AETC AIDS Education & Training Center Program Southeast

Hepatitis update

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Basic Features of Hepatitis Viruses

Virus	Transmission	Incubation Period (weeks)	Chronic Infection
A	fecal-oral	4 (2-6)	No
B	parenteral	8-12 (6-24)	Yes
C	parenteral	6-9 (2-24)	Yes
D	parenteral	? (2-10)	Yes
E	fecal-oral	4-5 (2-9)	No

Hepatitis Screening

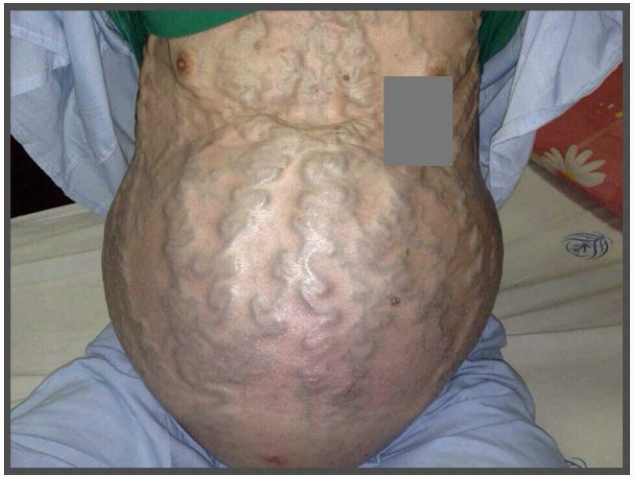
- **Hepatitis A Virus**
  - Screen with hepatitis A antibody (IgG or Total, NOT IgM)
  - To evaluate for evidence of prior HAV infection or immunity.
- **Hepatitis B Virus**
  - Hepatitis B surface antigen (HBsAg)- to look for chronic HBV
  - Hepatitis B surface antibody (HBsAb)- immunity or clearance
  - Hepatitis B core antibody (anti-HBc total, **NOT IgM**)
- **Hepatitis C Virus**
  - HCV antibody
    - If Positive then reflex to HCV Quantitative PCR (Viral Load)
  - Repeat annual testing or more frequent test is recommended for those who have ongoing risk of HCV acquisition.

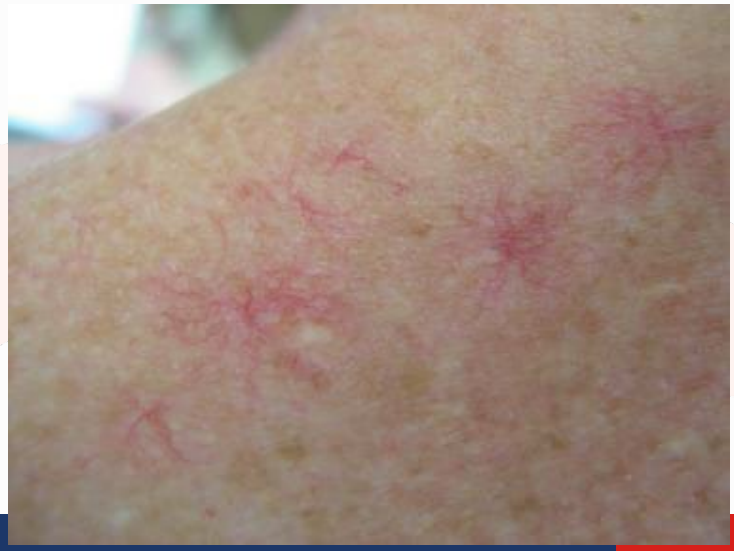
History from patient

- Date of onset of symptoms
- Occupation- sanitation worker, sex worker?
- If child, whether child attends childcare
- Household contacts- anyone sick?
- Restaurants attended 2-6 weeks
- Travel history- Asia, Africa?
- Sexual History- oral, anal,
- Hobbies-
- Pets- turtles, etc.?

Advanced Fibrosis/cirrhosis

- Cirrhosis
  - Palmar Erythema
  - Gynecomastia
  - Spider nevi
  - Thrombocytopenia
- Decompensated cirrhosis
  - Ascites
  - Caput medusa
  - Jaundice
  - Coagulopathy

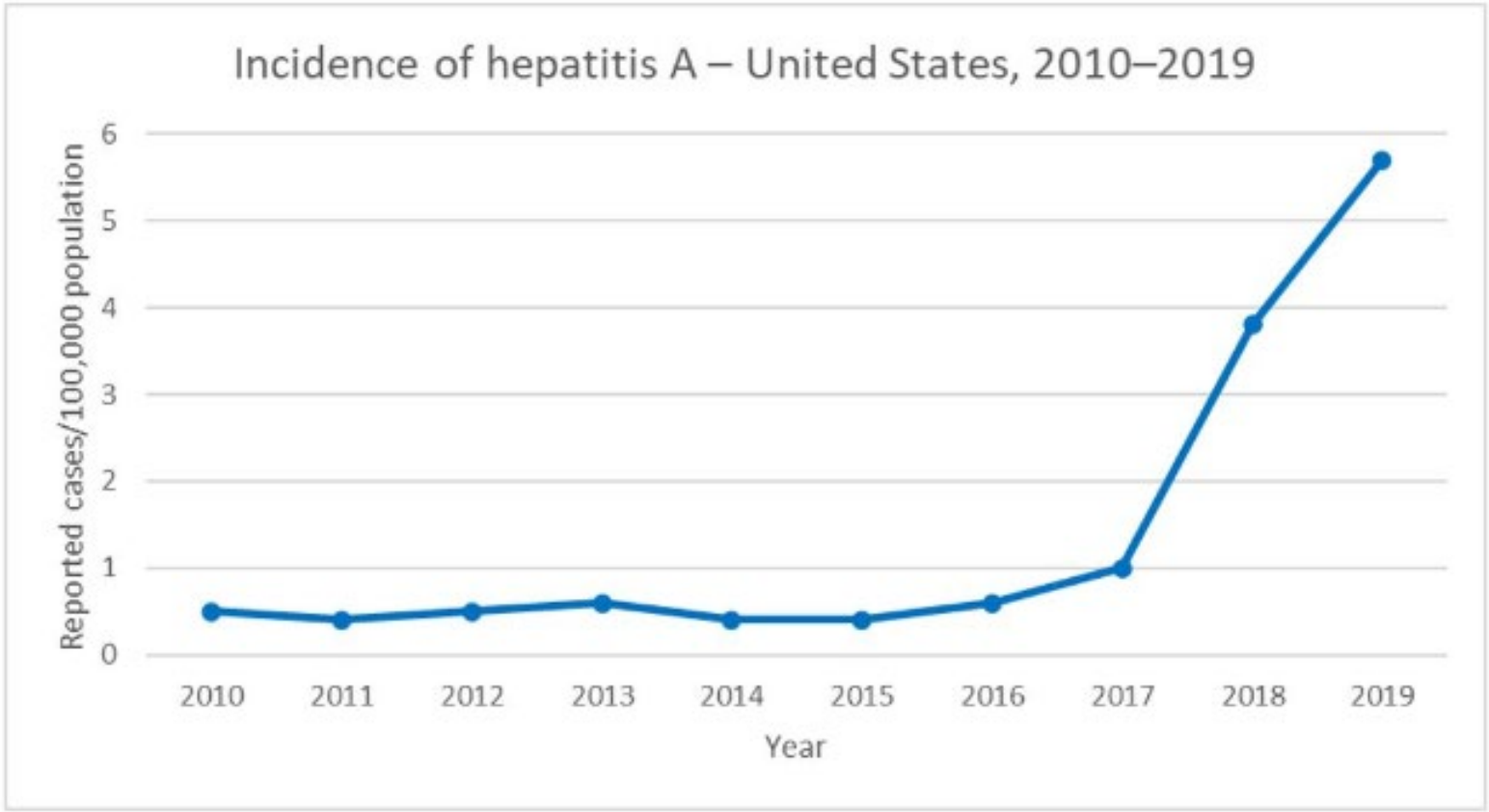




Hepatitis A

- Highly contagious.
- Usually transmitted by the fecal-oral route
  - Through person-to-person contact
  - Consumption of contaminated food or water.
- Hepatitis A is a self-limited disease
- Virus appears in feces 2 weeks before symptoms
- Symptoms
  - > 70% of adults have symptoms
- Diagnosis
  - Acute infection -diagnosed by HAV-IgM
  - Past Infection/ immunity -HAV-IgG by EIA (total Ab is cheaper).
    - Antibodies last for life and are protective

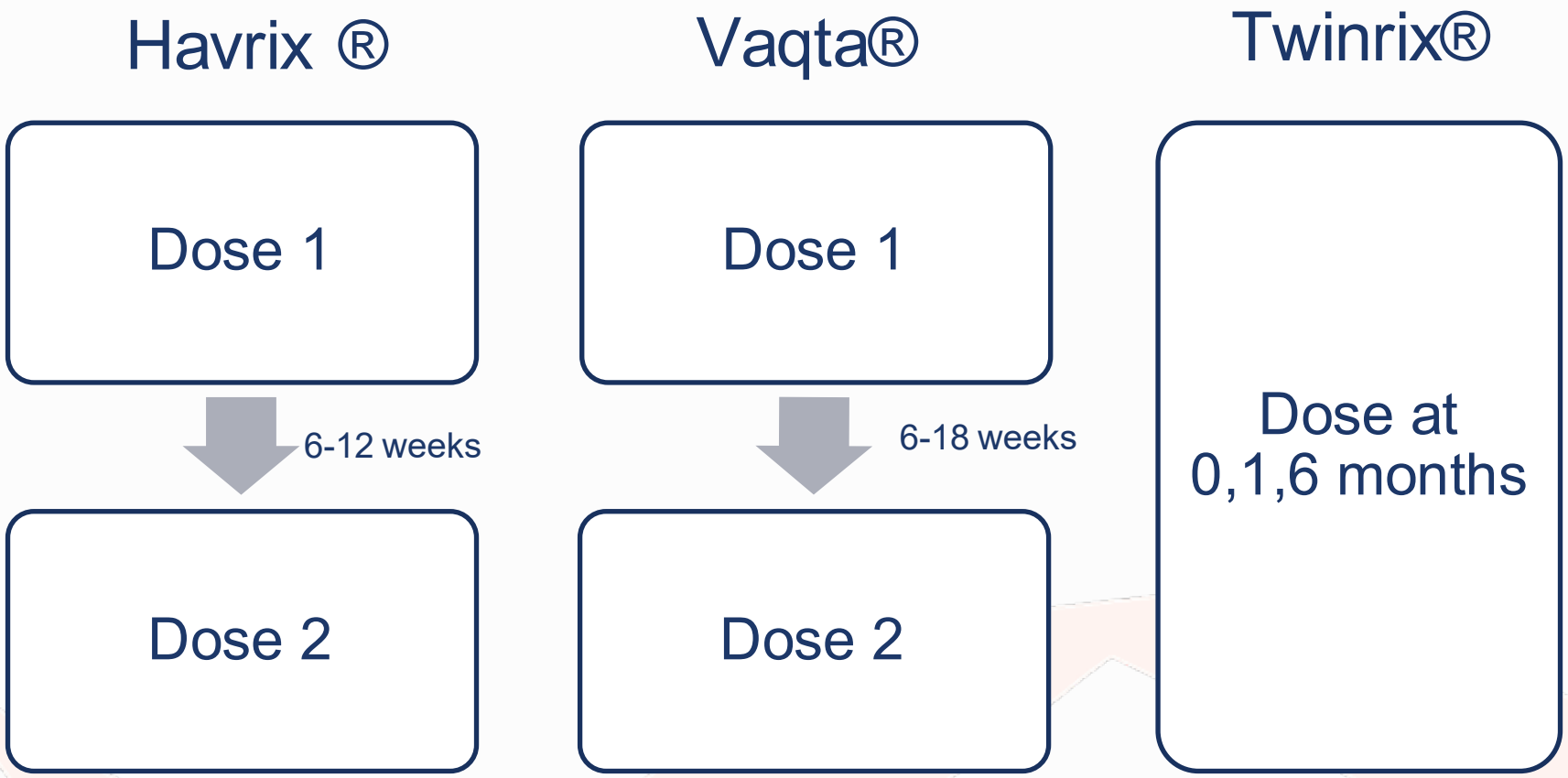
Incidence of Hep A in the US



Hepatitis A – prevention through vaccine

- New recommendations by CDC on February 15, 2019
  - All persons aged >/= 1 year, homeless, IVDU
- Vaccination (pre-exposure)
  - Two available inactivated vaccines,
    - HAVRIX
    - VAQTA
  - Combination vaccine
    - TWINRIX: combines hepatitis A and B vaccine
- Postexposure prophylaxis
  - Vaccine for healthy person's age 1- 40 years
  - GamaSTAN: (Immuneglobulin)
    - For persons > 40 years, at increased risk of severe hepatitis A

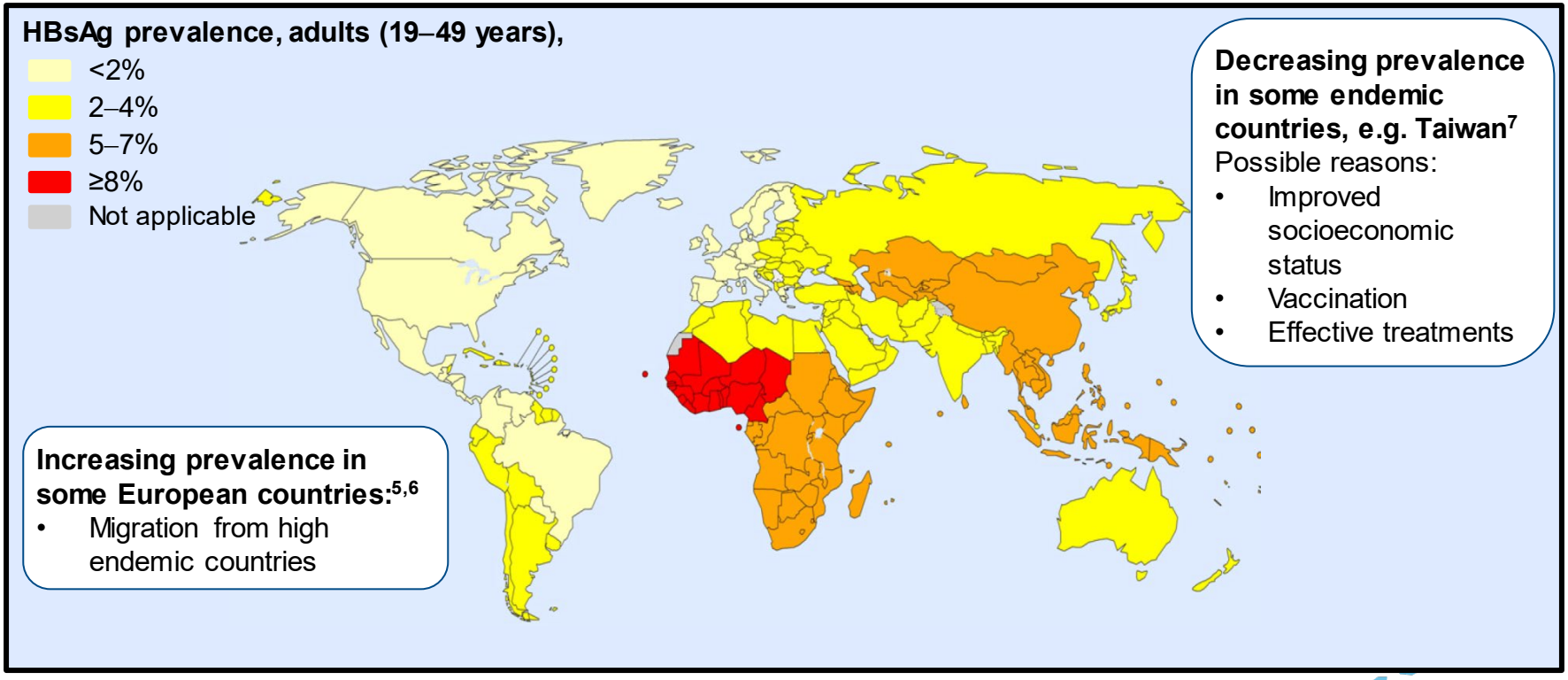
Hepatitis A Vaccine Options



CDC. Adults Immunization Schedule. Available from: https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html#note-hepb

Hepatitis B

- Hepatitis B affects approximately 300 million people worldwide.
- Hepatitis B contributes to an estimated 820,000 deaths every year.
- 25% of chronic hepatitis B infections progress to liver cancer.
- HBV is 50-100 times more infectious than HIV



1. EASL CPG HBV. J Hepatol 2017;67:370–98; 2. Schweitzer A, et al. Lancet 2015;386:1546–55;
3. Ott JJ, et al. Vaccine 2012;30:2212–9; 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71;
5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–83; 7. Chen C-L, et al. J Hepatol 2015;63:354–63.

EASL™ The Home of Hepatology

New Screening recommendations

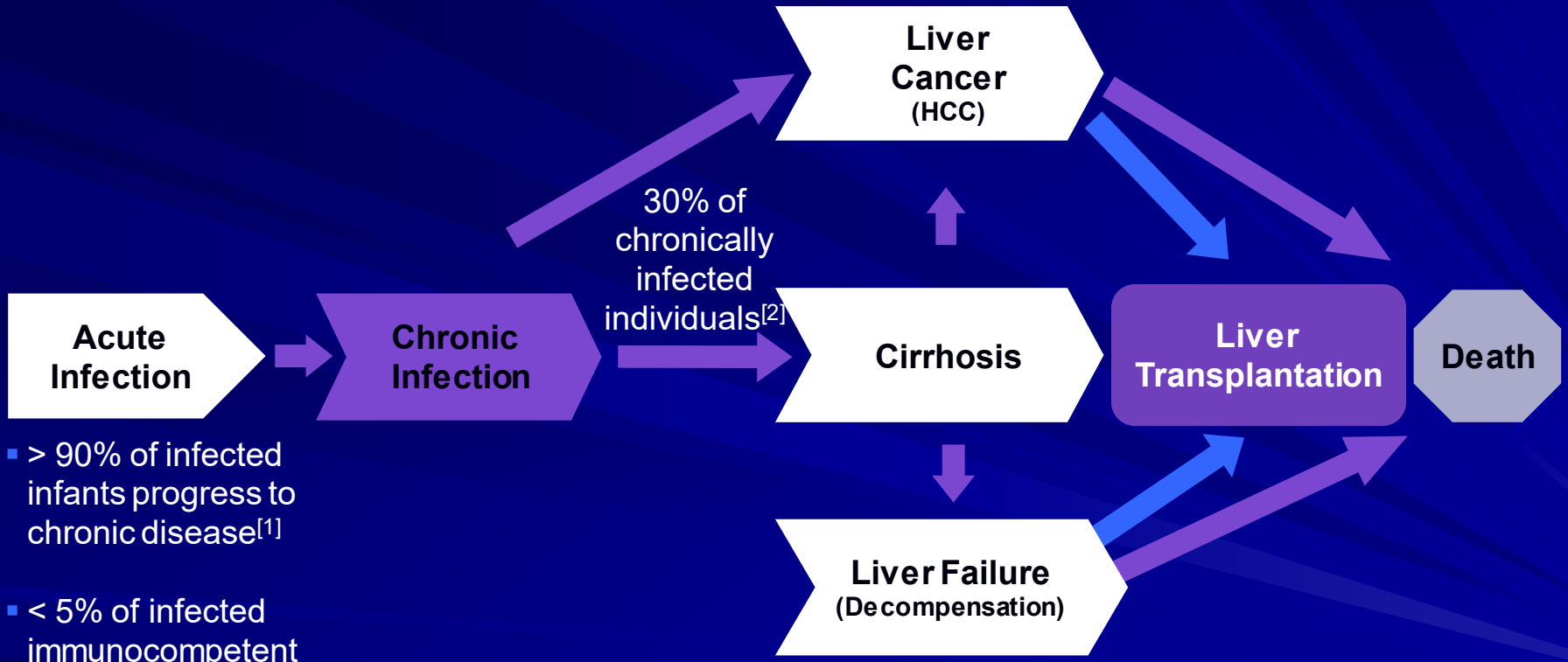
JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Hepatitis B Virus Infection in Adolescents and Adults
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

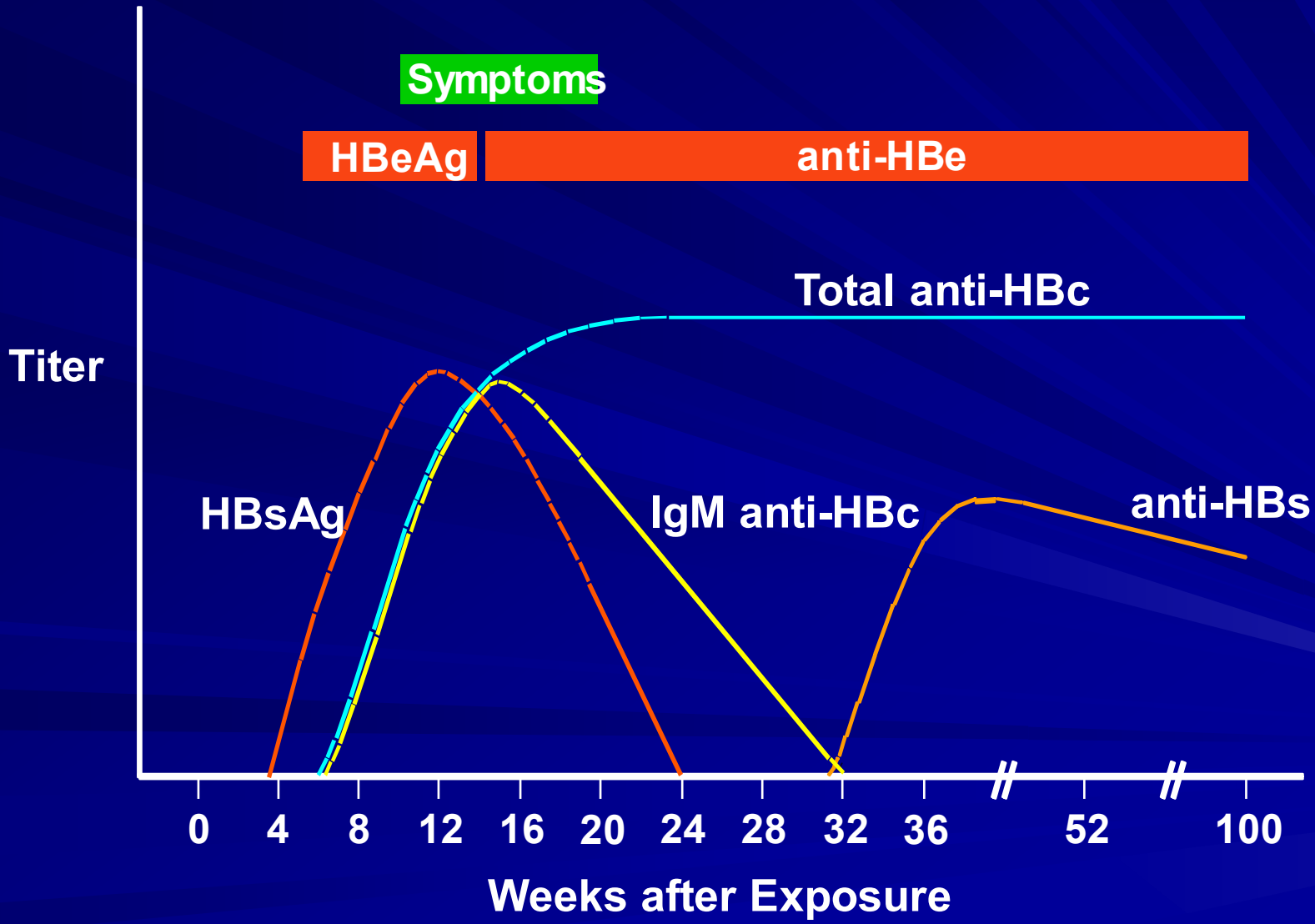
- Estimated 862 000 persons in the US with chronic hepatitis B virus
- Screen all persons :
  - Persons born in regions with a prevalence of HBV infection > 2%
  - Dialysis
  - All Pregnant women
  - Persistent Transaminitis
  - Starting immunosuppressive therapy
- Other high-prevalence populations
  - Persons who inject drugs; incarcerated
  - Men who have sex with men
  - HIV, HCV
  - Needle-sharing contacts and household contacts of persons with chronic HBV infection.
- Majority of HBV-infected persons are unaware of their infection

Hepatitis B Disease Progression

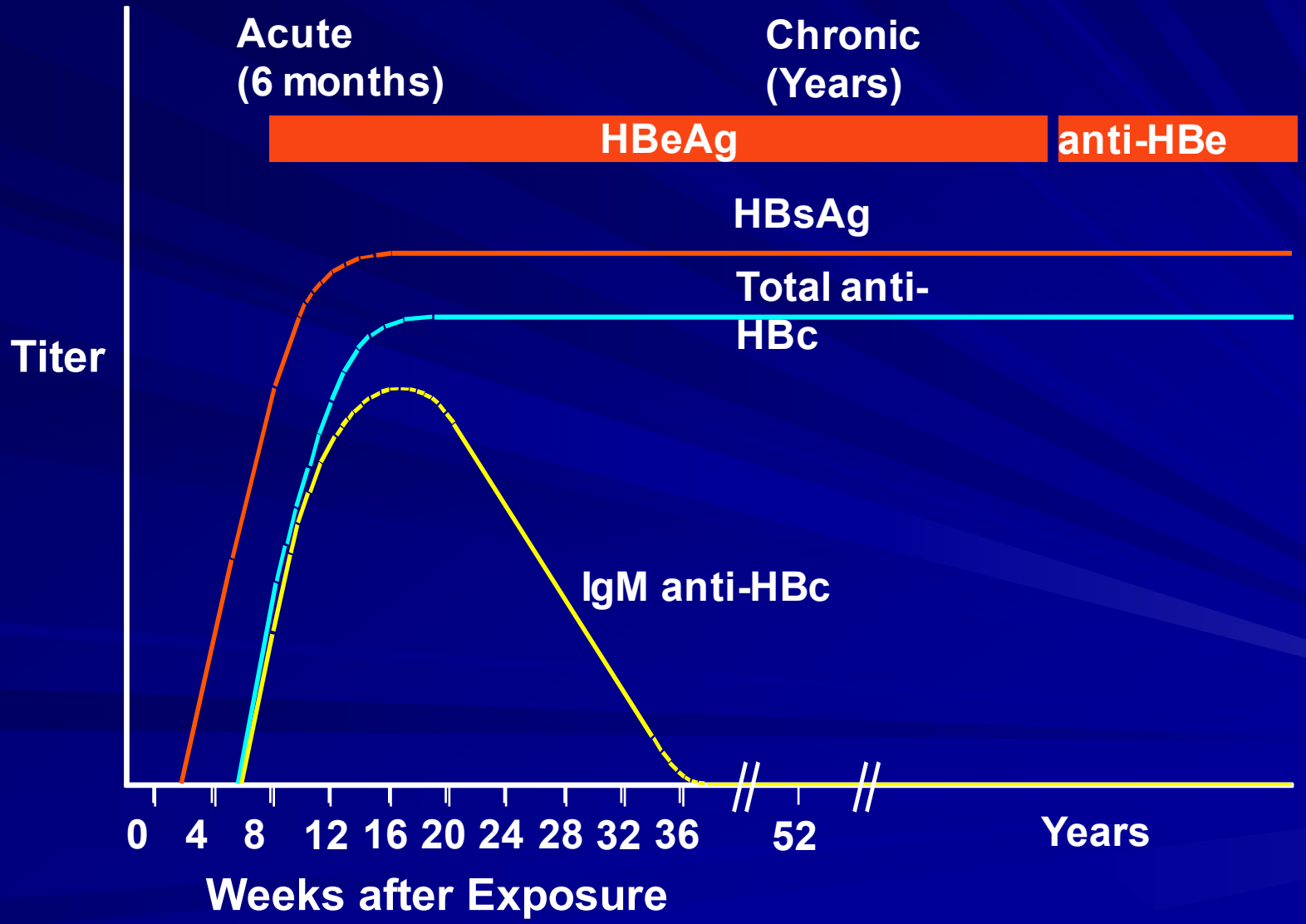


- > 90% of infected infants progress to chronic disease[1]
- < 5% of infected immunocompetent adults progress to chronic disease[1]

Acute HBV Infection with Recovery



Progression to Chronic HBV Infection



Interpretation of Serologic Results

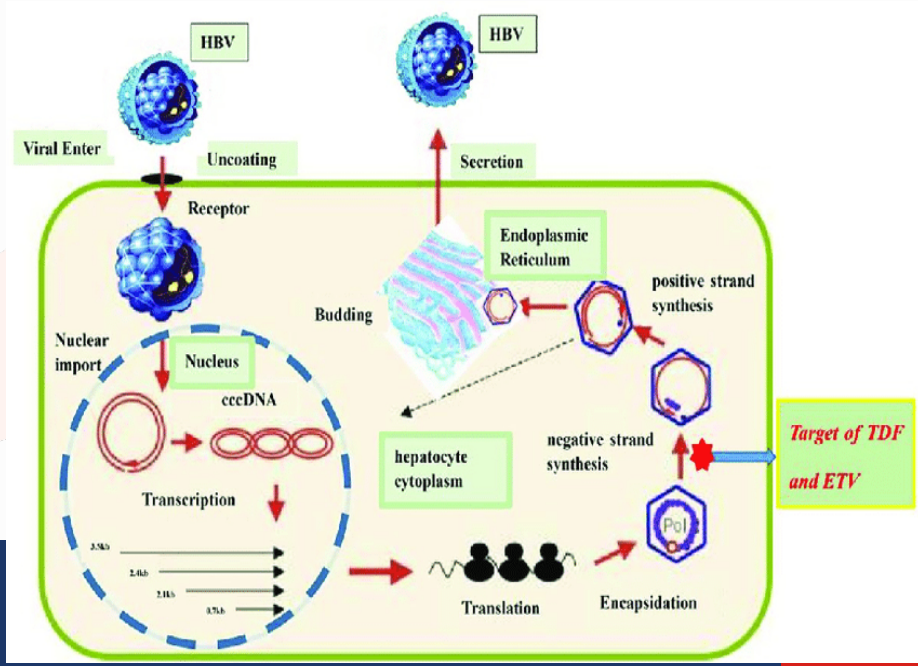
HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
Negative	Negative	--	Negative	Susceptible; offer vaccination
Negative	Positive	--	Positive	Immune due to natural infection
Negative	Negative	--	Positive	Immune due to hepatitis B vaccination
Positive	Positive	Negative	Negative	Chronic HBV infection
Positive	Positive	Positive	Negative	Acute HBV infection
Negative	Positive	--	Negative	Could be any one of the following: 1. Resolved infection (most common) 2. False-positive anti-HBc; susceptible 3. “Low-level” chronic infection 4. Resolving acute infection

CDC. Hepatitis B FAQs for Health Professionals.

HEPATOLOGY
AASLD
PRACTICE GUIDANCE | HEPATOLOGY, VOL. 67, NO. 4, 2018

Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance

- Preferred therapies
  - **Tenofovir disoproxil fumarate(TDF) 300 mg PO daily**
  - **Tenofovir alafenamide (TAF) 25 mg PO daily**
  - **Entecavir (0.5 mg qd; 1 mg if lamivudine resistance)**
  - Interferons
    - Non-Preferred therapies
      - Lamivudine (100 mg qd)
      - Telbivudine
      - Adefovir (10 mg qd)



Efficacy of treatment

- After 1 year of effective treatment
  - 75- 90% have undetectable viral loads
  - 65- 80% have normalized liver enzymes
- But Eradication of Hepatitis B is rare
  - Even in patients who have cleared hepatitis B on Rx:
    - Traces of HBV are detectable by serum PCR
    - HBV DNA can be detected in liver tissue
    - Stopping Treatment can lead to resurgence of viremia

- Therefore
  - Not everybody is started on Hepatitis B Rx
  - No well outlined stopping criteria
- Treatment is initiated in :
  - Patients with existing liver disease or cirrhosis
  - Raised liver enzymes (ALT > 2 ULN)
  - High Viral loads
    - (different for HBeAg negative and HBeAg positive disease)
  - Family history of HCC
  - Older age (> 40)
  - Extrahepatic complications

Hepatitis B prevention

- Primary Prophylaxis
  - Recombinant single-antigen formulation with a unique CpG adjuvant is the first new HBV vaccine approved for US adults in > 25 yrs
    - Requires 2 doses (vs 3 doses for previously available vaccines)
    - Can be completed in 1 mo (vs 6 mos for previously available vaccines)
  - Other HBV vaccines for adults remain effective
    - 2 single-antigen formulations, 1 combination with hepatitis A

Postexposure prophylaxis

Hepatitis B Immunoglobulin - used to protect persons who are exposed to hepatitis B

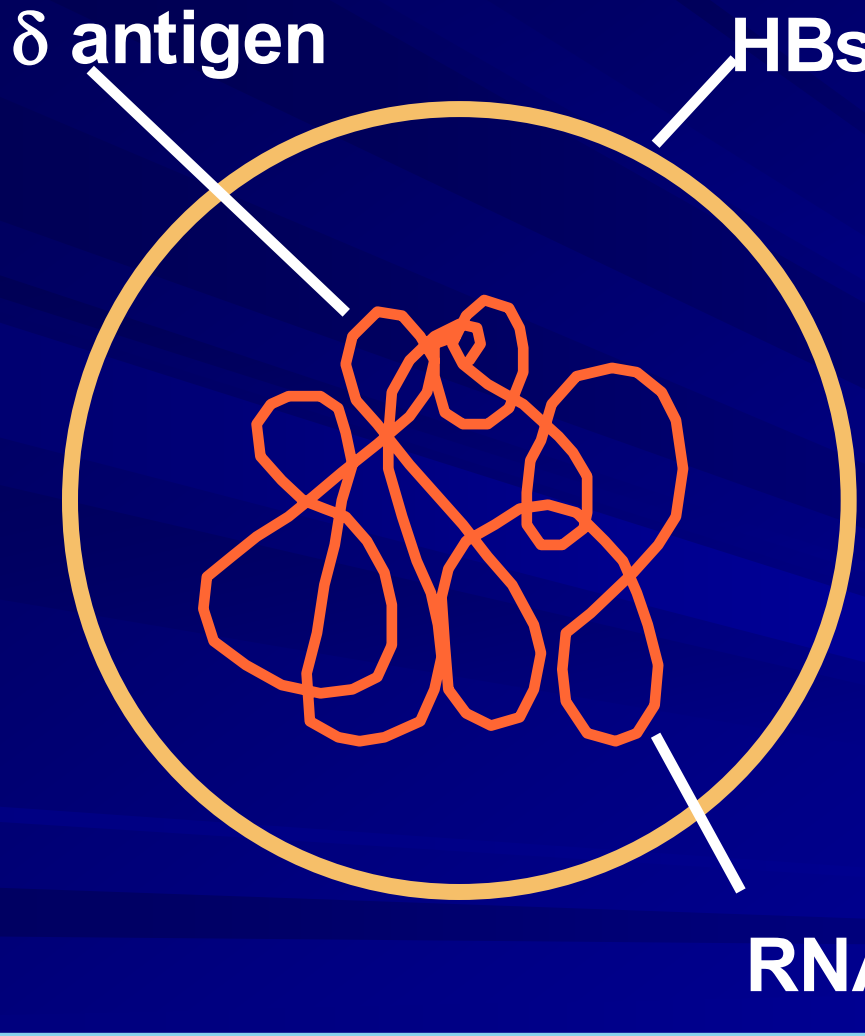
e.g., child born to Hep B positive mother

Schillie. MMWR Morb Mortal Wkly Rep. 2018;67:455. Schillie. MMWR Recomm Rep. 2018;67:1.

Hepatitis B – vaccination update 2021

- The following groups should receive hepatitis B vaccines:
  - Adults 19 through 59 years of age
  - Adults 60 years of age and older with risk factors for hepatitis B infection
- The ACIP recommends the following groups **may** receive hepatitis B vaccines:
  - Adults 60 years of age and older without known risk factors for hepatitis B infection

Hepatitis D (Delta) Virus



HDV is an incomplete virus that requires the helper function of HBV to replicate.

Hepatitis D Virus

- **Hepatitis D virus (HDV) affects globally nearly 5% of people who have a chronic infection with hepatitis B virus (HBV).**
- Hepatitis D is uncommon in the US.
- Hepatitis D only occurs among people who are infected with the Hepatitis B virus
- HDV can be
  - An acute, short-term infection
  - Or a long-term, chronic infection

Hepatitis C

- HCV - discovered in 1989 by scientists at CDC, NIH and industry
  - 1990: routine testing of the blood supply began
- Of every 100 people infected with HCV, approximately:
  - 75 to 85 will go on to develop chronic infection
  - 10 to 20 will go on to develop cirrhosis over a period of 20 to 30 years

At Risk

- **Risk behaviors**
  - Injection-drug or Intranasal illicit drug use
- **Risk exposures**
  - Persons on long-term hemodialysis (ever)
  - Persons with percutaneous/parenteral exposures
  - Needlesticks, sharps, or mucosal exposures to HCV-infected blood
  - Children born to HCV-infected women
  - Prior recipients of transfusions or organ transplants, including persons who:
  - Persons who were ever incarcerated
- **Other considerations**
  - HIV infection
  - Sexually active persons about to start PrEP for HIV
  - Unexplained chronic liver disease and/or chronic hepatitis including elevated alanine aminotransferase levels
  - Solid organ donors (deceased and living)

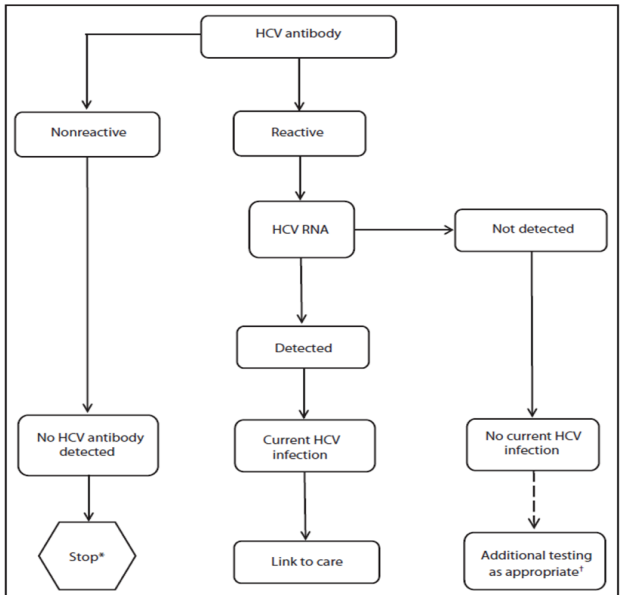
Hepatitis C Screening Recommendations

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

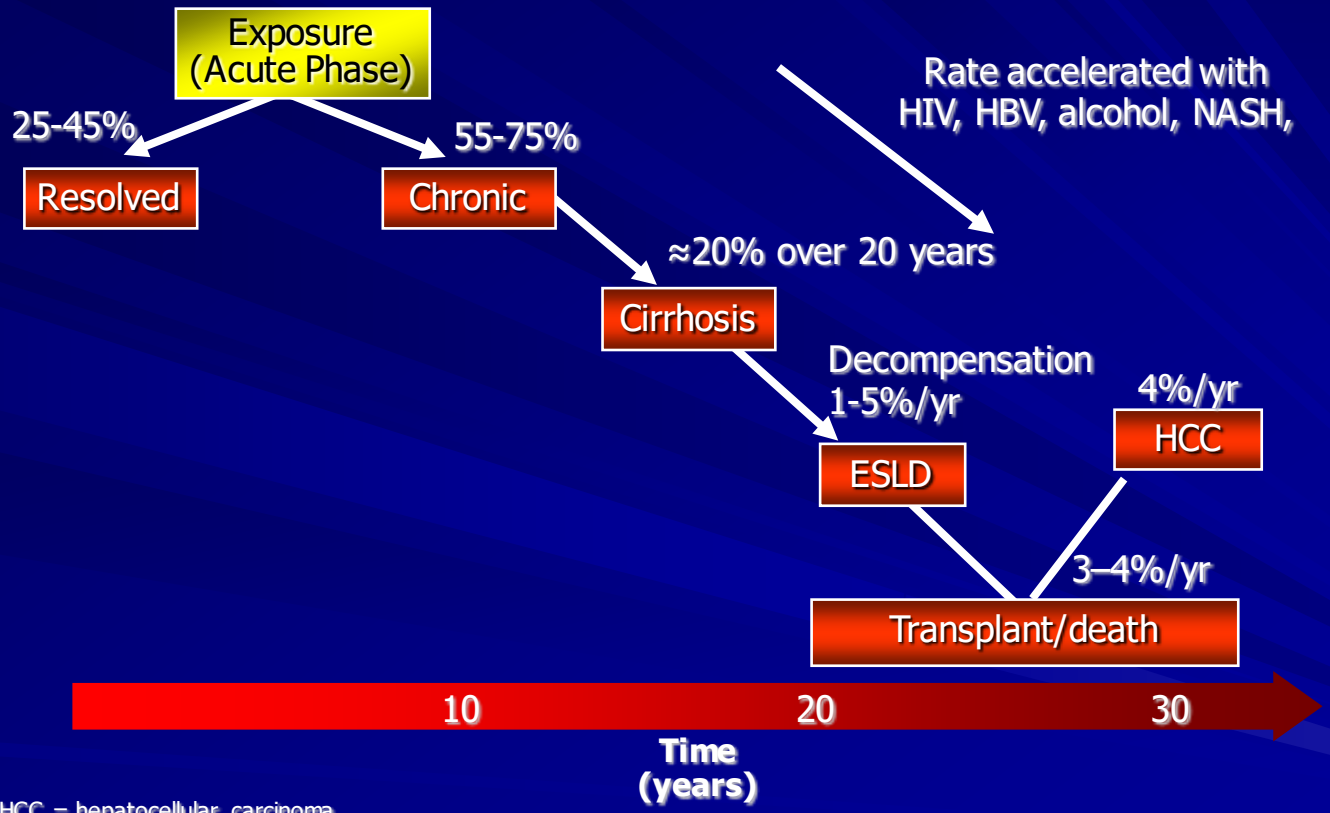
One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

FIGURE. Recommended testing sequence for identifying current hepatitis C virus (HCV infection



Natural History of HCV Infection



HCC = hepatocellular carcinoma
ESLD = end-stage liver disease

Modified from Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

Course of HCV

- **Acute infection**
  - Typically asymptomatic.
  - 15–30% may develop symptoms
  - 65-75% of persons will develop chronic infection

  Hoofnagle JH. Course and outcome of hepatitis C. Hepatology. 2002;36:S21-9
- **Cirrhosis**
  - May develop in 20-30% in the 3rd and 4th decades after infection
  - Metaanalysis of PWID with CHC
    - Estimated time to cirrhosis was 34 years

  Smith DJ, Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): A systematic review and meta-analysis. Int J Drug Policy. 2015;26(10):911–921
- **Hepatocellular Carcinoma**
  - HCV induced HCC is seen in 1% after 30 years
  - In cirrhotic patients risk is estimated to be 3.5%/year

Younassi et al:Aliment Pharmacol Ther 2014; 39: 518–531

Treatment of Chronic HCV

- **Treatment is recommended for ALL pts with chronic HCV**
  - Rare Exceptions:
- Goal of Treatment is - **Sustained Virological Response (CURE)**

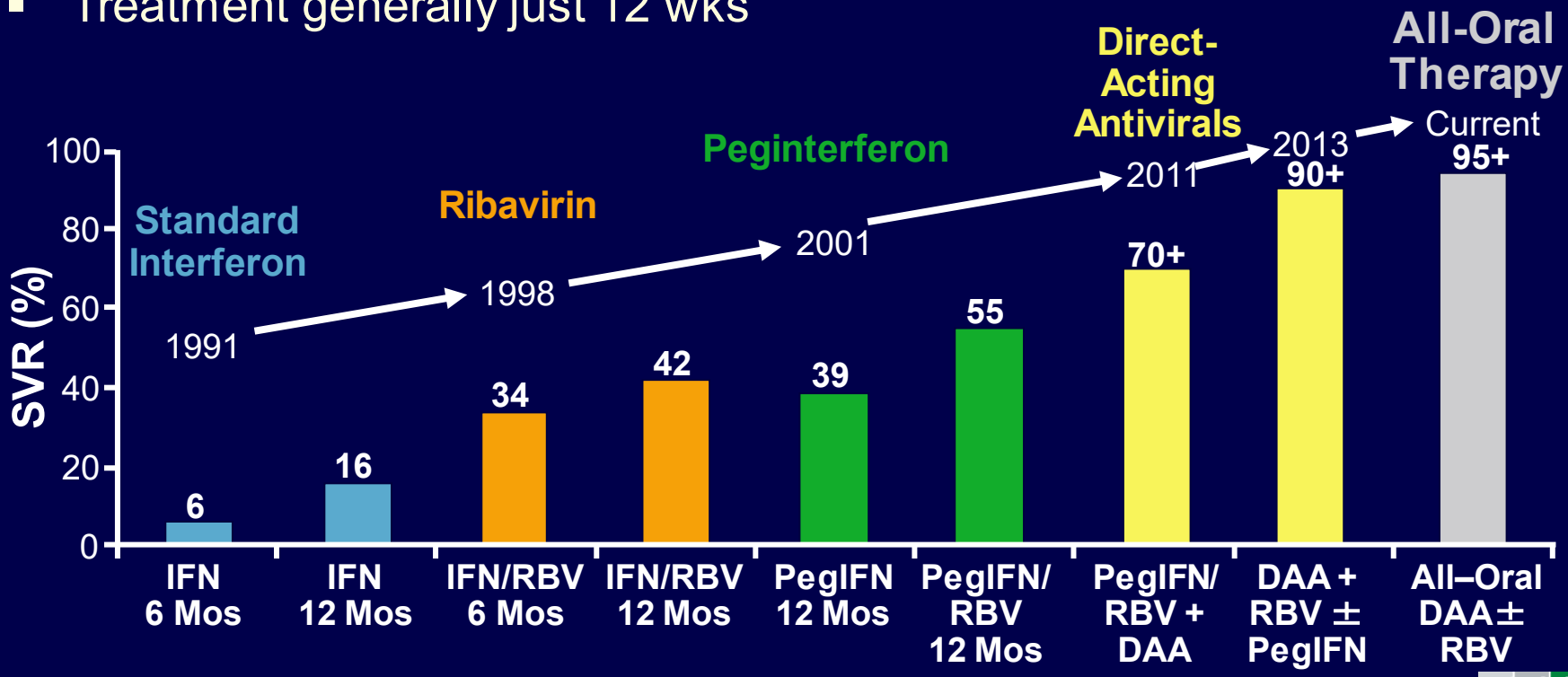
  SVR is defined as
  - *Undetectable HCV viral Load ≥12 weeks after treatment completion*
- **Current Directly acting antivirals have SVR > 98%**
  - 1-3 tablets, once a day, for 8-12 weeks
  - Very well tolerated

  Minimal monitoring needed during treatment

  Most patients don't need routine labs except those with cirrhosis or baseline lab abnormalities

Nearly Everyone With HCV Can Now Be Treated Successfully

- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every pt
- Treatment generally just 12 wks



Slide credit: clinicaloptions.com

HCV GUIDELINE SIMPLIFIED RECOMMENDATIONS

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

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4th Wednesday
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01:00pmpm-2:00pm EST
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South East Viral Hepatitis Interactive Case Conference

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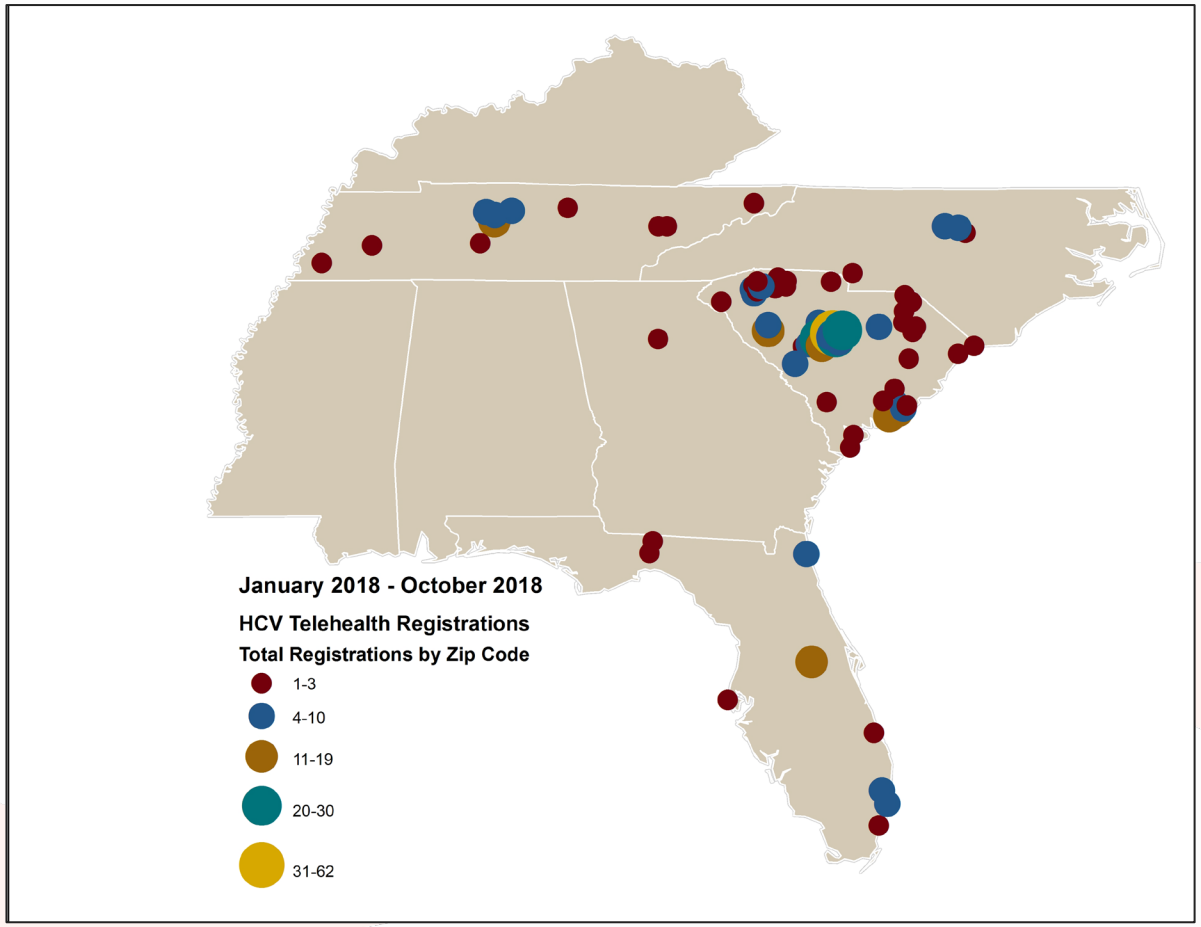
Reach of the HCV Telehealth



Liver Staging Modalities

APRI; FIB-4

- APRI

$$\mathbf{APRI} = \frac{\dfrac{\mathbf{AST}\ (U/L)}{\text{AST upper limit of normal}}}{\mathbf{Platelets}\ (10^9/L)} \times 100$$

- FIB-4

$$\mathbf{FIB-4} = \frac{\mathbf{Age}\ (years) \times \mathbf{AST}\ (U/L)}{\mathbf{Platelets}\ (10^9/L) \times \sqrt{\mathbf{ALT}\ (U/L)}}$$

Fibrosure

- Measurement of:
- *Alpha-2 macroglobulin, haptoglobin, GGT, ALT, apolipoprotein A1*
- Fibrosis score
  - >0.75 consistent with F4

FibroScan

- Ultrasound Transient elastography
- Accurate in measuring degree of liver inflammation and fibrosis as biopsy
- >9.5 considered F3
- >12.5 consistent with cirrhosis (F4)

AST/Platelet Ratio Index (APRI) Fibrosis-4 (Fib-4) Calculator

- APRI
  - The lower the APRI score (< 0.5), the greater the negative predictive value (and ability to rule out cirrhosis)
  - Higher the value (> 1.5) the greater the positive predictive value (and ability to rule in cirrhosis)
  - Midrange values are less helpful.
- FIB-4
  - FIB-4 score <1.45 has a negative predictive value of 90% for advanced fibrosis
  - FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis.

Non-invasive assessment of liver fibrosis

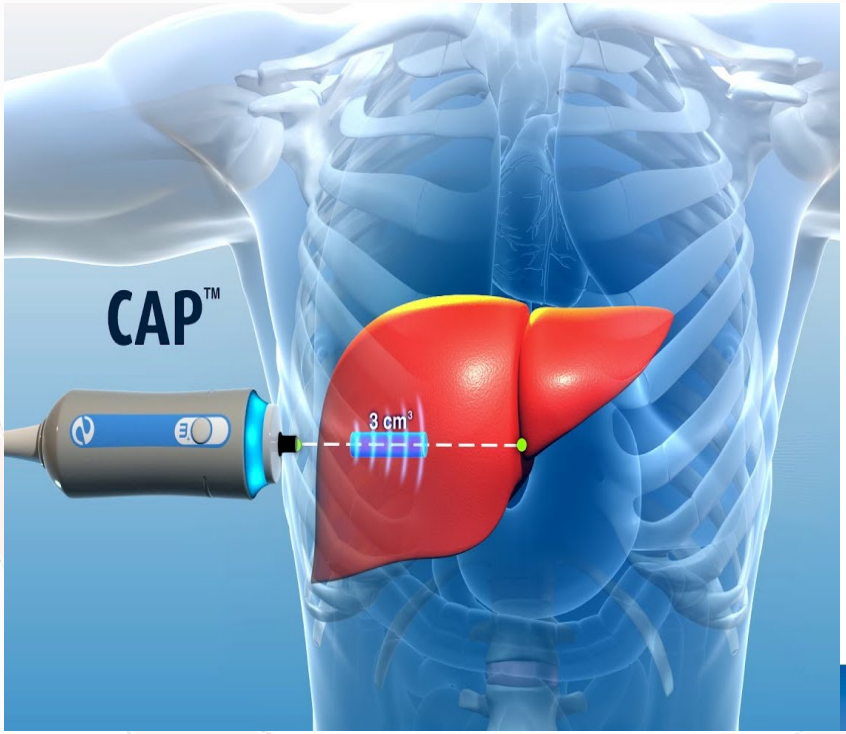
- None of the non-invasive blood tests are perfect
- Liver biopsy is almost never needed
  - unless ruling out other concomitant liver problems
- Better to combine 2 different staging modalities:

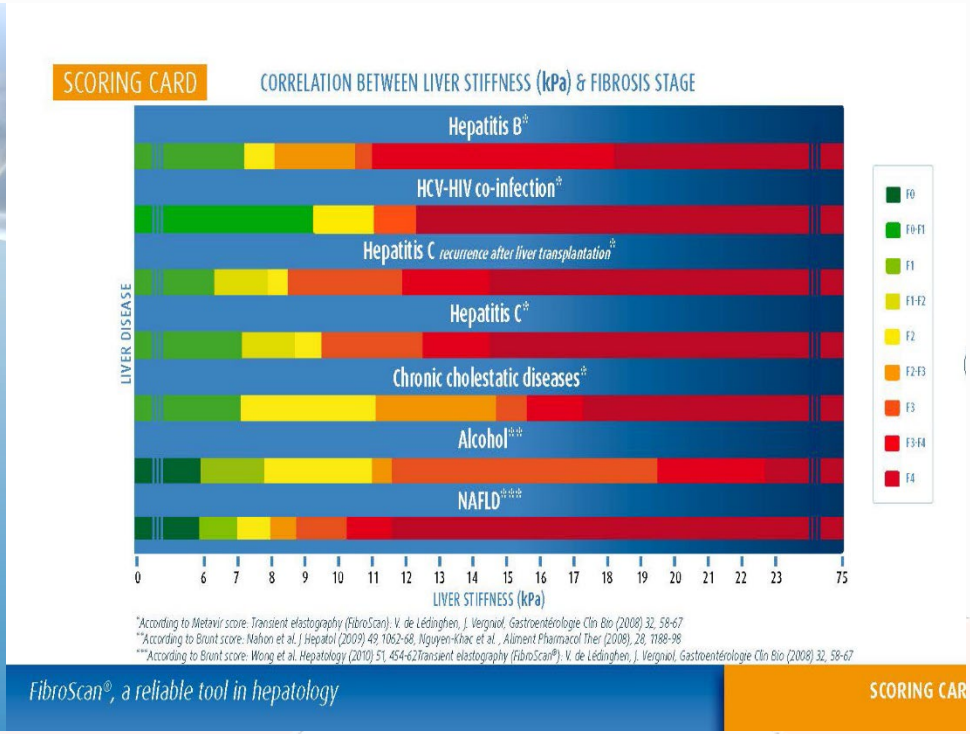
  APRI+ Fibrosure

  Or FIB-4 + Fibrosure

  Or APRI + Fibroscan

Transient Elastography





Genotypes

- **HCV**
  - GT 1 -77.%
  - GT 2- 13%
  - GT 3-12%;
  - GT 4 -1%
  - GT5 and GT6 < 1%
- *Germer JJ,et al: Hepatitis C virus genotypes in clinical specimens tested at a national reference testing laboratory in the United States. J Clin Microbiol. 2011;49(8):3040–3043.*
- GT3
  - Increase in GT 3 in IVDUs
- *Kanwal F, et al. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. Hepatology. 2014;60(1):98–105.*

AASLD guidance updated regularly

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING ⓘ
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Drug Interactions

	ELB/GZR	G/P	SOF/VEL	SOF/VEL/VOX
Aspirin	◆	◆	◆	◆
Duloxetine	◆	◆	◆	◆
Fluticasone	◆	◆	◆	◆
Gabapentin	◆	◆	◆	◆
Hydrochlorothiazide	◆	◆	◆	◆
Letrozole	◆	◆	◆	◆
Lisinopril	◆	◆	◆	◆
Metoprolol	◆	◆	◆	◆
Nifedipine	◆	◆	◆	◆

On-Treatment Monitoring

- Monitor blood glucose
  - Diabetics have the potential for hypoglycemia.
- Monitor INR if on Warfarin
- No laboratory monitoring is required for other patients
  - *Patients receiving elbasvir/grazoprevir should be monitored with a hepatic function panel at 8 weeks and again at 12 weeks if receiving 16 weeks of treatment*.
- Consider an in-person or telehealth/phone visit for patient support and adherence

Follow-Up After Achieving Virologic Cure (SVR)

- For patients without Cirrhosis who achieve SVR
  - No liver-related follow-up is recommended
- For patients with ongoing risk IVDU, MSM engaging in unprotected sex
  - Risk Reduction Counseling
  - Annual testing for HCV RNA.
- Advise patients to avoid excess alcohol use.

HIV/HCV Co-infection

- All persons living with HIV (PLWHIV) should be screened for HCV
- **Similar effectiveness rates of HCV drugs in the HIV/HCV co-infection population as with the HCV infected alone population**

Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. IDSA. 2018. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
Bersoff-Matcha et al. *Ann Intern Med*. 2017;166(11):792-798..
Wang C et al. *Clin Gastroenterol Hepatol*. 2017;15(1):132-136..

Prevention of transmission

- Treatment as Prevention
  - Avoid sharing toothbrushes, dental or shaving equipment, to stop using illicit drugs
  - Should be advised not to donate blood or body organs
- Counsel about Sexual transmission
- Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water.

HCV in corrections

- The burden of hepatitis C virus (HCV) infection is much higher in corrections compared to the general community.
- HCV Seroprevalence in prison inmates
  - Late 1990s, CDC estimated that 16 - 41%
  - 2003-2010 -23.3%
  - 2015- 18% in 2015
  - Probably around 12-15% but decreasing

WHO Vision: Eliminate Viral Hepatitis as a Major Health Threat by 2030

World Health Organization

"A world where viral hepatitis transmission is halted and everyone living with hepatitis has access to safe, affordable and effective care and treatment services"

90% reduction in new chronic HCV infections

Treatment of 80% of eligible persons with chronic HCV infection

65% reduction in mortality rates

WHO. https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Accessed November 17, 2020.

Hepatitis E

- HEV infection usually results in a self-limited, acute illness.
- It is widespread in the developing world.
  - Rare in developed countries

Hepatitis E

- Symptomatic Hepatitis E occurs among older adolescents and young adults (15–44 years).
  - Similar to Hepatitis A
- Pregnant women -more likely to have severe illness including fulminant hepatitis and death
- Most people with Hepatitis E recover completely.
- Overall case-fatality rate is < 1%

Hepatitis E - Epidemiologic Features

- Most outbreaks associated with fecally contaminated drinking water.
- Several other large epidemics have occurred since in the Indian subcontinent and the USSR, China, Africa and Mexico.
- In the United States and other non-endemic areas, a low prevalence of anti-HEV (<2%) has been found in healthy populations.
- Minimal person-to-person transmission.

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