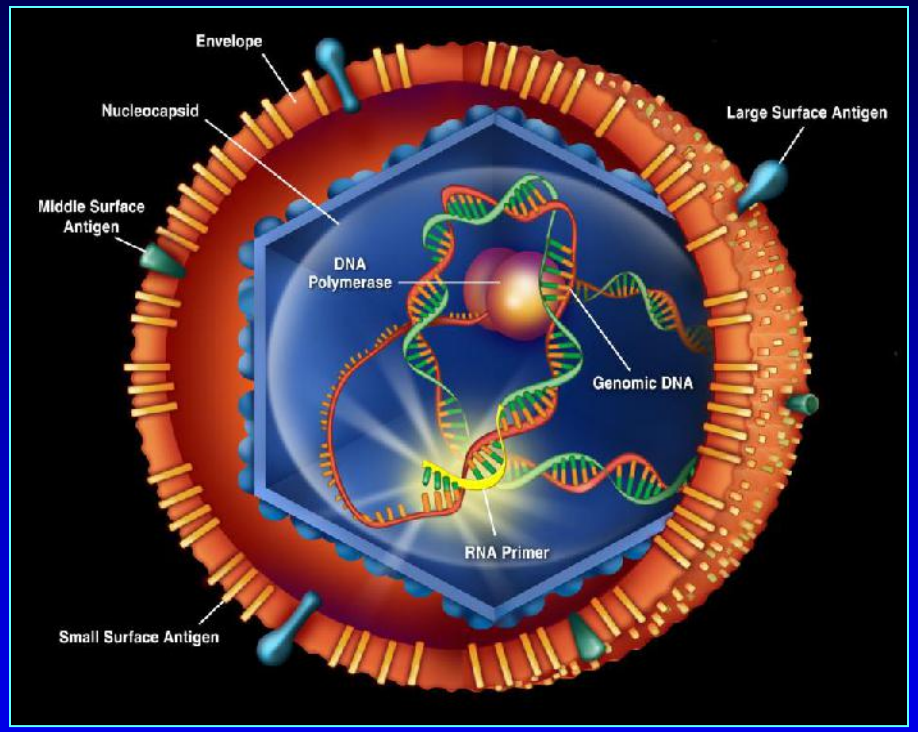
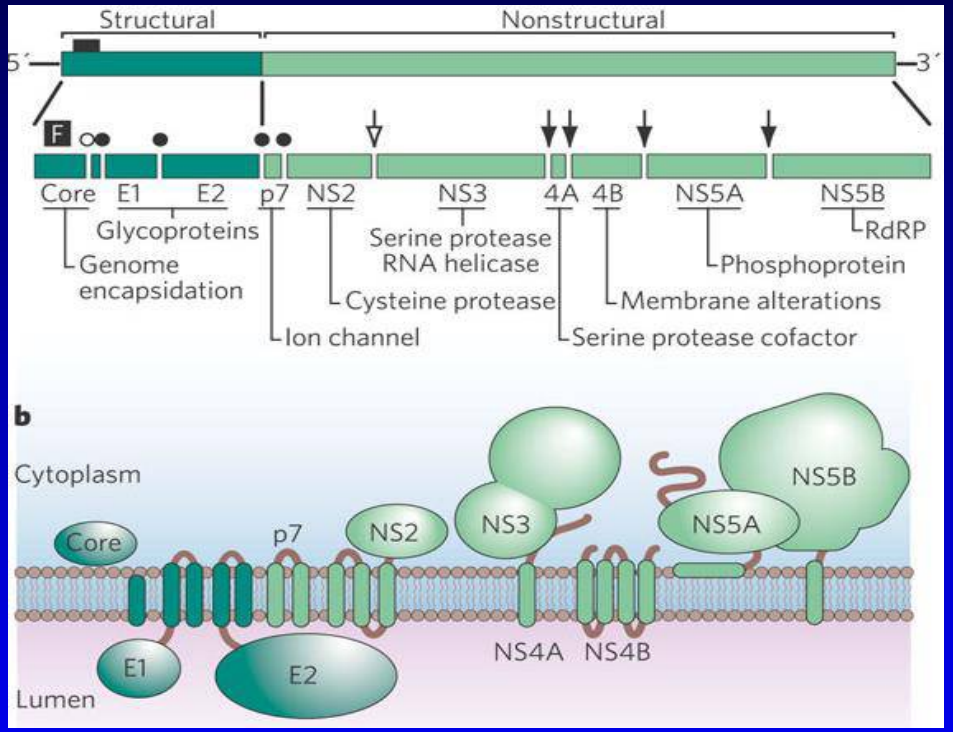
Viral Hepatitis Update 2022





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Gastrointestinal Unit
Massachusetts General Hospital
Harvard Medical School

Disclosures regarding my presentation today

During previous two years

- Consulting (incl. Scientific Advisory Boards)
  - Chroma Medicine
- Data monitoring/adjudicating committees
  - Janssen
  - Intercept, Genzyme/Sanofi, Alnylam—unrelated to my presentation

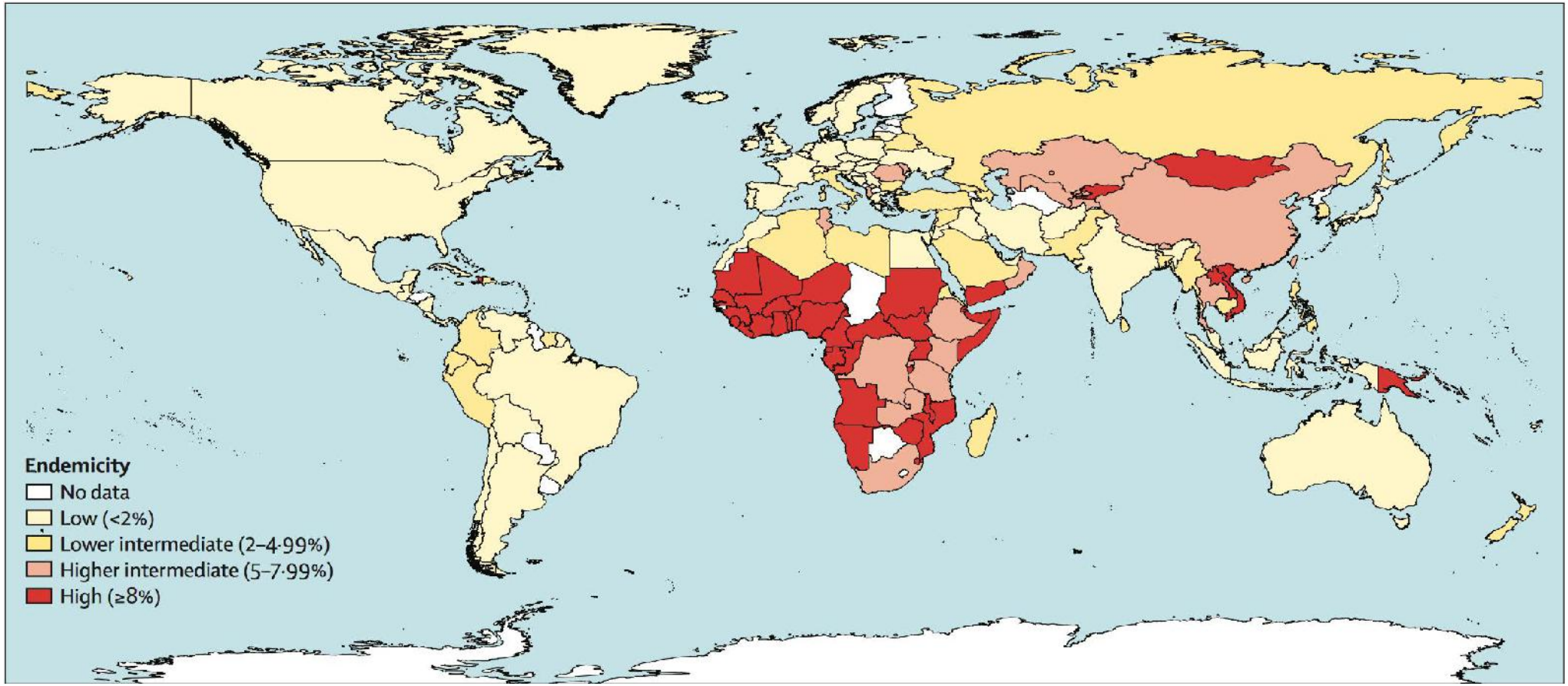
Learning Objectives

In chronic viral hepatitis …

1. Brief review of hepatitis virology, epidemiology.
2. Grasp the rationale for and approach to treatment (HBV vs HCV).
3. Recognize the driver of liver injury (viral replication).
4. Appreciate the impact of suppressing viral replication on natural history.
5. Understand the indications for therapy.

Global Prevalence of Chronic HBV Infection: Systematic review of published data 1965-2013

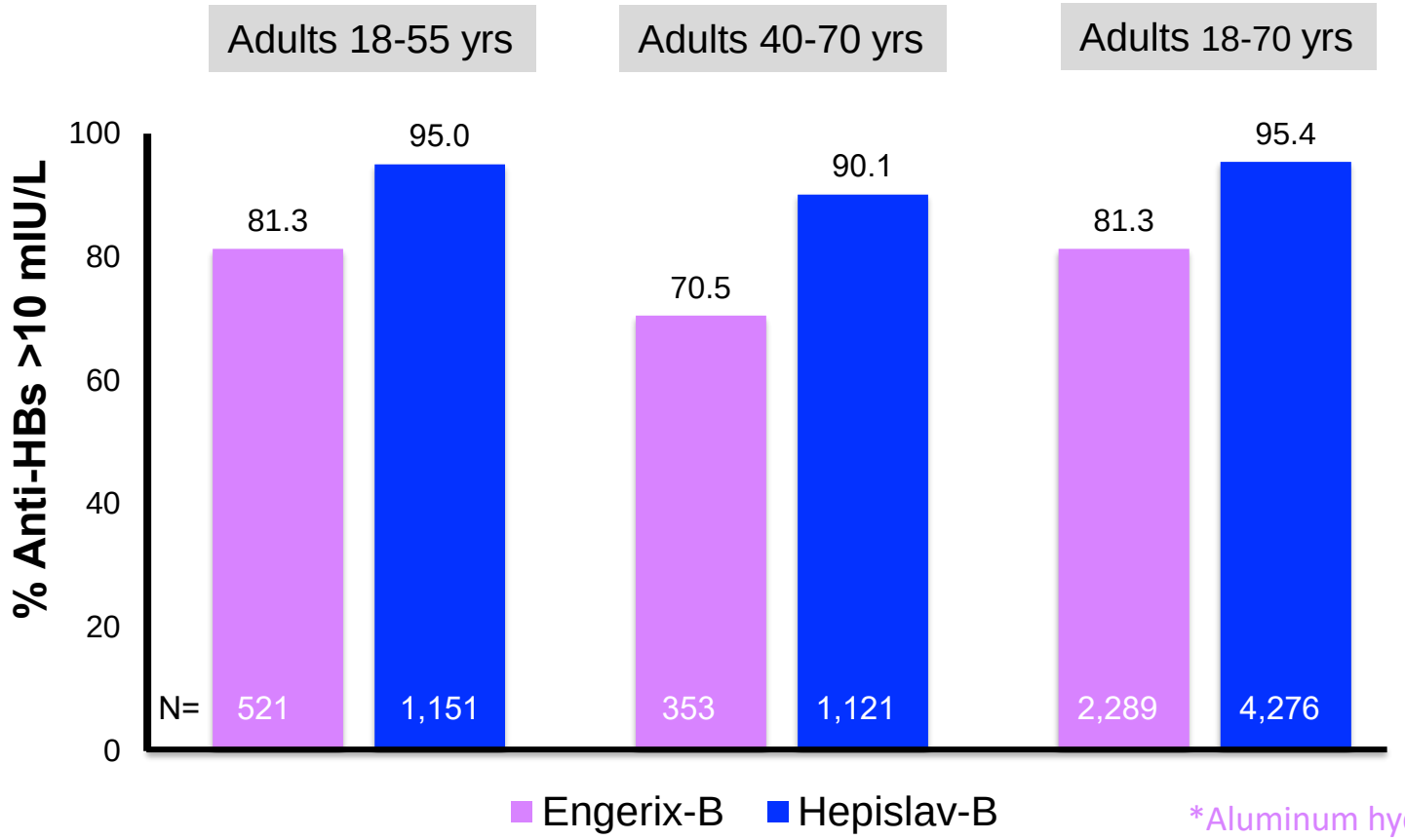
Global HBsAg seroprevalence 3.6% (248 million persons in 2010)
Highest: 8.8% Africa, 5.3% Western Pacific; lowest 0.2% Mexico; USA 0.27%



Global endemicity 1957-2013

Schweitzer A, et al. Lancet 2015;386:1546-55.

Engerix-B* (3 doses, 0, 1, & 6 mo) vs Hepislav-B† (2 doses, 0 & 1 mo)



*Aluminum hydroxide adjuvant

† Toll-like receptor CpG1018 adjuvant

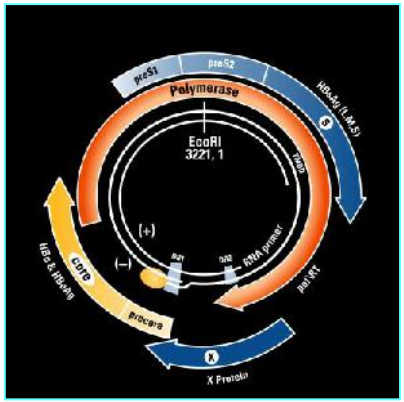
Halperin SA, et al. Vaccine 2012; 30:2556-63.
Heyward WL, et al. Vaccine 2013;31:5300-5.
Jackson S, et al. Vaccine 2018;36:668-74.

JAMA 2018;319:822-3 (reprinted from The Medical Letter 2018;60:17-8).
MMWR 2018;67:455-8.

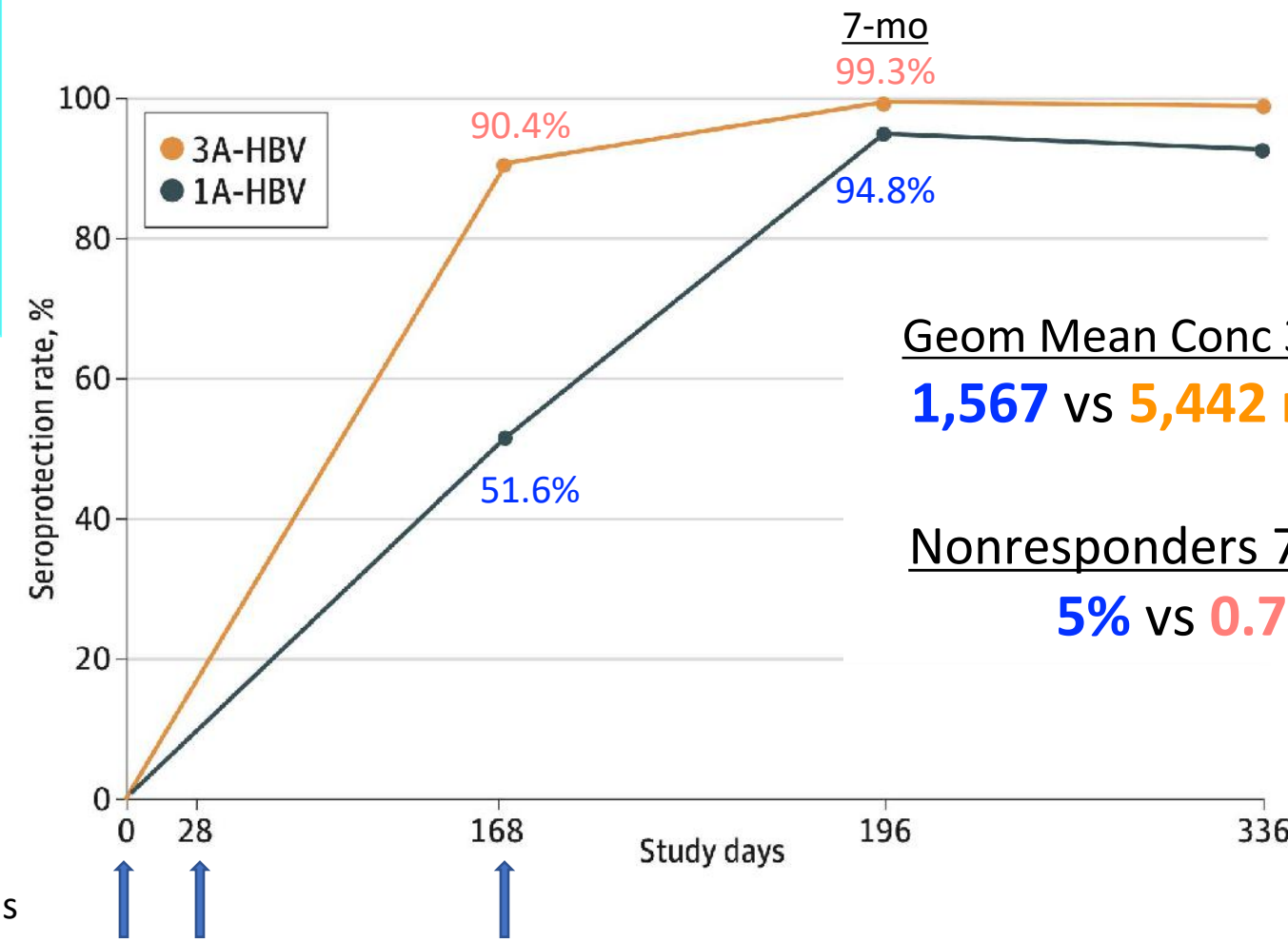
A three-antigen* vs a single-antigen hepatitis B vaccine (0, 1, 6 mo) in adults (CONSTANT): randomized, double-blind, phase-3 trial (n = 2,838, mean age 33.5 yrs)

*Pre-S1 (large), Pre-S2 (middle), S (small)
Mammalian posttranslational glycosylation (native conformation)

healthy young adults



Seroprotection rate (anti-HBs ≥10 mIU/ml)



Geom Mean Conc 3 x higher
1,567 vs **5,442 mIU/ml**

Nonresponders 7 x lower
5% vs **0.7%**

Vesikari T, et al. JAMA Network Open. 2021; 4(10):e2128652 doi:10.1001/jamanetworkopen.2021.28652

Approved Hepatitis B Vaccines

Hepatitis Vaccines Work Group, Advisory Committee on Immunization Practices, Wednesday February 23, 2022

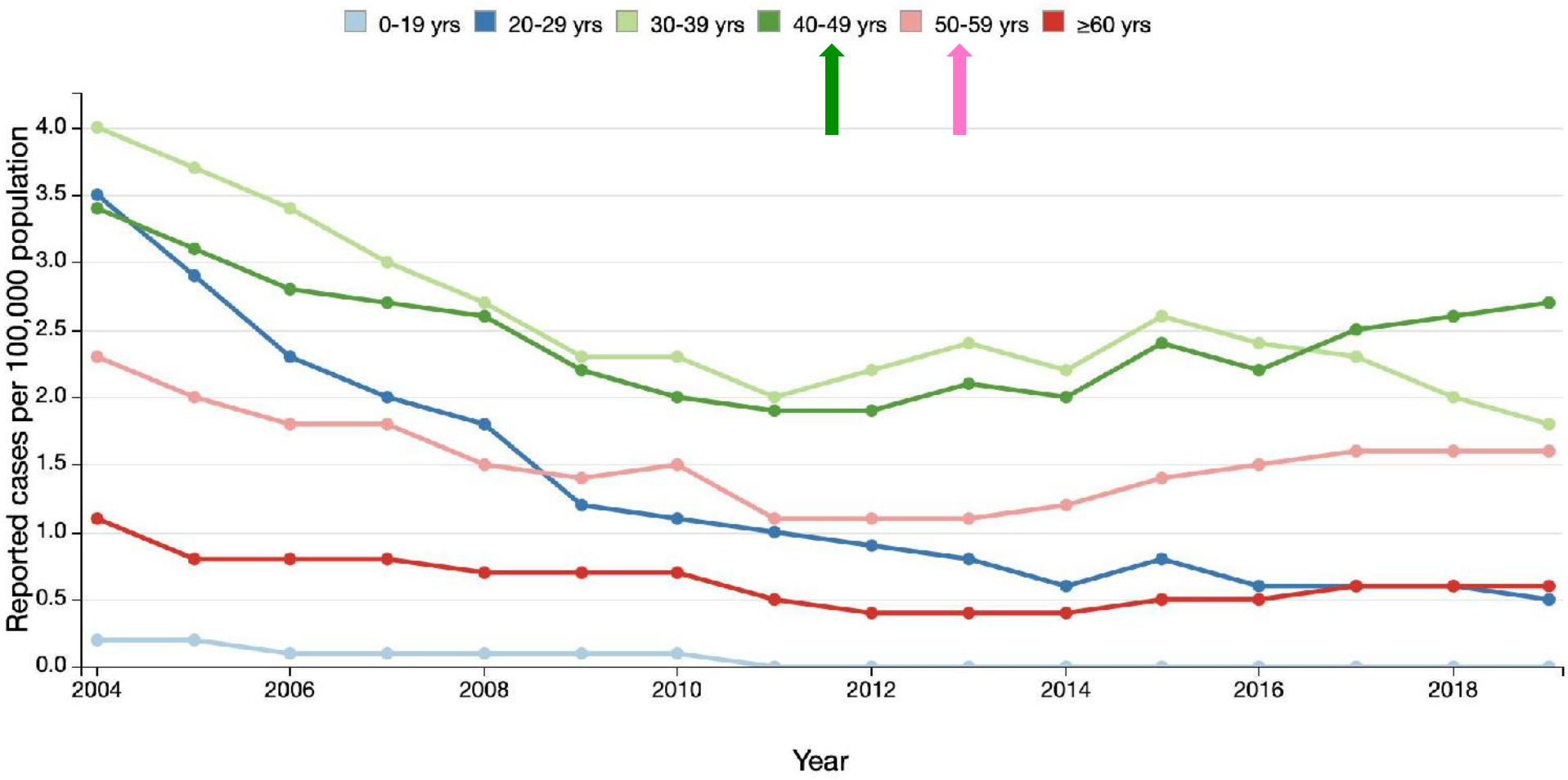
Adult HepB vaccine*	Derivation	Adjuvant	Dose of HBs Antigens	Schedule
PreHevbrio†	mammalian (Chinese hamster ovary) Cell	alum	10µg	3 doses at 0, 1, 6 mo
Engerix-B	yeast	alum	20µg	3 doses at 0, 1, 6 mo
Recombivax HB	yeast	alum	10µg	3 doses at 0, 1, 6 mo
Heplisav-B†	yeast	CpG 1018	20µg	2 doses at 0, 1 mo

*ACIP Recommended Immunization Schedule for Adults ≥19 Years — US, 2022 (http://dx.doi.org/10.15585/mmwr.mm7107a1)

Data on Heplisav-B and PreHevbrio currently insufficient to inform vaccine-associated risks in pregnancy—not recommended.

†Consider in reduced vaccine responsiveness: elderly, obese, DM, HIV, CLD, CKD, prior nonresponders

Rates of reported acute hepatitis B virus infection, by age group— US, 2004–2019



Source: CDC, National Notifiable Diseases Surveillance System.
Weng MK, et al. MMWR 2022;71:477-83 (April 1, 2022)

Universal Hepatitis B Vaccination in Adults Aged 19-59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices—US, 2022

- In 2018, vaccine coverage was only 30% among US adults age ≥19.
- Age 40-50 and 30-40 cohorts had the largest increases in reported acute hepatitis B (2014-2019).
- Hepatitis B vaccine coverage among adults with risk factors is suboptimal.
  - 37% of CDC-reported cases did not have identified risk factors.
- Risk factors assessed under prior recommendations included potential criminal or stigmatizing behavior, limiting effectiveness of risk assessment.
- Racial and ethnic disparities exist among persons with HBV infection.
- Non-US-born residents account for 69% with chronic HBV infection
  - 9 x more likely to have chronic hepatitis B than US-born persons
- Rates of hepatitis B among children and adolescents converged to a lower rate after universal vaccination implemented in this age group.
- Universal vaccination addresses these issues.*

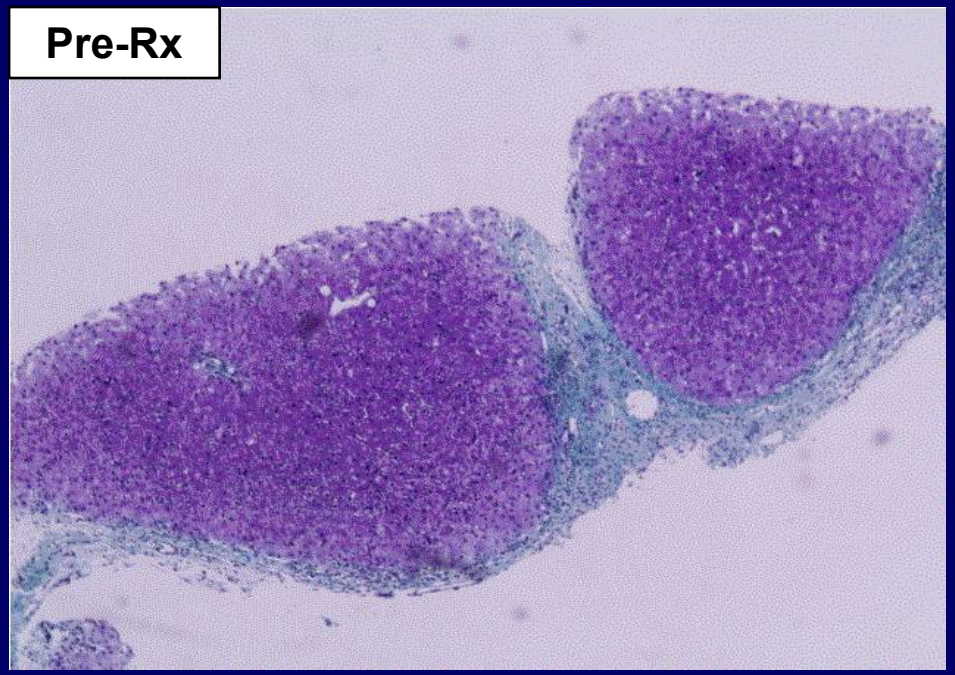
Murthy N. et al. Ann Intern Med (February 18, 2022) https://doi.org/10.7326/M22-0036
Weng MK, et al. MMWR 2022;71:477-83 (April 1, 2022)

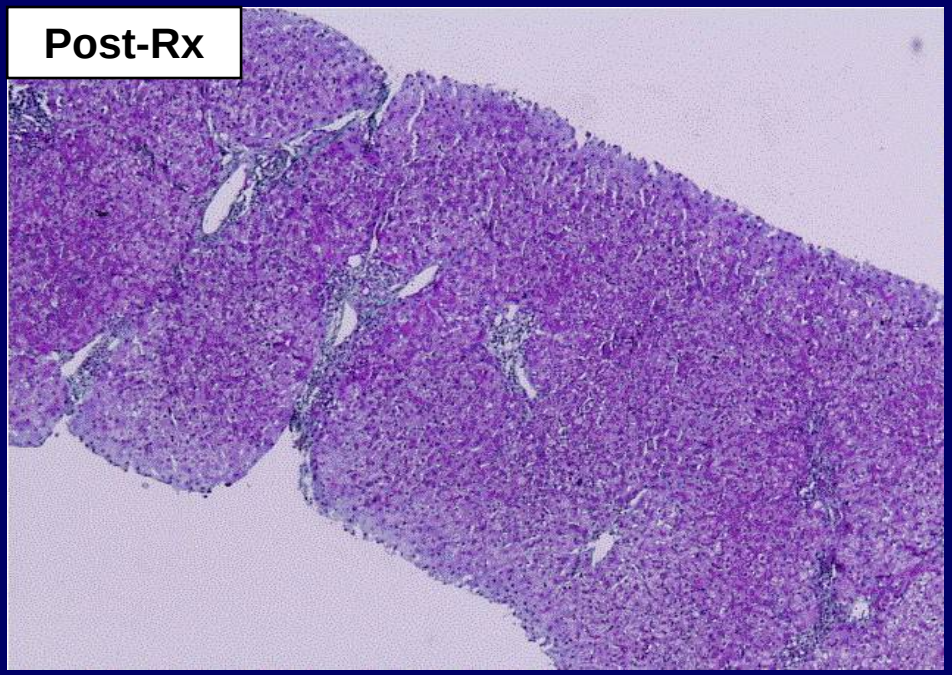
* For age >60, vaccination remains based on risk factors but may be offered even without risk factors.

All the following are true for antiviral therapy of chronic hepatitis B, except…

A. Involves very potent drugs with a high barrier to resistance
B. Can retard fibrosis but not reverse cirrhosis
C. Reduces the risk of hepatic decompensation and the need for liver transplantation
D. Reduces liver-related mortality, all-cause mortality, and HCC
E. Reduces the risk of hepatitis B reactivation after cytotoxic/immunosuppressive chemotherapy.

Histologic improvement in cirrhosis after 3 years of lamivudine therapy





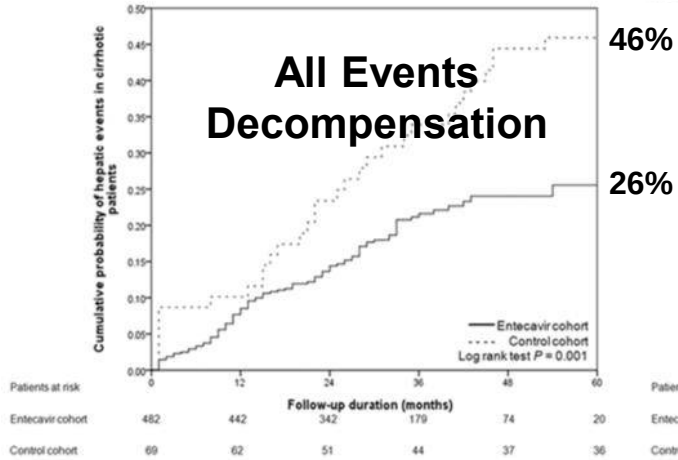
Wild-type HBV

ETV Antiviral Therapy Reduces Decompensation and Liver-related Mortality in Cirrhotic Patients with Chronic Hepatitis B

Retrospective-Prospective Cohort Study of 482 treated and 69 treatment-naïve patients

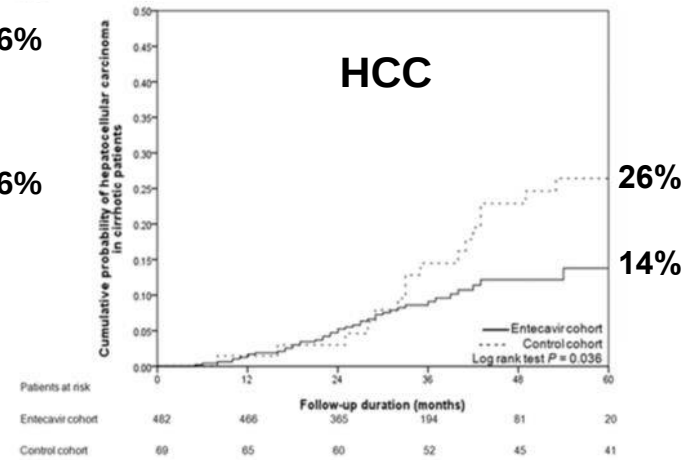
5-Year Cumulative Probability of Outcomes

HR* 0.51
(49% ↓)



46%

26%

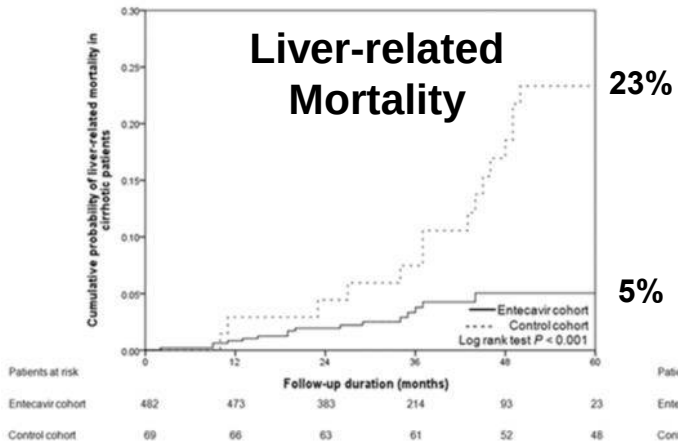


26%

14%

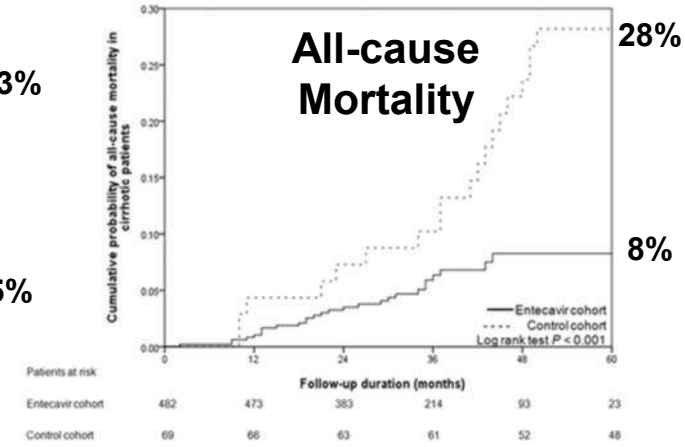
HR 0.55
(45% ↓)

HR 0.26
(74% ↓)



23%

5%



28%

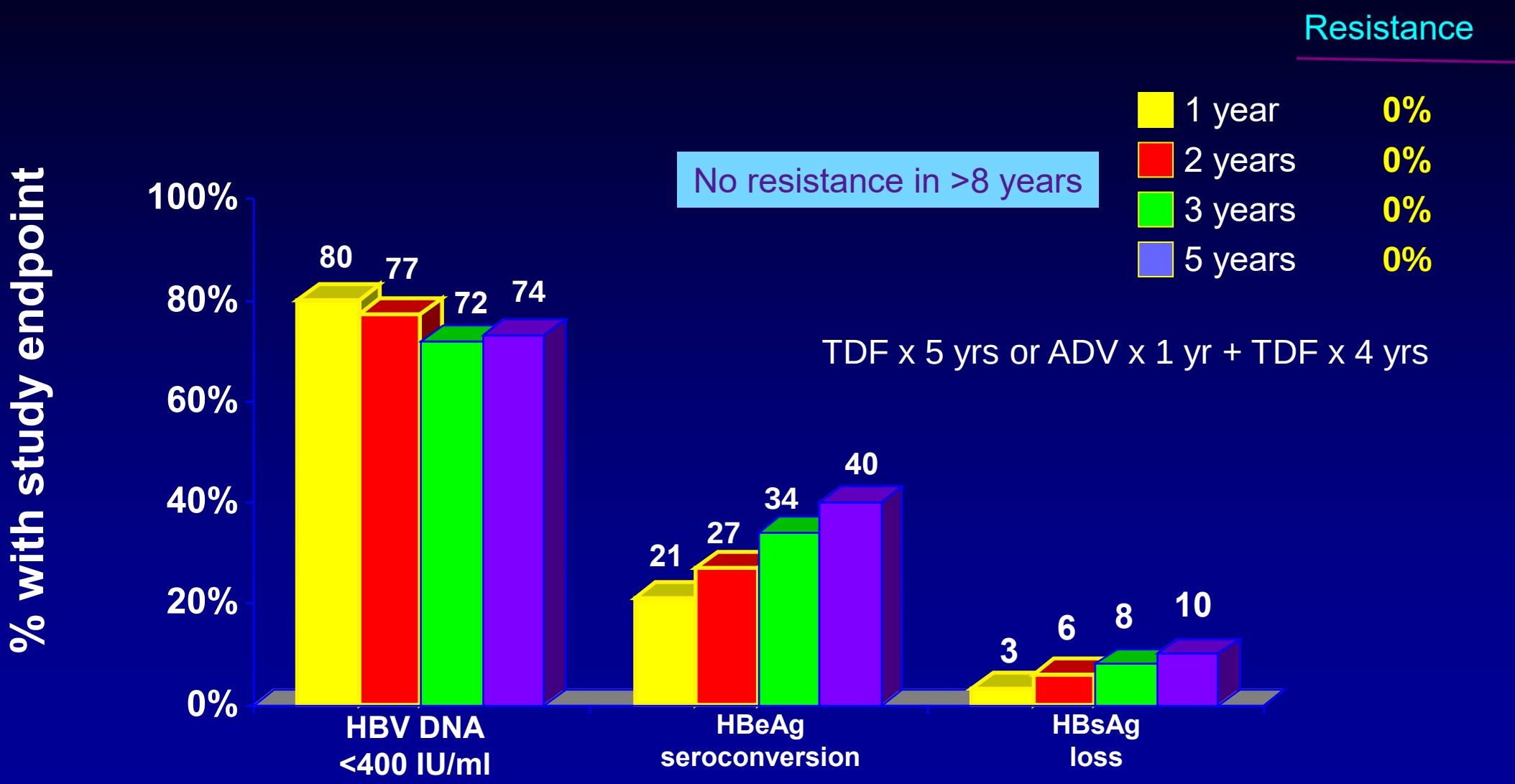
8%

HR 0.34
(66% ↓)

***Hazard Ratio**

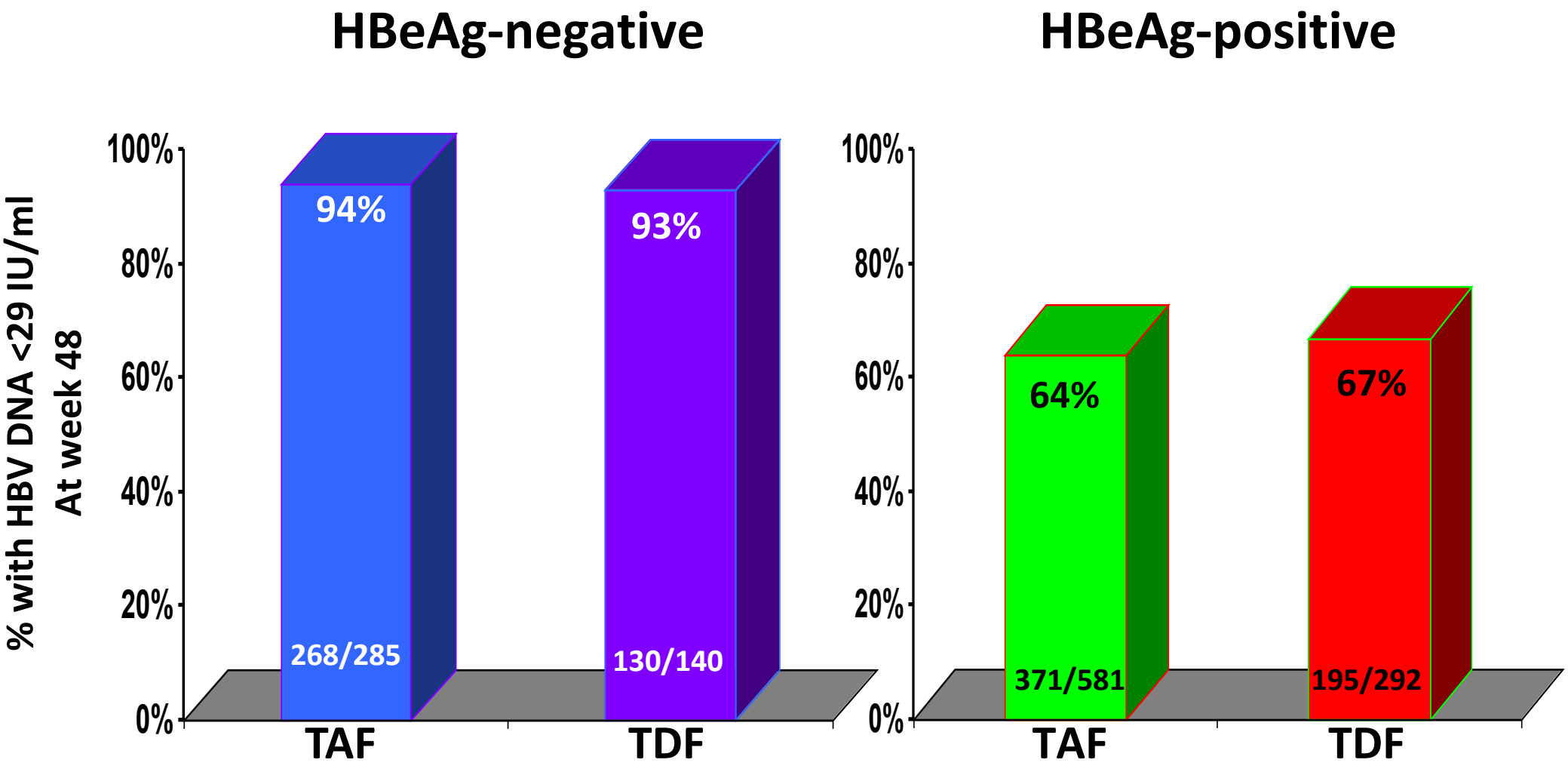
Wong GL-H, et al. Hepatology 2013;58:1537-47.

Tenofovir x 5 Yrs in HBeAg-Positive Chronic Hepatitis B



Snow-Lampart A et al. Hepatology 2011;53:763-73; Marcellin P et al. Lancet 2013; 381:468-75.

TAF* vs TDF in Chronic Hepatitis B



Buti M, et al. Lancet Gastroenterology Hepatology 2016;1:196-206.
Chan HLY, et al. Lancet Gastroenterology Hepatology 2016;1:185-95.

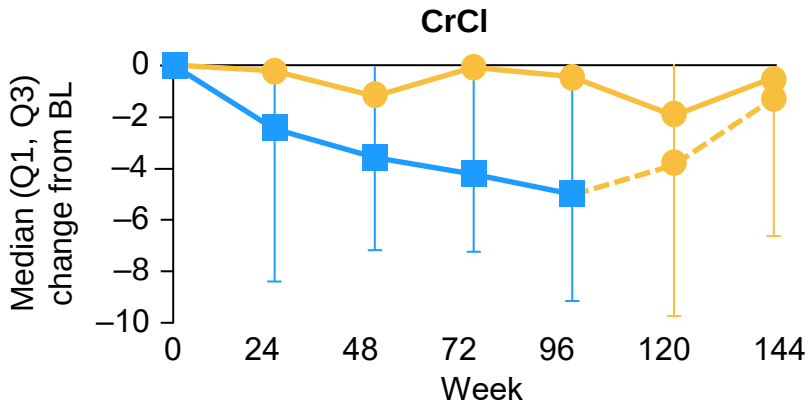
*Tenofovir Alafenamide

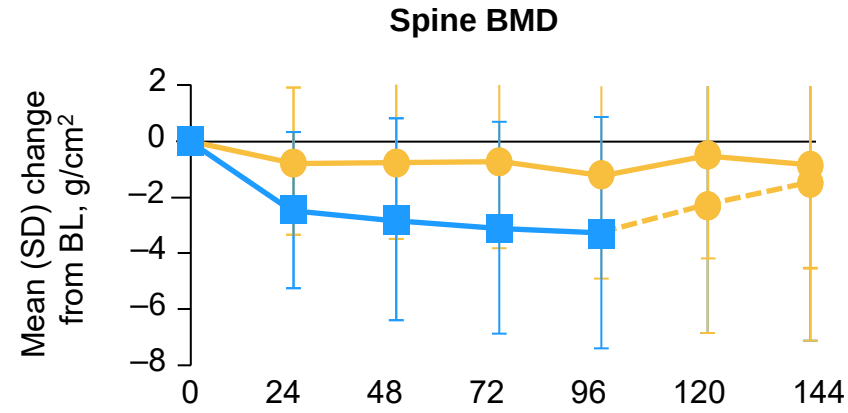
Impact of Switching from TDF to TAF on C_{Cr} and BMD

Creatinine Clearance

TAF (n = 360)
TDF (n = 180)
TDF→TAF

Bone Mineral Density





Gane E, et al. EASL 2018, Abstract PS-156.
Lampertico P, et al. Lancet Gastroenterol Hepatol 2020;5:441-53.

AASLD Hepatitis B Treatment Guidelines

HBeAg	HBV DNA	ALT	Management
+	>2 x 10^4 IU/mL	<2 x ULN	Low efficacy of current Rx*
+	>2 x 10^4 IU/mL	≥2 x ULN	Treat
-	>2 x 10^3 IU/mL	≥2 x ULN	Treat
-	>2 x 10^3 IU/mL	1- >2 x ULN	Low efficacy of current Rx*
-	≤2 x 10^3 IU/mL	≤ULN	Observe
+/-	+	Cirrhosis	Comp: Treat, regardless of ALT level Decomp: Treat, coordinate with Tx center
+/-	-	Cirrhosis	Comp: Observe Decomp: Treat, Refer for Liver Tx

*Consider Rx: except in patients >40, with family Hx cirrhosis or HCC, with extrahepatic manifestations, with a history of previous treatment, and/or liver biopsy (or noninvasive fibrosis determination) evidence for moderate to severe inflammation or fibrosis

Terrault NA, et al. Hepatology 2016;63:261-283 and Hepatology 2018;67:1560-99.

HBV Reactivation Risk Based on Serologic Status and Immunosuppressive Potency

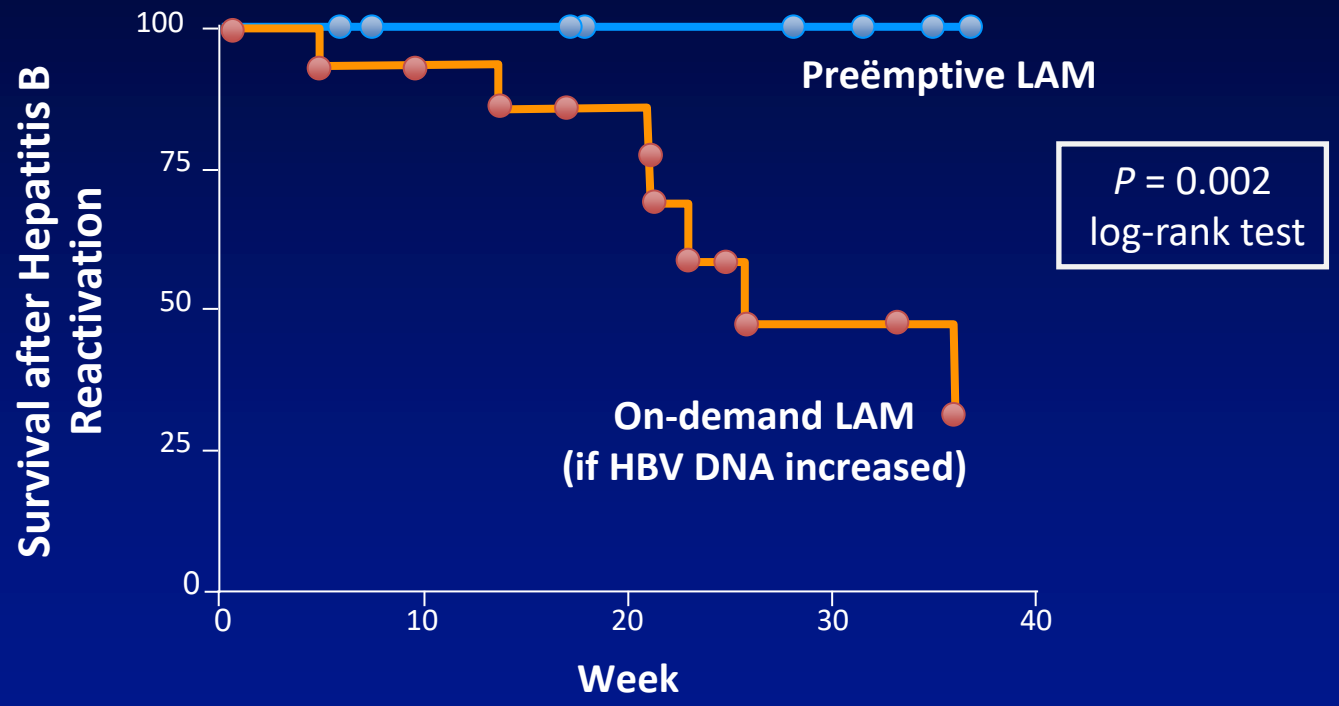
Risk Level	Serological Risk Status	Immunosuppressive Agent Risk Status
High (>10%)	HBsAg+, high HBV DNA, or HBeAg+	▪ B-cell–depleting agents (e.g., Rituximab) ▪ Systemic chemotherapy ▪ Moderate/high-dose corticosteroids*
Intermediate (1%-10%)	HBsAg- anti-HBc+ anti-HBs-	▪ Tumor necrosis factor (TNF) inhibitors ▪ T-cell activation inhibitors (e.g., Abatacept) ▪ Tyrosine kinase inhibitors ▪ Other cytokine and integrin inhibitors ▪ Transarterial chemoembolization ▪ Low/moderate/high-dose corticosteroids†
Low (<1%)	HBsAg- anti-HBc+ anti-HBs+	▪ Methotrexate ▪ Azathioprine ▪ 6-mercaptopurine ▪ Low-dose corticosteroids‡

*≥10 mg for ≥4 wks for HBsAg+/anti-HBc+
†<10 mg for ≥4 wks for HBsAg+/anti-HBc+; ≥10 mg for ≥4 wks for HBsAg-/anti-HBc+
‡<1 wk for HBsAg±/anti-HBc+; <10 mg for ≥4 wks for HBsAg-/anti-HBc+

Perrillo RP, et al. Gastroenterology 2015;148:221-44. Reddy KR, et al. Gastroenterology 2015;148:215-9.

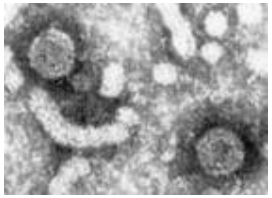
Preëmptive LAM Reduces Mortality in Hepatitis B Reactivation

HBsAg+ patients with lymphoma treated with high-dose chemotherapy randomized to preëmptive vs on-demand LAM



Patients at risk, n					
Preëmptive LAM	15	12	10	9	6
On-demand LAM	15	13	10	4	2

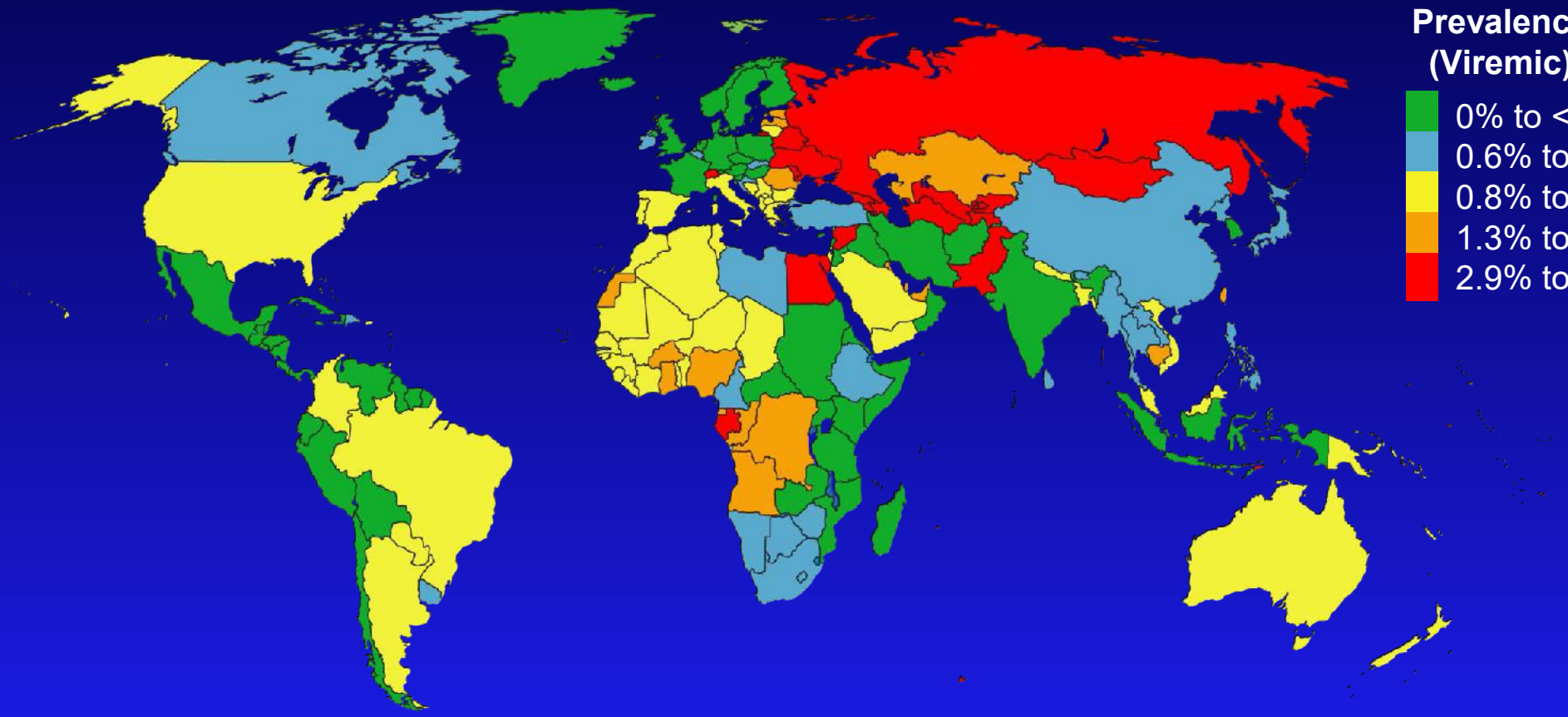
Lau GK, et al. Gastroenterology 2003;125:1742-9.



Evolving Hepatitis B Landscape: Take-Home Points

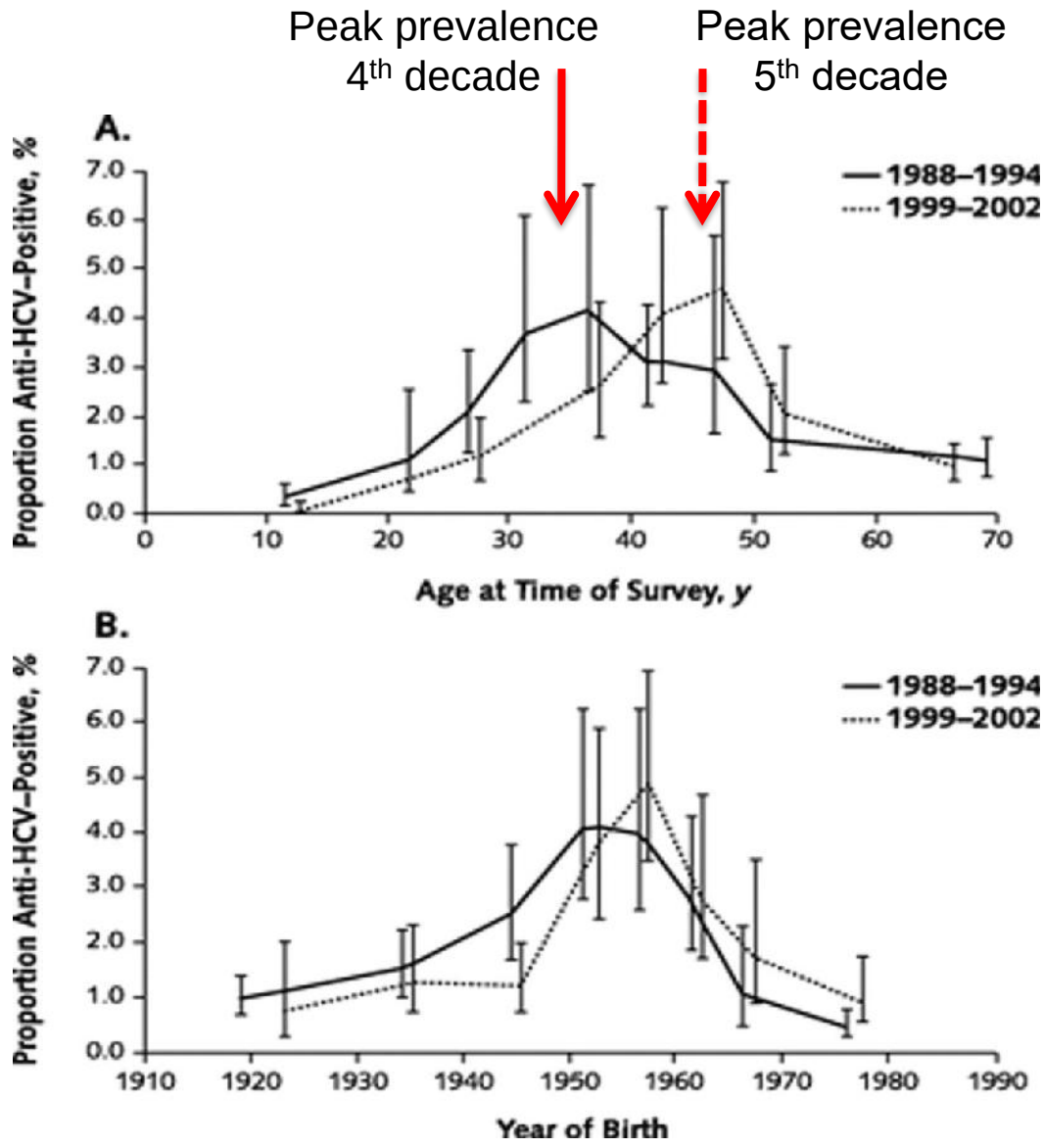
- HBV infection on the decline, but global burden remains high (250 million).
  - In the US, foreign-born persons account for the highest burden of infection.
- Hepatitis B vaccination introduced in the 1980s has reduced the prevalence, incidence, and disease burden of HBV infection.
  - In 2022, universal vaccination recommended (aged 19-59).
- Current generation antivirals—safe, well tolerated, highly potent, negligible resistance (ETV, TDF/TAF).
- Ultimately, chronic hepatitis B is a viral disease; viral suppression is the primary endpoint, but all other clinical endpoints follow.
  - Profound, durable HBV DNA suppression with oral antivirals reduces/reverses HBV-associated fibrosis progression, disease progression, HCC, and liver transplantation.
- Hepatitis B reactivation can complicate cytotoxic, immunosuppressive chemotherapy and antiviral therapy for hepatitis C—importance of preëmptive antiviral therapy.

Estimated 71 Million Persons Living with HCV Infection



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

Prevalence of HCV Infection in the US, NHANES 1988-1994 and 1999-2002

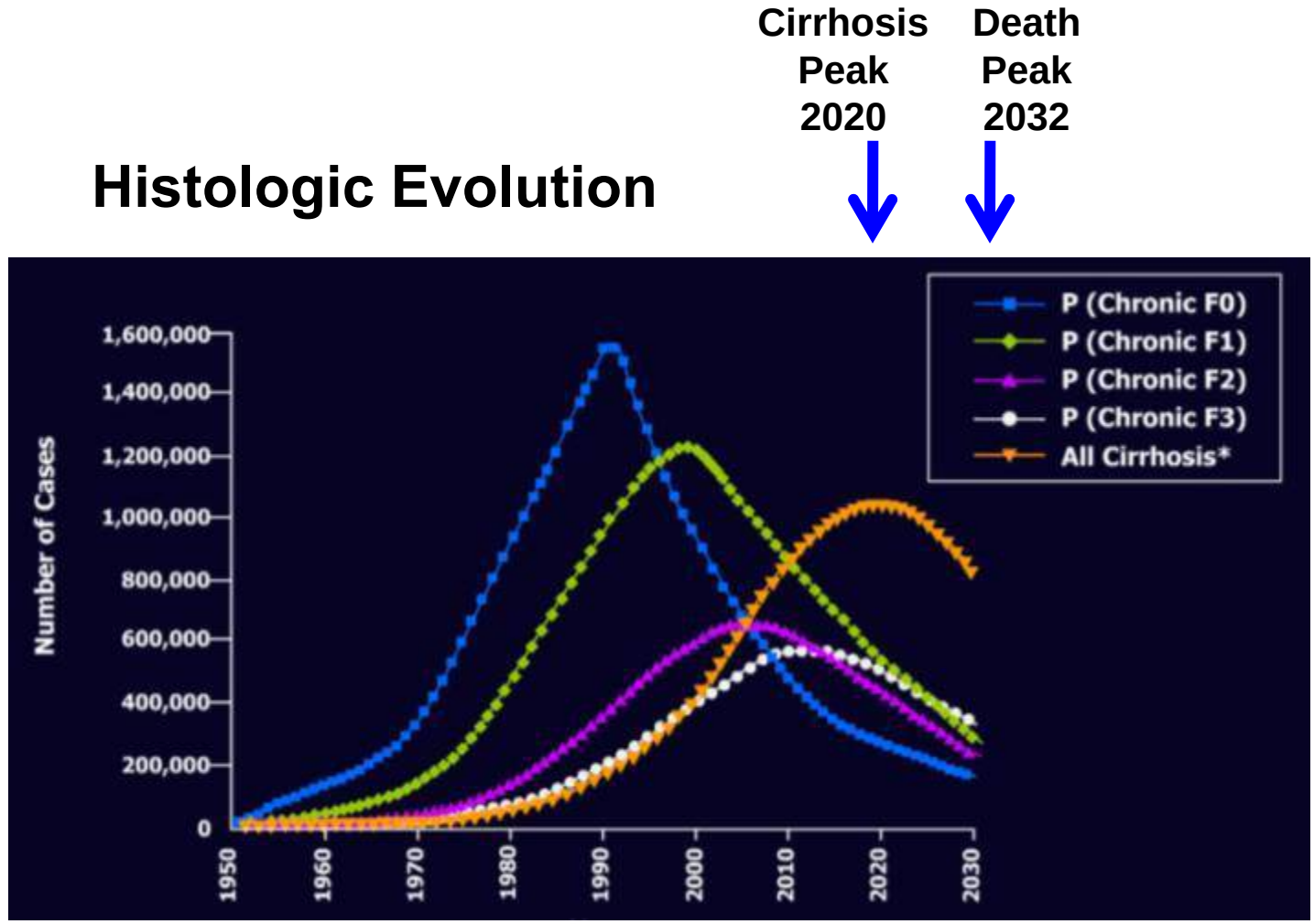


Peak prevalence
2015

Armstrong GL, et al**. National Health and Nutrition Examination Survey**. Ann Intern Med. 2006;144:705-14.

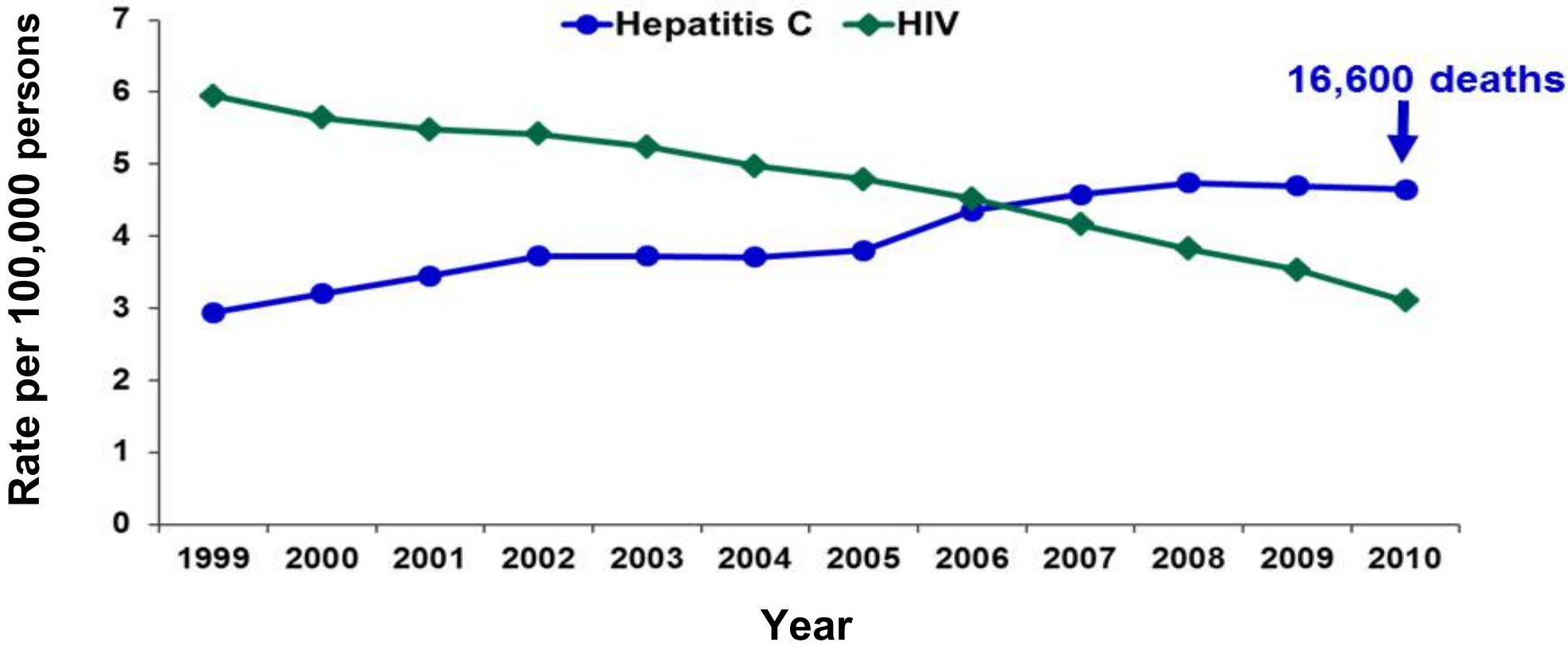
Aging of HCV-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression

Histologic Evolution



Davis GL, et al. Gastroenterology 2010;138, 513 –21

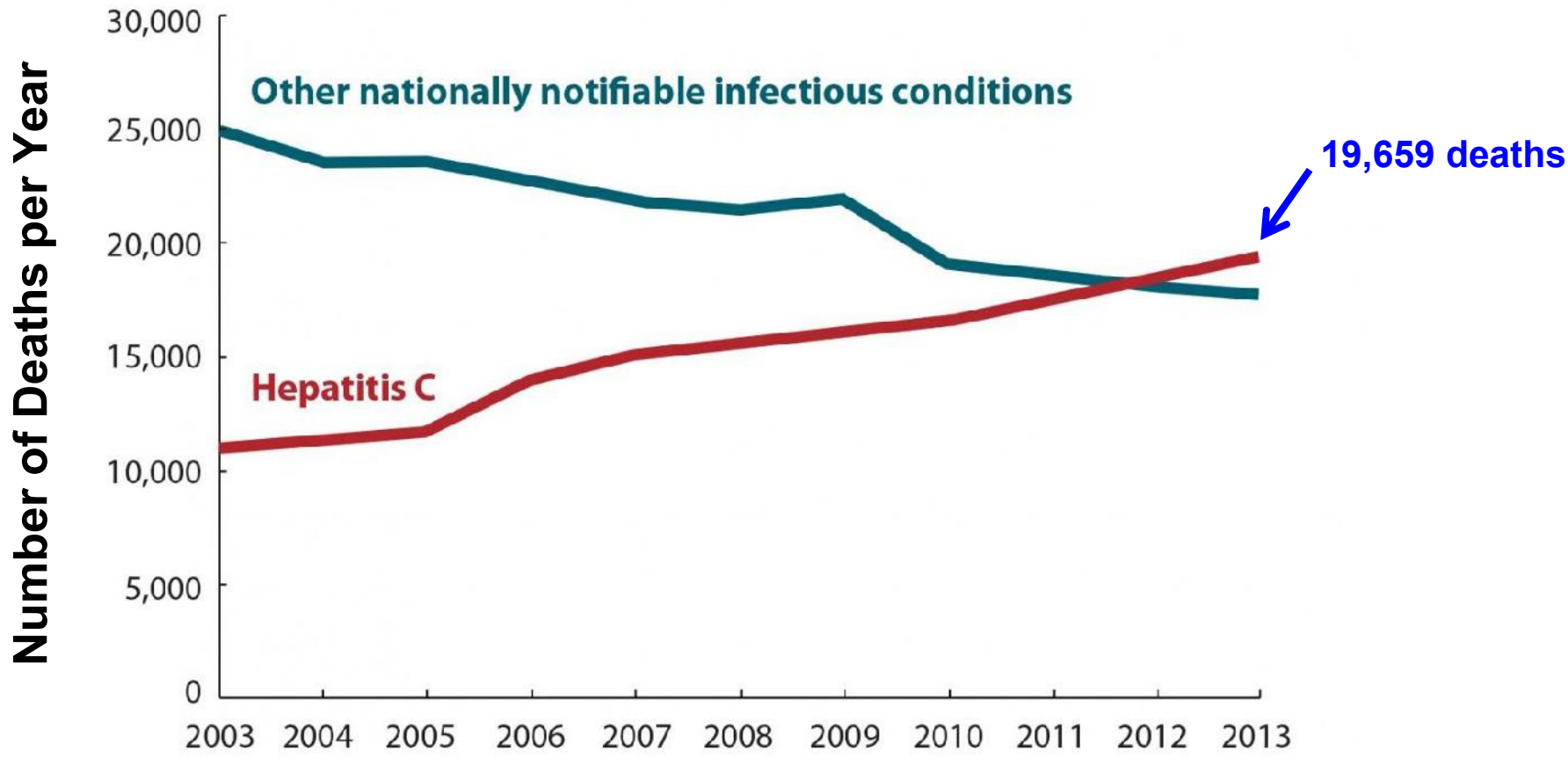
Annual age-adjusted mortality associated with HCV and HIV infections listed as causes of death in the United States,1999-2010



>70% of HCV-associated deaths occurred in people 45-64 years old

Ly KN, et al. Clin Infect Dis 2014;58:40-9.

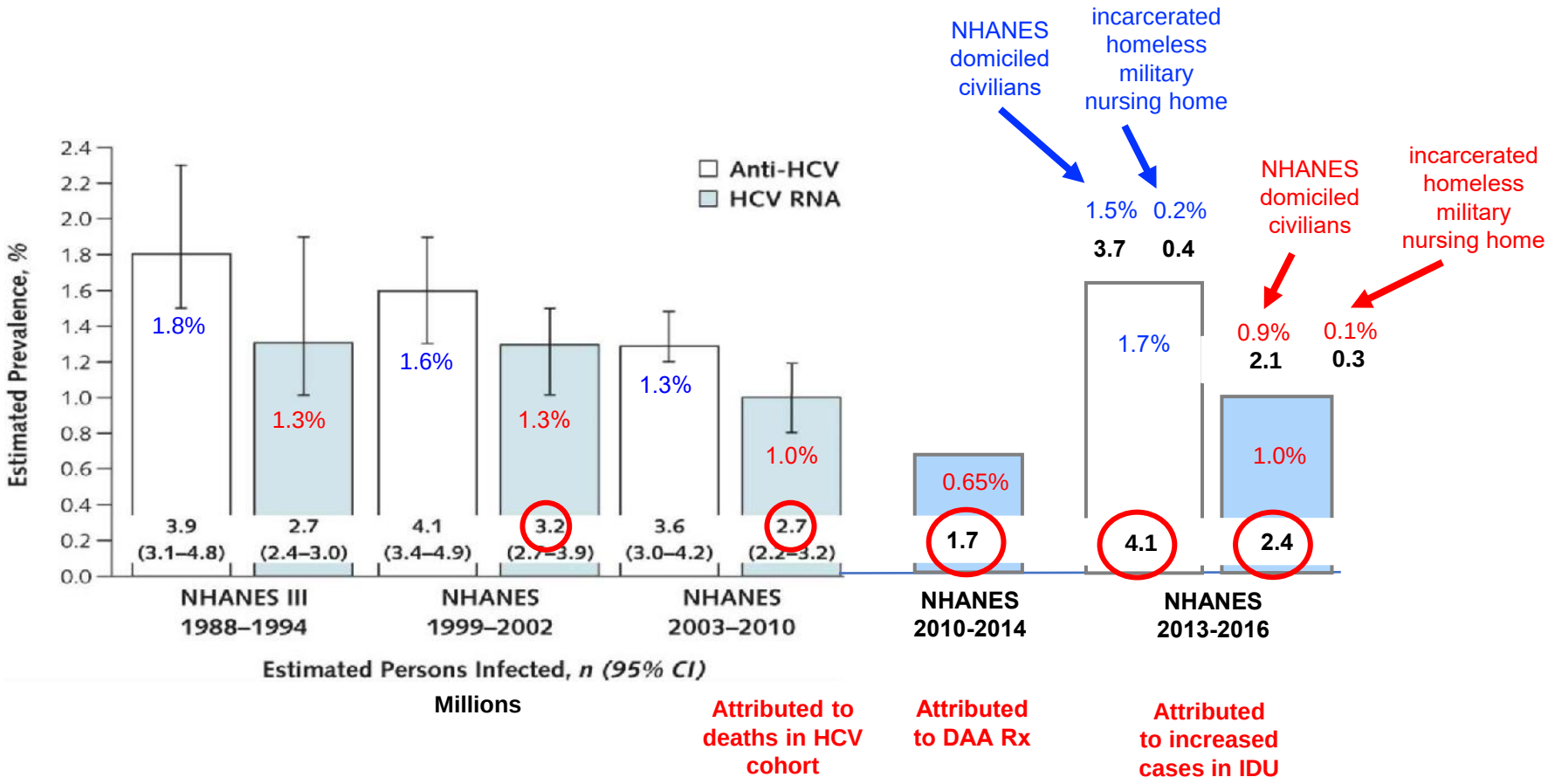
HCV Deaths and Deaths from Other Nationally Notifiable Infectious Diseases,* 2003- 2013



*TB, HIV, Hepatitis B, and 57 other infectious conditions reported to CDC

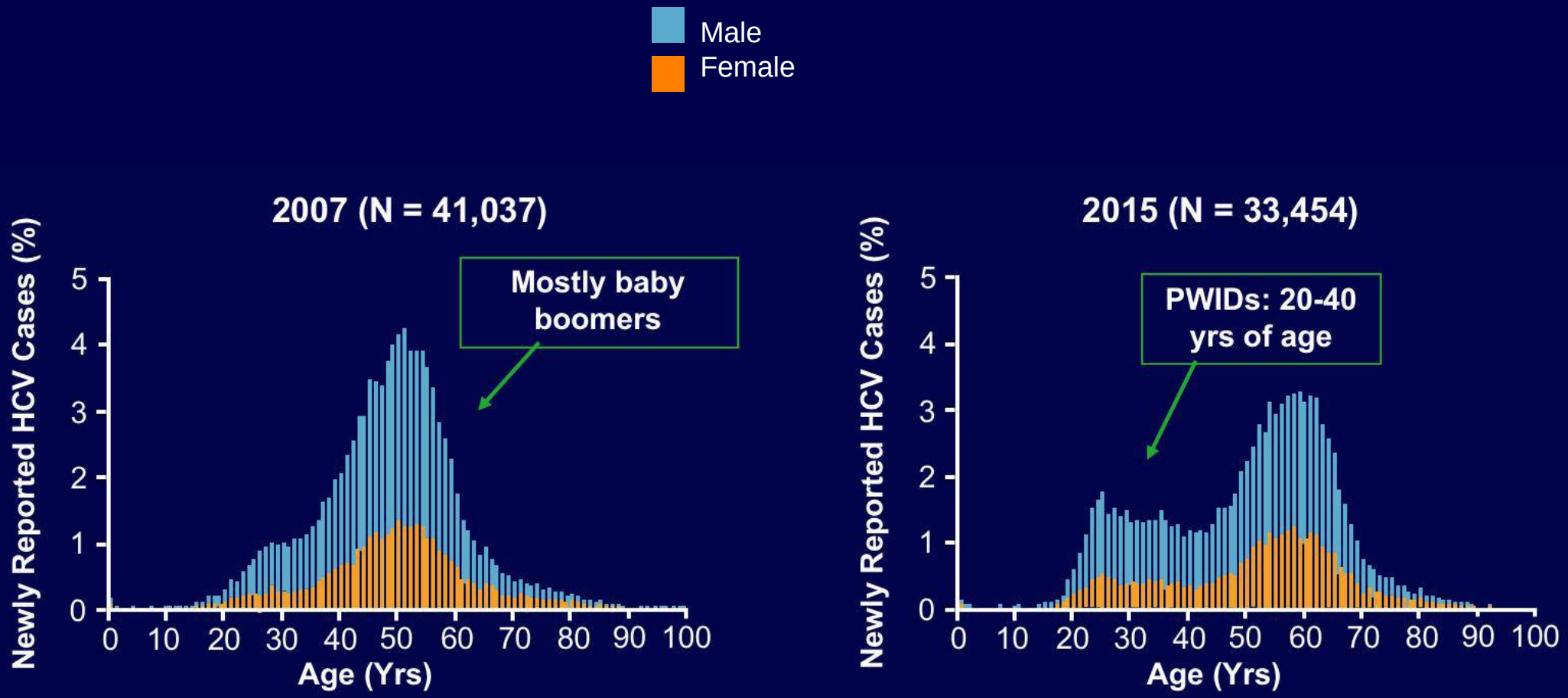
Ly KN et al. Clin Infect Dis 2016;62:1287-8.

Chronic Hepatitis C Virus Infection in the United States
National Health and Nutrition Examination Survey 2013 to 2016 Updated



Hofmeister MG, et al. Hepatology 2019;69:1020-31.

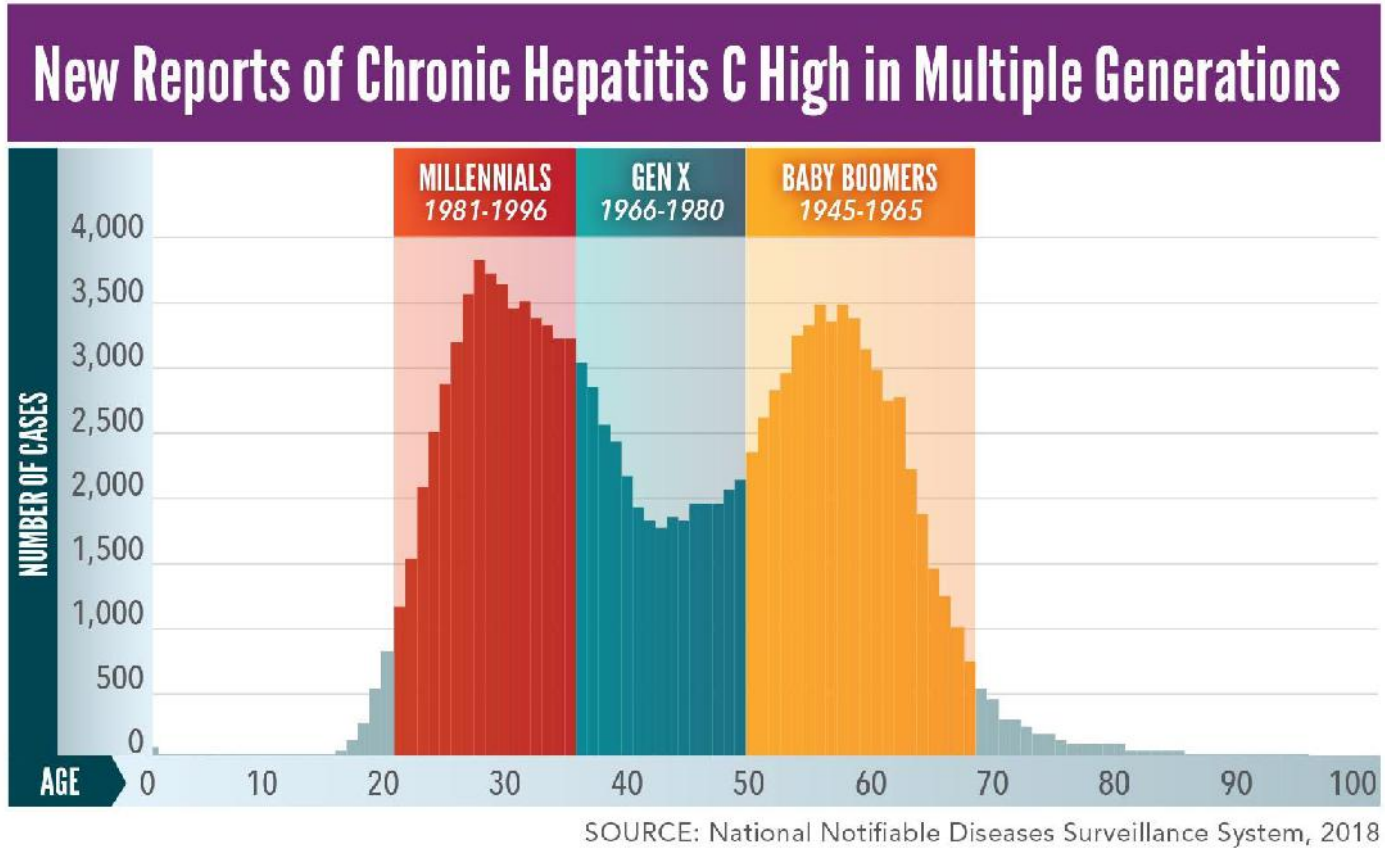
Changing Epidemiology of HCV Infection in the US



persons who inject drugs

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

2018 New Chronic Cases



36.5% of reported cases

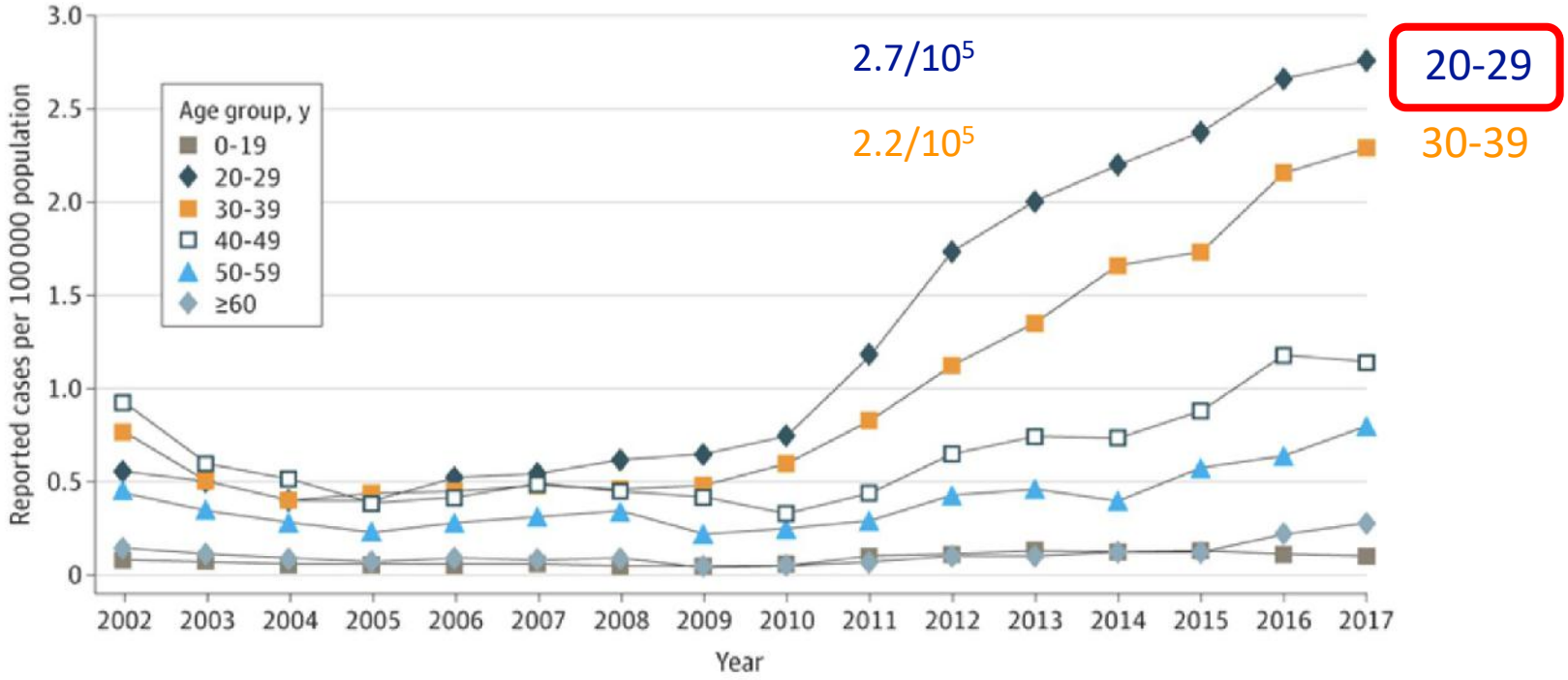
23.1% of reported cases

36.3% of reported cases

2020 recommendation by AASLD/IDSA, USPSTF, CDC:
Expansion of recommended hepatitis C screening to all adolescents and adults aged 18-79

US Preventive Services Task Force:
Universal screening for HCV infection in adolescents and adults ages 18-79
JAMA 2020; 323:970-5.

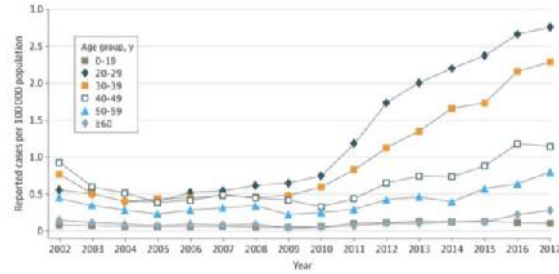
Rates of reported acute hepatitis C by age group in the US, 2002-2017



Source: Centers for Disease Control and Prevention, National Notifiable Diseases Surveillance System.

Price JC, Brandman D. JAMA Intern Med 2020;180:637-9. doi :10.1001/jamainternmed.2019.7334

New recommendation by AASLD/IDSA, USPSTF, CDC: Expansion of recommended hepatitis C screening to all adolescents and adults aged 18-79



Rationale

- Persons with chronic hepatitis C identified by 1945-1965 birth-cohort screening are older than 50—by the time they are identified, >20% already have advanced liver disease.
- Shifting demographics of HCV infection (since 2010), towards a younger population (highest, age 20-39*) exposed through injection-drug use
- 95-99% efficacy of all-oral, well tolerated, highly effective DAAs
- DAA therapy is associated with a marked decrease in liver and all-cause mortality, cirrhosis, and HCC
- Reduction in the initially high cost of DAA therapy
- Higher cost-effectiveness of screening all adults than birth-cohort screening

*Child-bearing years. Screening pregnant women recommended

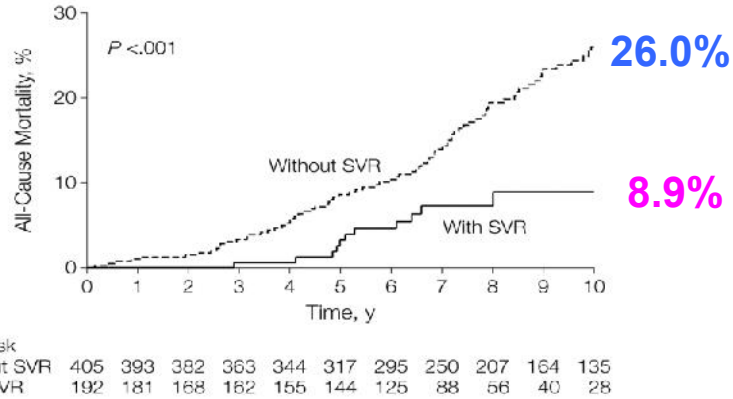
Price JC, Brandman D. JAMA Intern Med 2020;180:637-9. doi :10.1001/jamainternmed.2019.7334

Association between SVR and All-Cause Mortality among Patients with Chronic Hepatitis C and Advanced Hepatic Fibrosis

Survival outcomes with and without sustained virologic response (SVR)

530 pts with F4-6, IFN-based Rx, median f/u 8.4 Yrs

All-cause mortality

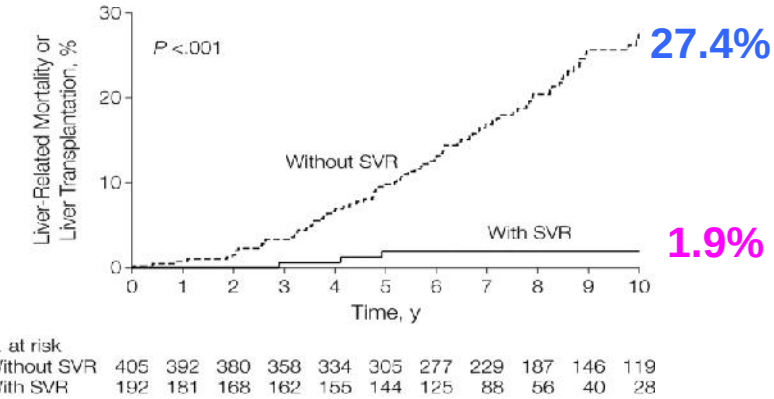


3-fold

26.0%

8.9%

Liver-related mortality and liver transplantation

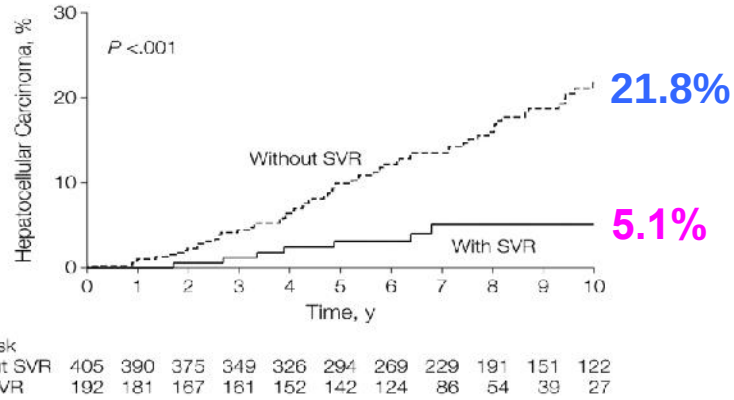


27.4%

1.9%

14-fold ↓

HCC

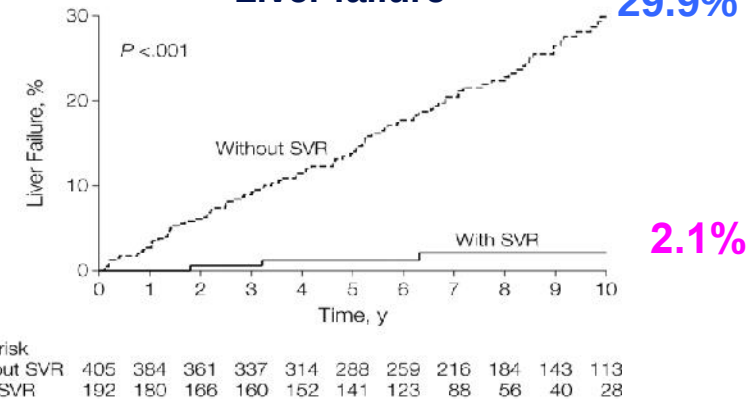


4-fold

21.8%

5.1%

Liver failure



29.9%

2.1%

14-fold ↓

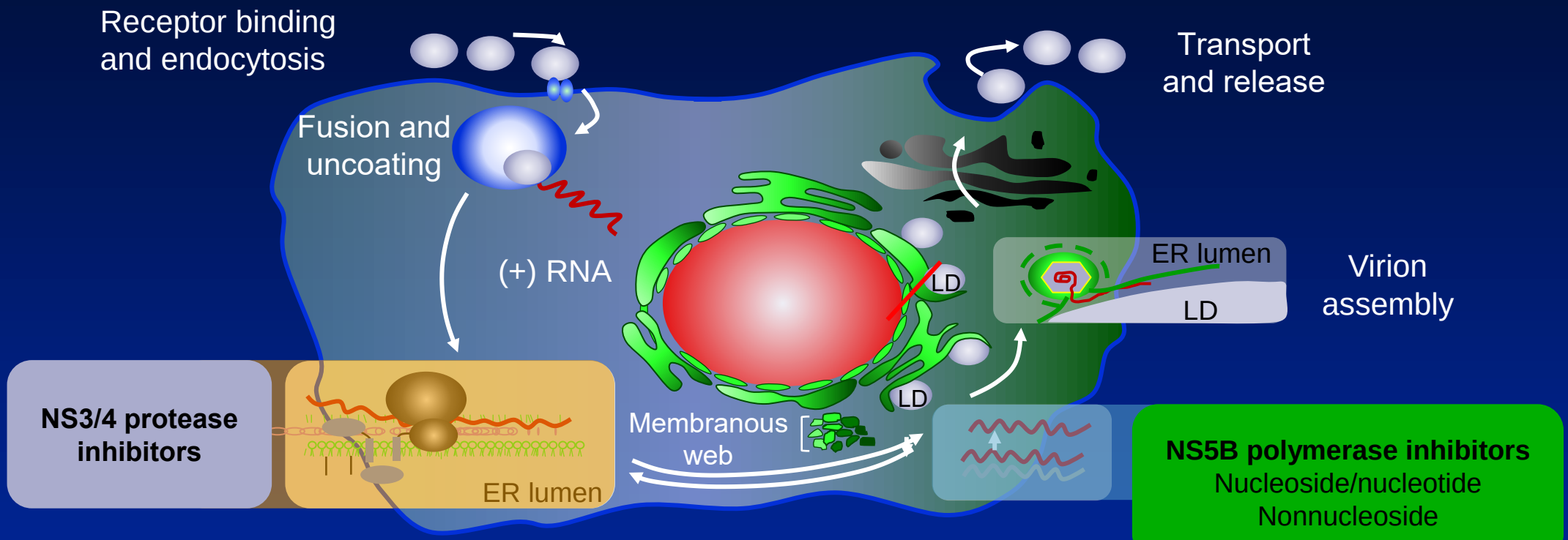
van der Meer AJ, et al. JAMA 2012;308:2584-93.

***10-yr cumulative occurrence rates**

Direct-acting antiviral (DAA) therapy for chronic hepatitis C: Which statement is accurate?

A. Current DAA combination therapy x 8-12 weeks can cure >95% of patients but must include a polymerase inhibitor.
B. DAA therapy results in an increase risk of HCC after therapy.
C. DAA therapy reduces liver-related mortality but not all-cause mortality or extrahepatic manifestations.
D. DAA Rx increases the risk of hepatitis B reactivation in HCV-HBV-coinfected persons.
E. DAA therapy is so expensive that it will have no impact on the disease burden of HCV infection.

HCV Life Cycle and Direct-Acting Antiviral Targets

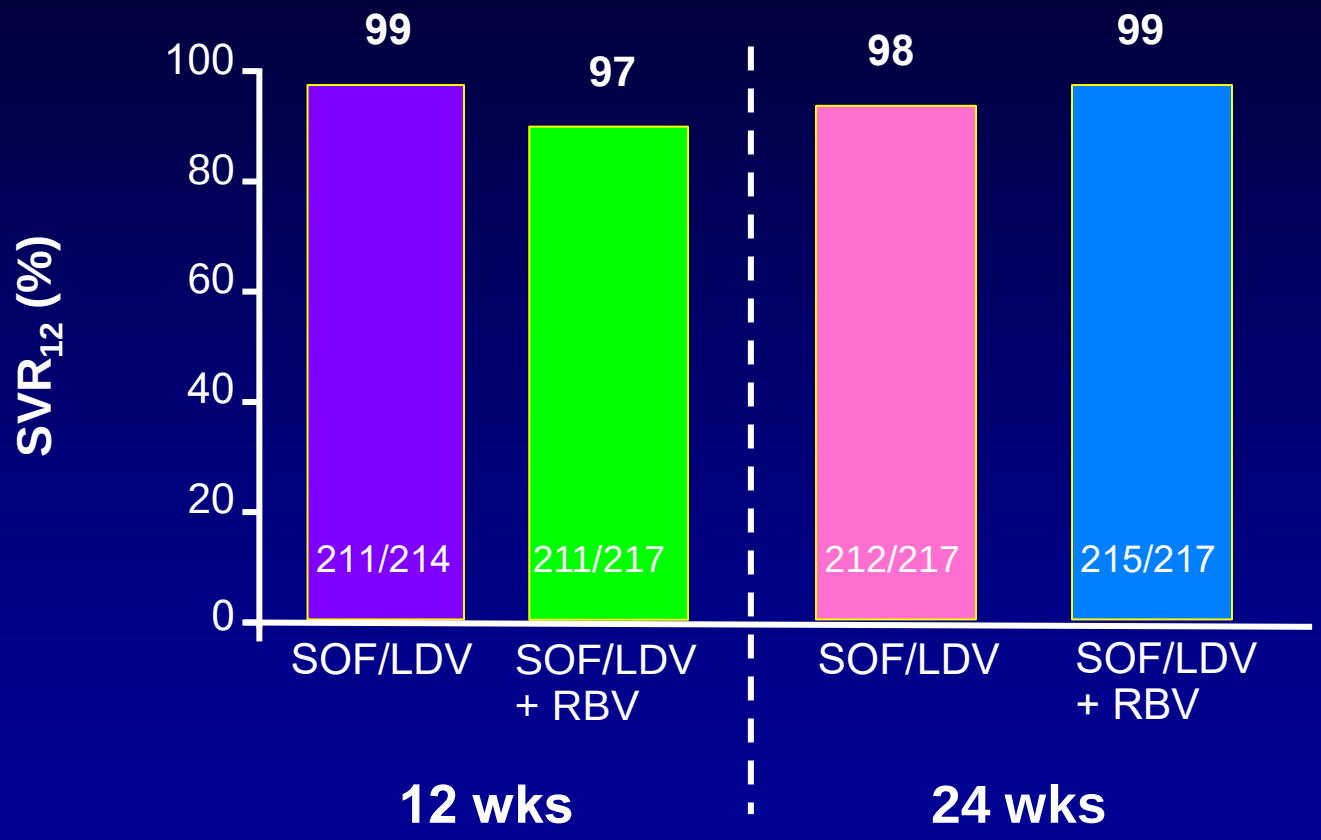


Adapted from Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Sofosbuvir (Nuc) + Ledipasvir (NS5A) ± RBV x 12-24 wks

IFN-free

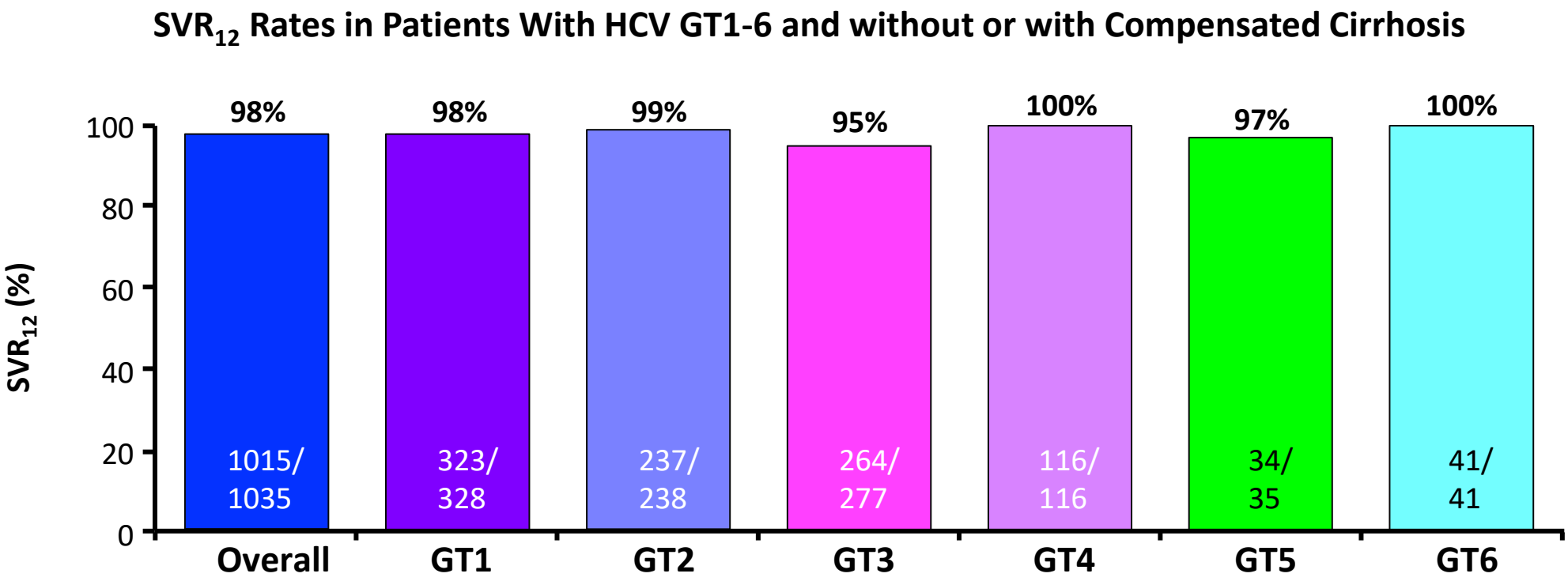
865 **Rx-naïve**,* 16% cirrhotic, 67% GT 1a, 33% GT 1b



No additional benefit with the addition of RBV or extension of Rx to 24 wks.

Afdhal N, et al. "**ION-1**," NEJM 2014;370:1889-98.

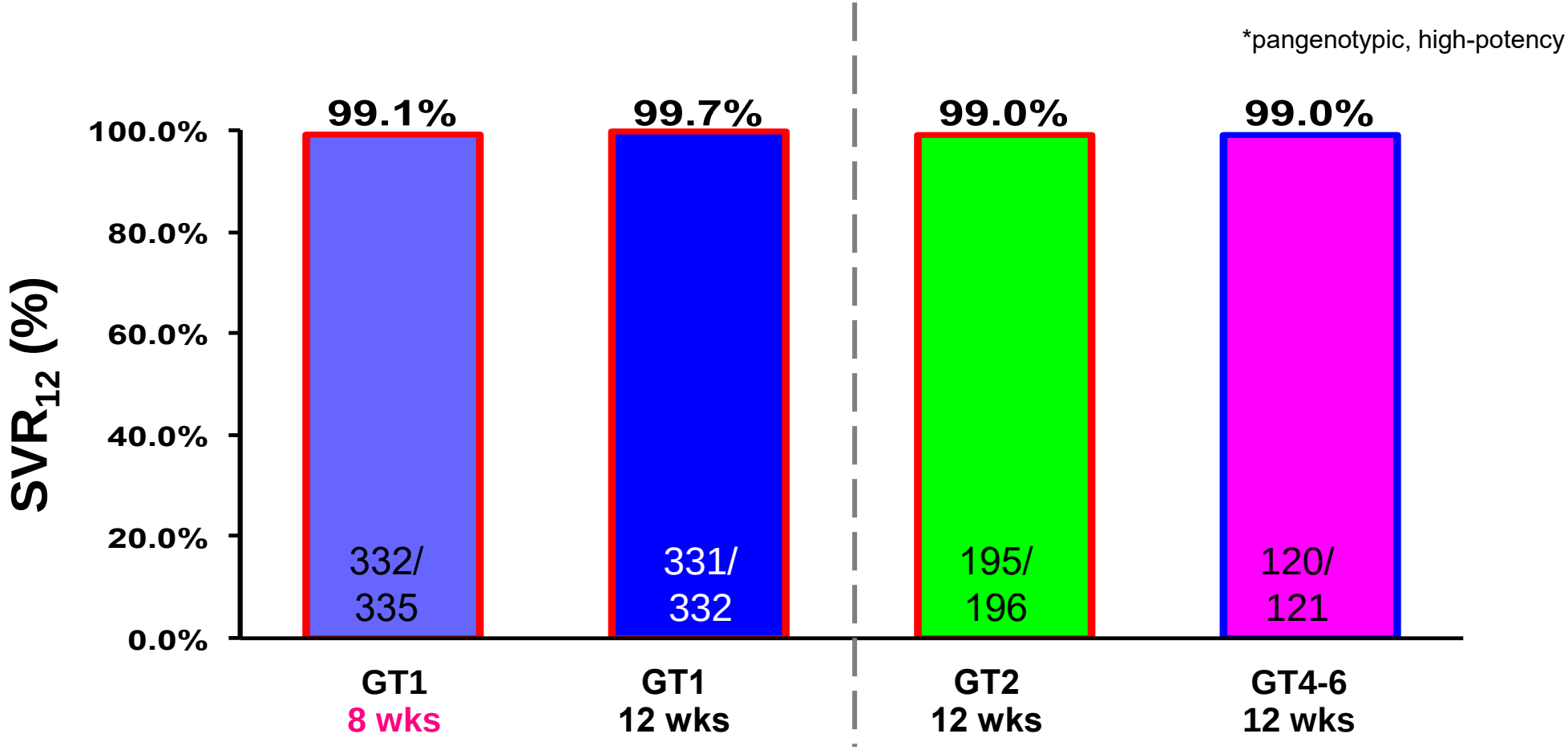
SOF/VEL x 12 Wks Effective across All HCV Genotypes



Feld JJ et al. N Eng J Med 2015;373:2599-607.
Foster GR, et al. N Engl J Med 215;373:2608-17.

Phase-III Trials of PI Glecaprevir*/NS5A Pibrentasvir* for Treatment of Noncirrhotic GT1, 2, 4, 5, 6 (Treatment-Naïve or Treatment-Experienced)

*pangenotypic, high-potency



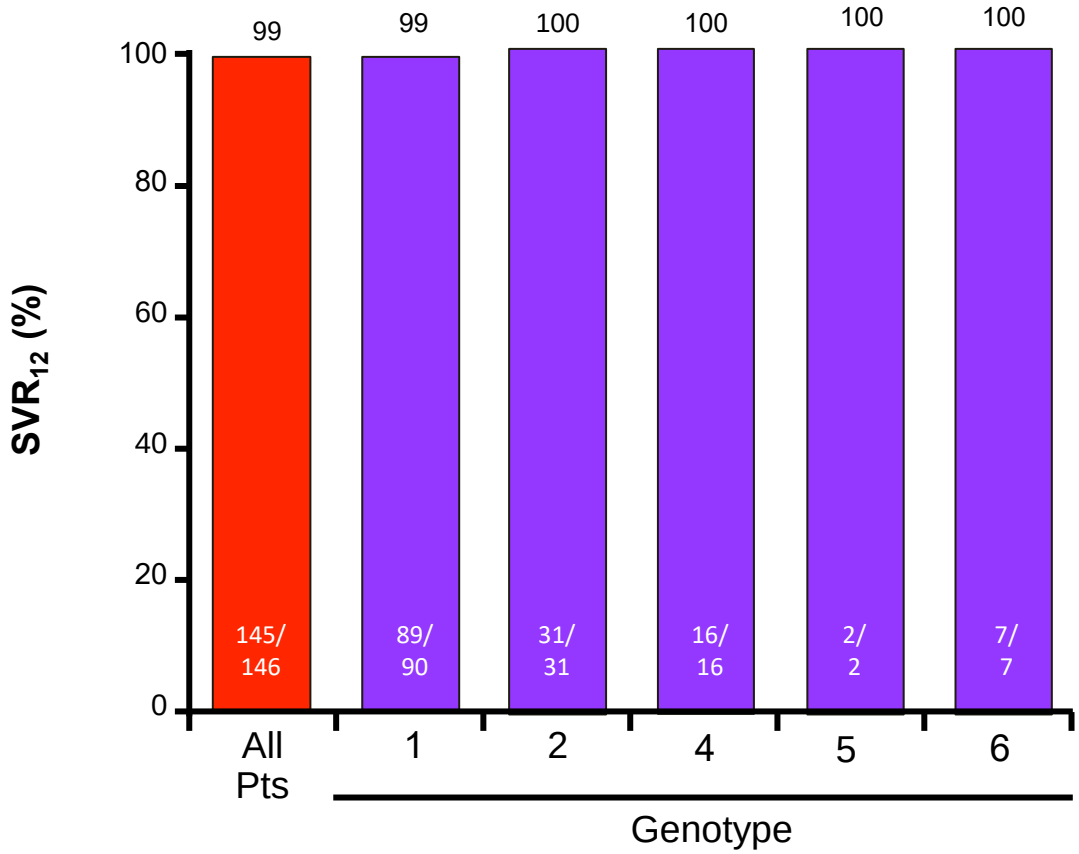
Zeuzem S, et al. N Engl J Med 2018;378:354-69.

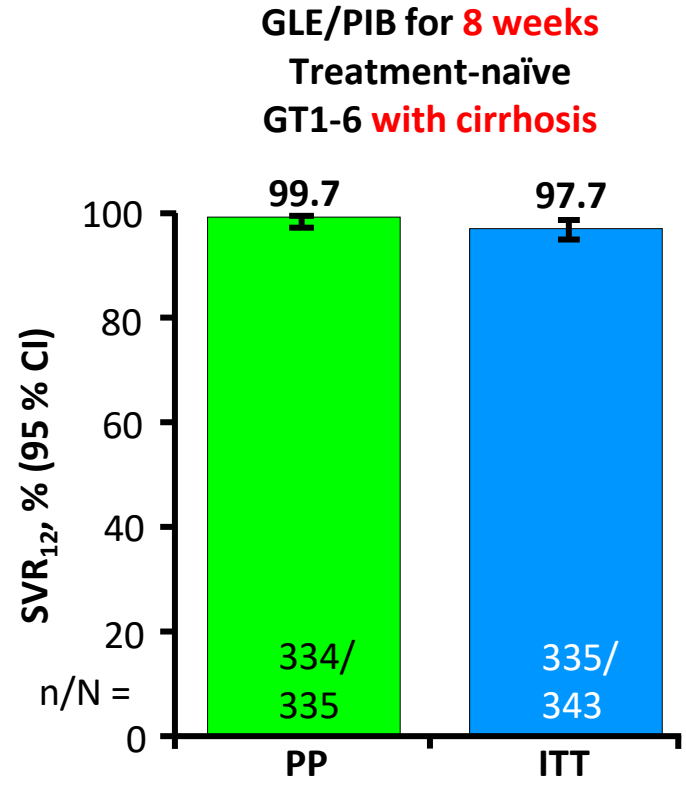
Asselah T, et al. Clin Gastroenterol Hepatol 2018;16:417-26.

Asselah T, et al. Lancet Gastroenterol Hepatol 2019;4:45-51.

Glecaprevir/Pibrentasvir x 12 Weeks in GT1, 2, 4, 5, and Compensated Cirrhosis*

Treatment-naive and treatment-experienced pts

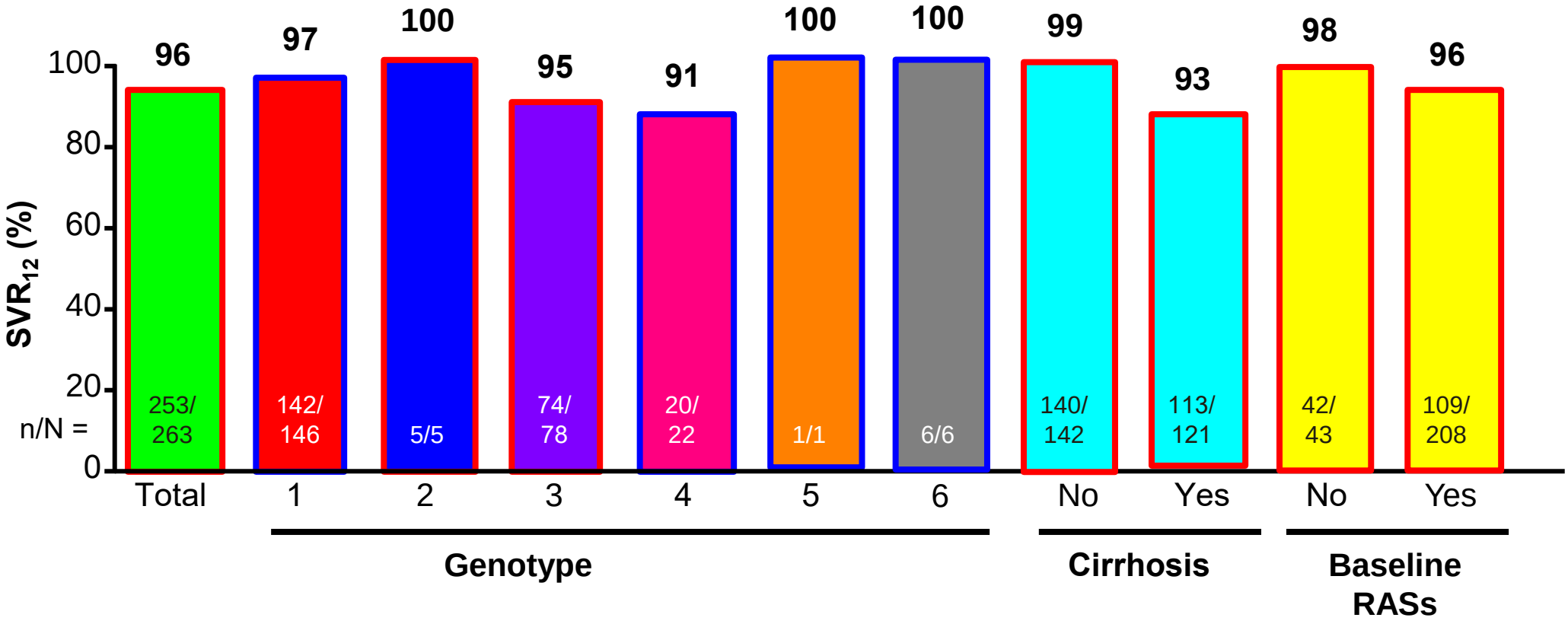




9/26/2019: FDA expanded GLE/PIB approval to **8 weeks** in compensated cirrhosis.

Forns X , et al. Lancet Infect Dis 17:1062-8, 2017

SOF/VEL/VOX Retreatment for 12 Wks after NS5A Failure in GT 1-6; Randomized, double-blind, placebo-controlled phase III trial



Boulière M, et al ("POLARIS-1"). NEJM 2017;376:2134-46.

Recommended First-line DAA Regimens: Treatment-naïve Patients, GT1a

Simplified regimens

Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 1a Patients Without Cirrhosis		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

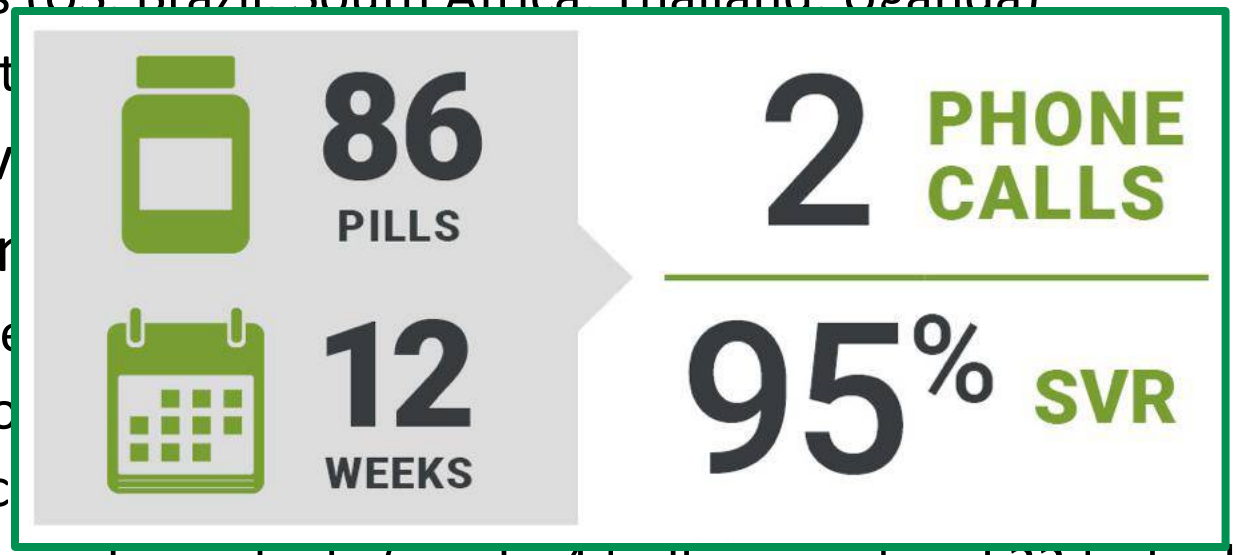
Compensated cirrhosis

Recommended regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, B

AASLD and IDSA. http://www.hcvguidelines.org

A Minimal Monitoring Approach for the Treatment of HCV Infection ("MINMON")

- Phase-4, open-label, single-arm trial
- 400 participants (399 initiated Rx)
  - 38 sites (US, Brazil, South Africa, Thailand, Uganda)
  - Eligibilit
- sofosbuv
- Minimal r
  1. No pre
  2. Full co
  3. No sc
  4. Two remote contacts (weeks 4 [adherence] and 22 [schedule SVR testing])
- SVR_{24} in 379/399 = 95% [CI 92.4-96.7]

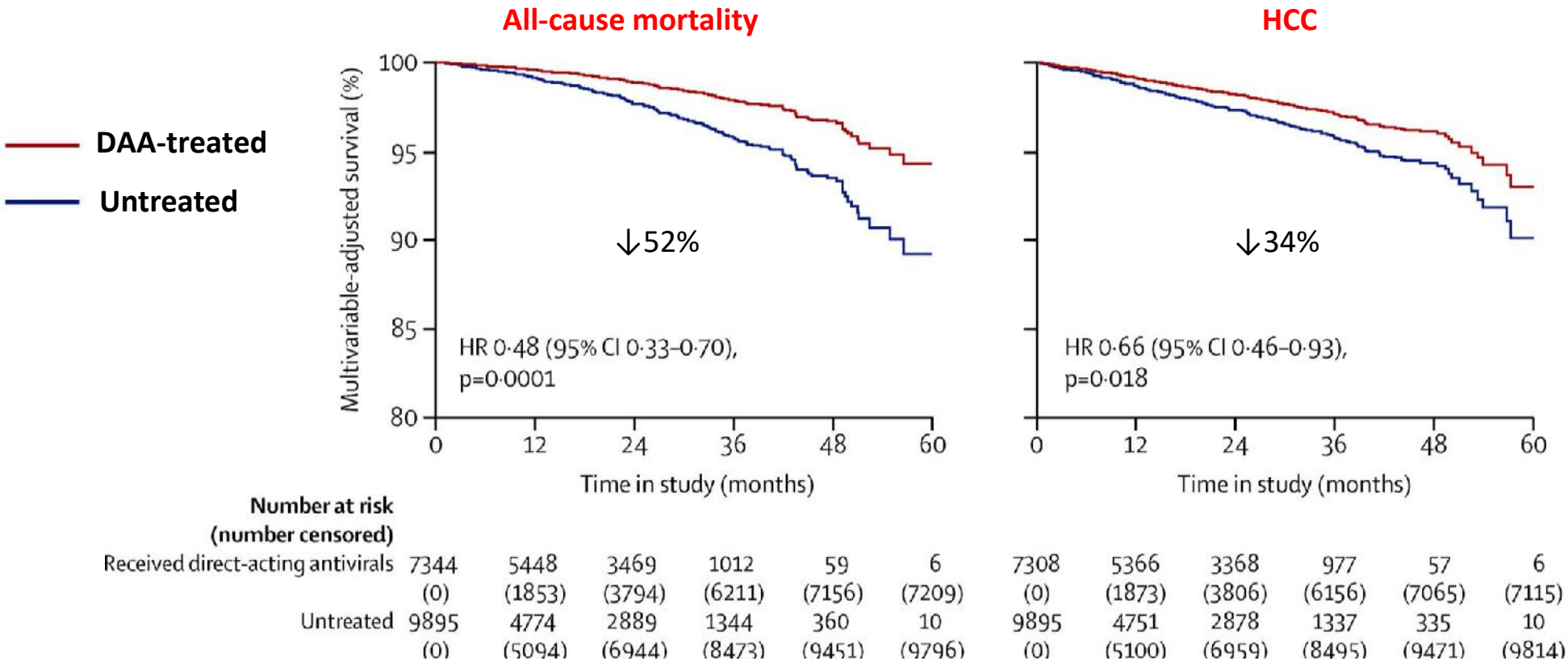


Solomon SS, et al. Lancet Gastroenterol Hepatol 2022. DOI:https://doi.org/10.1016/S2468-1253(21)00397-6

Clinical Outcomes in Patients with Chronic Hepatitis C after DAA Rx: A Prospective Cohort Study

Prospective 32-center cohort study in 10,166 French patients
Aug 2012-Dec 2015, median f/u 33.4 months

All patients analyzed multivariable-adjusted survival

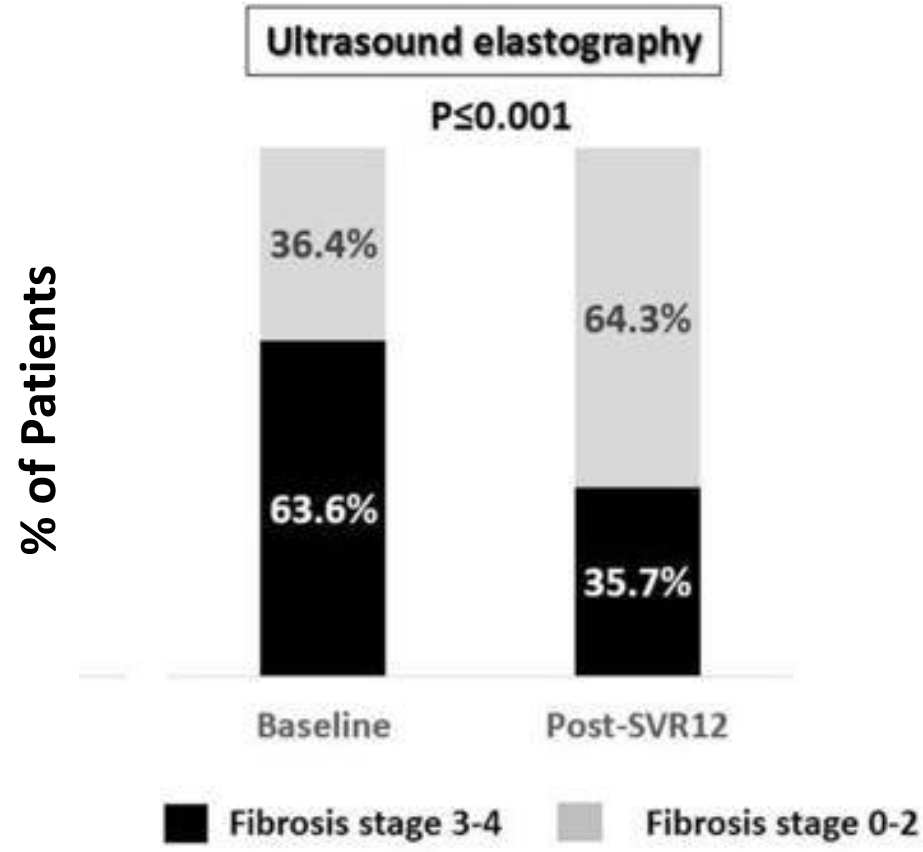


Carrat F, et al. Lancet 2019;393:1453-64.

Cirrhosis/Fibrosis Regression after SVR to Antiviral Therapy in Patients with Chronic Hepatitis C

Prospective study in 89 Thai patients* with SVR_{12} after DAA therapy (2017-2018)
Pre-Rx and 1 year after beginning Rx

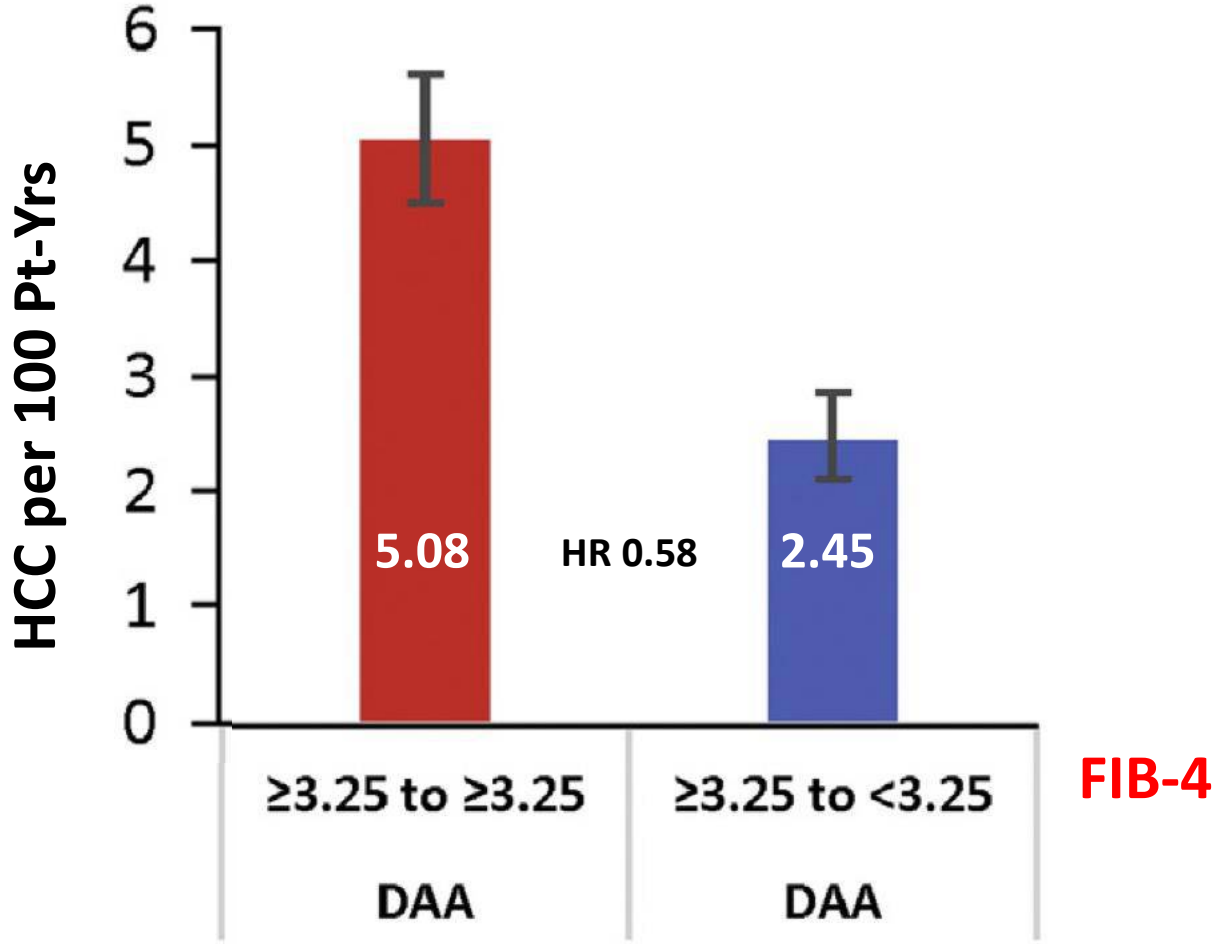
*43 (48.3%)
cirrhotic at baseline



Fibrosis regression in 44%

Thanapiroum K, et al. Scientific Reports 2022;12:4913 doi: 10.1038/s41598-022-08955-x

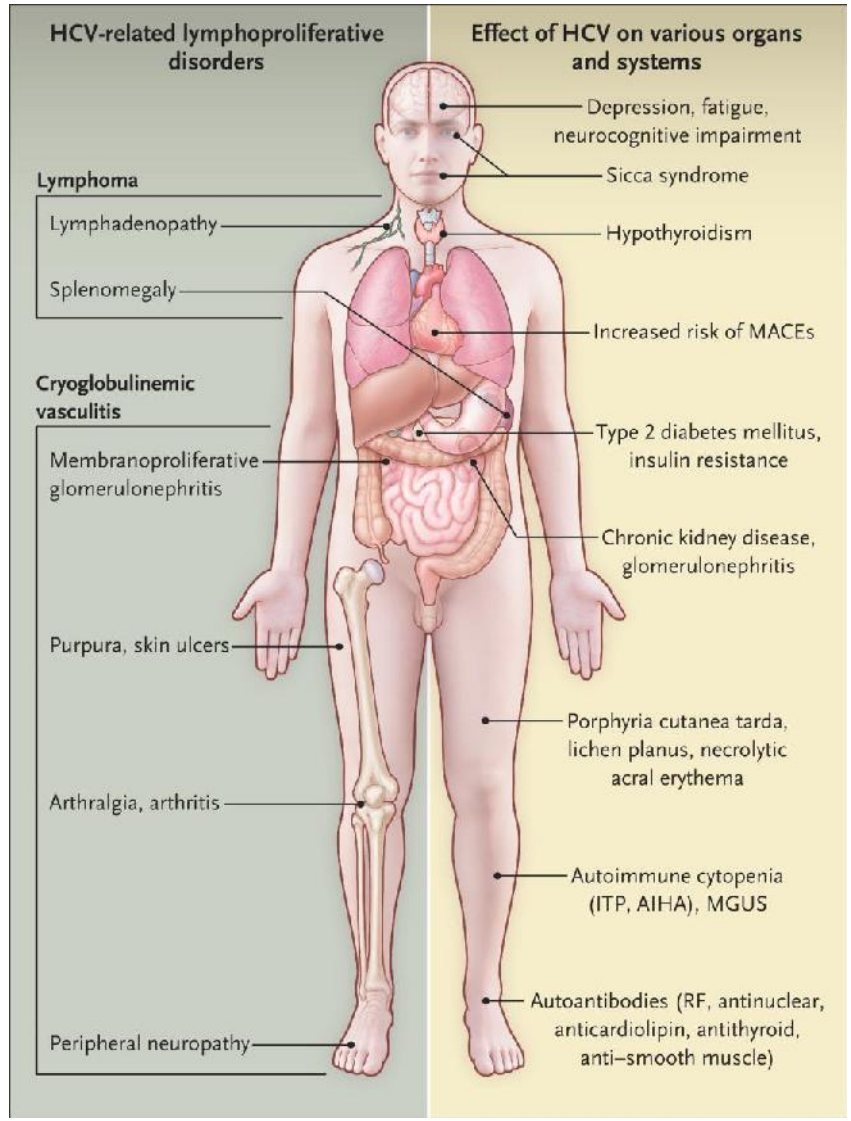
Persistently Increased HCC Risk up to 10 Years after SVR in 48,135 VAH Patients with Baseline Cirrhosis (2000-2015)



$$\text{FIB-4} = \frac{\text{Age (yrs)} \times \text{AST (U/L)}}{\text{PLT } (10^6/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

Ioannou GN, et al. Gastroenterology 2019;157:1264-78.

Extrahepatic Manifestations of Chronic HCV Infection



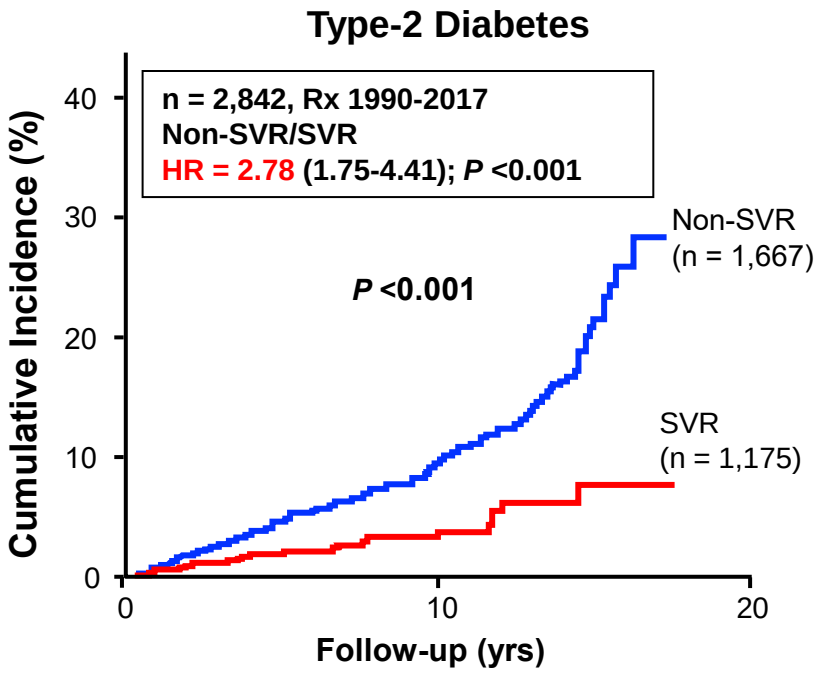
major adverse cardiac events

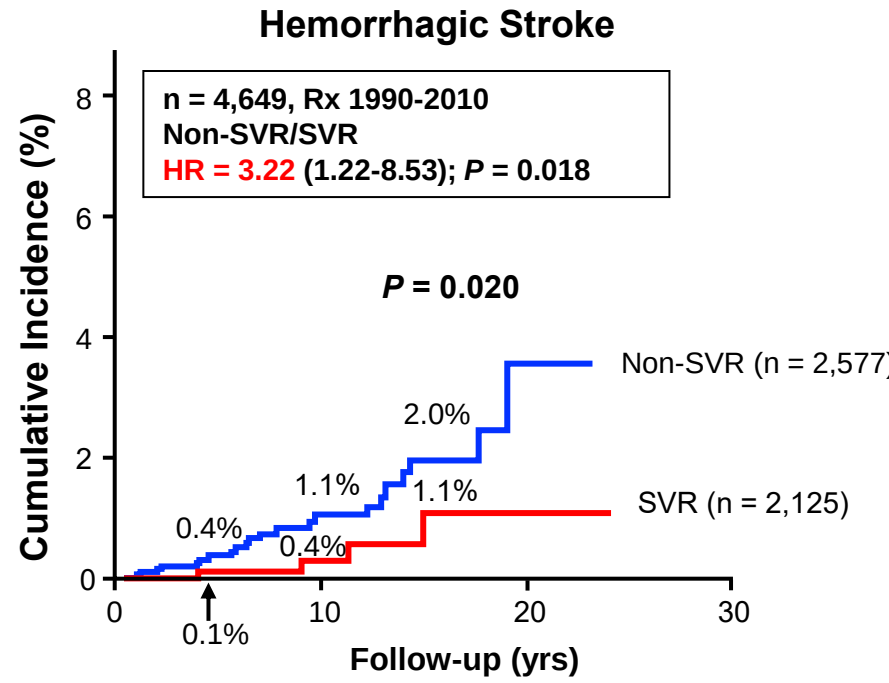
monoclonal gammopathy of undetermined significance
autoimmune hemolytic anemia

Cacoub P, Saadoun D. NEJM 2021;348:1038-52.

SVR associated with Lower Incidence of HCV-Related Nonhepatic Comorbidities

Retrospective studies in Japan among IFN-based-treated patients





Arase Y, et al. Hepatology 2009;49:739-44.

Arase Y, et al. J Med Virol 2014;86:169-75

DAA Therapy and HCC Risk

- HCC observed after DAA Rx in patients with advanced fibrosis (F3-4)
  - Early reports from Spain and Italy—raised concern.
  - Multiple studies (Australia, North America, UK, France, Italy) failed to confirm the finding.
  - Meta-analyses and systematic literature reviews did not show a DAA-associated risk that exceeded expected rates based on fibrosis stage.
  - Patients treated with DAAs tend to be older and sicker (more advanced fibrosis stage, including decompensated cirrhotics) than patients treated in the past with IFN-based regimens (a cohort bias).
    - *Confounding risk factors (more advanced liver disease), not DAA Rx, account for observation*.
- The opposite is supported by exhaustive data—DAA Rx reduces the risk of HCC.

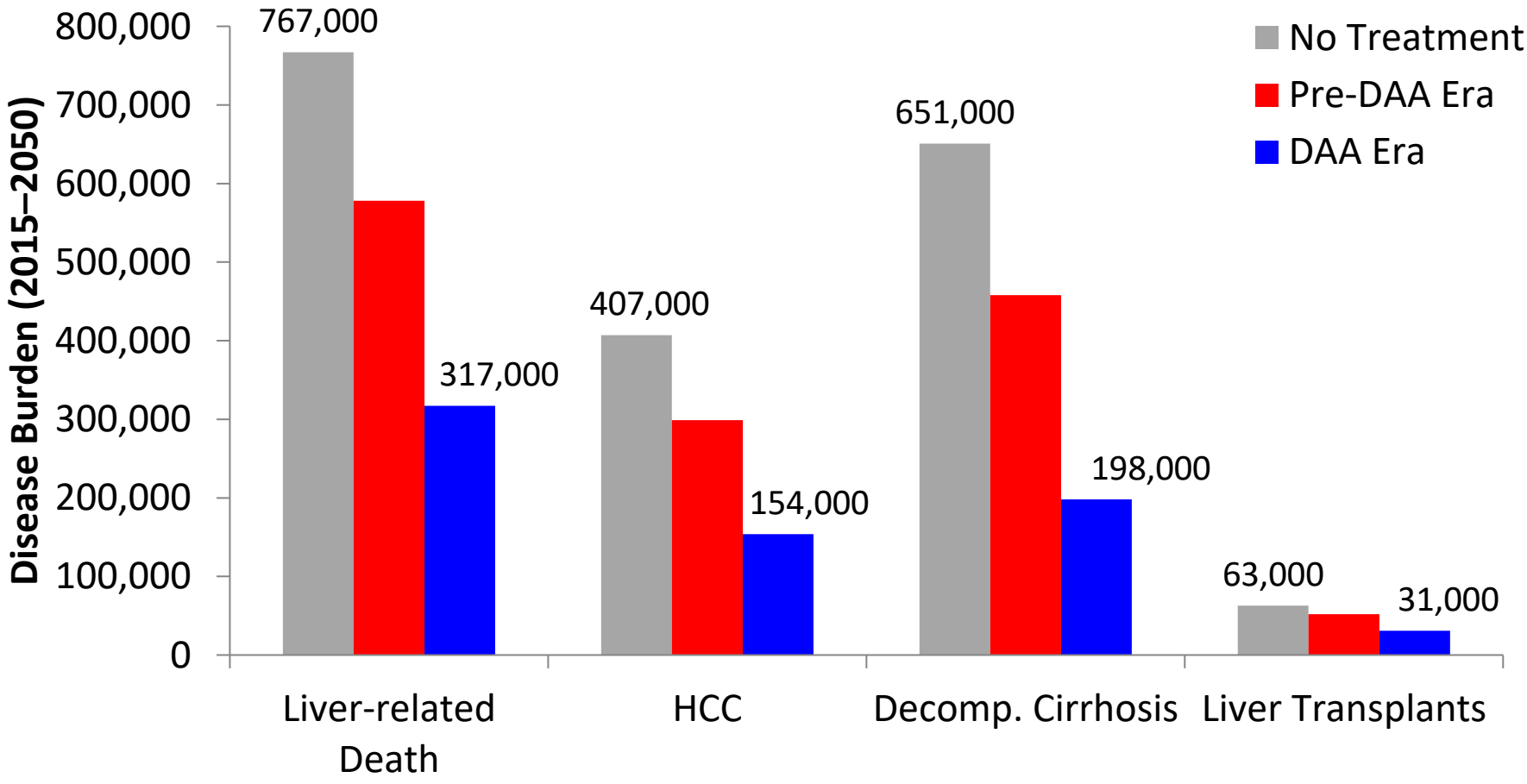
Alberti A, et al. AASLD 2016, abstract 19.

HBV Reactivation after DAA-associated SVR

- 24 cases reported by FDA
  - 22/24 cases $HBsAg^+$ at baseline
  - 3 cases with fulminant hepatitis/death (1 with isolated anti-HBc)
  - During weeks 4-12 of DAA therapy
- Accurate frequency unknown
- Mechanism not defined
  - ? competitive relation between viruses
  - ? altered immunologic milieu after DAA Rx
- HBV status (HBsAg) should be assessed in all patients.
- HBsAg+ patients should be carefully followed or treated.
  - Rely on criteria for HBV treatment in HBV-monoinfected persons

Bersoff-Matcha SJ, et al. Ann Intern Med 2017;166:792-8.

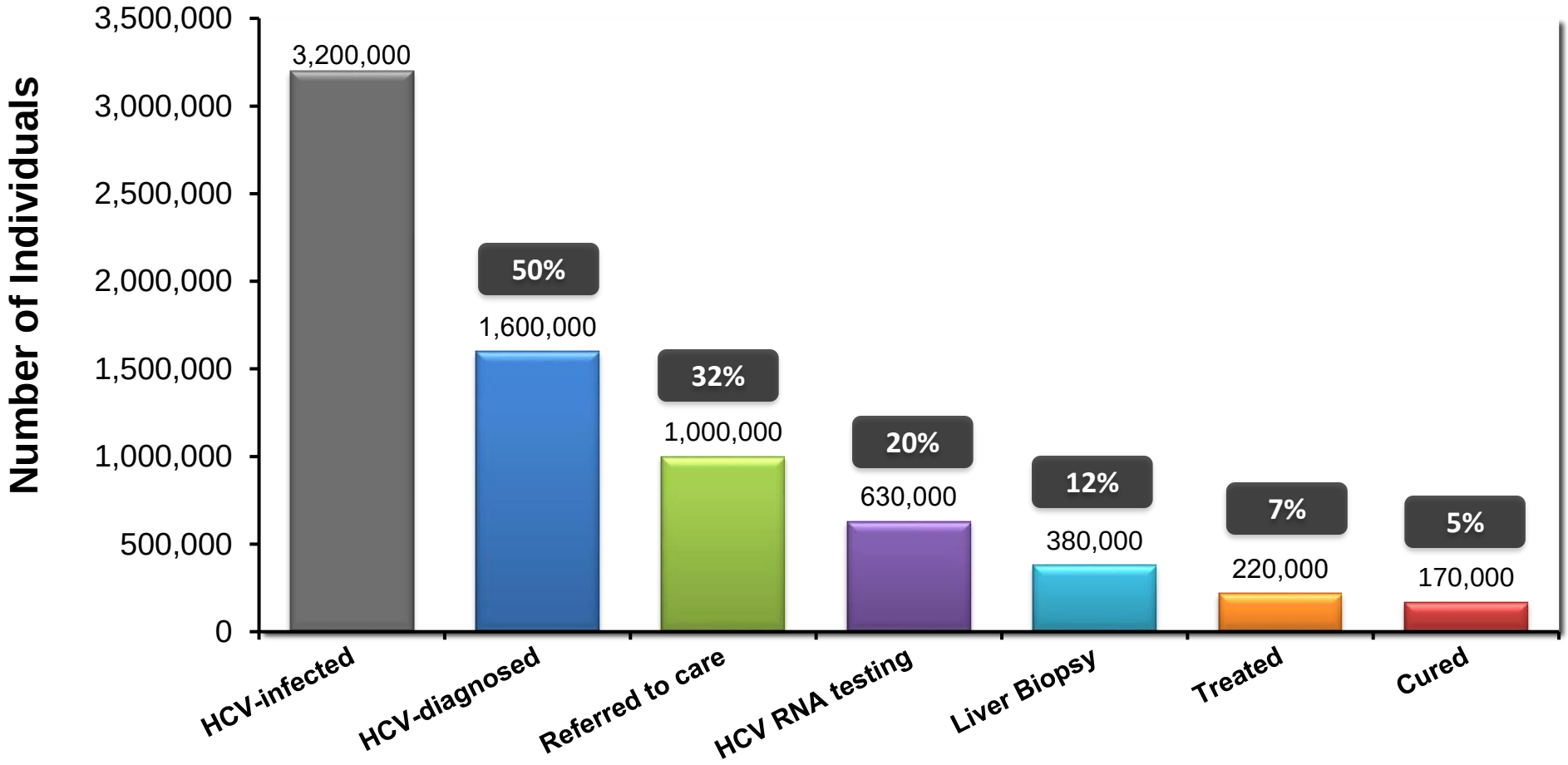
Modeling HCV-Associated Disease Burden (2015–2050)



50–70% reduction in HCV-associated disease burden

Chhatwal J, et al. Hepatology 2016; DOI: 10.1002/hep.28571.

"Porous" HCV Cascade of Care – United States
The Chronic Hepatitis Cohort Study



Holmberg S, et al. NEJM 2013;368:1859-61.

Marginalized Populations and Hepatitis C: Social Determinants of Disease

- Limited access to health care
  - Ethnic/racial minorities
  - Persons who use drugs
  - People experiencing homelessness
  - Neighborhood poverty, lower educational status, language barriers
  - Uninsured, underinsured
- Covid-19 pandemic impact
  - Even more limited access to health care
  - 1-yr 40% reduction in prescriptions for DAA Rx; estimated impact…
    - 72,300 xs HCV liver-related deaths*
    - 44,800 xs HCC cases*
  - Affected marginalized populations disproportionately
    - Contributed to by limited internet and telemedicine access

NHANES 2013-2016‡
Nonhispanic blacks:
12% of US population
23% of HCV infections

‡ Bradley H, et al. Hepatology Communic 2020;4:355-70.

*Blach S, et al. J Hepatol 2021;74:31-6.

Hepatitis C: Take-Home Points

- From discovery to cure in a quarter century
- The only human chronic viral infection that can be cured
  - GT1-6, naïve, experienced, RASs, cirrhosis, decomp cirrhosis, ESRD, acute, HIV co-infection
- Standard of care 2022*: Combination, orally administered DAAs (wks)
  - VEL/SOF (12); Glecaprevir/Pibrentasvir (8) for all genotypes
- Guidelines www.hcvguidelines.org
- Patients with advanced fibrosis require imaging/endoscopic monitoring after "cure."
- The SVR rate exceeds 90-95% and approaches 100%.
- The duration of therapy can be truncated to 12 and 8 weeks.
- Remaining challenge – implementation ("cascade of care")

Simplified treatment algorithm for treatment-naïve, noncirrhotic, cirrhotic, GT 1-6