Challenges in the Treatment of Hepatitis C and other Viral Hepatitis

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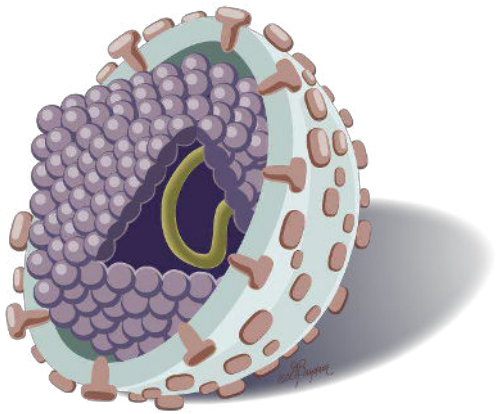

Disclosures

- No disclosures

Hepatitis A Infection

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Hepatitis A Infection

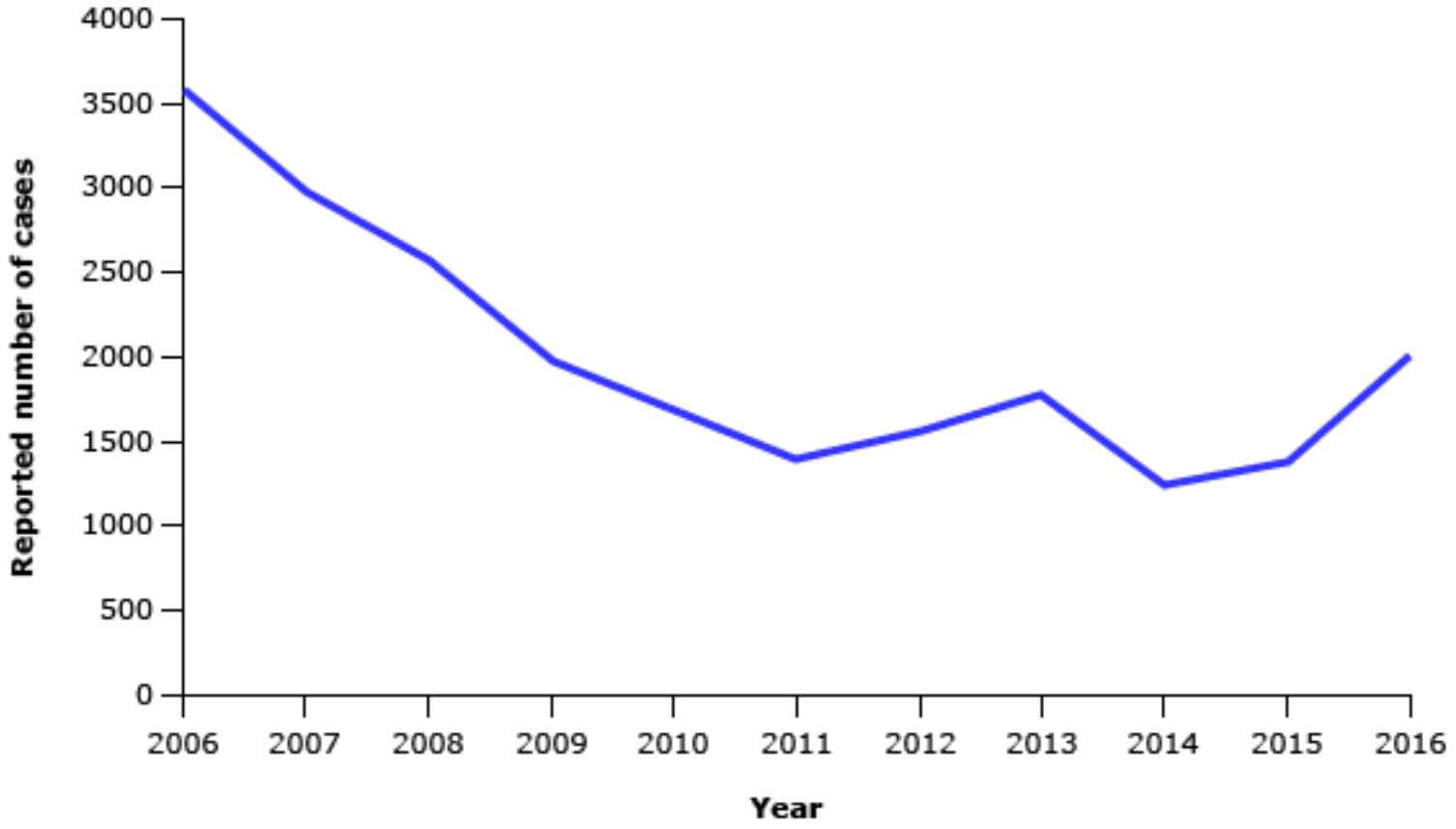
- Globally, an estimated 1.4 millions cases occur each year.

- 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

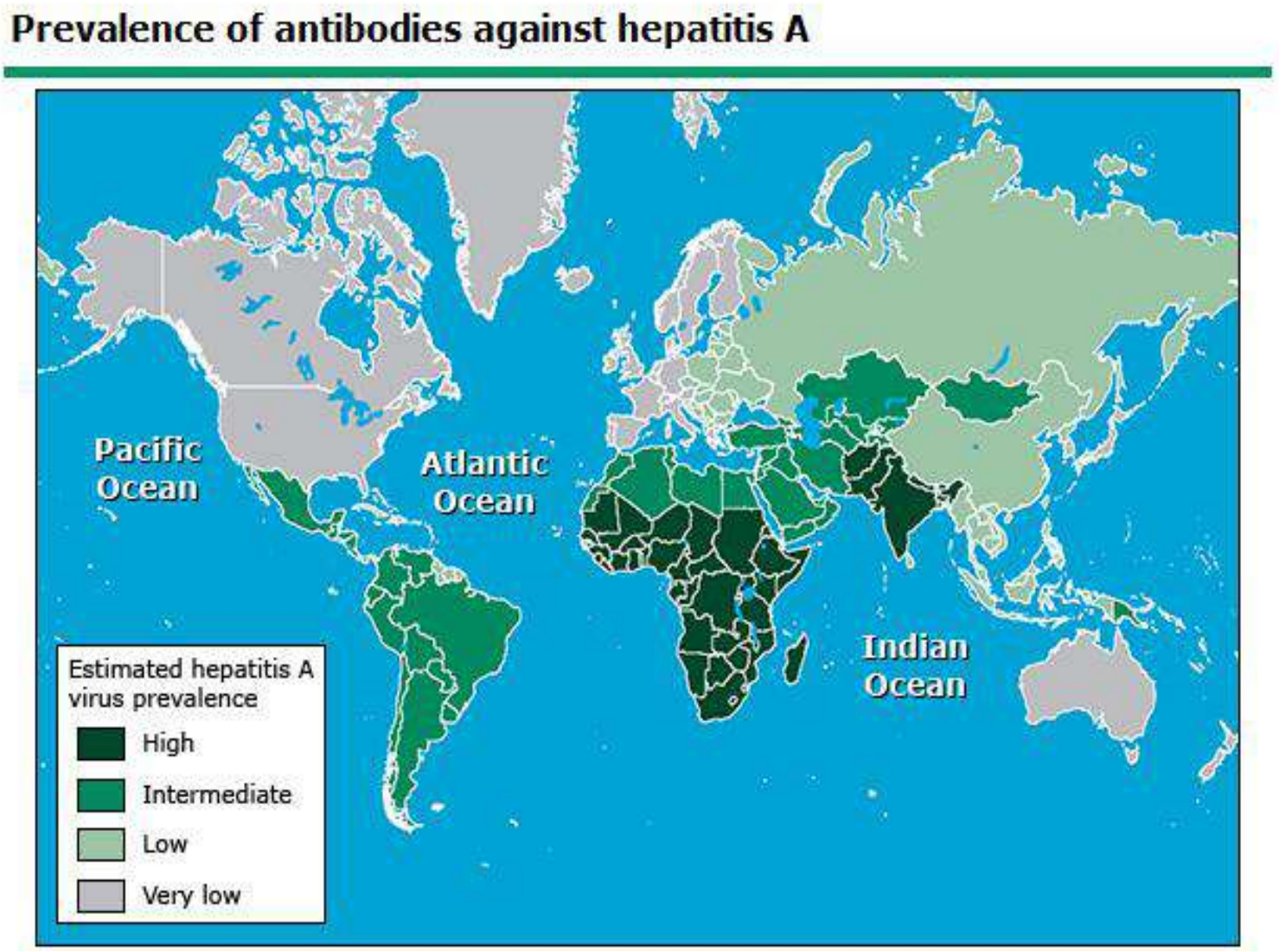
Incidence of hepatitis A, by year – United States, 2006-2016



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



Up to date Accessed on 10/13/20

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

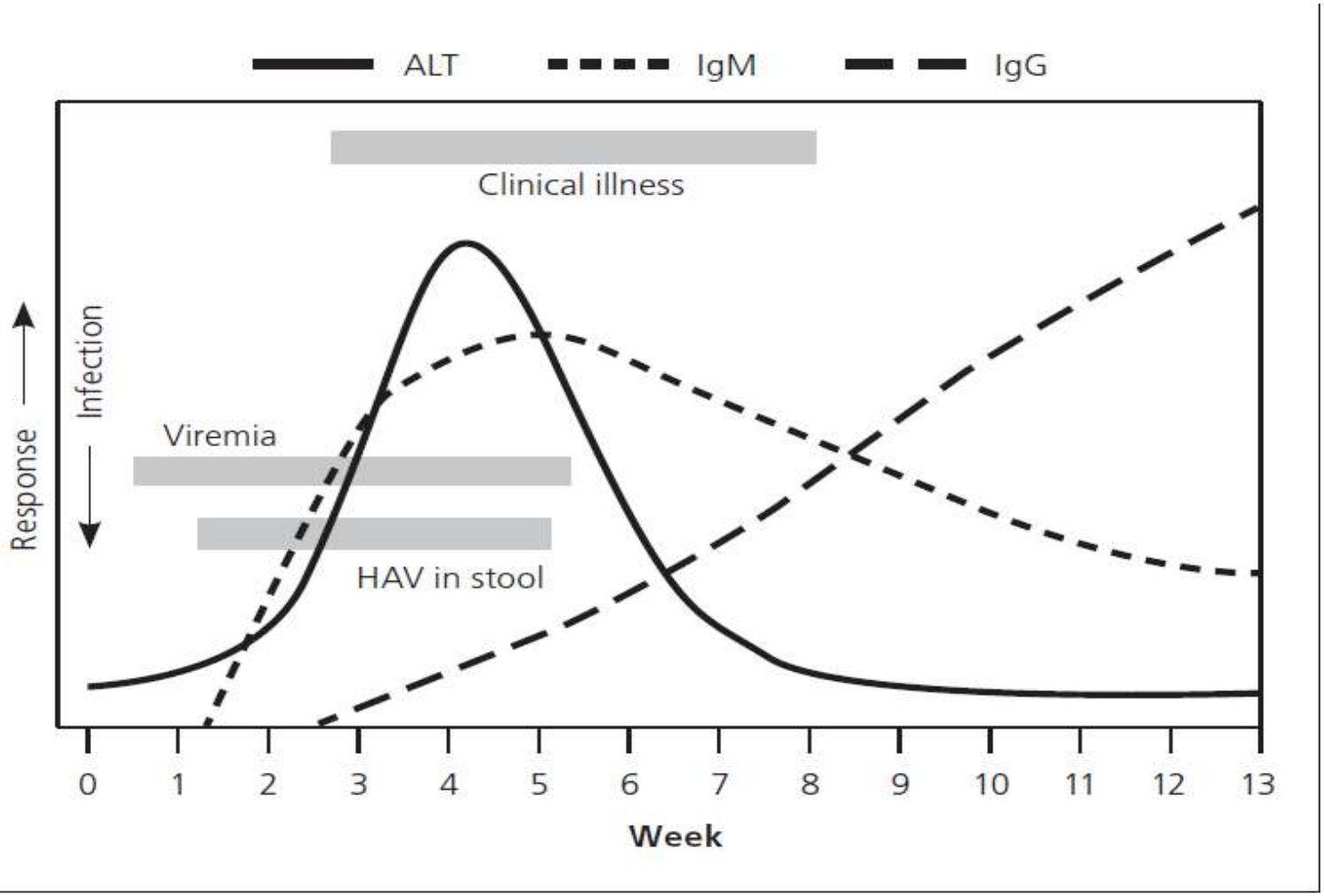
Clinical Variants of Hepatitis A Infection

- 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



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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

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

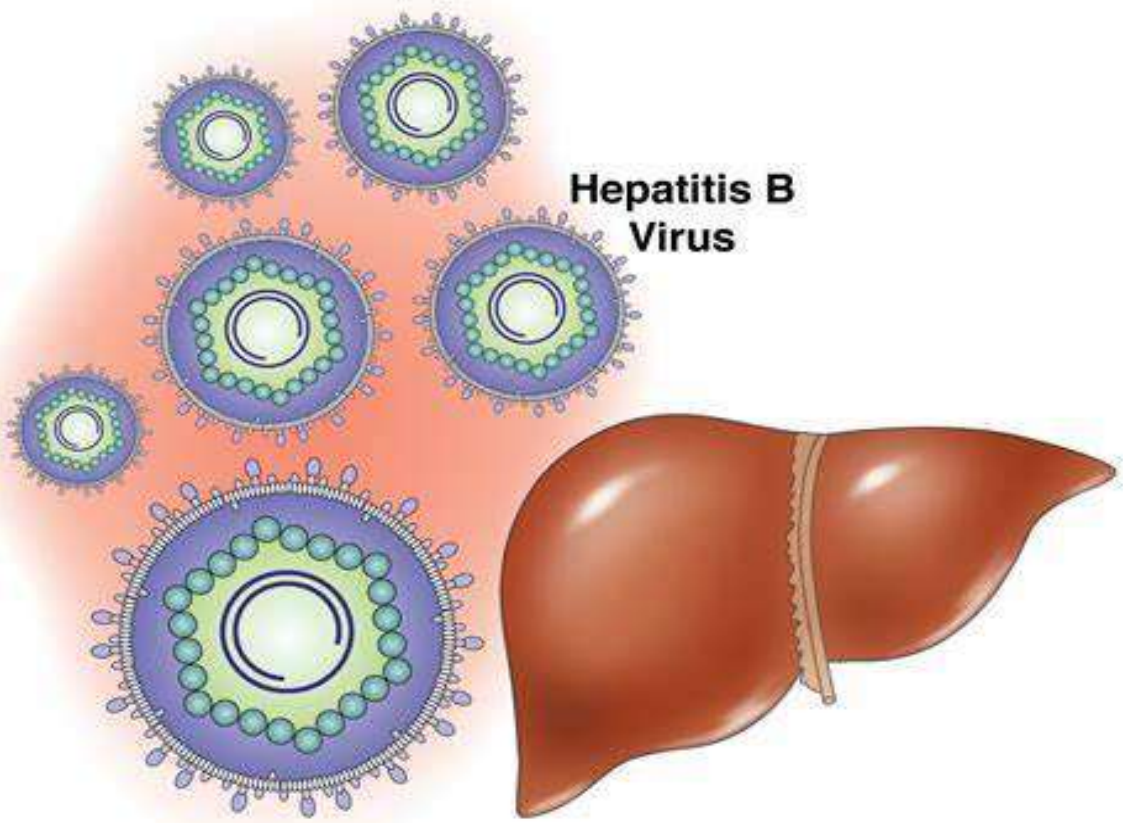
ELISA = enzyme-linked immunosorbent assay.

**—0 represents initial dose.*

†—*U.S.-approved schedule.*

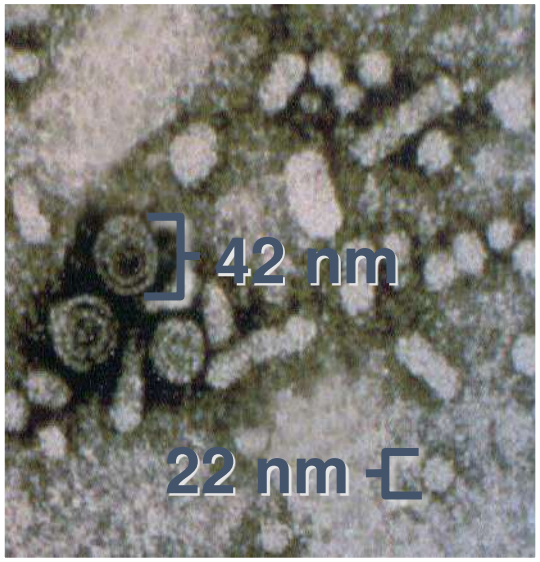
Information from references 7 and 30.

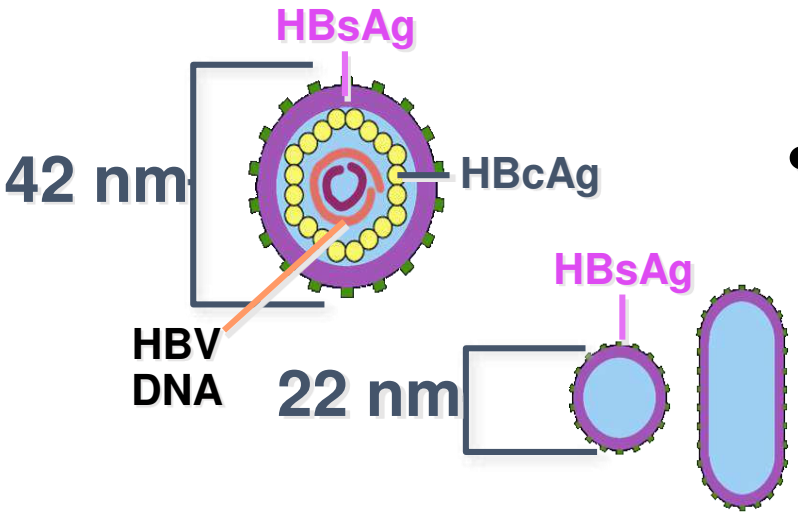
Hepatitis B Infection



dxline.info/img/new_ail/hepatitis-b_1.jpg

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

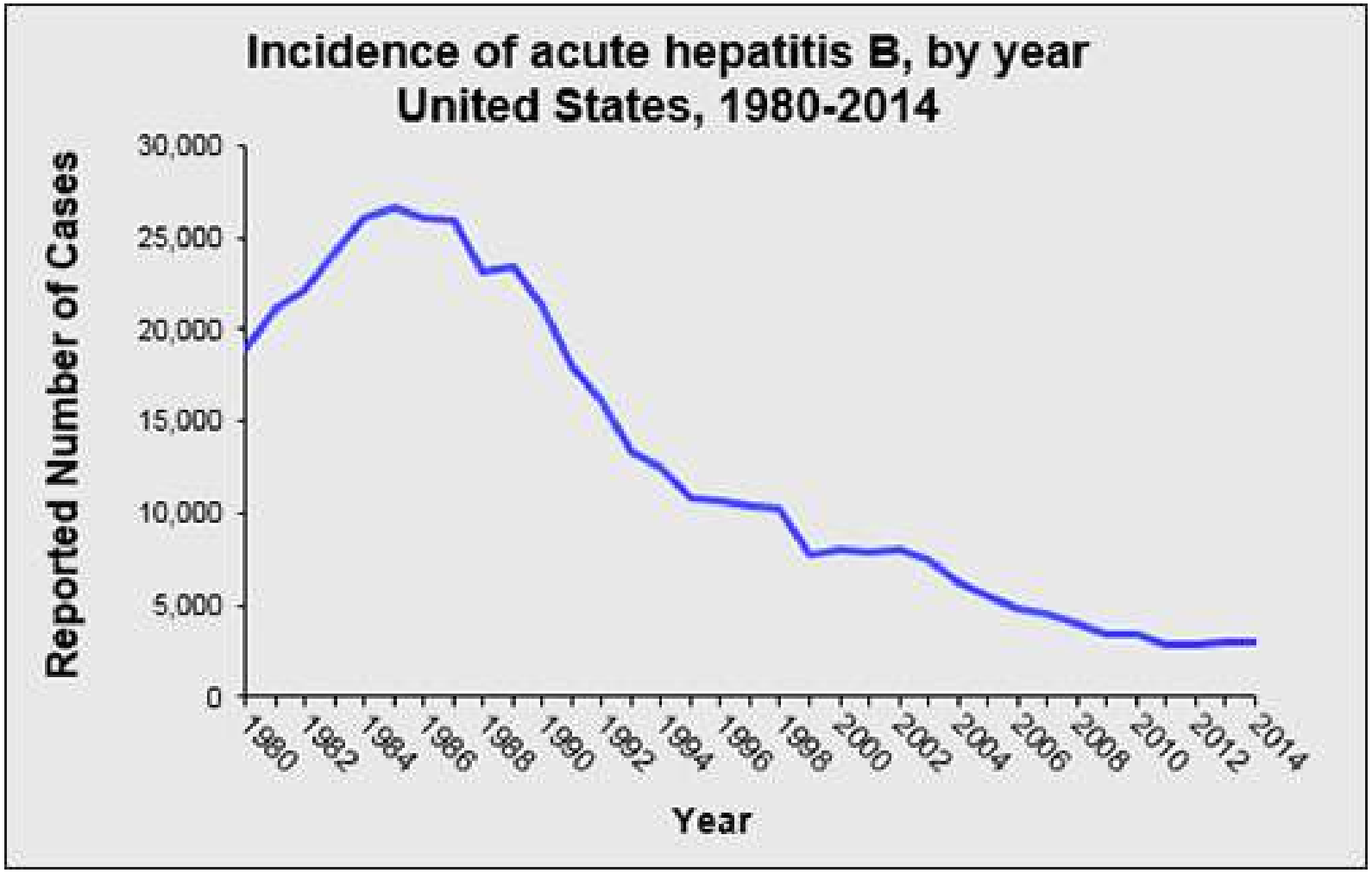
- It is estimated that there were about 257 millions of carriers worldwide and about 887,000 HBV-related liver disease deaths were reported that year.
- CDC estimated about 21,900 cases of **acute** hepatitis B in 2015.
- USA: 850,000 to 2.2 million cases of **chronic** hepatitis B

Hepatitis B Infection

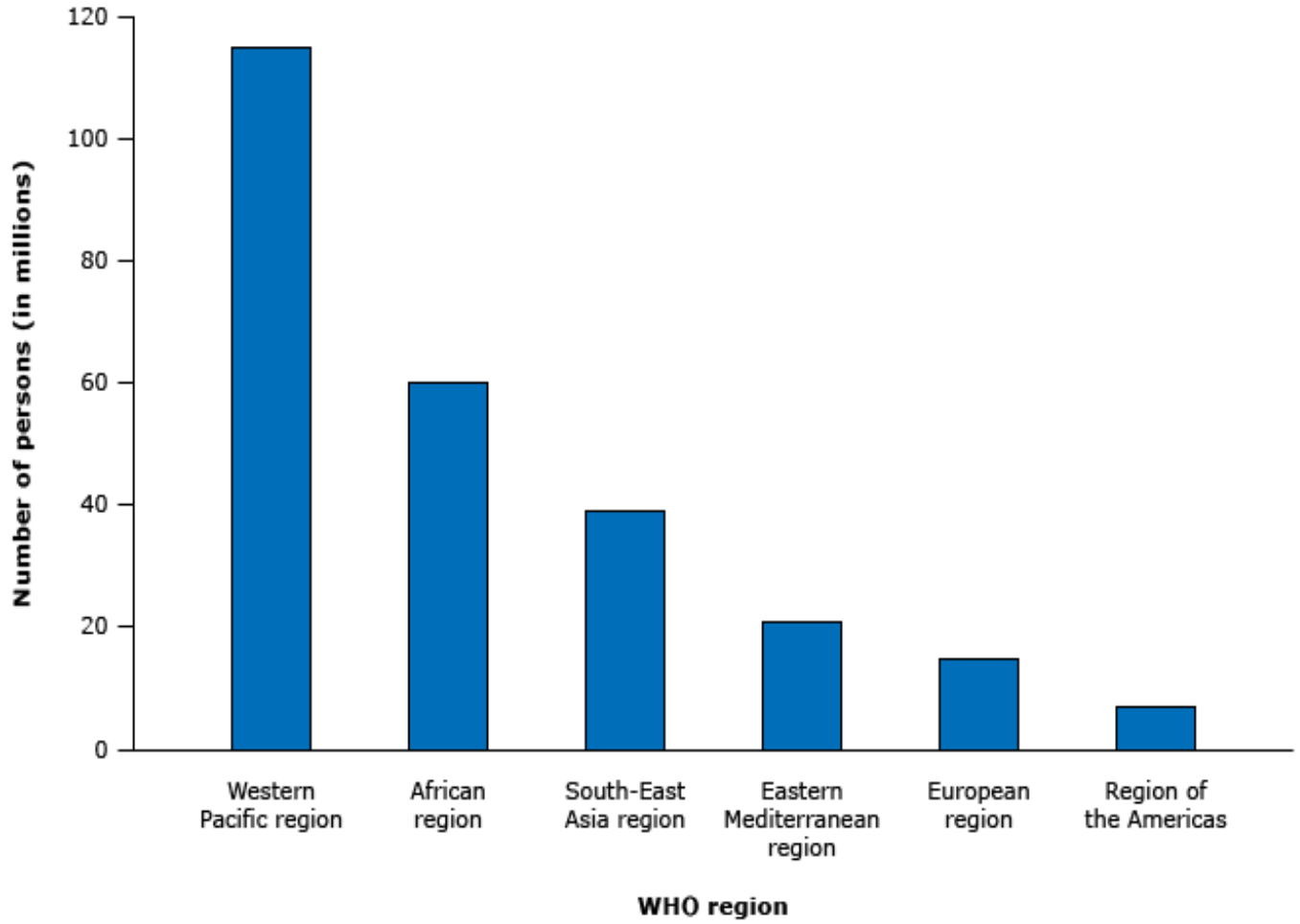
- The rate of new HBV infections has declined by approximately 82% since 1991

- The wide range in the prevalence of chronic hepatitis B in the world is related to different ages at diagnosis.
  - Age in 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



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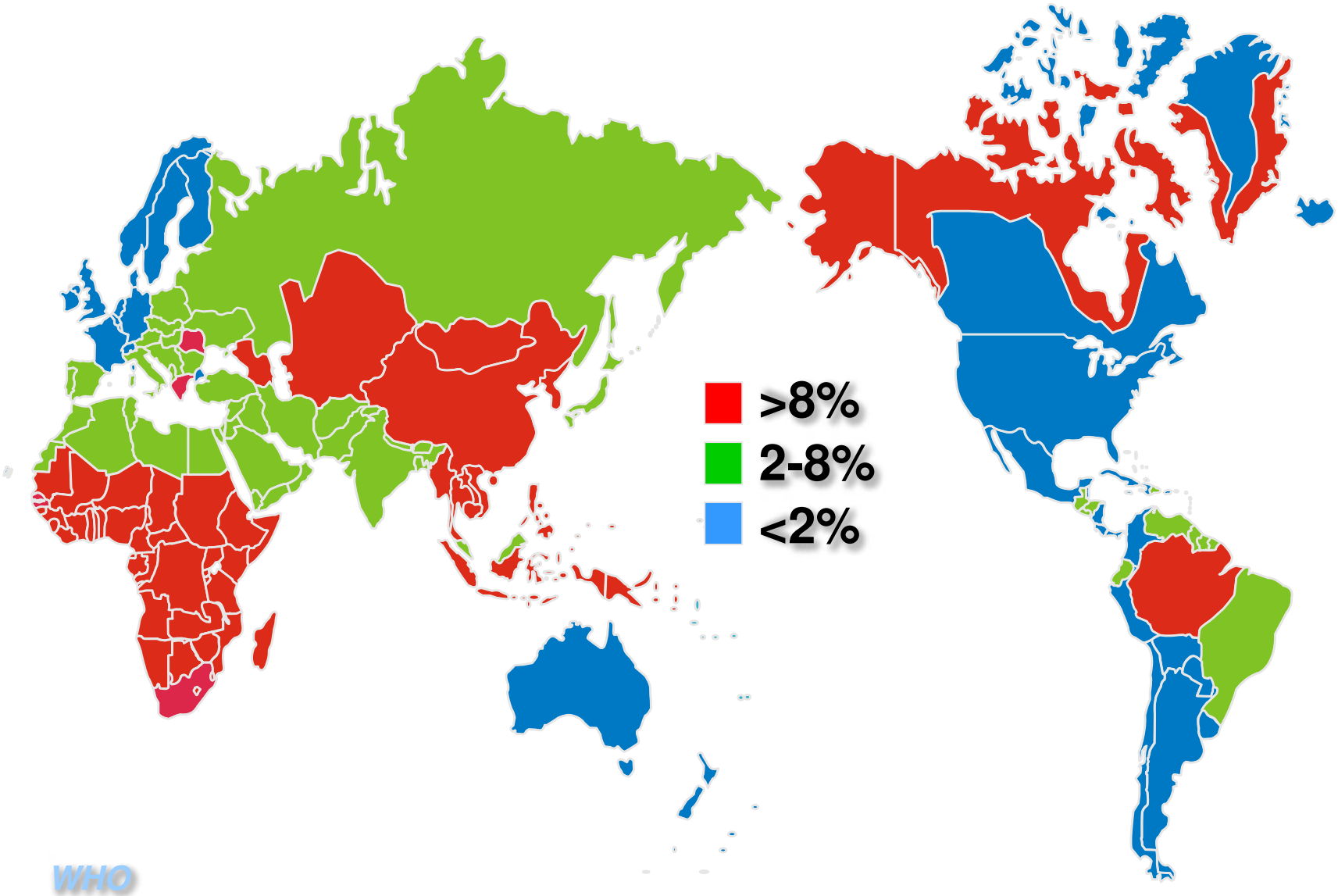
HBV - Epidemiology

Prevalence of HBsAg Carrier State



Risk Factors for Infection

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

- **Permucosal**
  - 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

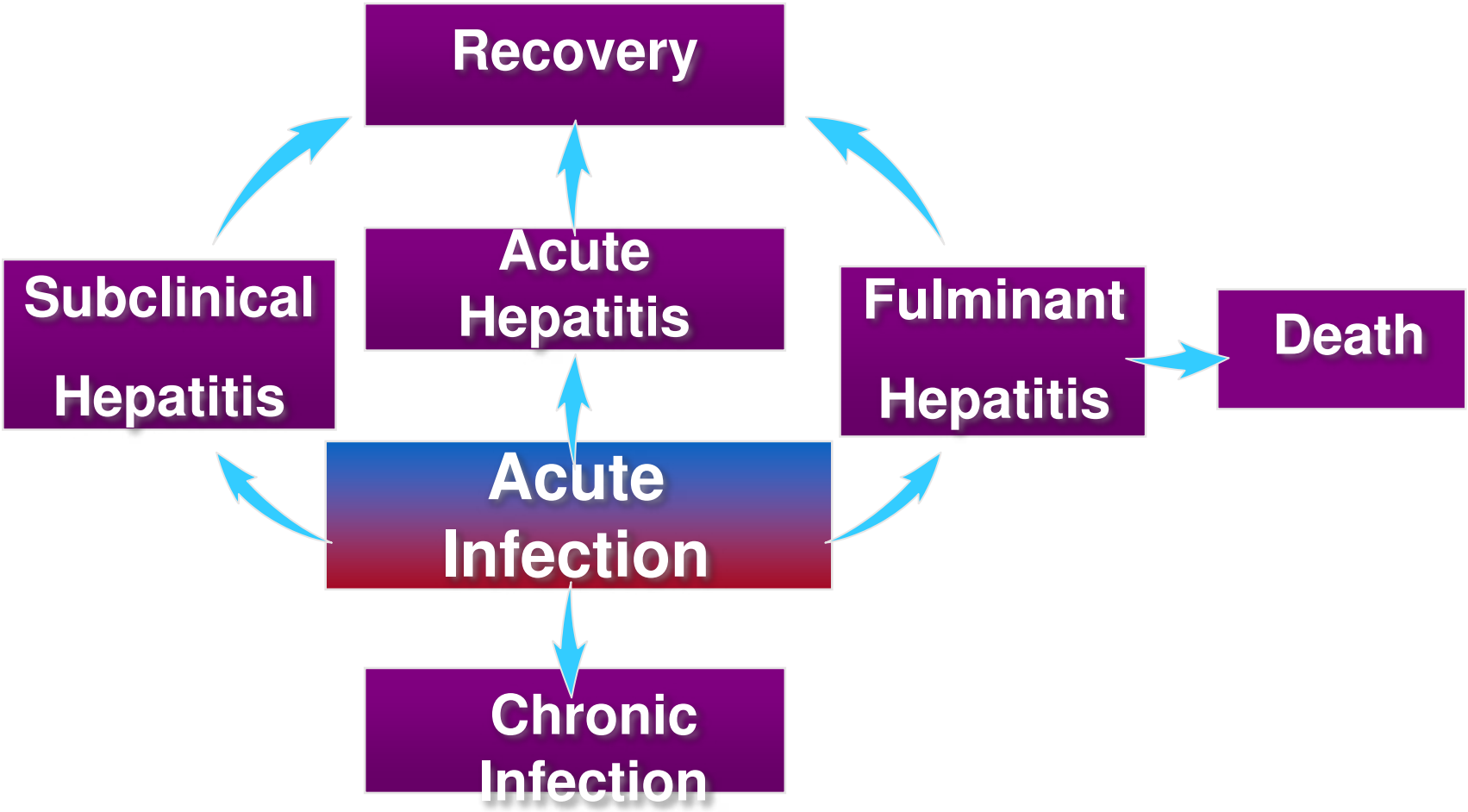
- Acute infection ranges from asymptomatic or mild disease to rarely fulminant hepatitis

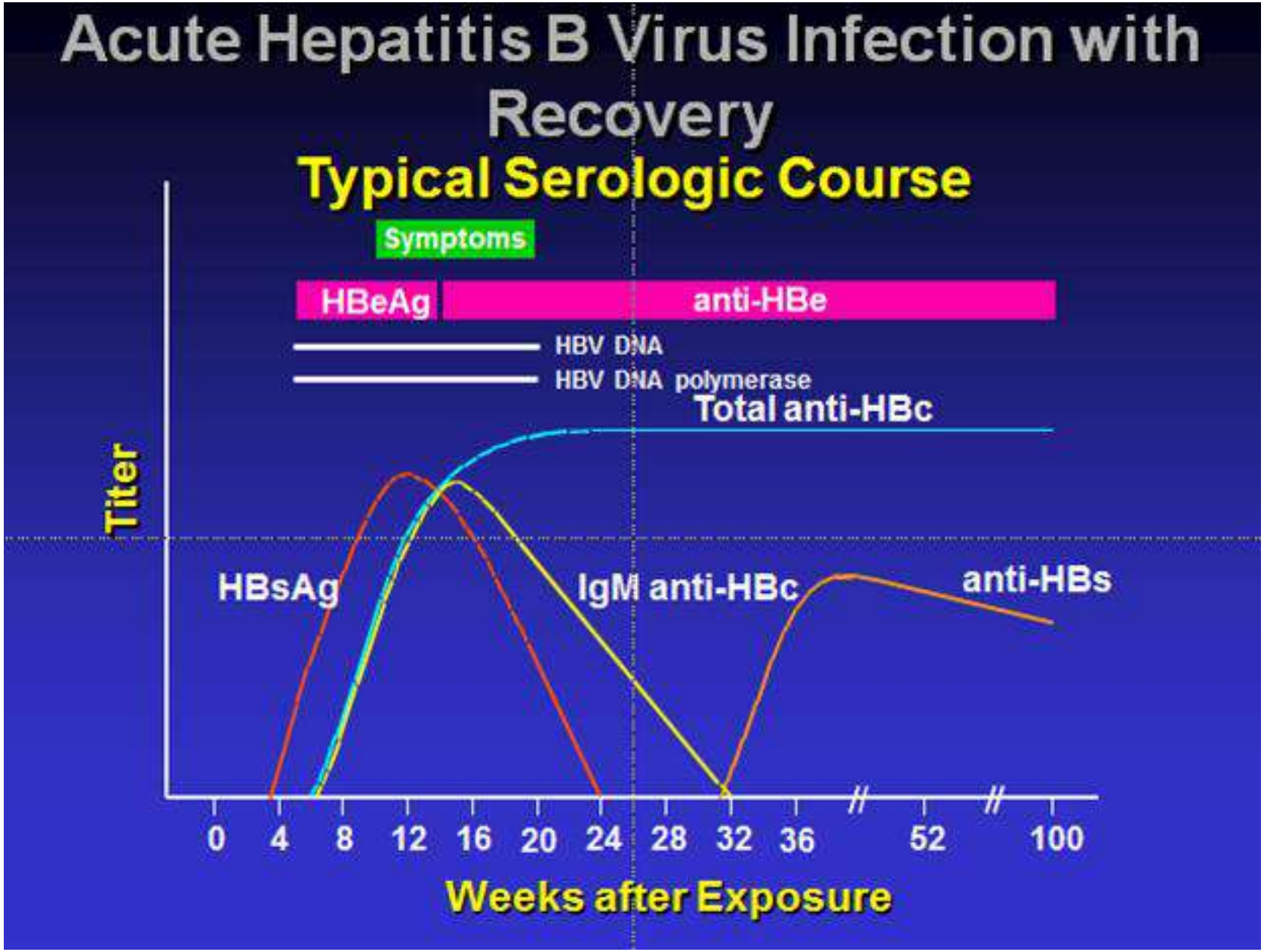
- Persons with chronic HBV infection:
  - might be asymptomatic
  - have no evidence of liver disease
  - have a spectrum of disease ranging from chronic hepatitis to cirrhosis or hepatocellular carcinoma

Signs and Symptoms of HBV Infection

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

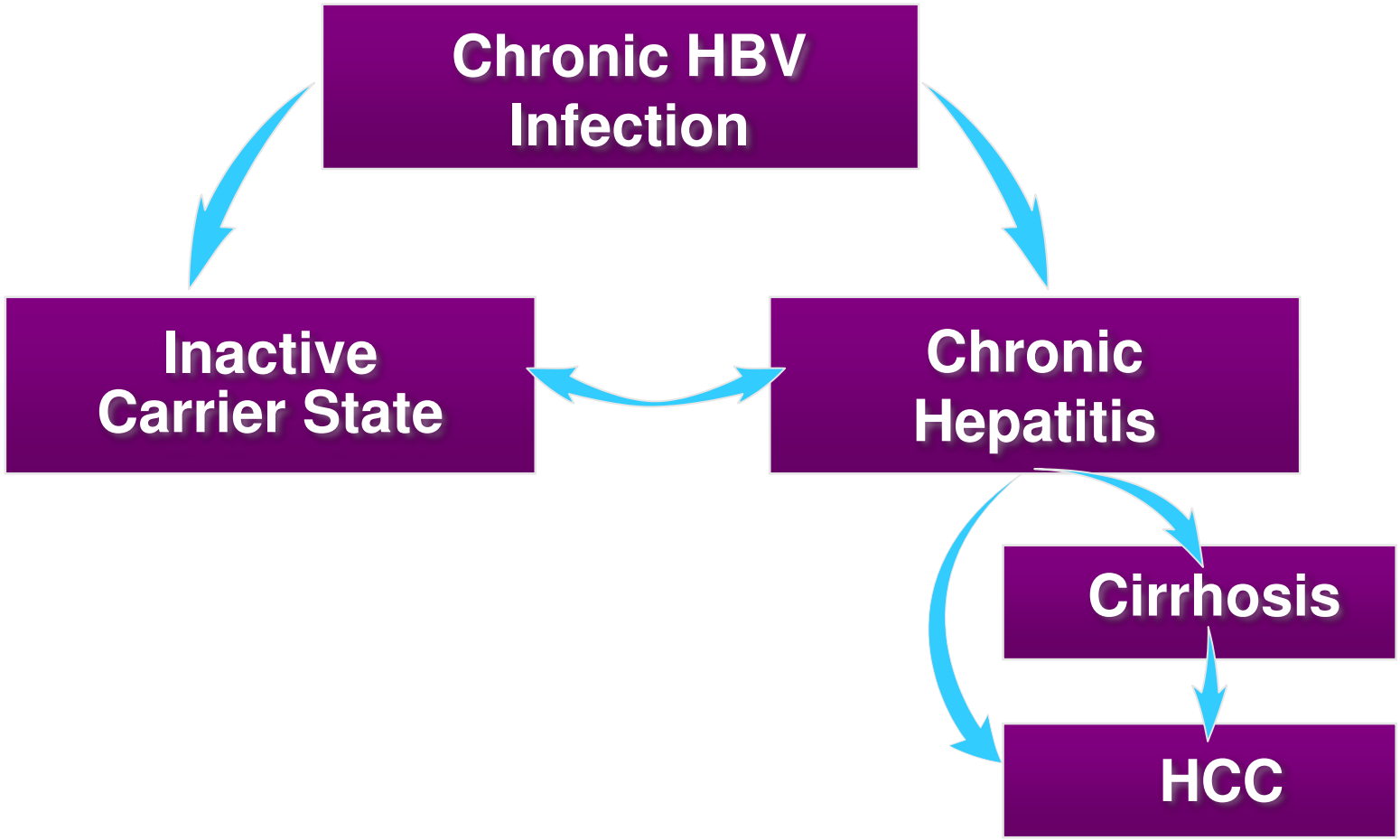
Outcome of Acute HBV Infection

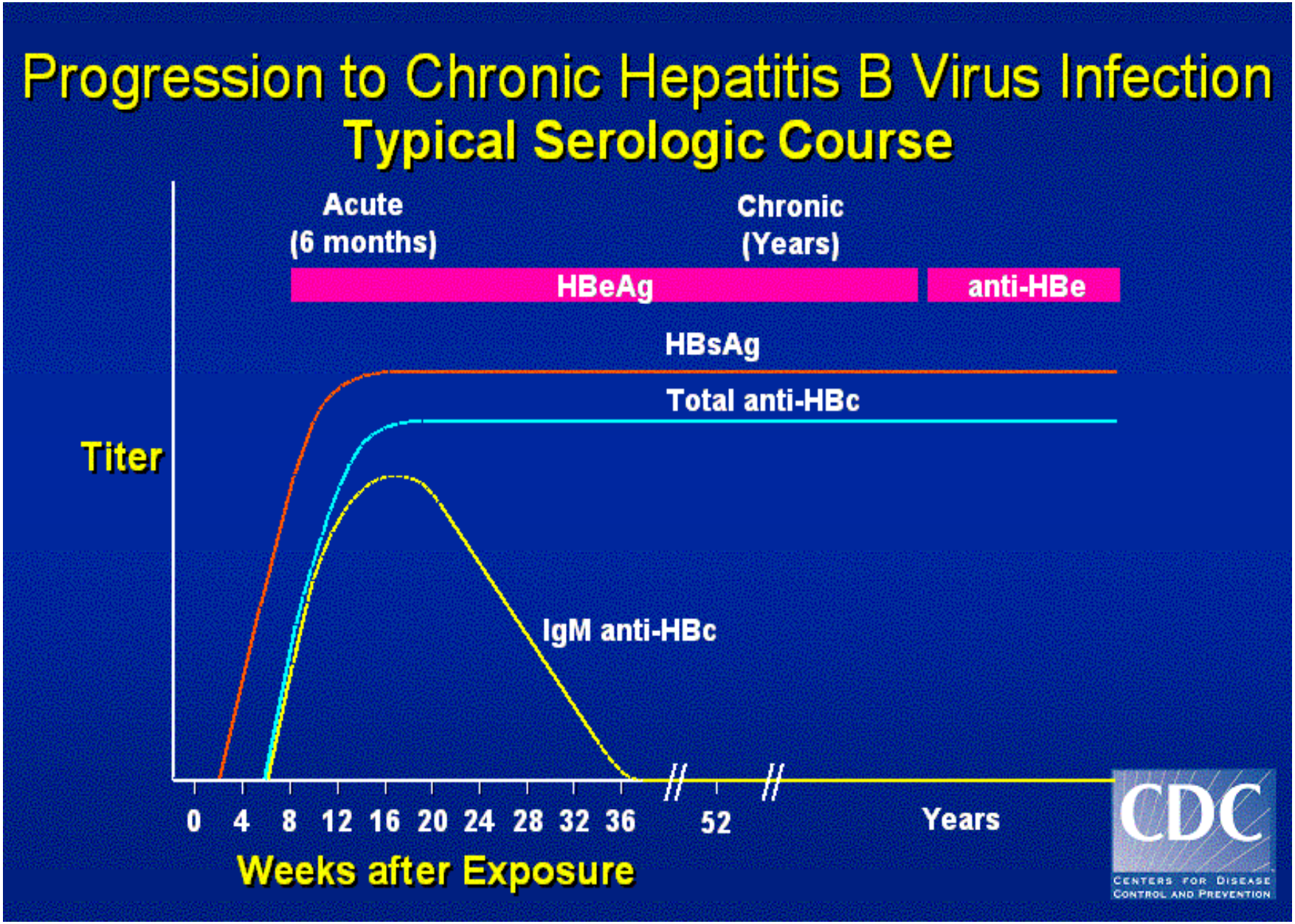




https://classconnection.s3.amazonaws.com/64/flashcards/261064/png/acute_hepb-1426834D5937988C10D.png

Outcome of Chronic HBV Infection





www.microbiologybook.org/virol/hepb-cd2.gif

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	Clinical Significance
HBsAg	Acute/Chronic
Anti-HBc IgM	Acute infection
HBeAg	High infectivity
Anti-HBe	Low infectivity
Anti-HBs	Immunity
Anti-HBc IgG and HBsAg	Chronic infection
Anti-HBc IgG and anti-HBs	Resolved infection

TABLE 4. Interpretation of Screening Tests for HBV Infection

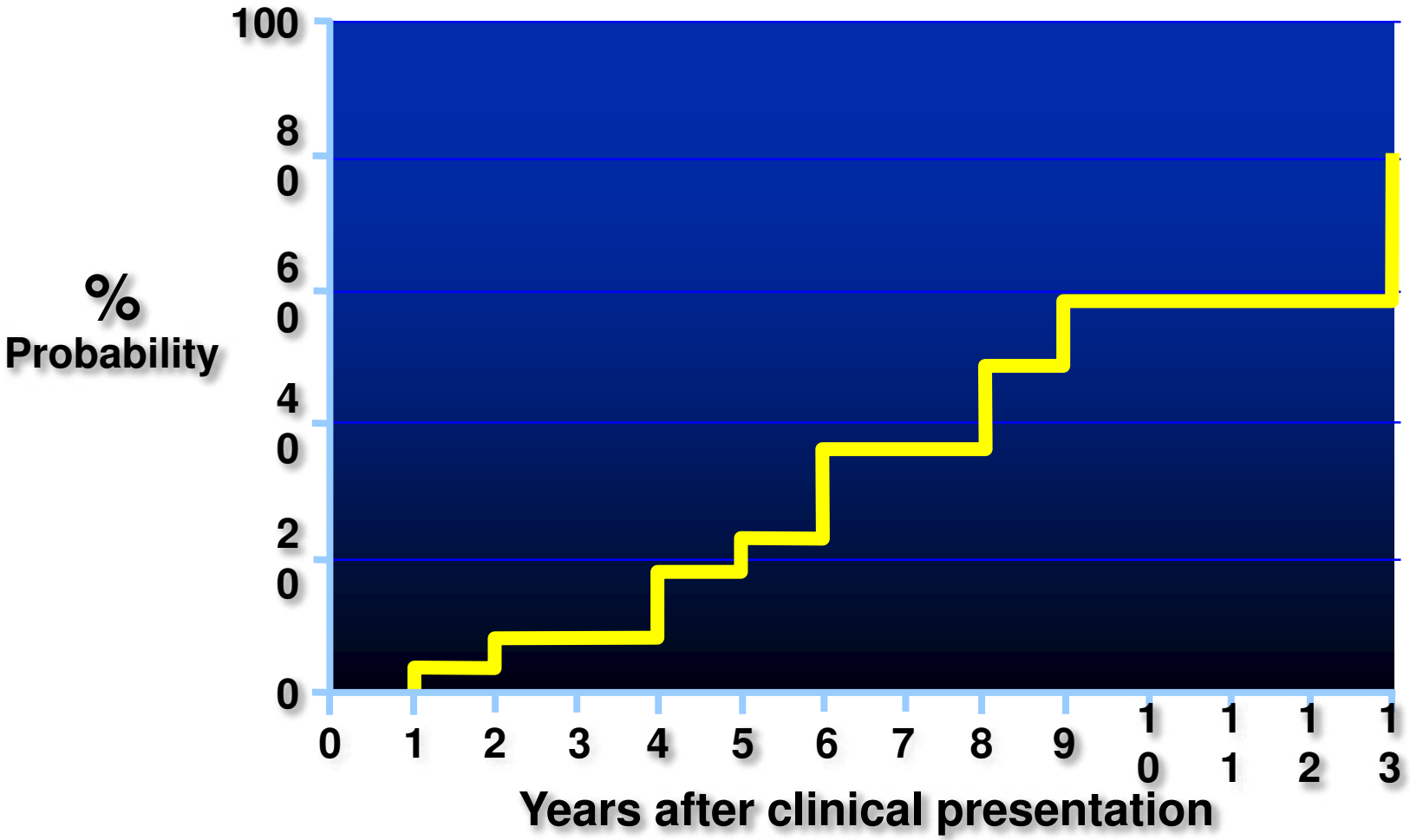
Screening Test Results					
HBsAg	Anti-HBc	Anti-HBs	Interpretation	Management	Vaccinate?
+	+	–	Chronic hepatitis B	Additional testing and management needed	No
–	+	+	Past HBV infection, resolved	No further management unless immunocompromised or undergoing chemotherapy or immunosuppressive therapy	No
–	+	–	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)

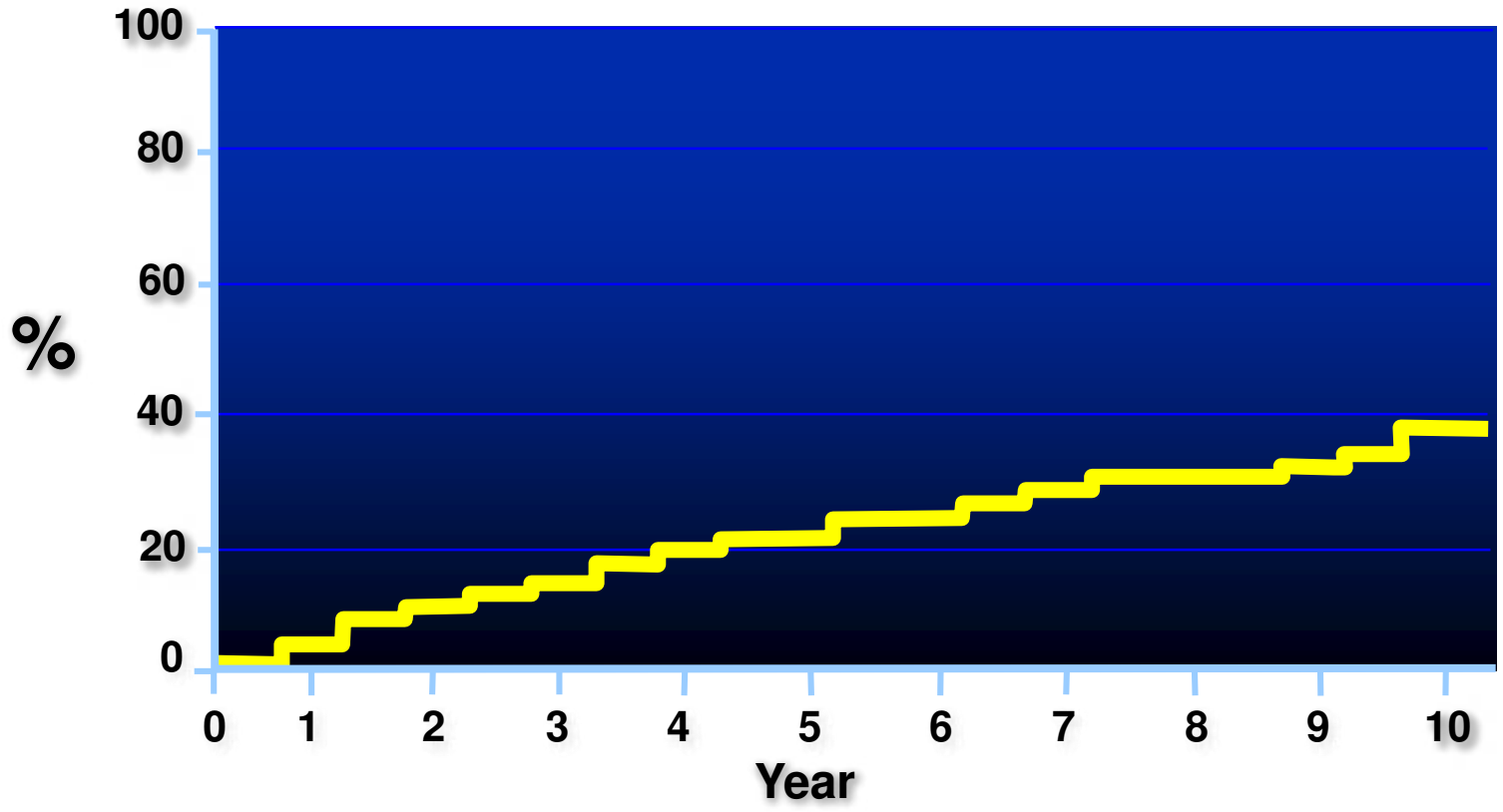
HBV - Natural History

Overall Risk of Progression to Cirrhosis



Fattovich G, Gut 1991; 32:294

Probability of Decompensation in HBsAg+ Patients with Cirrhosis



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

HBV - Natural History

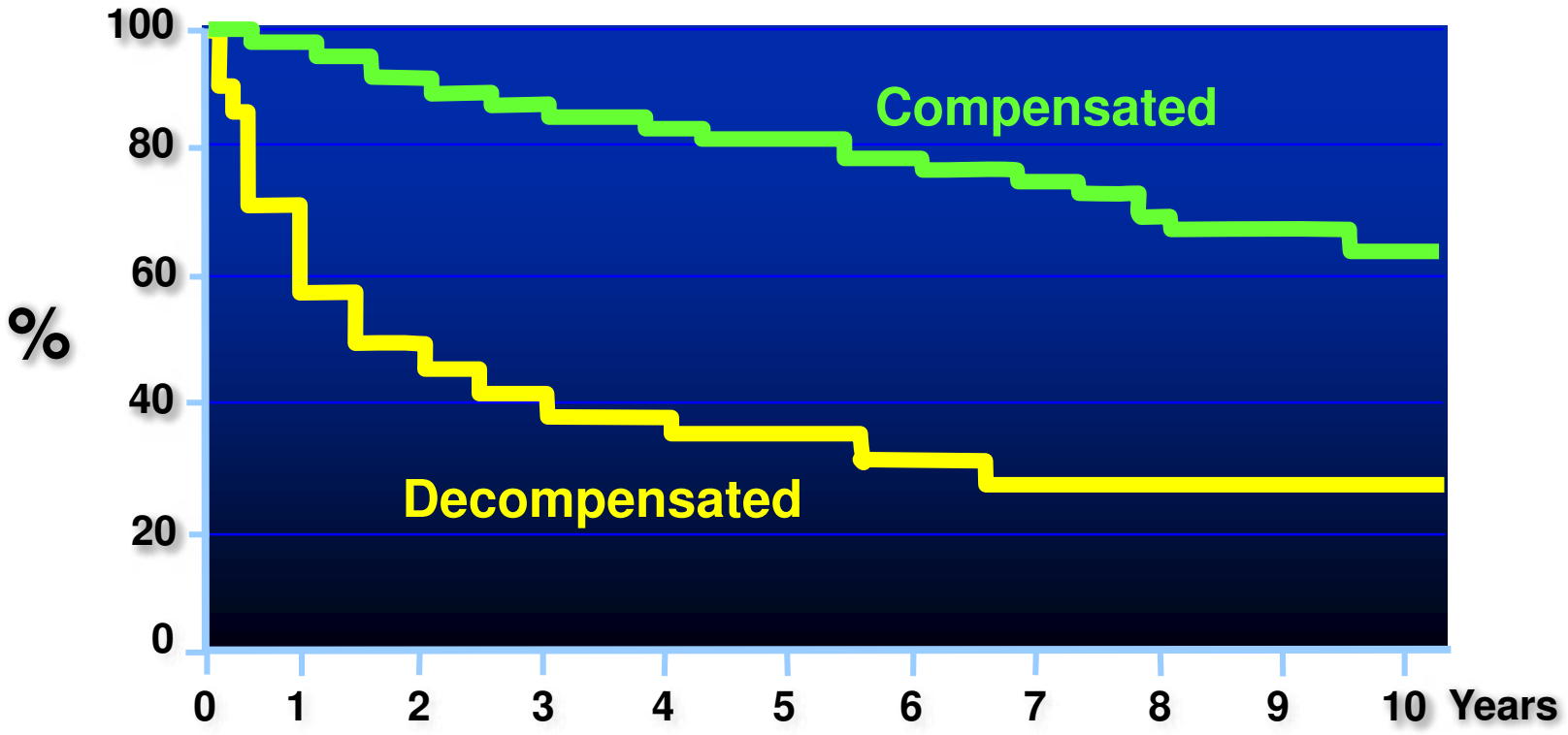
Survival of Patients with HBsAg+ Cirrhosis

Baseline variables associated with diminished survival

- Advanced age
- Low albumin
- Low platelets
- Splenomegaly
- Increased bilirubin
- HBeAg+

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

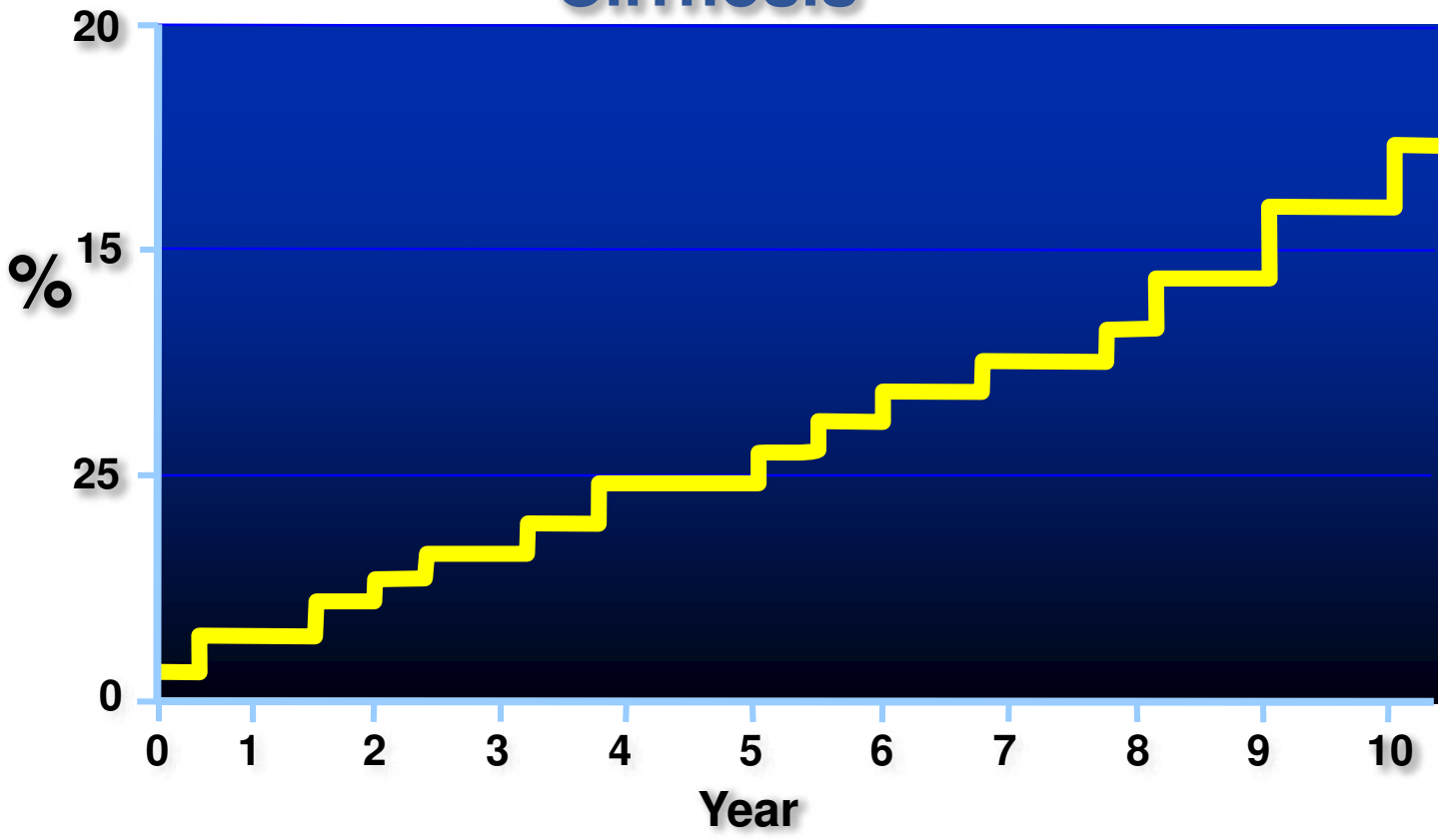
Effect of Decompensation on Survival of Patients with Cirrhosis



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***

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

Indications of Treatment

Chronic infection	**-**	**HBsAg+ >6 months**
Replicative infection	**-**	**HBV DNA > 10^5 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

Lok A, Gastroenterology 2001; 120:1828

Available Therapies for Hepatitis B

- Epivir-HBV (lamivudine)
- Intron A (interferon alfa 2-b)
- Pegasys (peginterferon alf 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

CDC and WHO

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

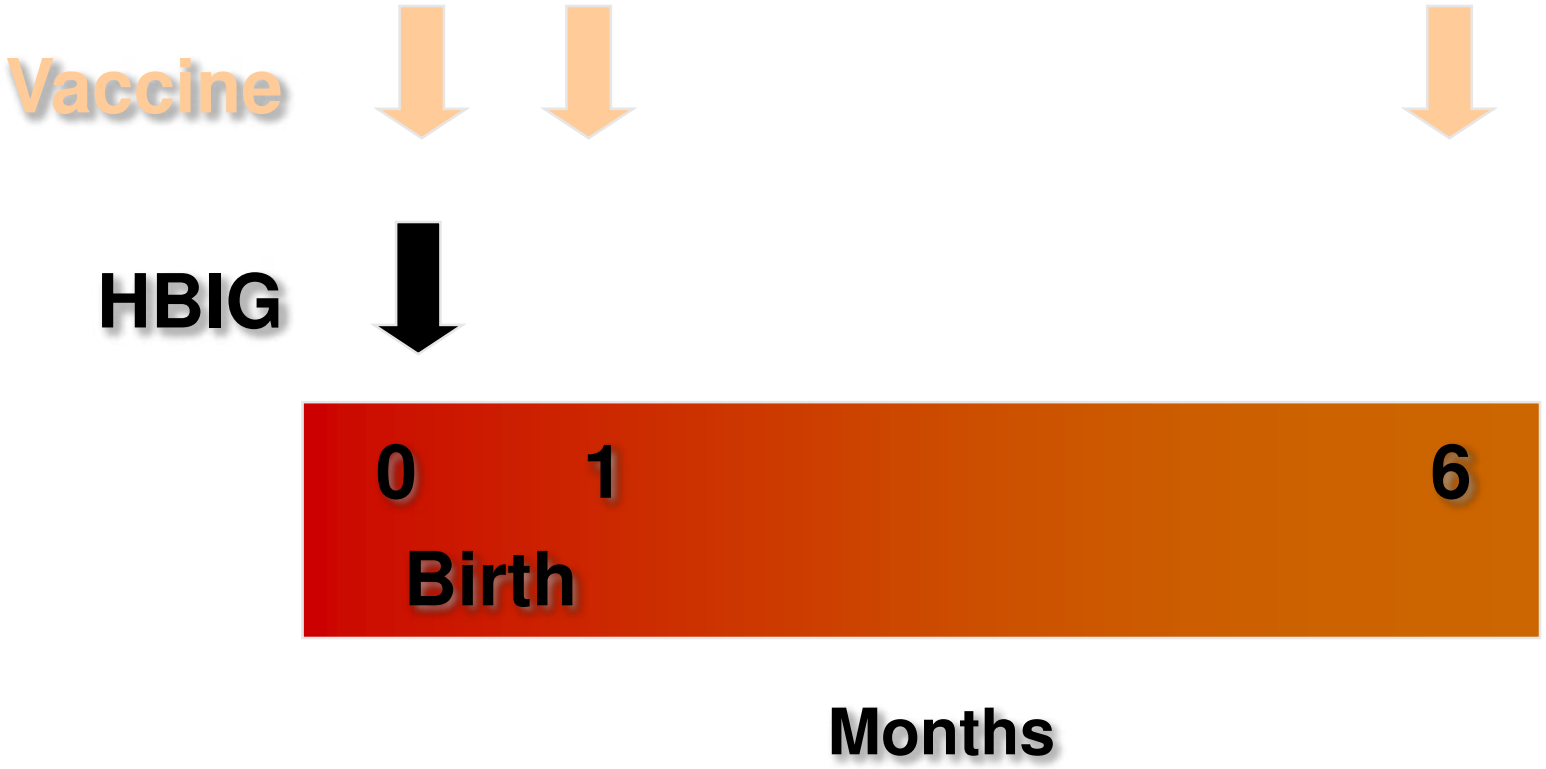
Dose Schedule

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	0-19 yr	5	0.5	3 (mo 0,1,6)
	≥ 20 yr	10	1.0	3 (mo 0,1,6)
(Optional 2-dose)	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



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

Knoll A, Vaccine 2000; 18:2029

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

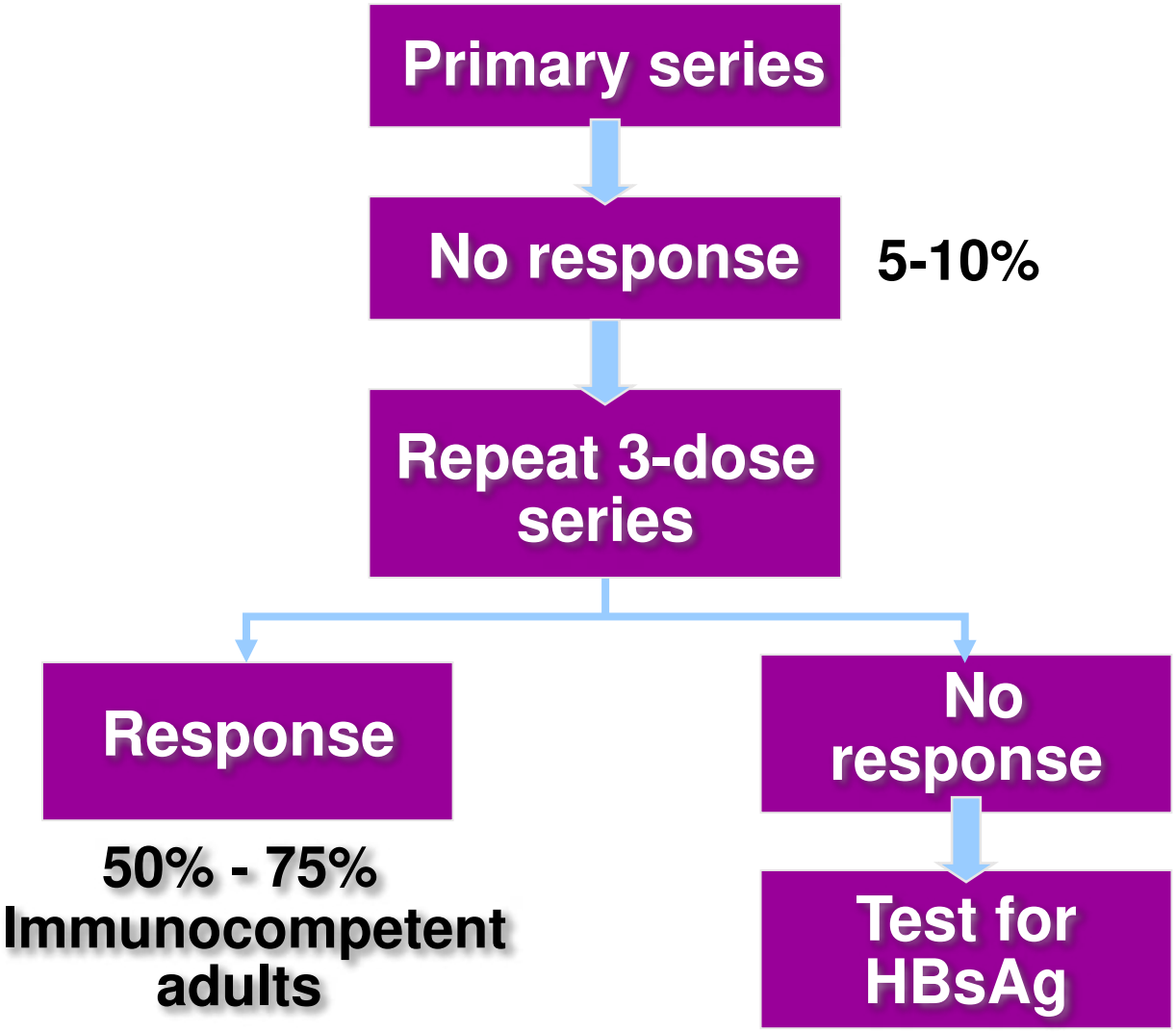
Booster Doses Recommended Only For

Hemodialysis patients

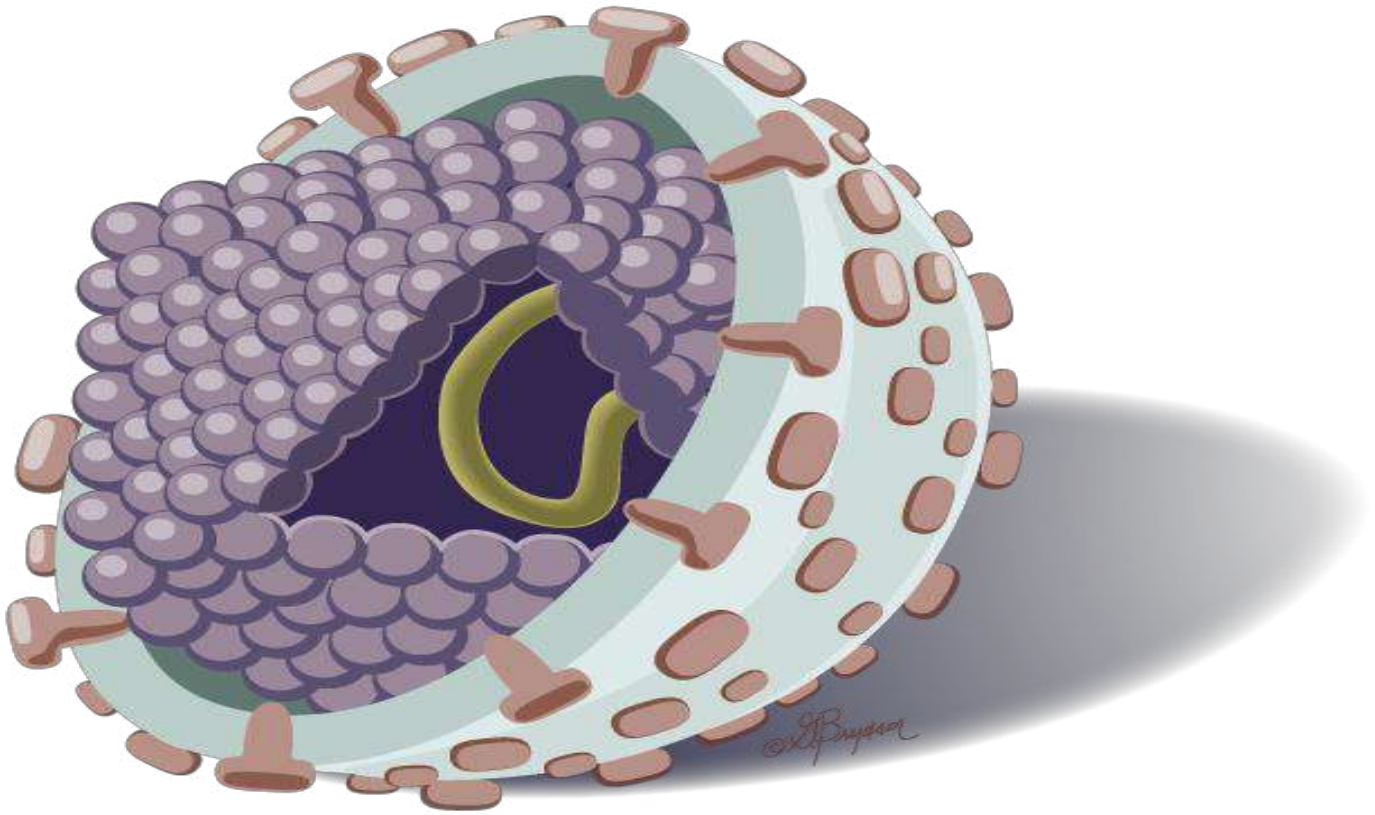
- Annual anti-HBs testing
- Booster dose when anti-HBs titer <10 IU/L

Immunocompromised persons with continuing increased risk of infection

Management of Non-responders

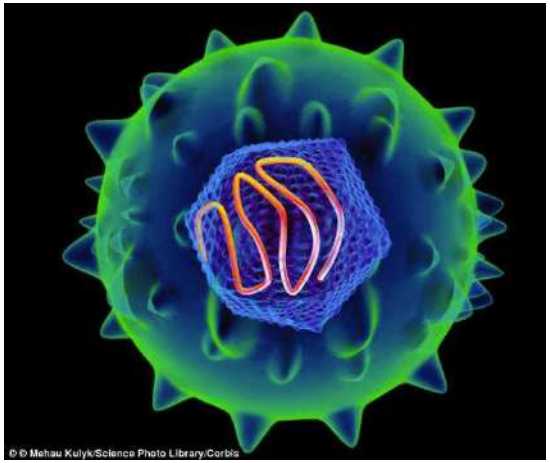


Hepatitis C Infection



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 distint genotypes



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

Prevalence

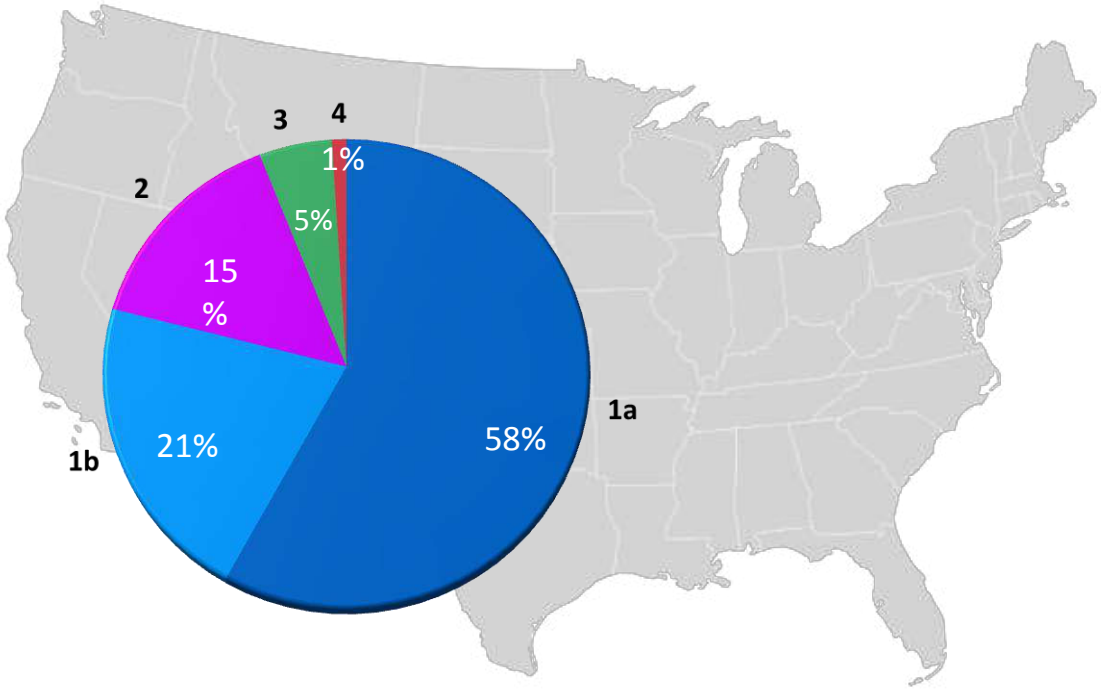
Worldwide 170 million (3%)

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



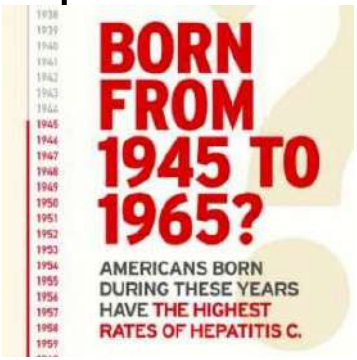
- Genotypes 1a and 1b account for 79%
- Genotype 2 accounts for 15%

Zein NN, et al. *Ann Intern Med*. 1996;125:634-639.

Prevalence

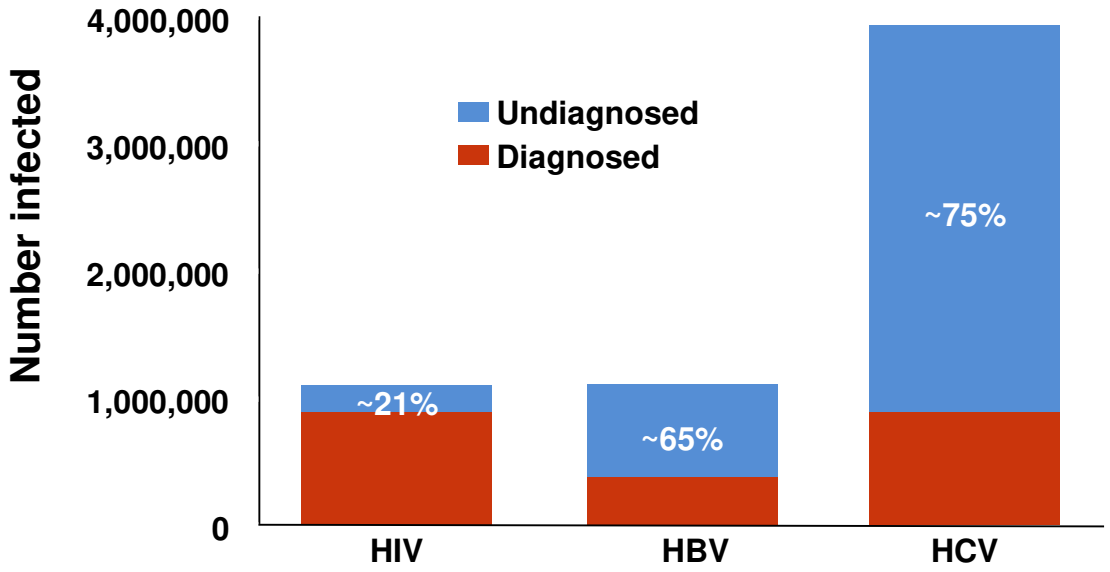
- Approximately 3.2 million people are chronically infected with HCV based on NHANES (2001-2008) population
  - ~ 70% born 1945- 1965

- 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



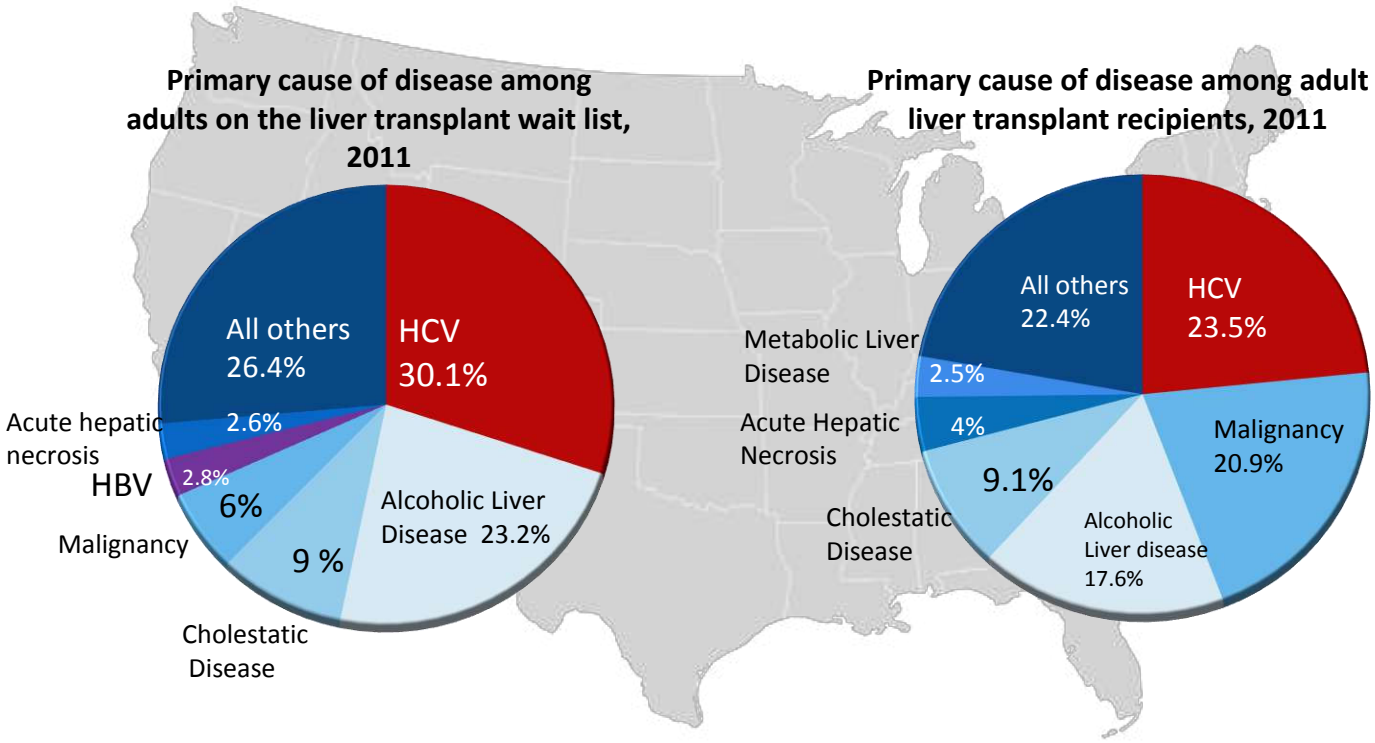
1. Armstrong GL, et al. Ann Intern Med. 2006;144:705-714 2.http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm;3. Chak E et al. Liver Int.2011;31:1090-1101

HEPATITIS C IS UNDER-DIAGNOSED IN US



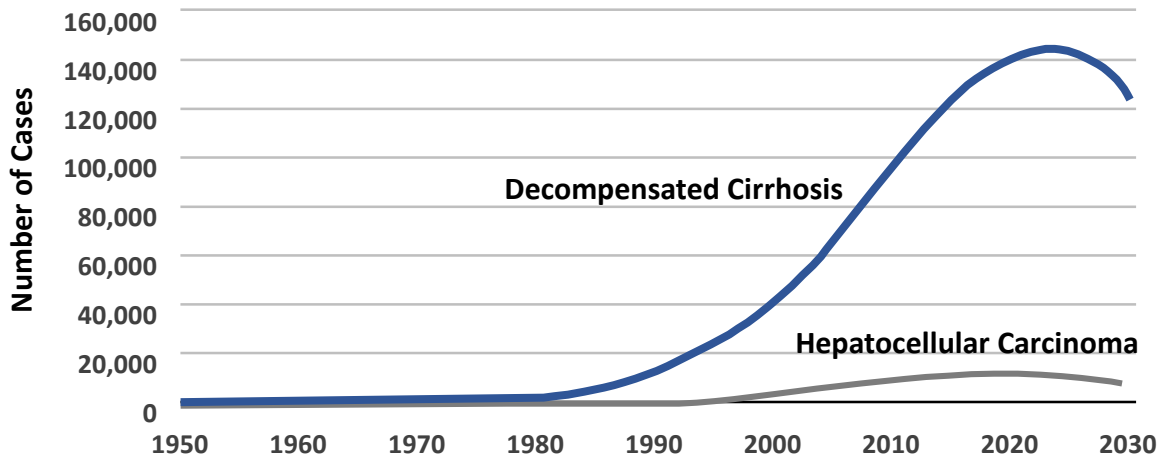
Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*; 2010.

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.

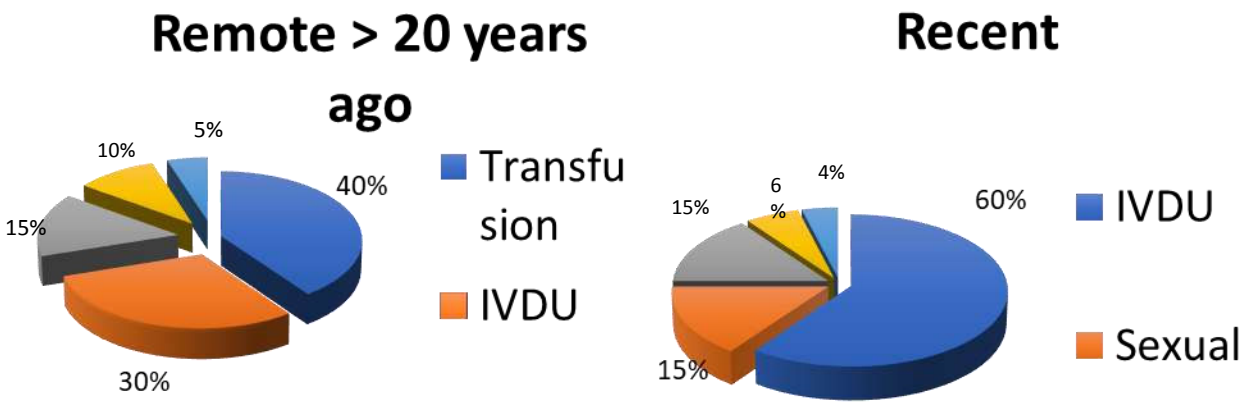
HCV- Related D-Cirrhosis and HCC Projected to Rise in the US



- HCV-related decompensated cirrhosis and HCC are rising as manifestations of liver disease in aging population[1]
- 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.

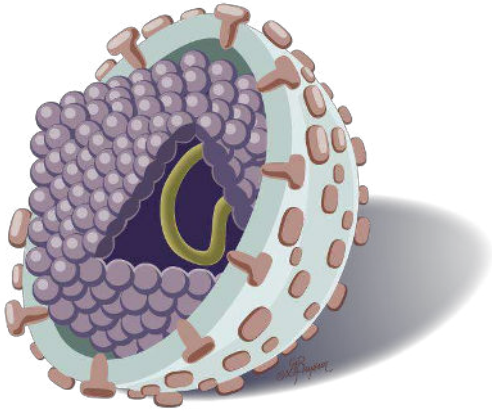
Risk Factors for HCV



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

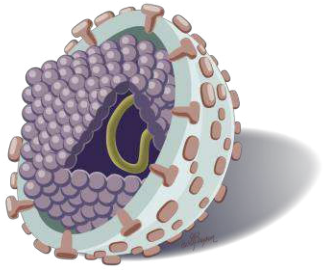
Epidemiology

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



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

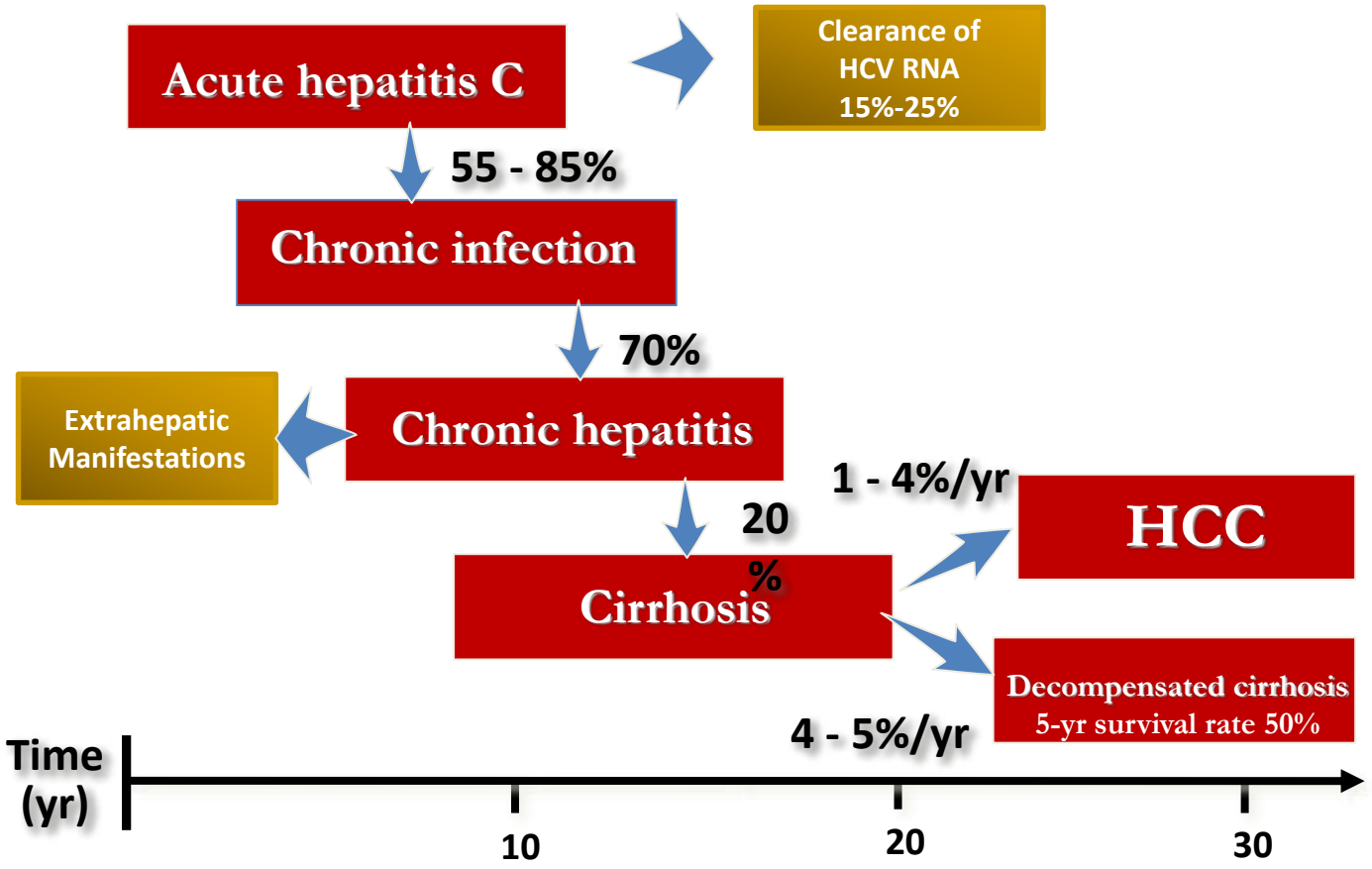
Epidemiology



- 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

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

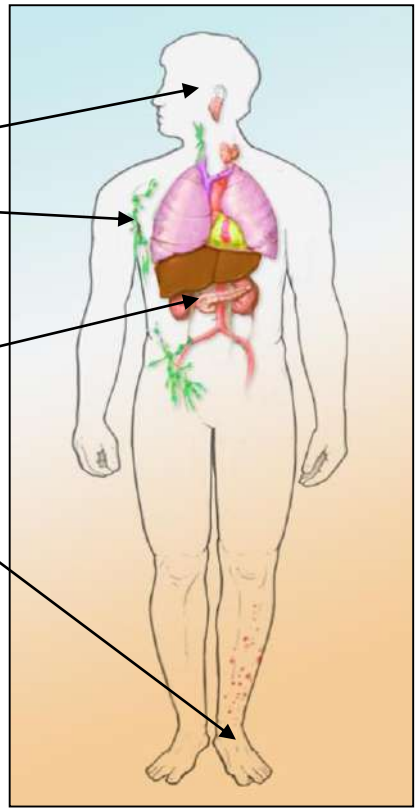
Natural History of HCV Infection



Extrahepatic Manifestations of HCV

Strongly associated

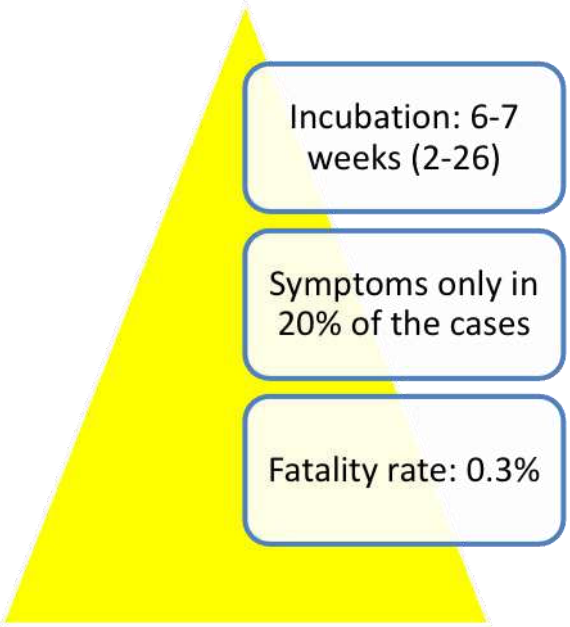
- Mixed cryoglobulinemia
- Sjögren (sicca) syndrome
- Lymphoproliferative disorders
- Porphyria cutanea tarda
- Neuropathy
- Membranoproliferative glomerulonephritis
- Cryoglobulinemic vasculitis



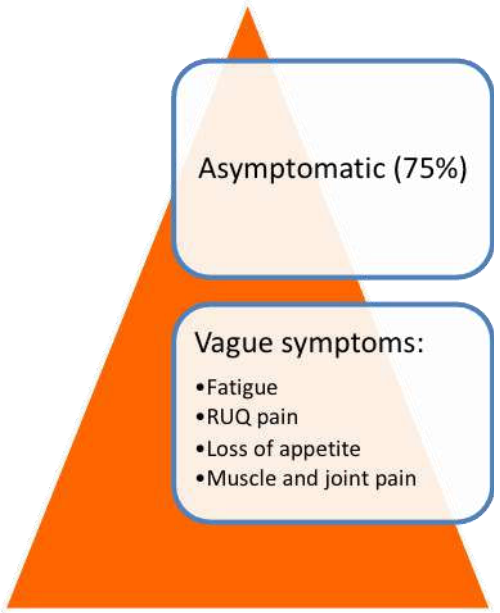
Adapted from Ali A, Zein NN. *Cleve Clin J Med.* 2005;72:1005-1008.

Presentation of Patients Infected with HCV

Acute Infection

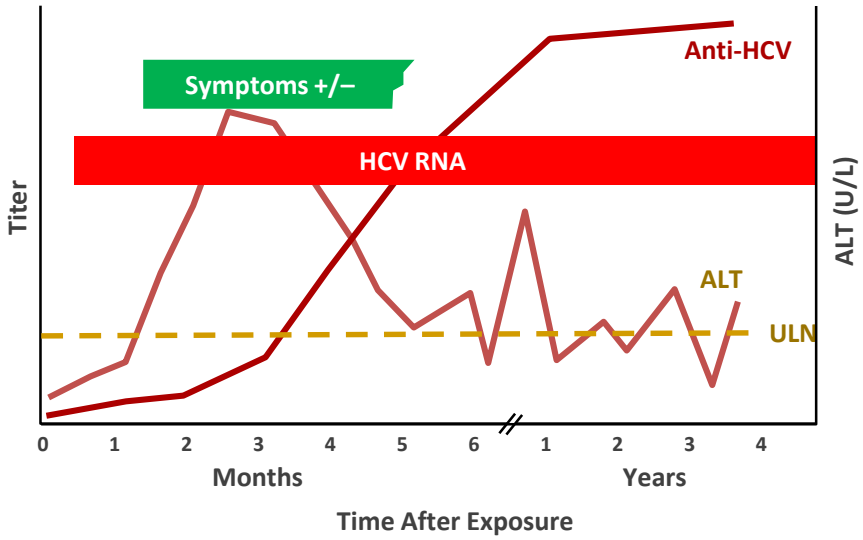


Chronic Infection



Laboratory Diagnosis of Chronic HCV Infection

- RNA testing identifies active disease in HCV-seropositive patients
- HCV antibodies appear by 6–8 weeks following infection[1]
  - Can be detected by EIA[2]
- Serum ALT is not a reliable indicator of liver damage[1]
- FDA-approved rapid point-of-care testing is available[3]
  - OraQuick® HCV Test

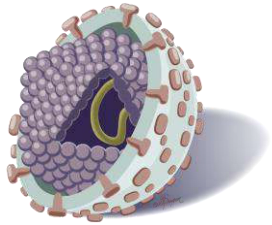


ALT=alanine aminotransferase; EIA=enzyme immunoassay; RNA=ribonucleic acid; ULN=upper limit of normal.

Image adapted from MicrobiologyBytes:Virology:HCV[1]

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
  - Immunosuppresion= HIV or post transplant

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

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”)

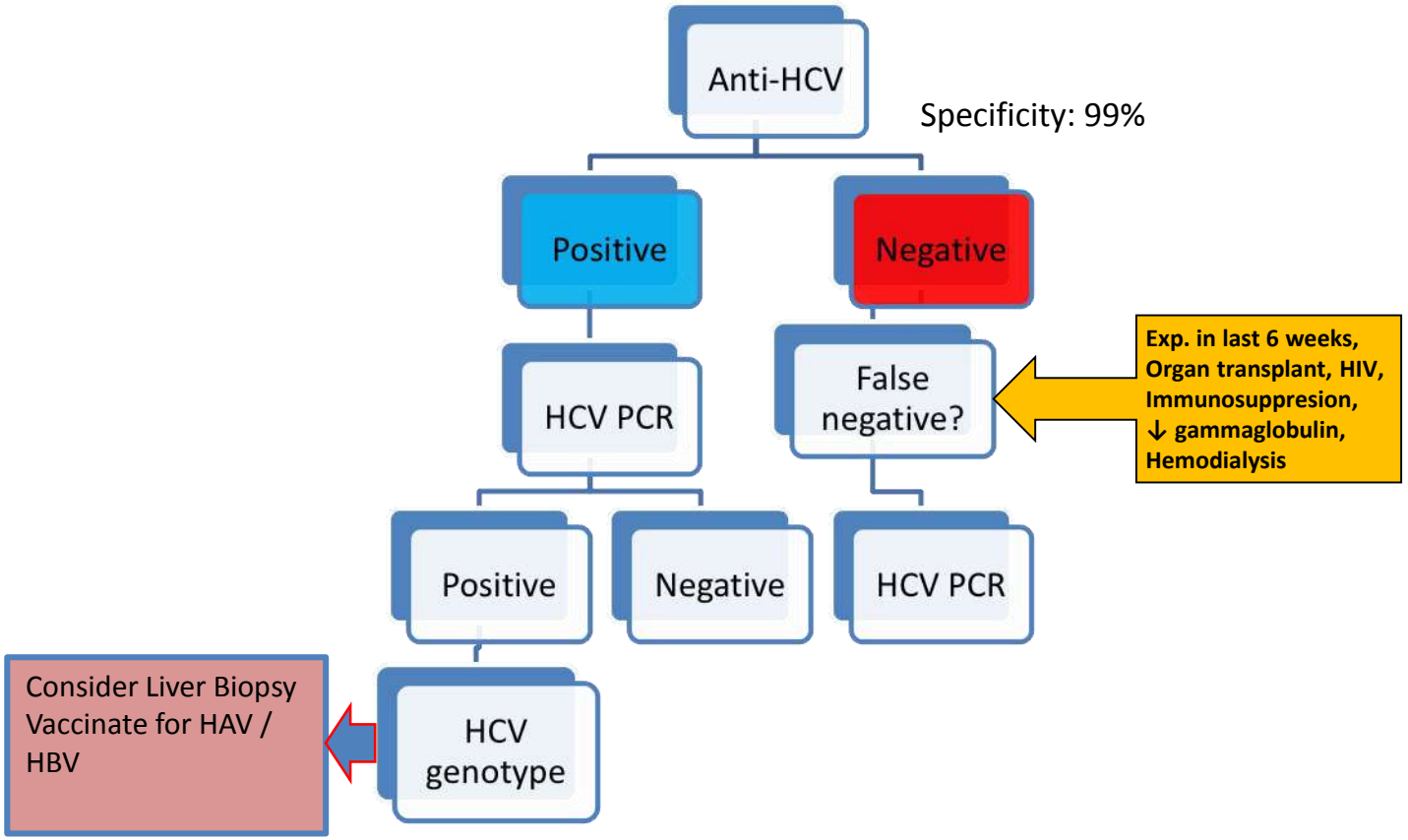
Current AASLD/IDSA Guidelines Screening Recommendations

✓ 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

AASLD/IDSA HCV Tx Guidance, May 2018

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

AASLD/IDSA HCV Tx Guidance, May 2018

Counseling Recommendations for HCV Infected Individuals

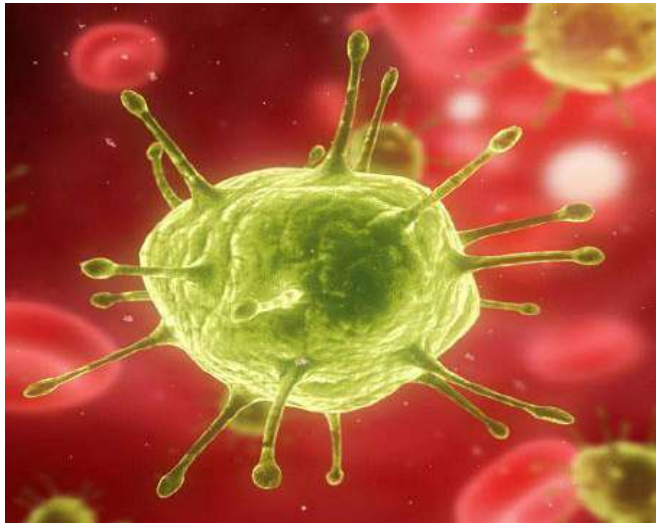
To Prevent HCV Transmission

- 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.

AASLD/IDSA HCV Tx Guidance, Sept 2017

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

AASLD/IDSA HCV Tx Guidance, Sept 2017

HBV testing/monitoring during Hepatitis C DAA Therapy

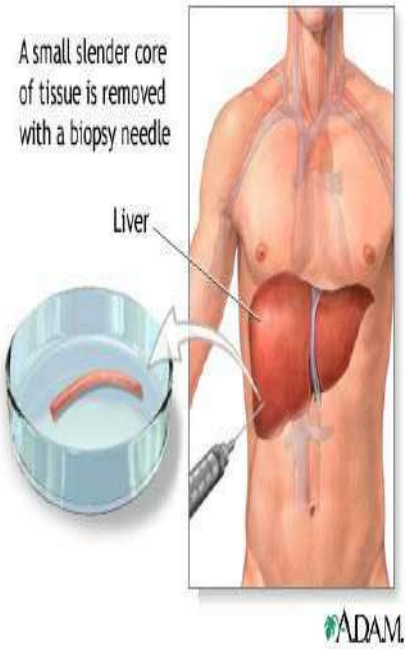
In HBsAg (+) patients in no HBV suppressive therapy

- 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.

AASLD/IDSA HCV Tx Guidance, Sept 2017

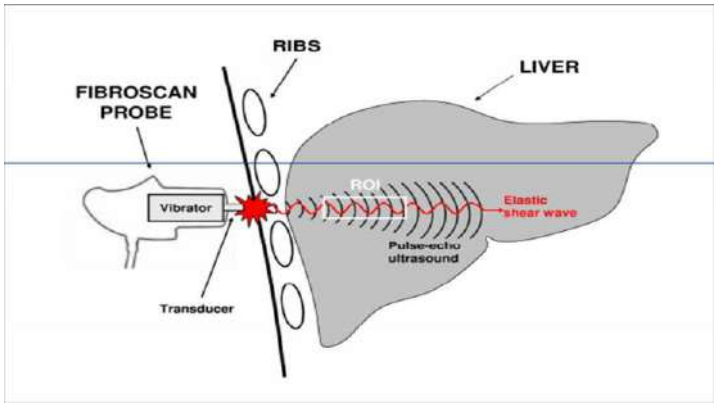
Clinical Staging: Liver Biopsy

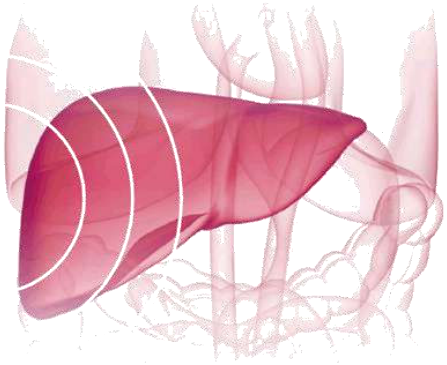
- Liver biopsy remains as the diagnostic standard
- Degree of inflammation
- Tissue damage or fibrosis staging
  - **THE MOST IMPORTANT PROGNOSTIC FACTOR IN DISEASE PROGRESSION**
- Coexistent liver diseases (iron, steatosis, etc.)
- Liver biopsy limitations:
  - **costly and invasive**
  - **complication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



Fibroscan- Transient Elastography

- **Transient elastography (Fibroscan)**
  - Uses ultrasound and low frequency elastic waves.

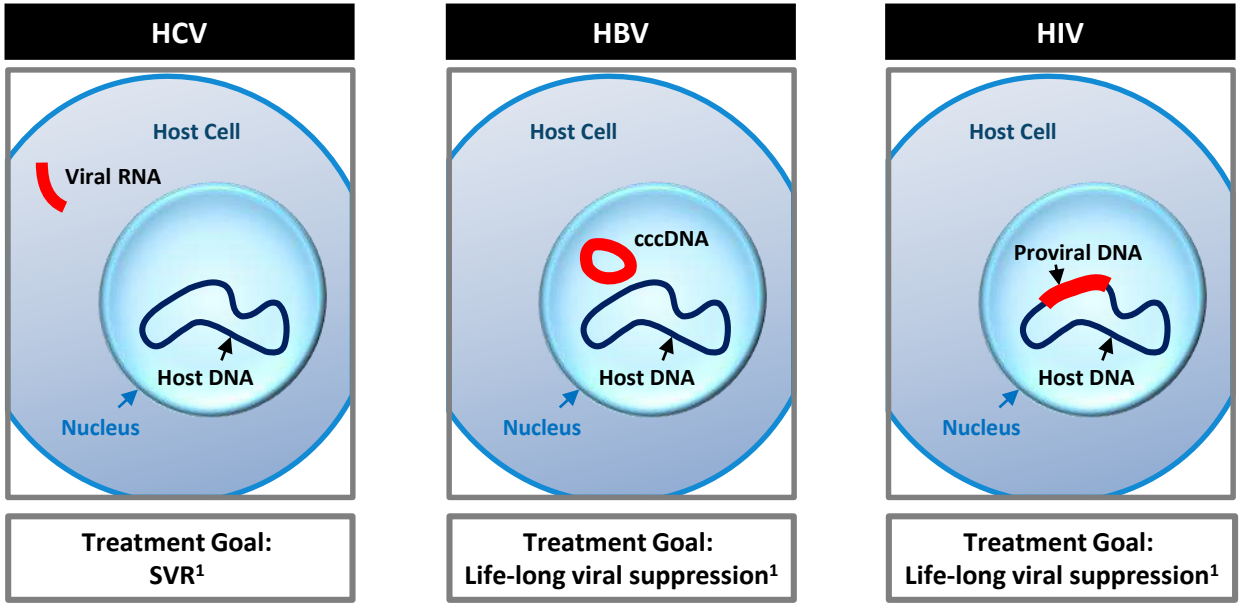




Antiviral Therapy

- 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 treatmet:
  - 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



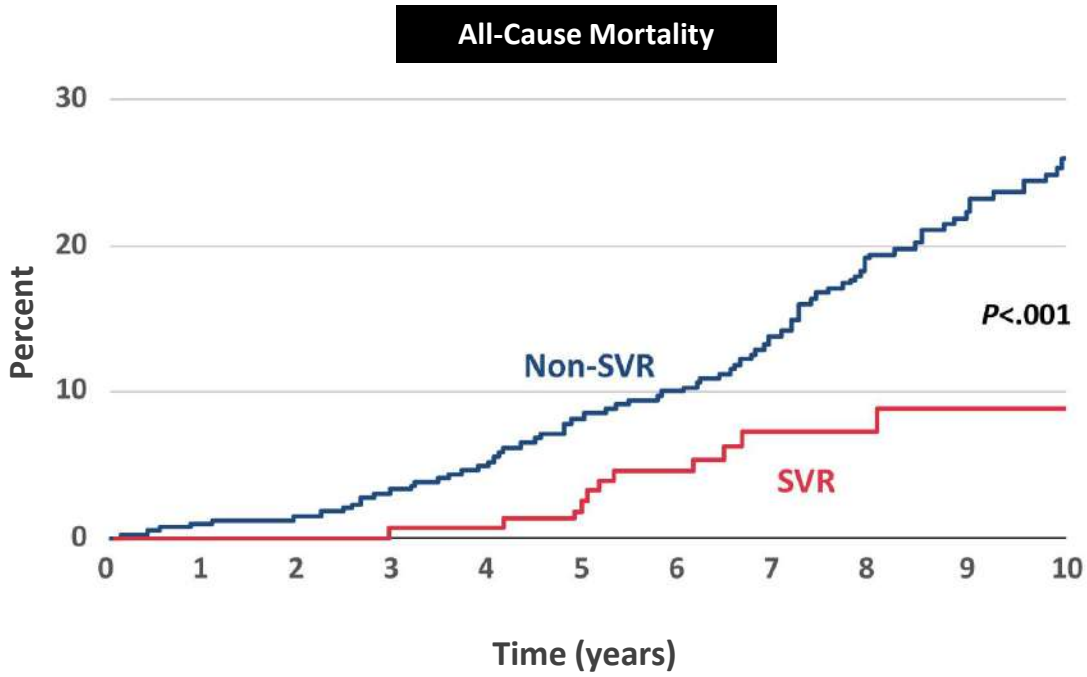
- **Majority of patients who achieve an SVR do not experience viral recurrence[2]**

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

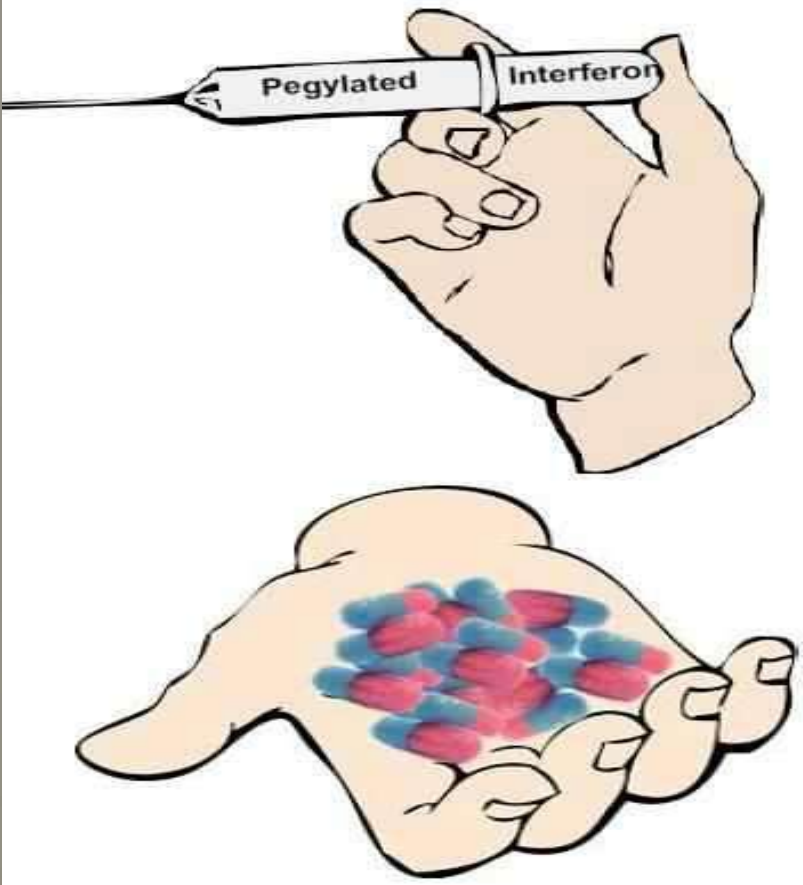


International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

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

Simplification of HCV Treatment

Past



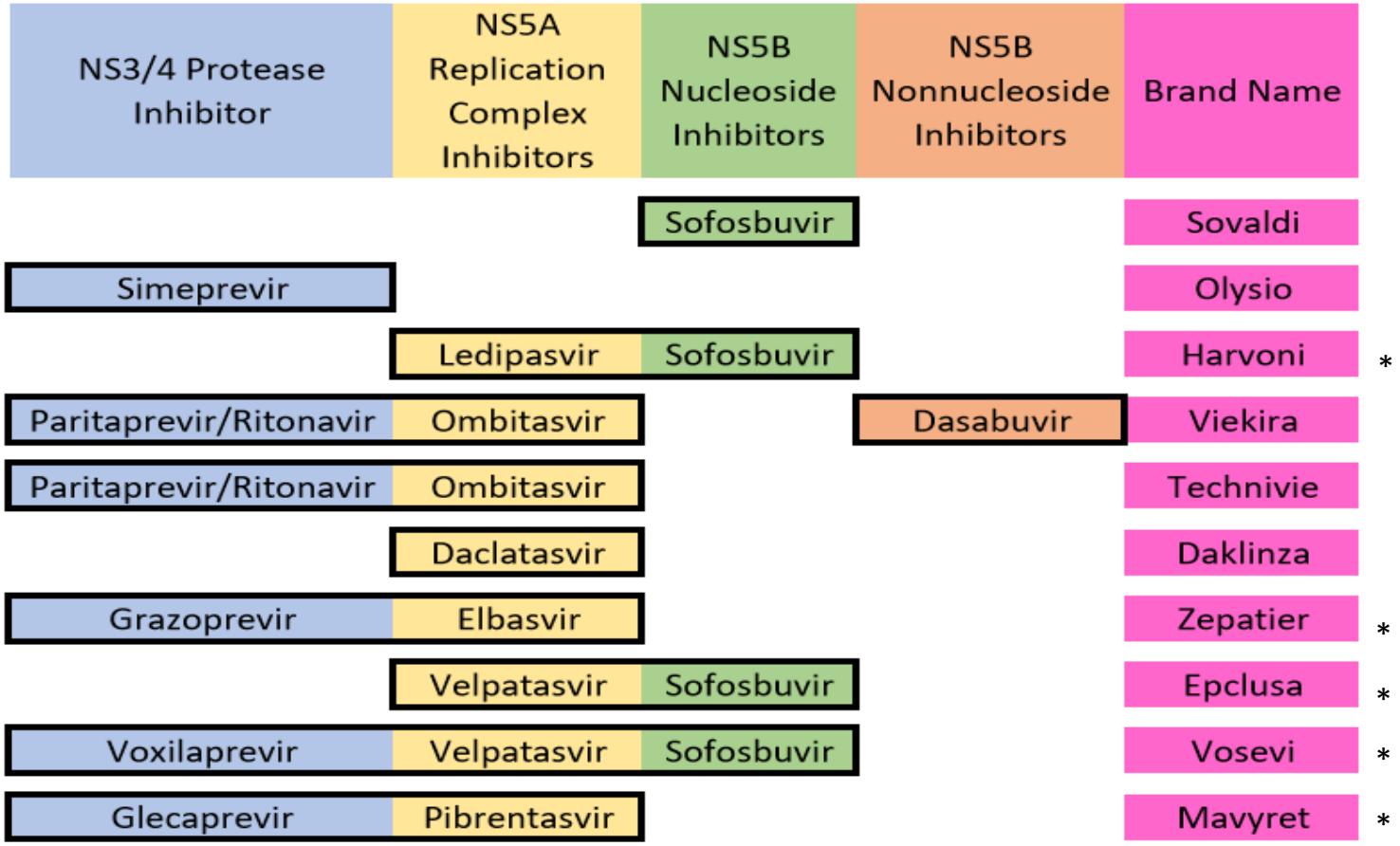
Present

PHARMASSET

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
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Voxilaprevir
Velpatasvir
Sofosbuvir
Vosevi
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Glecaprevir
Pibrentasvir
Mavyret
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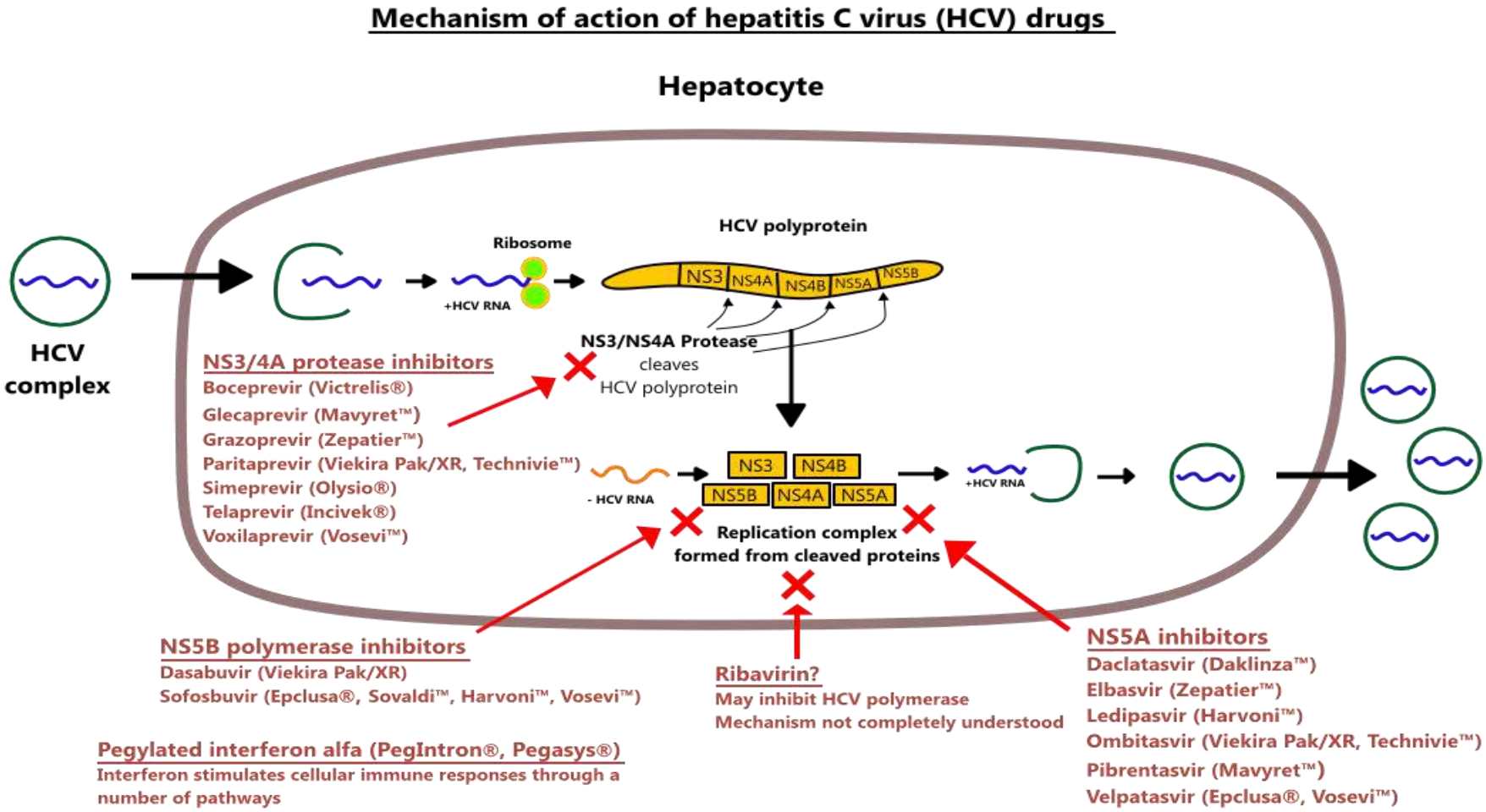


https://www.straighthealthcare.com/hepatitis-c-drug-moa.html

HCV Landscape

	Harvoni® (ledipasvir/sofosbuvir)	Zepatier® (elbasvir/grazoprevir)	Epclusa® (sofosbuvir/velpatasvir)	Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	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

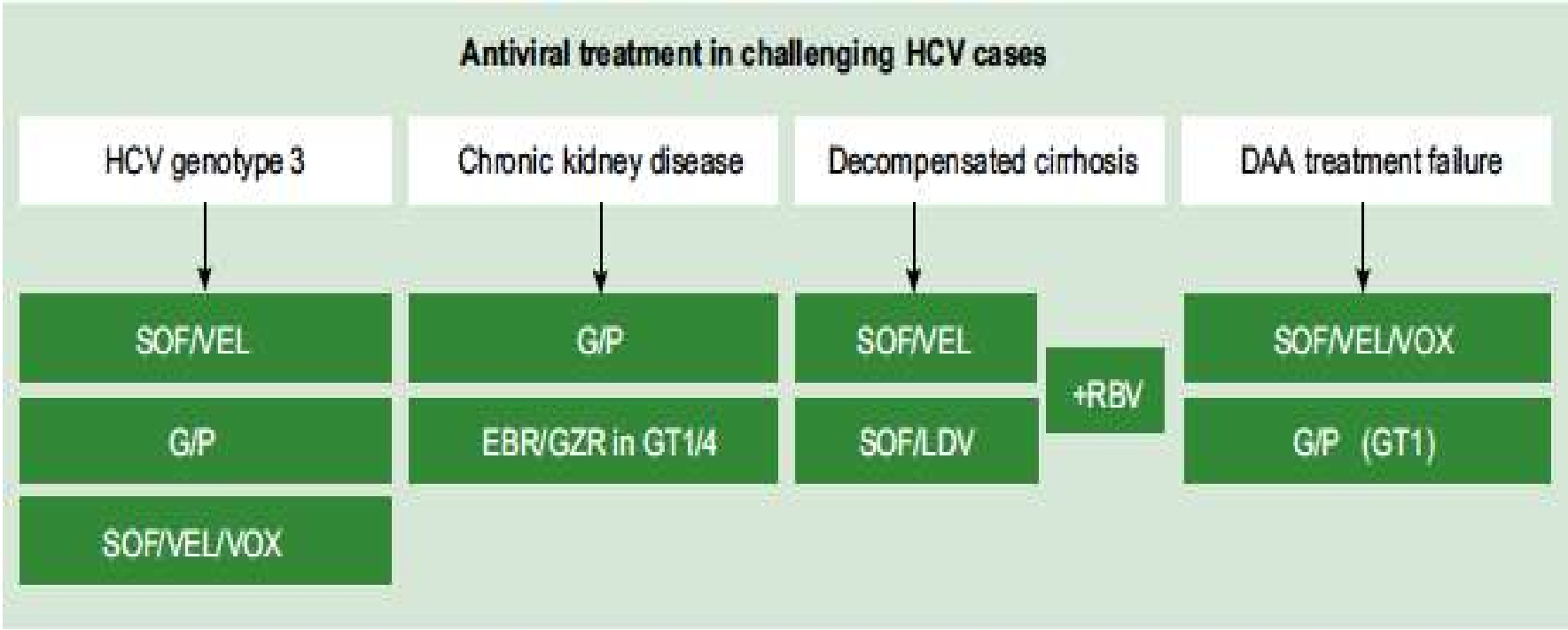
Drug to drug interactions

- 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



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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