

Infectious and Metabolic Hepatitis

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Disclosures

- Research Support/Grants
 - Abbvie
 - Gilead
 - Merck
 - Janssen
 - Boehringer Ingelheim
 - BMS
 - Roche
 - Synlogic
 - Kaleido

Liver disease an important cause of mortality

10 Leading Causes of Death by Age Group, United States – 2014											
Rank	Age Groups										Total
	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	
1	Congenital Anomalies 4,746	Unintentional Injury 1,216	Unintentional Injury 730	Unintentional Injury 750	Unintentional Injury 11,836	Unintentional Injury 17,357	Unintentional Injury 16,048	Malignant Neoplasms 44,834	Malignant Neoplasms 115,282	Heart Disease 489,722	Heart Disease 614,348
2	Short Gestation 4,173	Congenital Anomalies 399	Malignant Neoplasms 436	Suicide 425	Suicide 5,079	Suicide 6,569	Malignant Neoplasms 11,267	Heart Disease 34,791	Heart Disease 74,473	Malignant Neoplasms 413,885	Malignant Neoplasms 591,699
3	Maternal Pregnancy Comp. 1,574	Homicide 364	Congenital Anomalies 192	Malignant Neoplasms 416	Homicide 4,144	Homicide 4,159	Heart Disease 10,368	Unintentional Injury 20,610	Unintentional Injury 18,030	Chronic Low. Respiratory Disease 124,693	Chronic Low. Respiratory Disease 147,101
4	SIDS 1,545	Malignant Neoplasms 321	Homicide 123	Congenital Anomalies 156	Malignant Neoplasms 1,569	Malignant Neoplasms 3,624	Suicide 6,706	Suicide 8,767	Chronic Low. Respiratory Disease 16,492	Cerebro-vascular 113,308	Unintentional Injury 136,053
5	Unintentional Injury 1,161	Heart Disease 149	Heart Disease 69	Homicide 156	Heart Disease 953	Heart Disease 3,341	Homicide 2,588	Liver Disease 8,627	Diabetes Mellitus 13,342	Alzheimer's Disease 92,604	Cerebro-vascular 133,103
6	Placenta Cord. Membranes 965	Influenza & Pneumonia 109	Chronic Low. Respiratory Disease 68	Heart Disease 122	Congenital Anomalies 377	Liver Disease 725	Liver Disease 2,582	Diabetes Mellitus 6,062	Liver Disease 12,792	Diabetes Mellitus 54,161	Alzheimer's Disease 93,541
7	Bacterial Sepsis 544	Chronic Low Respiratory Disease 53	Influenza & Pneumonia 57	Chronic Low Respiratory Disease 71	Influenza & Pneumonia 199	Diabetes Mellitus 709	Diabetes Mellitus 1,999	Cerebro-vascular 5,349	Cerebro-vascular 11,727	Unintentional Injury 48,295	Diabetes Mellitus 76,488
8	Respiratory Distress 460	Septicemia 53	Cerebro-vascular 45	Cerebro-vascular 43	Diabetes Mellitus 181	HIV 583	Cerebro-vascular 1,745	Chronic Low. Respiratory Disease 4,402	Suicide 7,527	Influenza & Pneumonia 44,836	Influenza & Pneumonia 55,227
9	Circulatory System Disease 444	Benign Neoplasms 38	Benign Neoplasms 26	Influenza & Pneumonia 41	Chronic Low Respiratory Disease 178	Cerebro-vascular 579	HIV 1,174	Influenza & Pneumonia 2,731	Septicemia 5,709	Nephritis 39,957	Nephritis 48,146
10	Neonatal Hemorrhage 441	Perinatal Period 38	Septicemia 33	Benign Neoplasms 38	Cerebro-vascular 177	Influenza & Pneumonia 549	Influenza & Pneumonia 1,125	Septicemia 2,514	Influenza & Pneumonia 5,390	Septicemia 29,124	Suicide 42,773

Overview

- Viral hepatitis
- Nonalcoholic fatty liver disease (NAFLD)

Viral Hepatitis - Overview

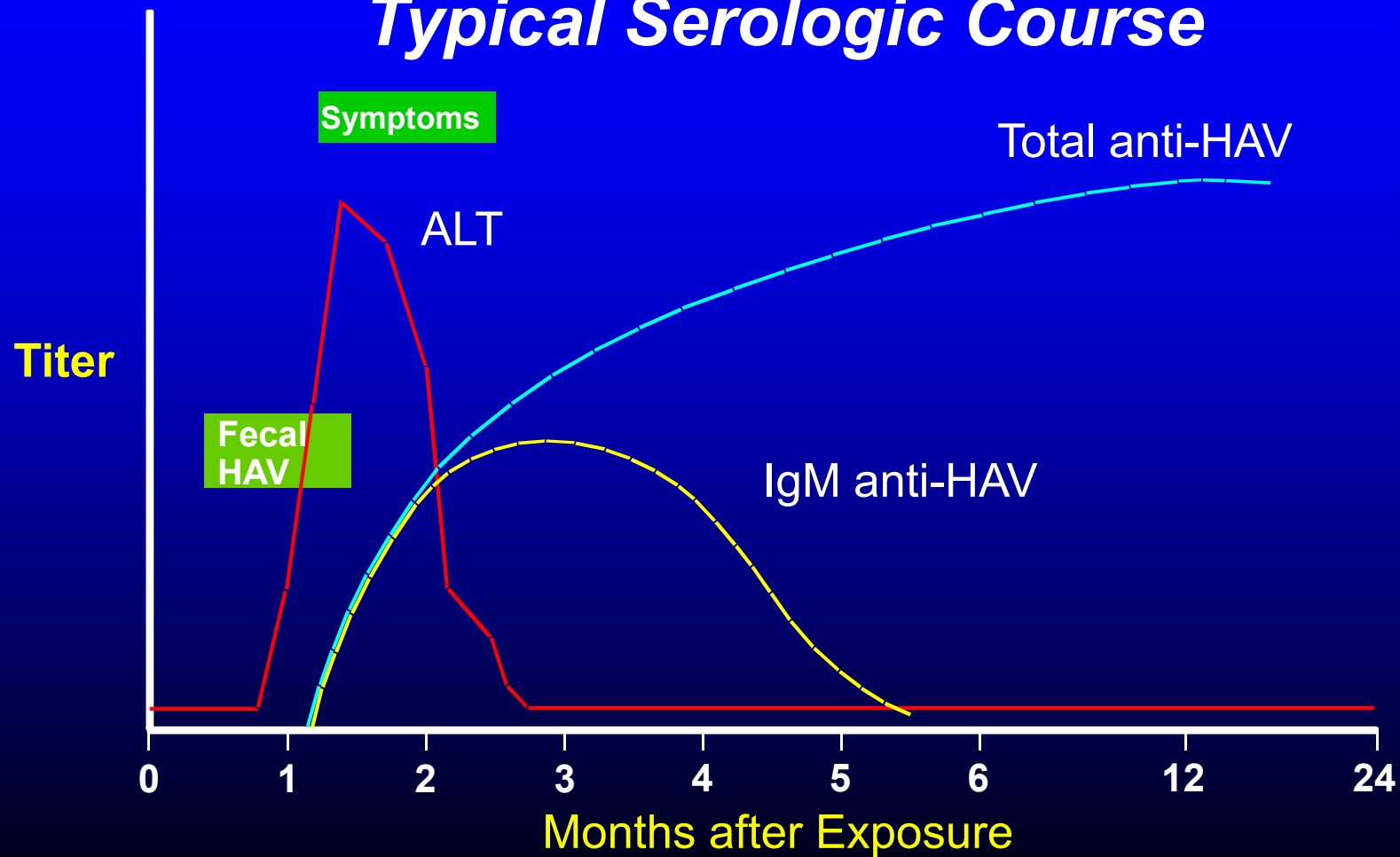
	Type of Hepatitis				
	A	B	C	D	E
Source of virus	feces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	feces
Route of transmission	fecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	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

Hepatitis A Virus Transmission

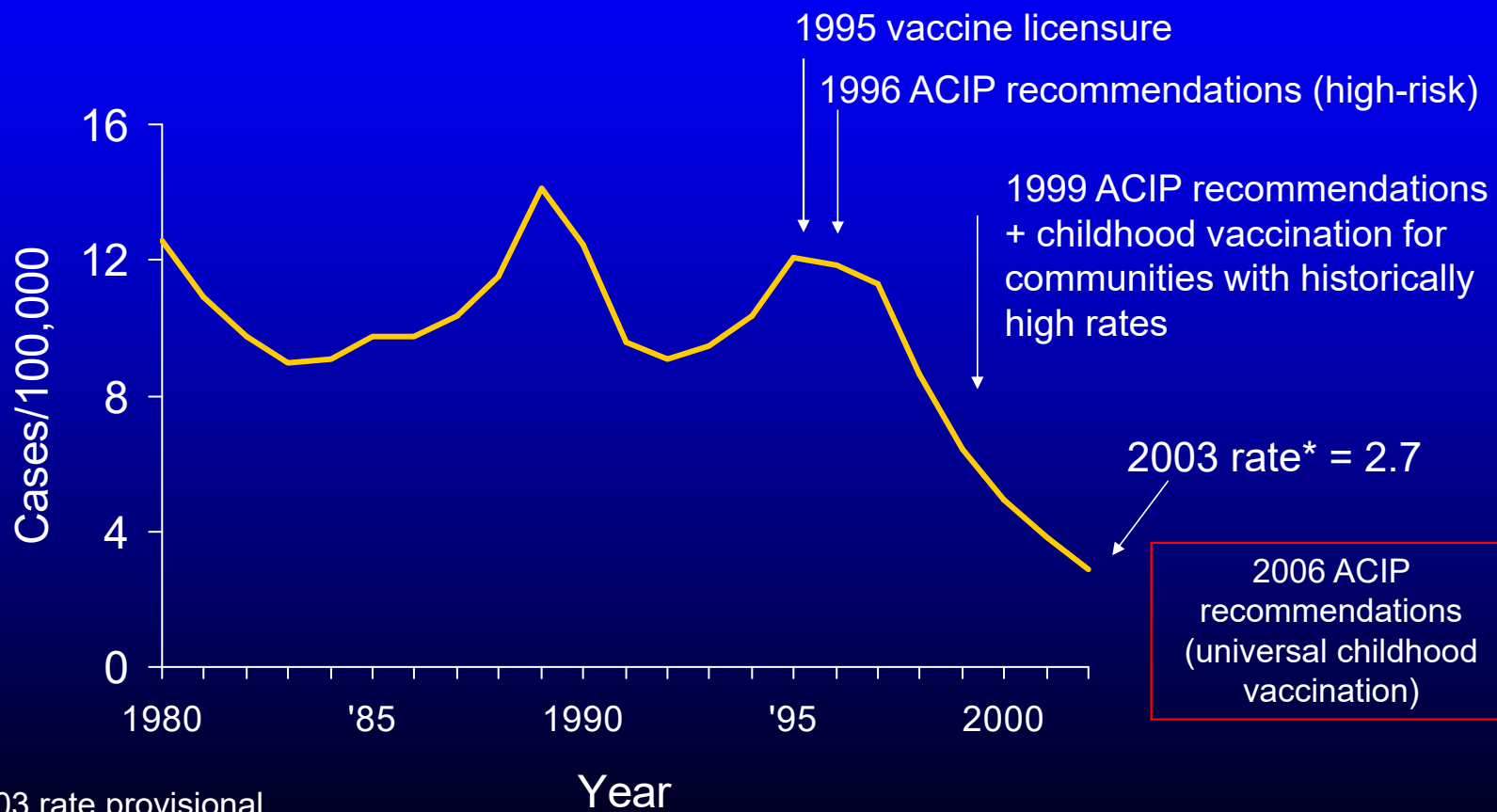
- Close personal contact
(household contact, sex contact, day care centers)
- Contaminated food, water
(infected food handlers, raw shellfish)
- Blood exposure (rare)
(injection drug use, transfusion)

Hepatitis A Virus Infection

Typical Serologic Course



Hepatitis A Incidence, United States, 1980-2003*



Monovalent Hepatitis A Vaccine, Inactivated

- Universal: all children 1-2yo
- recommended: travel to endemic areas (long notice), risk groups, CLD

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

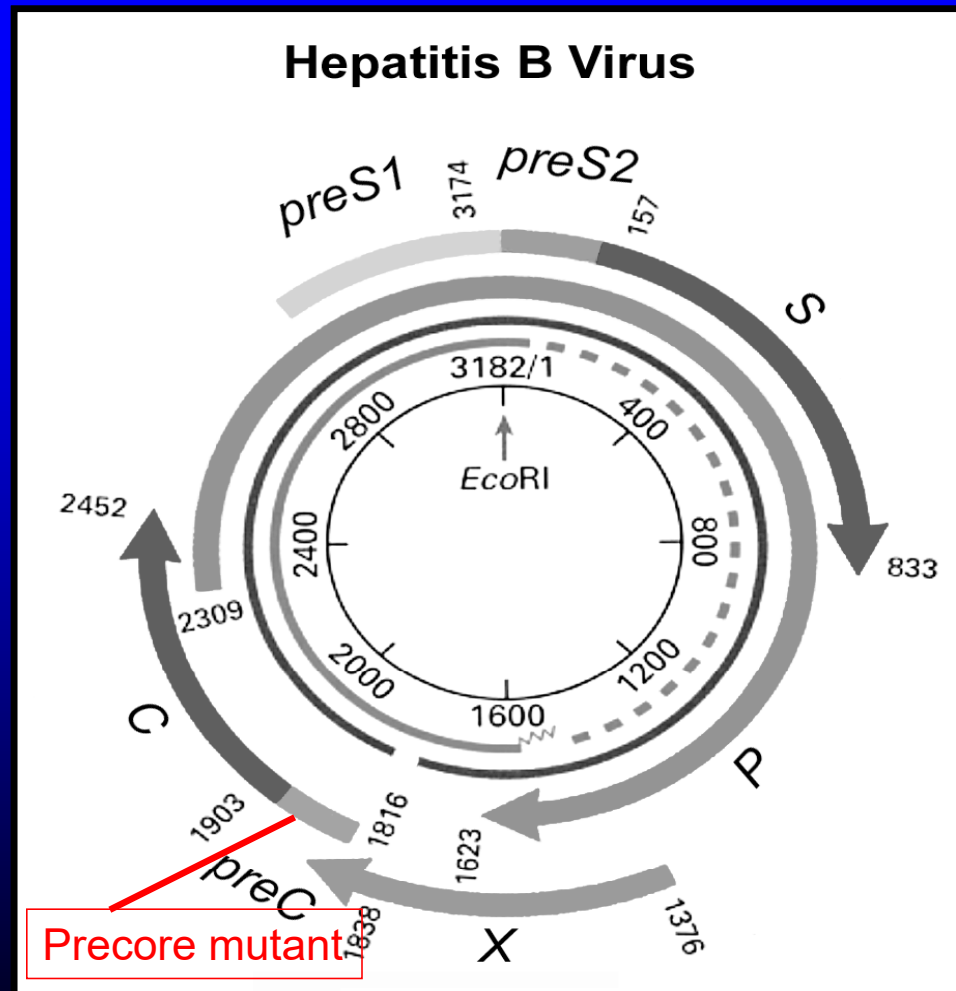
1. *Havrix* Prescribing Information. See Dosage and Administration. SmithKline Beecham Pharmaceuticals. Philadelphia, PA. Nov. 2001.

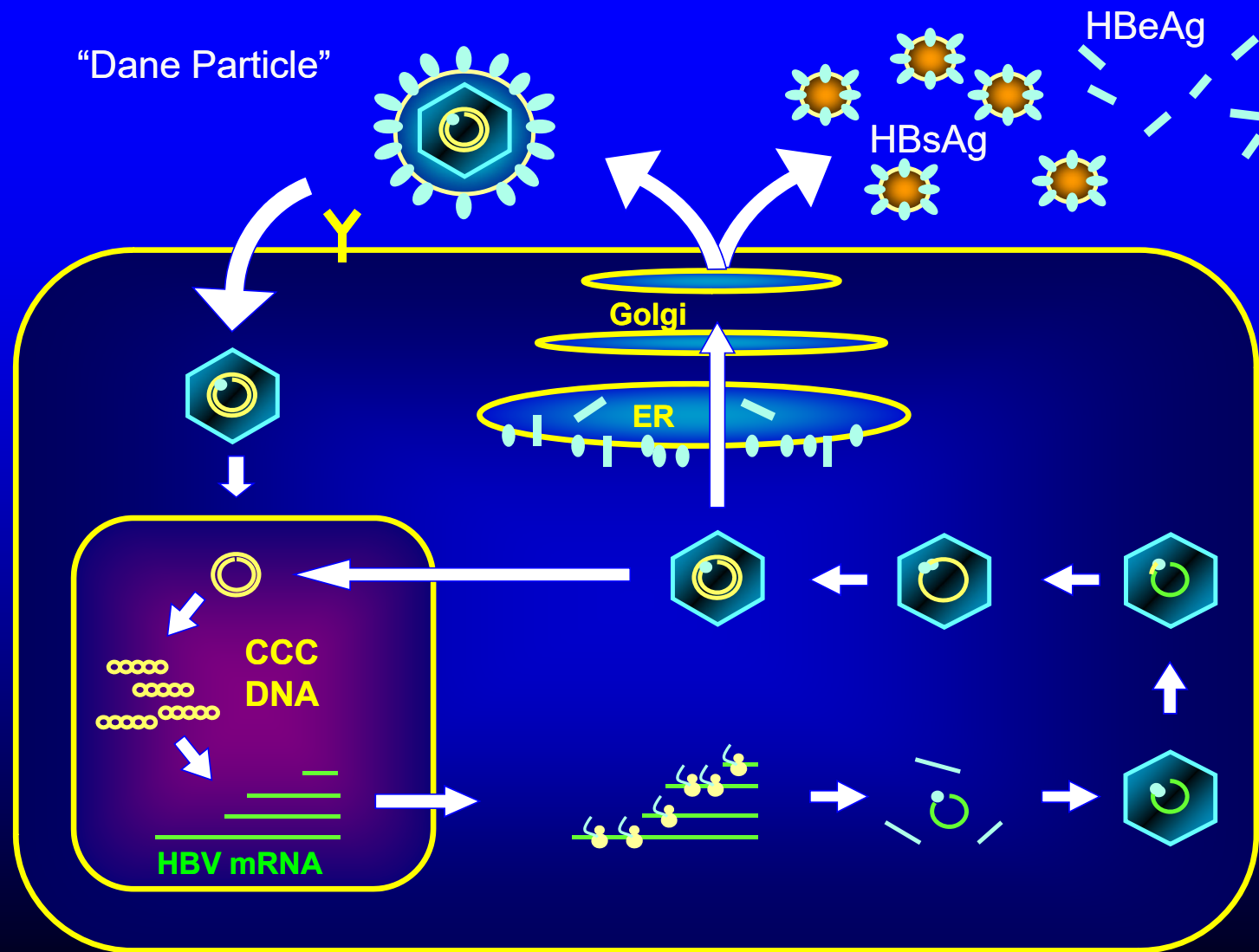
2. *Vaqta* Prescribing Information. Merck & Co, Inc. West Point, PA; 2001.

See complete prescribing information.

Hepatitis B Virus

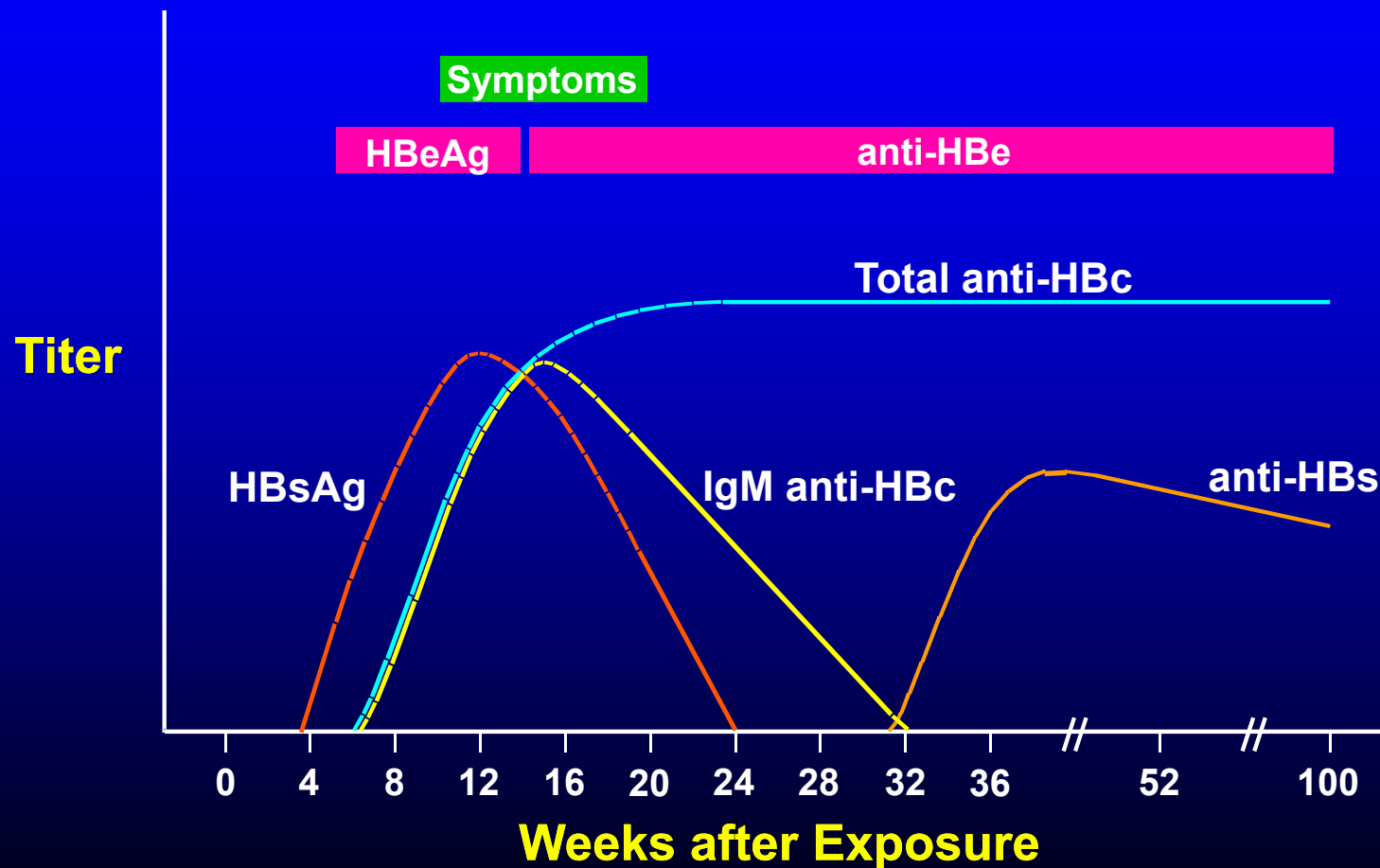
- Small partially double-stranded DNA virus
- Prototype of the *hepadnavirus* family
- 4 major gene products





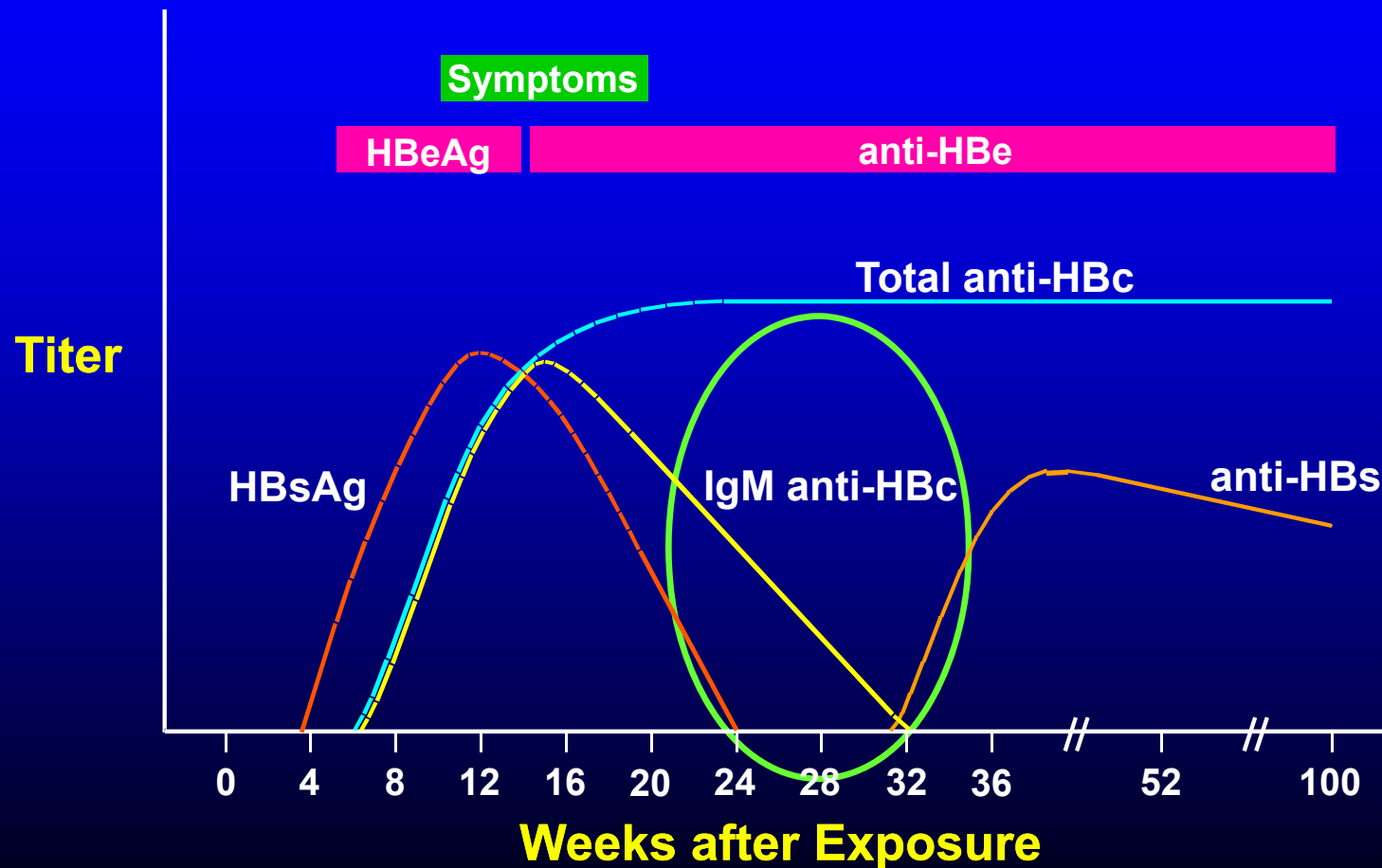
Acute HBV Infection with Recovery

Typical Serologic Course



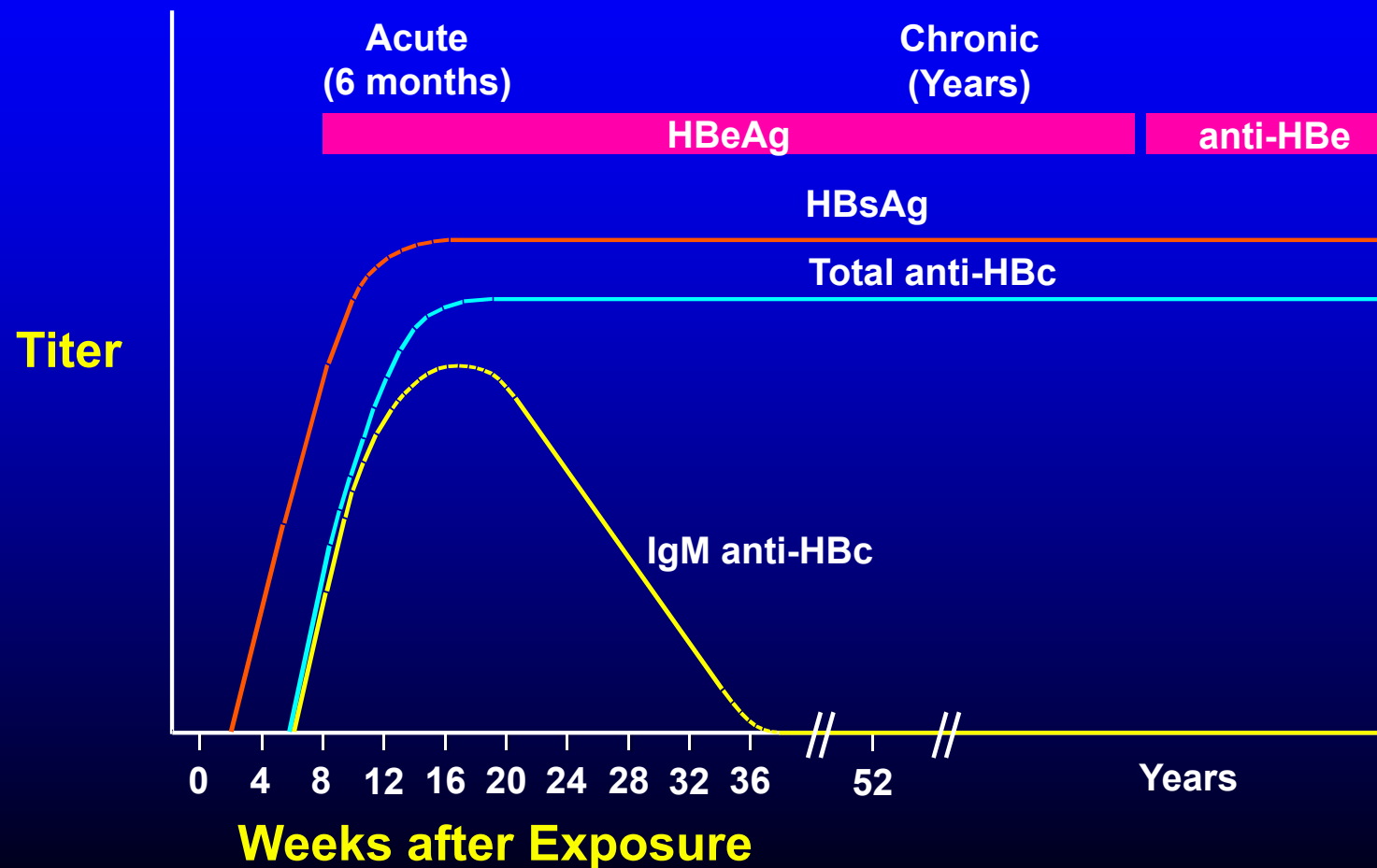
Acute HBV Infection with Recovery

Typical Serologic Course

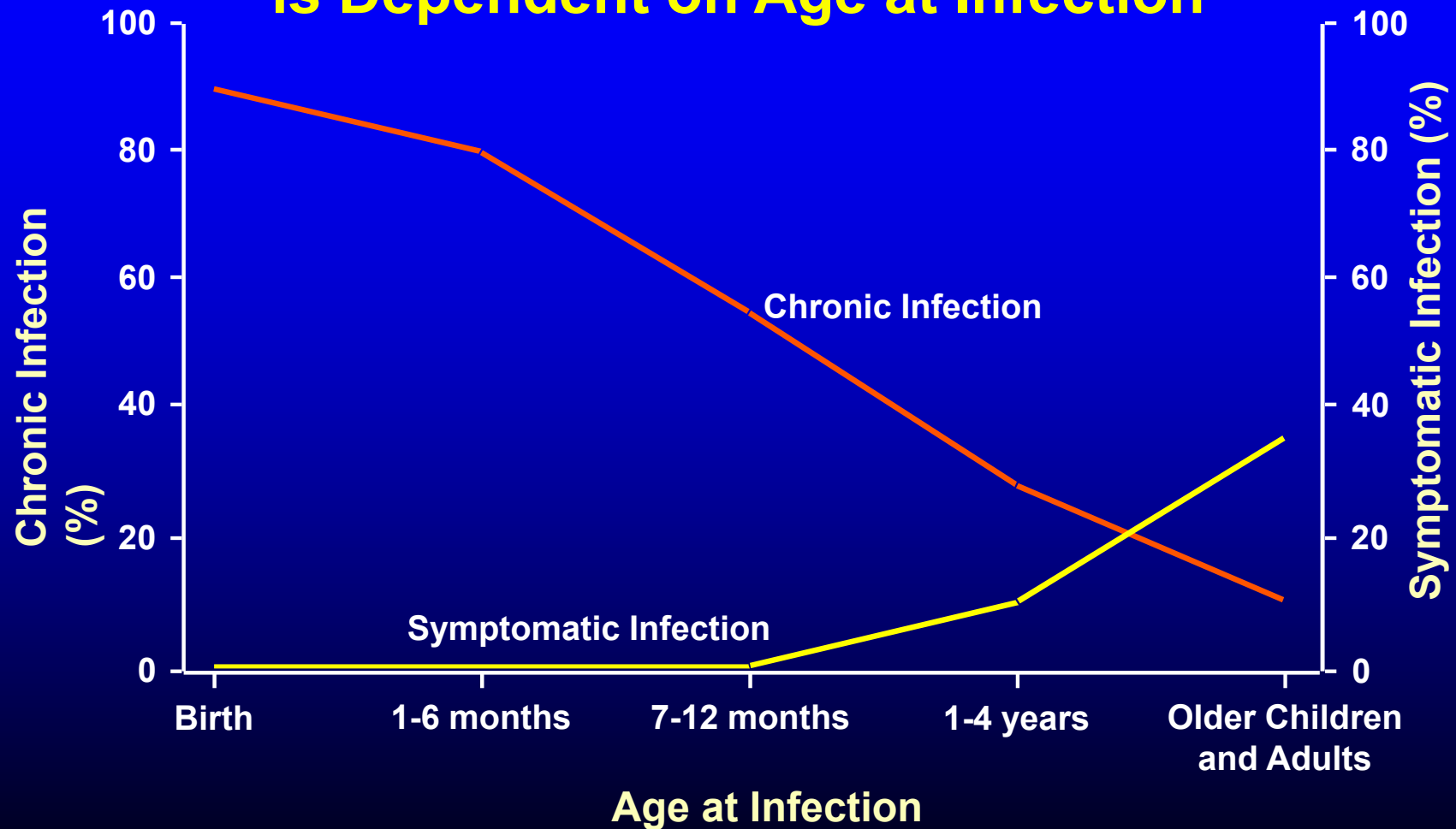


Progression to Chronic HBV Infection

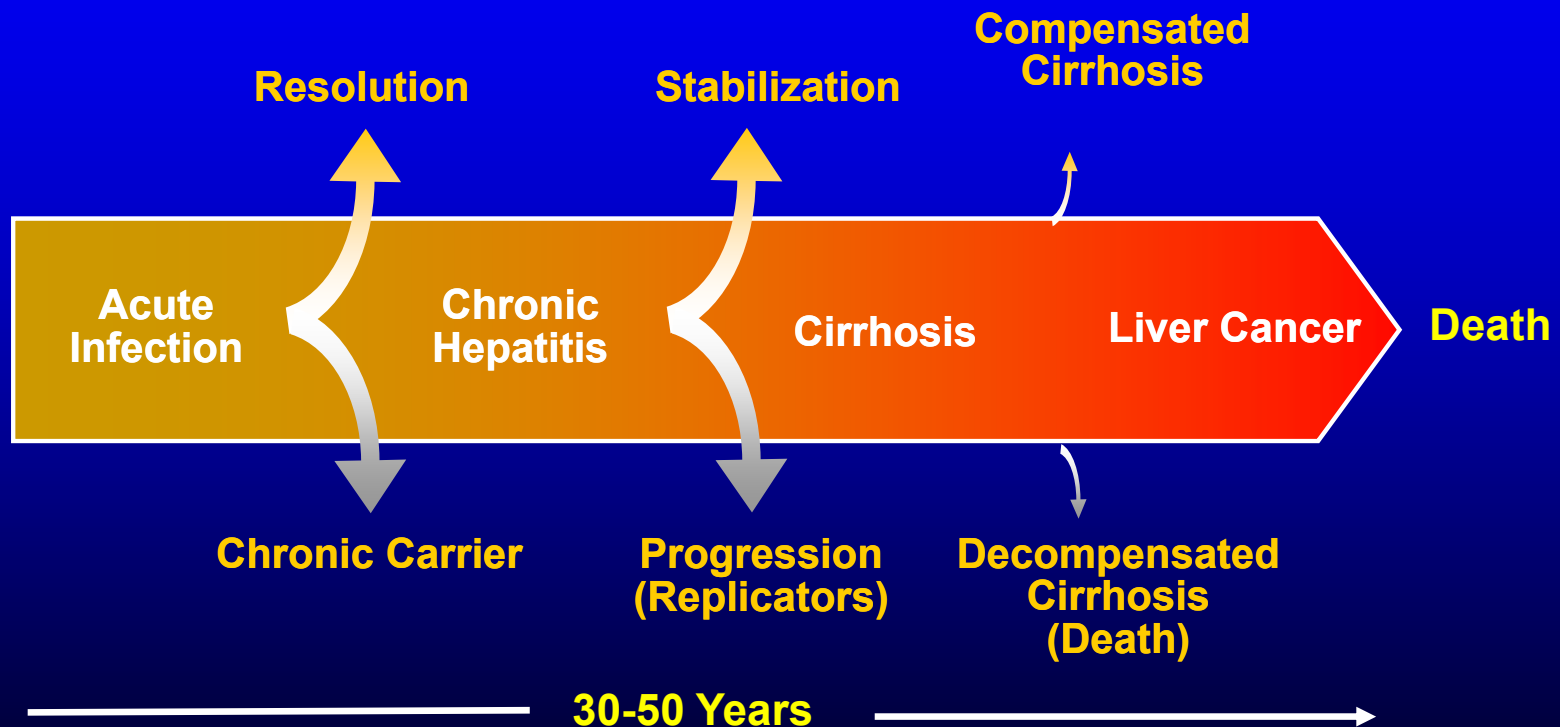
Typical Serologic Course



Outcome of HBV Infection is Dependent on Age at Infection



Natural History of Chronic HBV Infection



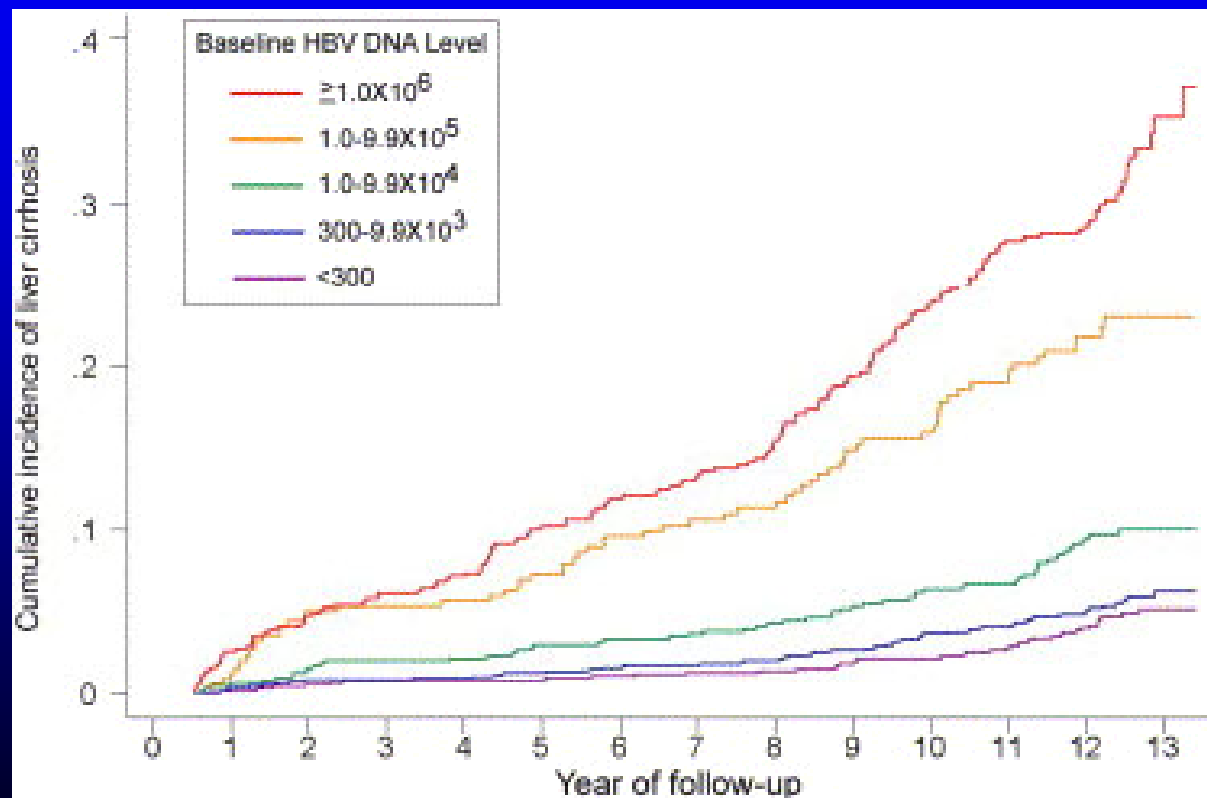
Adapted from Feitelson, *Lab Invest*, 1994.

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 DNA level predicts clinical outcome



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

Approved agents for chronic HBV

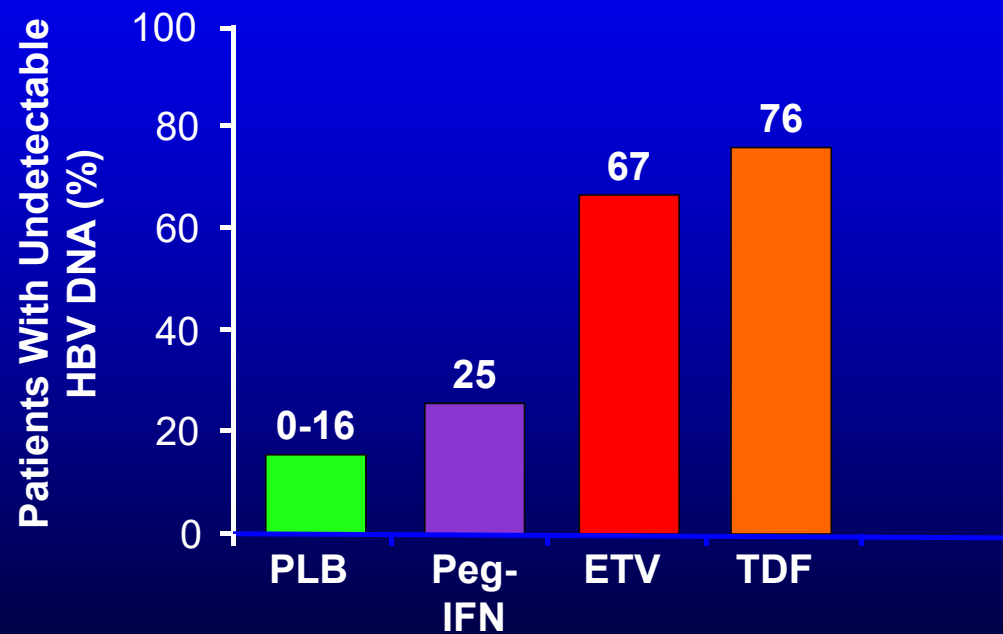
- Interferon-alfa-2b
- Lamivudine
- Adefovir
- Entecavir
- Tenofovir / tenofovir alafenamide
- Telbivudine
- PEG-interferon-alfa-2a

Other approved agents with anti-HBV activity

- Emtricitabine

Virologic Response in HBeAg+ Patients (Undetectable HBV DNA at Wk 48-52)

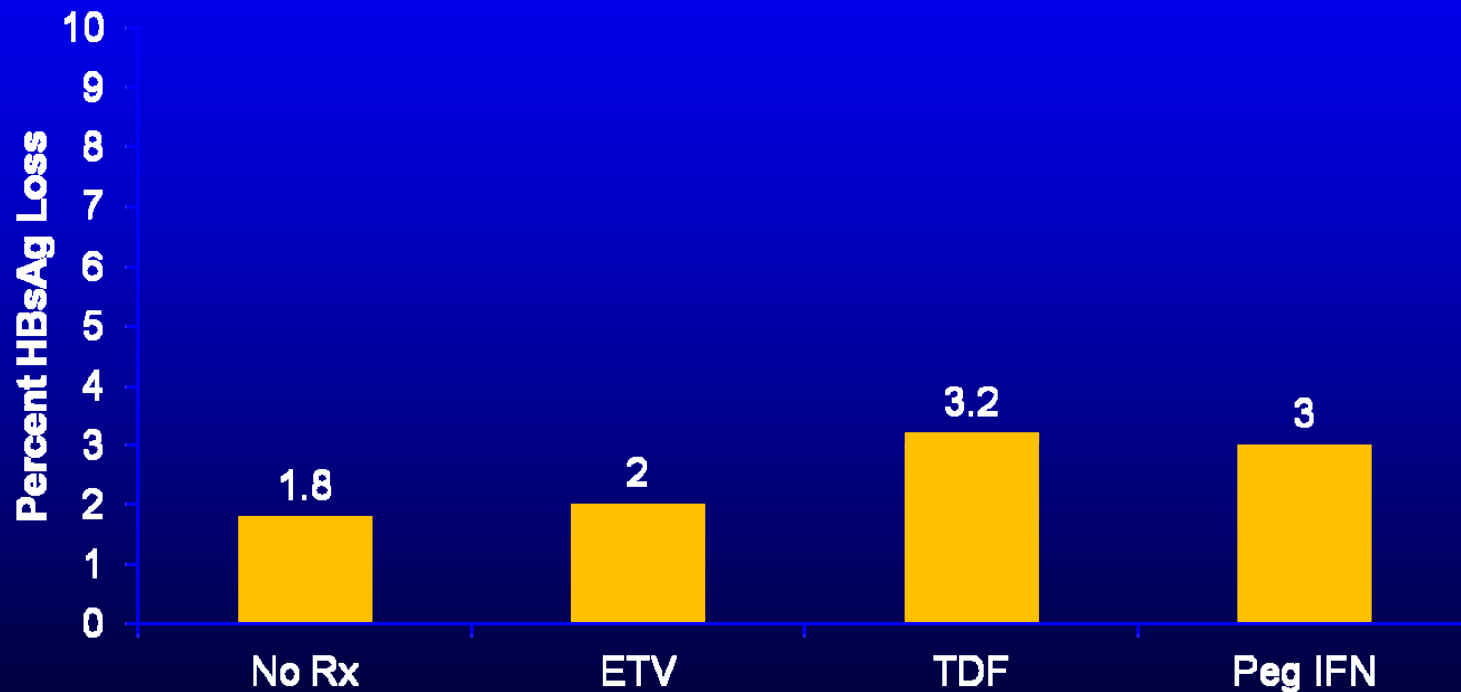
Not head-to-head trials



*By PCR based assay (LLD ~ 50 IU/mL).

Lok AS, et al. Hepatology. 2007;45:507-539.
Marcellin P et al NEJM 2008.

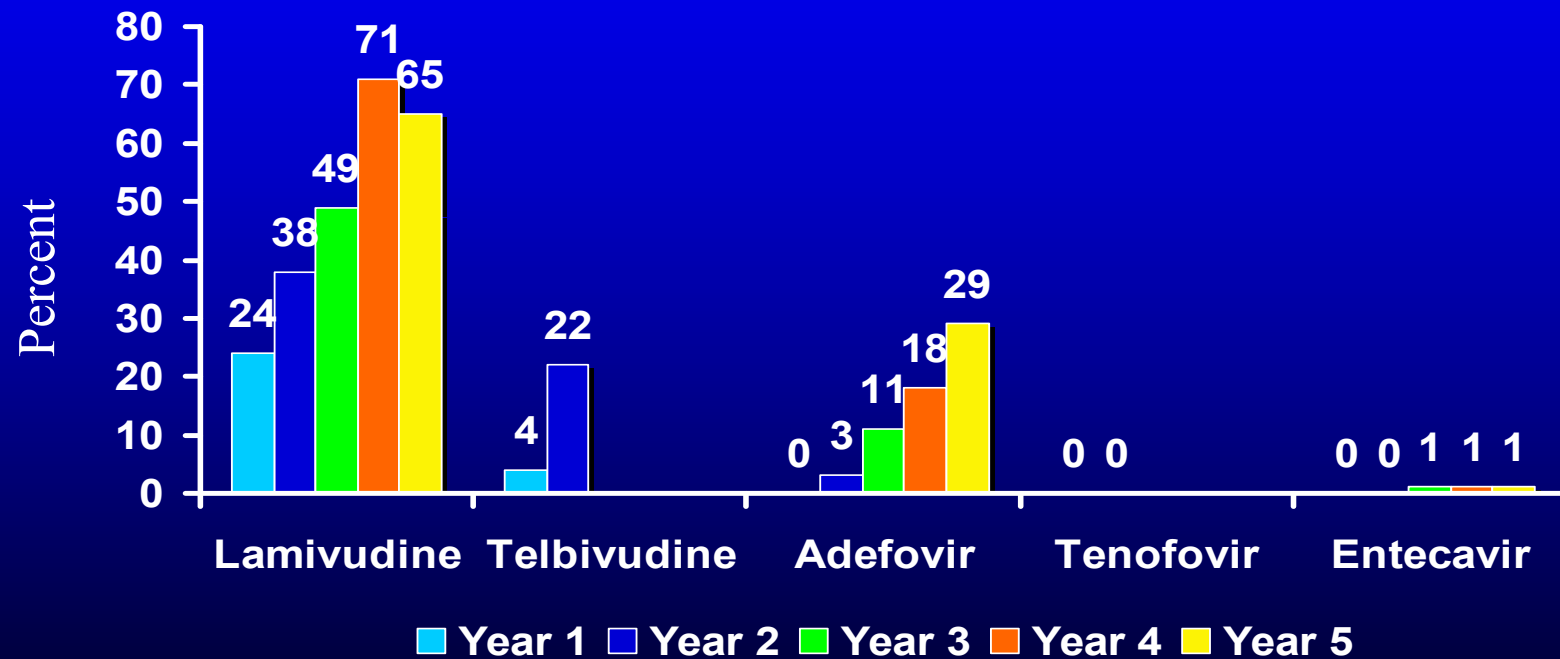
HBsAg loss During Therapy HBeAg positive CHB at 1 Year



Chang et al New Engl J Med 2006;354:1001; Lai et al New Engl J Med 2007;357:2576; Heathcote Hepatology 2007;46:LB6; Lau New Engl J Med 2005;352:2682;

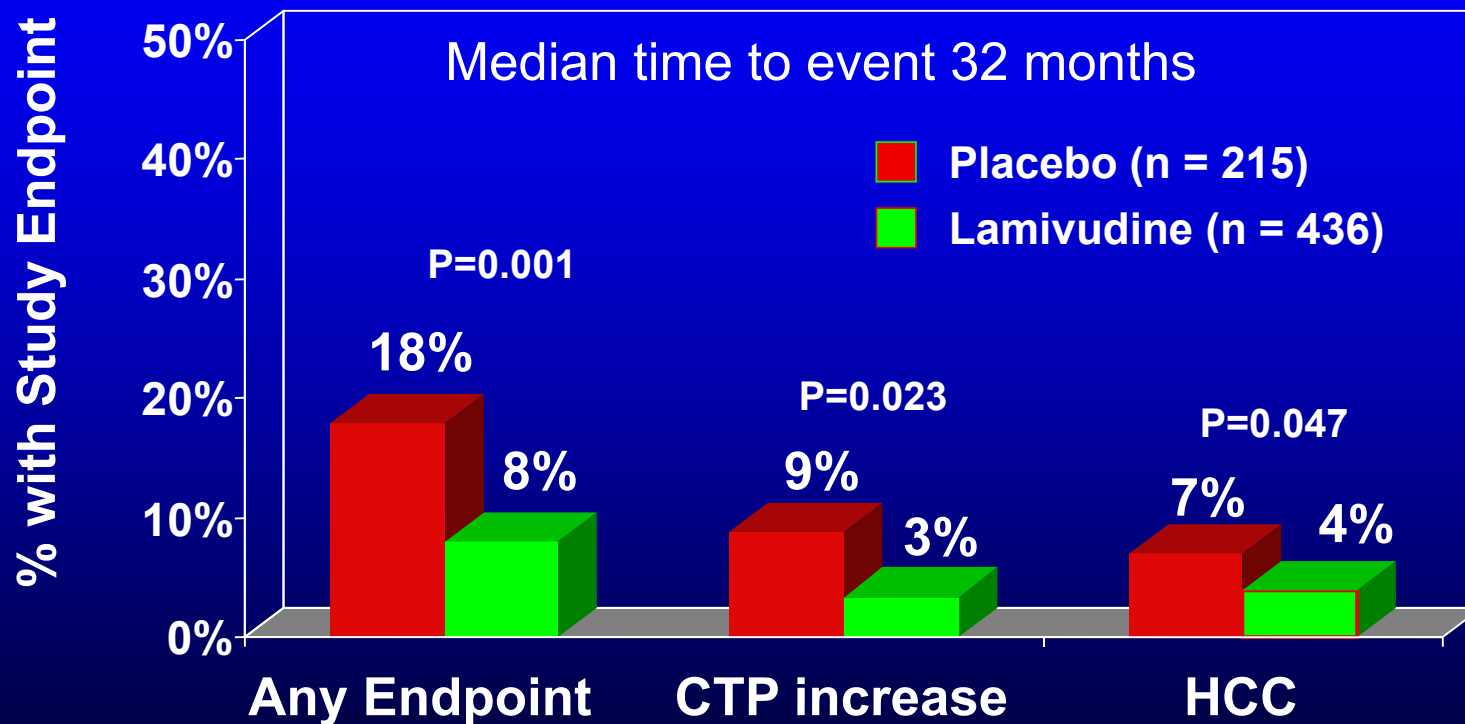
Rates of Genotypic Resistance

FDA approved nucs



Antiviral therapy prevents 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

HCC screening for HBV

Who?

- HBsAg carriers: Asian men >40, women >50
- HBV cirrhosis
- All HBsAg+ over 40yo with HBV DNA >2000 IU/mL
- 1st generation Africans >20yo
- Family History of HCC

How?

- Semiannual US +/- AFP

HBV immunization

- Confers protective immunity
- Universally offered at birth
- HBV vaccines – 3 doses over 6M
 - Engerix
 - Recombivax
 - Twinrix (with HAV)
- Heplisav-B approved 2018
 - Adjuvanted with TLR9 agonist
 - 2 dose schedule (0, 4 weeks)
 - Higher protection in those with DM, CKD

HBV Reactivation with I/S, Chemo: Suggested approach

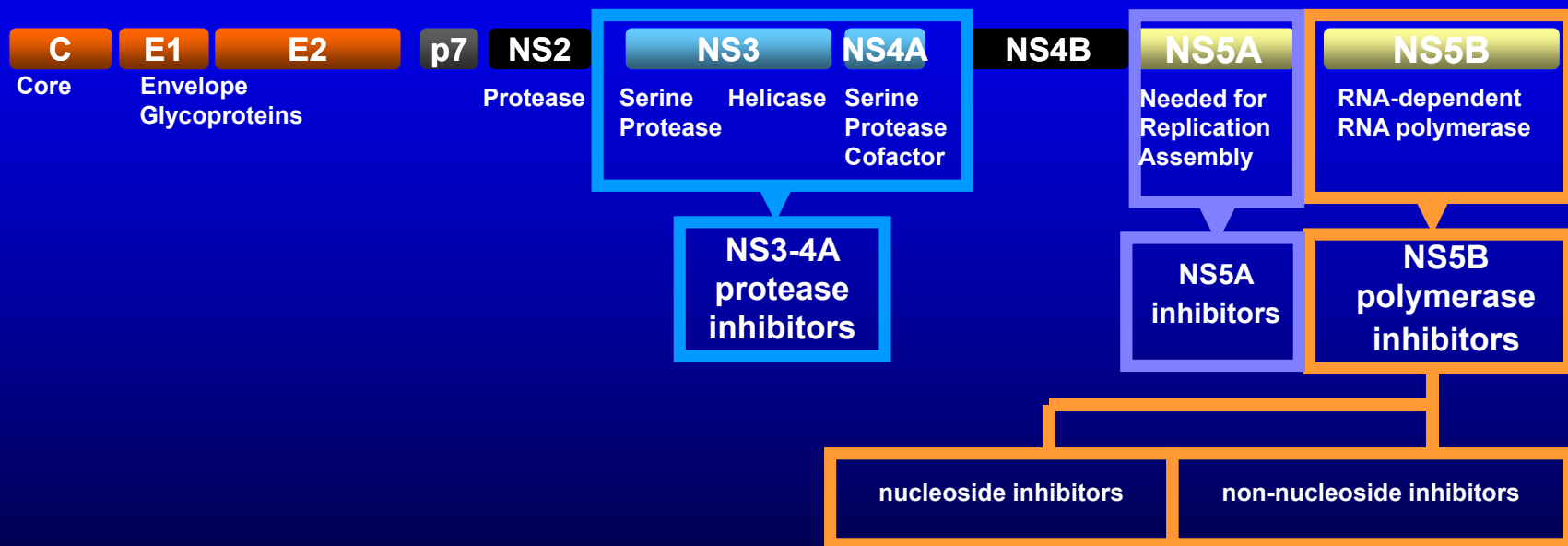
Test	Significance	Action
HBsAg	HBV infection	Prophylaxis indicated (ETV, TDF)
Anti-HBs alone	Immunity to HBV	None
Anti-HBc $\pm$ anti-HBs	Exposure to HBV	▪ **low risk for standard chemotherapy, monitor ▪ If rituximab and/or combined regimens for hematological malignancies or BMT or cirrhotic, prophylaxis indicated

**If observation is chosen, monitor liver tests, HBsAg and HBV DNA q1-3 months

HBV Management: Summary

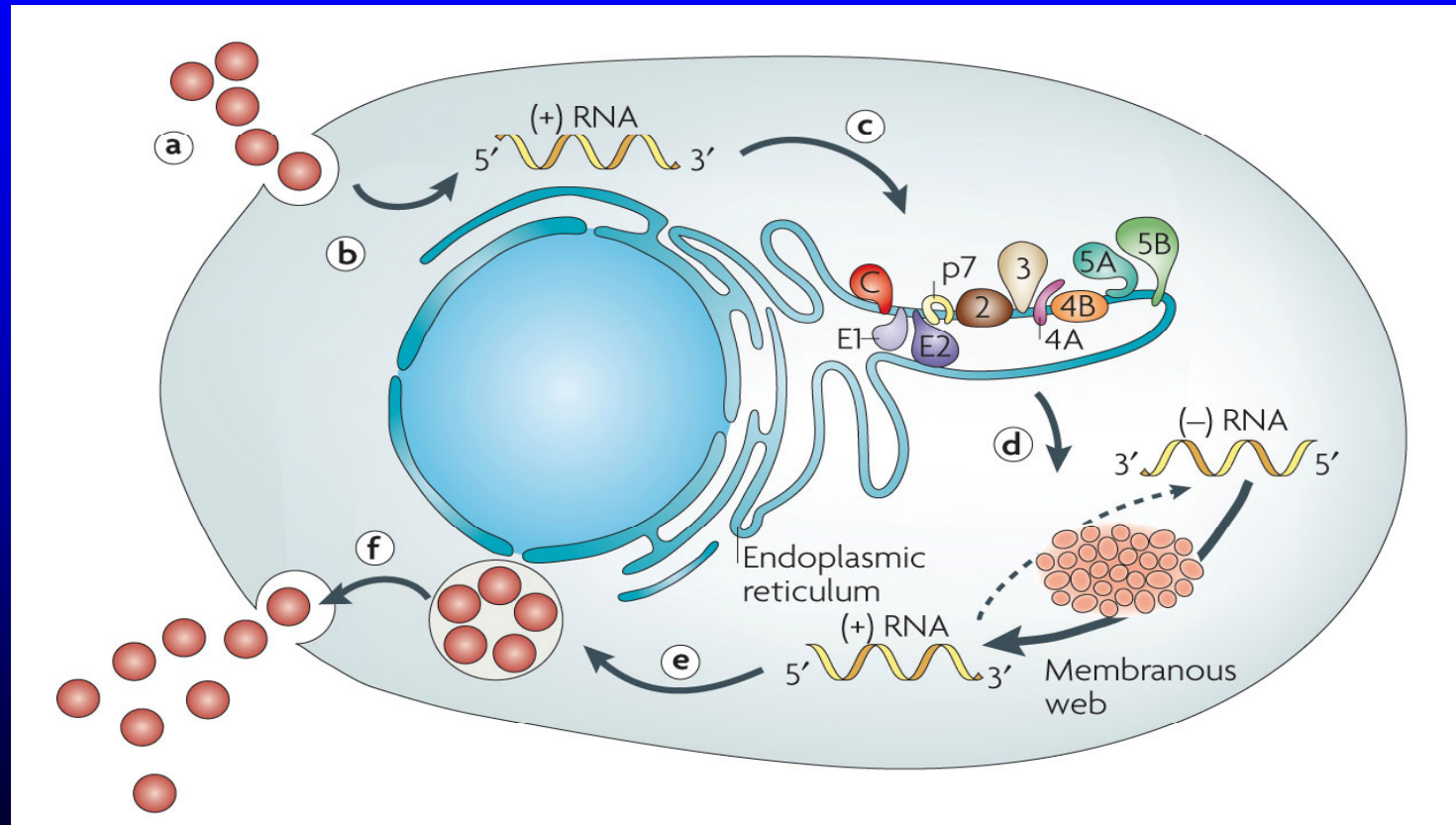
- HBsAg identifies chronically infected persons
- Screen patients from endemic areas, MSMs, pregnant women, HD, pts undergoing Rx with chemotherapy, steroids rituximab, biologics
- HBV DNA levels have prognostic value
- Treat *replicative, active* HBV (eAg+ or eAg-)
 - Entecavir, Tenofovir 1st line monotherapy agents
- Must be monitored!
- Vaccine preventable
- Screen for HCC
- We need curative strategies directed against other viral lifecycle steps

Hepatitis C Virus Polyprotein

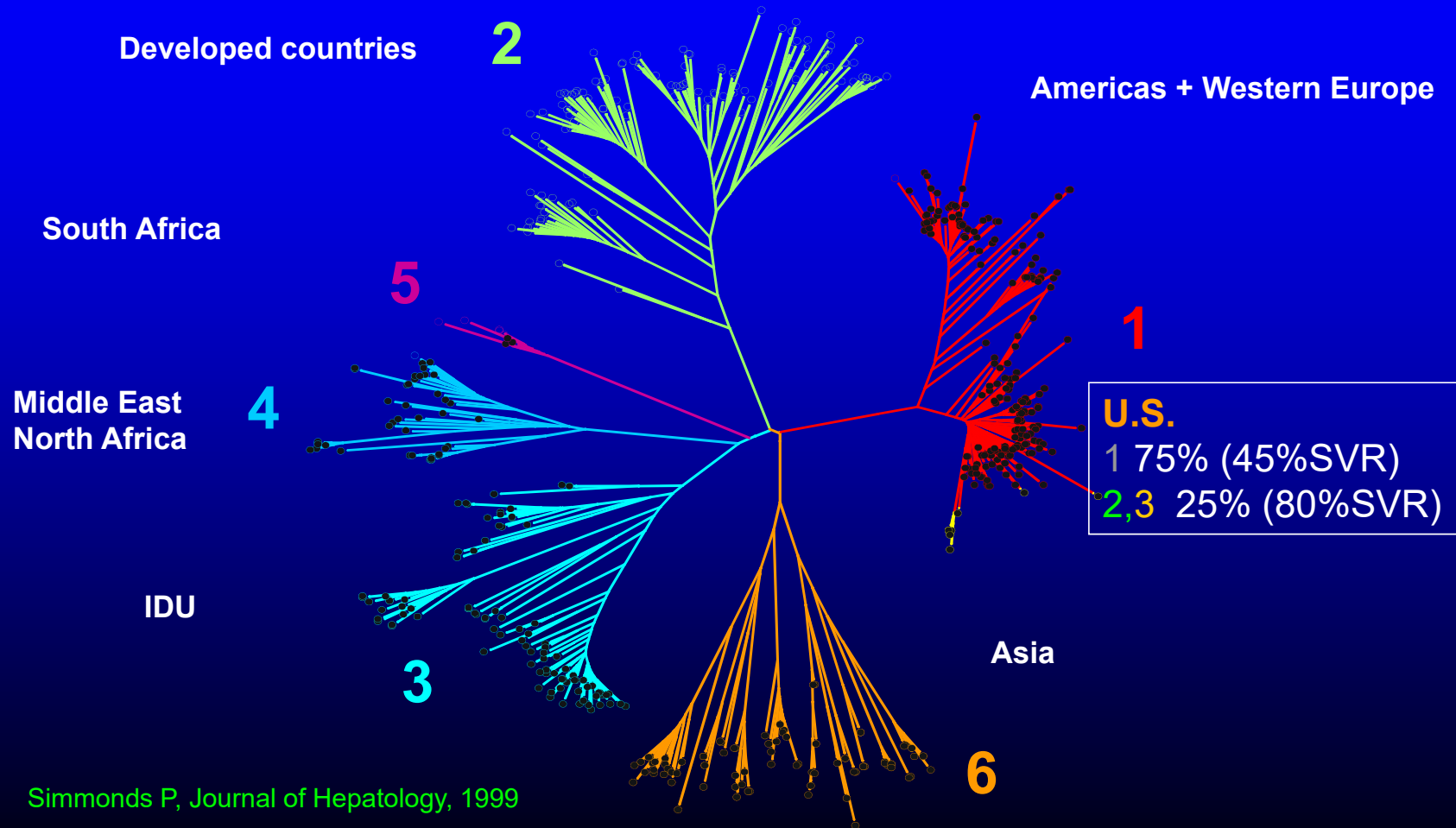


McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

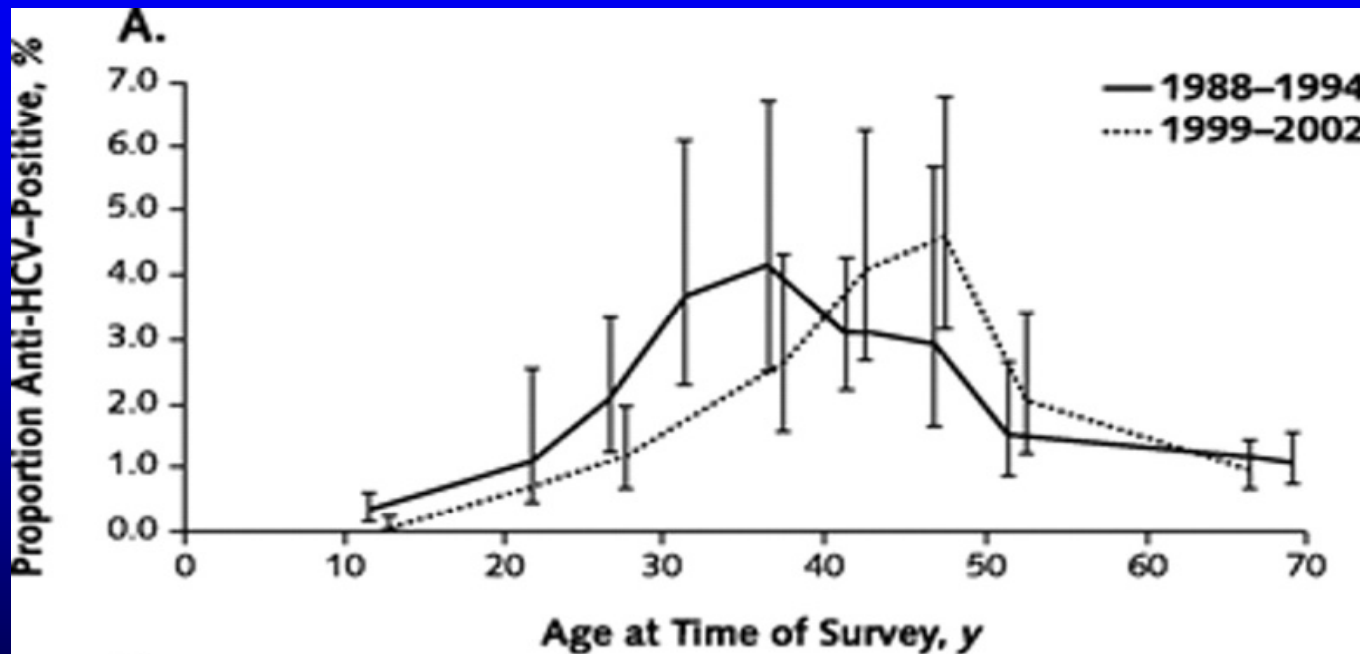
HCV life cycle



HCV Genotypes and Subtypes



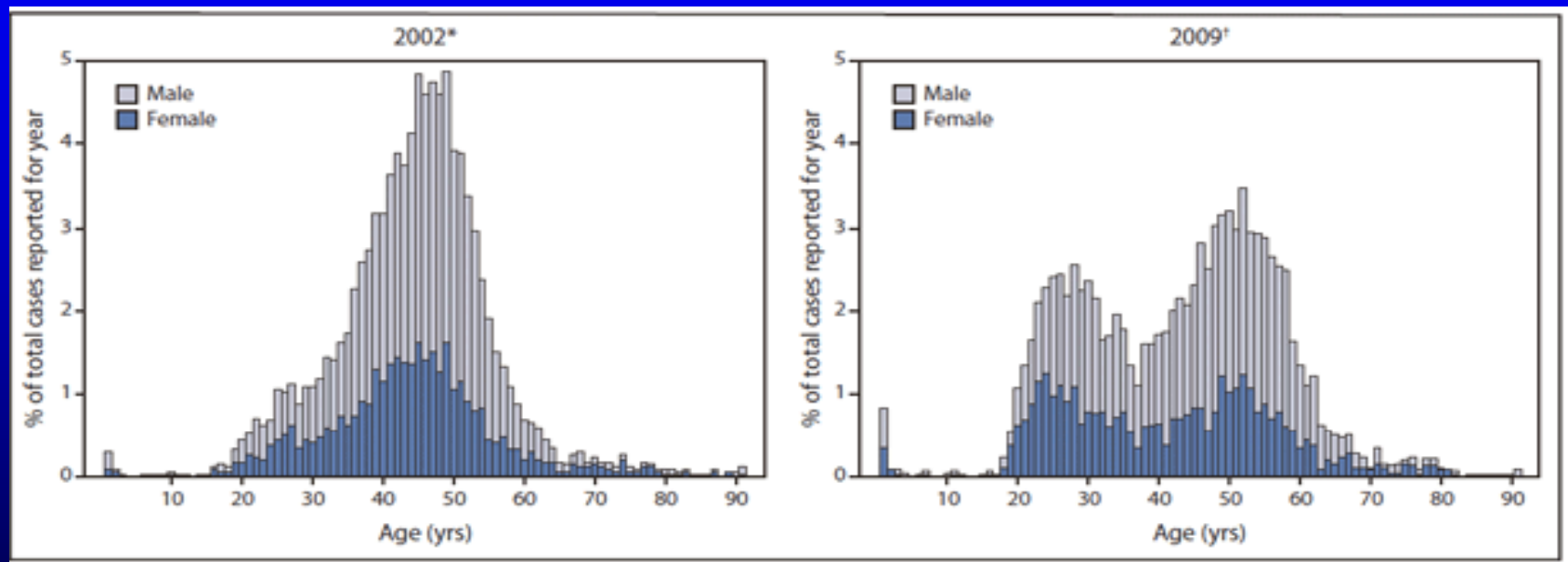
In general, the HCV cohort has aged...



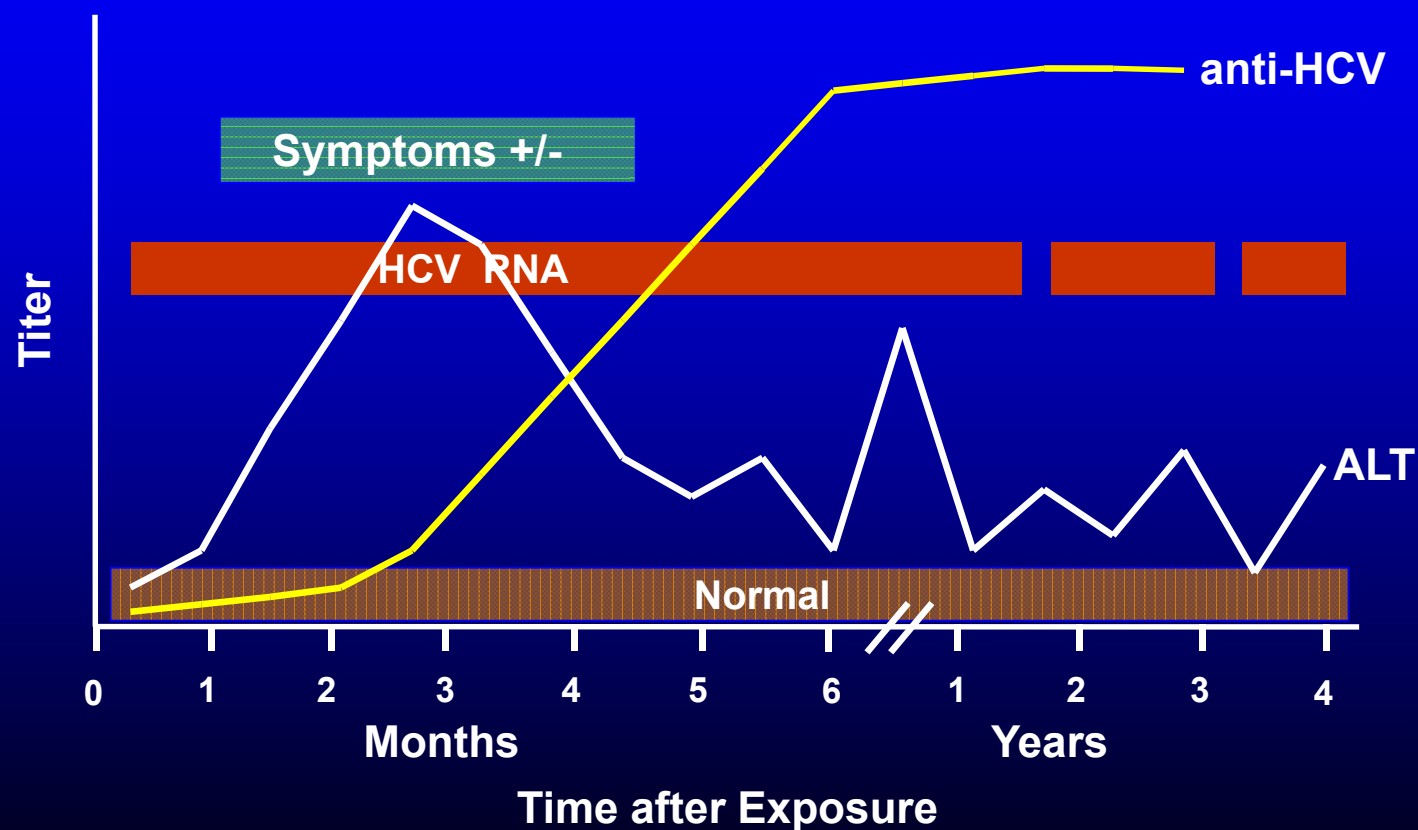
NHANES 2003-10: 2.7M chronically infected

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

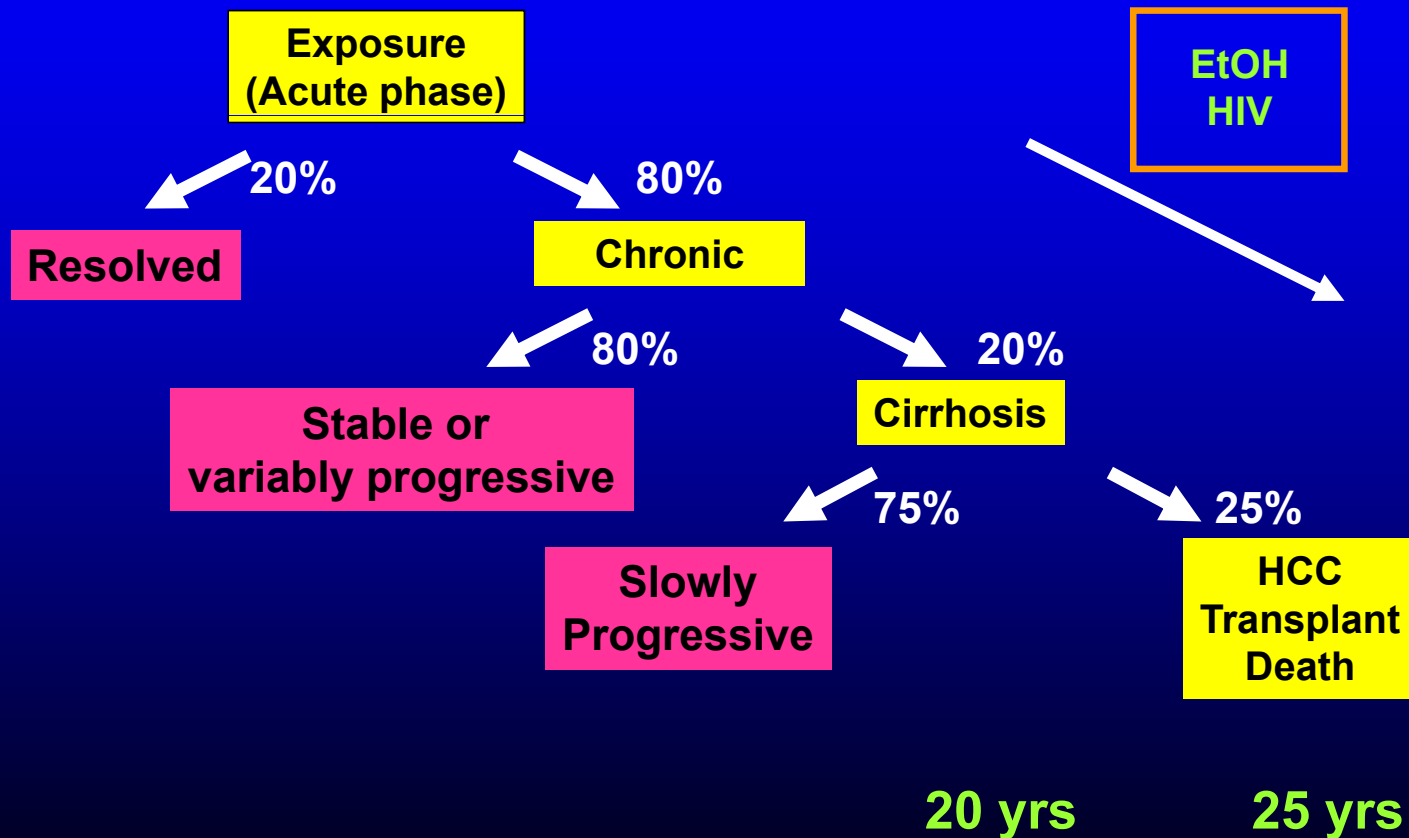


Serologic Pattern of Acute HCV Infection with Progression to Chronic Infection

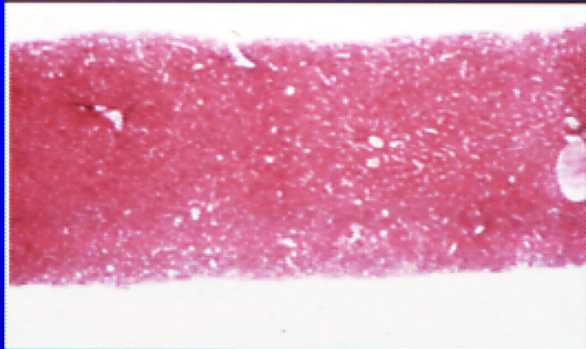


Adapted from MMWR 1998; 47(No. RR19)

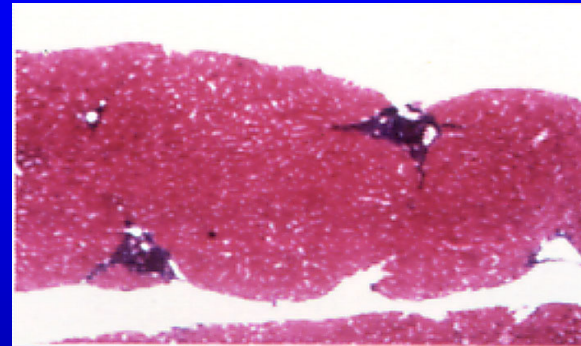
Natural History of HCV Infection



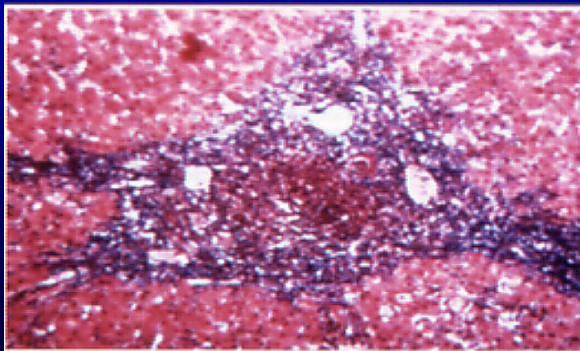
Histologic Progression of HCV



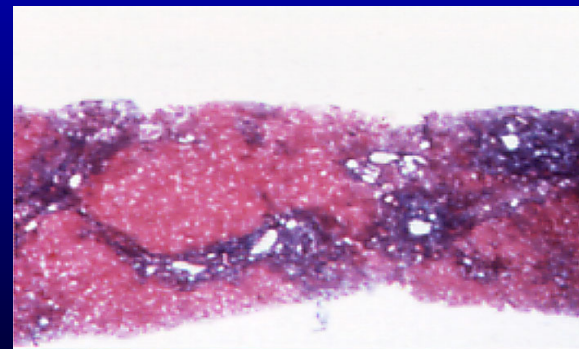
Normal



Mild Chronic Hepatitis (F1)



Moderate Chronic Hepatitis (F3)



Cirrhosis (F4)

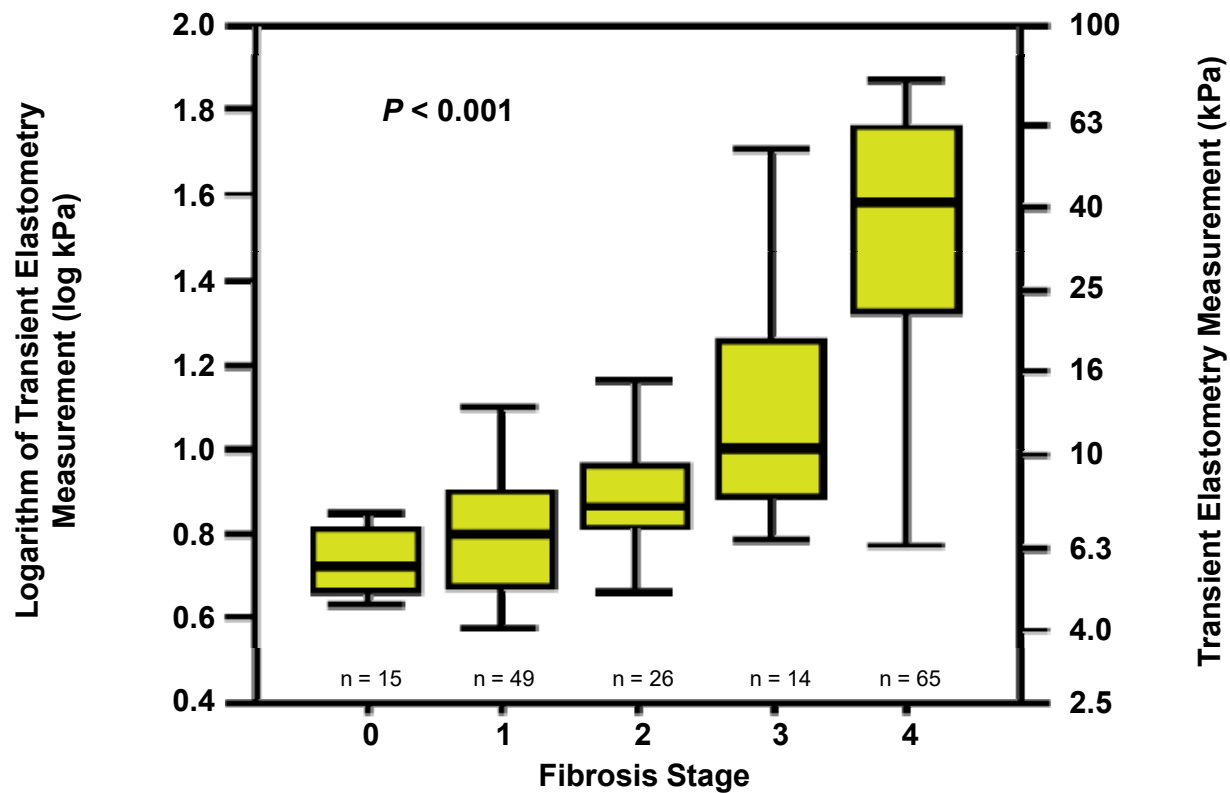
New Tools: Liver Stiffness by Transient Elastography

- 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



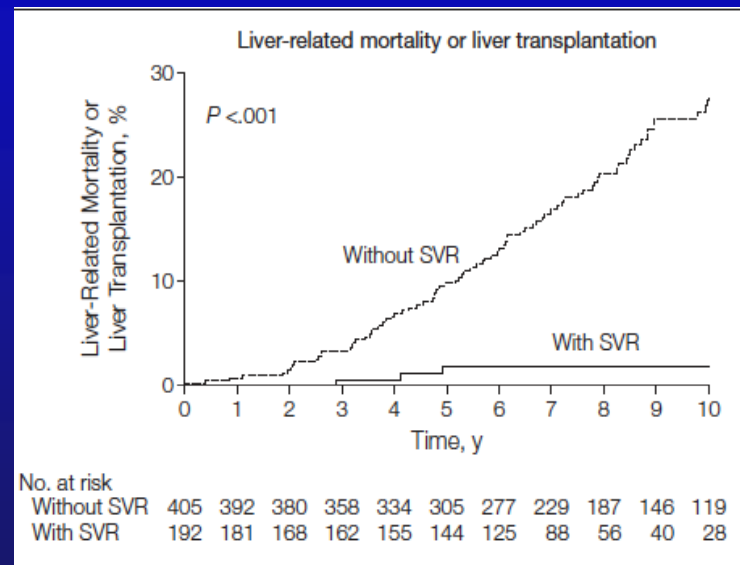
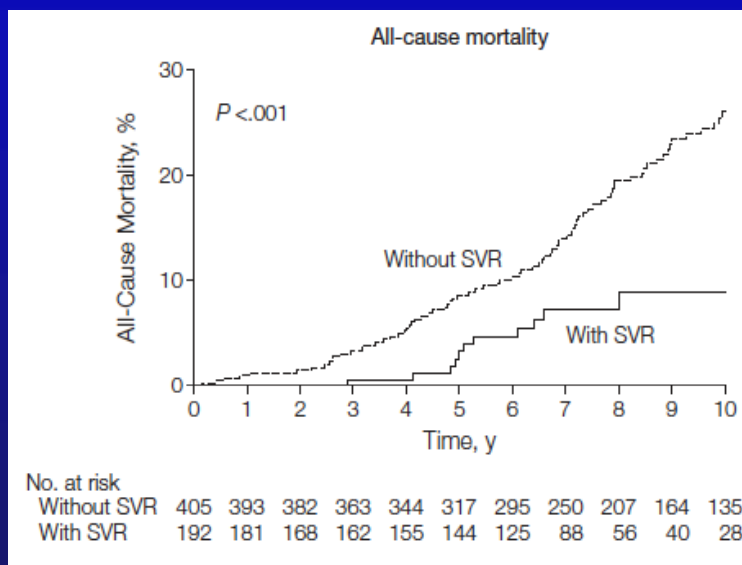
Liver Stiffness by Transient Elastography (Fibroscan)

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



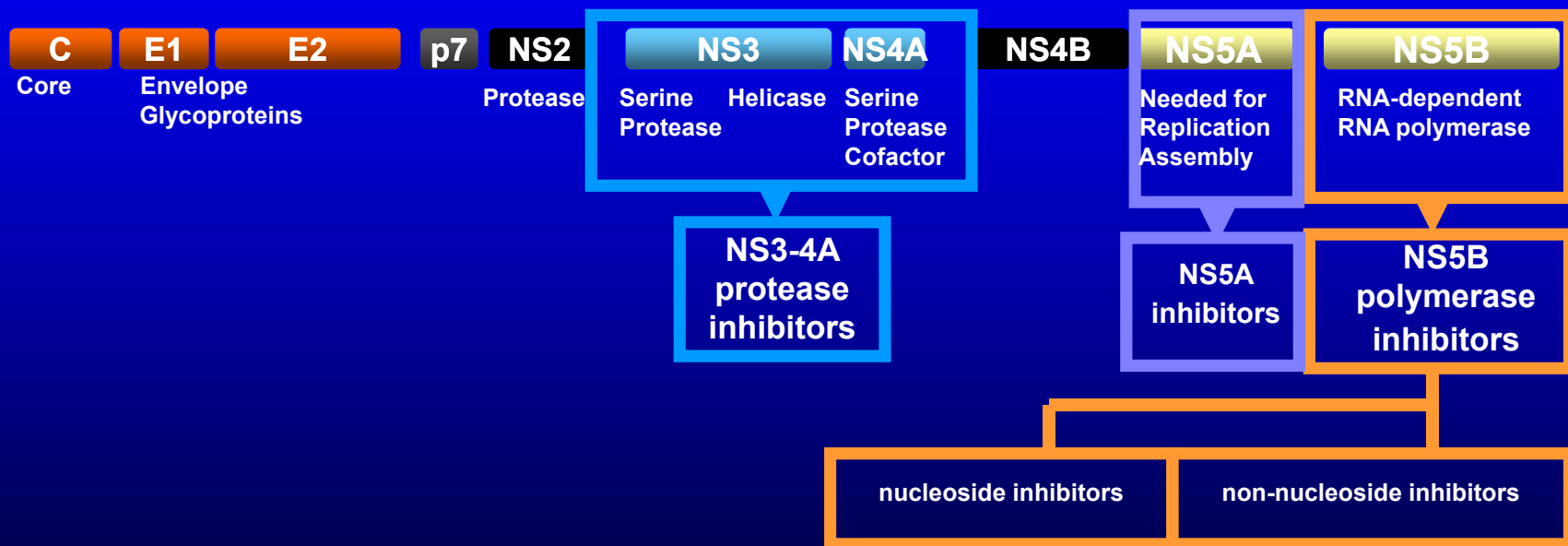
Good news: SVR Reduces All-Cause and Liver-Related Mortality

530 pts with F4-6, IFN-based Rx, median F/U 8.4Y



van der Meer A, JAMA, 2013

Targets for Direct Acting Antivirals (DAA)



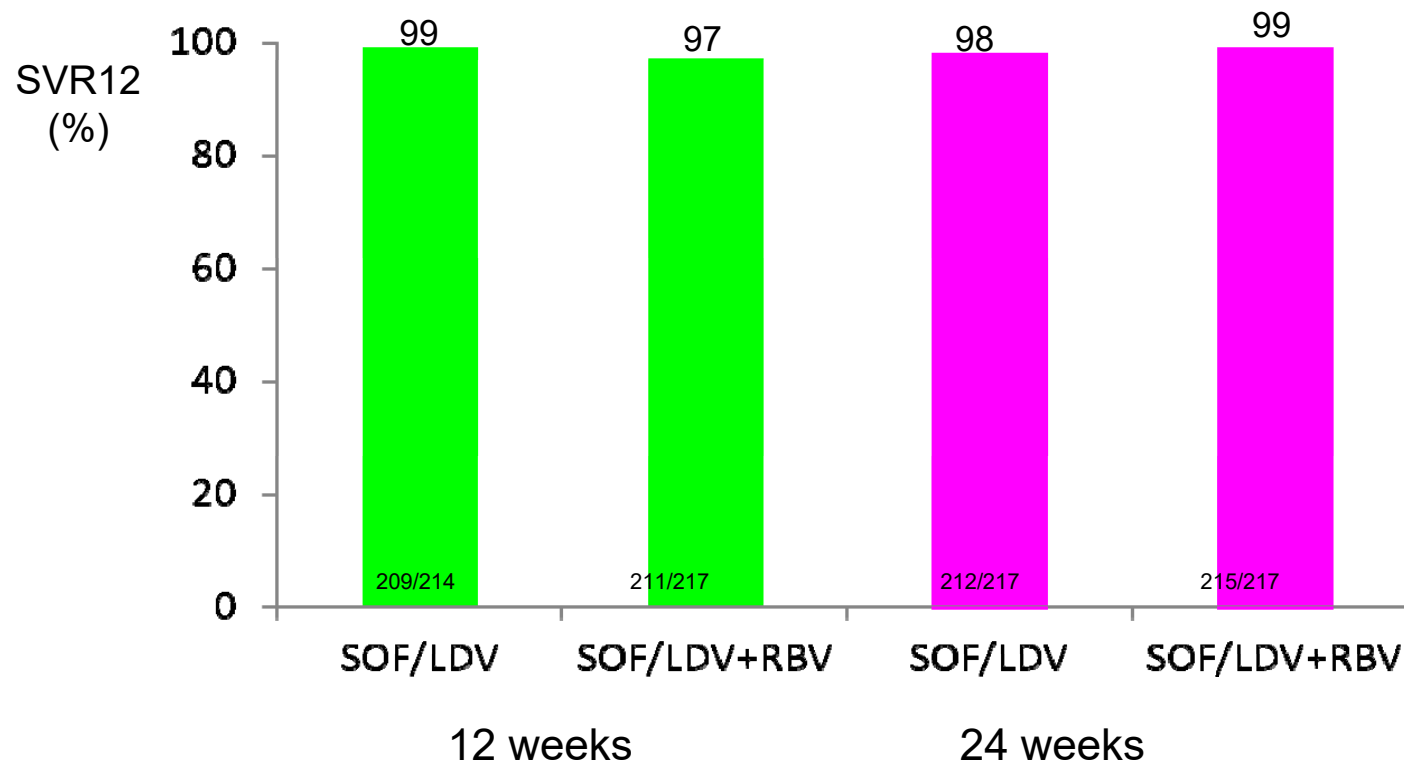
McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

ION-1: Sofosbuvir + Ledipasvir (NS5A Inhibitor)

Genotype 1: Treatment Naïve, n=865

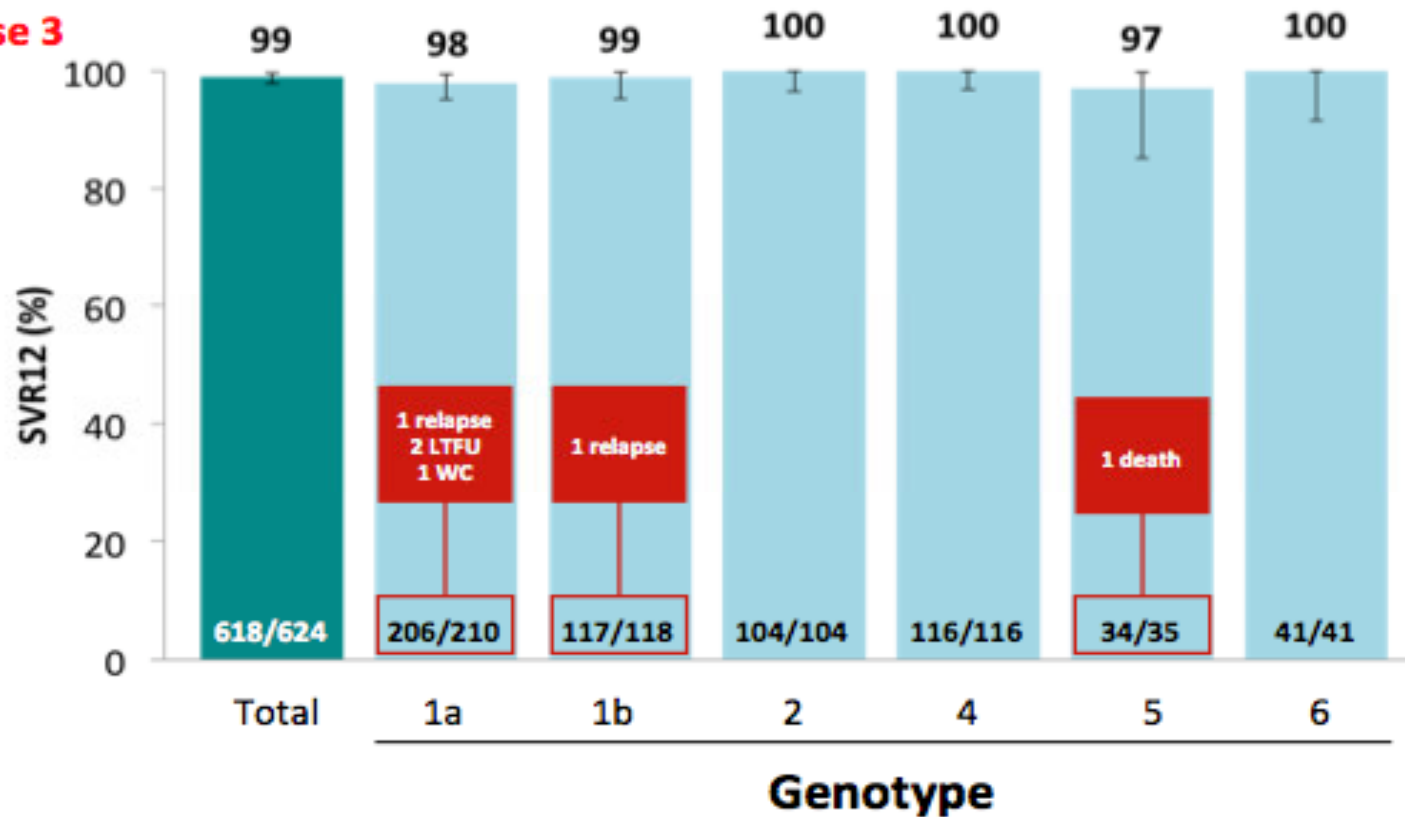
Cirrhosis in 16%

n=468



A Pangenotypic regimen: SOF + Velpatasvir (NS5A) x 12 wks

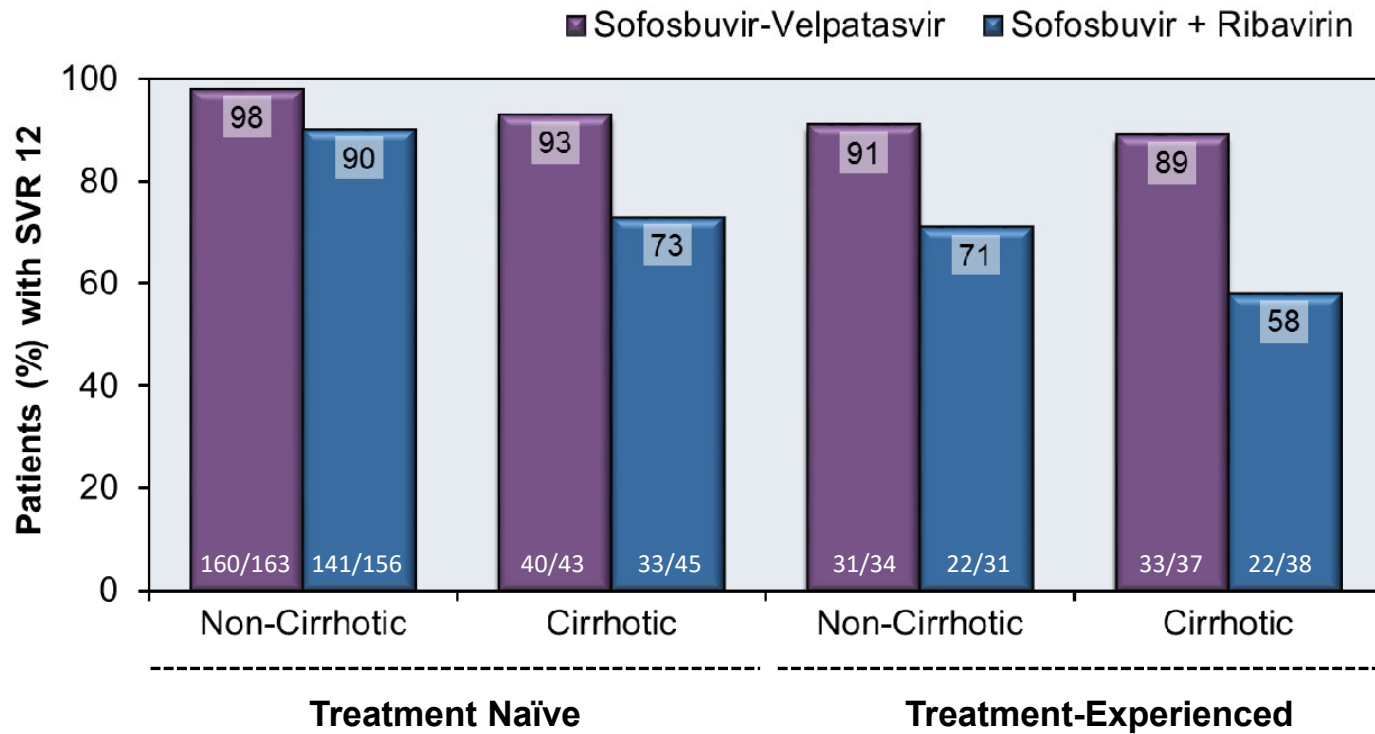
**ASTRAL-1:
Phase 3**



Feld J et al, NEJM 2015;373:2599

Sofosbuvir-Velpatasvir x 12W in HCV Genotype 3 ASTRAL-3

SVR12 Results by Cirrhosis & Treatment Experience



Foster GR, et al. N Engl J Med. 2015;373:2608-17

www.hcvguidelines.org



HCV Guidance: Recommendations for
Testing, Managing, and Treating
Hepatitis C



[Home](#) [Test, Evaluate, Monitor](#) [Treatment-Naïve](#) [Treatment-Experienced](#) [Unique & Key Populations](#) [About](#)



New and updated:
'HCV in Pregnancy' Updated
With the current increases in HCV among young adults, including women of childbearing age, there is now discussion about universal screening of pregnant women.

Search the Guidance

Genotype 1

Genotype 2

Genotype 3

Genotype 4

Genotype 5 or 6

GT3 : P/R : No Cirrhosis

GT3 : P/R : Compensated

GT3 : DAA

Start Here: Choose a

Wellcome to H

The AASLD and IDSA in p

easier and faster access t

click on a guidance sectio

+ Contents and Introduction - *Select a Page*

+ Testing, Evaluation, and Monitoring of Hepatitis C - *Browse Topics*

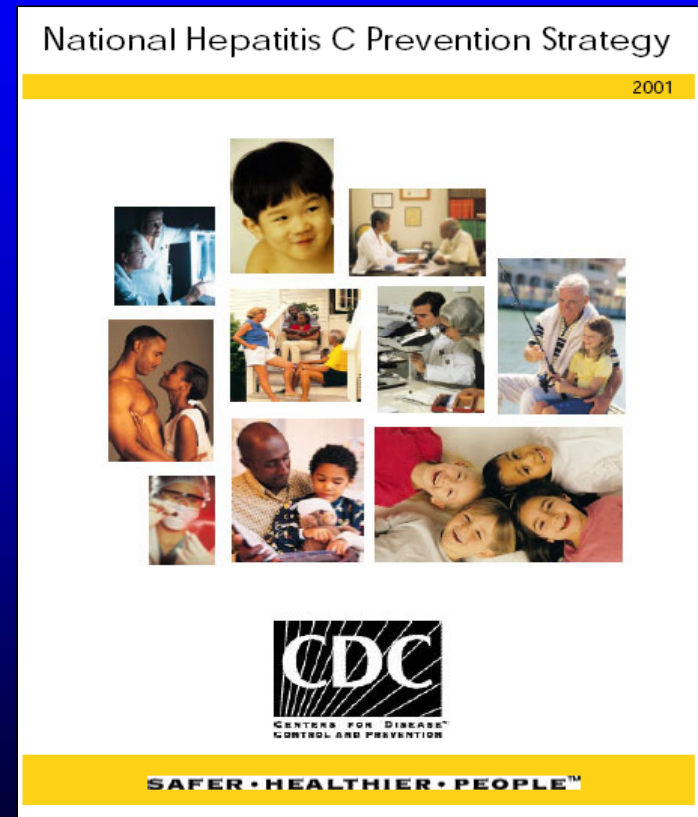
+ Initial Treatment of HCV Infection - *Choose Patient Genotype*

You can't treat them if you can't find them!

CDC recommendations (1998)

- Ever injected illegal drugs
- Received clotting factors made before 1987
- Received blood/organs before July 1992
- Ever on chronic hemodialysis
- Evidence of liver disease (elevated ALT)
- Infants born to HCV infected mothers
- HIV infection

MMWR 1998;47 (No. RR-19)



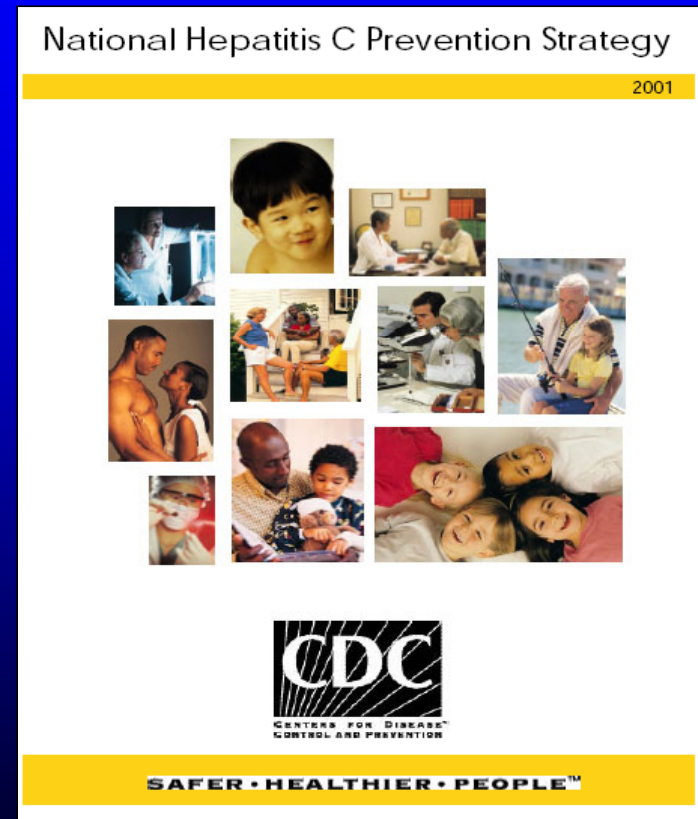
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- Evidence of liver disease (elevated ALT)
- Infants born to HCV infected mothers
- HIV infection

• CDC (2012)

- Born between 1945-64 (80% of adults with HCV)
- Single time screening
- Expected to identify up to 1M new cases of prevalent HCV
- USPSTF has now issued draft recs to screen the entire adult population



HCC screening for HCV

Who?

- Patients with F3-4 disease
 - Continue screening after cure of HCV

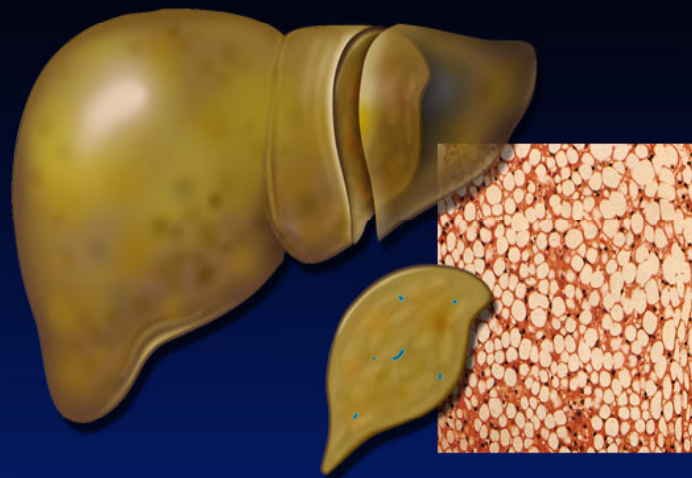
How?

- Semiannual US +/- AFP

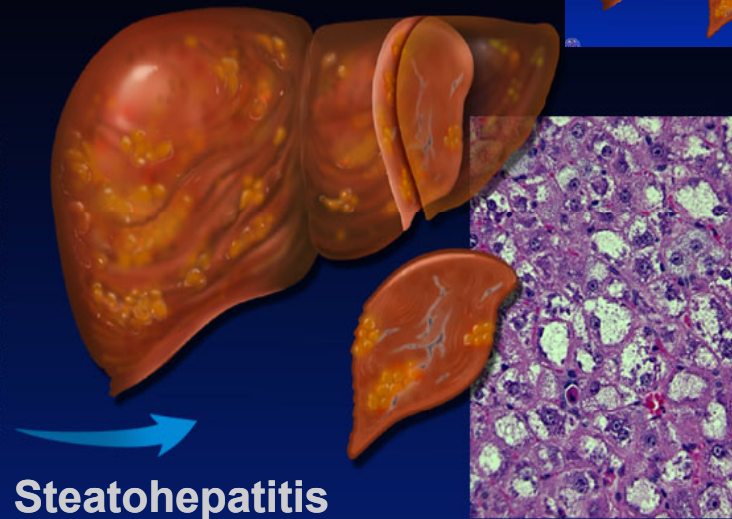
HCV: Summary

- Minimally symptomatic acute infection but high chronicity
- HCV RNA distinguishes chronic from cleared infection
- All HCV RNA+ should be treated
- All oral, tolerable, high efficacy regimens (>95% cure) now available for all genotypes
- High cure rates now possible in historically difficult populations (cirrhotics, decompensated, post-LT, HIV)
- Not yet vaccine preventable
- Screen all born between 1945-65 and those with RFs
- Can be noninvasively staged (serum tests, elastography)
- Advanced fibrosis (F3-4) should be screened for HCC with semiannual US +/- AFP
 - HCC screening should be continued even after HCV cure

Nonalcoholic Fatty liver Disease



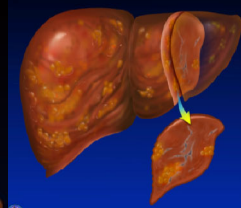
Steatosis



Steatohepatitis



Cirrhosis



NAFLD Global Prevalence: 25%



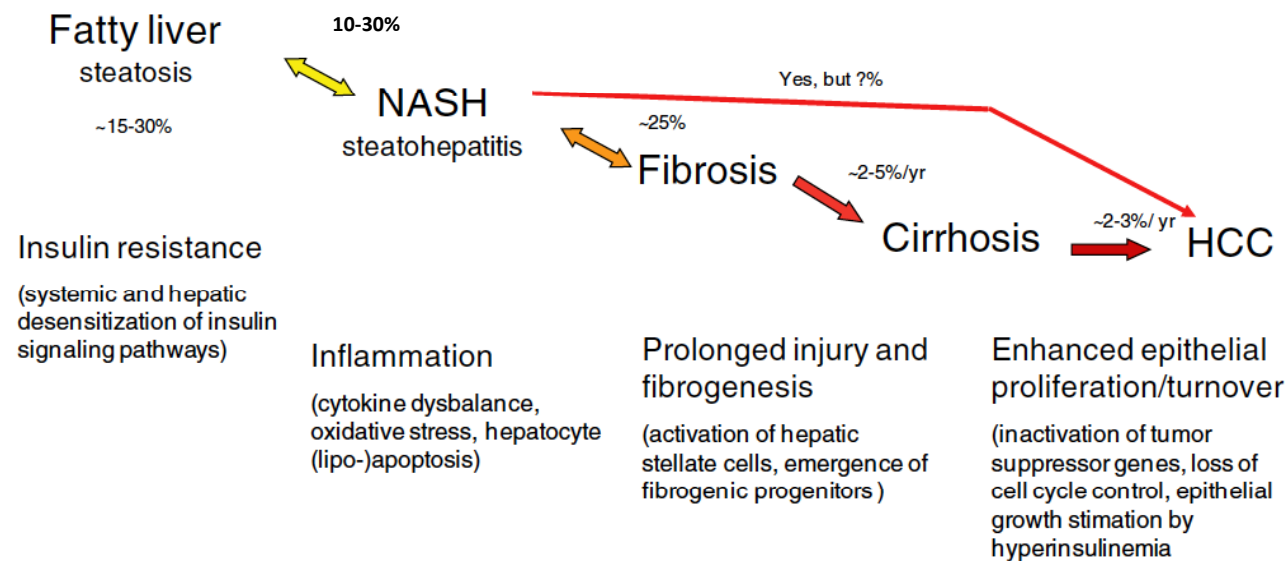
Region	N	Prevalence (%)
Africa	2	13.48
Asia	14	27.37
Europe	11	23.71
Middle East	3	31.79
North America	13	24.13
South America	2	30.45
Overall	45	25.24

NASH Prevalence: 1.5-6.6%

Demographics of NAFLD

- Most common chronic liver disease in US
- 3rd most common indication for liver transplant
 - Projected to be the most common within 10 years
- NASH (10-30% of steatosis)
 - 3% of adults
 - 15-20% of obese adults
 - 25-70% of those undergoing bariatric surgery

Progression of NAFLD



- Recent evidence in NASH underscores prognostic significance of fibrosis but not other histologic features

Risk factors: Established association

- Obesity
- Type 2 DM: insulin resistance (IR)
- Dyslipidemia
- Metabolic syndrome (MS)
- Polycystic ovary syndrome

Risk factors: Emerging associations

- Hypothyroidism
- Obstructive sleep apnea
- Hypopituitarism
- Hypogonadism
- Psoriasis

Medications that can produce fatty liver

- Amiodarone
- Methotrexate
- Tamoxifen
- Corticosteroids
- Diltiazem
- Valproic acid
- Antiretroviral therapy (PIs)

Screening Recommendations

AASLD Guidelines

- Who?
 - abnormal LFTs
 - Existing risk factors (T2DM, MetS, obesity)
- Imaging (>5% fat)
 - Ultrasound
 - CT
 - MRI
- Staging
 - NAFLD fibrosis score
 - Fibroscan (CAP > 250)
 - Liver biopsy

NAFLD fibrosis score

Age	Albumin
BMI	AST
Hyperglycemia	ALT
Platelet count	

<http://nafldscore.com>

- < -1.455: **absence** of significant fibrosis (F0-F2)
- ≤ -1.455 to ≤ 0.675 : indeterminate
- > 0.675: **presence** of significant fibrosis (F3-F4)

Liver biopsy

- Should be prompted by abnormal findings on noninvasive markers
- Normal ALT does not preclude NASH or fibrosis! (19% F2-3, 7% cirrhosis in NASH CRN)
- Presence of metabolic syndrome, T2DM, BMI>35 or persistently elevated biochemistries may benefit from liver biopsy
- Patients with biopsy proven NASH cirrhosis should be screened routinely for esophageal varices and HCC

Lifestyle Interventions

- **Weight loss** by lower caloric intake and increased physical exercise
 - 10% weight loss → 30% improvement in steatosis and improvements in necrosis and inflammation, possibly fibrosis
- Alcohol consumption
 - heavy intake should be avoided
 - light intake (<1 drink/day), mixed data, avoid in advanced fibrosis

Promrat, et al. Hepatology 2010

Dunn, et al. Hepatology 2008

Gunji. et al. Am J Gastro 2009

Moriya, et al. Alim Pharm Ther 2011

Ruhl, et al. Clin Gastro Hepatol 2005

AASLD recommendations for treatment

- **Pioglitazone** can be used to treat biopsy-proven NASH who do or do not have DM but may have undesirable AEs (wt gain)
- **Vitamin E** 800 IU improves liver histology in nondiabetic NASH
 - Not recommended in those with diabetes, NASH cirrhosis, NAFLD without biopsy
 - Slight increased RR for prostate CA, hemorrhagic CVA
- **Bariatric surgery**: resolves NASH in 85%, improves fibrosis in 33% at 1 year in morbidly obese (AASLD Guidance 2018)
- **Ongoing trials**
 - Many compounds, including obeticholic acid (FXR agonist), cenicriviroc (CCR2/5 antagonist), elafibrinor (PPAR α/δ agonist)

NAFLD: Summary

- Remarkably common
- Subset will produce progressive liver disease
- Challenge remains to identify at-risk population
- Screen for NAFLD in high risk pts, those with abnormal LFTs
- Low threshold for liver biopsy to identify those with fibrosis
- Management: lifestyle changes difficult, await other therapies
- May be at reciprocal risk for CVD (particularly in cirrhosis)
- Low threshold for referral to stratify risk!
- HCC screen: F2-4, diabetes