Viral Hepatitis 2015

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Viral Hepatitis - Overview

	Type of Hepatitis				
	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	yes, in I/C
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking water; immunization

Estimates of Acute and Chronic Disease Burden for Viral Hepatitis, United States

	HAV	HBV	HCV	HDV
Acute infections /year*	21,000 falling	38,000 falling	35-180 falling	1,000
Fulminant deaths/year	20	50	?	10
Chronic infections	0	1.25 million	3.5 million	70,000
Chronic liver disease deaths/year	0	3,000	14,000 rising	600

* CDC, estimated annual incidence, 2009

Hepatitis A

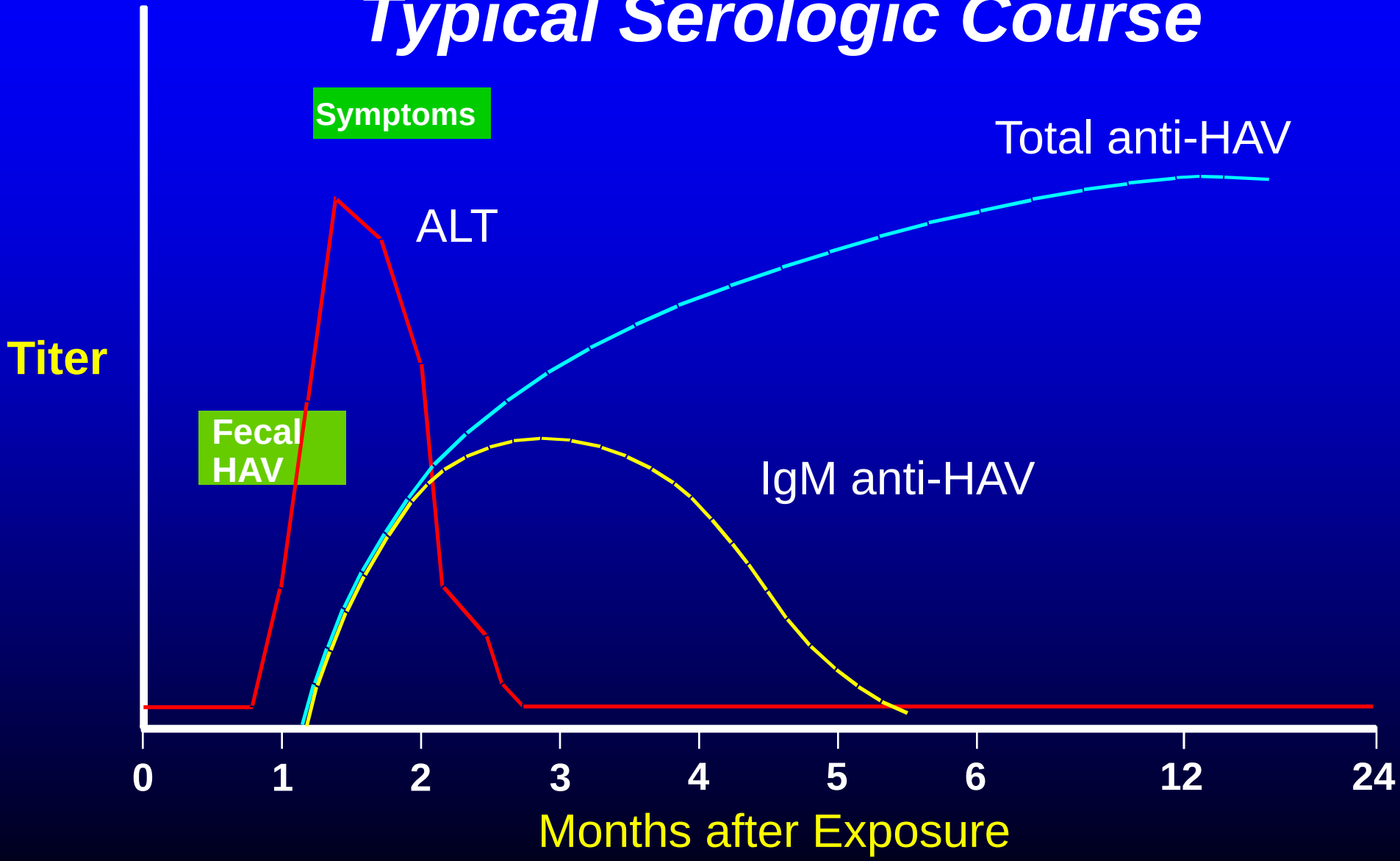
- Virology: picornavirus
- Incubation period: Average 30 days
  Range 15-50 days
- Jaundice by age group: <6 yrs <10%
  6-14 yrs, 40%-50%
  >14 yrs, 70%-80%
- Complications: Fulminant hepatitis
  Cholestatic hepatitis
  Relapsing hepatitis
- Chronic sequelae: None

Hepatitis A Virus Transmission

- Close personal contact
  (household contact, sex contact, day care centers)
- Contaminated food, water
  (infected food handlers, raw shellfish)
- Blood exposure (rare)
  (injection drug use, transfusion)

Hepatitis A Virus Infection

Typical Serologic Course



Age-specific Mortality Due to Hepatitis A

Age group (years)	Case-Fatality (per 1000)
<5	3.0
5-14	1.6
15-29	1.6
30-49	3.8
>49	17.5
Total	4.1

Source: Viral Hepatitis Surveillance Program, 1983-1989

Monovalent Hepatitis A Vaccine, Inactivated

- recommended: travel to endemic areas (long notice), risk groups, CLD

	Dose	Schedule
Havrix®[1]	1440 EL.U. in 1.0 mL IM	0, 6 to 12 months
Vaqta®[2]	~50 U in 1 mL IM	0, 6 to 12 months

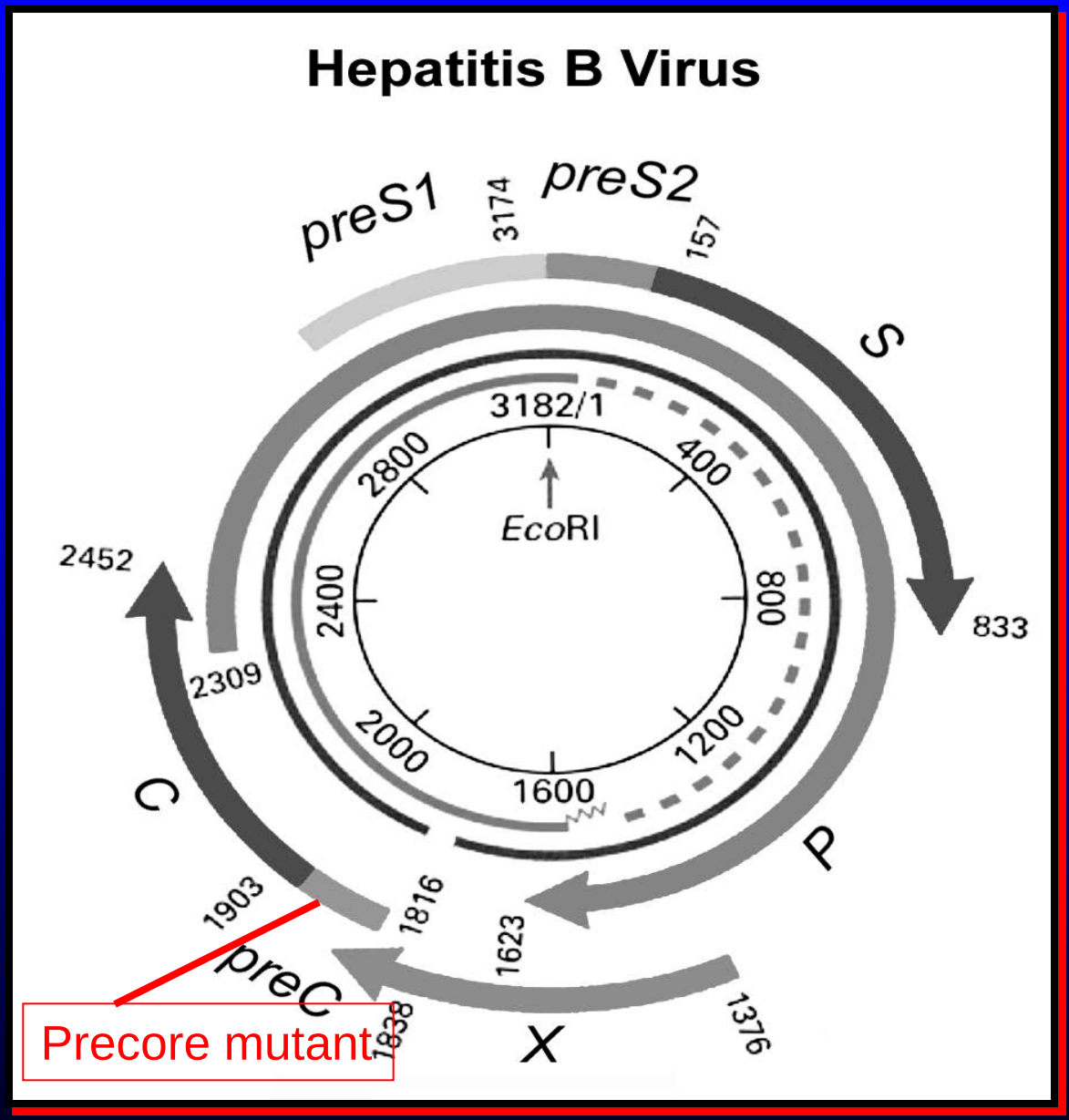
1. Havrix Prescribing Information. See Dosage and Administration. SmithKline Beecham Pharmaceuticals. Philadelphia, PA. Nov. 2001.
2. Vaqta Prescribing Information. Merck & Co, Inc. West Point, PA; 2001.
See complete prescribing information.

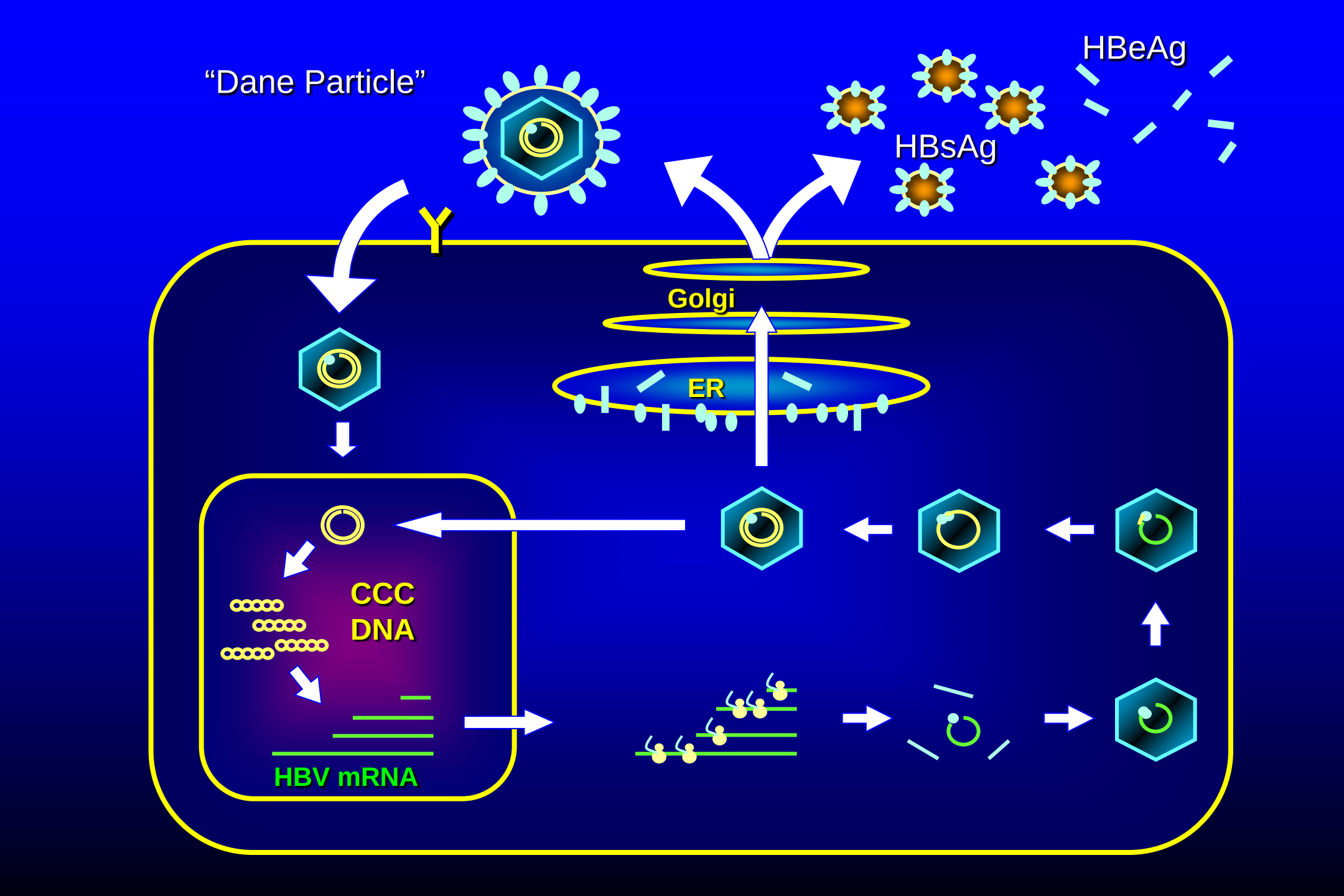
Hepatitis A Prevention - Immune Globulin

- Preexposure
  - travelers to intermediate and high HAV-endemic regions (short notice <2 wks)
- Postexposure (within 14 days)
  - Routine
    - household and other intimate contacts
  - Selected situations
    - institutions (e.g., day care centers)
    - common source exposure (e.g., food prepared by infected food handler)

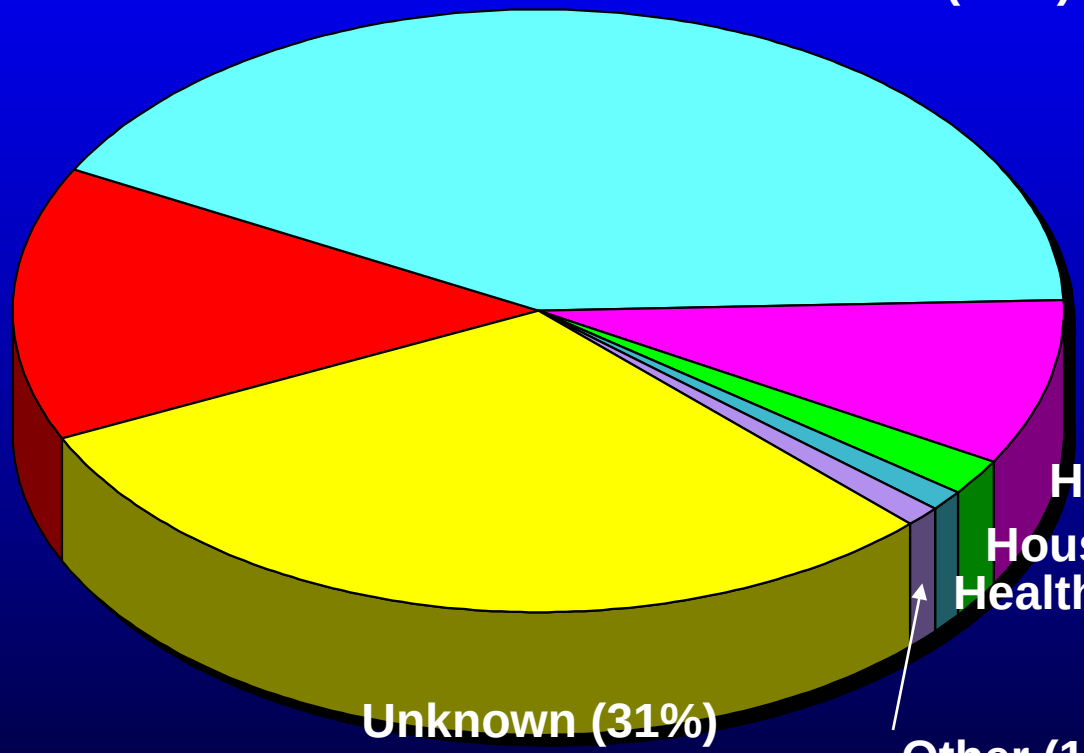
Hepatitis B Virus

- Small partially double-stranded DNA virus
- Prototype of the *hepadnavirus* family
- 4 major gene products



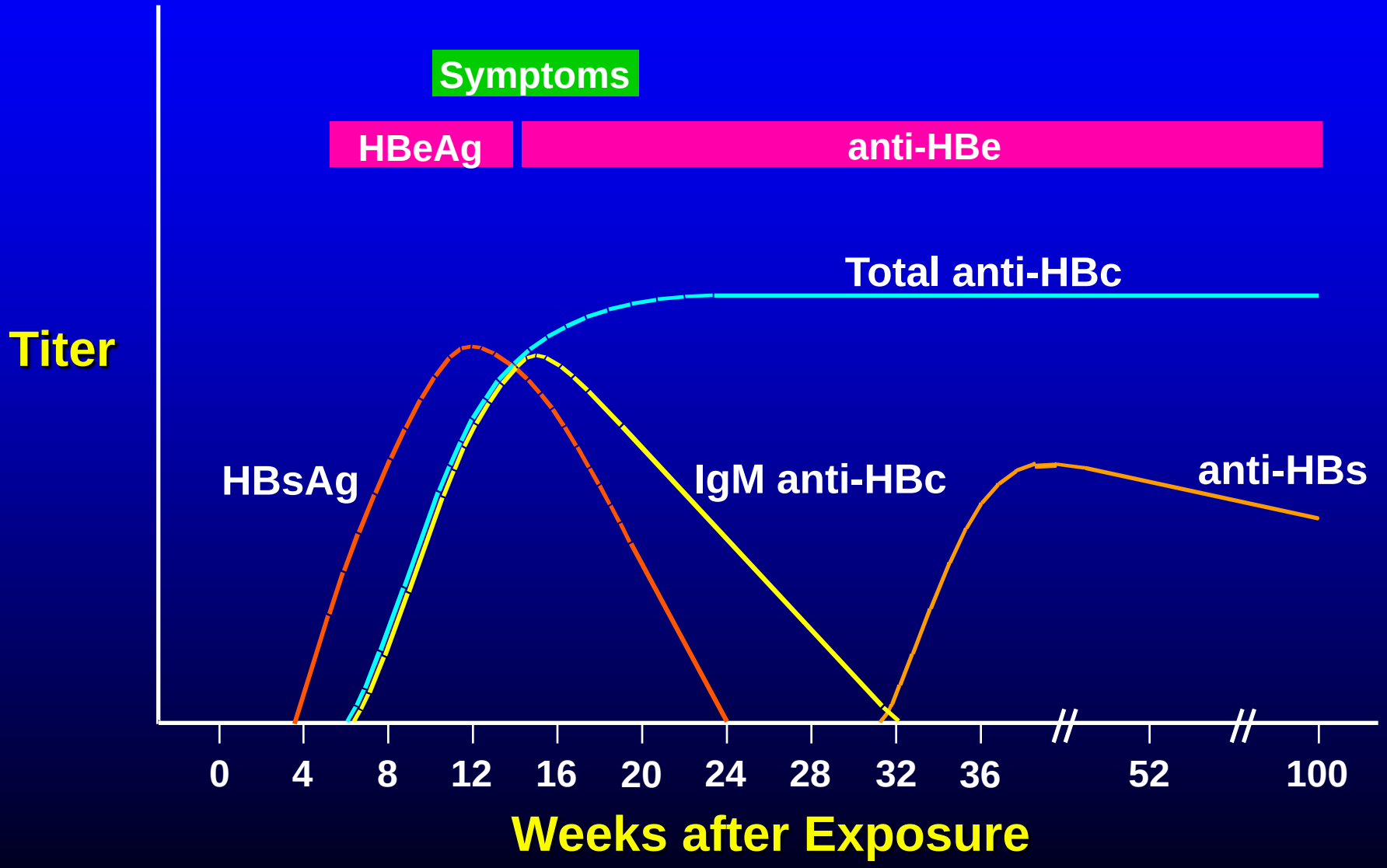

"Dane Particle"
HBeAg
HBsAg
Golgi
ER
CCC
DNA
HBV mRNA

Risk Factors for Acute Hepatitis B United States, 1992-1993

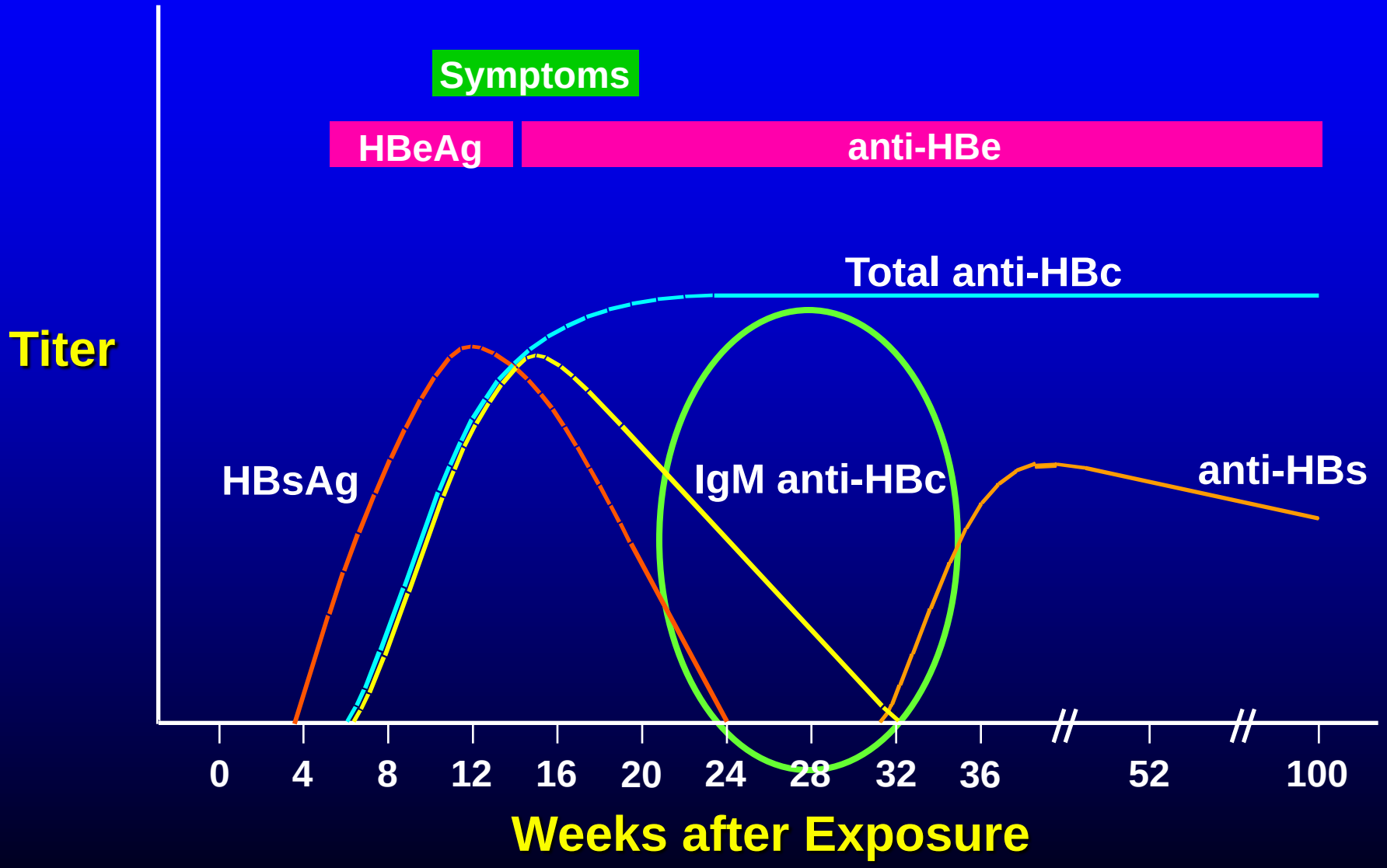


* Includes sexual contact with acute cases, carriers, and multiple partners.
Source: CDC Sentinel Counties Study of Viral Hepatitis

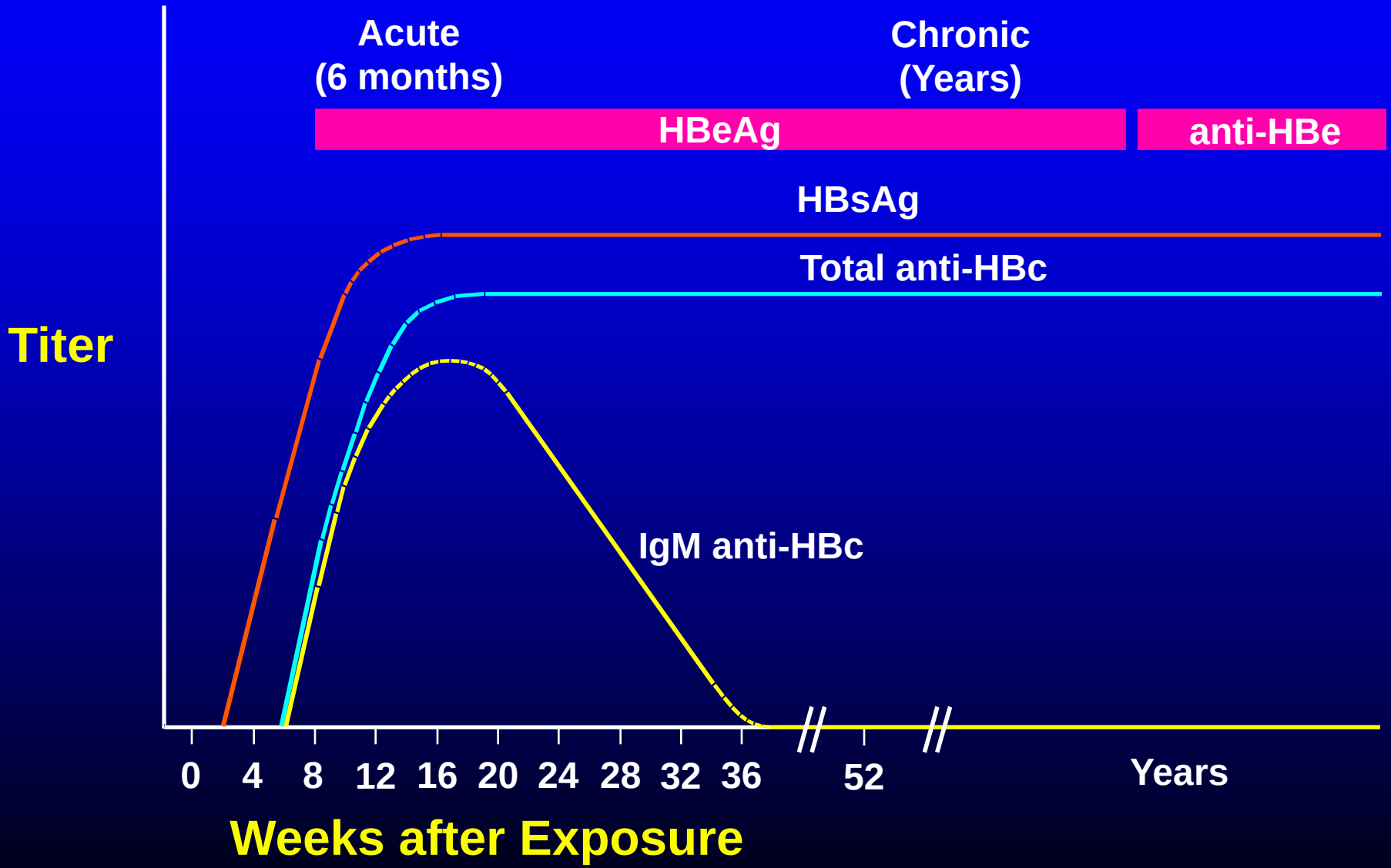
Acute HBV Infection with Recovery
Typical Serologic Course



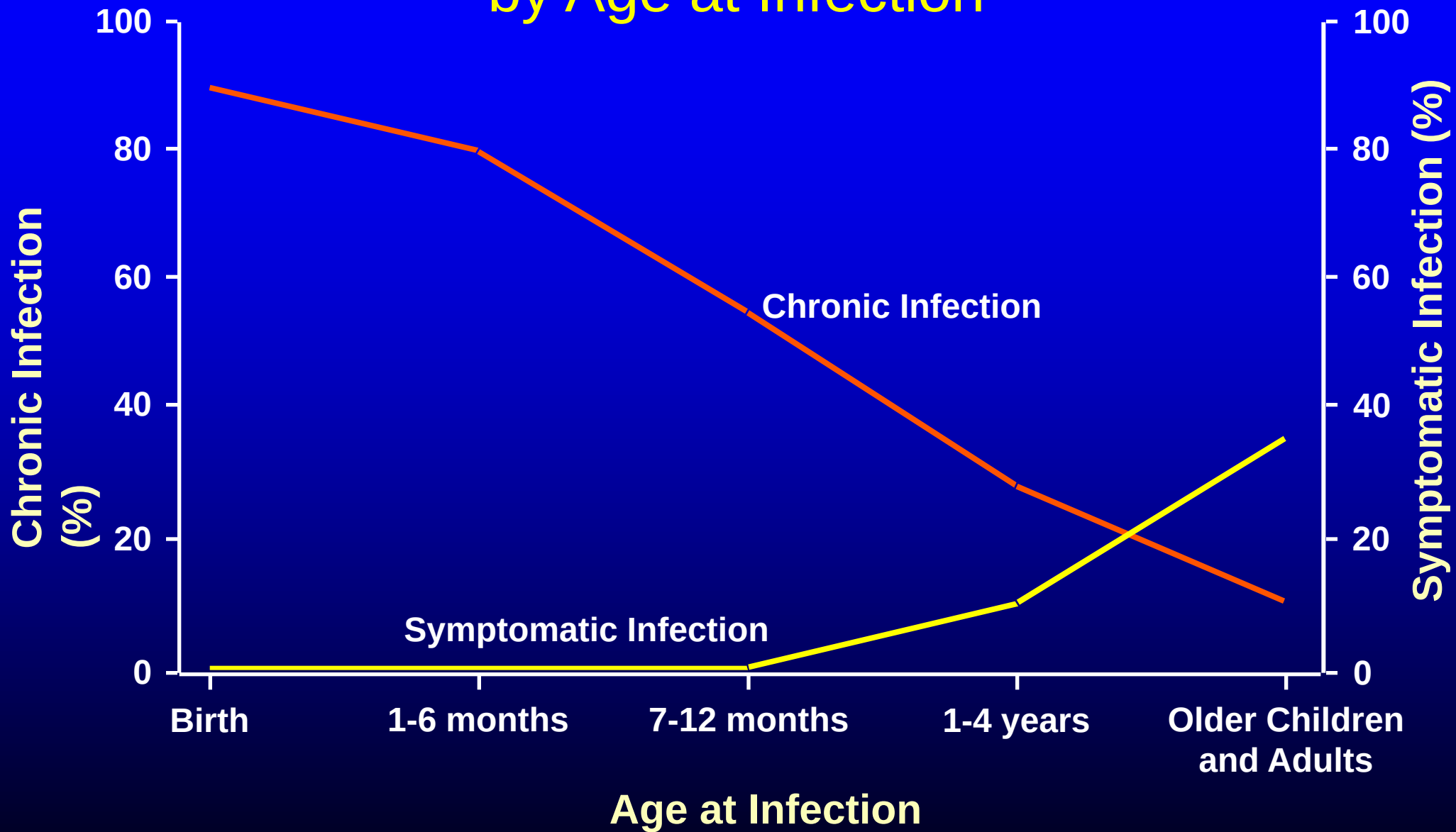
Acute HBV Infection with Recovery
Typical Serologic Course



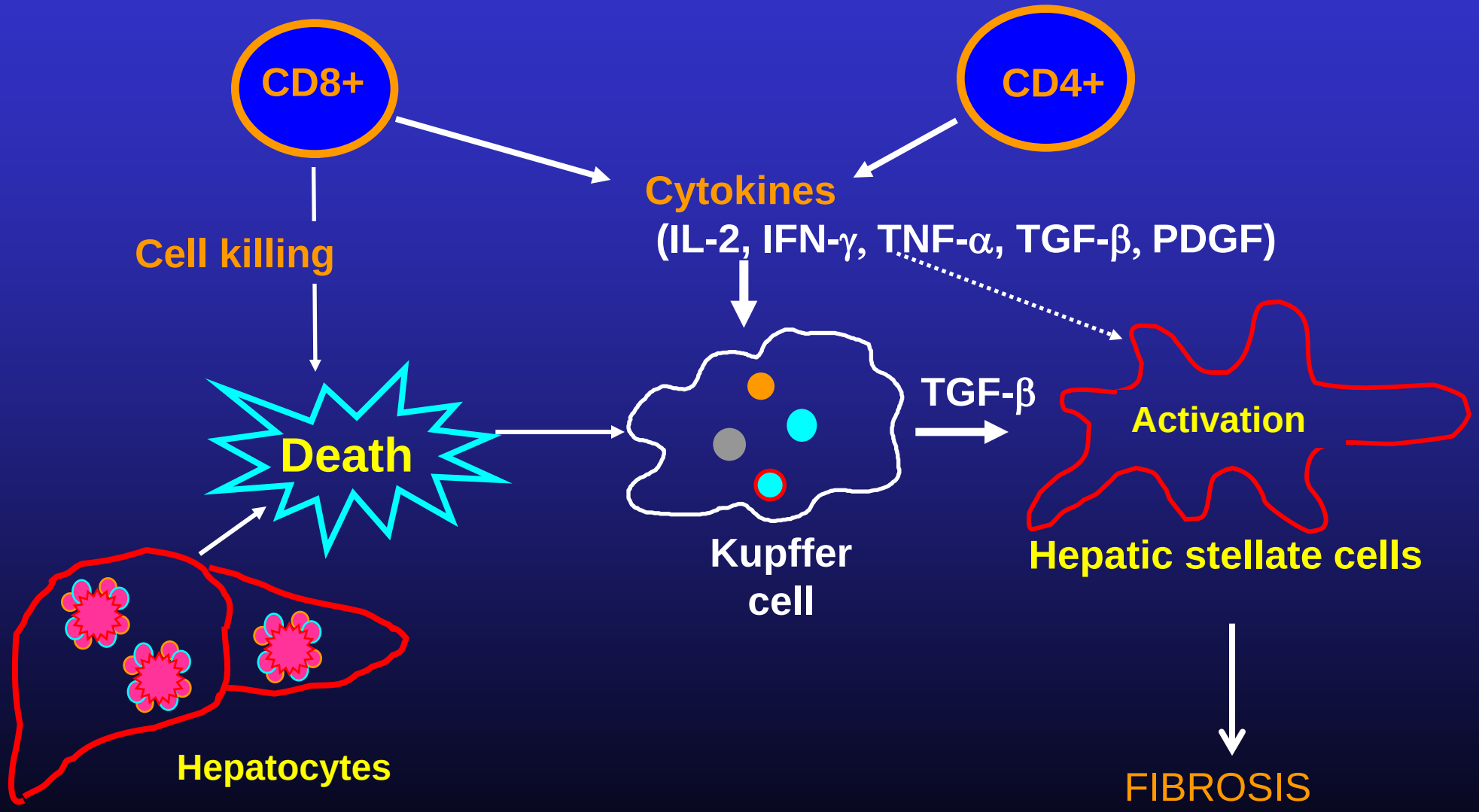
Progression to Chronic HBV Infection
Typical Serologic Course



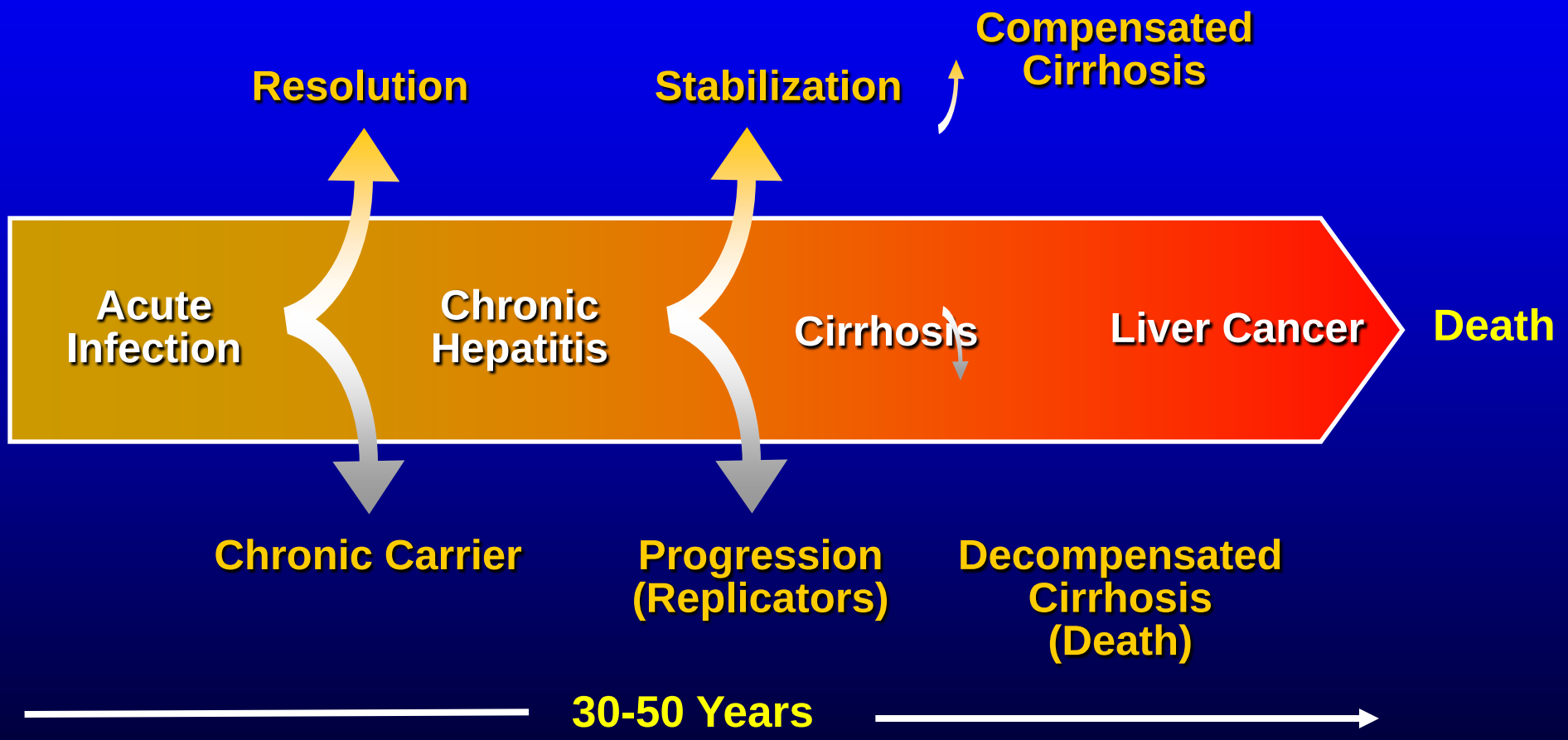
Outcome of HBV Infection by Age at Infection



Hepatitis B disease pathogenesis

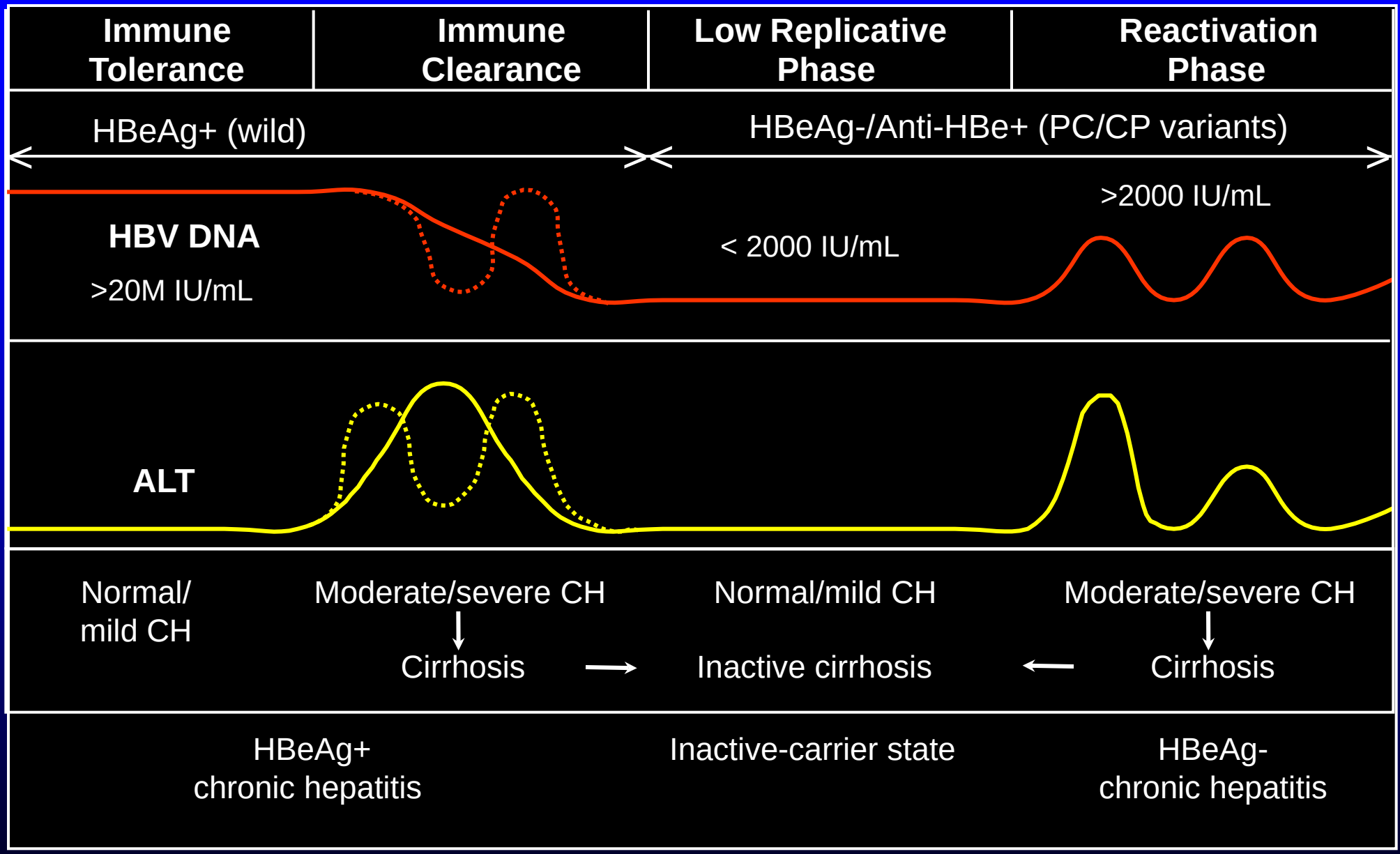


Natural History of Chronic HBV Infection



Adapted from Feitelson, *Lab Invest,* 1994.

Stages of Chronic HBV Infection



PC, precore; CP, core promoter; CH, chronic hepatitis

Adapted from G Fattovich, MD

Interpretation of HBV Diagnostic Tests

Test	Acute Hepatitis B	Past Exposures (Immunity)	Vaccinated	Chronic* eAg(+) (replicative)	Chronic* eAg(-) (replicative)	Inactive Carrier
HBsAg	+	-	-	+	+	+
Anti-HBs	-	+	+	-	-	-
HBeAg	+	-	-	+	-	-
anti-HBe	-	+/-	-	-	+	+
anti-HBc	+	+	-	+	+	+
IgM anti-HBc	+	-	-	-	-	-
HBV DNA (PCR)	+	-	-	>20,000 IU/mL	>2,000 IU/mL	- or low +
ALT	Elevated	Normal	Normal	Elevated	Elevated	Normal

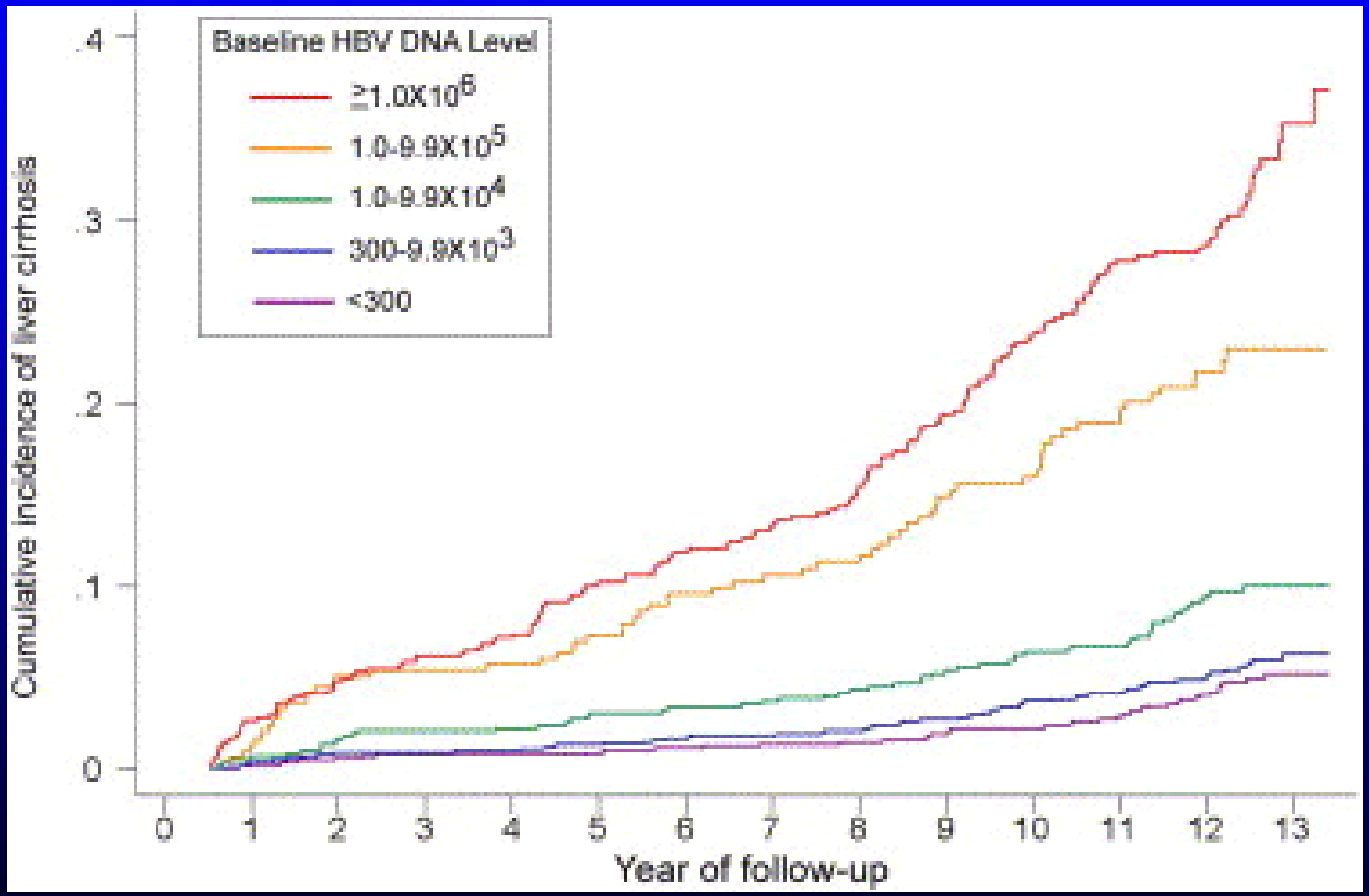
*indicated for antiviral therapy

HBV replicators are at highest risk of disease progression

- Study of HBV progression and HCC in 11,893 men in Taiwan
- Likelihood of HCC 3.9x higher in patients with detectable HBV DNA vs undetectable
  - Risk associated with increasing HBV DNA levels
- Relative risk of HCC vs uninfected individuals
  - HBsAg(+) and HBeAg(+) 60.2x
  - HBsAg(+) but HBeAg(-) 9.6x
- Antiviral therapy to decrease risk of outcomes

Yang HI, et al. *N Engl J Med*. 2002;347:168-174.

HBV DNA level predicts clinical outcome



Iloeje U, Gastro 2006;130:678-86.

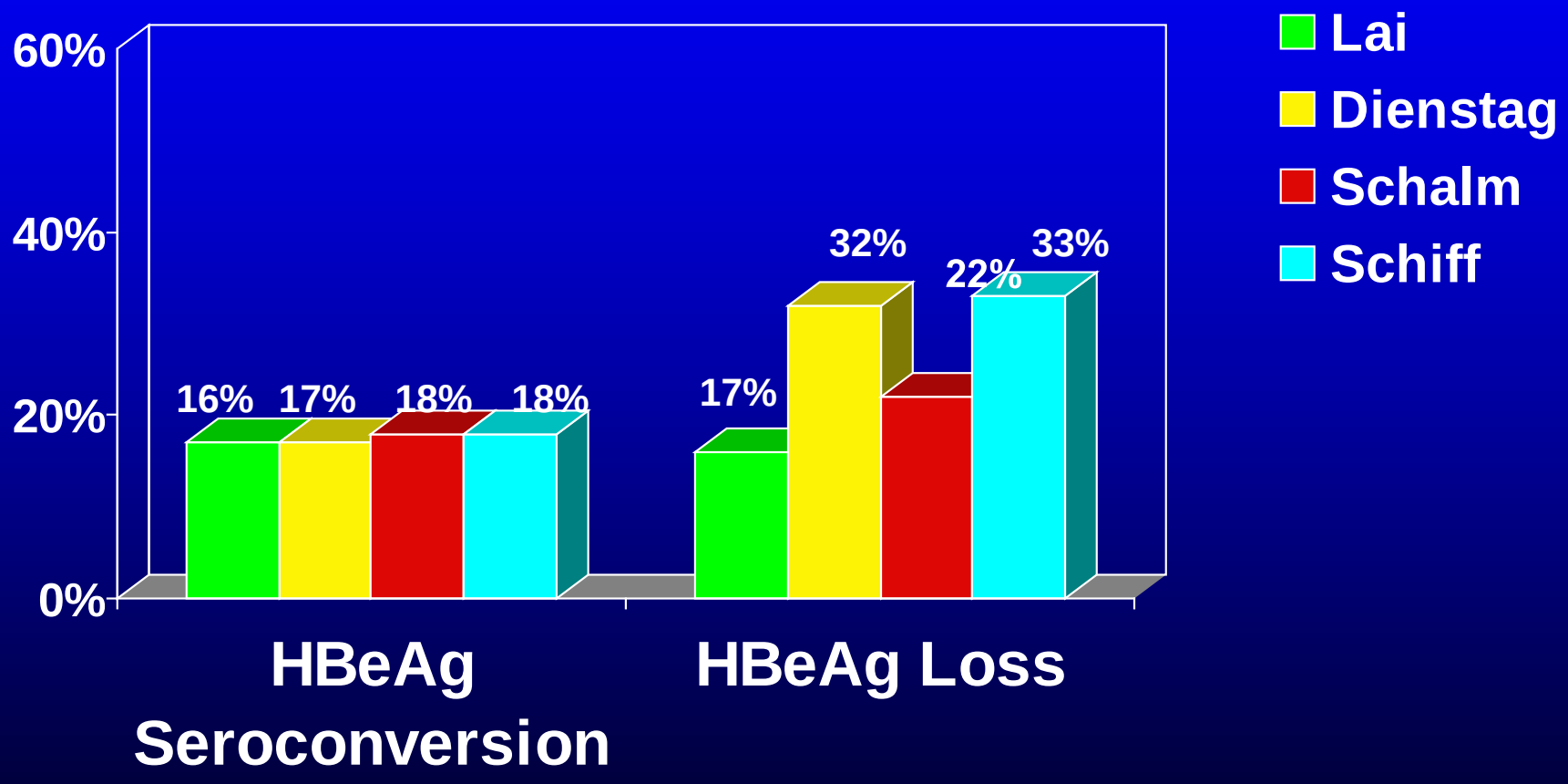
Approved agents for chronic HBV

- Interferon-alfa-2b
- Lamivudine
- Adefovir
- Entecavir
- Tenofovir
- Telbivudine
- PEG-interferon-alfa-2a

Other approved agents with anti-HBV activity

- Emtricitabine

HBeAg Responses in Phase-III Trials of Lamivudine (100 mg/d x 52 weeks)

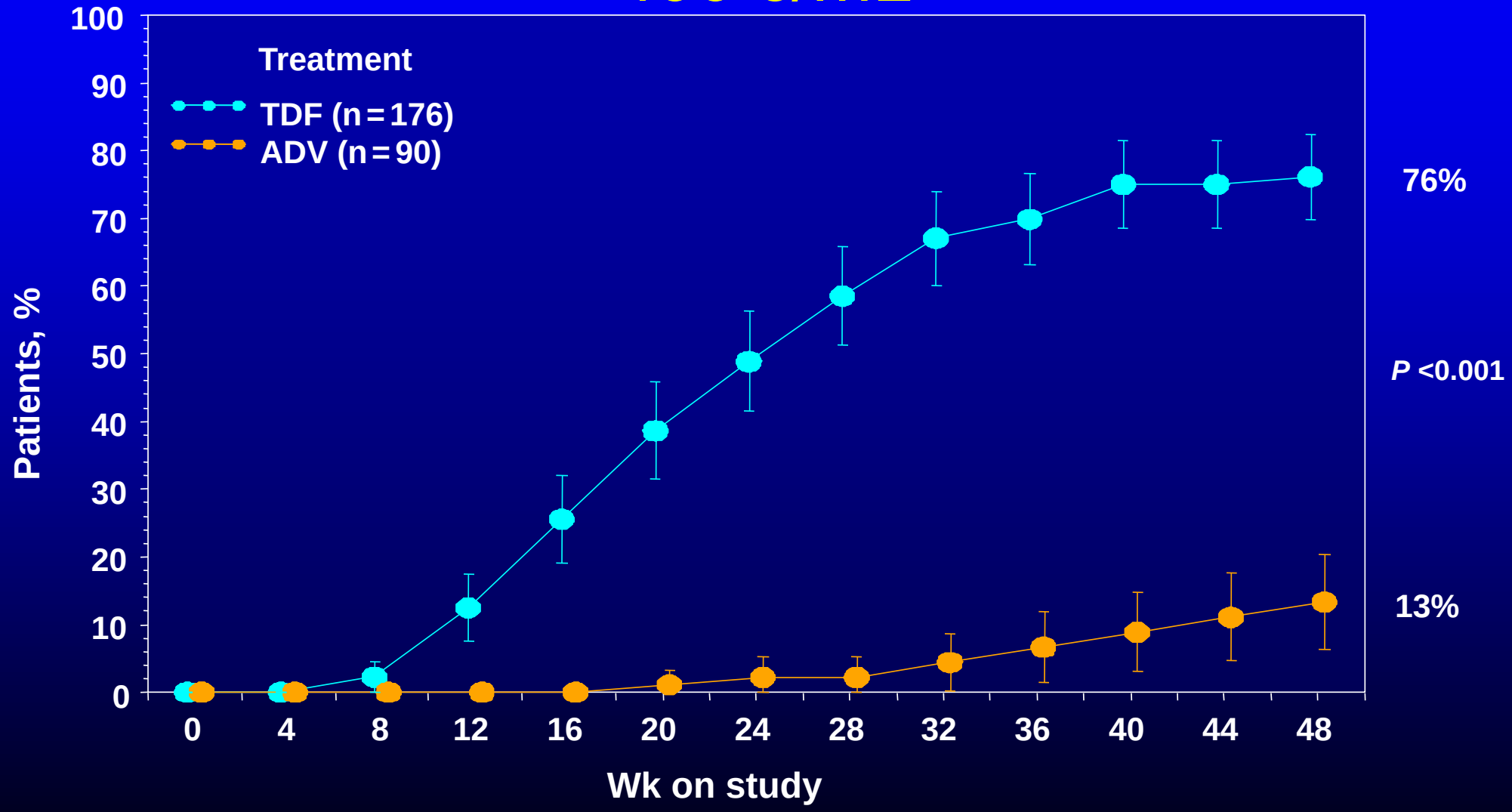


Entecavir vs Lamivudine in HBeAg(+) patients

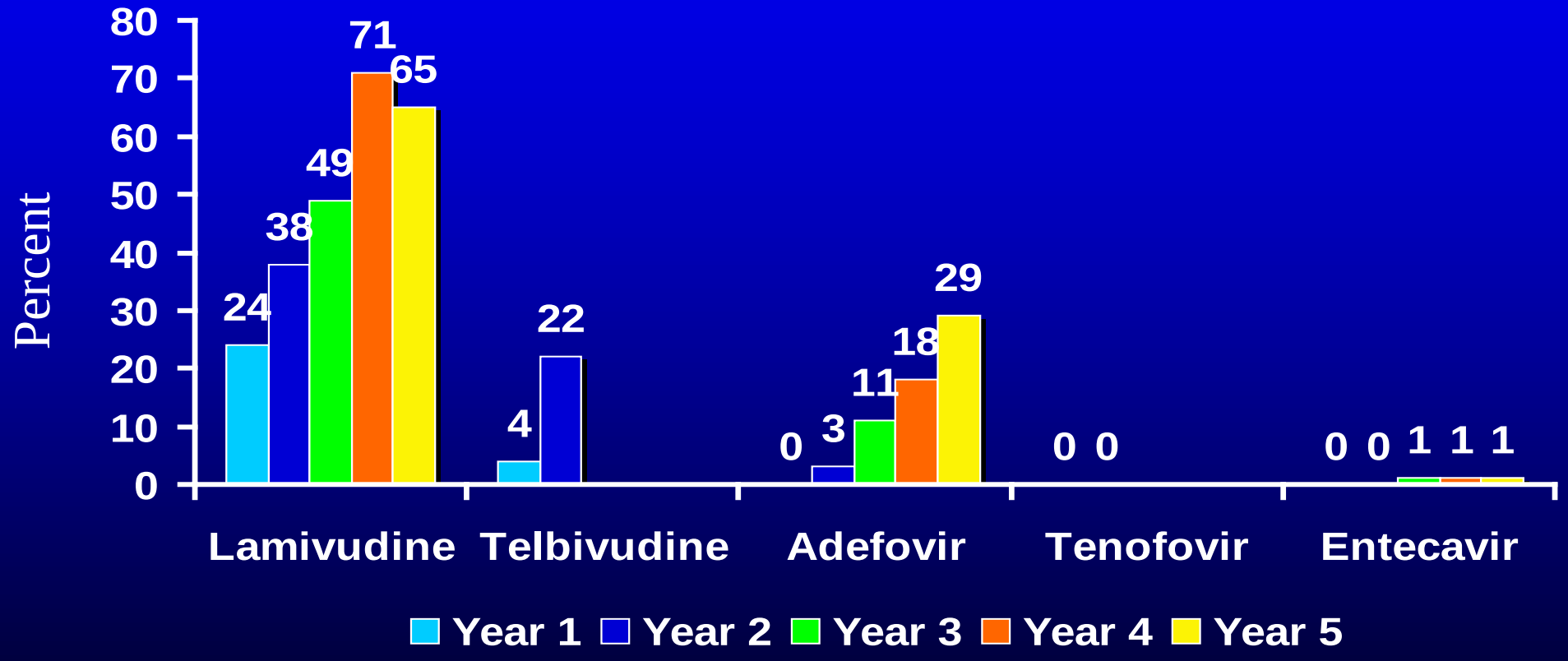
	Entecavir (n = 354)	Lamivudine (n = 355)	*P* Value
Histologic improvement, %	72	62	.0085
Median change in HBV DNA from baseline, log_{10} copies/mL	-6.98	-5.46	< .0001
HBV DNA < 0.7 mEq/mL, %	91	65	< .0001
HBV DNA < 400 copies/mL, %	69	38	< .0001
HBeAg seroconversion, %	21	18	NS

Chang T, et al. NEJM 2006

Tenofovir vs Adefovir in HBeAg-positive CHB: Patients With HBV DNA Levels of <400 c/mL

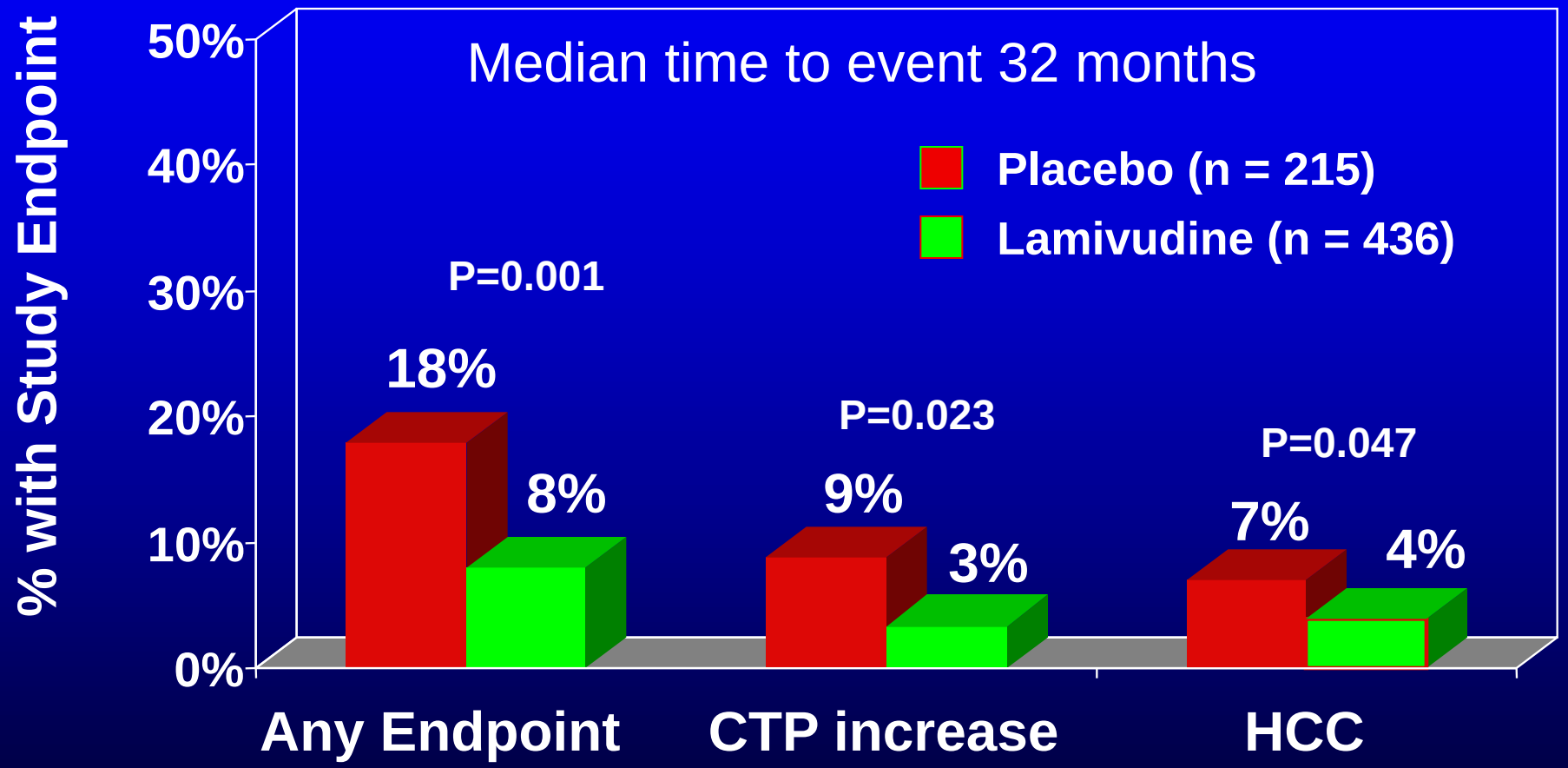


Rates of Genotypic Resistance FDA approved nucs



Antiviral therapy postpones clinical outcomes in cirrhotic HBV

Study terminated early after 72 endpoints



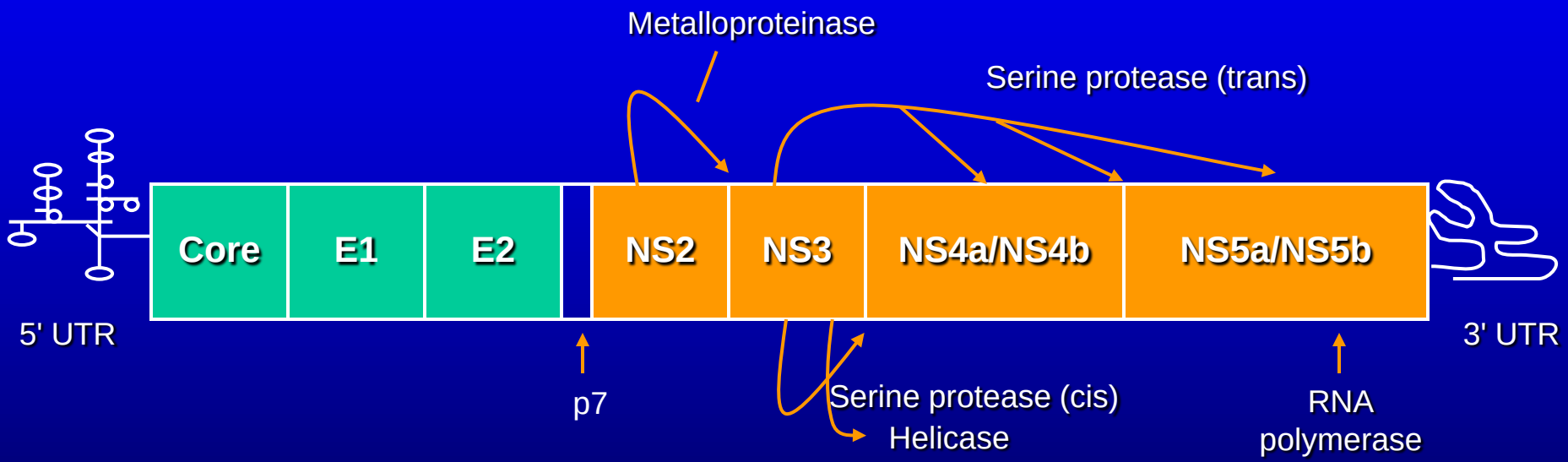
≥2 point CTP elevation, HCC, SBP, renal insufficiency, bleeding varices

Liaw Y-F et al. N Engl J Med 2004; 351:1521

HBV Management

- HBV DNA levels have prognostic value
- Treat *replicative, active* HBV
- Goal is eAg seroconversion or HBV DNA suppression
  - sAg seroconversion elusive
- Entecavir, Tenofovir 1st line monotherapy agents
- PEGIFN can be considered in young persons with low HBV DNA, inc ALT
- In any HBsAg+ pt undergoing chemo, steroids, rituximab, biologics, prophylax!
- We need curative strategies directed against other viral lifecycle steps

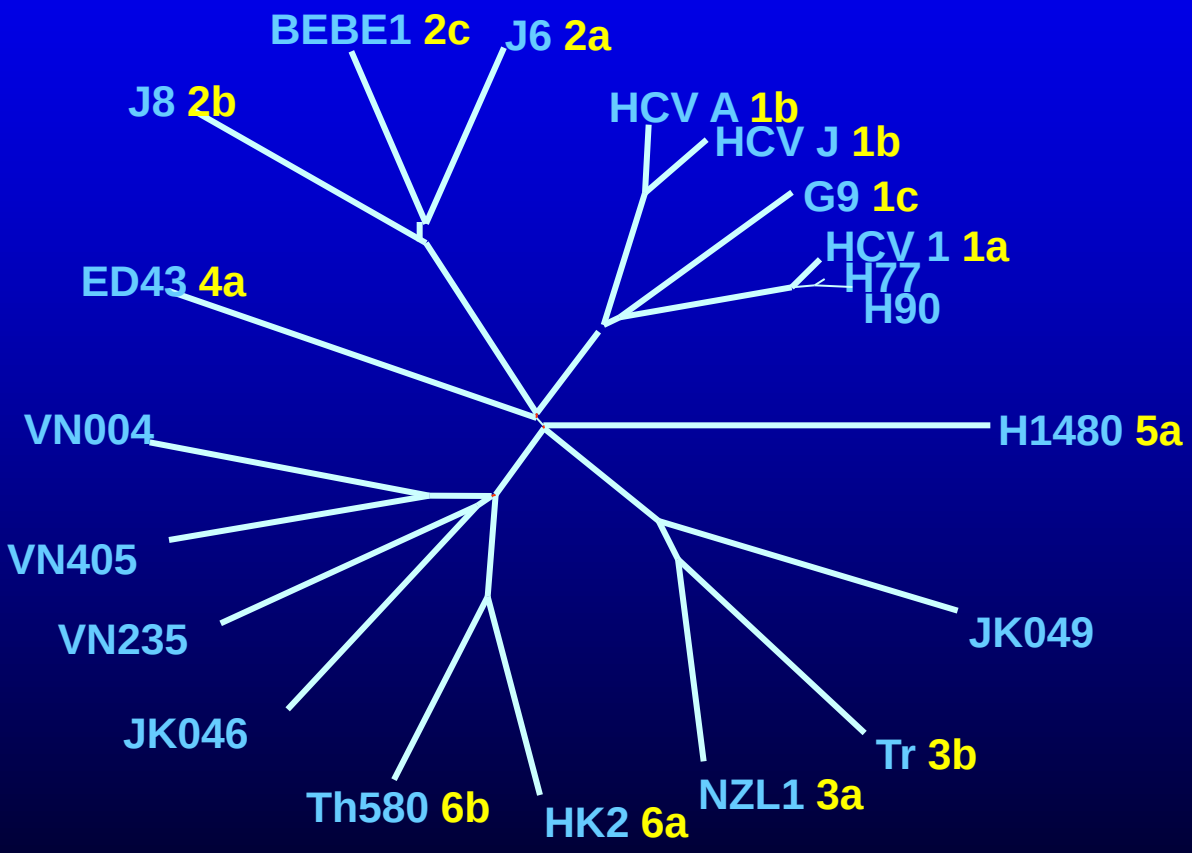
HCV Genomic Organization



Structural proteins **Nonstructural proteins**

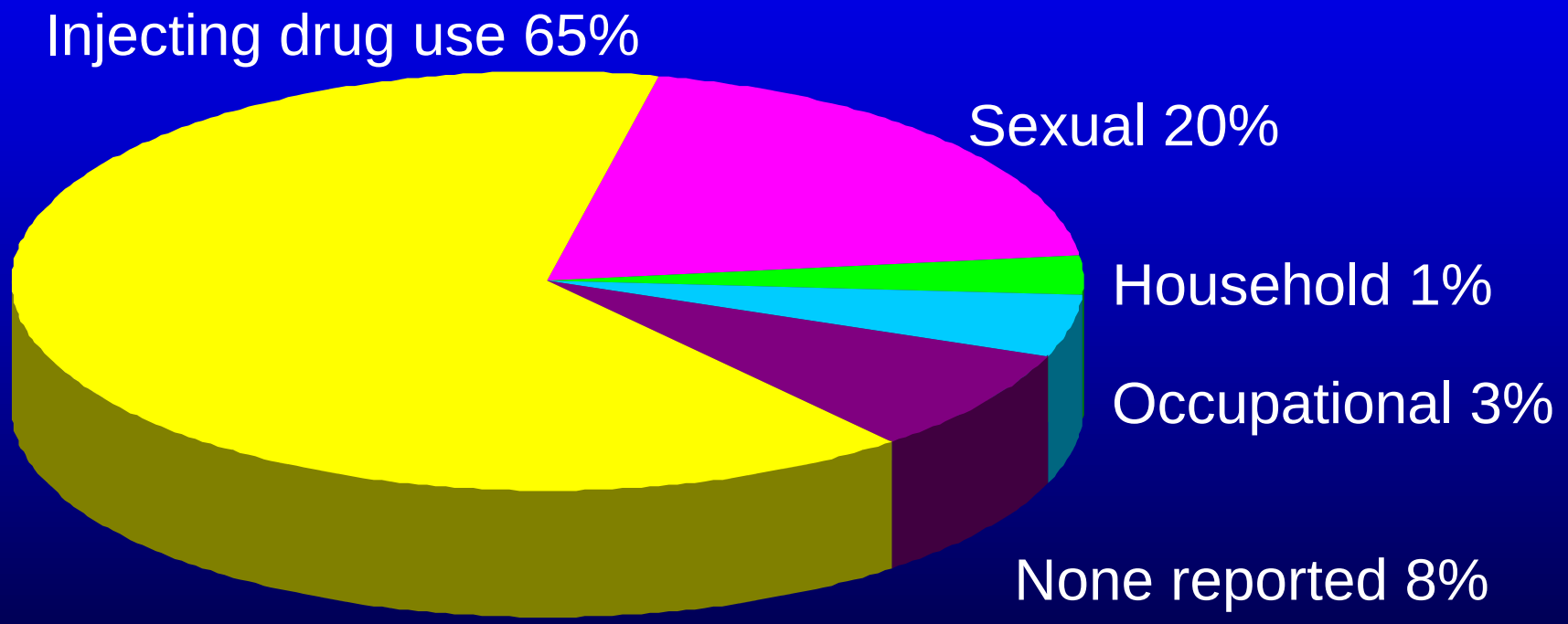
RNA virus does not integrate into genome – *curable*
RNA polymerase error-prone – *high genetic diversity*

Genetic Diversity of HCV



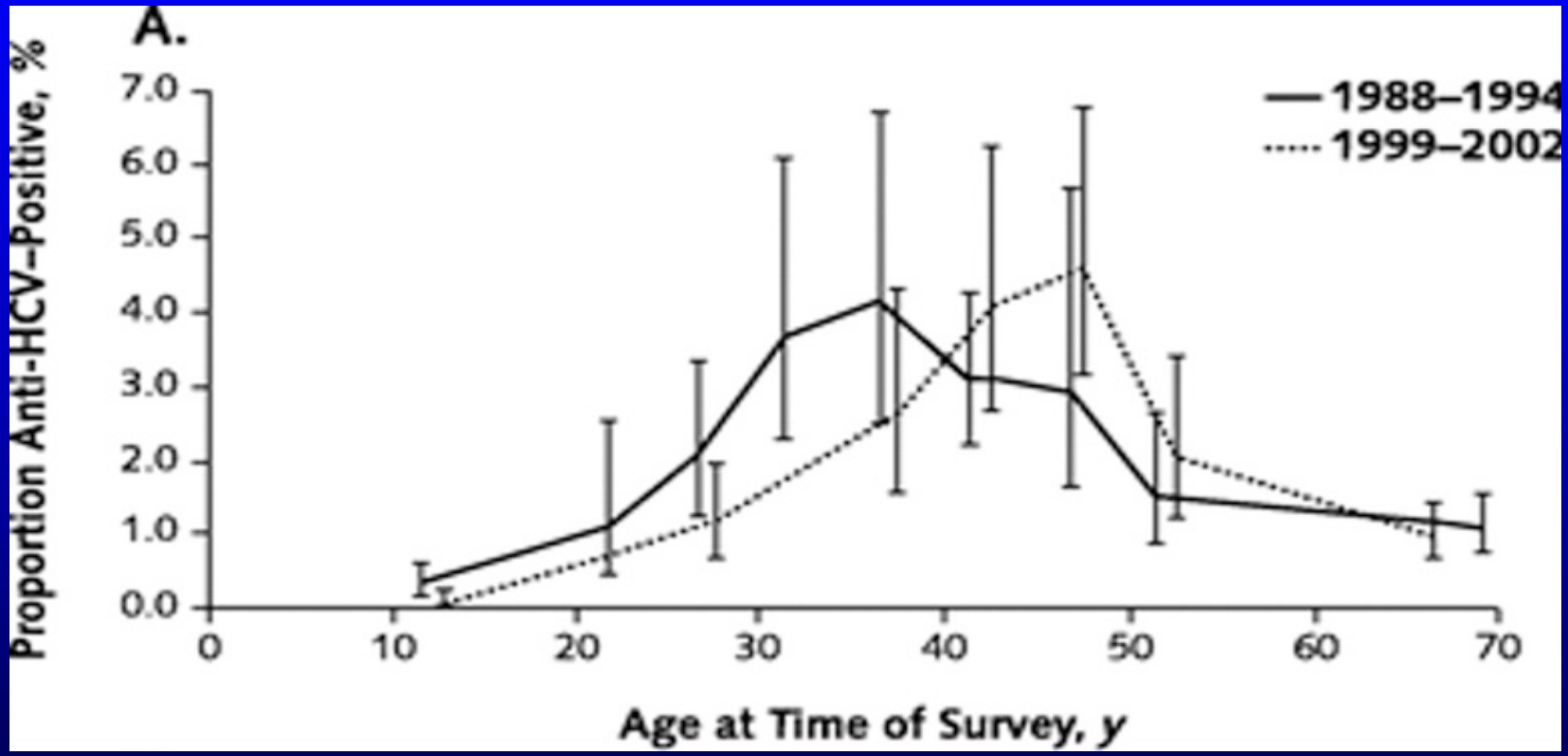
- 6 major genotypes
- many subtypes
- in US,
  - gt 1 75%
  - gt 2,3 25%

Sources of Infection for Persons With Acute Hepatitis C in 6 Months Prior to Illness Onset, 1994-2006



Williams IT, et al. Arch Intern Med. 2011;171:242-248

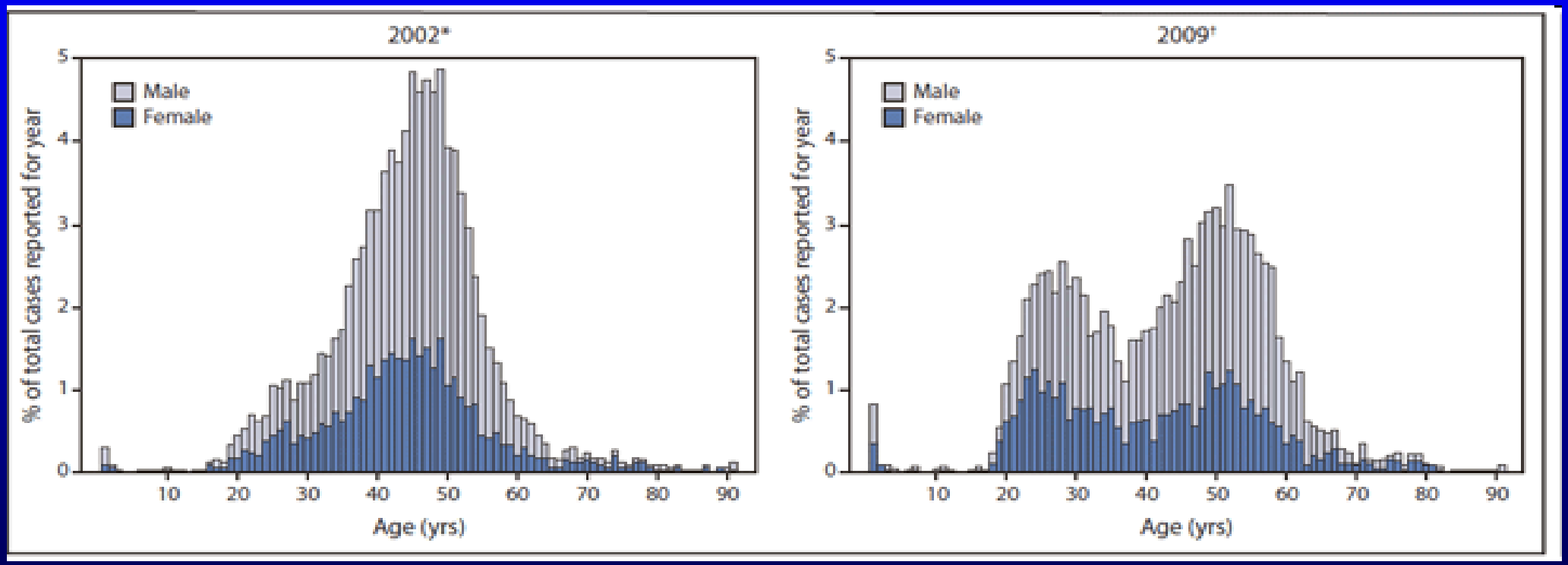
In general, the HCV cohort has aged…



NHANES 2003-10: 2.7M chronically infected

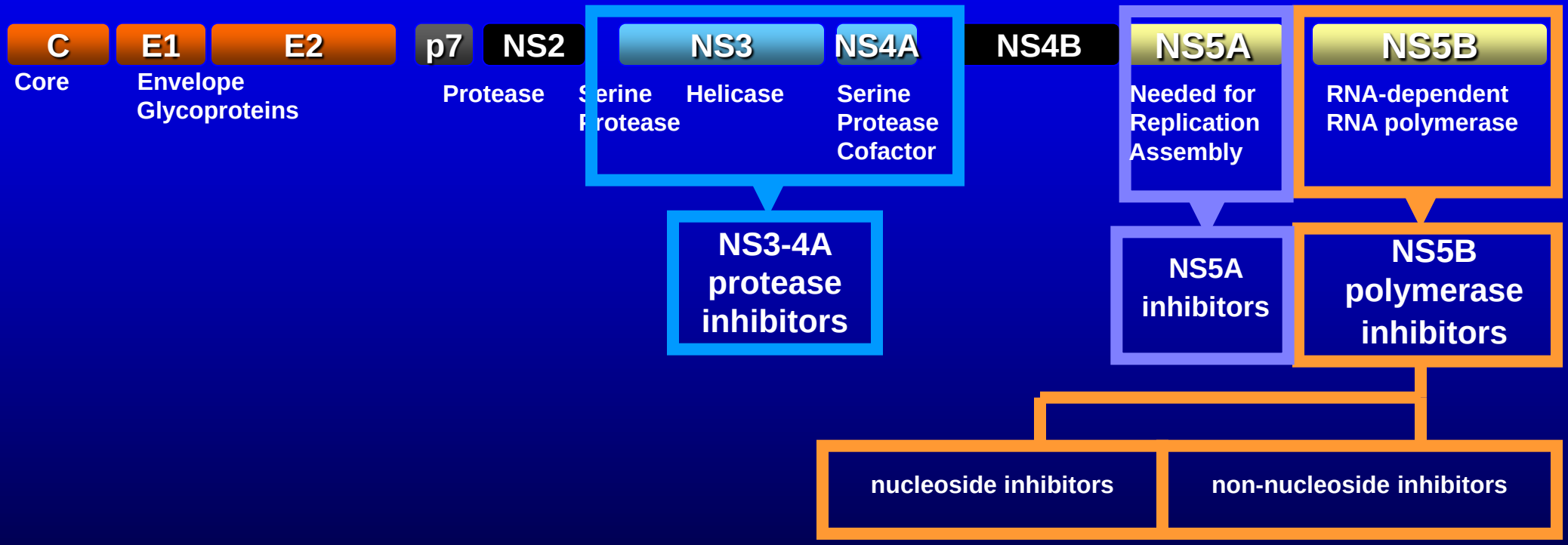
CDC data. Armstrong GL et al. Ann Intern Med 2006;144:705-14
Denniston MM et al, Ann Intern Med 2014; 160:293-300

…but there has been a youthful spike



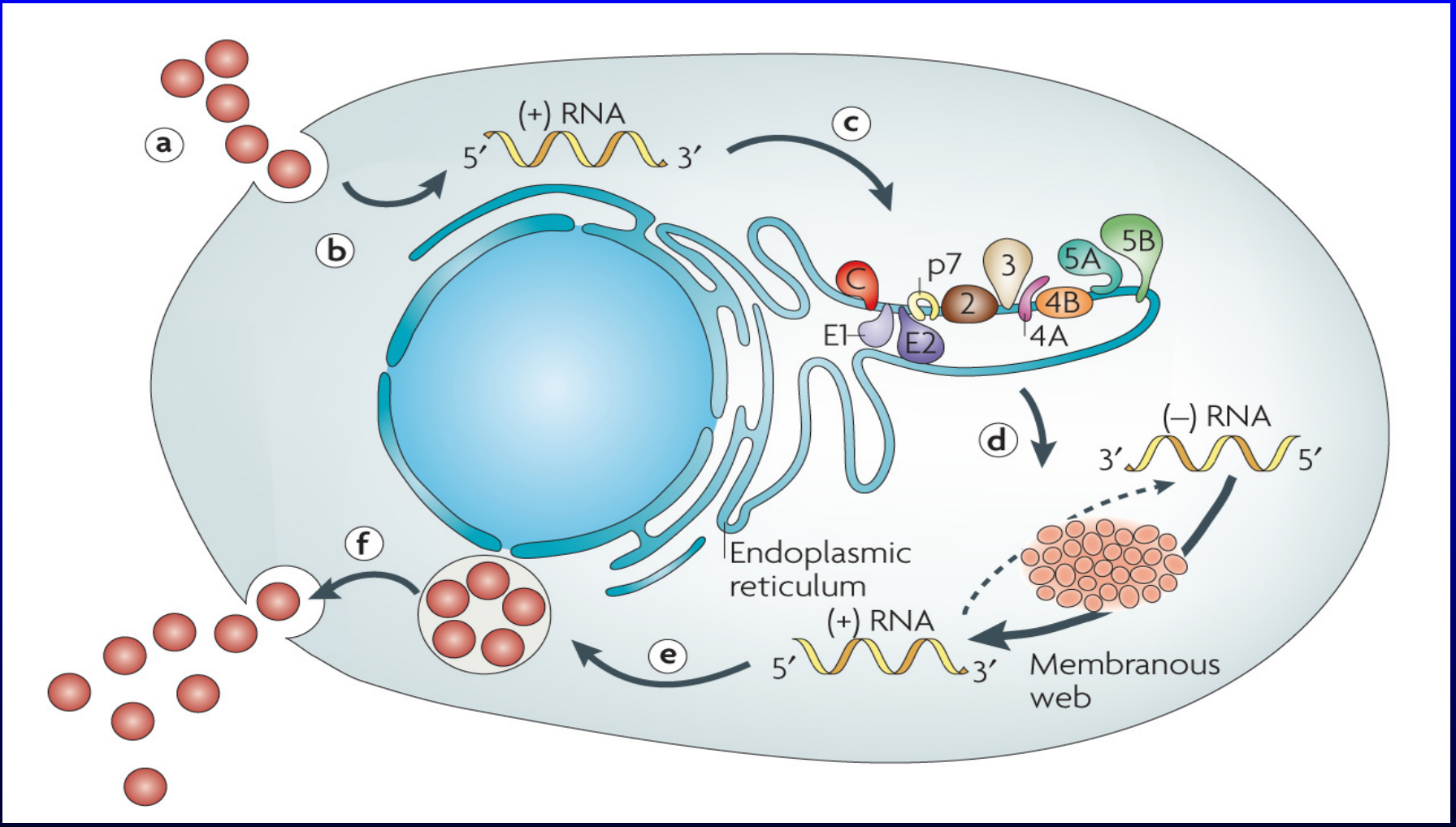
Onofrey et al. MMWR May 6, 2011 / 60(17);537-541

Targets for Direct Acting Antivirals (DAA)



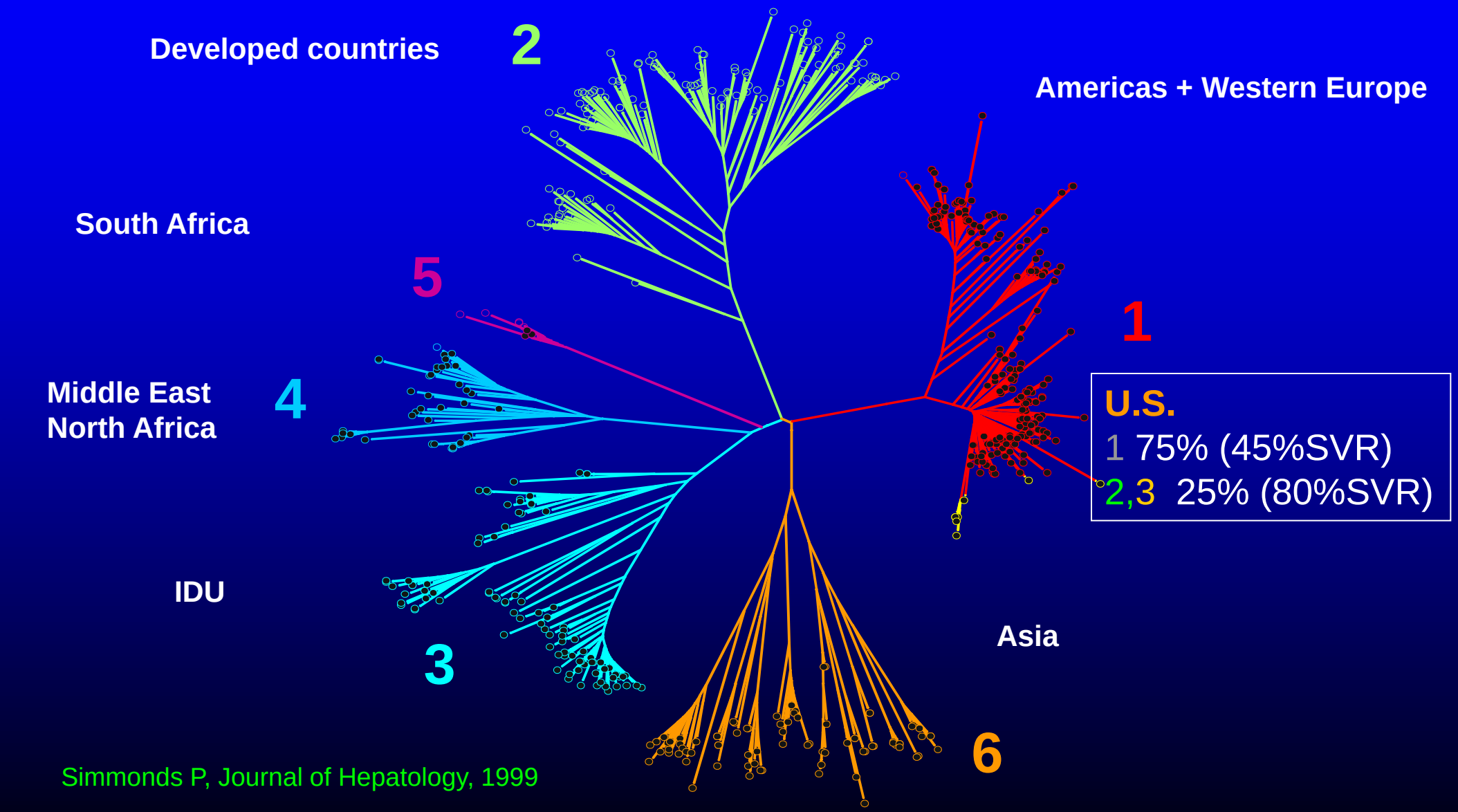
McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

HCV life cycle



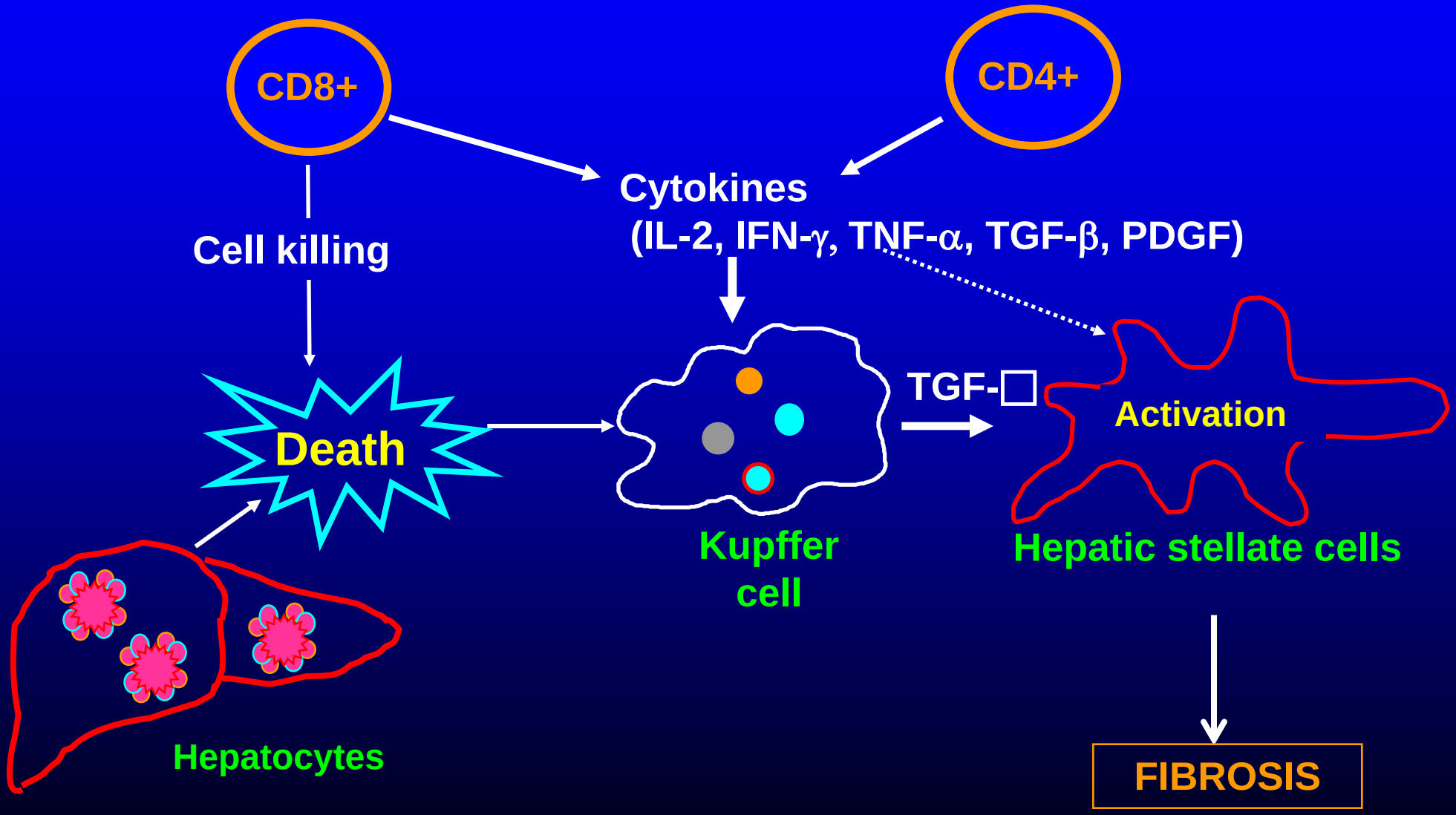
Moradpour, Nat Rev Microbiol 2007;5:453

HCV Genotypes and Subtypes

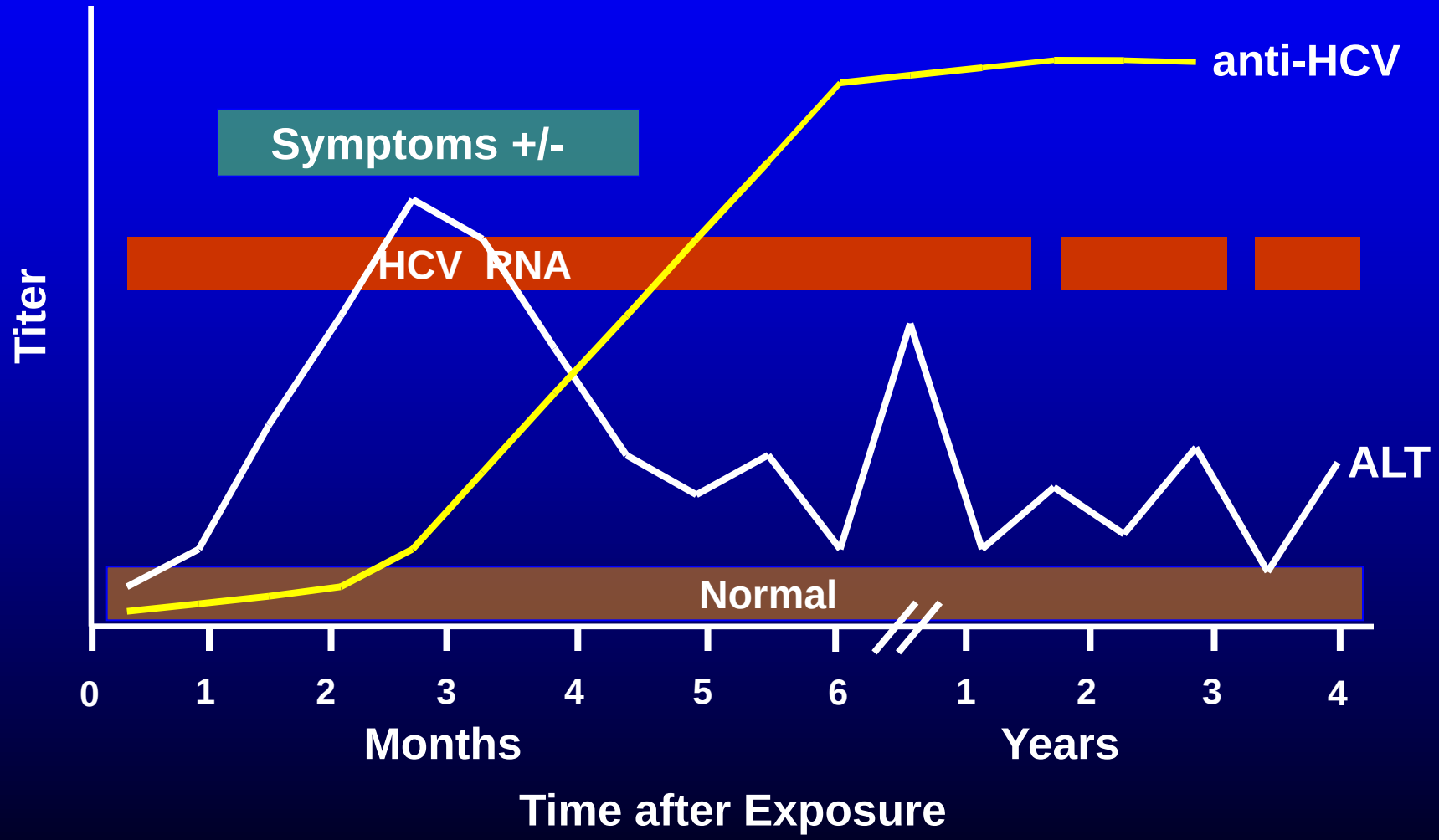


Simmonds P, Journal of Hepatology, 1999

Hepatitis C disease pathogenesis

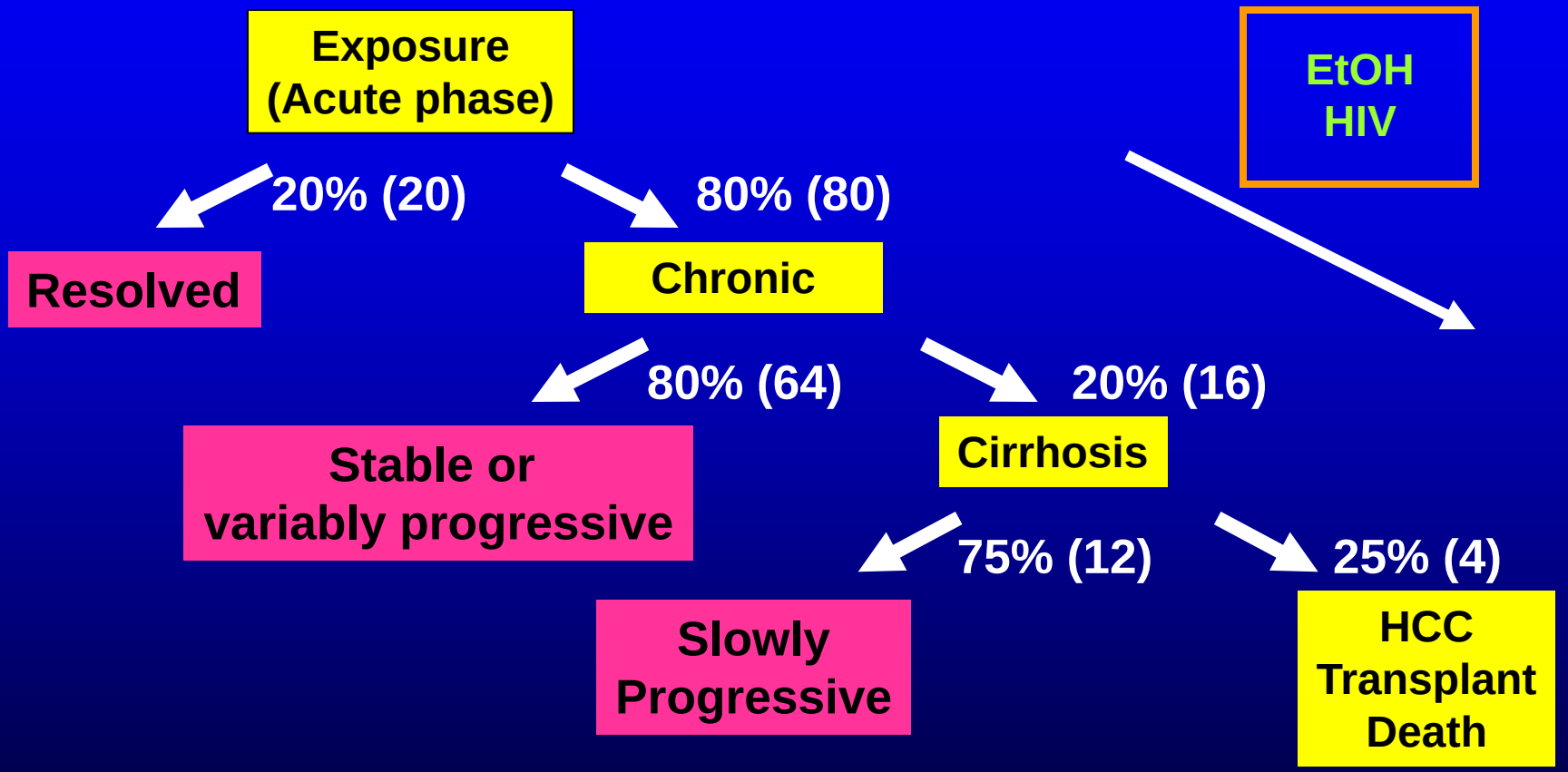


Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

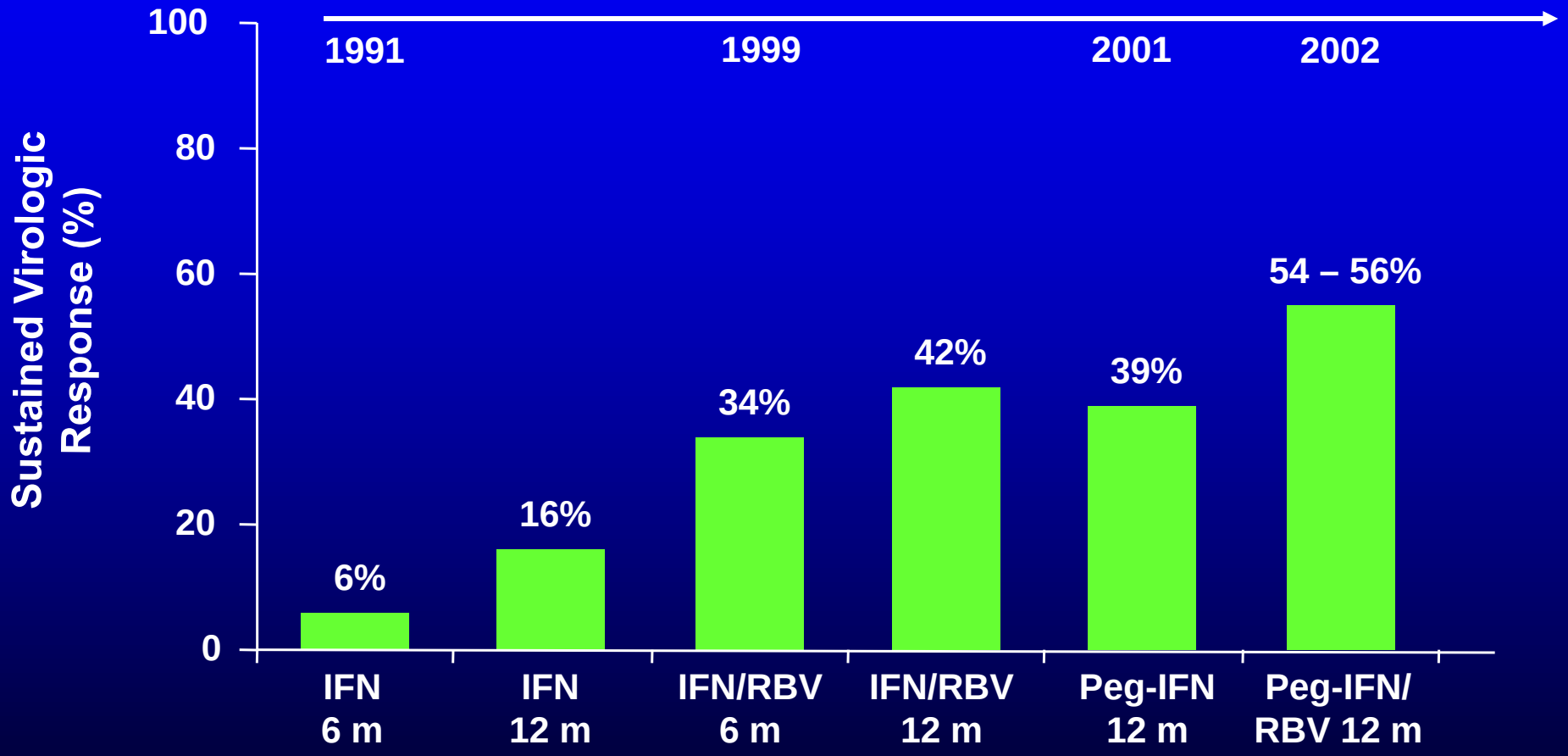


Adapted from MMWR 1998; 47(No. RR19)

Natural History of HCV Infection

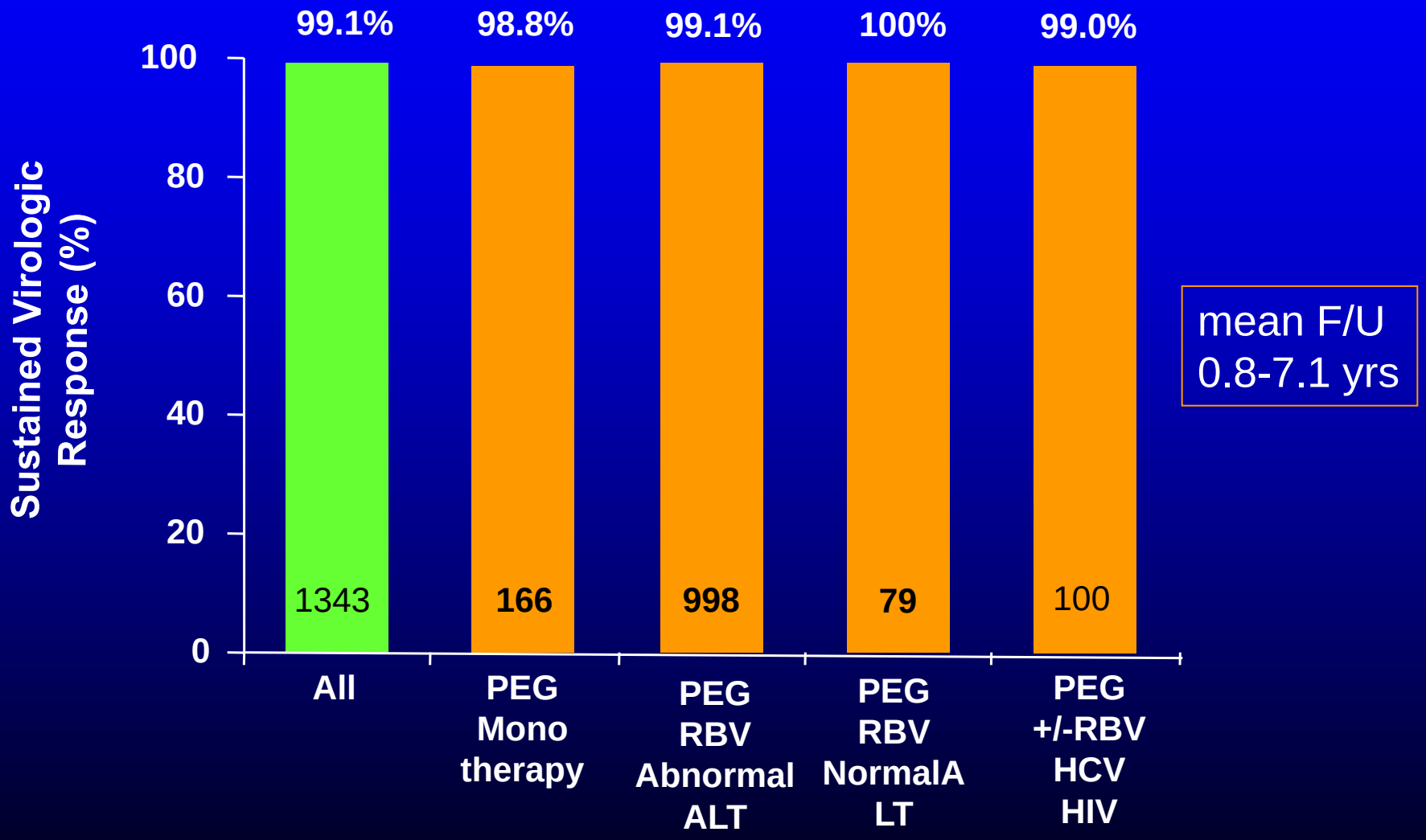


PEG-IFN-α and RBV Produce SVR in About Half of Patients with HCV



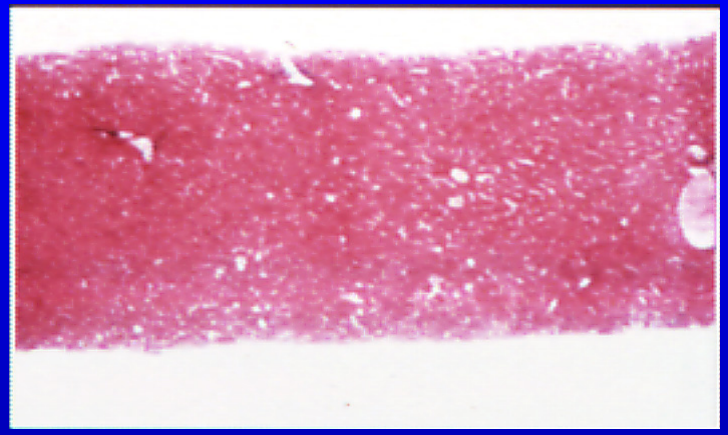
Adapted from Strader DB, et al. *Hepatology.* 2004;39:1147-71

The good news: a sustained response is truly sustained

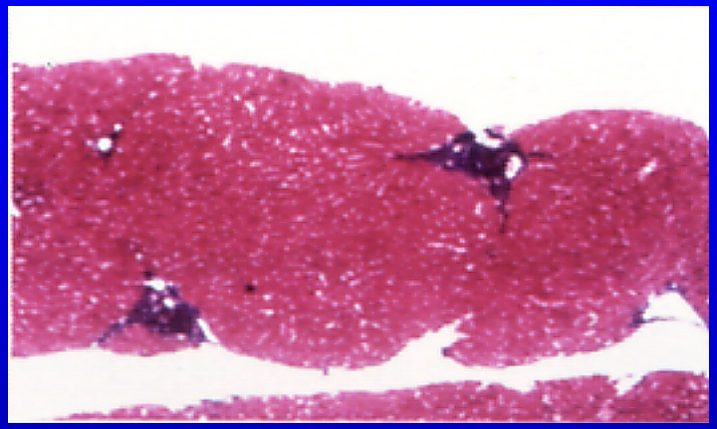


Swain M, et al. *Gastroenterology* 2010;139:1593

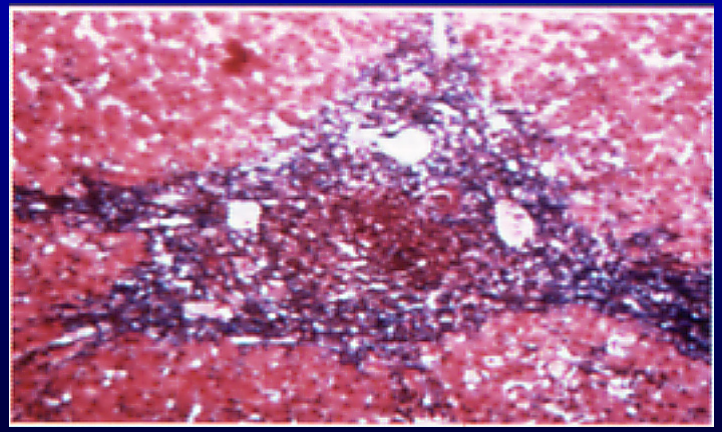
Histologic Progression of HCV



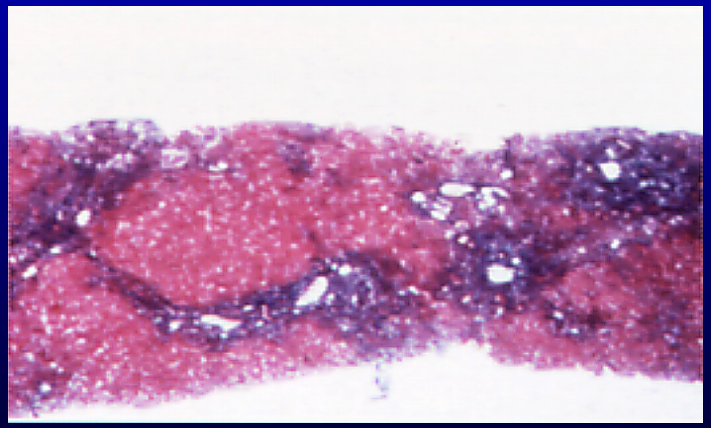
Normal



Mild Chronic Hepatitis (F1)



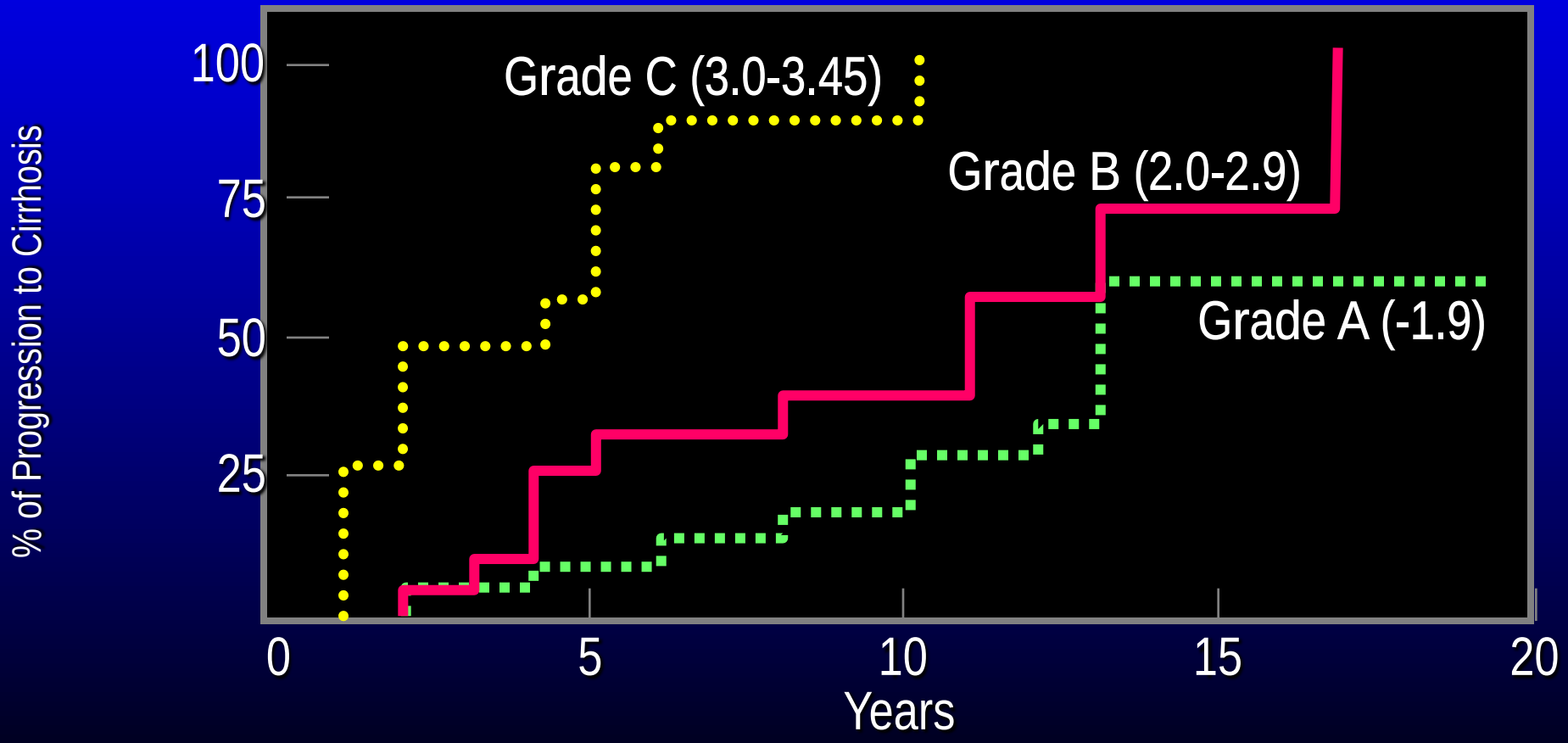
Moderate Chronic Hepatitis (F3)



Cirrhosis (F4)

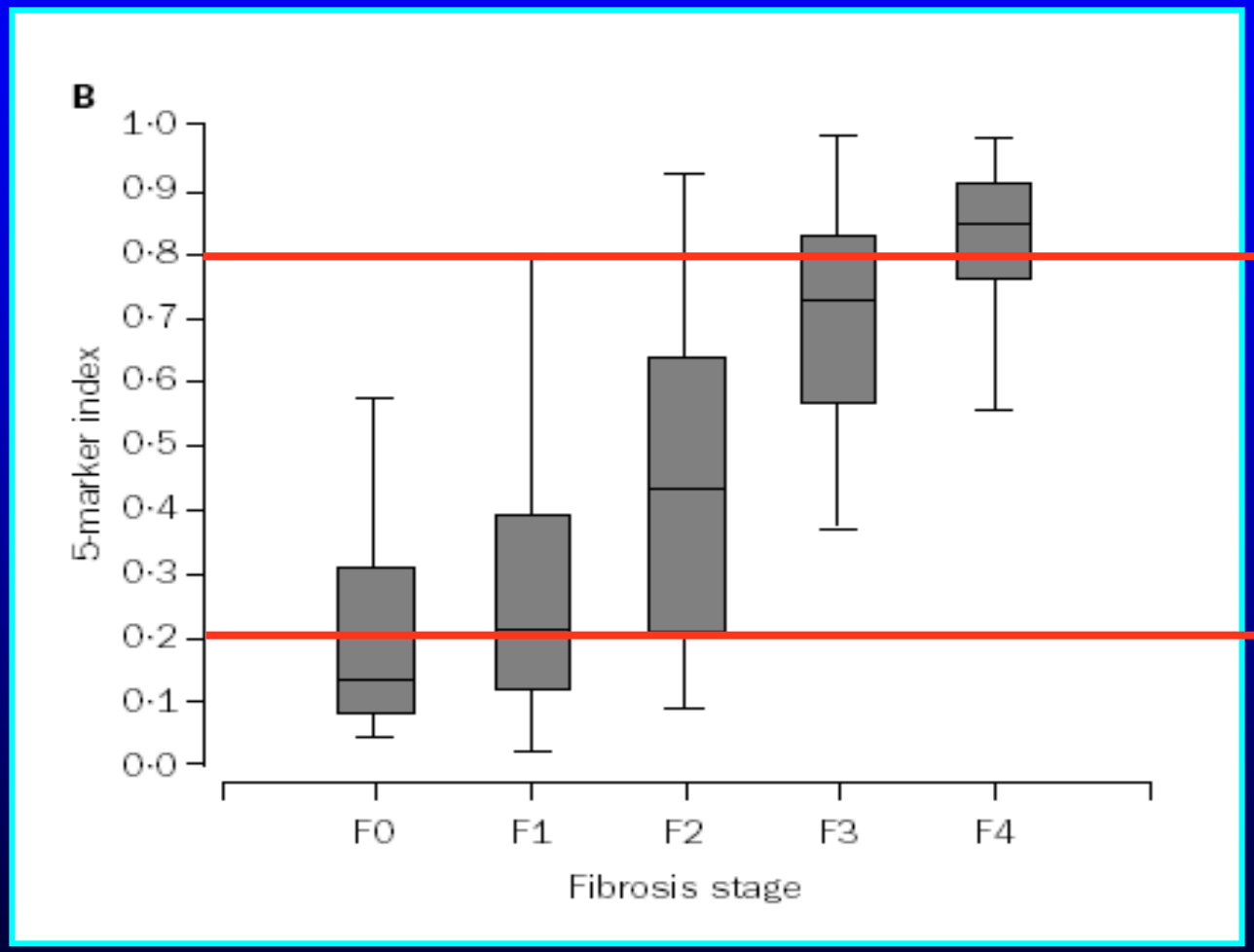
Rate of Progression to Cirrhosis from Chronic Hepatitis C

Degree of Fibrosis on Initial Liver Biopsy



Yano M et al. *Hepatology*. 1996;23:1336

≈ 50% of Biopsies Avoidable with FibroTest



FT > 0.80
Spec 97%
PPV 92%

Indeterminate
54%

FT ≤ 0.20
Sens 92%
NPV 87%

n=134
F2-F4 fibrosis: 45%

TBili, α-2-MG, hapto, GGT, ApoA1

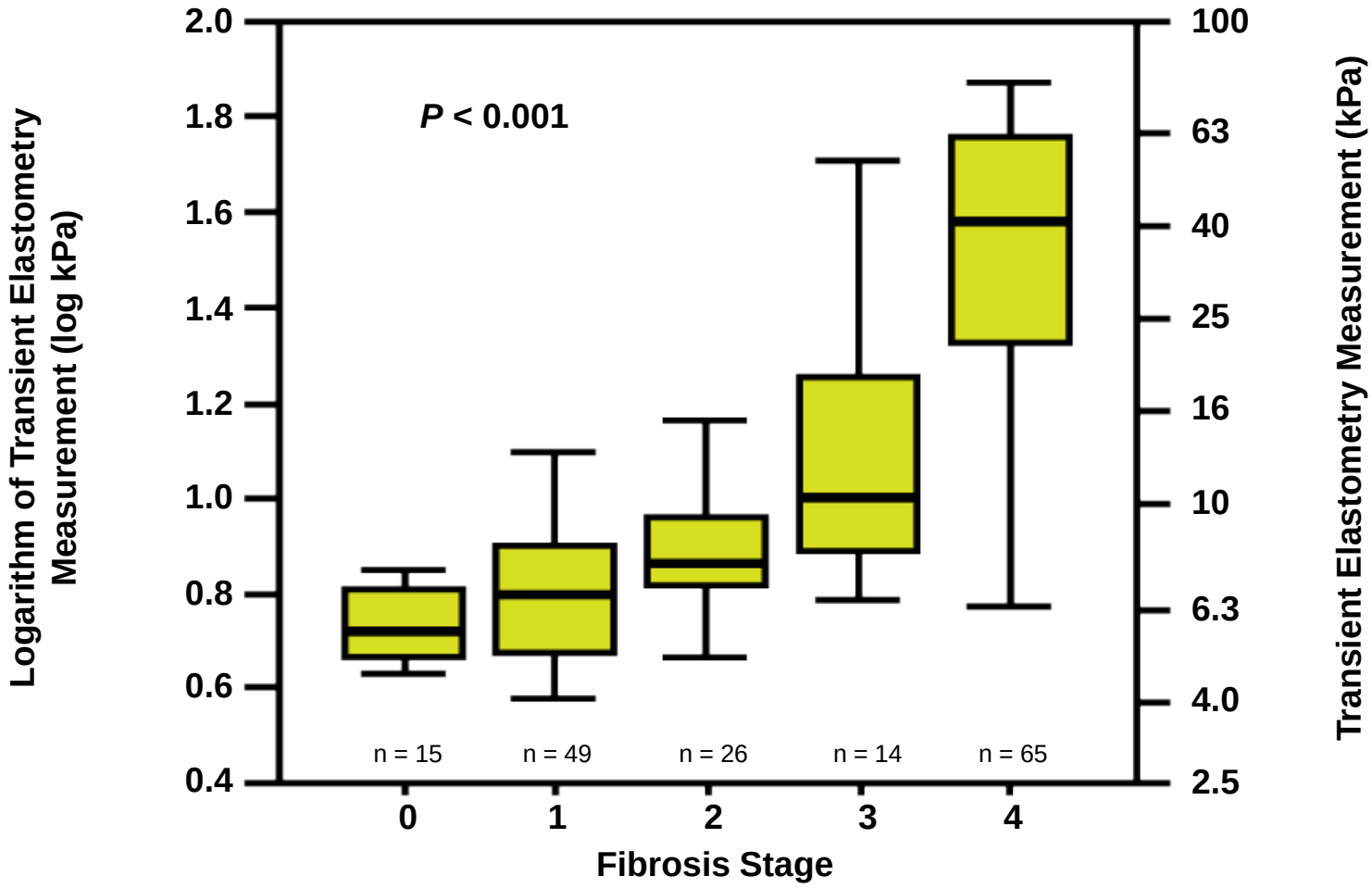
Imbert-Bismut. Lancet 2001;357:1069-75

New Tools:
Liver Stiffness by Transient Elastography

- Ultrasound-based technique
- Determines liver “stiffness”
- Correlates well with fibrosis
- No ceiling, ie, increases with worsening cirrhosis → predicts complications (eg, varices)
- Simple to use – minimal training

Liver Stiffness by Transient Elastography (Fibroscan)

- Very good for minimal fibrosis (F0-2) vs cirrhosis (F4)



Vergera. *CID.* 2007.

HHS Action Plan for the Prevention, Care and Treatment of Viral Hepatitis

By 2020, goal will be to achieve

- an increase in the proportion of persons who are aware of their hepatitis B virus infection, from 33% to 66%
- elimination of mother-to-child transmission of HBV
- an increase in the proportion of persons who are aware of their hepatitis C virus infection, from 45% to 66%
- Birth cohort initiative: screen all persons born between 1945-65 (75% of epidemic in this group)
- 25% reduction in the number of new cases of HCV infection

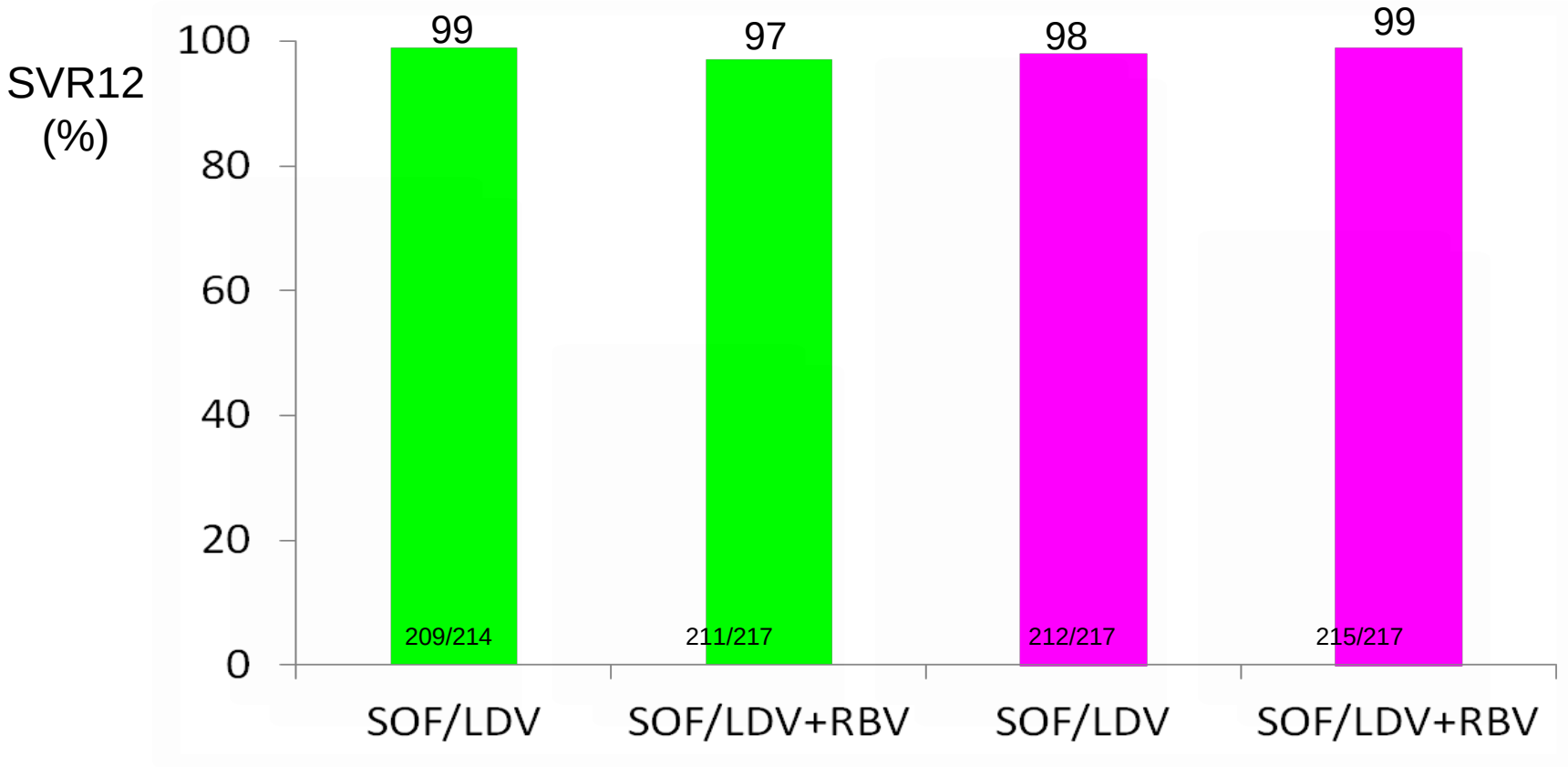
HHS Action Plan. May 12, 2011. www.hhs.gov

ION-1: Sofosbuvir + Ledipasvir (NS5A Inhibitor)

Genotype 1: Treatment Naïve, n=865

Cirrhosis in 16%

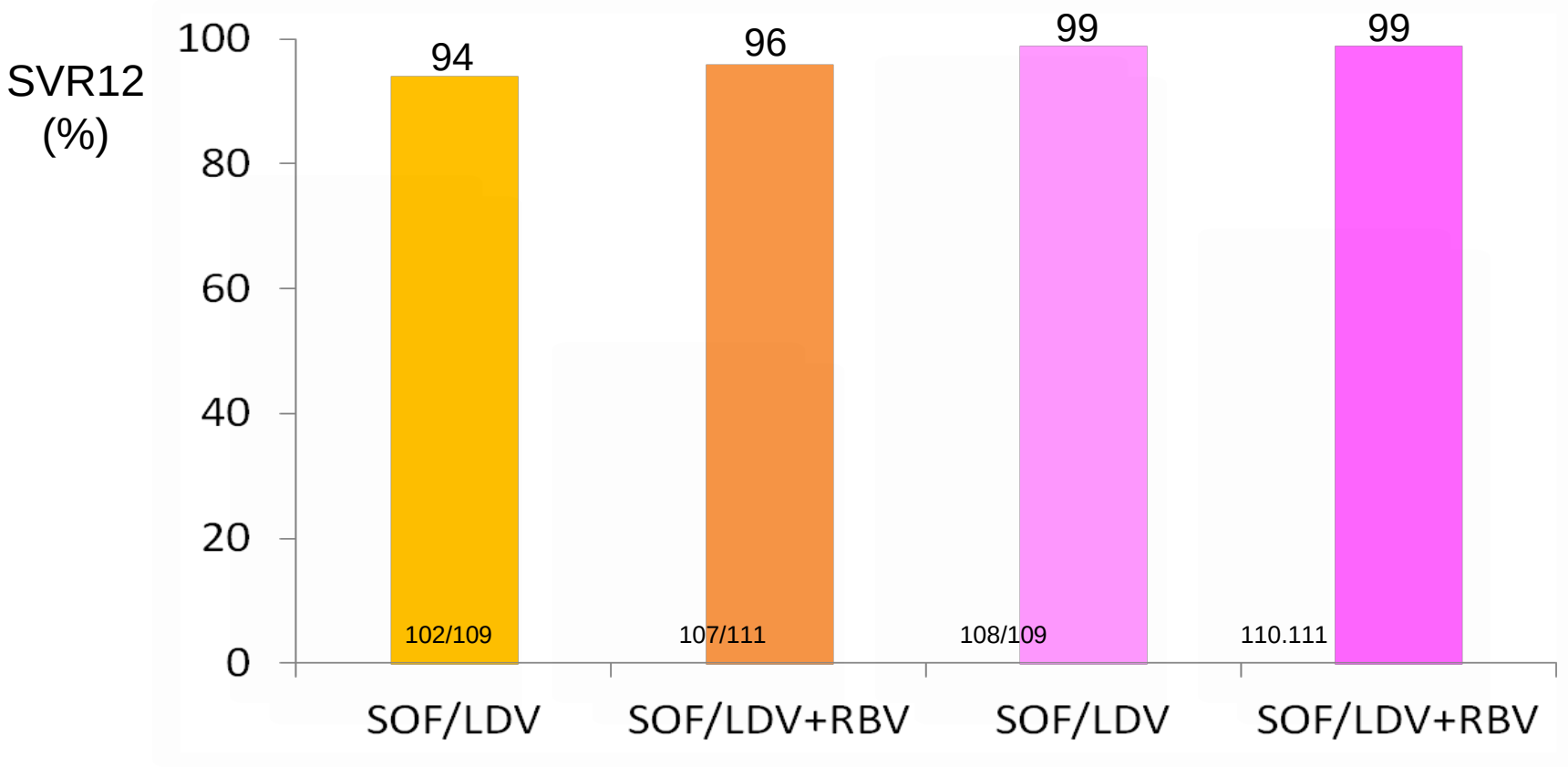
n=468



Afdhal N et al, N Engl J Med 2014;370:1889

ION-2: Sofosbuvir + Ledipasvir ± RBV

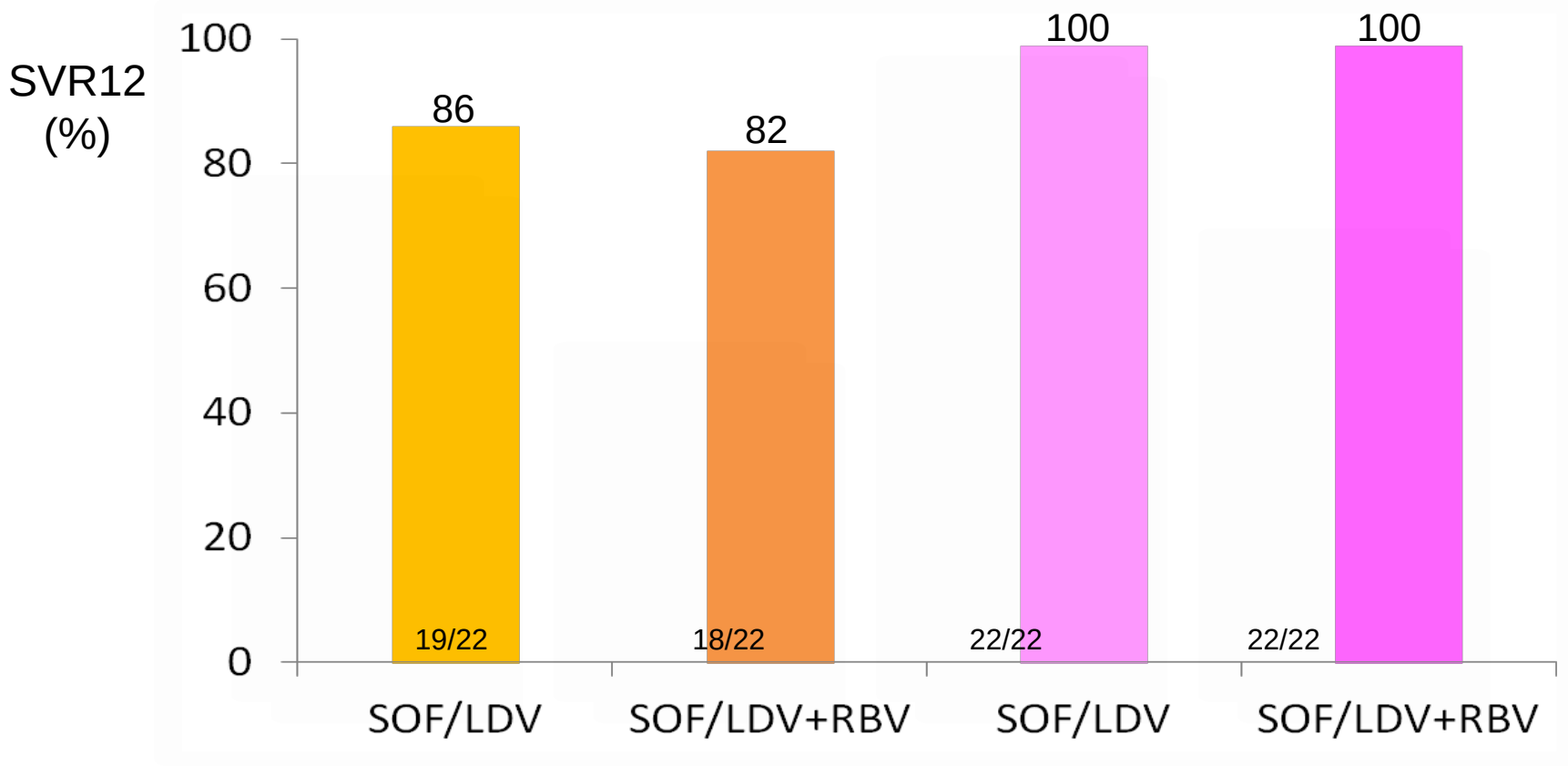
Genotype 1 Treatment Experienced
Cirrhosis in 20%
n=440



Afdhal N et al, N Engl J Med 2014;370:1483

ION-2: Sofosbuvir + Ledipasvir ± RBV

Genotype 1 Treatment Experienced
Patients With Cirrhosis

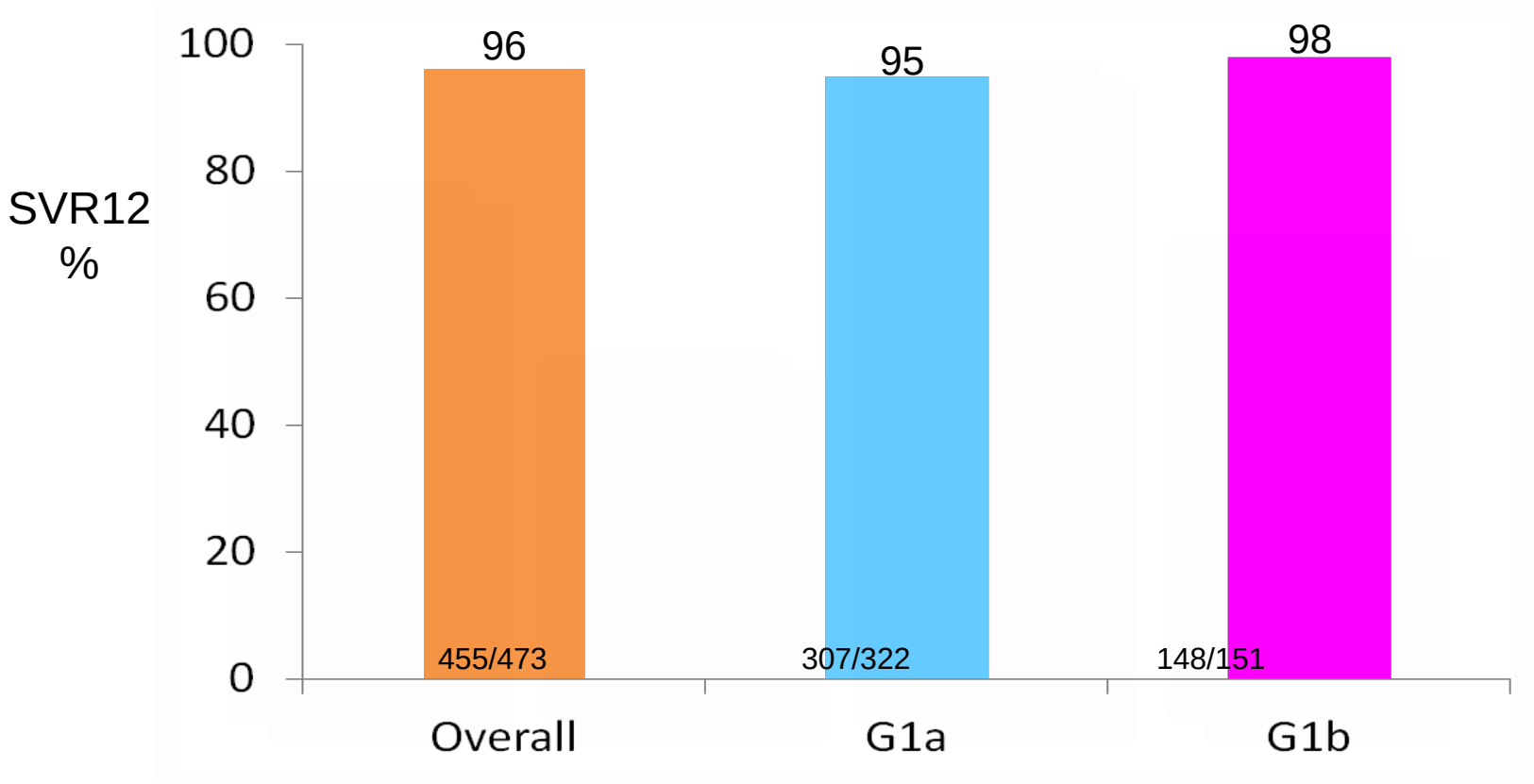


Afdhal N et al, N Engl J Med 2014;370:1483

Paritaprevir (PI)/ritonavir/Ombitasvir (NS5A) + Dasabuvir (NNI) + RBV

SAPPHIRE-1

Genotype 1, treatment naïve, noncirrhotic,12 weeks, n=473



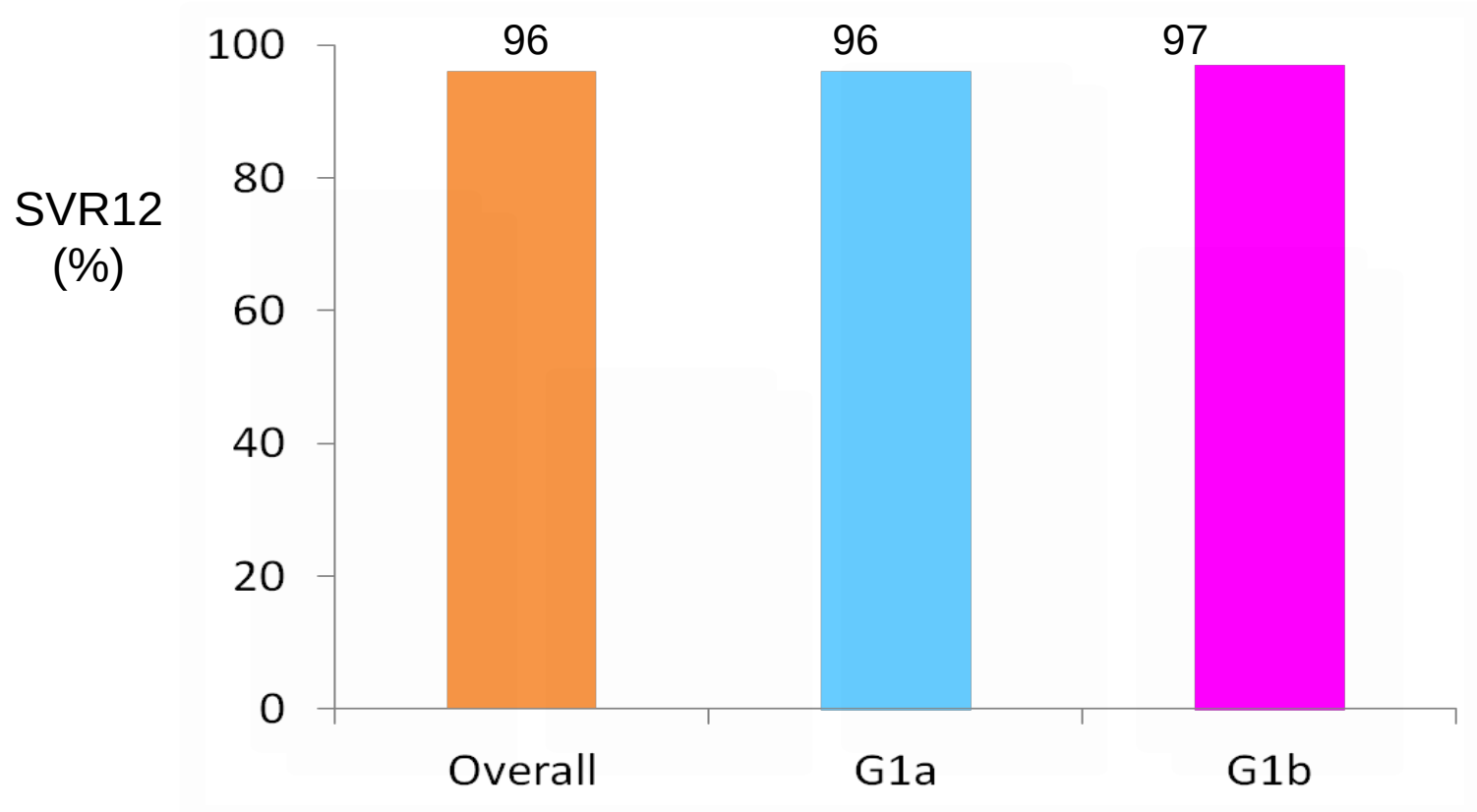
PEARL III Trial, gt1b treatment naïve (n=419): 3DAA + RBV 99%, 3DAA no RBV 99%

Feld JJ et al, N Engl J Med 2014;370:1594-1603

Paritaprevir (PI)/ritonavir/Ombitasvir (NS5A) + Dasabuvir (NNI) + RBV

SAPPHIRE-2

Genotype 1, treatment experienced, noncirrhotic, 12 weeks, n=394



PEARL II Trial, gt1b treatment experienced (n=179): 3DAA + RBV 97%, 3DAA no RBV 100%

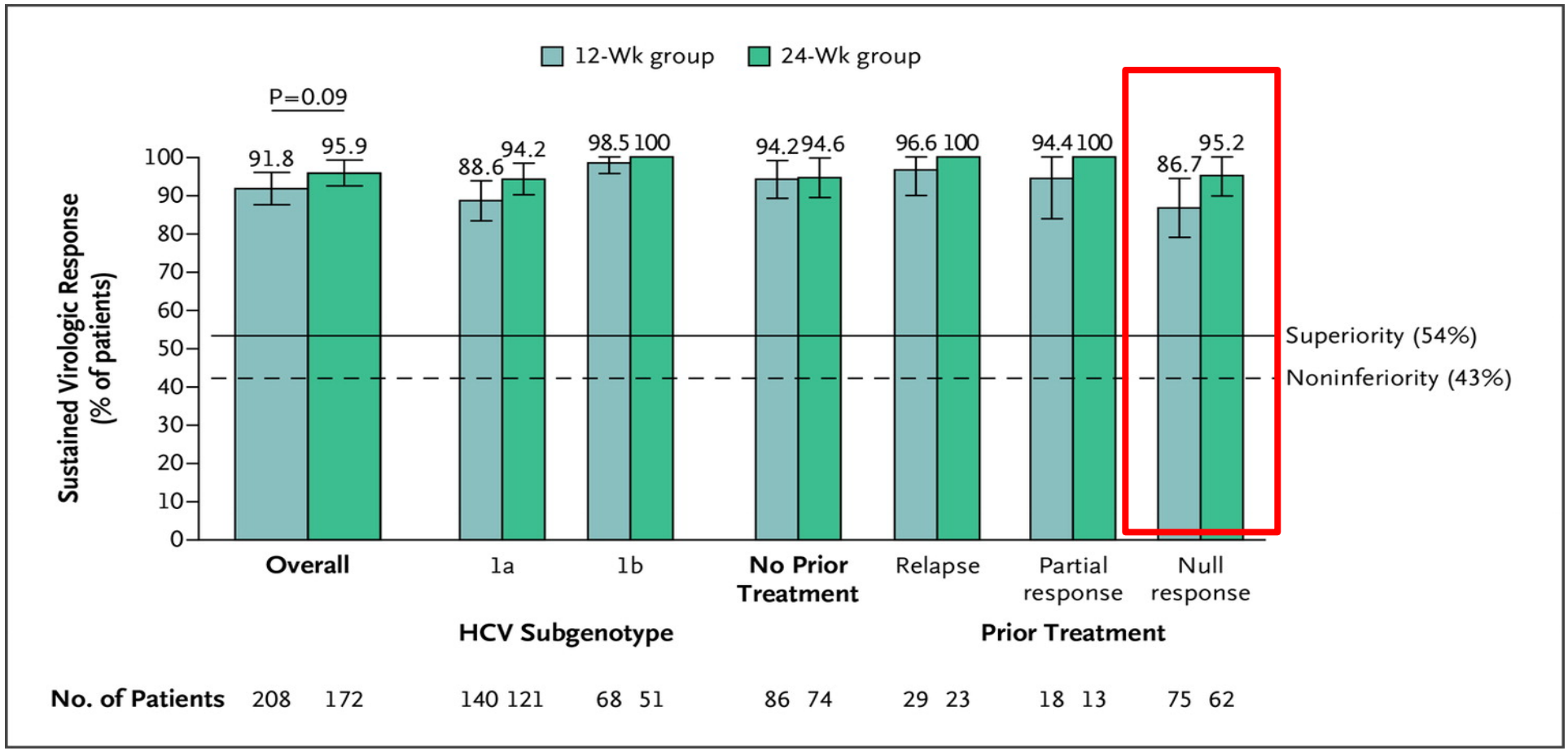
Zeuzem S et al, N Engl J Med 2014; 370:1604

Paritaprevir (PI) + Ombitasvir (NS5A) + Dasabuvir (NNI) + RBV

TURQUOISE-II

Gt1 compensated cirrhosis (naïve and experienced)

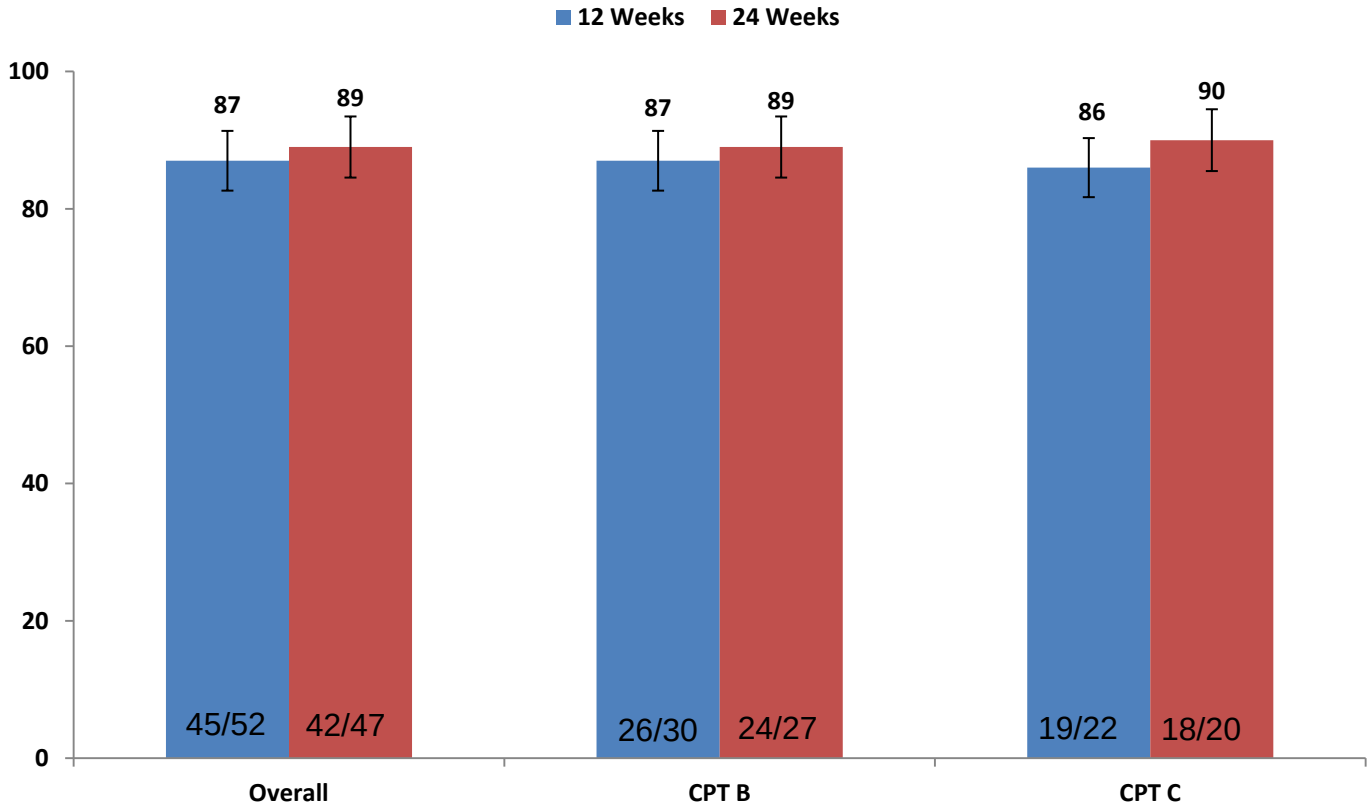
n=380



Poordad F et al, EASL 2014; NEJM 2014 370:1973

Sofosbuvir/Ledipasvir + RBV in Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

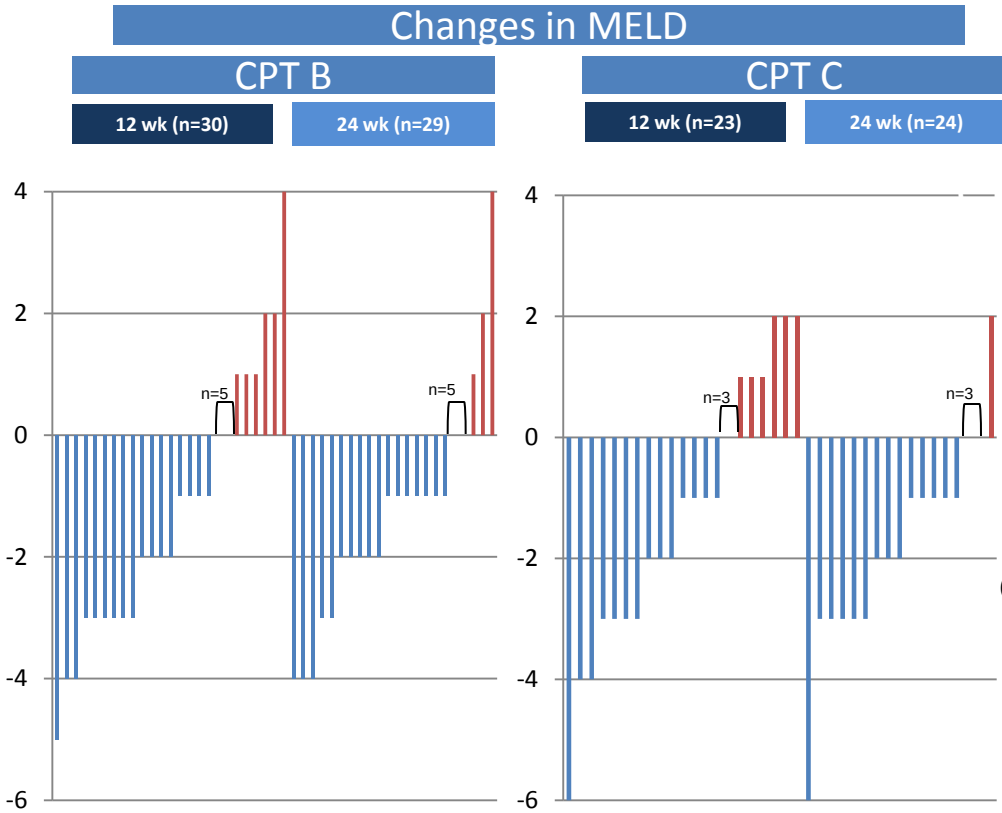
- n=99
- Randomized to SOF + LDV + RBV (600 mg w/escalation) for 12 or 24 wks
- Patients with GT 1 or 4 and decompensated cirrhosis
- Median albumin = 2.6-3.0 g/L; Median platelets = 71-88K

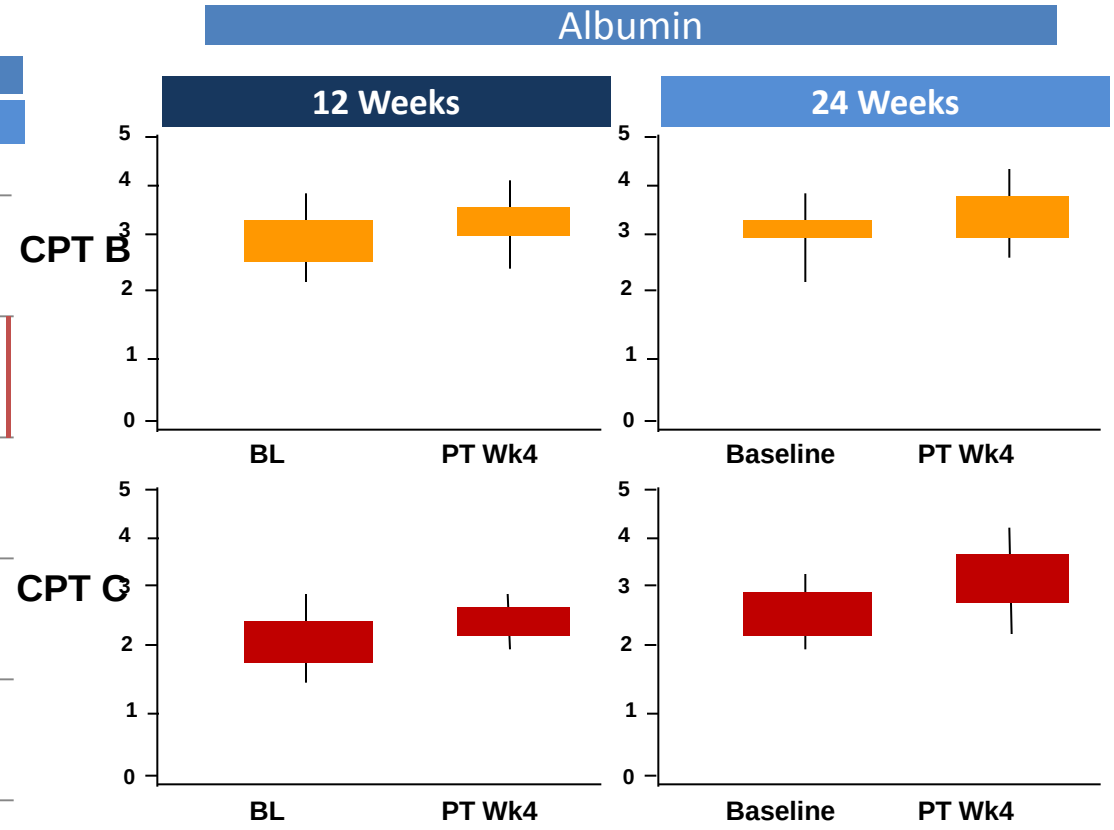


Flamm, Abst# 239, AASLD 2014

Sofosbuvir/Ledipasvir + RBV in Patients with Decompensated Cirrhosis: improved clinical status

- SAE = 10%-42% (only 4 considered treatment-related)
- 5 deaths: Septic shock (4), renal failure/cardiac arrest

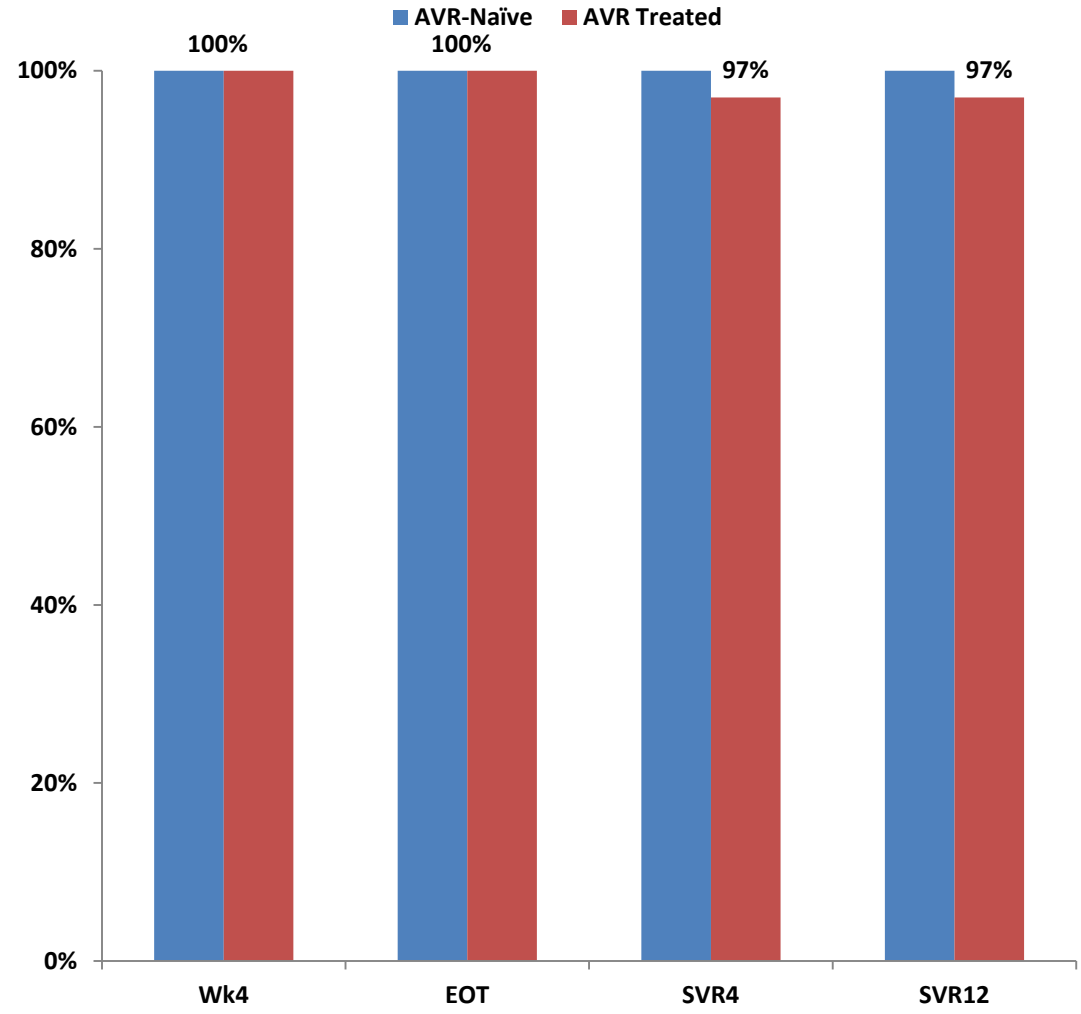




Flamm, Abst# 239, AASLD 2014

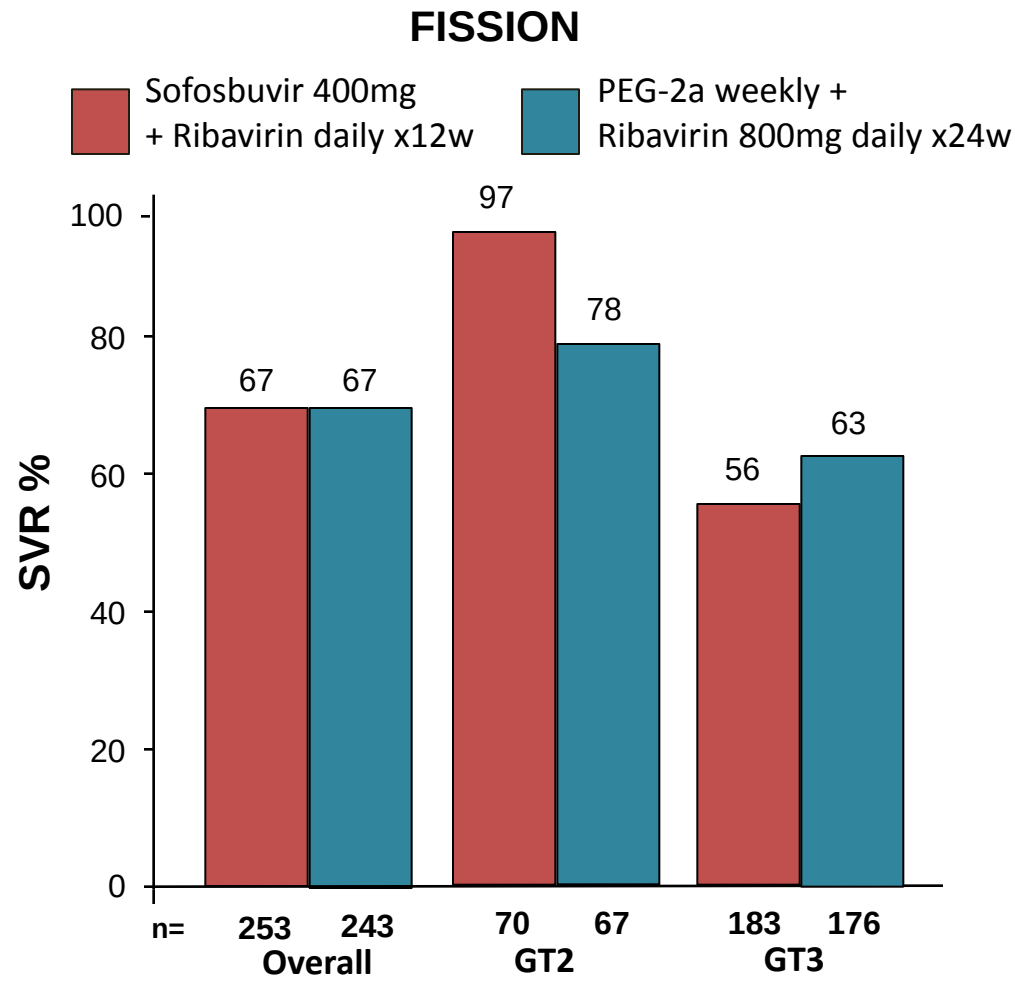
High Efficacy of Sofosbuvir/Ledipasvir for HCV GT1 in Patients Coinfected With HIV: NIAID ERADICATE Trial

- HCV, GT1, tx naïve noncirrhotic subjects (n=50) treated with SOF/LDV x12 wks
  - GT1a =74%
  - African American = 84%
  - F0-2 78%
- Arm A (n=13): ARV naïve
- Arm B (n=37): ARV treated
  - ARV: Tenofovir/FTC with Efavirenz, Rilpivirine or Raltegrevir
- No change in CD4 or HIV RNA
- No SAE or early DC due to AE



Osinusi, Abst# 84, AASLD 2014

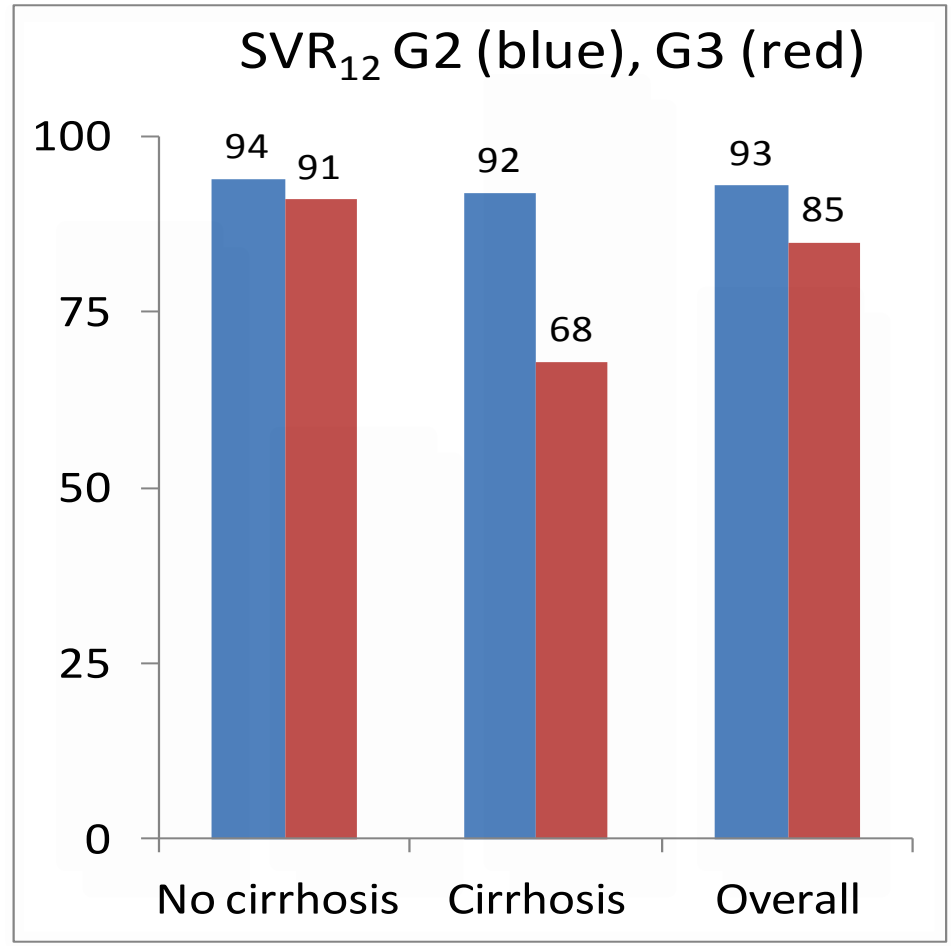
Sofosbuvir in Treatment Naïve GT 2,3 Patients



Lawitz E et al., NEJM 2013; 368:1878-87

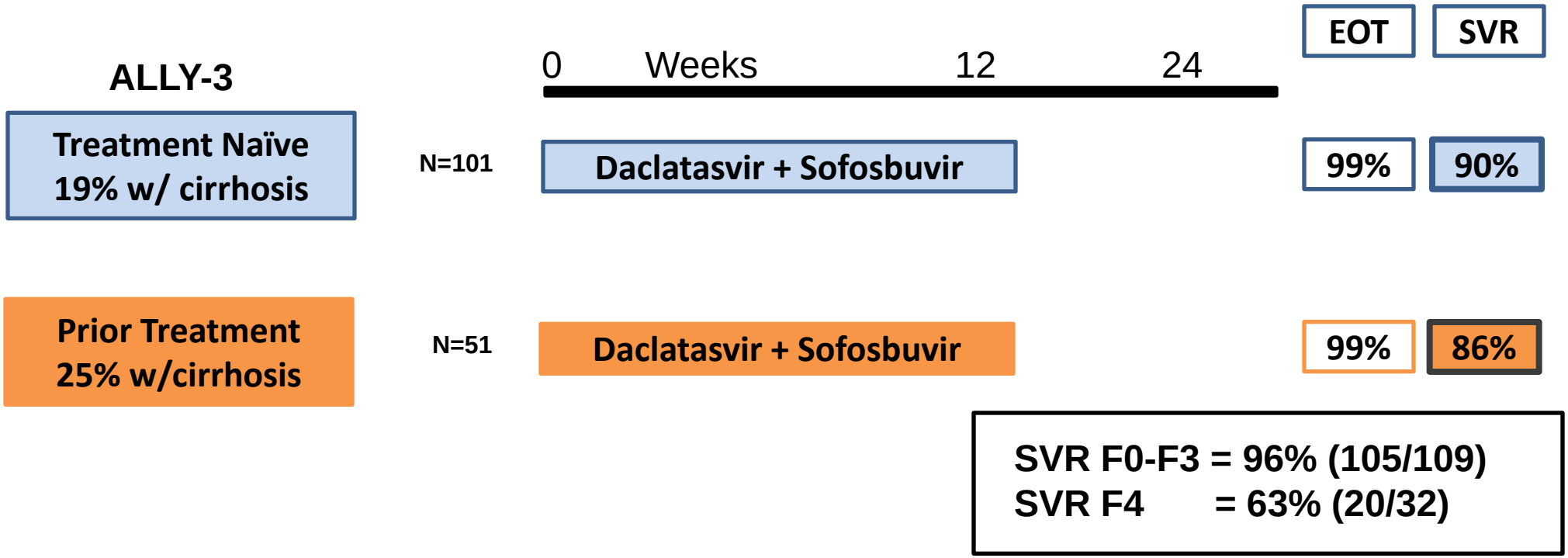
Sofosbuvir/Ribavirin for Treatment-Naïve and Experienced Patients with Genotype 2 or 3: VALENCE

- Phase 3 trial in Europe
  - Amended to treat GT3 for 24 weeks
- SOF/RBV x12W (GT2, n=73) or 24W (GT3, n=250)
  - Cirrhosis 14–23%
  - Treatment experienced 58%
- Discontinuation due to AE, n=2



Zeuzem et al, N Engl J Med 2014; 370:1993

All-Oral Combination of Daclatasvir (NS5A) and Sofosbuvir in Patients with GT 3: ALLY-3



- No SAEs related to treatment, no premature D/C due to AEs
- Most AE mild: fatigue, headache, nausea, diarrhea

Nelson, LB-3, AASLD 2014

Summary

- All oral, tolerable, high efficacy regimens (>90% cure) now available
- Several roads to the same IFN-free destination
  - High barrier compounds desirable for simplified regimens but can be matched by combinations of DAA classes
  - High SVR rates now possible in historically difficult populations (nulls, cirrhotics, decompensated, post-LT, HIV)
- Timelines for FDA approval
  - Dec 2013
    - Sofosbuvir + P/R, Simeprevir + P/R for gt 1
    - Sofosbuvir + RBV for gt 2/3
  - Oct 2014
    - Sofosbuvir + simeprevir for gt1
    - Sofosbuvir/ledipasvir for gt1
  - Dec 2014
    - Paritaprevir/r/ombitasvir + dasabuvir +/- RBV for gt 1
  - July 2015
    - Daclatasvir + sofosbuvir for gt 3
- Beyond: grazoprevir/elbasvir +/- RBV, ASV/DCV/BCV

Who should be treated and how?

- Genotype 1
  - Sofosbuvir + ledipasvir x 8-24W (TE cirrhosis)
  - 1a: Paritaprevir/r/ombitasvir + dasabuvir + RBV x 12-24W (cirrhosis)
  - 1b: Paritaprevir/r/ombitasvir + dasabuvir x 12W
  - Sofosbuvir + simeprevir x 12-24W (cirrhosis)
- Genotype 2
  - SOF/RBV x 12W (naïve and experienced)
  - Extend to 16W in cirrhotics
- Genotype 3
  - SOF/RBV x 24W
  - PEG/RBV/SOF x 12W
  - Daclatasvir and Sofosbuvir x 12 wks (noncirrhotic)
- Ideally: all treated
- Priority: F3-4, extrahepatic disease, symptomatic
- www.hcvguidelines.org

Summary

- HAV
  - vaccine-preventable
- HBV
  - vaccine-preventable
  - chronicity dictated by age at exposure
  - replication is associated with more severe outcomes
  - therapeutic strategies therefore aimed at replicative HBV
- HCV
  - not likely to be vaccine-preventable
  - much more likely to be clinically silent
  - highest rates of chronicity
  - curable!
  - strongly consider evaluating with liver biopsy (gt 1)