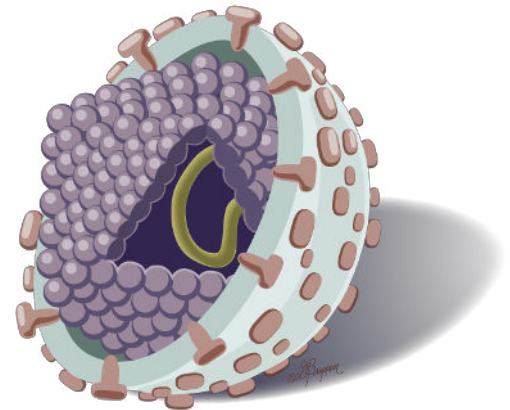


Challenges in the Treatment of Hepatitis C and other Viral Hepatitis

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PRIVATE PRACTICE, CAGUAS PR**



Disclosures

- No disclosures

Hepatitis A Infection



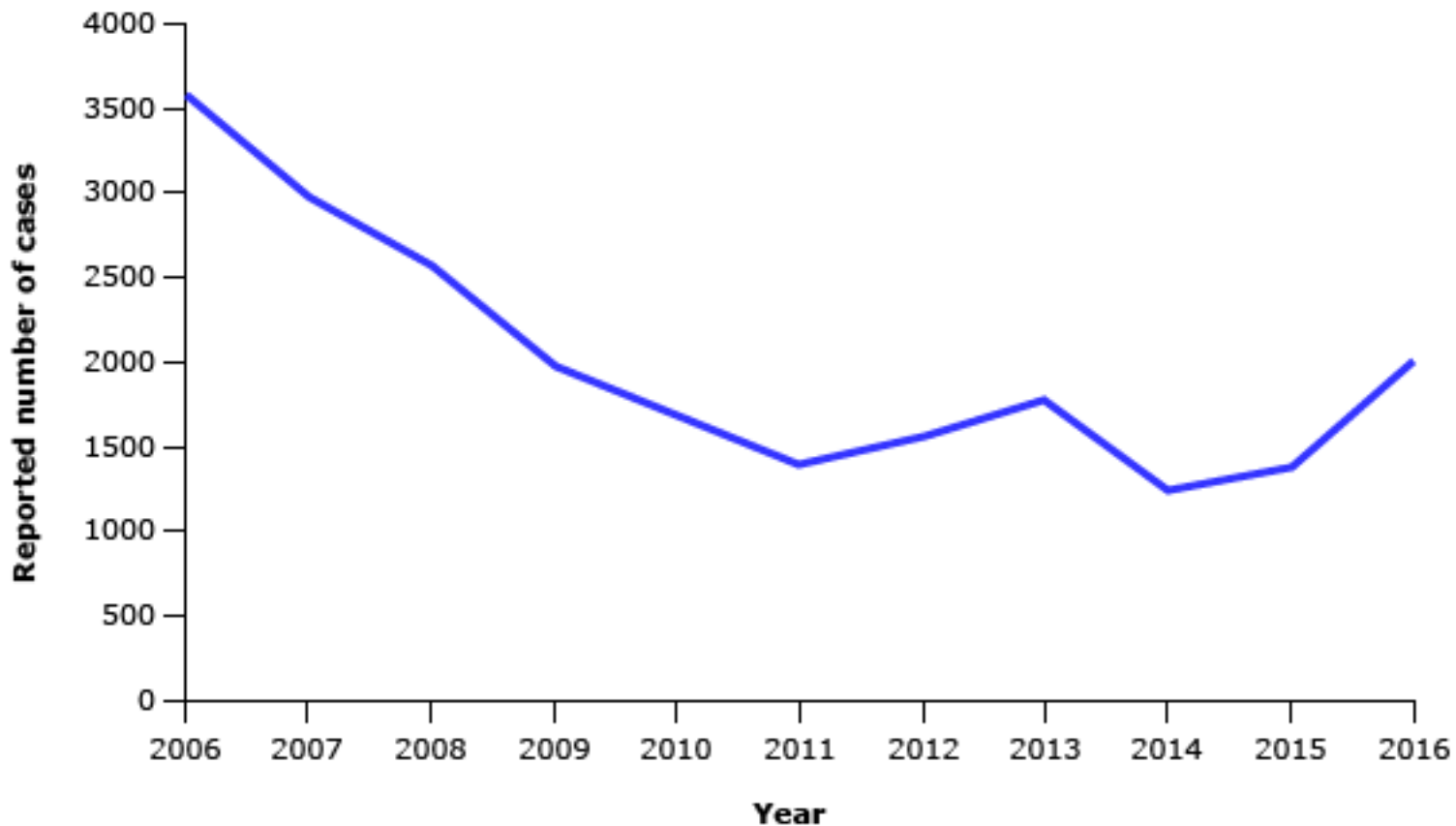
Hepatitis A Infection

- Globally, an estimated 1.4 million cases occur each year.
- Hepatitis A rates in the United States have declined by 95% since Hepatitis A vaccine first became available in 1995.

Hepatitis A Infection

- Between 2016 to 2018 hepatitis A infection increased in USA by 294 percent compared to 2013 to 2015.
 - Drugs users, homeless, men who have sex with men, outbreaks associated with contaminated foods
 - 2017 : largest outbreak in US in the last two decades
 - 417 hospitalizations; 21 deaths

Incidence of hepatitis A, by year – United States, 2006-2016

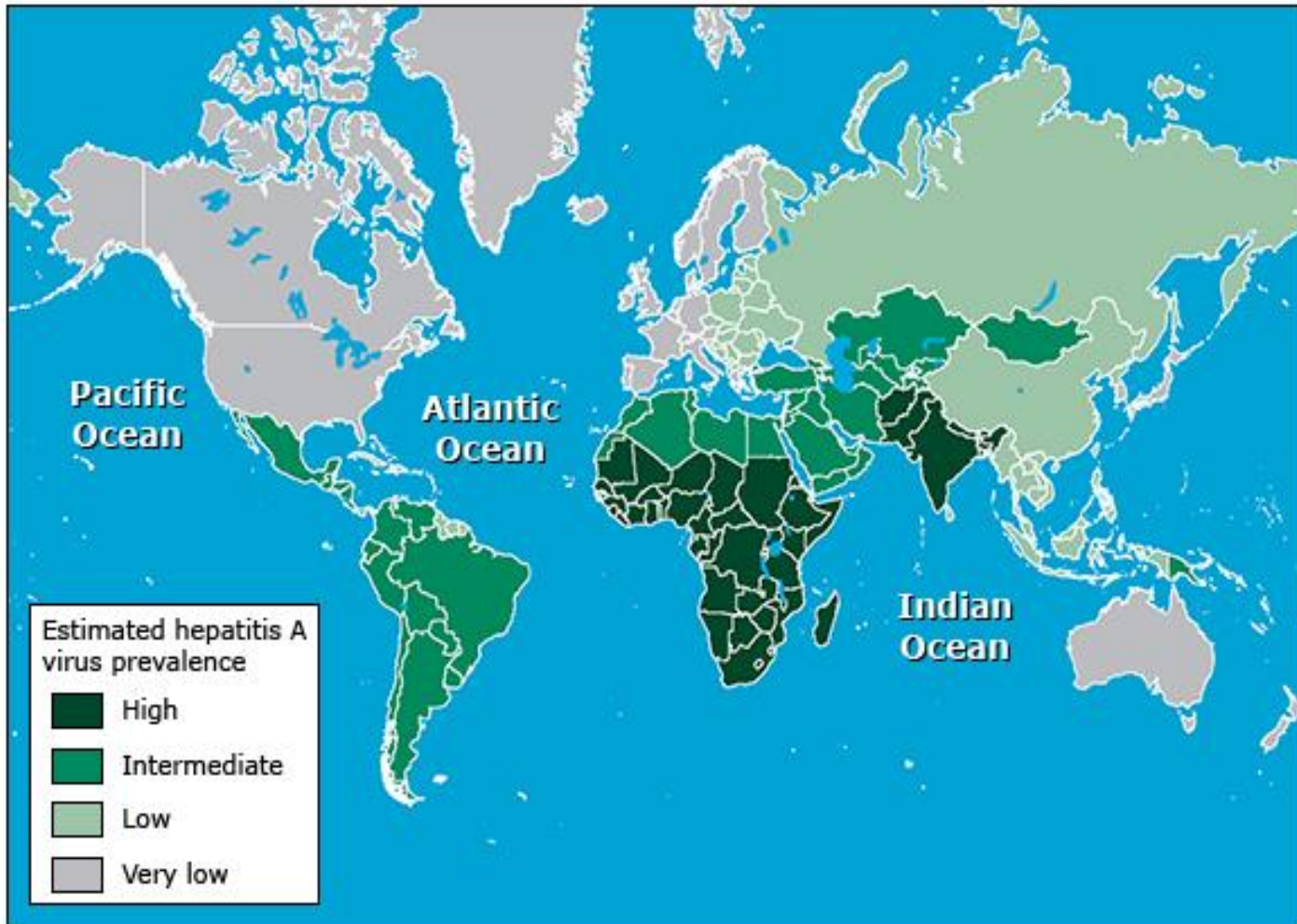


Reproduced from: Centers for Disease Control and Prevention. Hepatitis A Questions and Answers for Health Professionals. Available at: <https://www.cdc.gov/hepatitis/hav/havfaq.htm> (Accessed on December 17, 2018).

UpToDate®

HAV - Epidemiology

Prevalence of antibodies against hepatitis A



Hepatitis A Transmission

- **Close personal contact**
 - Household, sexual contact, residential institution, daycare, military personnel
 - Person-to-person transmission through the fecal-oral route
 - Primary means of HAV transmission in the United States
- **Fecal-oral contamination of food or water**
 - Food handlers
 - Raw shellfish
 - Travel to endemic areas
- **Blood-borne (rare)**
 - Injecting drug users

Signs and Symptoms of HAV Infection

- In children aged <6 years, 70% of infections are asymptomatic
- Among older children and adults, infection is typically symptomatic, with jaundice occurring in >70% of patients.
- The average incubation period for Hepatitis A is 28 days (range: 15–50 days).
- Symptoms usually last less than 2 months, although 10%–15% of symptomatic persons have prolonged or relapsing disease for up to 6 months
- Hepatitis A does not become chronic

Signs and Symptoms of HAV Infection

- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Clay-colored bowel movements
- Joint pain
- Jaundice

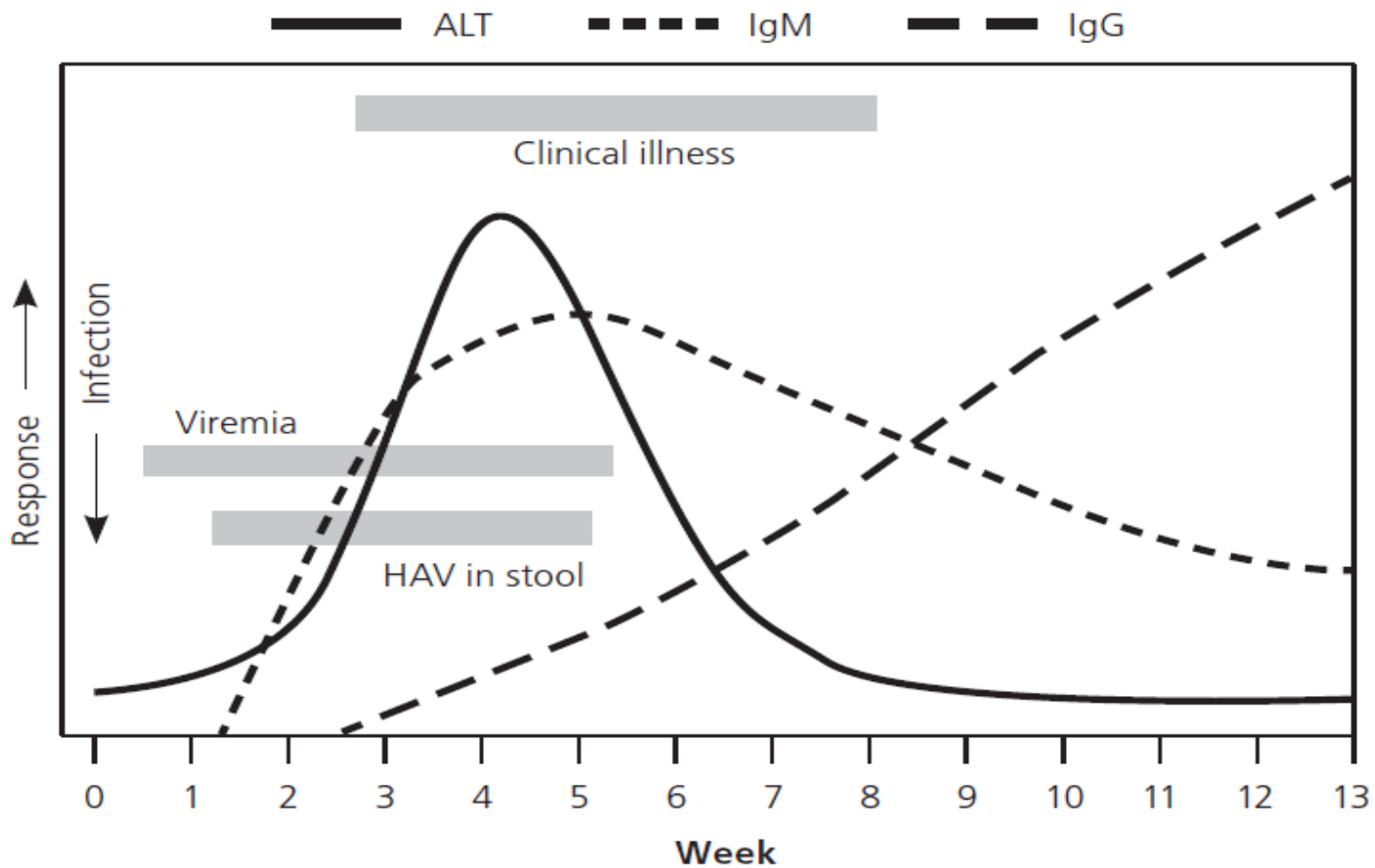
Clinical Variants of Hepatitis A Infection

- Asymptomatic (anicteric) disease
 - Children under 6 years of age, > 90%
 - Children from 6-14 years old, 40-50%
- Symptomatic (icteric) disease
 - Adults and children over 14 y/o, 70-80%

Clinical Variants of HAV Infection

- **Cholestatic hepatitis (< 5% of the cases)**
- **Relapsing hepatitis (up to 10% of the cases)**
- **Fulminant hepatic failure (<1 % of the cases)**

Timeline for Hepatitis A Manifestations



Hepatitis A: Vaccination

- All children at age 1 year (i.e., 12–23 months)
- Children and adolescents ages 2–18 who live in states or communities where routine Hepatitis A vaccination has been implemented because of high disease incidence

Hepatitis A: Vaccination

Persons at increased risk or danger of infection

- Travelers to intermediate and high HAV prevalence areas
- Men having sex with men
- Injecting drug users
- Persons with chronic liver disease
- Persons who have occupational risk for infection
- Persons who have clotting-factor disorders
- Families of adoptees from endemic areas

HAV

Hepatitis A: Pre-vaccination Serology

Likely to be cost-effective for:

- Adults who were born, or lived, in high endemic areas
- Adults >40 years of age

Table 3. Active Immunization Schedule for Hepatitis A

Vaccine	Age	Dose	Number of doses	Schedule
Havrix	12 months to 18 years	720 ELISA units per 0.5 mL	2	0* and 6 to 12 months
	18 years and older	1,440 ELISA units per mL	2	0* and 6 to 12 months
Vaqta	12 months to 18 years	25 U per 0.5 mL	2	0* and 6 to 18 months
	18 years and older	50 U per mL	2	0* and 6 to 18 months
Twinrix† (hepatitis A/B)	18 years and older, regular schedule†	720 ELISA units/20 mcg per mL	3	0,* 1, and 6 months
	18 years and older, accelerated schedule†	720 ELISA units/20 mcg per mL	4	Days 0,* 7, and 21 to 30, with a booster at 12 months

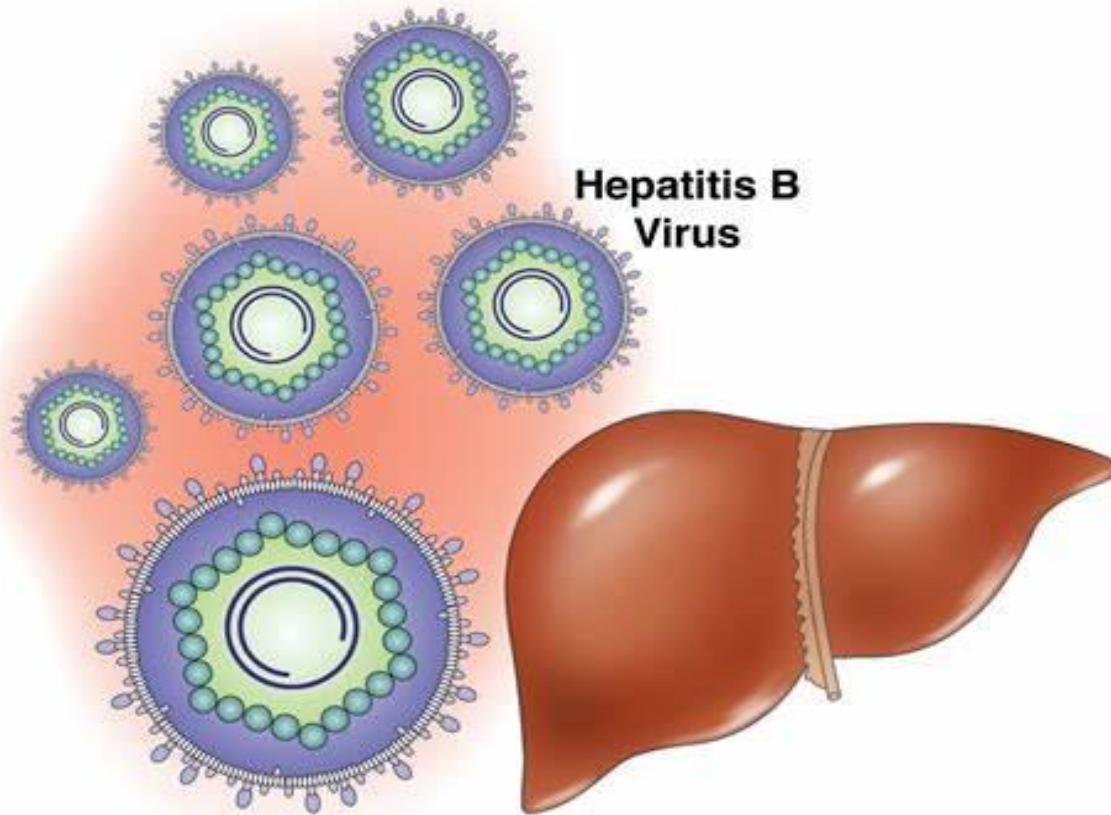
ELISA = enzyme-linked immunosorbent assay.

*—0 represents initial dose.

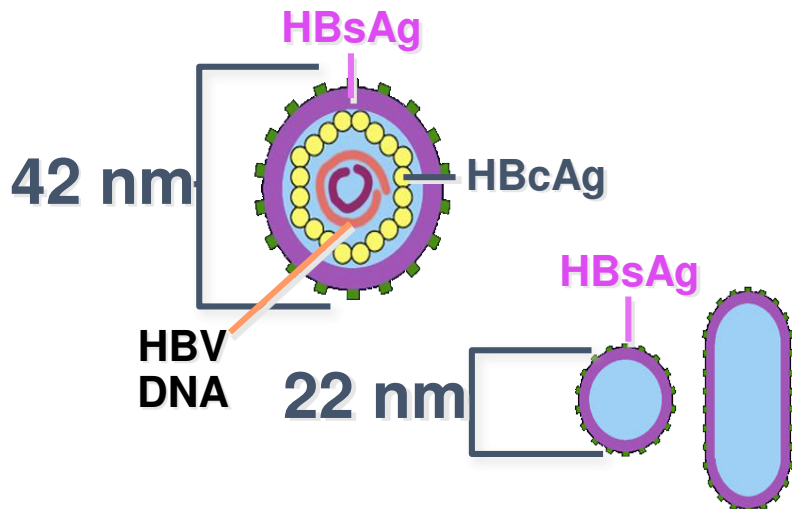
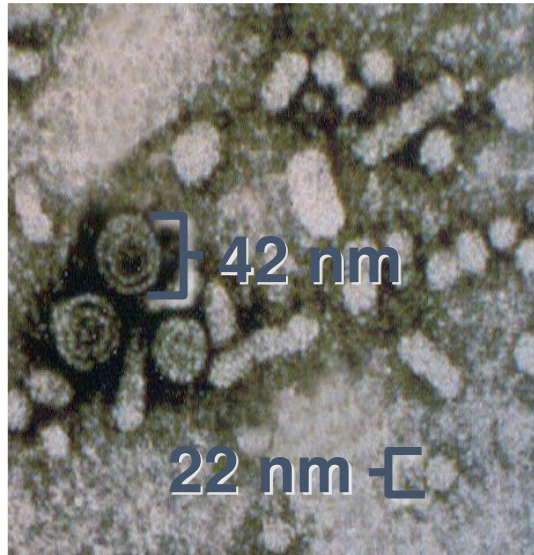
†—U.S.-approved schedule.

Information from references 7 and 30.

Hepatitis B Infection



Hepatitis B Virus



- Nucleic Acid: 3.2 kb DNA
- Classification: *Hepadnaviridae*
- Multiple serotypes and genotypes A-J
- Enveloped
- In vitro model: primary hepatocyte culture and transfection of cloned HBV DNA
- In vivo replication: in cytoplasm, cccDNA in nucleus; hepatocyte and other tissues, human and other primates

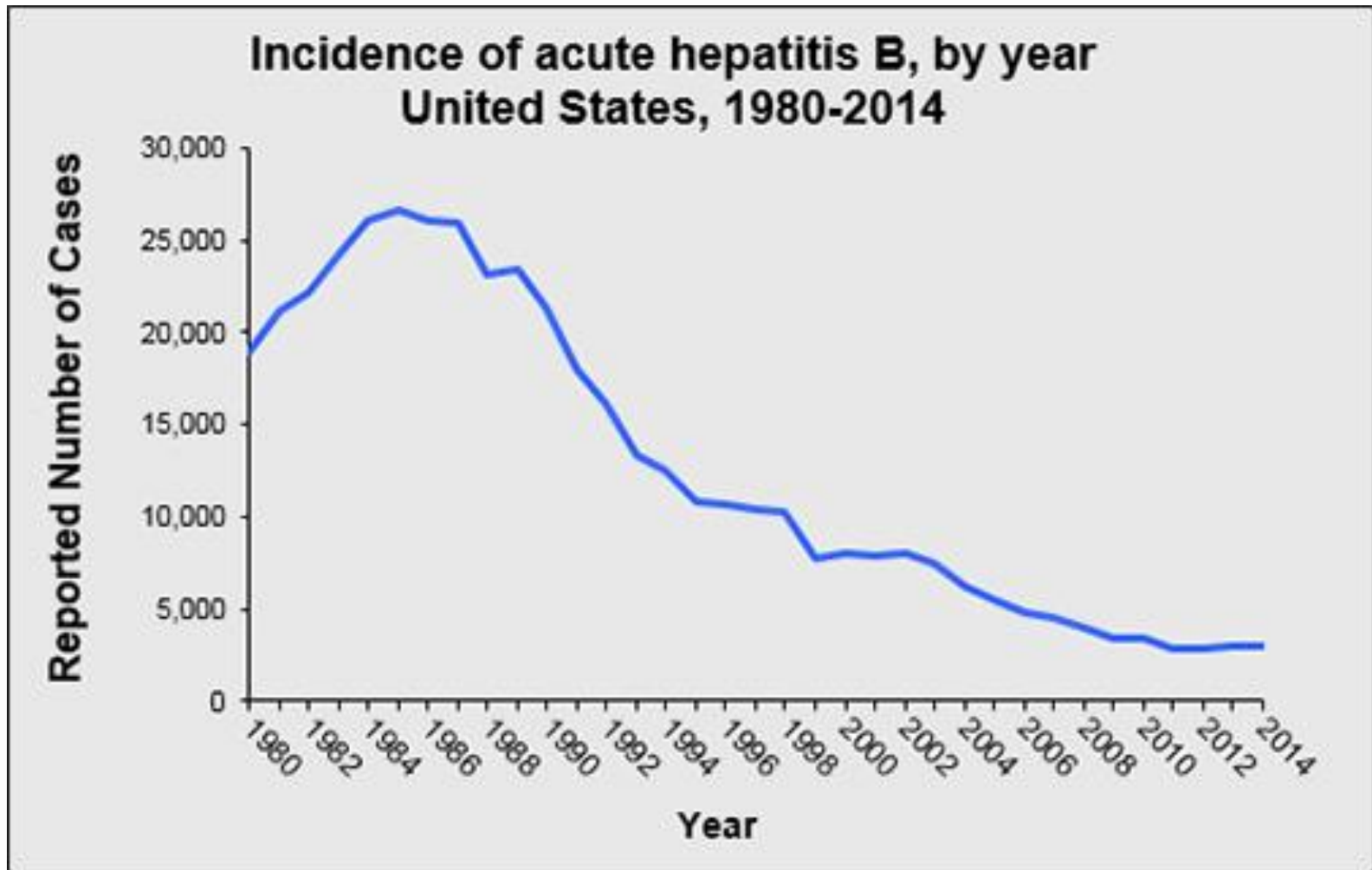
Hepatitis B Infection

- It is estimated that there were about 257 millions of carriers worldwide and about 887,000 HBV-related liver disease deaths were reported that year.
- CDC estimated about 21,900 cases of acute hepatitis B in 2015.
- USA: 850,000 to 2.2 million cases of chronic hepatitis B

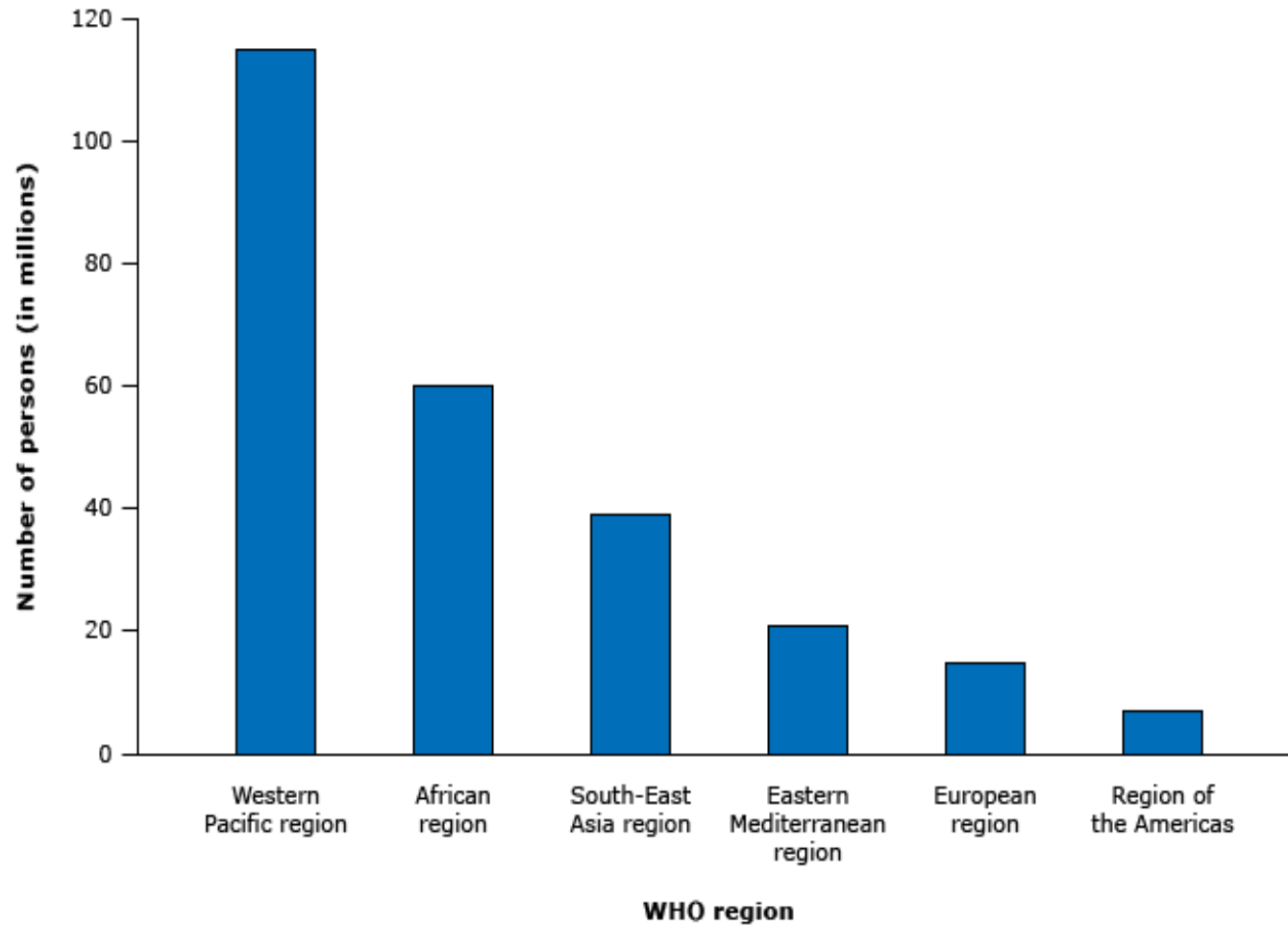
Hepatitis B Infection

- The rate of new HBV infections has declined by approximately 82% since 1991
- The wide range in the prevalence of chronic hepatitis B in the world is related to different ages at diagnosis.
 - Age is inversely related to the risk of chronicity
 - Perinatally HBV infection → 90% risk of chronicity

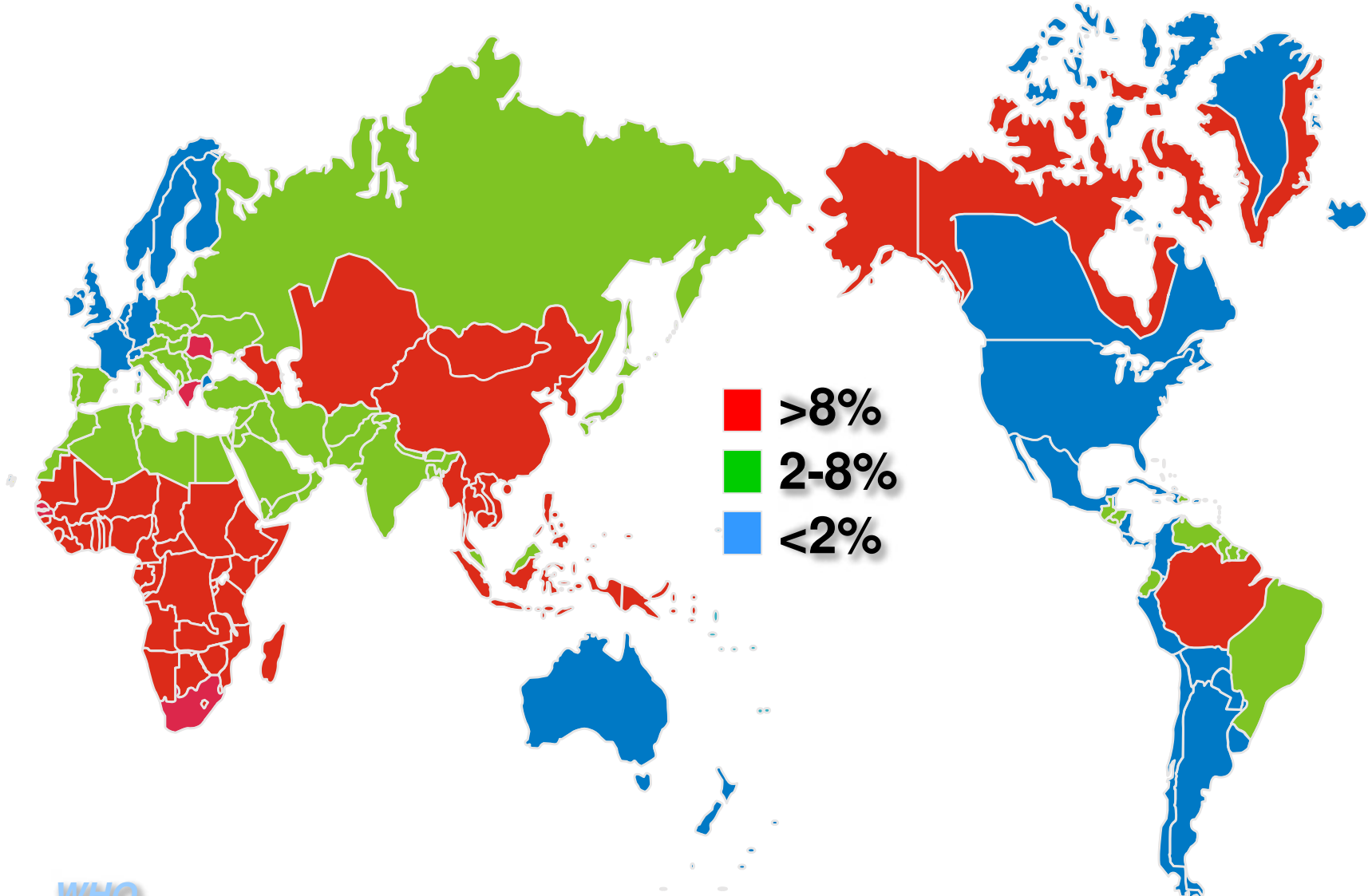
HBV - Epidemiology



Prevalence of chronic HBV infection in the general population by WHO region, 2015



Prevalence of HBsAg Carrier State



Risk Factors for Infection

- Percutaneous

- Injection drug use
- Transfusion or transplant
- Occupational exposure
- Parenteral practices

- Per mucosal

- Perinatal
- Sexual
- Household contact

HBV - Epidemiology

Populations at increased risk of becoming infected with HBV

- Infants born to infected mothers
- Sex partners of infected persons
- Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., >1 sex partner during the previous 6 months)
- Men who have sex with men
- Injection drug users
- Household contacts of persons with chronic HBV infection

HBV - Epidemiology

Populations at increased risk of becoming infected with HBV

- Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids
- Hemodialysis patients
- Residents and staff of facilities for developmentally disabled persons
- Travelers ***to countries with intermediate or high prevalence of HBV infection***

Signs and Symptoms of HBV Infection

- Most children under age 5 years and newly infected immunosuppressed adults are asymptomatic
- 30%–50% of persons aged ≥ 5 years have initial signs and symptoms
- Symptoms begin an average of 90 days (range: 60–150 days) after exposure to HBV
- Symptoms typically last for several weeks but can persist for up to 6 months.

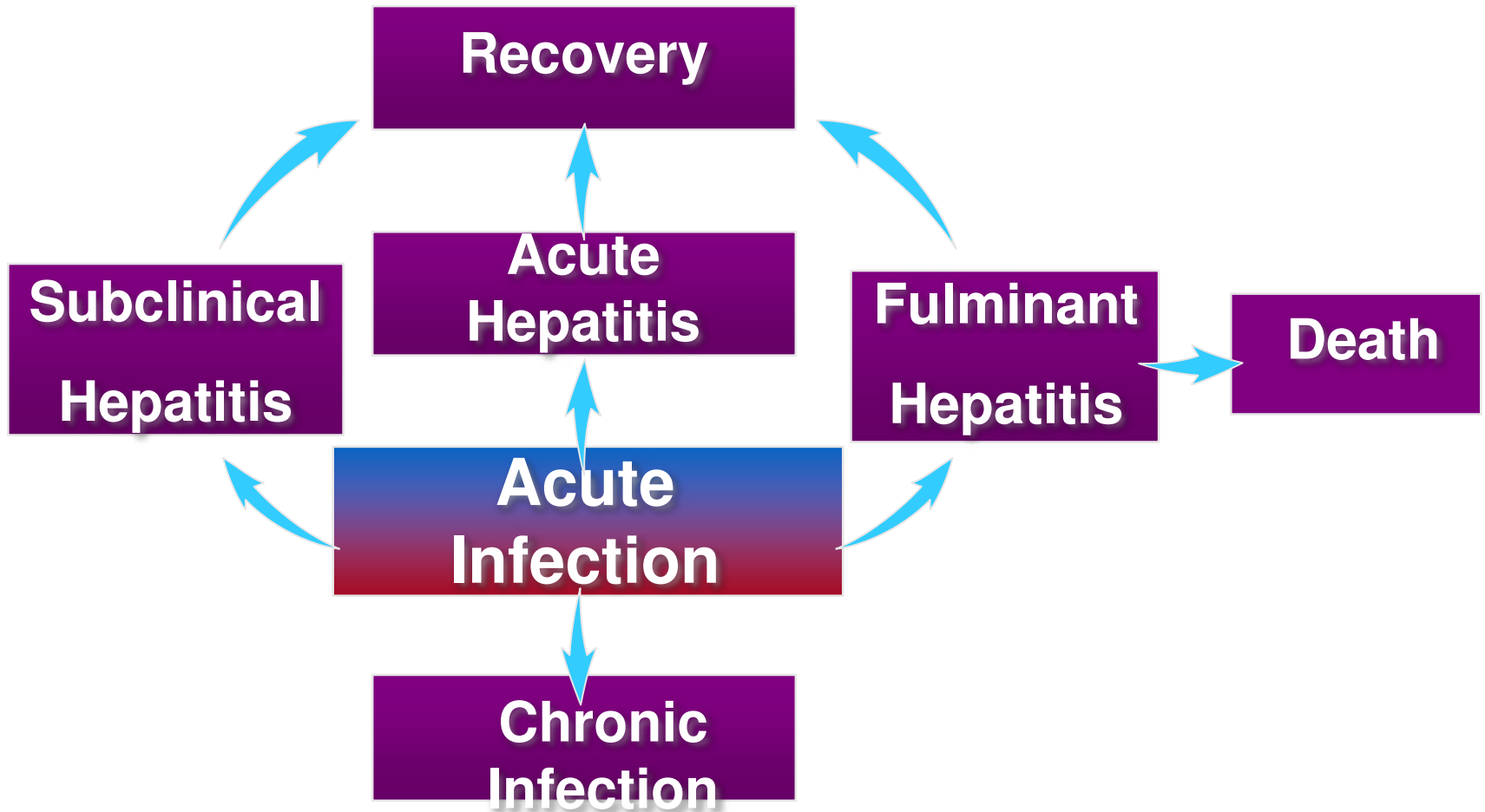
Signs and Symptoms of HBV Infection

- Acute infection ranges from asymptomatic or mild disease to rarely fulminant hepatitis
- Persons with chronic HBV infection:
 - might be asymptomatic
 - have no evidence of liver disease
 - have a spectrum of disease ranging from chronic hepatitis to cirrhosis or hepatocellular carcinoma

Signs and Symptoms of HBV Infection

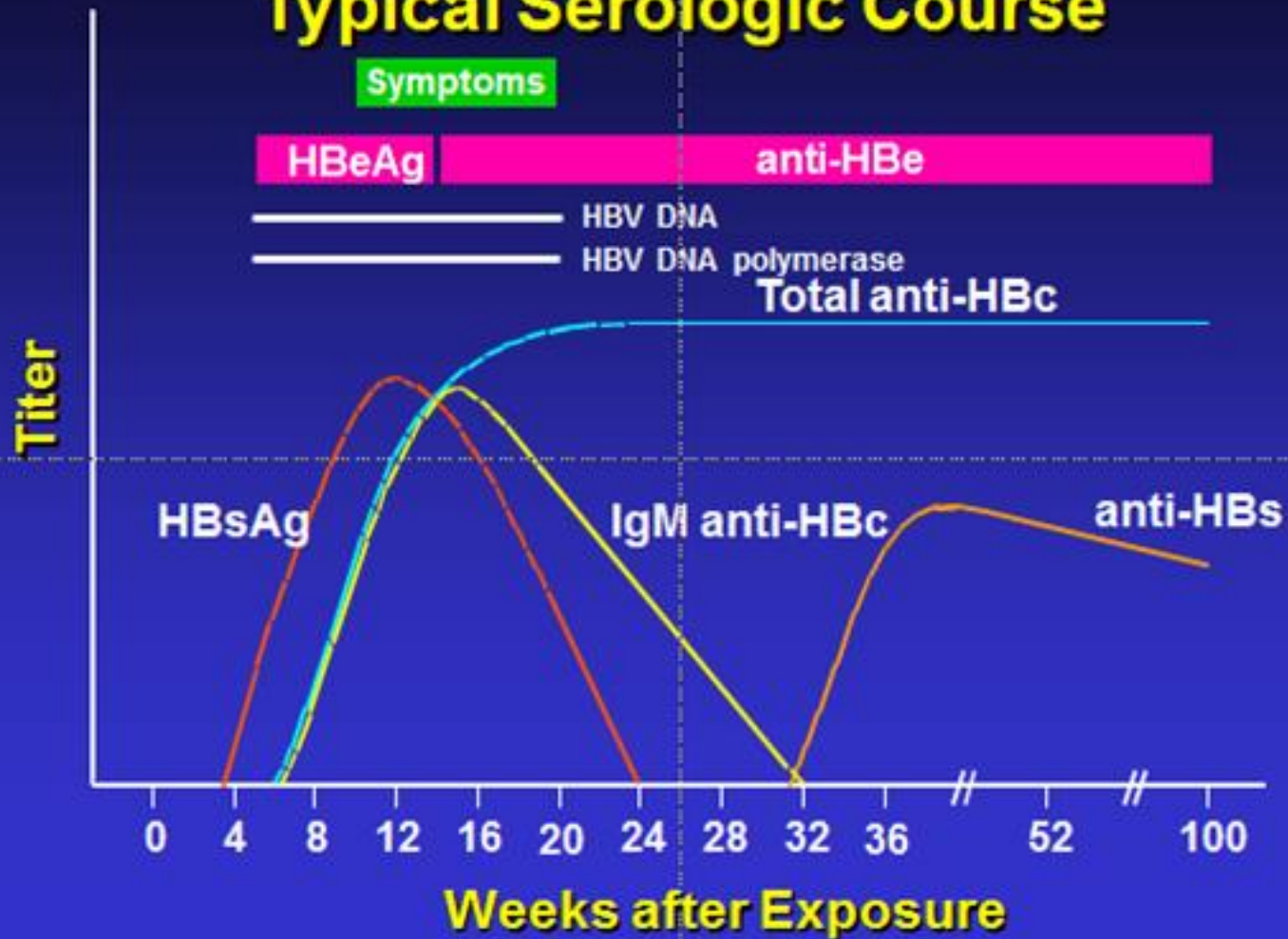
- Fever
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Abdominal pain
- Dark urine
- Clay-colored bowel movements
- Joint pain
- Jaundice

Outcome of Acute HBV Infection

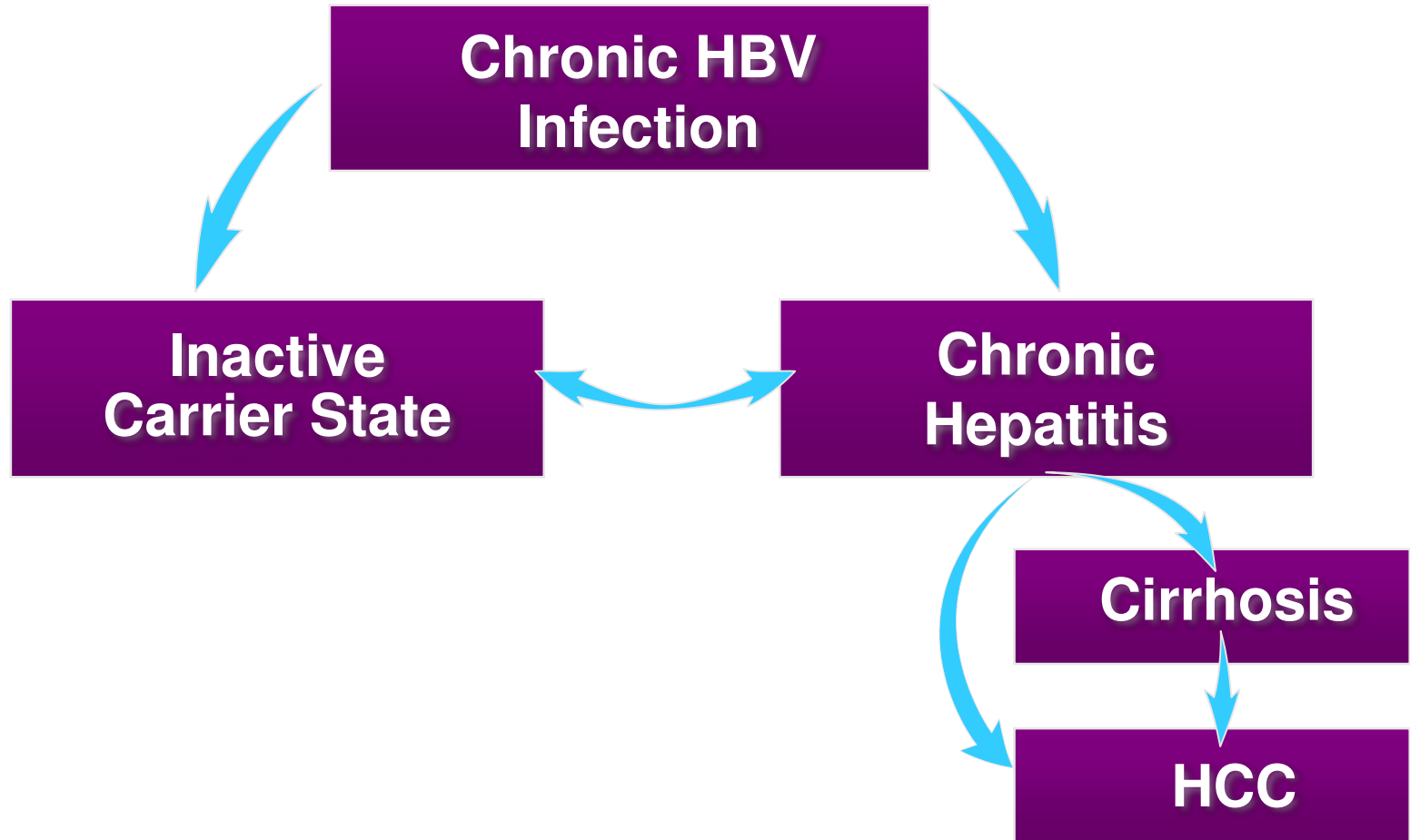


Acute Hepatitis B Virus Infection with Recovery

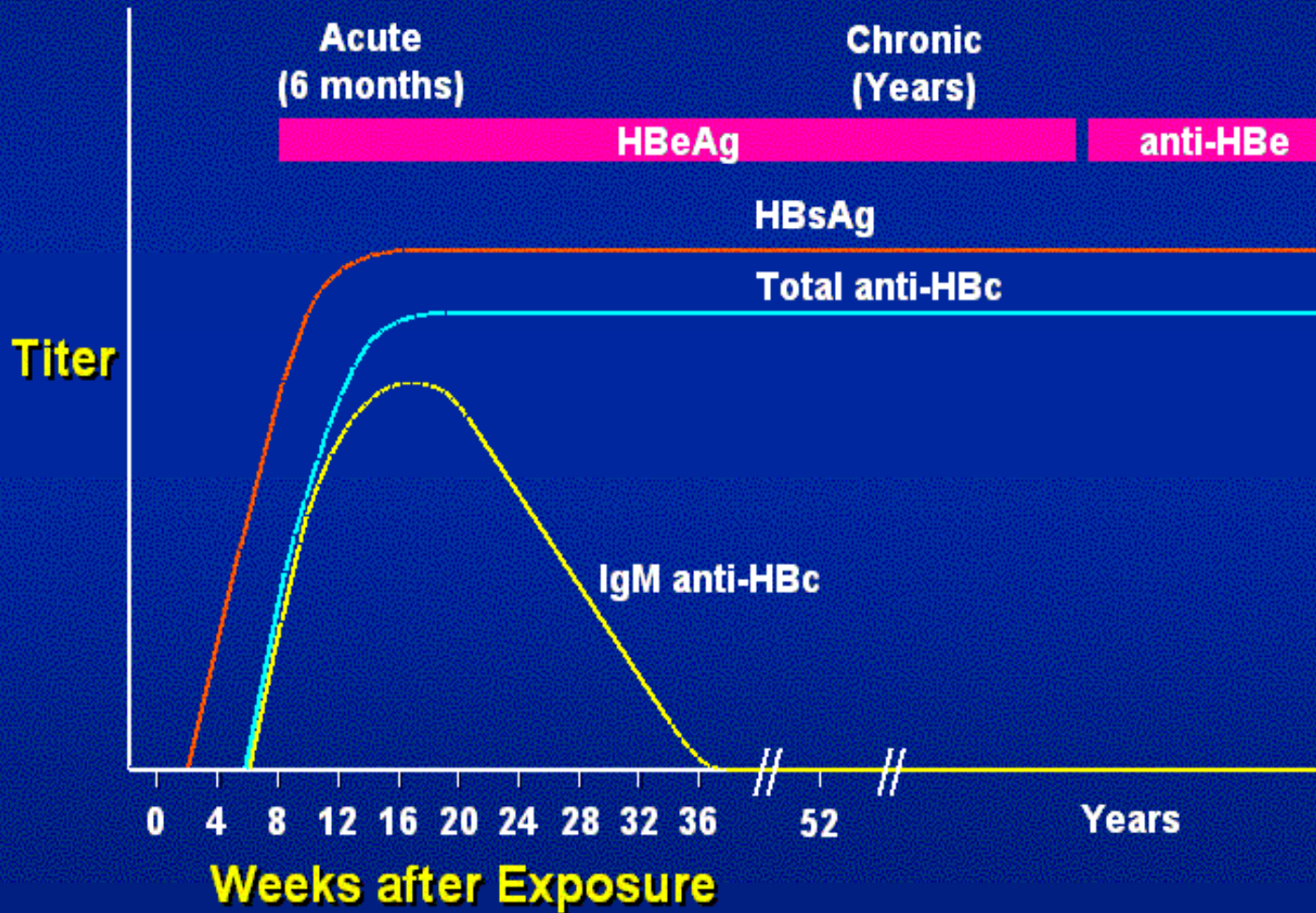
Typical Serologic Course



Outcome of Chronic HBV Infection



Progression to Chronic Hepatitis B Virus Infection Typical Serologic Course



Diagnostic Criteria *Resolved Hepatitis B*

- Previous history of acute or chronic hepatitis B
- HBsAg-
- Anti-HBc+ , anti-HBs+
- Serum HBV DNA < 10^3 copies/ml
- Normal ALT

Diagnostic Criteria *Chronic Hepatitis B*

- HBsAg+ > 6 months
- Serum HBV DNA > 10^5 copies/ml
- Persistent or intermittent elevation in ALT
- Liver biopsy HAI \geq 4 (optional)

Diagnostic Criteria *Inactive HBsAg Carrier State*

- HBsAg+ > 6 months
- HBeAg- , anti-HBe+
- Serum HBV DNA < 10^5 copies/ml
- Persistently normal ALT

HBV - Diagnosis

Serological Markers

HBsAg

Anti-HBc IgM

HBeAg

Anti-HBe

Anti-HBs

Anti-HBc IgG and HBsAg

Anti-HBc IgG and anti-HBs

Clinical Significance

Acute/Chronic

Acute infection

High infectivity

Low infectivity

Immunity

Chronic infection

Resolved infection

TABLE 4. Interpretation of Screening Tests for HBV Infection

Screening Test Results

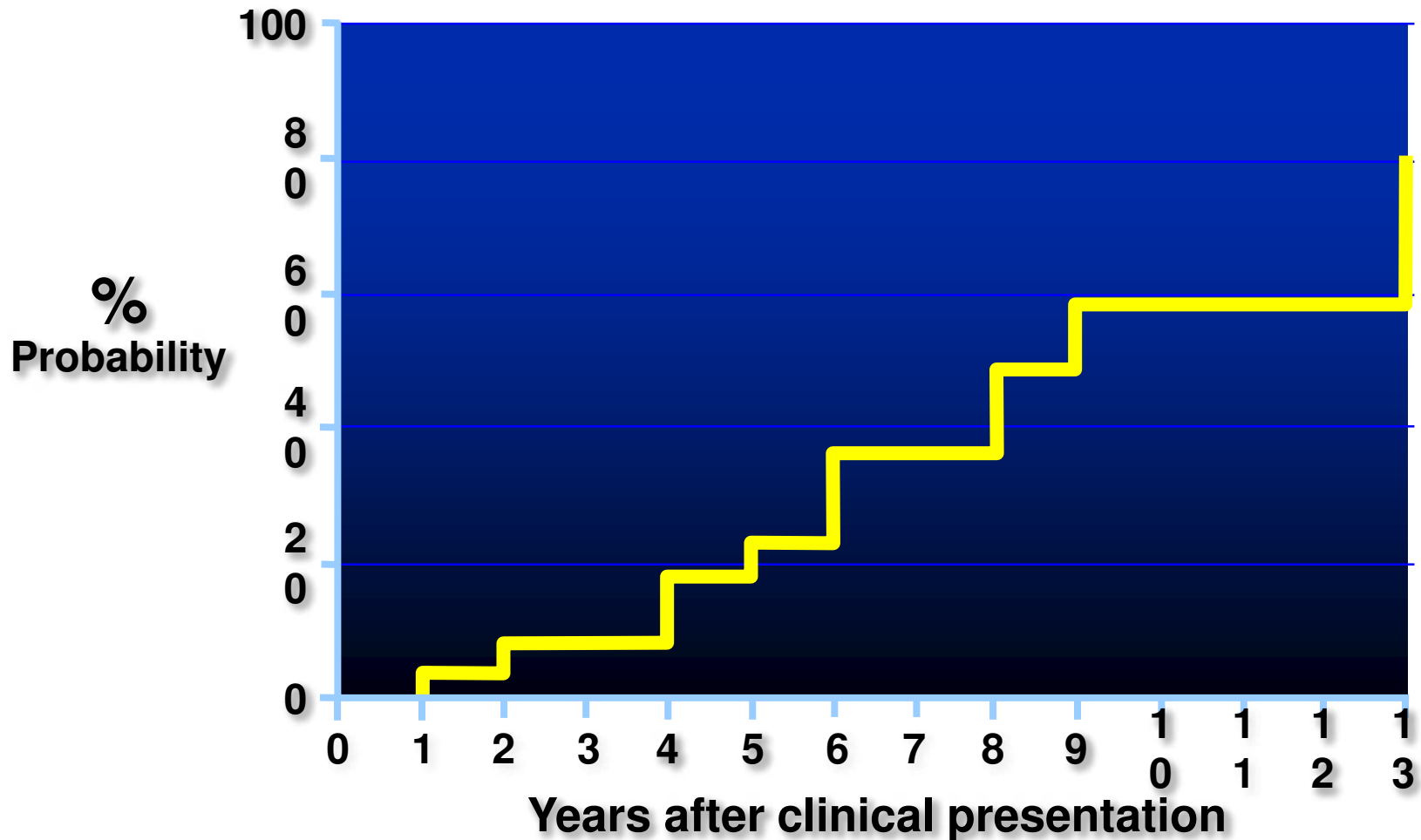
HBsAg	Anti-HBc	Anti-HBs	Interpretation	Management	Vaccinate?
+	+	-	Chronic hepatitis B	Additional testing and management needed	No
-	+	+	Past HBV infection, resolved	No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy	No
-	+	-	Past HBV infection, resolved or false-positive	HBV DNA testing if immunocompromised patient	Yes, if not from area of intermediate or high endemicity
-	-	+	Immune	No further testing	No
-	-	-	Uninfected and not immune	No further testing	Yes

Evaluation of Patients with Chronic Hepatitis B

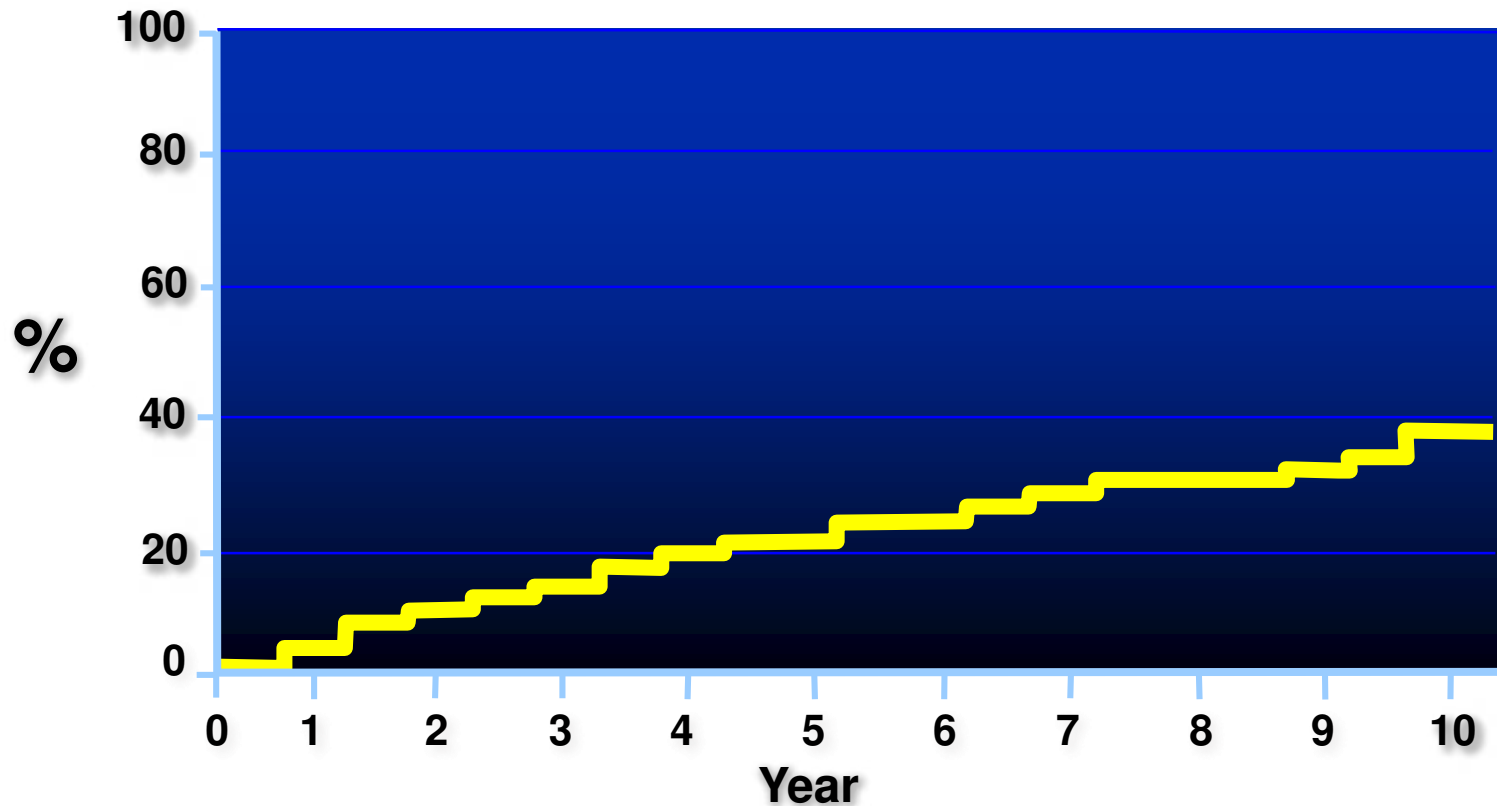
- History and physical exam
- Assessment of liver disease activity and liver function
- HBV DNA PCR quantitative
- Tests for possible co-infection with HIV, HDV and HCV
- Liver biopsy
- Fibrosure, Fibroscan
- Imaging studies (abdominal ultrasound, CT scan or MRI)

HBV - Natural History

Overall Risk of Progression to Cirrhosis



Probability of Decompensation in HBsAg+ Patients with Cirrhosis



HBV - Natural History

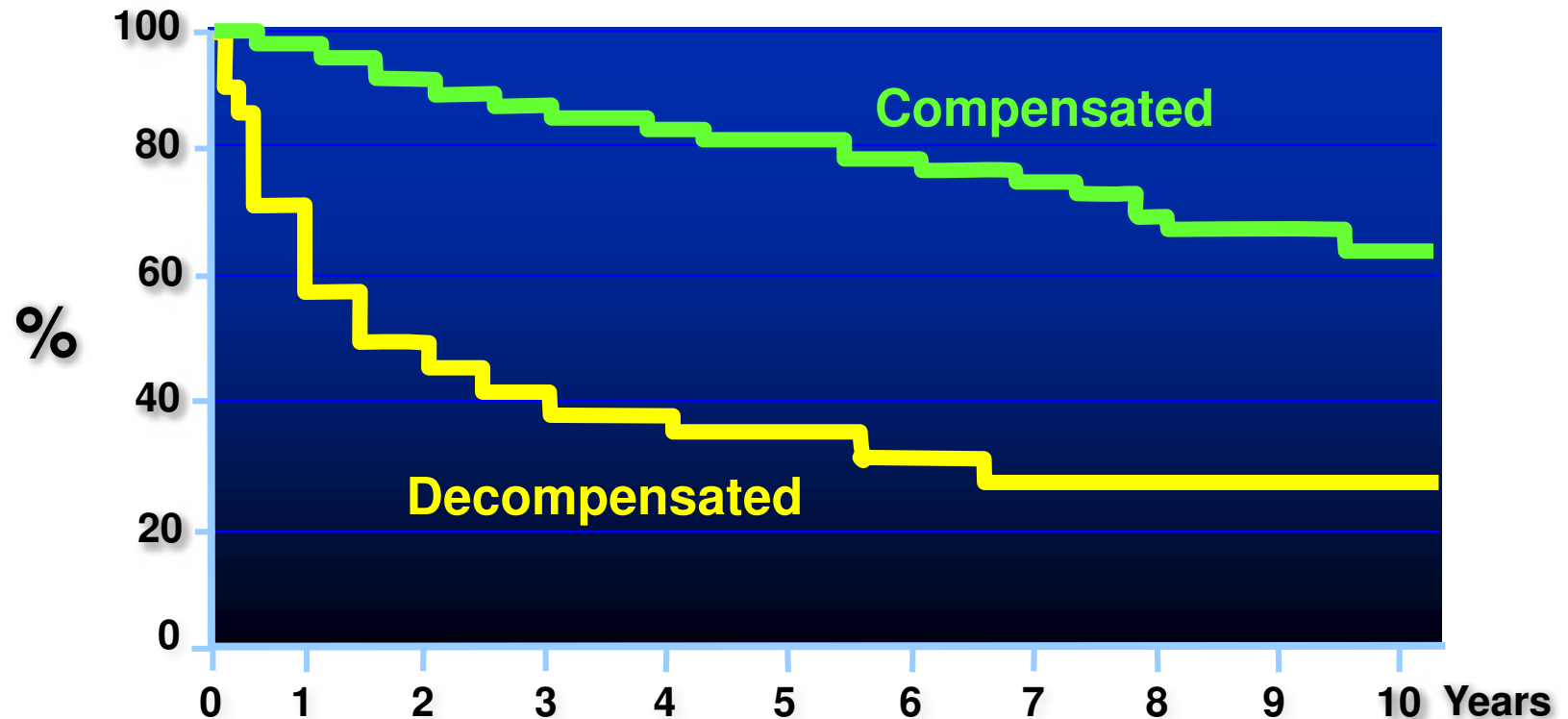
Survival of Patients with HBsAg+ Cirrhosis

Baseline variables associated with diminished survival

- Advanced age
- Low albumin
- Low platelets

- Splenomegaly
- Increased bilirubin
- HBeAg+

Effect of Decompensation on Survival of Patients with Cirrhosis

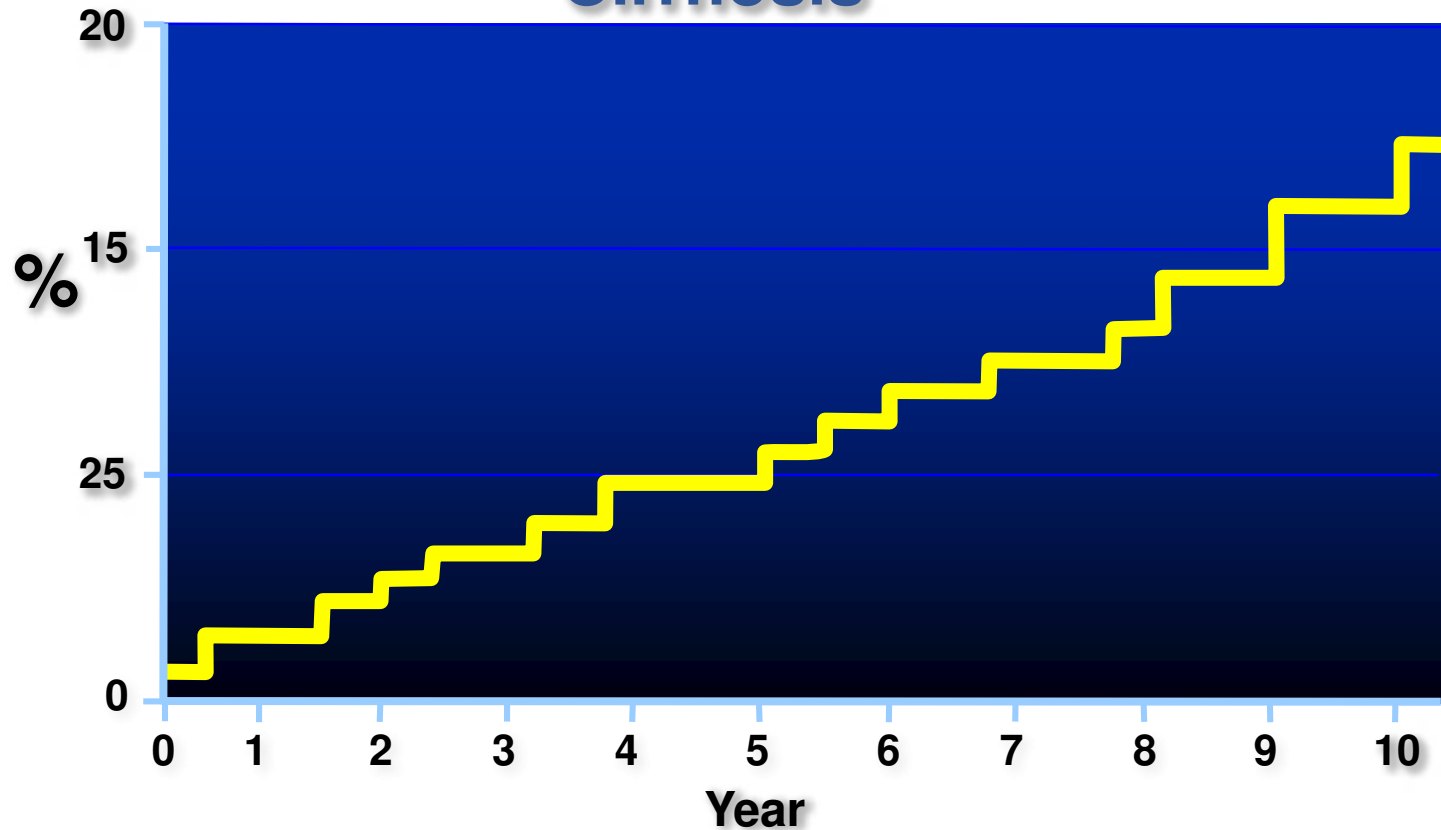


Fattovich G, et al., Hepatology 1995; 21:77

Realdi G, et al., J Hepatol 1994; 21:656

HBV - Natural History

Cumulative Probability of Developing HCC in Patients with HBsAg + Compensated Cirrhosis



Fattovich, et al., Hepatology 1995; 21:77

Survival of HBsAg+ Patients with Compensated Cirrhosis

Events during follow-up associated with improved survival

- *Biochemical remission*
- *HBeAg clearance*
- *HBV DNA clearance*

Indications of Treatment

Chronic infection

- **HBsAg+ >6 months**

Replicative infection

- **HBV DNA > 10⁵ copies/ml**
HBeAg positive or negative

Active liver disease

- **ALT >2 x normal**
Chronic hepatitis ±cirrhosis

Goals of Antiviral Treatment of Chronic Hepatitis B

1. Sustained suppression of HBV replication

Decrease in serum HBV DNA to $<10^5$ copies/ml

HBeAg to anti-HBe seroconversion

HBsAg to anti-HBs seroconversion

2. Remission of liver disease

Normalization of serum ALT levels

Decreased necroinflammation in liver

3. Improvement in clinical outcome

Decreased risks of developing cirrhosis, liver failure and HCC

Increased survival

Definition and Criteria of Treatment Response

Categories of Response:

- Biochemical - ALT decrease to normal
- Virological - HBV DNA decrease to $< 10^5$ copies/ml
- Loss of HBeAg in HBeAg+ patients
- Histological - Decrease in necroinflammatory score by 2 points or more

Timing of Assessment:

- On Therapy - During treatment
- Sustained - 6 - 12 months post-treatment

Available Therapies for Hepatitis B

- Epivir-HBV (lamivudine)
- Intron A (interferon alfa 2-b)
- Pegasys (peginterferon alfa 2-a)
- Hepsera (adefovir dipivoxir)
- Baraclude (entecavir)
- Viread (tenofovir disoproxyl fumarate)
- Vemlidy (tenofovir alafenamide)

HBV and HCV Coinfection

WARNING



- Test all patients for evidence of previous Hepatitis B infection before start HCV therapy. There is a risk of HBV reactivation with direct acting antivirals (DAAs) that could lead to fulminant hepatitis, hepatic failure, and eventually dead.

Vaccine Indications

- HBIG and HB vaccine to infants of HBsAg+ mothers
- Routine vaccination of infants and adolescents
- Catch-up vaccination of children
- Vaccination of adults at risk of infection

Indications in Adults

- Sexual and household contacts of carriers
- Sexually active individuals with multiple sex partners
- Men who have sex with men
- Injection drug users
- Hemodialysis patients
- Recipients of clotting factor concentrates
- Families of adoptees from endemic areas

Indications in Adults (con' t.)

- Health care and public safety workers with occupational risks
- Persons in institutions for the developmentally disabled or in long-term correctional facilities
- Travelers to countries endemic for hepatitis B who plan to stay > 6 months
- Transplant candidates before transplantation
- Patients with chronic liver disease

HBV - Vaccine

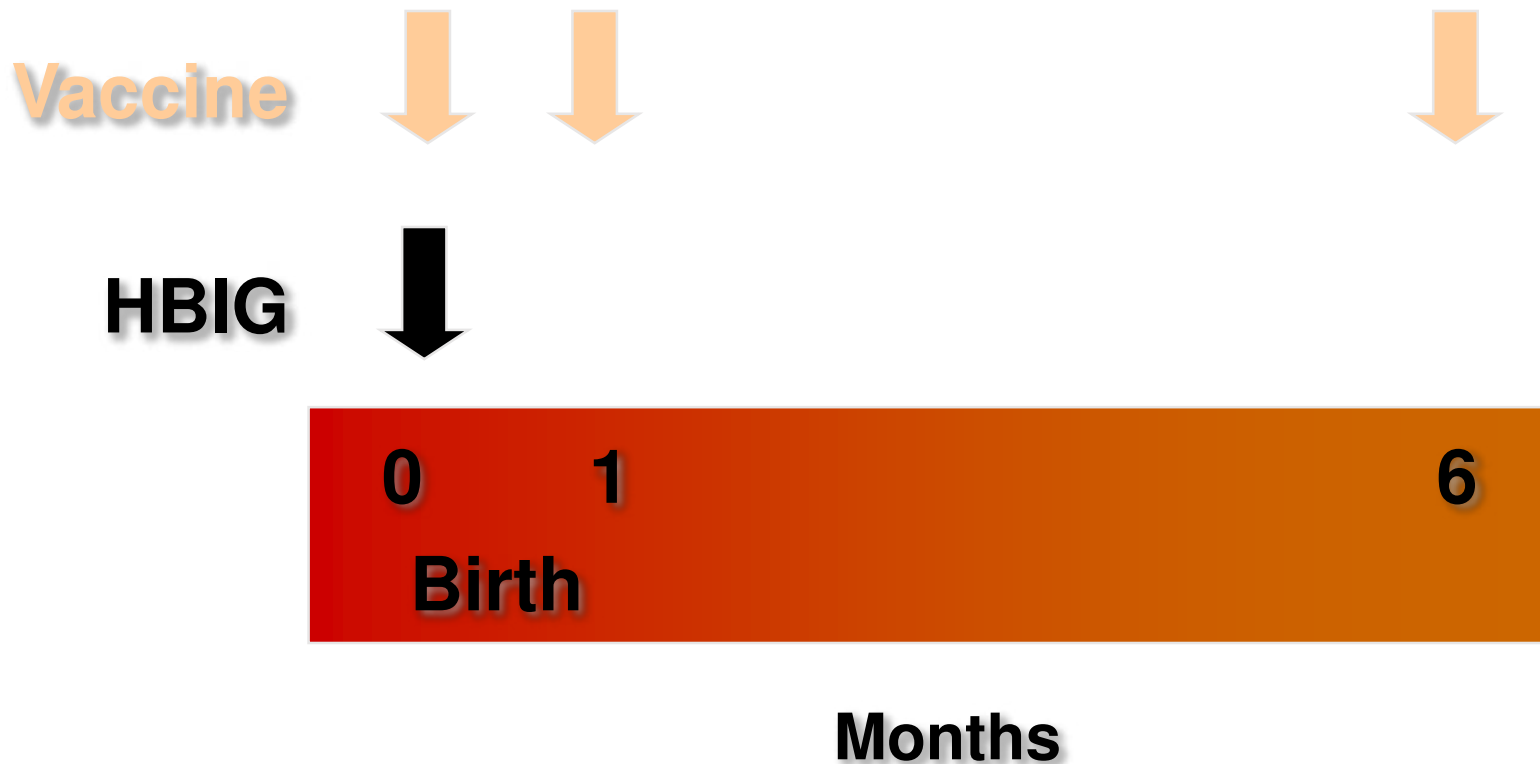
Dose Schedule

Vaccine	Age Group	Dose (ug)	Volume (ml)	# Doses
Engerix-B	0-19 yr	10	0.5	3 (mo 0,1,6)
	≥ 20 yr	20	1.0	3 (mo 0,1,6)
	Adults on hemodialysis	40	2.0	4 (mo 0,1,2,6)
Recombivax HB (Optional 2-dose)	0-19 yr	5	0.5	3 (mo 0,1,6)
	≥ 20 yr	10	1.0	3 (mo 0,1,6)
	11-15 yr	10	1.0	2 (mo 0, 4-6)
	Adults on hemodialysis	40	1.0*	3 (mo 0,1,6)

*Special Formulation

HBV - Vaccine

Neonates of HBsAg+ Mothers



Combined HAV and HBV - Vaccine

Twinrix

- Bivalent HAV and HBV vaccine
- 1ml contains 720 ELISA Units of inactivated HAV and 20 ug of recombinant HBsAg protein
- Dosage: 1 ml at 0, 1, 6 months
- Recommended for all susceptible persons ≥ 18 years at risk of exposure to both HAV and HBV, including travelers to areas of high/intermediate endemicity for both viruses

Pre-vaccination Testing

Not recommended for:

- Routine infant, childhood or adolescent vaccination
- Worker at occupational risk

May be cost-effective in adult populations with:

- HBsAg carrier rate $> 2\%$, or
- Overall infection (anti-HBc+) rate $> 30\%$

Vaccine Efficacy

Definition of
protective response

Anti-HBs >10 IU/L

Prevention of infection

- Pre-exposure - Immunocompetent adults and children >95%
- Post-exposure - Infants born to HBsAg + mothers
 - Vaccine alone 65%-95%
 - Vaccine + HBIG 85%-95%

Post-vaccination Anti-HBs Testing

Recommended for

- Infants born to HBsAg+ mothers
- Dialysis patients
- Immunocompromised persons at continued risk
- Sexual partners of HBsAg+ carriers
- Persons with occupational risk of blood exposure

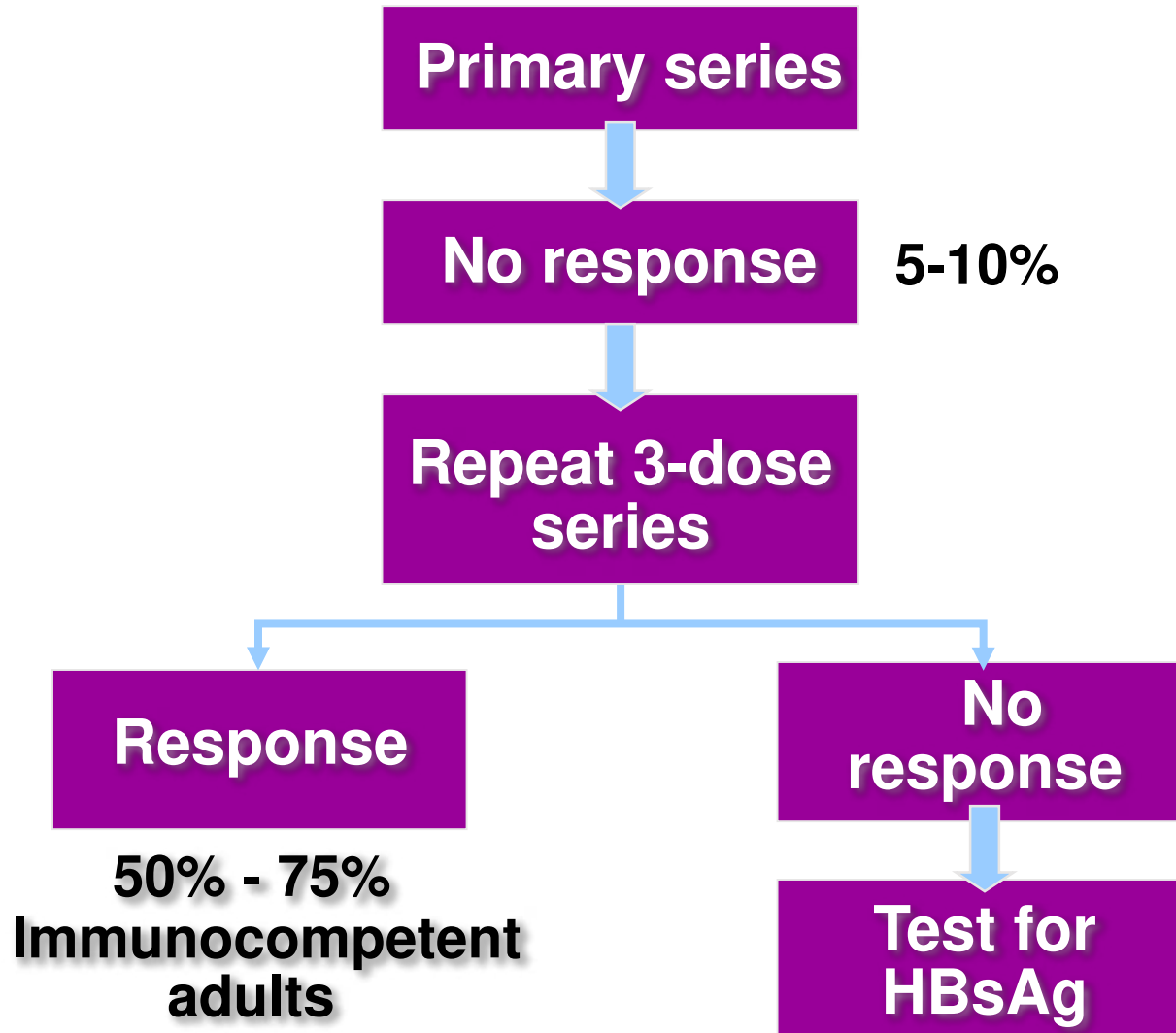
Booster Doses Recommended Only For

Hemodialysis patients

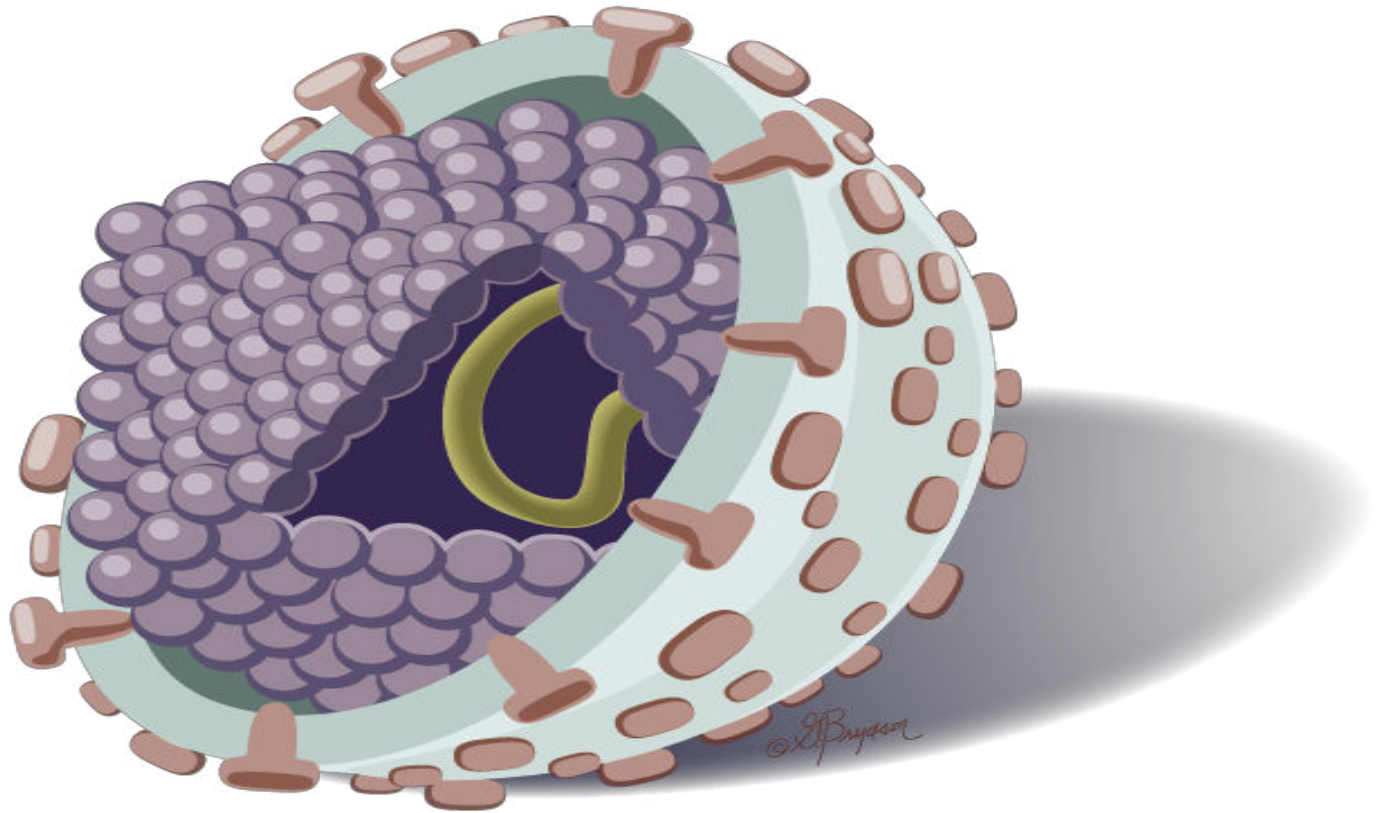
- Annual anti-HBs testing
- Booster dose when
anti-HBs titer <10 IU/L

**Immunocompromised persons with continuing
increased risk of infection**

Management of Non-responders

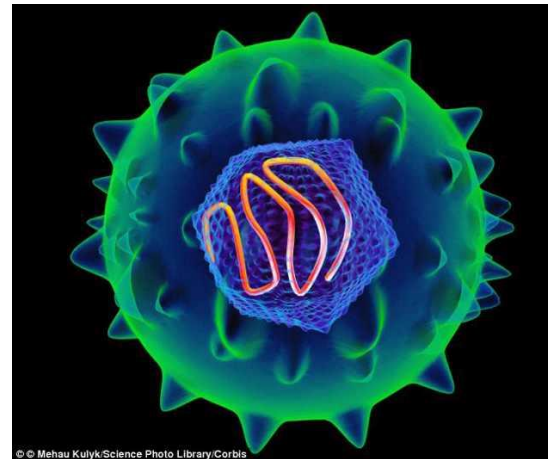


Hepatitis C Infection



Hepatitis C Virus

- Single stranded ribonucleic acid (RNA virus)
- Initially described as Non A Non B Hepatitis
- Has a rapid replication rate
- Lacks proofreading ability
- High degree of genetic diversity
- Six distinct genotypes



Prevalence

Worldwide 170 million (3%)



United States 3.2 million (1.9%)

Puerto Rico (2.3%); San Juan (6%)

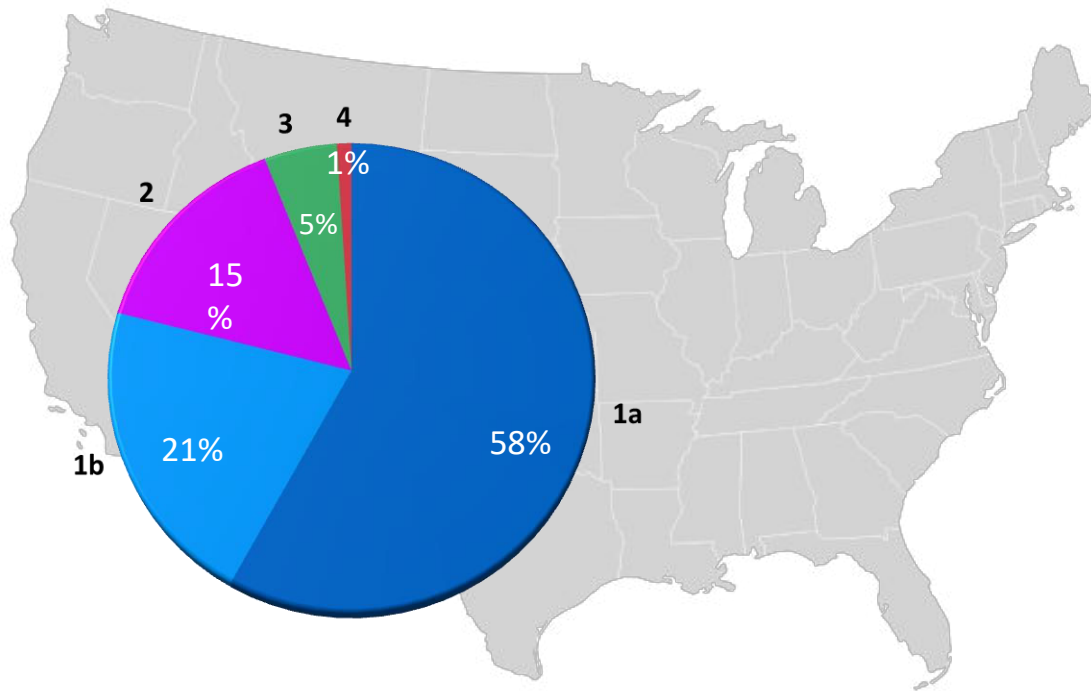
Alter MJ et al., New Engl J Med 1999; 341:556

Lavanchy D & McMahon B, In: Liang TJ & Hoofnagle JH (eds.);

Denniston 2014

Perez Cynthia 2010

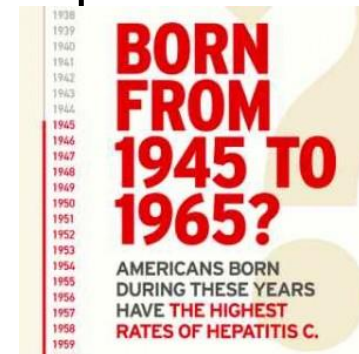
Distribution of HCV Genotypes in US



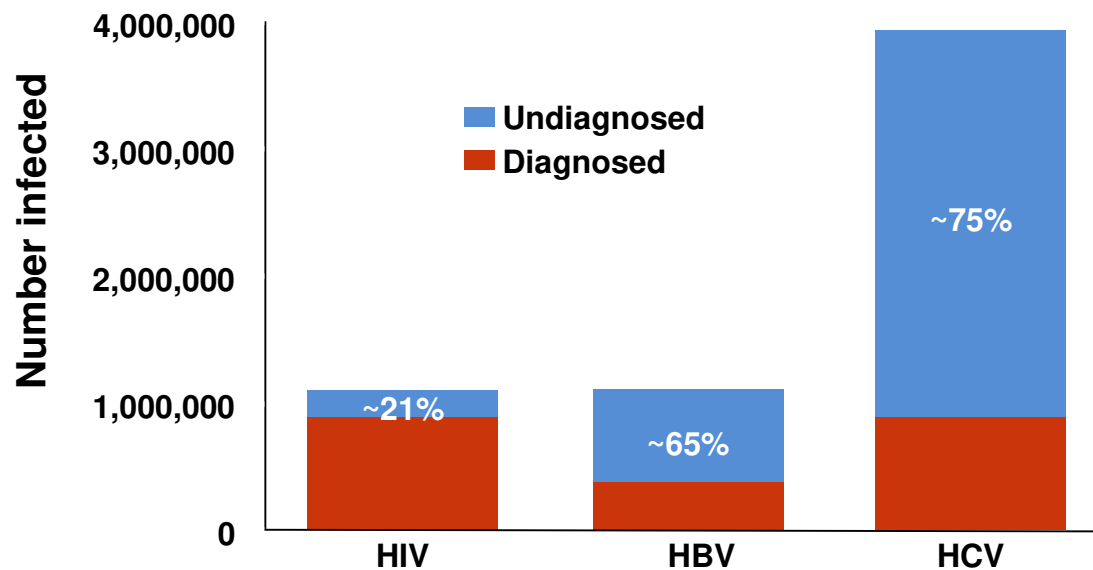
- Genotypes 1a and 1b account for 79%
- Genotype 2 accounts for 15%

Prevalence

- Approximately 3.2 million people are chronically infected with HCV based on NHANES (2001-2008) population
 - ~ 70% born 1945- 1965
- The number chronically infected with HCV in the US may be even higher.
 - Accounting for populations not sampled in NHANES
 - Incarcerated
 - Homeless
 - Nursing Home Residents
 - Hospitalized
 - Those on active military duty

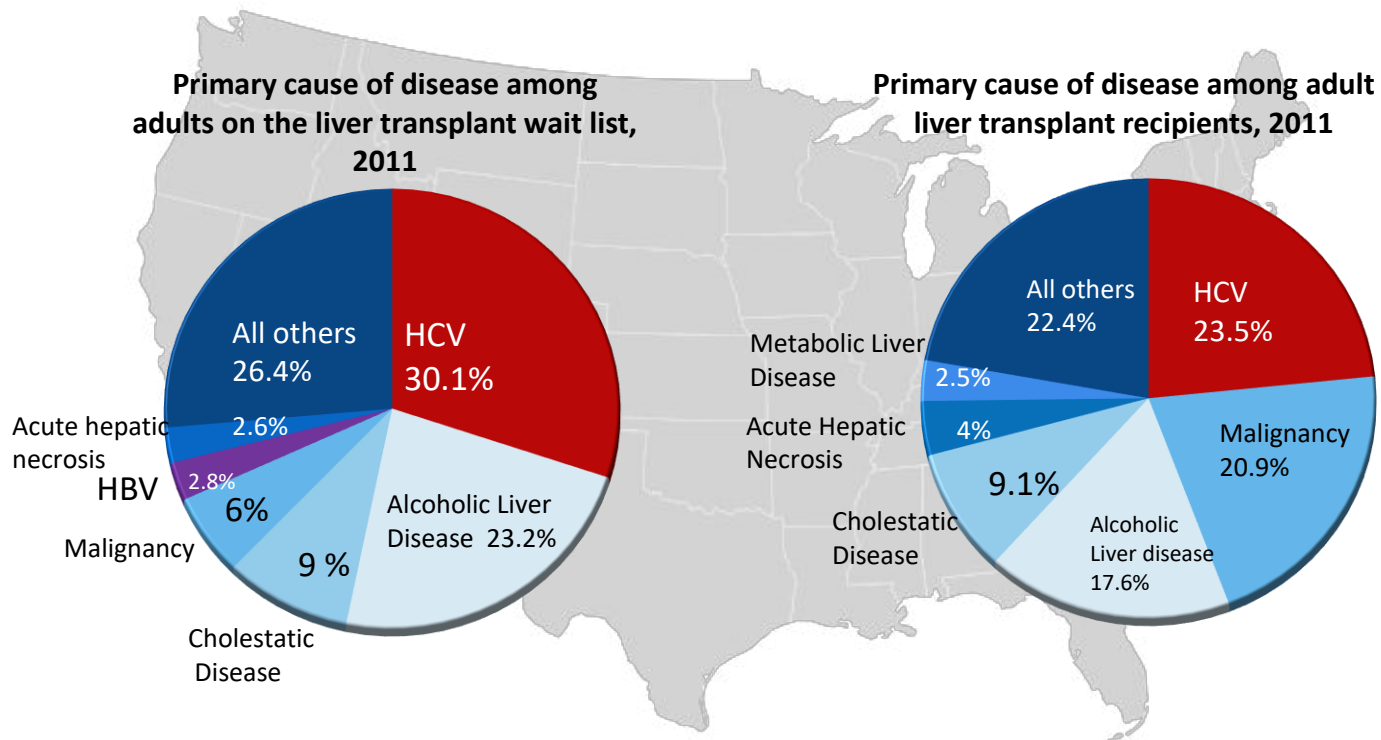


HEPATITIS C IS UNDER-DIAGNOSED IN US



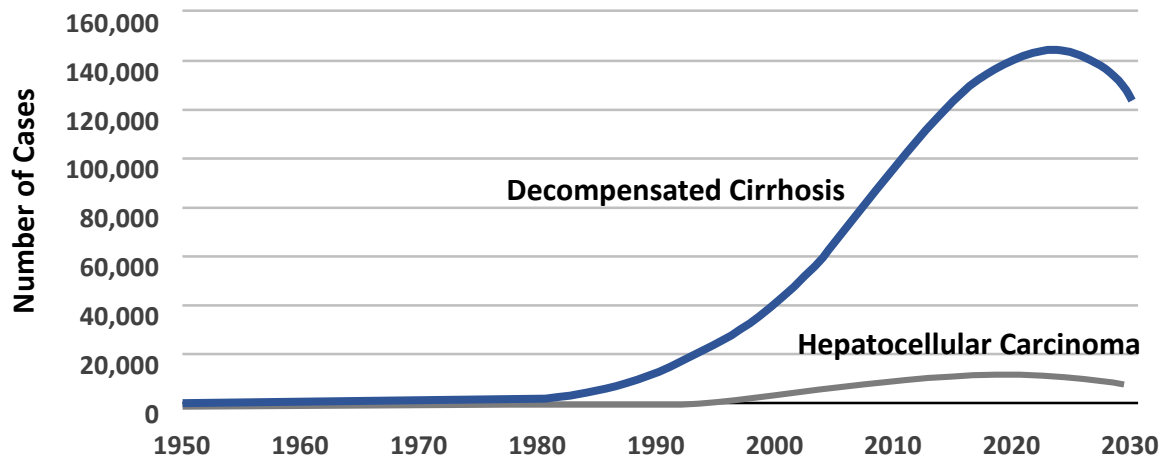
Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*; 2010.

HCV is the leading cause of Liver Transplants in the US



Available at: http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/03_%20liver_12.pdf.

HCV- Related D-Cirrhosis and HCC Projected to Rise in the US

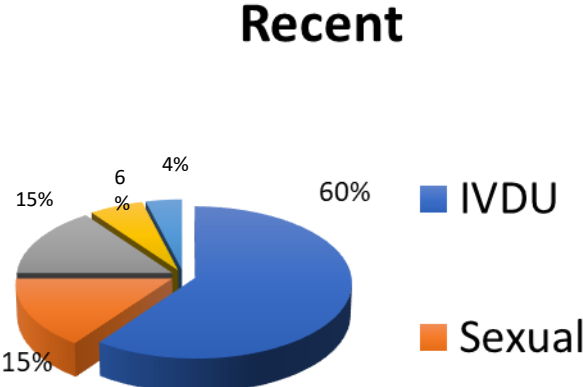
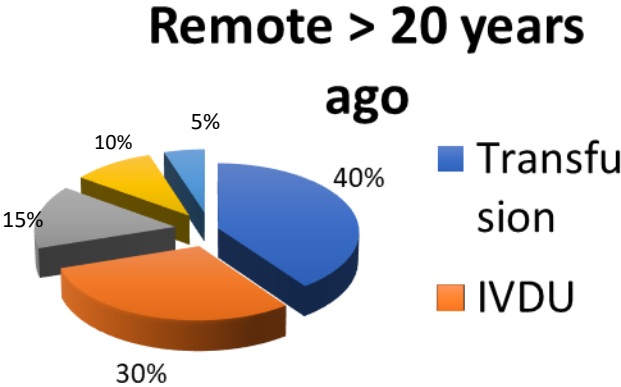


- HCV-related decompensated cirrhosis and HCC are rising as manifestations of liver disease in aging population¹
- 73.4% of HCV-related deaths occurred among persons 45-64 years of age
 - **Median age was 57 years; ~20 years less than the average lifespan of persons living in the US^{2,*}**

Projection based on a dynamic, multicohort, natural history model of data from the CDC, NHANES, and a review of the medical literature, with conservative estimates of disease progression and complications. Model assumes first-year mortality of 80%-85% for HCC.

*During the period from 1999 to 2007.

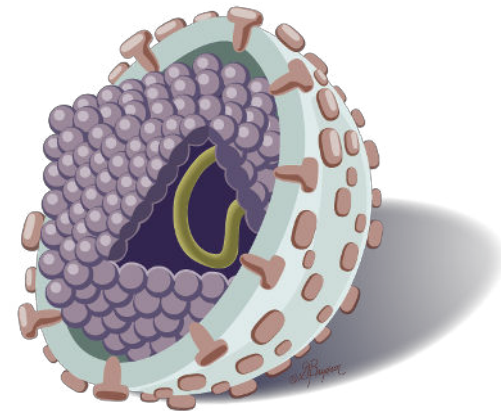
Risk Factors for HCV



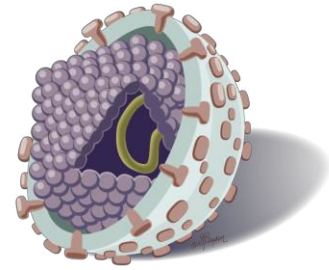
Schiff, Sorrell, Maddrey. Diseases of the liver. 2007; 807-847

Epidemiology

- Incidence of new infection:
 - Most common in young people (20-39 y/o)
 - Hispanics
 - Slight predominance in men
 - 60 % due to IVDU
 - 10-40 % no clear risk factor

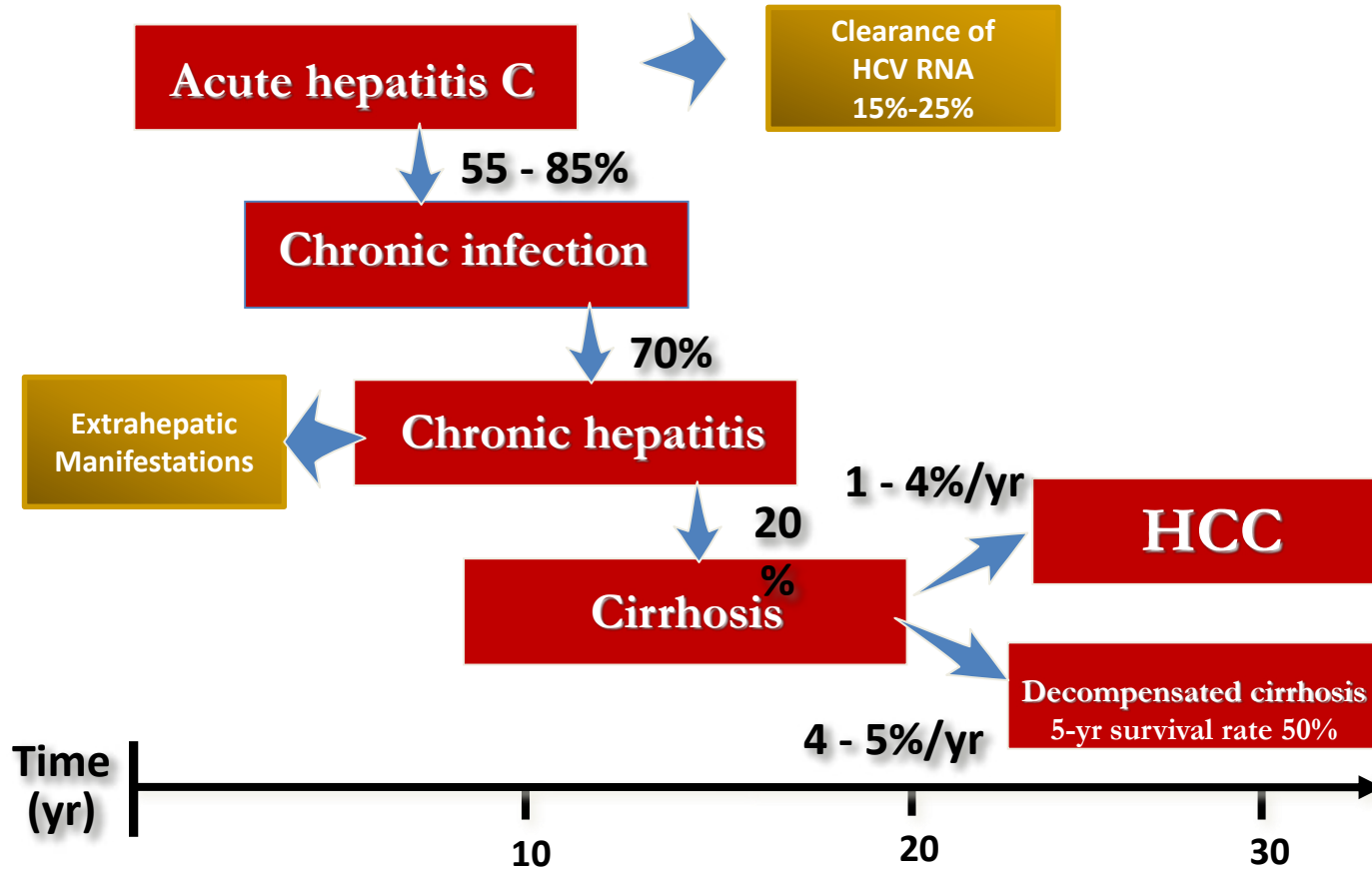


Epidemiology



- Incidence new infection:
 - Blood transfusion now: 0.01%-0.001%
 - Accidental needle stick/sharp exposures: 1.8%
 - Sexual transmission : near zero in monogamous heterosexual couples
 - Perinatal transmission:
 - Ab from mother can last for 1 year in baby's serum
 - In viremic mother: 3.2% risk for baby
 - In viremic mother with HIV: 7.9 % risk for baby
 - HCV not transmitted by breastfeeding

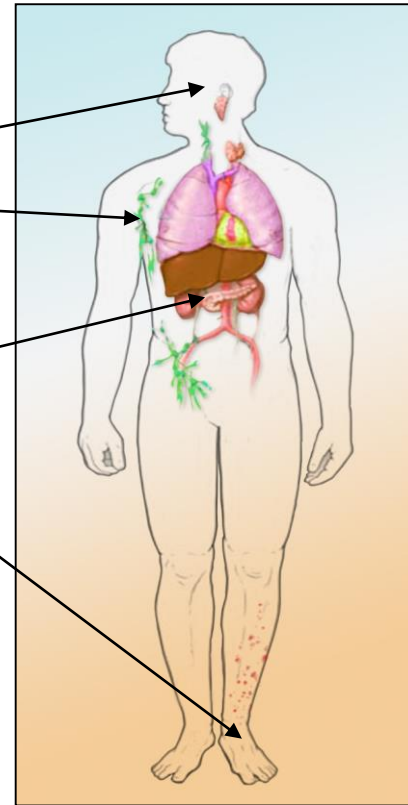
Natural History of HCV Infection



Extrahepatic Manifestations of HCV

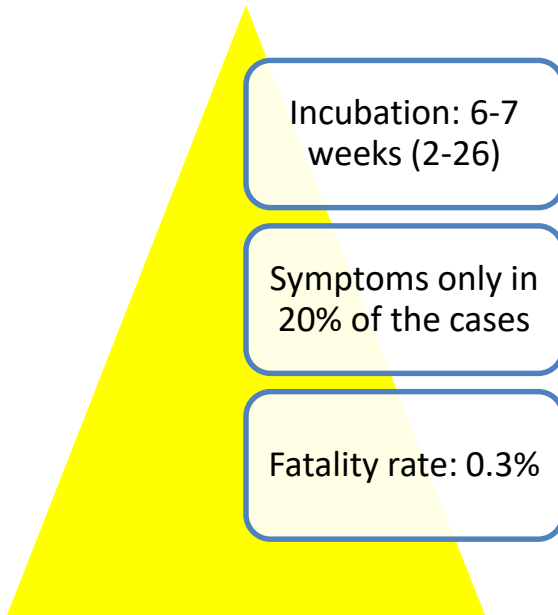
Strongly associated

- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis

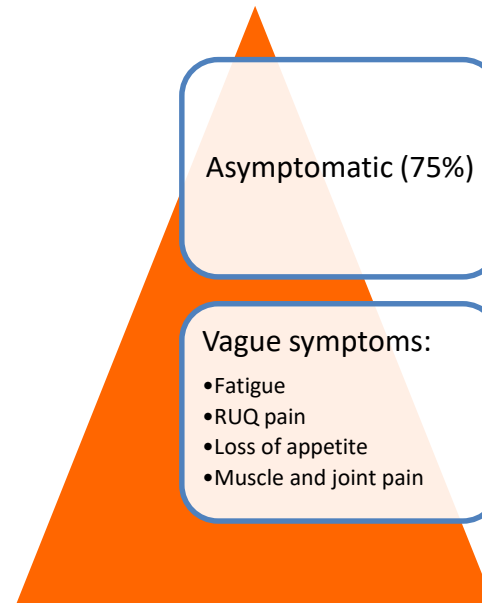


Presentation of Patients Infected with HCV

Acute Infection

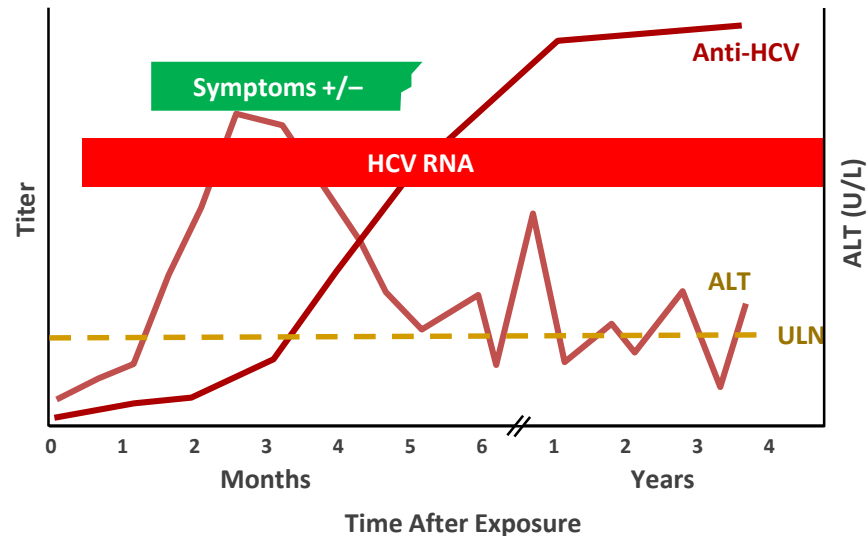


Chronic Infection



Laboratory Diagnosis of Chronic HCV Infection

- RNA testing identifies active disease in HCV-seropositive patients
- HCV antibodies appear by 6–8 weeks following infection¹
 - Can be detected by EIA²
- Serum ALT is not a reliable indicator of liver damage¹
- FDA-approved rapid point-of-care testing is available³
 - OraQuick® HCV Test



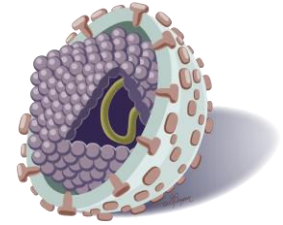
ALT=alanine aminotransferase; EIA=enzyme immunoassay; RNA=ribonucleic acid; ULN=upper limit of normal

Image adapted from MicrobiologyBytes:Virology:HCV¹

1. www.microbiologybytes.com/virology/HCV.html; 2. Alter MJ, et al. *MMWR Recomm Rep.* 2003;52(RR-3):1-13, 15;

3. Shivkumar S, et al. *Ann Intern Med.* 2012;157:558-566.

Natural History HCV



- Usually has a slow progression
- Factors associated to more rapid progression:
 - Alcohol=1.5 to 3 times higher
 - Age= worse if acquired after 50-55 y/o
 - Ethnic background= hispanics and whites
 - Immunosuppression= HIV or post transplant

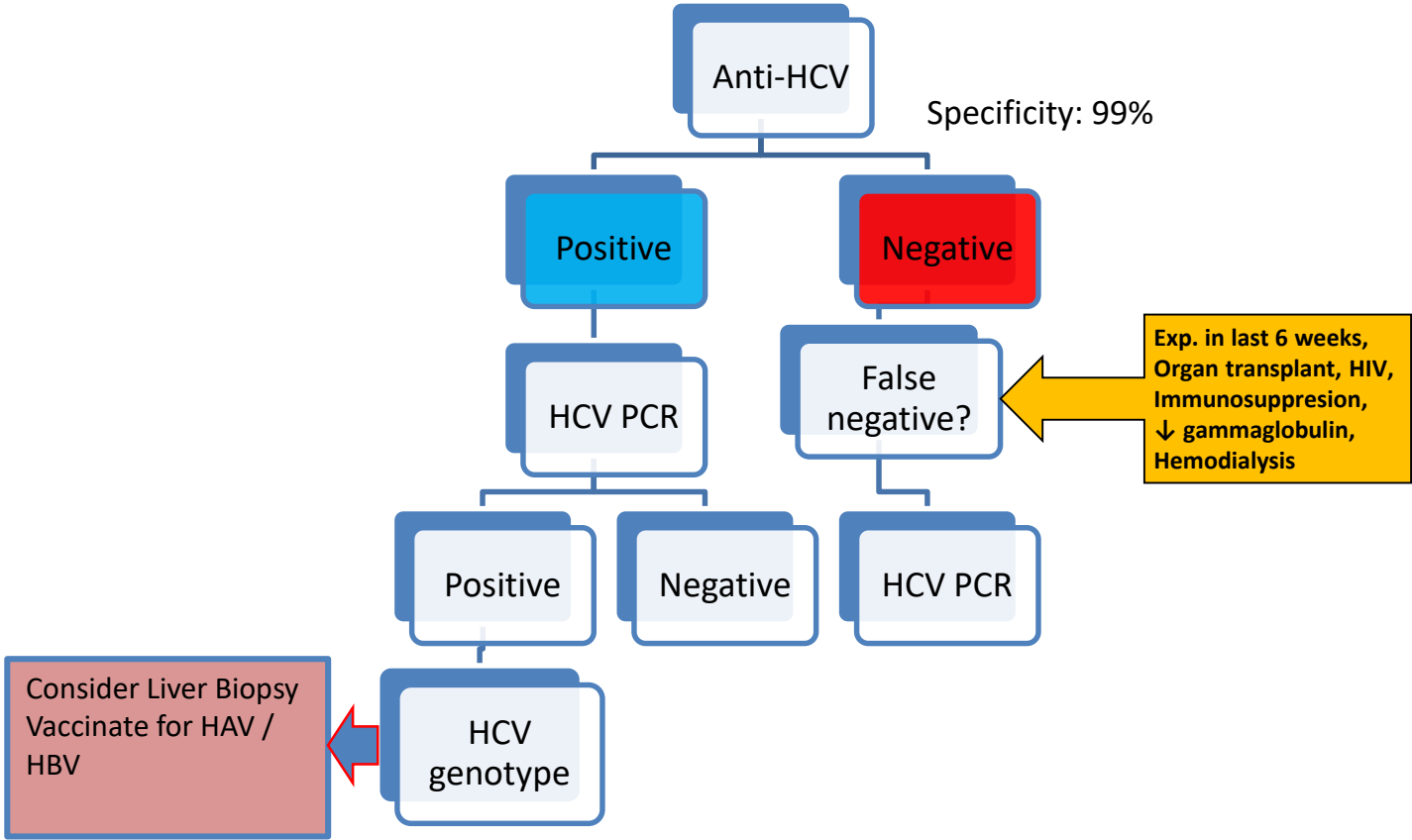
Current AASLD/IDSA Guidelines Screening Recommendations

- Those at high risk for HCV infection:
 - Most important risk factor is past or current injection drug use
 - Intranasal drug use
 - Additional risk factors include:
 - Receiving a blood transfusion before 1992 or clotting factor concentrate before 1987
 - Long-term hemodialysis
 - Being born to an HCV-infected mother
 - Incarceration
 - Getting an unregulated tattoo, and other percutaneous exposures
 - Healthcare workers after needle sticks, sharps, or mucosal exposures
 - HIV or HBV infection
 - High risk or unsafe sexual practices
 - Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
 - Solid organ donors (deceased or living)
- Adults born between 1945 and 1965 (“Baby Boomers”)

Current AASLD/IDSA Guidelines Screening Recommendations

- ✓ Annual HCV Testing is recommended for:
 - Persons who inject drugs
 - HIV seropositive men who have unprotected sex with men
 - Other persons with ongoing risk factors for HCV exposure

HCV Diagnostic Algorithm Based on Serologic Testing



COUNSELING FOR PATIENTS WITH ACTIVE HEPATITIS C

- Education regarding how to reduce liver disease progression and transmission
- Abstinence of alcohol
- Evaluation for other conditions that could accelerate liver fibrosis (HIV, Hepatitis B)
- Evaluation for advanced liver fibrosis (liver bx, fibroscan, imaging, markers, etc)
- Vaccination for hepatitis A/B infection
- Vaccination for streptococcal pneumonia in patients with cirrhosis

Counseling Recommendations for HCV Infected Individuals

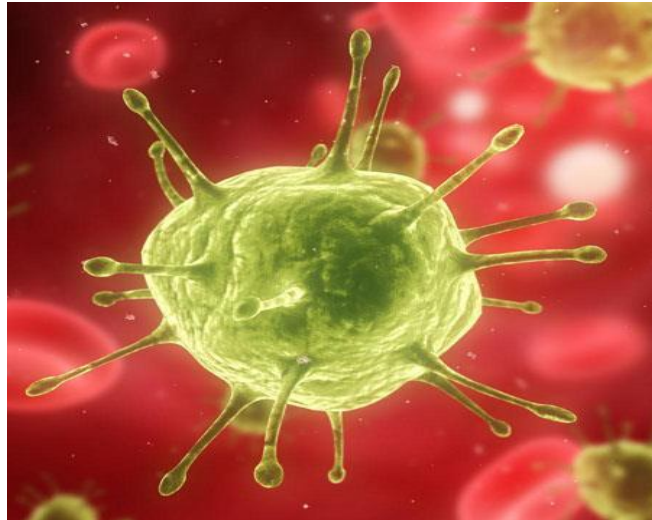
To Prevent HCV Transmission

- Avoid sharing toothbrushes and dental or shaving equipment
- Prevent blood contact with others
- Stop using illicit drugs; those who continue to inject drugs should take precautions to avoid viral transmission
- Risk of sexual transmission is low, but practice “safe sex”

Additional Recommendations

- Avoid alcohol consumption
 - Excess alcohol may lead to progressive liver disease, increased HCV RNA replication, and reduced response to treatment
- Vaccinate for hepatitis A and B
- Get tested for HIV
- Encourage family members to get screened
- If cirrhosis vaccinate for Pneumococcal infection

Antiviral Treatment



GENERALLY ACCEPTED INDICATIONS FOR HCV TREATMENT

- HCV RNA positive
- Acceptable hematologic and biochemical indices
- Willingness to be treated and to adhere to treatment requirements
- No contraindications
- Do not tx: Patients with a short life expectancy that can not be remediated by: HCV tx, liver transplantation or another direct therapy.

Information Needed Before Initiating Therapy for HCV

- ✓ Confirm diagnosis with HCV RNA: viral load
- ✓ HCV Genotype: 1 (1a or 1b) to 6
- ✓ Histologic staging: biopsy vs fibroscan
- ✓ Treatment history: Naïve vs Experienced
 - IFN based vs DAA (NS5A/NS3/4/polymerase inhibitor)
- ✓ Test for resistance-associated substitutions (RAS)-NS5A, NS3/4 (for some products)
- ✓ Hepatitis B profile for all patients

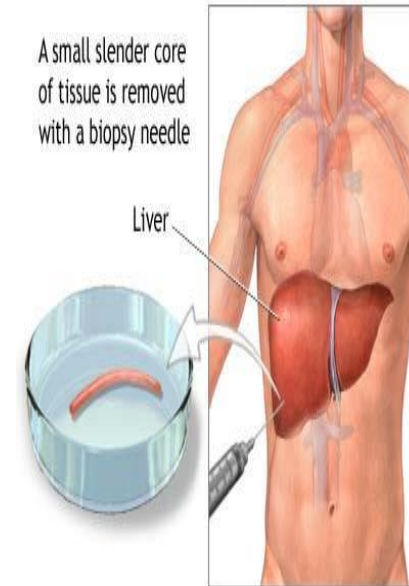
HBV testing/monitoring during Hepatitis C DAA Therapy

In HBsAg (+) patients in no HBV suppressive therapy

- If Hep B DNA level meets AASLD criteria for tx- start tx
- If low Hep B DNA:
 - Initiate prophylactic antiviral therapy and continued until 12 weeks after completion of DAA therapy
 - Monitor HBV DNA levels during and immediately after DAA therapy
 - Start tx for Hep B if HBV DNA > 10 fold above baseline or to > 1000 IU/ml in those with previously undetectable or unquantifiable DNA level.

Clinical Staging: Liver Biopsy

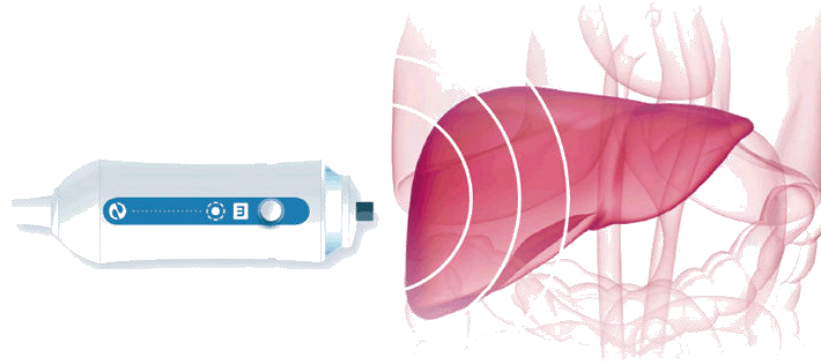
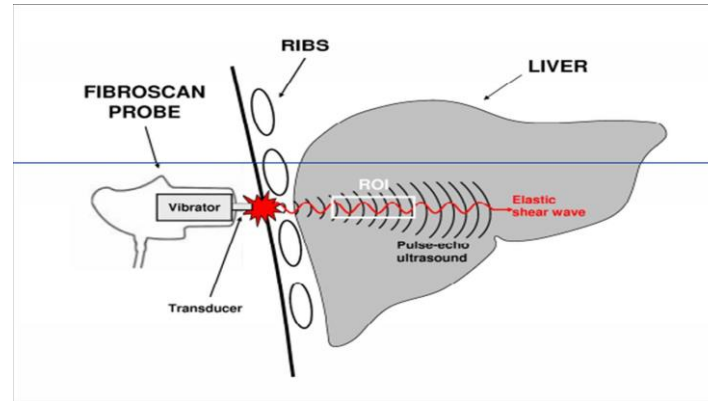
- Liver biopsy remains as the diagnostic standard
- Degree of inflammation
- Tissue damage or fibrosis staging
 - **THE MOST IMPORTANT PROGNOSTIC FACTOR IN DISEASE PROGRESSION**
- Coexistent liver diseases (iron, steatosis, etc.)
- Liver biopsy limitations:
 - **costly and invasive**
 - **complication rate up to 5%**
 - **Sampling error**
 - **Inter-observer variability**



Fibroscan- Transient Elastography

- **Transient elastography (Fibroscan)**

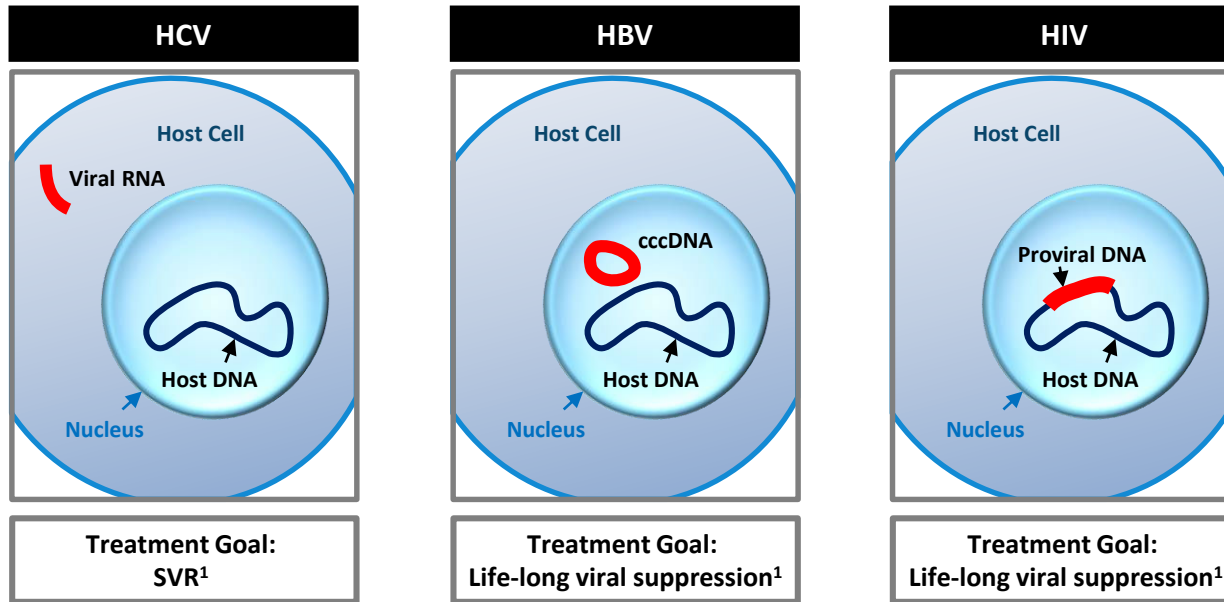
- Uses ultrasound and low frequency elastic waves.



Antiviral Therapy

- Goal of treatment= SVR (negative VL after 12 wks of treatment completion)
 - Suppression of viral replication
 - Decrease hepatic inflammation
 - Inhibition of progressive liver injury
 - Reduction the need for liver transplant
- Major goal of treatment:
 - Prevent development of End stage liver disease, Hepatocellular Carcinoma and death
- If SVR, HCV RNA in serum is not detectable, but HCV antibodies still positive

Treatment Goal in HCV is SVR



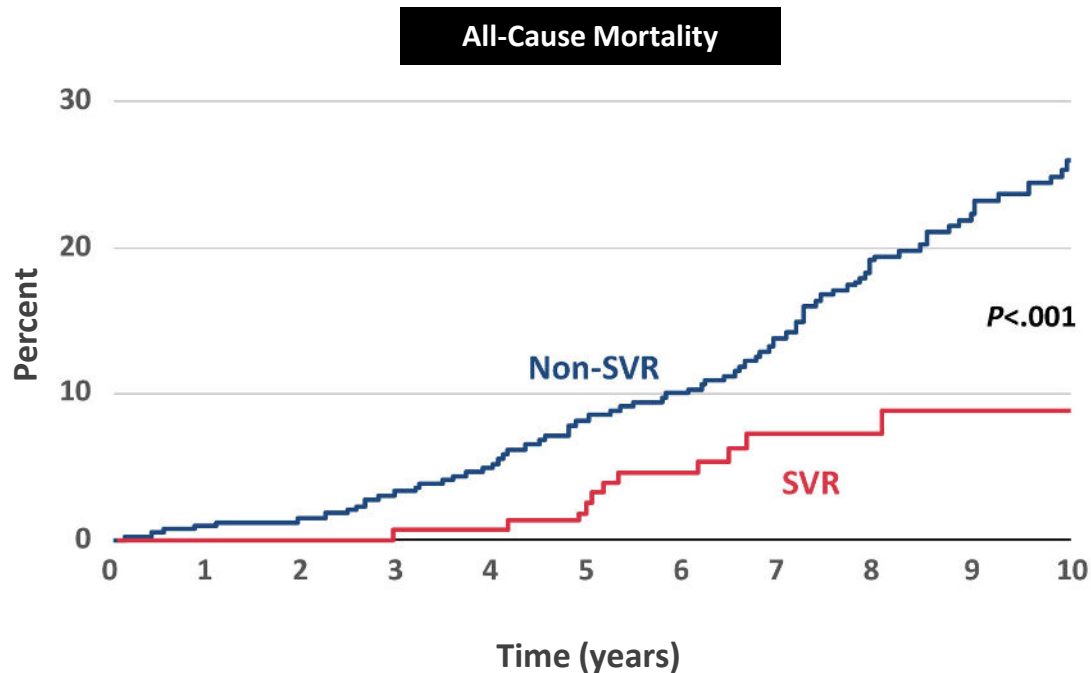
- Majority of patients who achieve an SVR do not experience viral recurrence²

cccDNA=covalently closed circular DNA; HBV=hepatitis B virus.

Images adapted from Soriano V, et al.¹

1. Soriano V, et al. *J Antimicrob Chemother.* 2008;62:1-4; 2. Swain MG, et al. *Gastroenterology.* 2010;139:1593-1601.

SVR was Associated with Reduced Long-Term Risk of All-Cause Mortality in an International, Multicenter Study

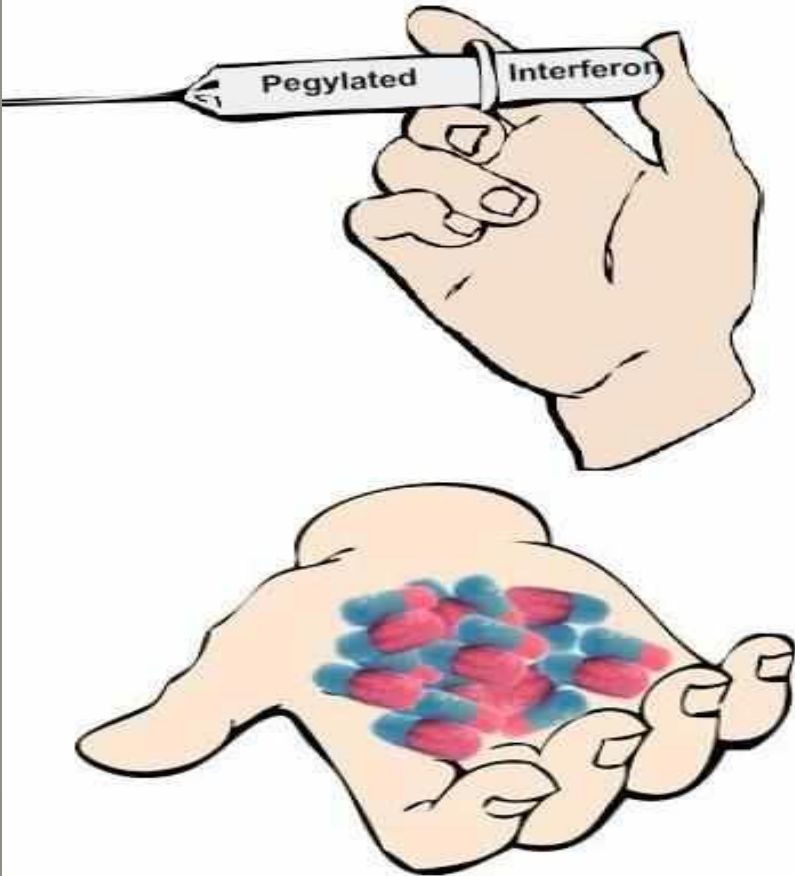


International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

Simplification of HCV Treatment

Past



Present



Antiviral Therapy 2017

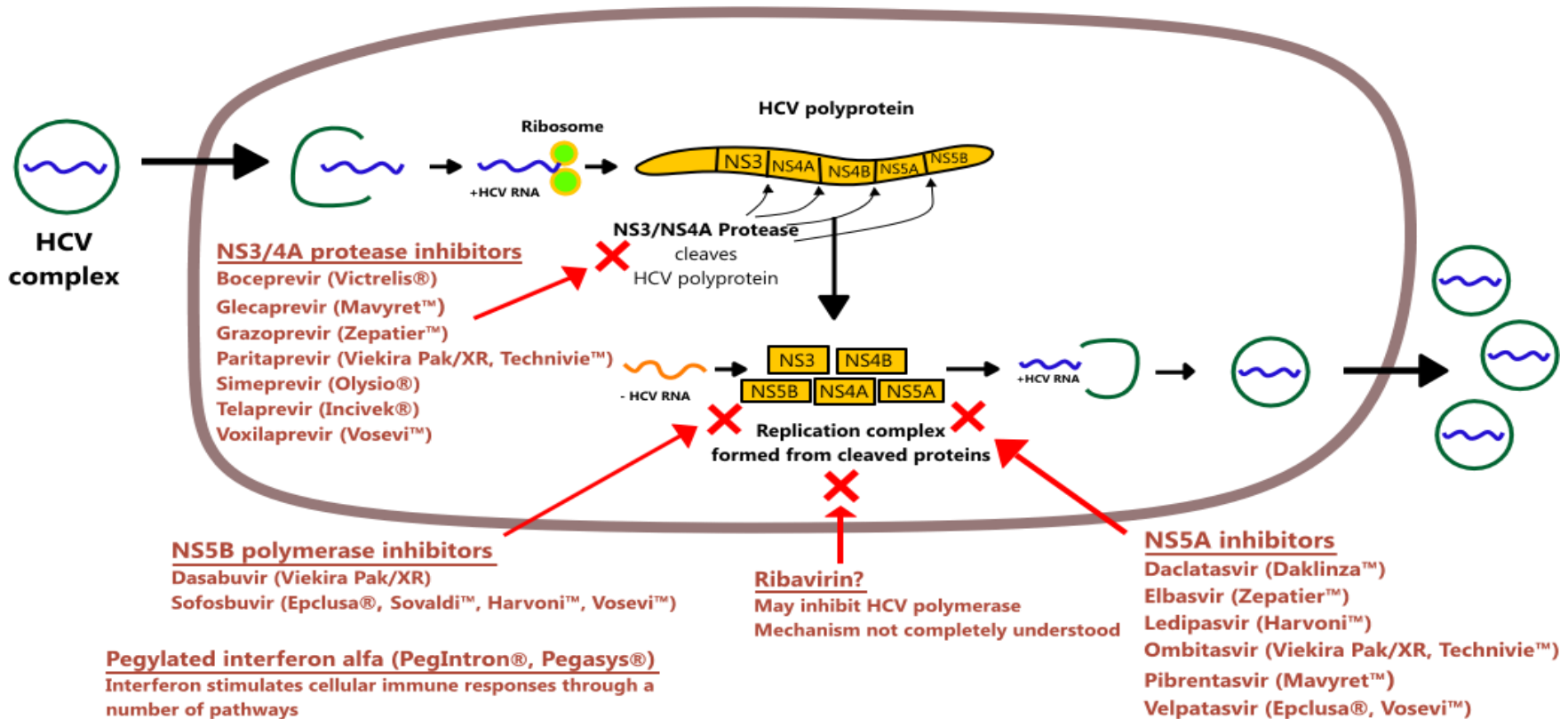
- **Direct Acting Antivirals:**
 - Pangenotypic
 - Short duration of treatment
 - Efficacy
 - Increase tolerability
 - Decrease resistance
 - INF free - oral regimen

Available Agents /Combination Regimens

NS3/4 Protease Inhibitor	NS5A Replication Complex Inhibitors	NS5B Nucleoside Inhibitors	NS5B Nonnucleoside Inhibitors	Brand Name
		Sofosbuvir		Sovaldi
Simeprevir				Olysio
	Ledipasvir	Sofosbuvir		Harvoni *
Paritaprevir/Ritonavir	Ombitasvir		Dasabuvir	Viekira
Paritaprevir/Ritonavir	Ombitasvir			Technivie
	Daclatasvir			Daklinza
Grazoprevir	Elbasvir			Zepatier *
	Velpatasvir	Sofosbuvir		Epclusa *
Voxilaprevir	Velpatasvir	Sofosbuvir		Vosevi *
Glecaprevir	Pibrentasvir			Mavyret *

Mechanism of action of hepatitis C virus (HCV) drugs

Hepatocyte



HCV Landscape

	Harvoni® (ledipasvir/sofosbuvir)	Zepatier® (elbasvir/grazoprevir)	Eplclusa® (sofosbuvir/velpatasvir)	Vosevi (sofosbuvir/velpatasvir/v oxilaprevir)	MAVYRET (glecaprevir/pibrentasvir)
Manufacturer	Gilead	Merck	Gilead	Gilead	AbbVie
Approval	October 2014	January 2016	June 2016	July 2017	August 2017
MOA	NS5B + NS5A	PI + NS5A	NS5B + NS5A	NS5B + NS5A + PI	PI + NS5A
Genotype coverage	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Dosing of DAAs	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (1 pill)	Once daily (3-pill blister pack)
Overcomes baseline RAVs, including Y93H	✗	✗	✗	✓	✓
8-week duration	1* 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6	1 2 3 4 5 6
Efficacy in some types of DAA failures	GT1 PI failures only	GT1 PI failures only	PI failures only	✓	✓
No Ribavirin	Treatment- experienced cirrhotics, decomp cirrhosis	Cirrhotics and GT1a with resistance	Decomp cirrhosis	✓	✓
Decomp cirrhosis	✓	✗	✓	✗	✗
Renal: Severe or ESRD	✗	✓	✗	✗	✓

*GT1 treatment naïve, non-cirrhotic, <6 million baseline viral load

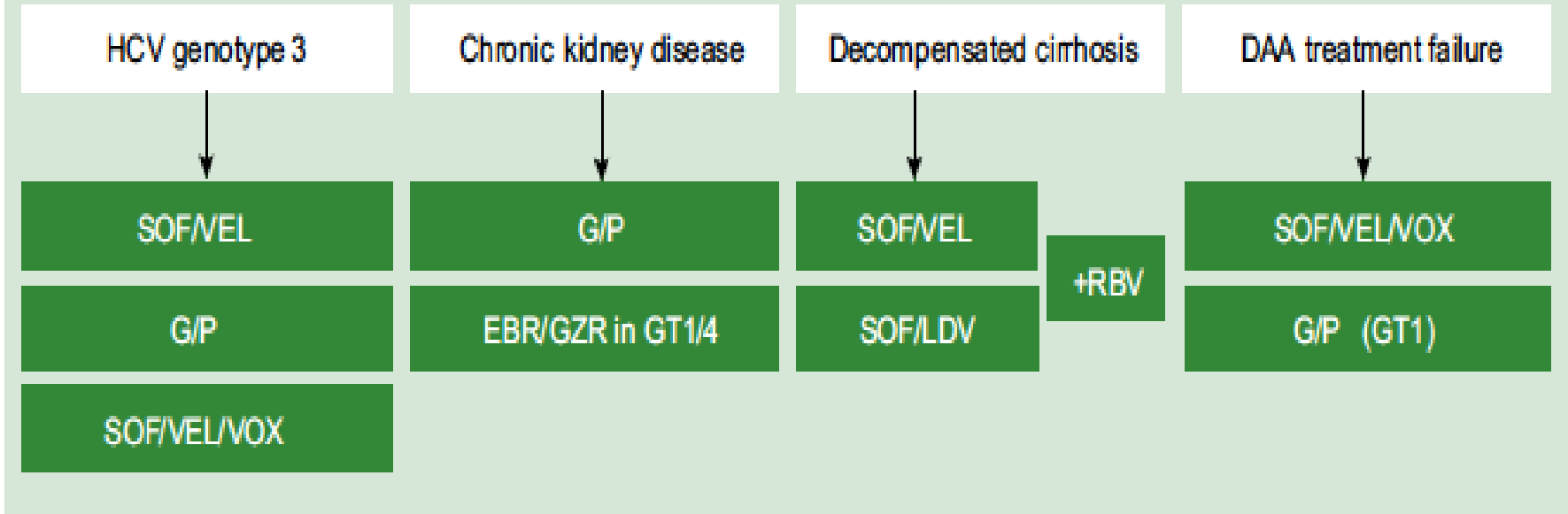
Drug to drug interactions

- Be aware of the risk of drug interactions with DAA's and other concomitant medications
 - Ask about over the counter drugs:
 - Milk thistle
 - St. John's Wort
 - Increase toxicity or loss of efficacy can be observed
 - Amiodarone
 - Acid suppressors/inhibitors
 - Statins
 - Medications used for treatment of HIV infection
- www.hep-druginteractions.org

Challenges in therapy

- ✓ Genotype 3
- ✓ Chronic kidney disease
- ✓ Decompensated Liver Disease
- ✓ Failure to previous DDA therapy

Antiviral treatment in challenging HCV cases



Hepatitis B/C and COVID-19

- COVID-19 positive patients could have elevated liver enzymes. An evaluation should be done, and always other non-COVID-19 etiologies should be considered.
- All hepatitis C/B patients negative to COVID-19 should continue their therapies unless a physician gives another recommendation.
- Patients with chronic hepatitis C and COVID-19 negative should be treated as per guidelines. Therapy should not be delayed taking in consideration risks vs benefits.
- Some medications used to treat COVID-19 (most off label) could cause reactivation of hepatitis B infection.
- Patient with **advanced chronic liver disease** could experience severe COVID-19 symptoms and difficult clinical course.



THANK YOU