Viral Hepatitis

Peter Gulick, DO, FACP, FIDSA, FACOI
Professor of Medicine
Michigan State University

Disclosures

I have no disclosures

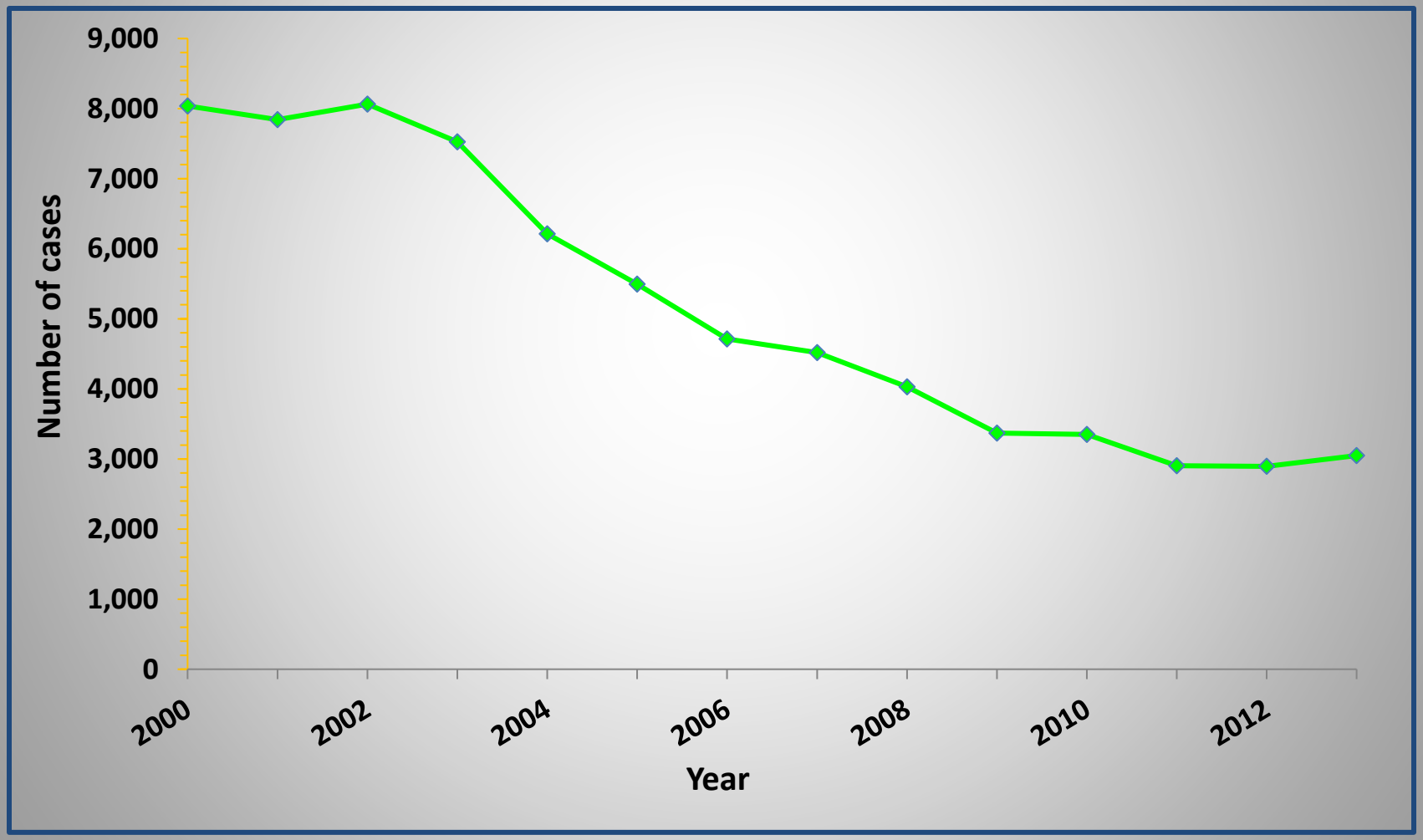
Objectives

1. To describe the basic characteristics of Hepatitis B
2. To describe the ways it is spread and natural history
3. To describe the serological analysis of Hepatitis B diagnosis and how to interpret the serologies
4. To describe the therapies to treat Hepatitis B
5. To discuss cases of Hepatitis B

Hepatitis B Virus Infection in USA

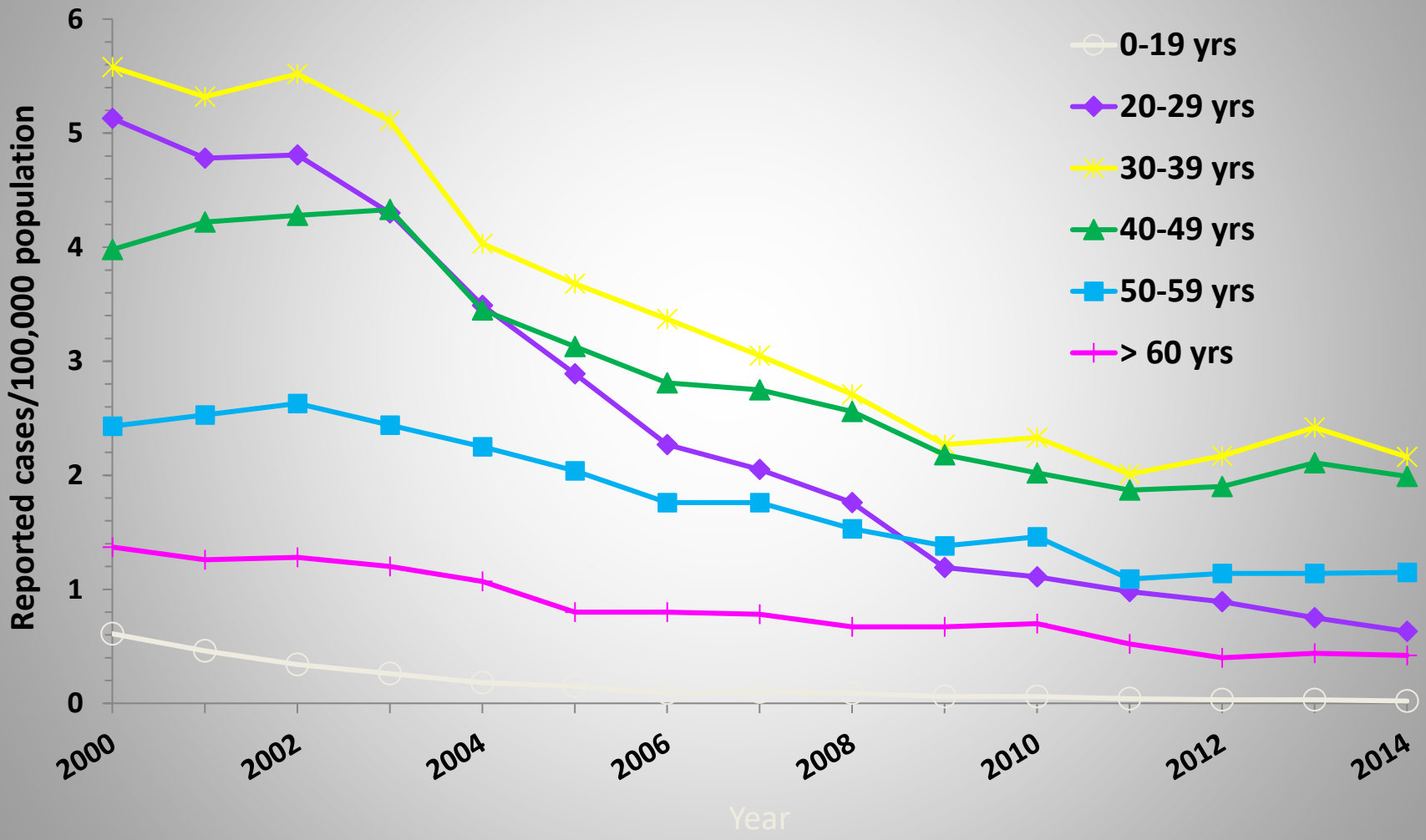
Transmission	**Percutaneous, mucosal**
Main risk factors	**Multiple sex partners, MSM, IDU, sexual and household contacts; perinatal exposure**
Symptomatic	**~0% <5 years; 30%-50% >5 years;**
Chronic infection	**90% <1 year; 5% >5 years;**
Mortality	**0.5%-1% (acute fatality)** **15-25% (chronic liver disease)**
# of chronic infections	**800,00 - 1.25 million**
# of annual deaths	**3,000**

Reported number of acute hepatitis B cases United States, 2000–2013



Source: National Notifiable Diseases Surveillance System (NNDSS)

Incidence of acute hepatitis B, by age group
United States, 2000–2014



Source: National Notifiable Diseases Surveillance System (NNDSS)

How is hepatitis B spread?

- **HBV is significantly more contagious than HIV and can be spread:**
  - **By unprotected sex**
  - **By tattooing, ear piercing or body piercing with infected needles**
  - **By sharing needles or equipment to inject drugs**
  - **By sharing personal items such as razors**
  - **From an infected mother to her baby during childbirth**

Stages of hepatitis B

Acute hepatitis B[1]

- Begins with a short-term infection that can last up to six months
- 95% of adults clear the virus from their bloodstream and develop immunity

Chronic hepatitis B[1]

- People who still have the virus after six months (HBsAg+) are considered to have chronic hepatitis B

1 Lok A, McMahon BJ. Chronic hepatitis B. *Hepatology.* 2001;34:1225-1241

Serological Markers of HBV Infection

HBsAg	Acute/chronic infection
Anti-HBc IgM	Recent infection
HBeAg	High infectivity
Anti-HBe	Low infectivity
Anti-HBs	Immunity
Anti-HBc IgG + HBsAg	Chronic infection
Anti-HBc IgG + anti-HBs	Resolved infection

Screening for HBV infection: HBsAg and anti-HBs +/- anti-HBc IgG

Interpretation of HBV Serology

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Not been exposed
+	+	–	–	Chronic infection
+	+	+	–	Acute Infection
–	+	–	+	Immunity from past infection
–	–	–	+	Immunity after vaccination
–	+	–	–	Occult / past HBV infection

Concurrent HBsAg and Anti-HBs

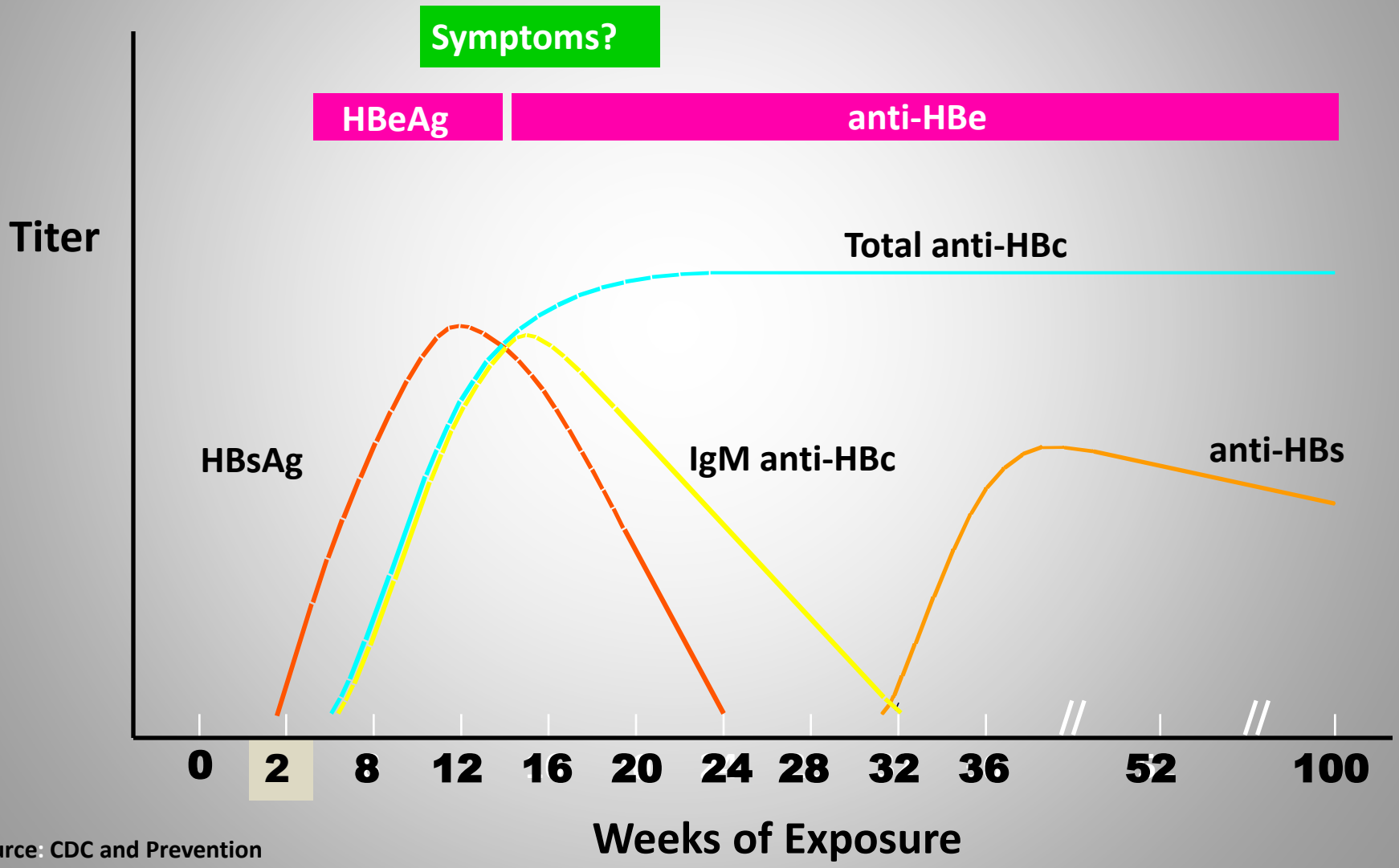
- Prevalence
  - 5%-60%
  - 6.6% in NIH-funded Hepatitis B Research Network (HBRN)
- Clinical characteristics
  - No differences in country of birth, modes of transmission, AST, ALT, HBeAg, HBV DNA, HBV genotype; but lower HBsAg level
  - Anti-HBs not neutralizing, management as for other chronic HBV patients who are anti-HBs-

HBV Genotypes

- A-J, difference in geographical distribution
- B/C most common in the US followed by A, D, & E
- Genotype C associated with delayed spontaneous HBeAg seroconversion
- Genotype C (F) associated with increased risk of HCC
- Genotype A associated with highest rate of interferon-related HBeAg and HBsAg loss
- No impact on response to nucleos(t)ide analogue therapy
- Testing not clinically indicated except for patients in whom treatment is indicated and are potential candidates for interferon therapy

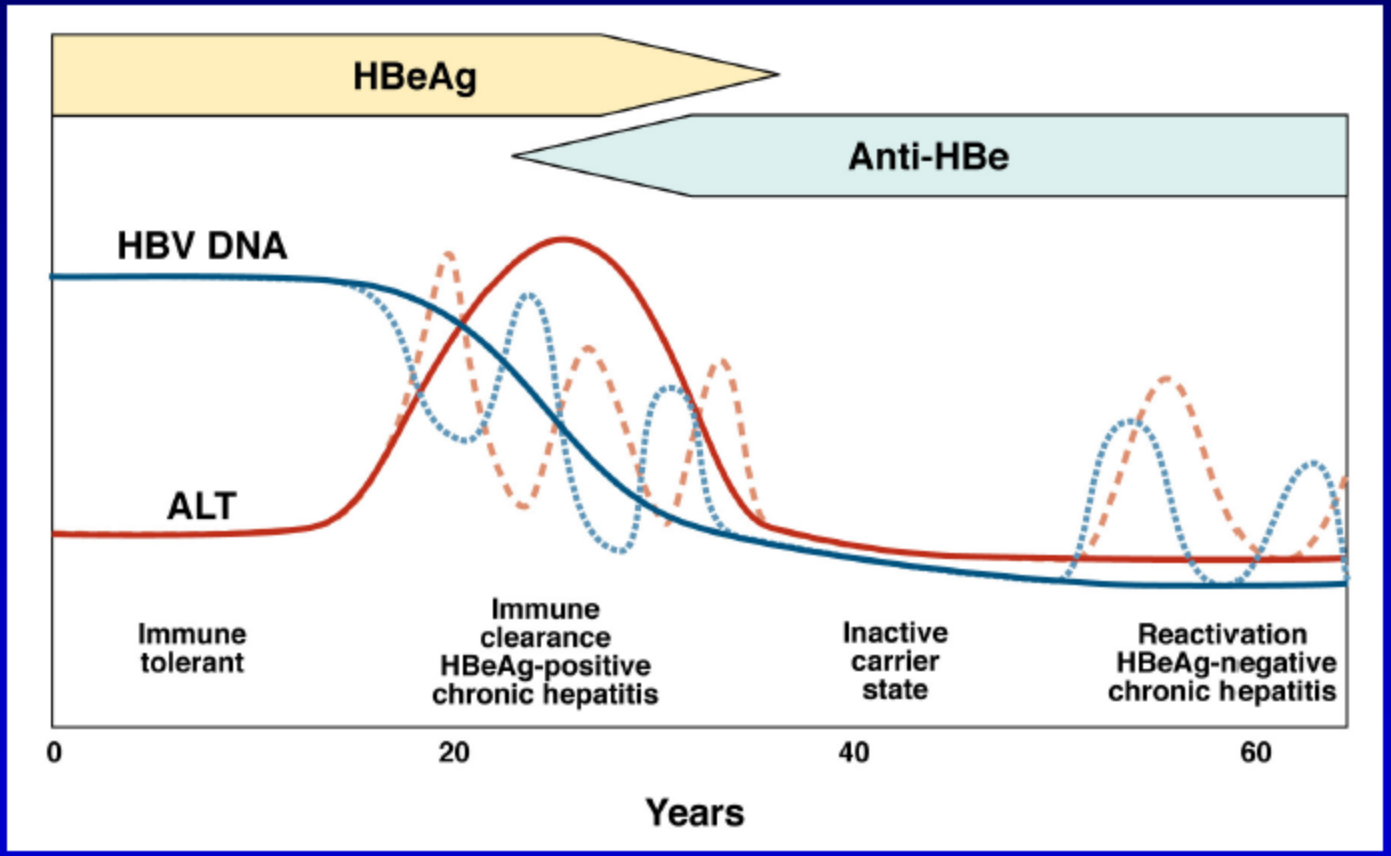
Acute HBV Infection With Recovery

Typical Serologic Course



Source: CDC and Prevention

Phases of Chronic HBV Infection



Serological Markers

Serological Markers

- **HBsAg** – Hepatitis B surface antigen is first serologic marker to appear –acute infection, if present > 6 months indicates chronic infection
- **HBeAg** – Hepatitis B e antigen indicates active viral replication
- **HBsAb–** Documents recovery and/or immunity to HBV. Present in vaccinated persons, conferring immunity. If present with AntiHBc IgG indicates resolved infection with immunity.
- **Anti-HBe** – Antibody to hepatitis Be antigen, can be present with HBsAg.
- **Anti-HBc (IgM)** – Antibody to hepatitis B core antigen, marker acute infection.
- **Anti-HBc (IgG)** – Antibody to hepatitis B core antigen, can indicate chronic (occult) infection if present or NOT with HBsAg.
- **HBV-DNA** – Viral load, present in chronic infection, used to monitor treatment progress.

Recommended screening for HBV infection

- **HBsAg, anti-HBs and anti-HBc IgG**

HBV Treatment: for Whom and When?

Efficacy of Currently Available HBV Therapies

- Potent viral suppression
- Reverse hepatic fibrosis / cirrhosis
- Prevent progression to liver failure

BUT

- Low rate of HBsAg loss
- Decrease but not eliminate incidence of HCC

Approved HBV Treatments

- Interferons (IFN)
  - Standard IFN alfa - 1992
  - Pegylated IFN alfa - 2005
- Nucleos(t)ide analogues
  - Lamivudine - 1998
  - Adefovir - 2002
  - Entecavir - 2005
  - Telbivudine - 2006
  - Tenofovir disoproxil fumarate - 2008
  - Tenofovir alafenamide - 2016

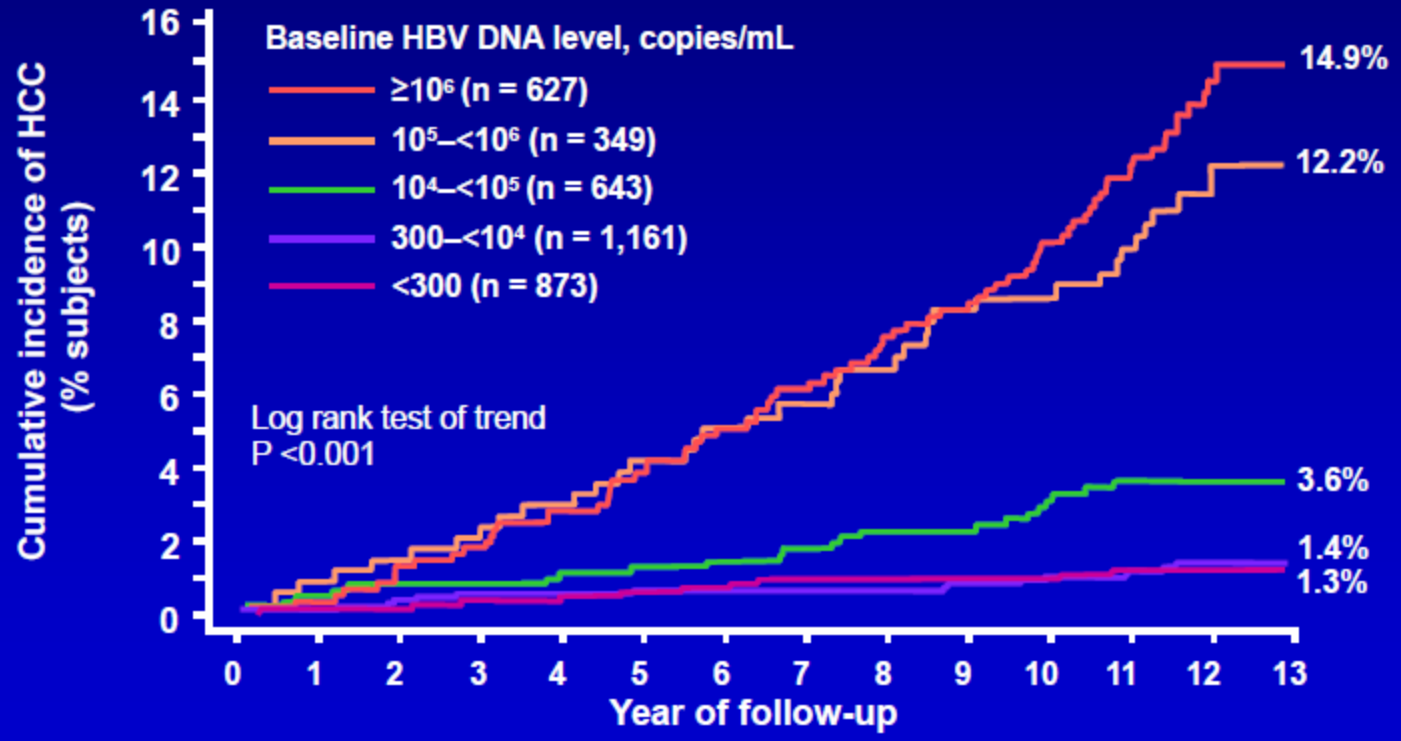
Case Study: Immune Tolerant

- 21 y.o. refugee Somalia, female
- Married desires pregnancy
- Screening +HBsAg, +HBcAb, +HBeAg, HBV load-5 million,- HDV Ab
- Unknown risk factor, ? Perinatal through mother at birth
- ALT-18, AST-20, Plt -258, Alb-4.5
- Liver ULS normal

- Assessment: No Tx at present
- If becomes pregnant needs treatment in third trimester
- Can Tx with lamivudine/Epivir HB 100 mg daily.
- Best outcome for infant with mother undetectable during delivery
- Mother can breast feed
- Tx can be stopped postpardum
- Requires yearly ULS liver with AFP and every 6 month HBV serology, metabolic panel and CBC

High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n = 3,653), mean age 43



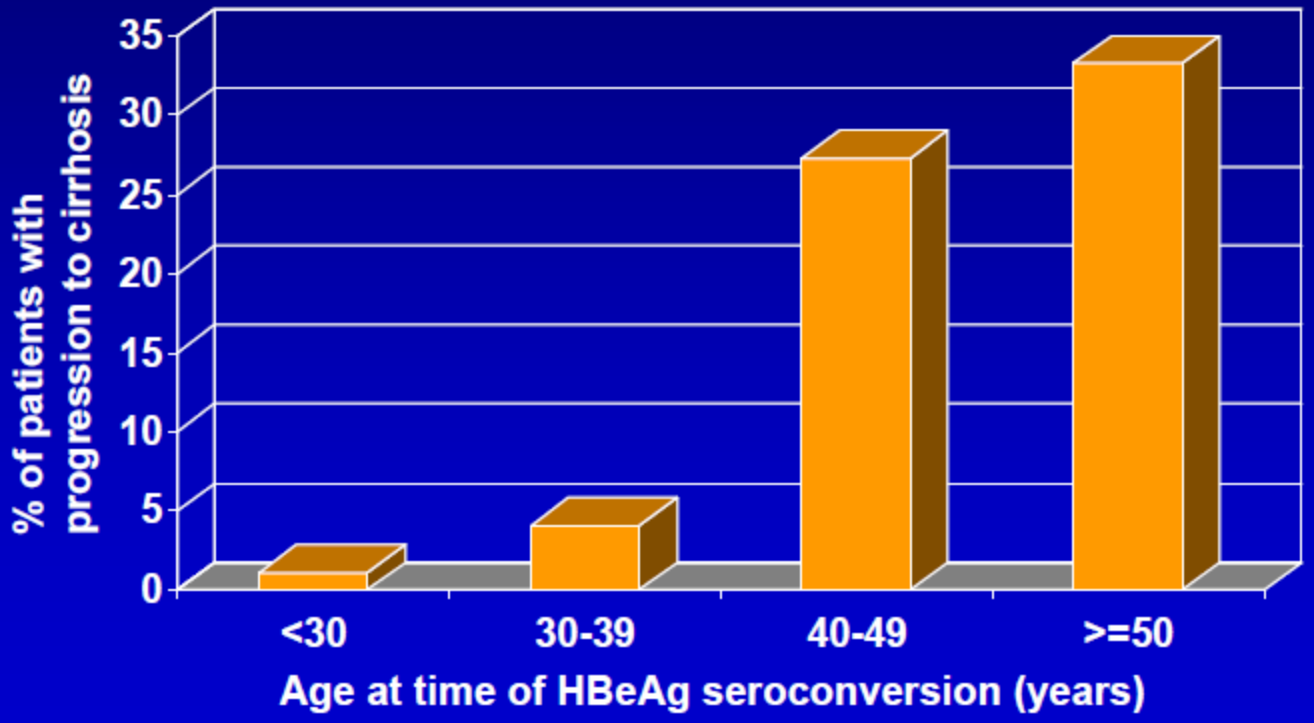
Chen CJ, et al. JAMA. 2006; 295:65

Case Study: Precore mutant-Low replicator

- 48 y.o. Asian male
- Family Hx negative for liver cancer
- Risk factor: transfusion 1970
- Married, US citizen since 2000, wife is immune with +HBsAb
- Serology for patient:+HBsAg, +HBcAb, +HBeAb,-HBeAg. HBV load-20,000, AFP-3.2
- Liver ULS-mild echogenicity
- Fibrosure: F-2
- ALT-65, AST-55,Plt-135,Alb-3.6
- Naïve to Tx

- Patient meets criteria for Tx per AASLD
- Showing some Fibrosis and inflammation and HBV>2,000 iu/ml
- Treat options:
  - Baraclude .5 mg daily (naïve) 1mg daily (experienced) or
  - Viread 300 mg daily or
  - Vemlidy 25 mg daily
- Monitor yearly ULS liver and AFP
- Labs: HBV load, metabolic panel, CBC every 3-4 months
- Low chance clearance HBsAg
- Life-long Tx with medications

Persistence of HBeAg after Age 40 Associated with Increased Risk of Cirrhosis



Chu & Liaw J Viral Hepat 2007; 14: 147

Case Study: High Replicator-Immune Active

- 50 y.o. caucasian male, Hx Rheumatoid arthritis
- High risk sexual activities
- Dx with HBV 2006
- Serology: +HBsAg,+HBcAb,+HBeAg,-HBeAb,HBV load-5 billion, ALT-200,AST-180,Plt-103,Alb-3.5
- Liver ULS shows coarse liver
- Fibrosure-F3/4

- Assessment: high replication in person>40 years-high risk for HCC/cirrhosis
- Treatment is recommended by guidelines indefinitely
- Tx options:
  - Baraclude
  - Viread
  - Truvada
  - Vemlidy
- Monitor for HCC every 6 months with ULS liver and AFP
- Monitor HBV serology, CBC,CMP every 3-4 months

Isolated Anti-HBc+ (HBsAg-, anti-HBs-)

- Most common scenario: past HBV with spontaneous loss of HBsAg, particularly in
  - Persons from endemic areas
  - Persons with risk factors for HBV
    - Risk behaviors
    - HCV or HIV infection
- HBV DNA
  - Usually not detected in serum except for those who are HIV+
  - Often detected in liver

Case Study: Occult HBV

- 42 y.o. AA female, IVDU,
- Single, currently in rehab for 1 year
- Dx with Chronic HCV 1998-naïve to Tx
- +HCV genotype 1, HCV load-1.2 million
- ULS liver mild echogenicity, fatty liver
- Serology: -HBsAb, +HBcAb, -HBeAb, -HBeAg, HBV load-detectable, ALT-80,AST-65, Plt-240,Alb-4.8
- Desires HCV Tx

- Many options for HCV Tx:
  - Harvoni
  - Mavyret
  - Zepatier
  - Epclusa
- All require HBV to be Tx prior to HCV Tx
  - Warning on all HCV products: can cause exacerbation occult HBV infection
- Tx HBV wit:
  - Baraclude
  - Viread
  - Vemlidy
- Vaccination has shown to be ineffective

HIV and HBV

- **In HIV/HBV co-infected patients, there are many reasons to treat both viruses**
  - **Co-infected patients have**
    - **Faster rates of fibrosis progression**
    - **Increased risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma**
- **Agents that have antiviral activity against HBV and HIV include:**
  - **Tenofovir/Emtricitabine-Truvada**
  - **TAF/Emtricitabine-descovy**
  - **Lamivudine**
    - **Not recommended as single agent due to high resistance**
- **These medications fall within the NRTI class and are:**
  - **The backbone of fully suppressive HIV combination therapy**
  - **Well tolerated**
  - **Not associated with mitochondrial toxicity**

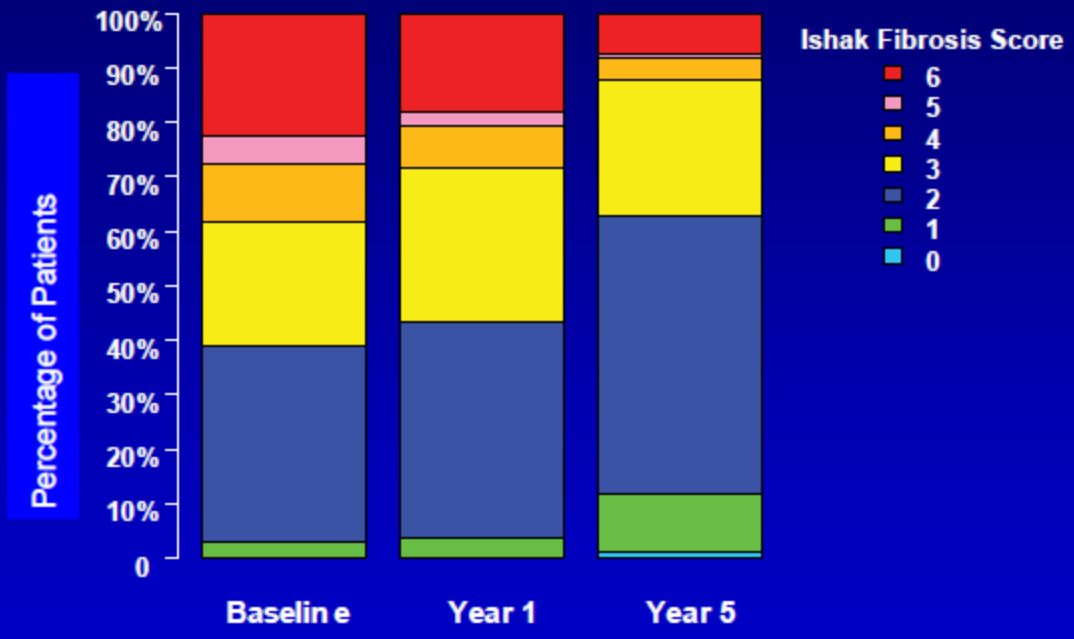
Case Study: Co-infection

- 32 y.o. MSM
- High risk sex
- Hx multiple partners
- Screening: +HIV combo test with +confirmation
- HIV load-120,000, CD4-250
- +HepA Ab
- +HBsAg
- +HBcAb
- +HBeAg
- -HBeAb
- -HBsAb
- HBV load: 4 million
- -HCV Ab
- Liver ULS negative
- Desires Tx

- Assessment: Need to Tx both HBV and HIV virus
- Current medications:
  - Odefse
  - Genvoya
  - Stribild
  - Complera (STR)
  - Descovy with 3rd agent
- IF unable to take above can add baraclude to the HIV regimen
- Monitor every 3-4 months HIV/HBV loads
- Yearly liver ULS with AFP

Reversal of Fibrosis and Cirrhosis

Tenofovir Phase III Trial: Biopsies at Years 0, 1, 5



- 348/641 (54%) had liver biopsy at baseline and Year 5
- 71/96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5

Marcellin, P, Lancet 2013; 381: 468

Case Study-Inactive "Carrier"

- 38 y.o. refugee from Middle East
- Married
- Asymptomatic
  - Found +HBsAg on screening to US
- +HBeAb
- -HBeAg,
- +HBcAb
- -HBsAb
- HBV load: 200
- ALT-25
- ALT-20
- ALB-4.5
- Plt-280
- Fibrosure: F-0
- Ultrasound liver negative

- Assessment:
  - Per AASLD guidelines, no Tx at this time
- Monitor every 6 months with labs
  - CBC
  - CMP
  - HBV load
- Screening: Liver ULS yearly
- Immunize for Hep A if needed
- Screen family, especially husband for immunity/infection

Clear-Cut Cases in Which Treatment Should Be Initiated Now

- Life-threatening liver disease (regardless of HBV DNA and ALT level)
  - Fulminant hepatitis B
  - Severe exacerbations of chronic hepatitis B
  - Decompensated HBV cirrhosis
- High risk of liver failure/HCC in the near future
  - Compensated cirrhosis (any HBV DNA level?)
- HBsAg+ patients who will be starting immunosuppressive therapy
- HBsAg+ pregnant women with HBV DNA >200,000 IU/mL
- Noncirrhotics at high risk of progressive liver disease

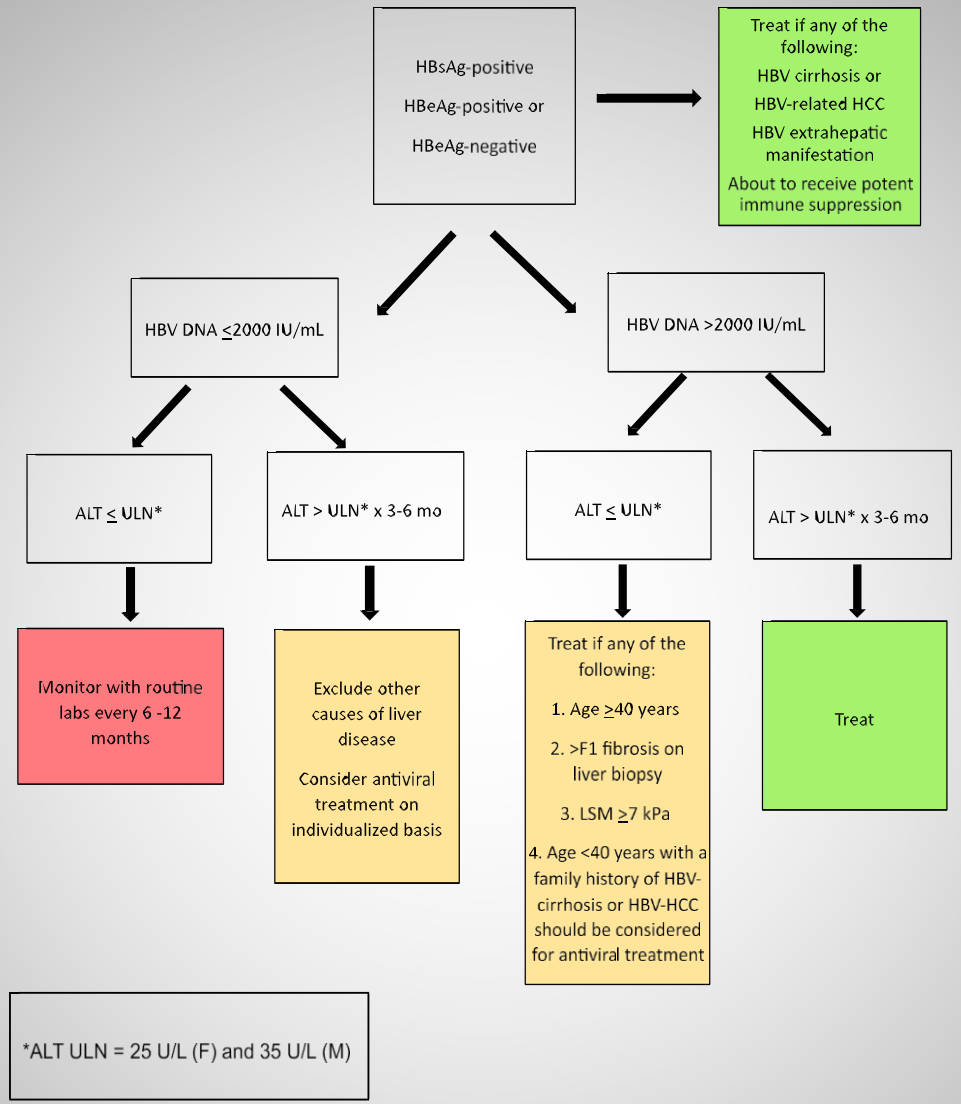


Figure 1 Summary of Recommendations for Hepatitis B Treatment Initiation
ALT = Alanine transaminase; F = Female; HBeAg = Hepatitis B e antigen; HBsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HCC = Hepatocellular carcinoma; M = Male

Tailoring Treatment to Patient

IFN

- No contraindications
- Willing to try
- Genotype A
- High ALT

Nucleos(t)ide analogues

- Cirrhosis
- Severe flares of chronic hepatitis
- Contraindications to IFN
- Unwilling to try IFN
- Willing to accept long-term treatment

Entecavir, tenofovir: potent antiviral activity, high barrier to resistance.
Tenofovir alafenamide: less renal and bone toxicity vs tenofovir disoproxil fumarate

Hepatitis B Vaccination: Recommendations

- Routine infant
- Ages 11-15 catch up, and through age 18
- Over 18: high risk
  - Occupational risk
  - Hemodialysis patients
  - All STD clinic clients
  - Multiple sex partners or prior STD
  - Inmates in correctional settings
  - MSM and HIV positive persons
  - IDU
  - Institutionalized for developmental disability
- Pre-vaccination testing, if cost effective
- Post-vaccination testing, 1-2 months after last shot, if establishing response critical (HCW)

What health maintenance measures are needed?

- Administer Hepatitis A vaccine if not already immune
- Encourage a healthy diet
- Avoid alcohol
- Limit acetaminophen to 2 grams a day
- Encourage exercise program
- Weight loss if Fatty Liver
- Yearly monitoring of liver ultrasound and alpha fetoprotein for hepatocellular carcinoma (HCC)
- Immunize partners, close friends, family, and especially sexual contacts

Hepatitis D

- Only people with Hepatitis B infection can contract Hepatitis D (satellite virus)
- Hepatitis D can cause severe liver disease with rapid progression to cirrhosis and HCC
- HBV vaccination provides protection against HBV as well as HDV
- Hepatitis D is uncommon the USA
  - Eastern, Southern Europe (Turkey, Moldova)
  - Central, Northern Asia (Mongolia, Iran)
  - Amazon Basin
  - Africa (Central, West)
- Risk Factors
  - IVDA
  - Coinfected HIV and HBV
  - MSM
  - Household or close contact with HDV

Hepatitis D

Testing

- Antibody Testing
  - ELISA, RIA
  - IgM: Acute infection persists 2-3 weeks
  - IgG Anti-HDV: Persists long after viral clearance
- Antigen testing
  - HDV-RNA qualitative or quantitative PCR tests
  - Measure active viral infection
  - Used to measure and monitor treatment response

Samples	Markers	
Serum	**Anti-HDV IgG**	**HDV RNA**
Acute HDV Coinfection	+	+
Acute HDV Superinfection	+	+
Chronic HDV	+	+ (10^5-10^7 copies/mL)
Chronic Active HDV-HBV	+	+ (10^5-10^7 copies/mL)
Cirrhosis	+	+ (10^3-10^7 copies/mL)
HDV Recovery	+	-
Liver	**HDV RNA**	
Chronic HDV	+	

Hepatitis D

Treatment and Prevention

- Treatment
  - Peg interferon
    - May work in 30% or less
  - New drugs in development
- Prevention
  - Vaccination of hepatitis B
  - Percutaneous and mucosal precaution

Questions?

THANK YOU FOR YOUR ATTENTION

1. A 30-year-old presents for evaluation of his hepatitis B. He immigrated from China 35 years ago with his parents. His mother and father both have chronic hepatitis B, and his father was diagnosed with liver cancer. It was felt that the patient acquired hepatitis B from his mother at birth. He is otherwise healthy with no PMH. Labs: CBC 14.3/5.4/185,000; CMP: SGOT 85 (8-48); SGPT 90 (7-55); total bilirubin 0.8; albumin 4.8; INR normal. He had staging of hepatitis B and is stage 2 with minimal fibrosis. Hepatitis B DNA is 10 million. What would you advise him?

2. If you decide to treat, what would you use?

    a) Viread disoproxil fumarate
    b) Viread alafenamide
    c) Entecavir
    d) Emtricitabine
    e) Pegylated interferon

3. How would you treat him long term?

4. A patient comes into your office complaining of nausea, vomiting for 2 days with severe fatigue. He has no prior medical history. His social history is positive for a STD and being bisexual. He also had been to a restaurant 1 week ago. On exam he has jaundice, but no other findings. Labs: CBC 14.0/5.3/190,000; CMP: SGOT 800 (8-48); SGPT 980 (7-55); total bilirubin 10.5 (0.1-1.2).

   Hepatitis screen:

   Hepatitis A: IgM+, IgG-

   Hepatitis B: Hepatitis B core Ab-

   Hepatitis B surface Ab+, Hepatitis B surface Ag-

   Hepatitis C Antibody-

   a) What is the diagnosis?
   b) What other tests do you want?
   c) What therapy can you give?
   d) What chronic changes can occur?

5. A 35-year-old comes in for routine evaluation. He has no complaints. Social history is positive with prior history of IVDA, STD's. Labs: CMP – SGOT 85 (8-48); SGPT 90 (7-55); CBC Hb 14.2; WBC 5.5; platelets 120.

   Hepatitis panel:

   Hepatitis A: IgM-, IgG+

   Hepatitis B: Hep B core Ab+, Hep B surface Ag+, Hep B surface Ab-

   Hepatitis C: Antibody+

   a) How do you interpret this lab work?
   b) What other tests do you want?
   c) What is the likely diagnosis?