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begins**



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- Each month a new topic will be held from 12:00 p.m. to 1:00 p.m. CST on the fourth Wednesday of the month, with exceptions during holidays.**
  
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  - HIV/AIDS in American Indian Communities**
  - March 25th, 2015**
  - Register: <http://www.ndhealth.gov/HIV/events.htm>**



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# *Hepatitis B Update*

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*Division of infectious Diseases*

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# Overview of Current Presentation

- **Epidemiology**
- **Screening and Vaccination**
- **Natural History and Diagnosis**
- **Update on Treatment and special populations**



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## HBV: A Global Problem

- **2 billion people worldwide have been infected with HBV<sup>[1]</sup>**
- **~ 350 million chronic carriers<sup>[2]</sup>**
- **Leading cause of cirrhosis and HCC worldwide<sup>[2]</sup>**
- **Causes 80% of all HCC in Asian Americans<sup>[3]</sup>**
- **30% to 50% of HCC associated with HBV in the absence of cirrhosis<sup>[4]</sup>**
- **Second only to tobacco in causing the most cancer deaths<sup>[5]</sup>**
- **HBV is 50-100 times more infectious than HIV<sup>[1]</sup>**

1. World Health Organization. HBV fact sheet. 2. Conjeevaram HS, et al. J Hepatology. 2003;38(suppl 1):s90-s103. 3. Stanford Asian Liver Center. For hepatitis B and liver cancer patients. 4. Bosch FX, et al. Clin Liver Dis. 2005;9:191-211. 5. World Health Organization. Global alert and response: hepatitis B—Introduction.



## Estimated HBV Prevalence Among Foreign-Born Americans

Foreign-Born Population	HBV Prevalence, %	HBV Prevalence, n
All regions	3.7	1,522,798
<b>Asia</b>	<b>7.9</b>	<b>862,779</b>
Central America	1.3	208,804
<b>Caribbean</b>	<b>2.3</b>	<b>82,000</b>
South America	1.6	46,614
<b>Africa</b>	<b>11.8</b>	<b>196,338</b>
Europe	2.2	114,174
<b>Oceania</b>	<b>5.4</b>	<b>9424</b>
North America	0.3	2665

Welch S, et al. AASLD 2008. Abstract 853.



# Chronic Hepatitis B in the US: Undiagnosed and Undertreated

**~ 2 million people have chronic hepatitis B**



**400,000-600,000 diagnosed**



**200,000-300,000  
entered into care**

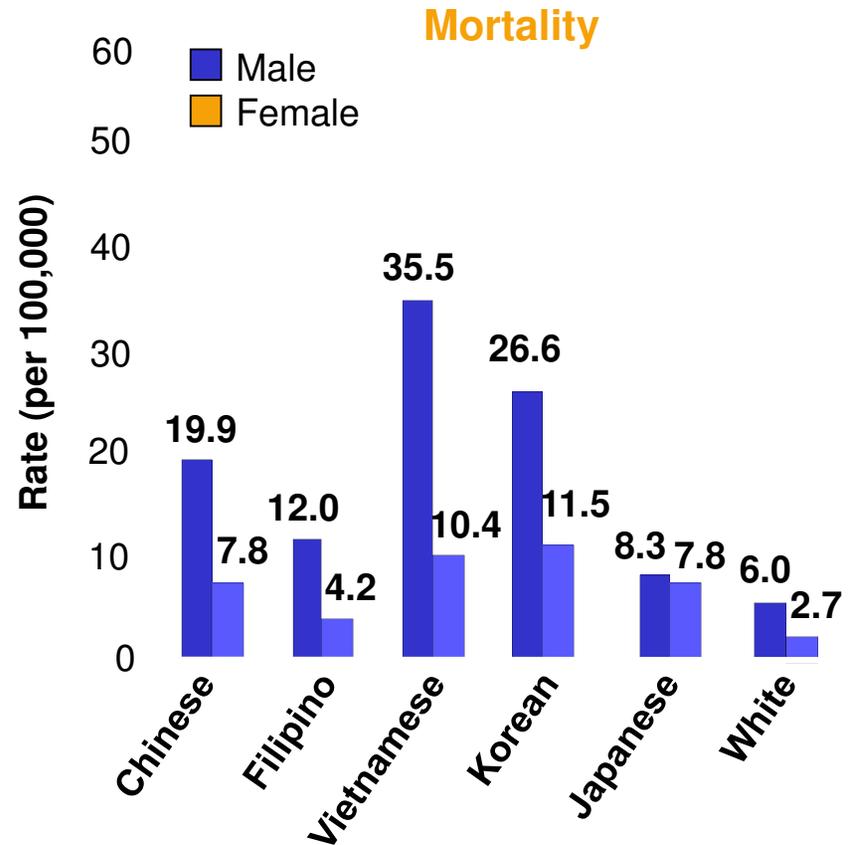
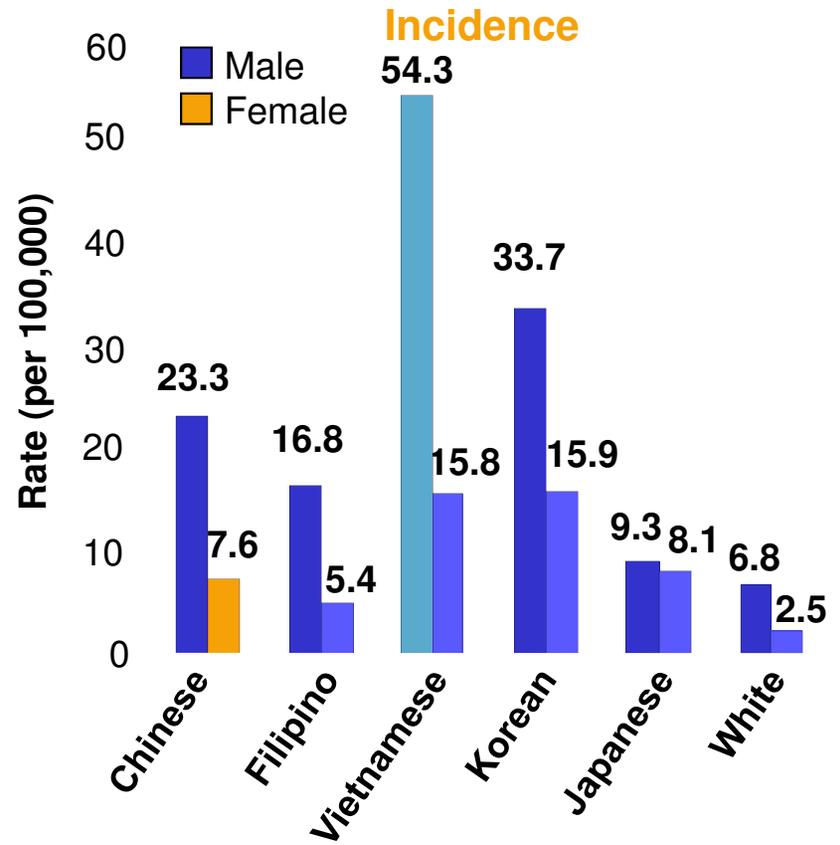


**< 50,000 are  
receiving antiviral  
treatment**



# Asian American Age-Adjusted Liver Cancer Rates (California 2000-2002)

- ~ 3.7 million Asians in California; data from Los Angeles Cancer Surveillance Program and California Cancer Registry



McCracken M, et al. CA Cancer J Clin. 2007;57:190-205.



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## Candidates for HBV Screening

- **Persons born in high and intermediate endemic areas ( $\geq 2\%$  prevalence)**
- **US-born children of immigrants from high endemic areas ( $\geq 8\%$ ; only if not vaccinated as infants in the US)**
- **Household and sexual contacts of HBV carriers**
- **Persons who have injected drugs**
- **Persons with multiple sexual partners or history of STDs**

Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.  
Lok AS, et al. Hepatology. 2009;50:661-662.



## Candidates for HBV Screening

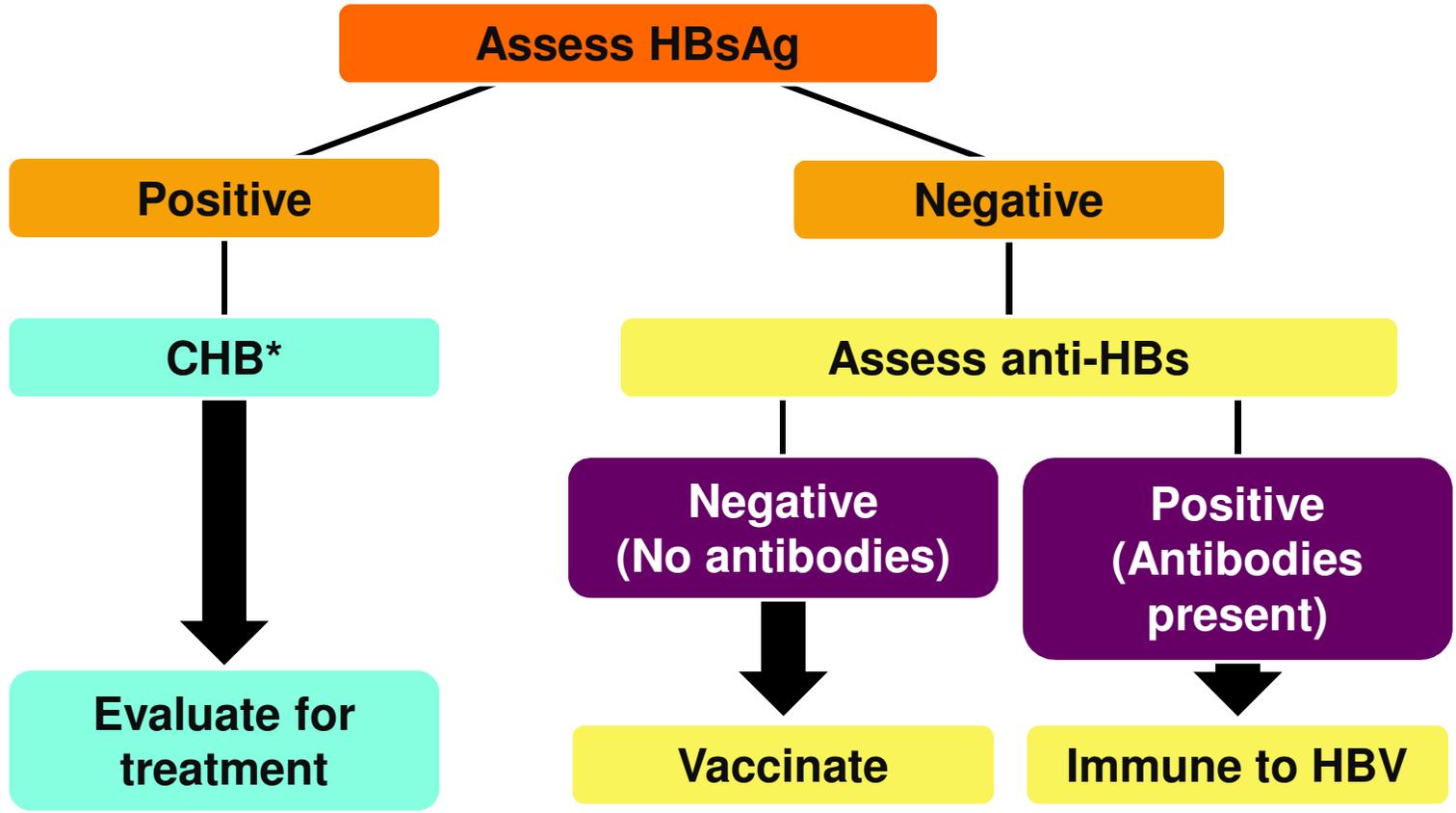
- **Men who have sex with men**
- **Inmates of correctional facilities**
- **Individuals with chronically elevated ALT/AST**
- **Individuals infected with HIV or HCV**
- **Patients undergoing dialysis**
- **Patients undergoing immunosuppressive therapy**
- **All pregnant women**
- **Infants born to HBV carrier mothers**

Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.

Lok AS, et al. Hepatology. 2009;50:661-662.



# HBV Screening Algorithm



\*Time from positive HBsAg test to diagnosis of CHB is 6 mos.  
Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.



## **What Are the Barriers to HBV Screening in Primary Care Clinics?**

- **Accurate identification of candidates for screening**
- **Time constraints in busy practice setting**
- **Awareness of benefits of HBV diagnosis for patient health**
- **Issues regarding reimbursement of cost of testing**
- **Patient willingness**
- **Others?**



## **Practical Strategies for Implementing Screening in Your Practice**

- **Add “Have you ever been tested for HBV?” to standard questionnaire for new patients**
- **Add “HBV test” as check box to standard blood test order**
- **If you have an electronic medical records program, add HBV testing to the history and physical form**
- **Make educational materials on hepatitis B easily accessible to all patients in the office**
- **Offer screening to family members of those known to be infected**



## **Which of the Following Patient(s) Should Be Screened for HBV?**

- A. 20-yr-old, US-born Korean student who was vaccinated against HBV at birth**
- B. 64-yr-old, US-born white male with lymphoma currently undergoing evaluation for chemotherapy**
- C. 42-yr-old businessman from South Africa**
- D. 28-yr-old, US-born white female who is 6 mos pregnant**



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## HBV: 1 Virus or More?

- **8 well-documented genotypes**
- **Wild-type virus**
- **Naturally occurring mutants**
  1. Precore
  2. Basal core promoter
- **Drug-resistant mutants**



# Hepatitis B Virus Variants

- **Wild type**
  - Usually HBeAg+ hepatitis
- **Precore mutation (27% US patients)<sup>[1]</sup>**
  - Abolishes HBeAg production
- **Core promoter mutation (44% US patients)<sup>[1]</sup>**
  - Down-regulates HBeAg production
- **Treatment-induced mutations**
  - YMDD: induced by lamivudine (~ 20%/yr)<sup>[2,3]</sup>
  - N236T and A181V: induced by adefovir (0% at Yr 1, 3% at Yr 2, 11% at Yr 3, 18% at Yr 4, and 29% at Yr 5)<sup>[4]</sup>

1. Chu CJ, et al. Hepatology. 2003;38:619-628. 2. Chang TT, et al. J Gastroenterol Hepatol. 2004;19:1276-1282. 3. Lok AS, et al. Gastroenterology. 2003;125:1714-1722. 4. Hadziyannis SJ, et al. Gastroenterology. 2006;131:1743-1751.



# HBV Genotypes: Epidemiology

- **HBV classified into 8 well-documented genotypes (A-H)**
  - A: North America, Western Europe, and Africa
  - B and C: Asia
  - D: Southern Europe, Africa, and India
  - E: West Africa
  - F: Central and South America and Alaska
  - G: United States, France, and Germany
  - H: Central America



## HBV Genotypes: Epidemiology

- **Genotype B associated with less active disease, slower progression, and lower incidence of HCC than genotype C**
- **Genotypes A and B respond better to IFN than genotypes C and D**

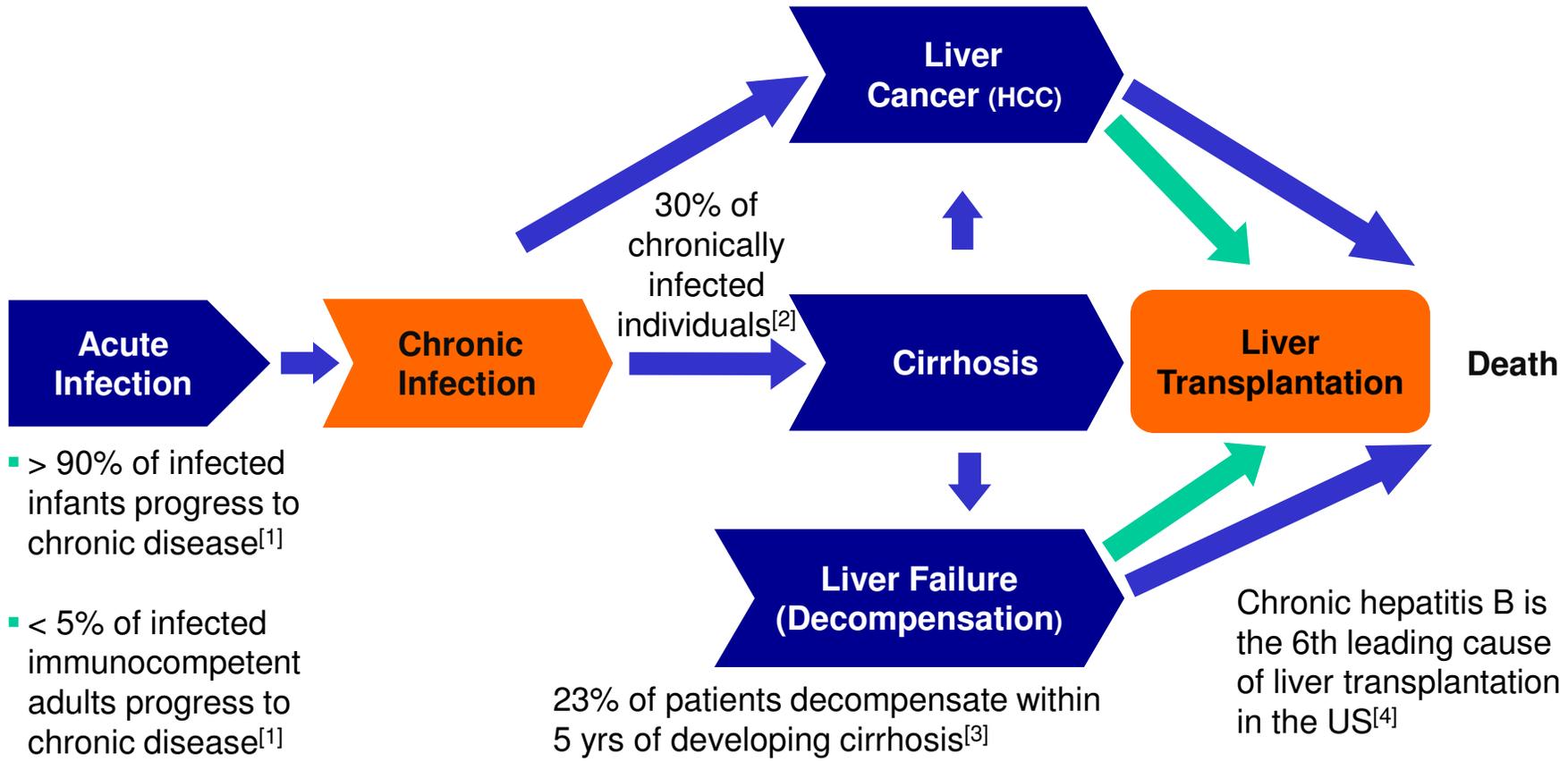


## **Modes of HBV Transmission**

- **Spread via exposure to blood and bodily fluids**
- **Need a break in skin or mucus membrane**
- **Found in semen, saliva, vaginal mucus, and tears but at levels 1000-fold lower than in serum**
- **Not found in urine, sweat, or stool**



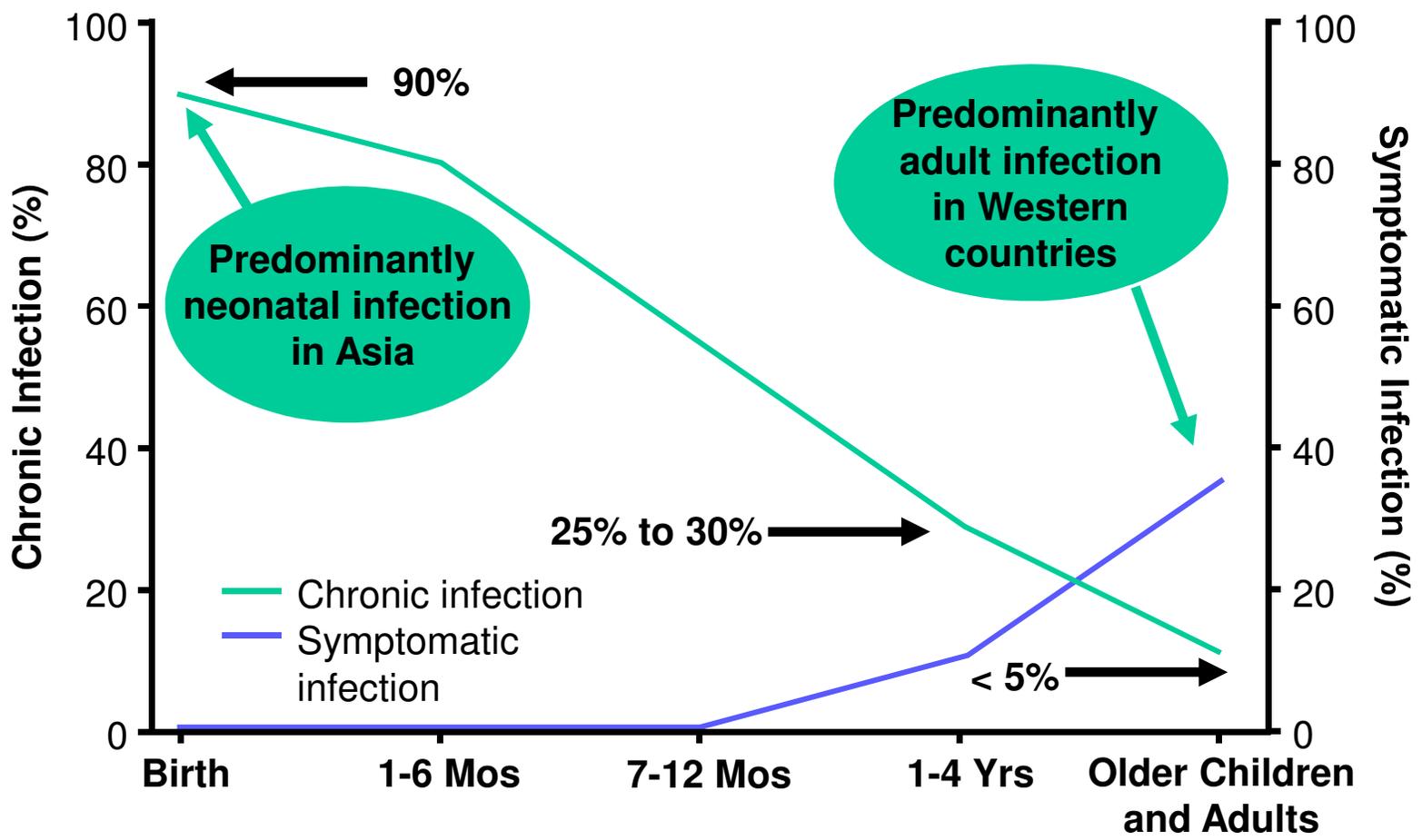
# Hepatitis B Disease Progression



1. CDC. HBV FAQs for health professionals. 2. Torresi J, et al. Gastroenterology. 2000;118(2 suppl 1):S83-S103. 3. Fattovich G, et al. Hepatology. 1995;21:77-82. 4. Seaberg EC, et al. Clin Transpl. 1998:17-37.



# Outcome of HBV Infection by Age of Transmission



Stanford Asian Liver Center. 2007 physician's guide to hepatitis B: a silent killer.



## Geographic Differences in Epidemiologic and Clinical Characteristics

<b>Characteristic</b>	<b>Asia/Sub-Saharan Africa</b>	<b>N America/W Europe</b>
Endemicity	High	Low
Age of infection	Birth, toddler	Early adulthood
Primary mode of transmission	Perinatal, horizontal	Percutaneous, sexual
Chronicity	Common	Rare
Risk of cirrhosis	High	Low
Risk of HCC	High	Low

Mast EE, et al. MMWR Recomm Rep. 2006;55:1-33.

Custer B, et al. J Clin Gastroenterol. 2004;38(10 suppl):S158-S168.

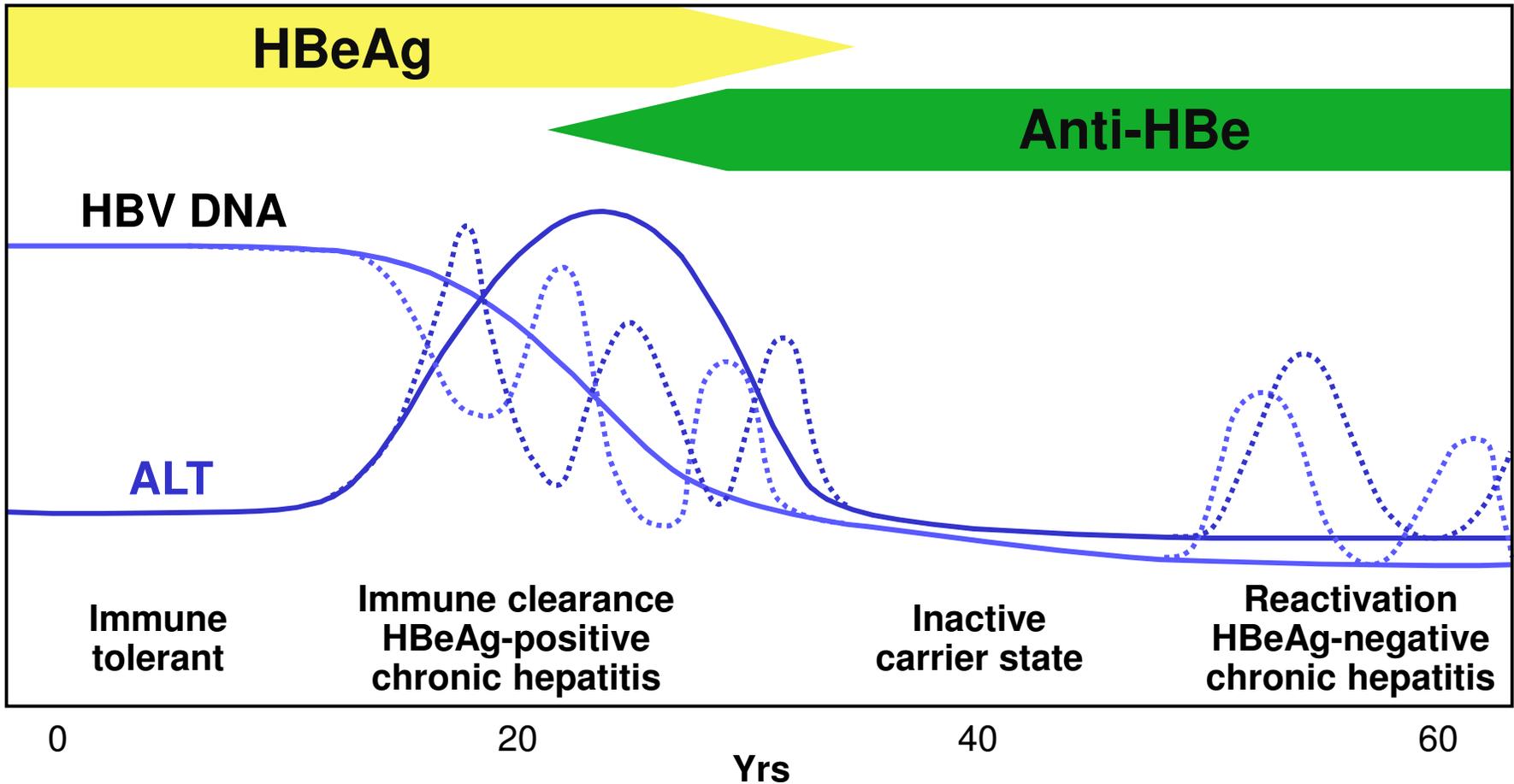


# Serologic Markers in HBV Infection

- **HBsAg**
  - Marker of chronic hepatitis B when found in serum > 6 mos
- **Anti-HBs**
  - Marker of immunity
- **HBeAg**
  - An index of active viral replication and high infectivity
- **Anti-HBe**
  - Appears in recovery phase or reactivation phase
- **Anti-HBc**
  - Marker of past and possibly current infection



# Phases of Chronic HBV Infection

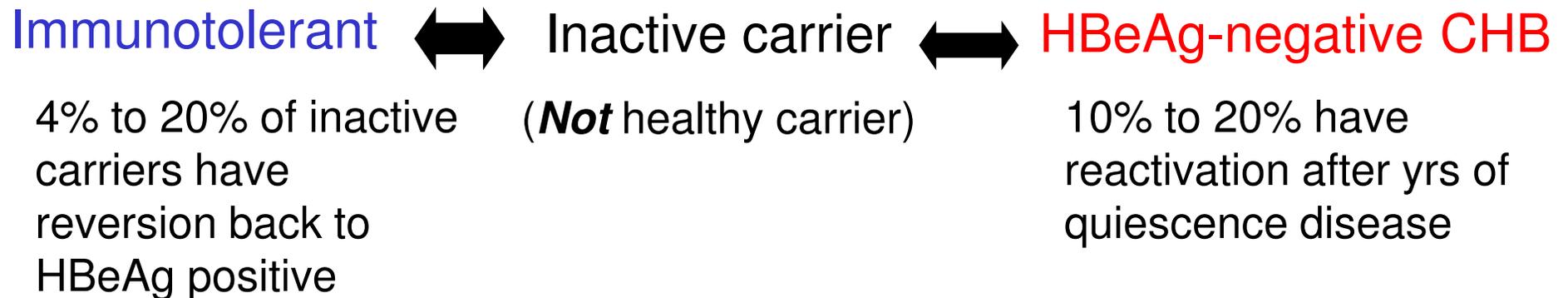


Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. *Hepatology*. 2006;43:S173-S181. Copyright © 1999–2012 John Wiley & Sons, Inc. All Rights Reserved.



## Dynamic Nature of Carrier State

After spontaneous HBeAg seroconversion,  
67% to 80% of carriers remain in inactive carrier phase



Serial testing is necessary during the  
“inactive carrier state”



# Differentiating HBeAg-Negative Chronic Hepatitis B From Inactive Carrier State

Status	HBeAg-Negative Disease	Inactive Carrier
HBsAg positive	✓	✓
Anti-HBe positive	✓	✓
Anti-HBc positive	✓	✓
HBV DNA	Moderate, often fluctuating levels; serum HBV DNA > 2000 IU/mL	Low or undetectable; serum HBV DNA negative or < 2000 IU/mL
ALT	Elevated, often fluctuating levels	Normal



# Interpretation of Diagnostic Tests

Test	HBsAg	Anti-HBs	Anti-HBc	IgM Anti-HBc	HBV DNA
Acute infection, high infectivity	+	-	+	+	+
Recovery from infection	-	+	+	-	-
Immunization	-	+	-	-	-
Chronic infection	+	-	+	-	+/-
Unclear*	-	-	+	-	-

\*4 possibilities: 1) resolved infection (most likely), 2) false-positive anti-HBC, 3) “low level” chronic infection, 4) resolving acute infection.



# Initial Testing in Patients Diagnosed With Chronic HBV Infection

## Testing for Patients Who Are HBsAg Positive<sup>[1]</sup>

Lab tests to assess liver disease: CBC, hepatic panel, and INR (prothrombin time)

Tests for HBV replication: HBeAg/anti-HBe, HBV DNA

Tests to rule out viral coinfections: anti-HCV, anti-HDV (in persons from countries where HDV infection is common and in those with history of injection drug use), and anti-HIV in those at risk

Tests for screening and surveillance for HCC: AFP and ultrasound as appropriate

Consider liver biopsy to grade and stage liver disease for patients who meet criteria for chronic hepatitis

- **Consider core and precore assays and testing for HBV genotype**
- **CDC guidelines recommend HIV testing in ALL chronic HBV patients<sup>[2]</sup>**

1. Lok AS, et al. Hepatology. 2009;50:661-662.

2. Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.



## Upper Limit of Normal ALT Levels

- **Updated upper limits**
  - Males: 30 U/L (-25% from previous ULN)
  - Females: 19 U/L (-37% from previous ULN)
- **Based on retrospective cohort study**
  - 6835 first time blood donors 1995-1999
    - Anti-HCV negative and no contraindication to donation
- **ALT activity independently related to**
  - BMI
  - Abnormal lipid or carbohydrate metabolism



# HCC Surveillance in Chronic Hepatitis B: AASLD Recommendations

- **Asian men older than 40 yrs of age**
- **Asian women older than 50 yrs of age**
- **Patients with cirrhosis**
- **Patients with family history of HCC**
- **African/North American blacks**
- **Those with other risk factors such as high HBV DNA, coinfection with HCV or HIV, or presence of other liver diseases**



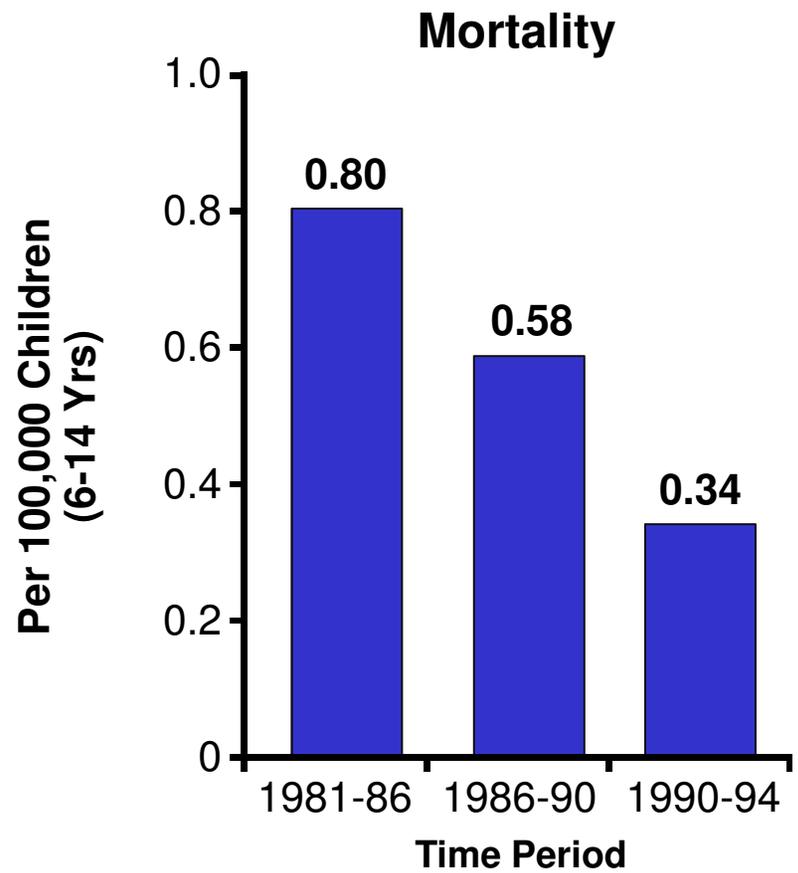
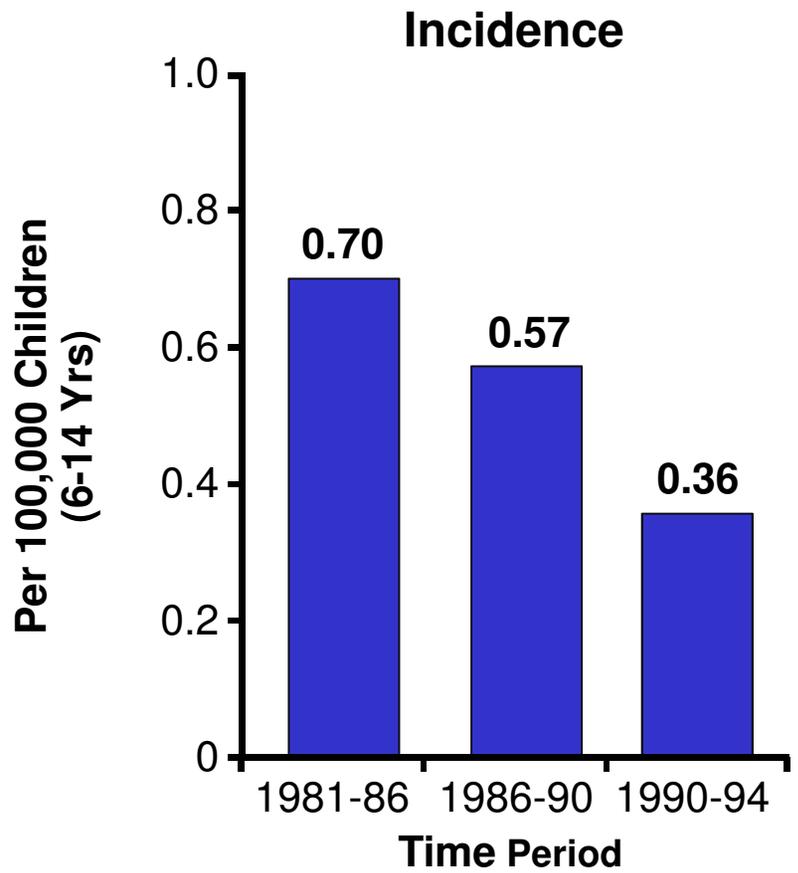
## Who should be vaccinated?

- All infants, beginning at birth
- All children aged <19 years who have not been vaccinated previously
- Susceptible sex partners of HBsAg + persons
- Susceptible household contacts of HBsAg + persons
- Persons seeking evaluation or treatment for STD
- Health care/ public safety workers at risk for exposure to blood-contaminated body fluids
- Residents and staff of facilities for developmentally disabled persons
- Travelers to HBV endemic areas
- Unvaccinated adults with DM < age 60
- HIV+
- MSM
- IVDU
- ESRD, Chronic liver disease
- Sexually active persons who multiple sexual partners(>1 partner in previous 6 m)
- All other persons seeking protection from HBV infection
  - acknowledgment of a specific risk factor is not a requirement for vaccination

**ACIP Update: Everyone should be screened and offered vaccination !!**



# Effect of HBV Vaccination on HCC Incidence and Mortality\*



\*Nationwide vaccination in Taiwan, implemented July 1984.  
Chang MH, et al. N Engl J Med. 1997;336:1855-1859.

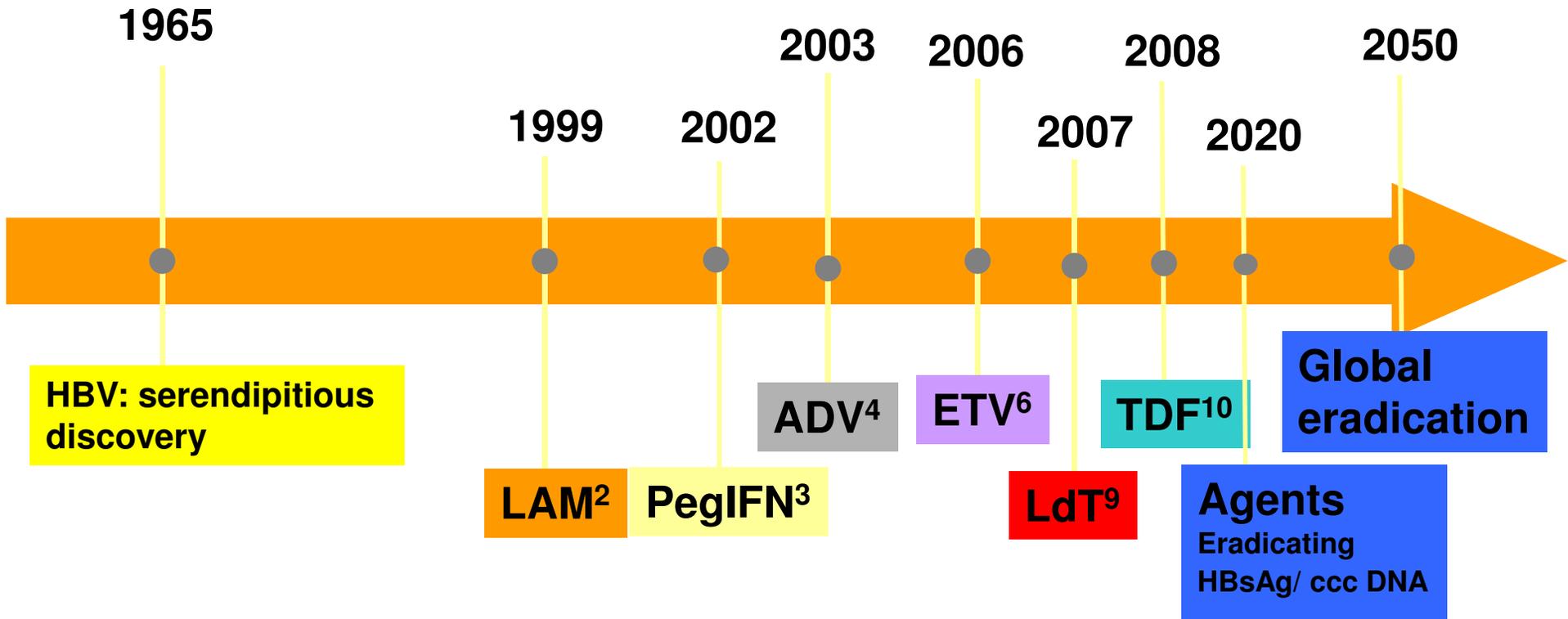


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# Unlike HCV, HBV is easy to treat, difficult to understand





# HBV Treatment

## Whom Do We Treat??

- **Moderately active disease with significant fibrosis**
- **ALT elevation**
- **Viral Load:**
  - **>2,000 IU/mL for HBeAg (-)**
  - **> 20,000 IU/mL for HBeAg (+)**
- **FH+ for HBV related HCC**

## Why Not Treat Everyone??

- **Limitations of current Rx**
- **Does not eradicate infection**
- **Long term treatment needed**
- **Unfavorable cost benefit ratio (direct/indirect costs, long-term safety)**
- **Implications for drug resistance**

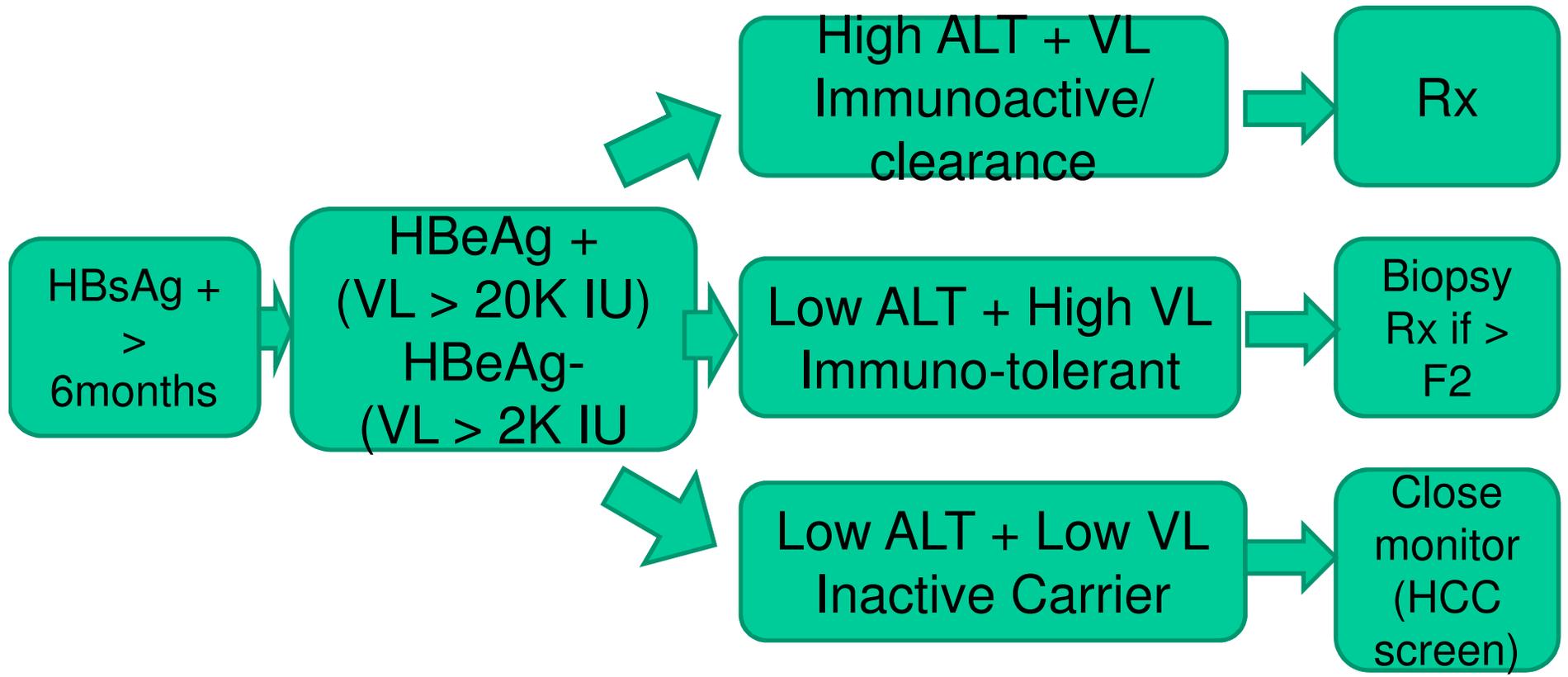


## Special Groups

- **Co-infected (HIV, HCV, HDV)**
- **Pregnancy (selected)**
- **Pre-emptively for immunosuppressive Rx**
  - Cancer chemotherapy
  - Steroids, Biologics, Rituximab, Etanercept
  - BMT recipients
- **Liver Transplant Recipients**
  - Pre and post for HBsAg carriers
  - Some recipients of anti-HBc (+) livers



# My Algorithm





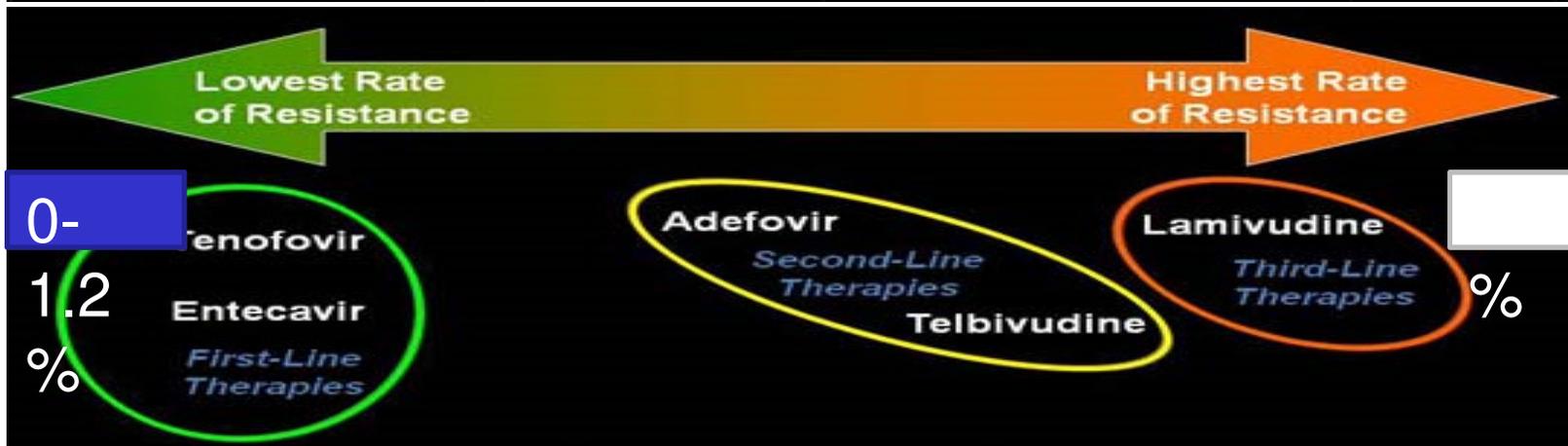
## 49-Yr-Old Korean Male Presents at Your Clinic

- He was born in Korea and immigrated to the US at 15 yrs of age
- Test results
  - HBsAg positive HBV DNA 100 IU/mL
  - HBeAg negative AFP 5.1 ng/mL
  - HBeAb positive Liver U/S: no mass lesion detected
  - ALT 17 IU/L

1. Which phase of chronic hepatitis B is the patient in?
2. How would you manage this patient?



First-Line Therapy			
Peginterferon alfa-2a	PEGASYS®	Roche Laboratories	2005
Entecavir	BARACLUDE™	Bristol-Myers Squibb	2005
Tenofovir	VIREAD®	Gilead Sciences	2008
Second-Line Therapy			
Adefovir dipivoxil	HEPSERA™	Gilead Sciences	2002
Telbivudine	TYZEKA™	Idenix and Novartis	2006
Third-Line Therapy			
Lamivudine	EPIVIR-HBV®	GlaxoSmithKline	1998





# HBV TREATMENT OPTIONS

## Nucleot (s)ides

### Pros:

- Oral administration
- Well tolerated
- Maintained response
- Decreases HBV DNA

### Cons:

- Resistance
- Duration ?
- Long term safety ?

## Peg-IFN

### Pros:

- Finite duration
- No obvious resistance
- Sustained response
- Decreases DNA & HBsAG

### Cons:

- Injection
- Side effects
- Contraindicated in pregnancy/ cirrhosis/ post KTx



# HBV: Current Oral Agents

Table 1 Efficacy of nucleoside/nucleotide analogs treatment for chronic hepatitis B (HBeAg-positive/HBeAg-negative)

	Lamivudine [20, 22, 23, 32]	ADV [39–41, 45]	Telbivudine [48, 52]	Entecavir [59–63]	TDF [71, 72, 74, 75]
Rate of HBeAg seroconversion (%)					
1 year	16/–	12/–	23/–	21/–	21/–
2 year	29/–	29/–	30/–	31/–	27/–
4 (or 5 <sup>a</sup> ) year	47/–	48/– <sup>a</sup>	NA/–	44/– <sup>a</sup>	29/–
ALT normalization (%)					
1 year	72/96	48/72	77/74	68/78	68/76
2 year	NA/60	74/73	70/77	87/89	NA/NA
4 (or 5 <sup>a</sup> ) year	69/NA	NA/69 <sup>a</sup>	NA/NA	80/NA <sup>a</sup>	NA/NA
Undetectable HBV DNA by PCR (%)					
1 year	36/68	21/51	60/88	67/90	76/93
2 year	NA/42	40/71	56/82	80/94	89/91
4 (or 5 <sup>a</sup> ) year	NA/NA	NA/67 <sup>a</sup>	NA/NA	94/NA <sup>a</sup>	96/100
<hr/>					
	Lamivudine [20, 22, 32]	ADV [39–41, 45]	Telbivudine [48, 52]	Entecavir [59–63]	TDF [71, 72, 74, 75]
Resistance (%)					
1 year	14	0	2.2–5	0	0
2 year	39	3	10.8–25.1	<1	0
5 year	60–70	20–29	NA	1.2	NA

Lam et al; Curr Hepatitis Rep 2011



# HBV: Pregnancy



## Hepatitis B: Pregnancy

### Effect of HBV on Pregnancy:

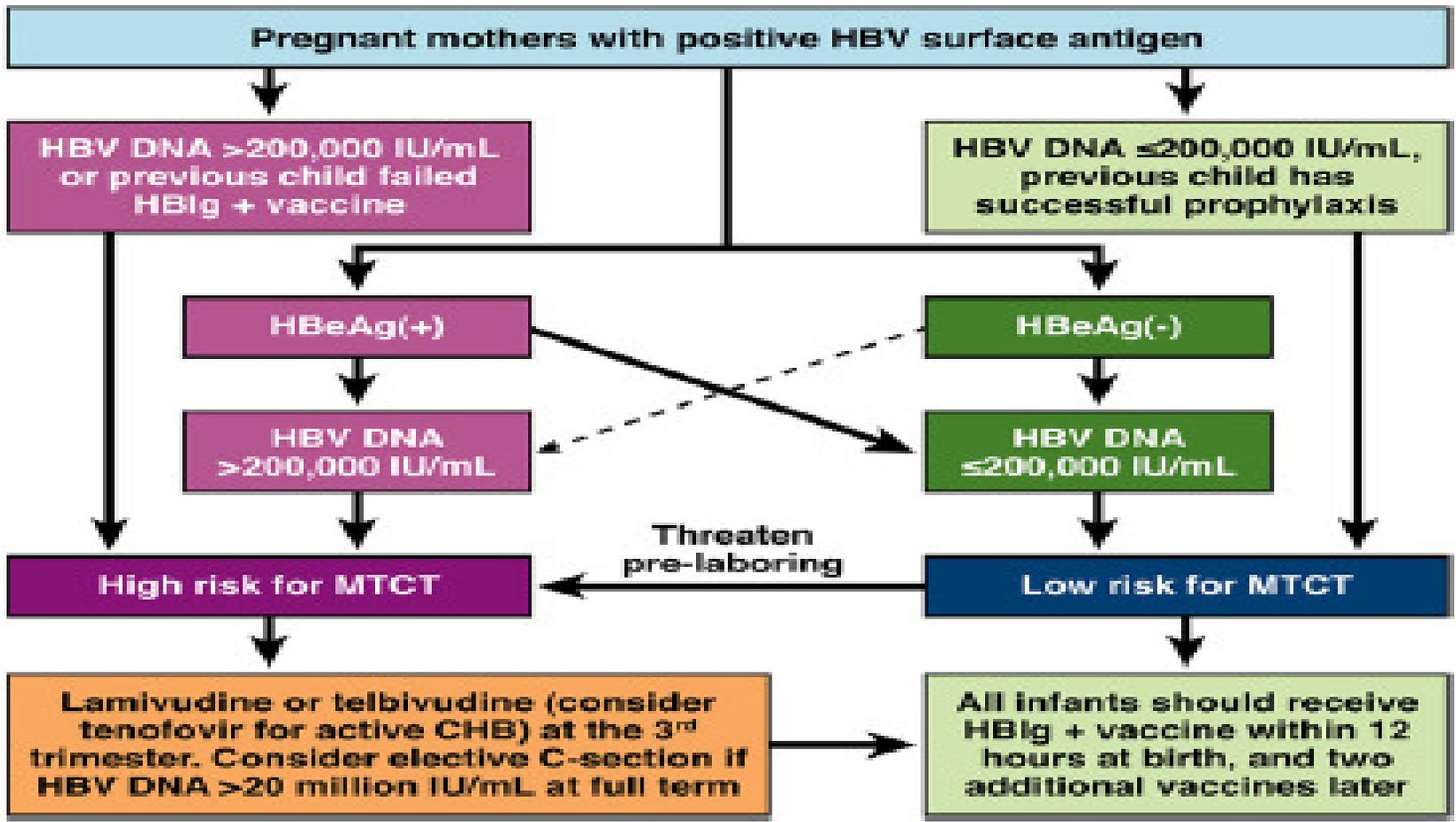
- **HBV per se doesnot affect fertility or conception**
- **HBV w/ cirrhosis:**
  - 30-40% spontaneous abortions
  - Hepatic decompensation
- **Recent study (Tse et al; 2005):**
  - Antepartum H'age
  - Pre-term labor
  - LBW

### Effect of Pregnancy on HBV:

- **Hormone/ cytokine alterations in pregnancy → mild increase in ALT upto high ULN in late trimester**
- **Increased HBV DNA**
- **HBV hepatitis flares, cholestasis, liver failure reported but RARE**
- **HBV related HCC: Hormone effect**
  - Rare but poorest outcome
  - Increased maternal mortality
- **Peripartum/ postpartum hepatitis flares: very frequent**
  - Hepatic decompensation possible
  - Seroconversion rates (12-17%)
  - Need close monitoring



# Algorithm for HBV in Pregnancy





# HBV: Immunocompromised



## Reactivation of Hepatitis B

**Definition: An abrupt increase in HBV replication in a person with chronic or past HBV infection**

**Depends on intensity of immunosuppression**

**Types of HBV reactivation**

**•HBsAg+ persons**

- Exacerbation of chronic hepatitis B
- Reactivation of inactive hepatitis B

**•HBsAg-, anti-HBc  $\pm$  anti-HBs+**

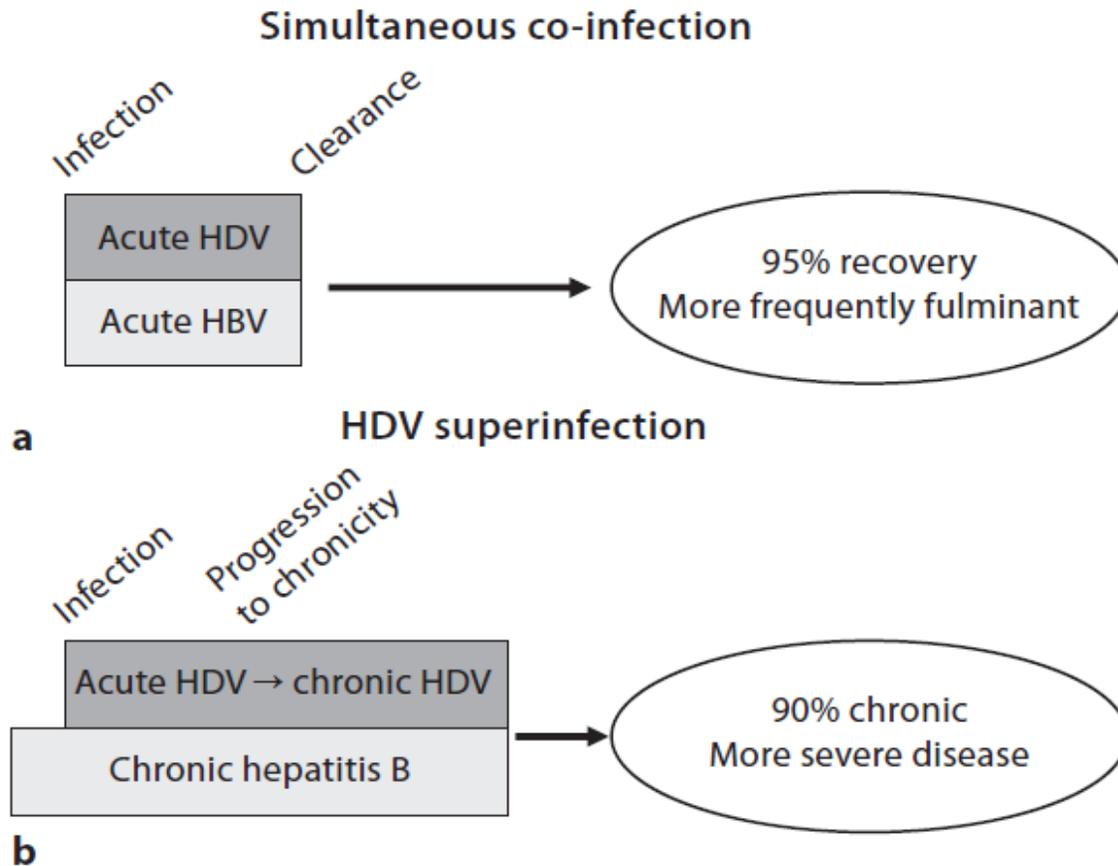
- Reverse seroconversion (reappearance of HBsAg)
-



# Hepatitis Delta



# HDV: Natural History & Rx



- **Defective Virus**
- **5-10% HBsAg+**
- **Treatment:**
  - **Peg IFN Only**
    - SVR: 17-47%
    - High relapse rate
  - **Control HBV**
  - **No novel Rx**



## Summary

- **Screen those at risk and vaccinate if not immune**
- **HBV carrier state is not static but dynamic**
- **Routine monitoring with serology, ALT, and HBV DNA measurements is essential for all HBV carriers**
- **We have discussed when and how to treat HBV.**



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*Thank You*

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