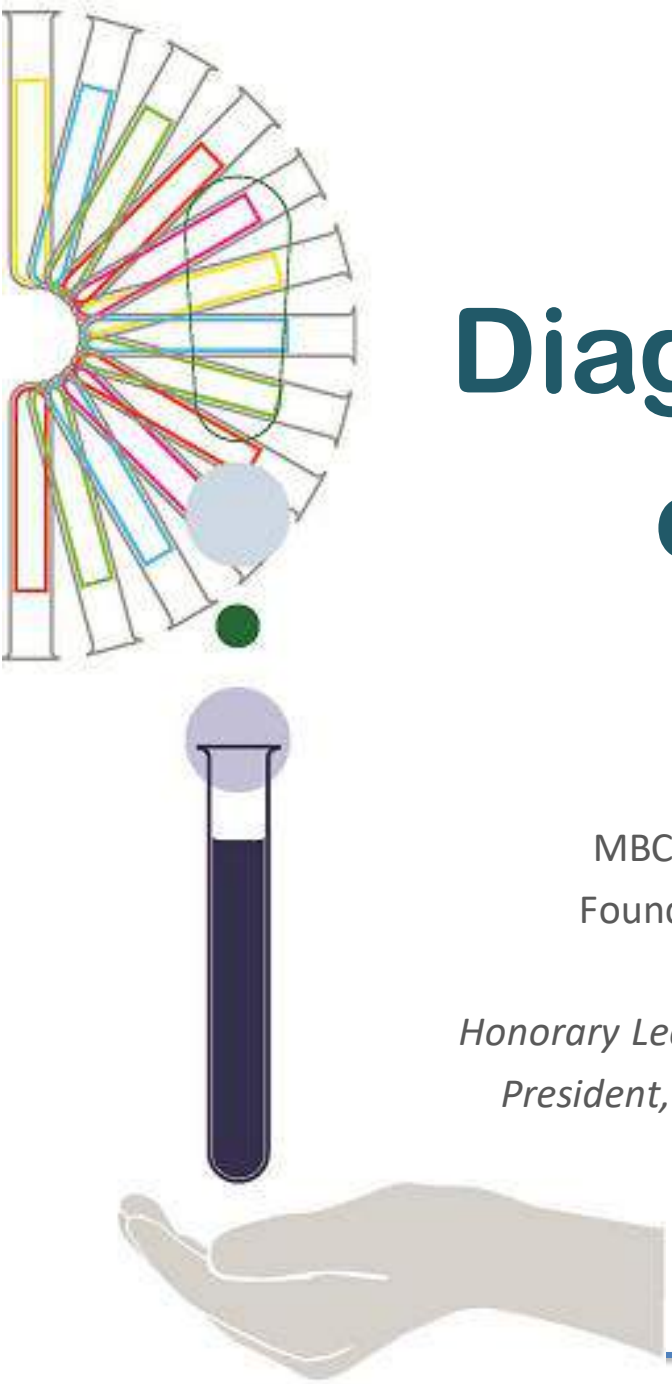

Updates on Lab Diagnosis & Monitoring of Hepatitis B

Dr Ahmed Kalebi

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President, International Academy of Pathology – East African Division

Rwanda Military Hospital CME, November 2018

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COI Declarations

- We are consultant pathologists in a private independent laboratory group that offers referral laboratory services thus the subject matter herein is of business interest to us.
- *However, our presentation is based on current scientific literature and factual experiences with* ***the aim of sharing information,*** *rather than being influenced by our practice's financial interests*.
- A lot of the text and images in the slides have been obtained from colleagues and also from the internet.

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Lancet Group of Laboratories

- Established 1950s
- ~30 partners in SA
- >120 pathologists
- >30000 patients per day
- 12 Reference Labs
- >150 branch labs & >500 centers
- ISO15189 Accreditation Standards
- Kenya hub in East Africa Group
- **60+ service centers in <u>East Africa</u>**

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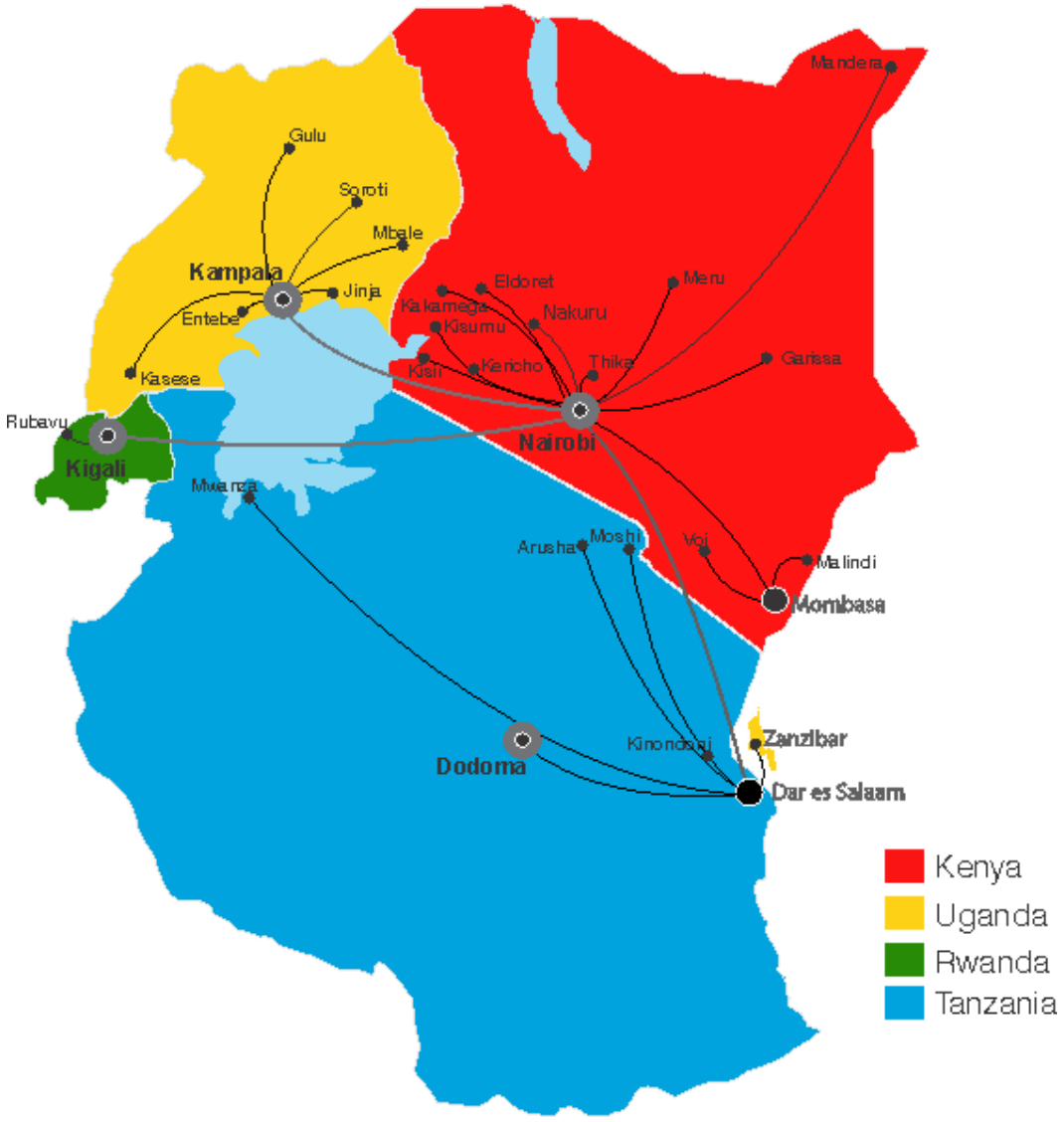
East Africa Footprint



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Footprint in East Africa

KENYA

- Nairobi (9)
- **Mombasa (5)**
- Nakuru (1)
- Thika (1)
- Garissa (1)
- Eldoret (1)
- Kisumu (2)
- Kisii (1)
- Malindi (2)
- Voi (2)
- Meru (1)
- Kakamega (1)

UGANDA

- Kampala (7)
- Mukono (1)
- Jinja (1)
- Entebbe (1)
- Entebbe Rd (1)
- Mbale (2)
- Gulu (1)
- Mbarara (2)
- Tororo(1)
- Fort Portal (1)
- Masaka (1)

TANZANIA

- Dar es Salaam (5)
- Kigamboni (1)
- Zanzibar (2)
- Dodoma (2)
- Arusha (2)
- Moshi (1)

RWANDA

- Kigali (1)
- Gisenyi/Goma (1)

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What we've developed

- Wider footprint in East Africa **>50 sites**
- Extensive test menu **>4300 tests**
- Quality, Reliability & Consistency
- Internationally accepted ISO15189 quality
- >100 pathologists/PhD scientists
- Innovative Electronic report delivery

24h Lab

sanas Medical Laboratory M0402
Our Main Lab is SANAS Accredited

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Quality Assurance & Accreditation

sanas
Medical Laboratory
M0462
ISO15189
SANAS accreditation

Our Main Reference Lab is SANAS accredited since 2010

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Proud moment receiving the ISO15189 SADCAS certificate in Tanzania

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Test Offering

- Chemistry, Endocrinology & Serology
- Haematology
- Coagulation
- Microbiology
- Histology & Cytology
- Molecular Biology
- Cytogenetics
- Newborn screening
- Occupational health
- Clinical trial lab - BARC

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Meet Our Team of Pathologists

Dr Ahmed Kalebi
General & Anatomic Pathologist
Group Managing Director/ CEO
MBChB, Mmed Anat Path, FCPath Anat path (SA) FCPath (ECSA)

Dr Muthoni Kirimi
Anatomic Pathologist
MBChB, MMed Anat Path, FCPath (ECSA)

Dr Charles Wahome
Anatomic Pathologist
MBChB, MMed Anat Path. FCPath (ECSA)

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Veterinary Pathologist
BVM, MSc. Vet. Path

Dr Charles Maina Ngari
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Mmed General Path

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BSc. Med Hons (UCT), PhD (University of Liverpool)

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MBChB, MMed.Path, PhD FCPath (ECSA)

Dr Jamilla Rajab
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MBChB, MMed Path, MPH, FCPath (ECSA)

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Clinical Pathologist/ Haematologist
MBChB, MMed Clin Path FRCP

Dr Valerie Magutu
Clinical Pathologist
MBChB, MMed Clin Path.

Dr Albet Gachau
General & Anatomic Pathologist
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Dr Susan Aketch
Anatomic Pathologist
Mmed General Path

Dr. Susan E. Mbugua
Cytotechnologist
Registry of Medical Technologists American Society of Clinical Pathology (ASCP)

Dr. Evelynn Chege
MBChB, MMed (Human Pathology) Arbitrator (DCI)

Dr. Sima Rugarabamu *(Tz)*
Microbiologist
DDS, M.Sc Microbiology & Immunology. PhD fellow

Prem Ratna Gupta *(Tz)*
Consultant Pathologist
M.B.B.S., DNB Path Theory

Dr Robert Lukande *(Ug)*
General & Anatomic Pathologist
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Dr Ntakirutimana Gervais *(Rwanda)*
Anatomic Pathologist
Mmed Anat Path

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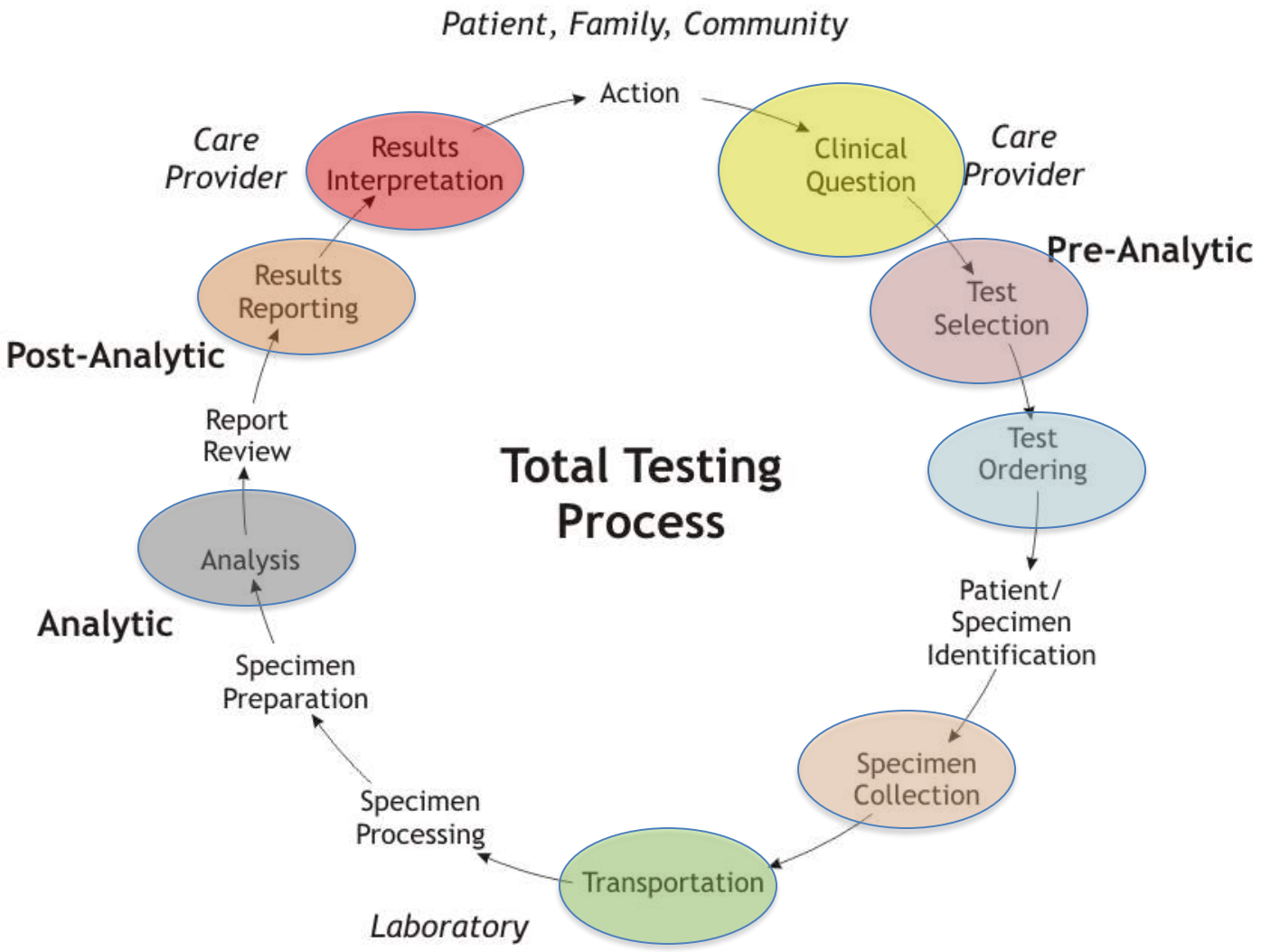
Laboratory Test Pathway



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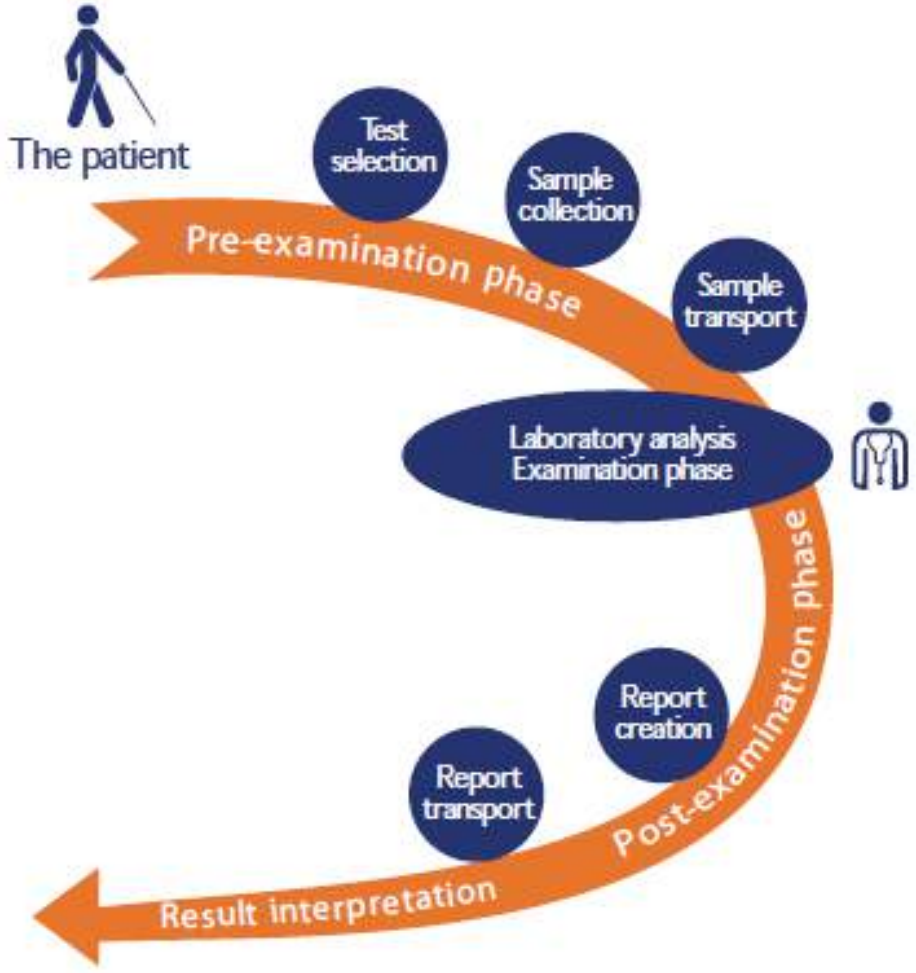
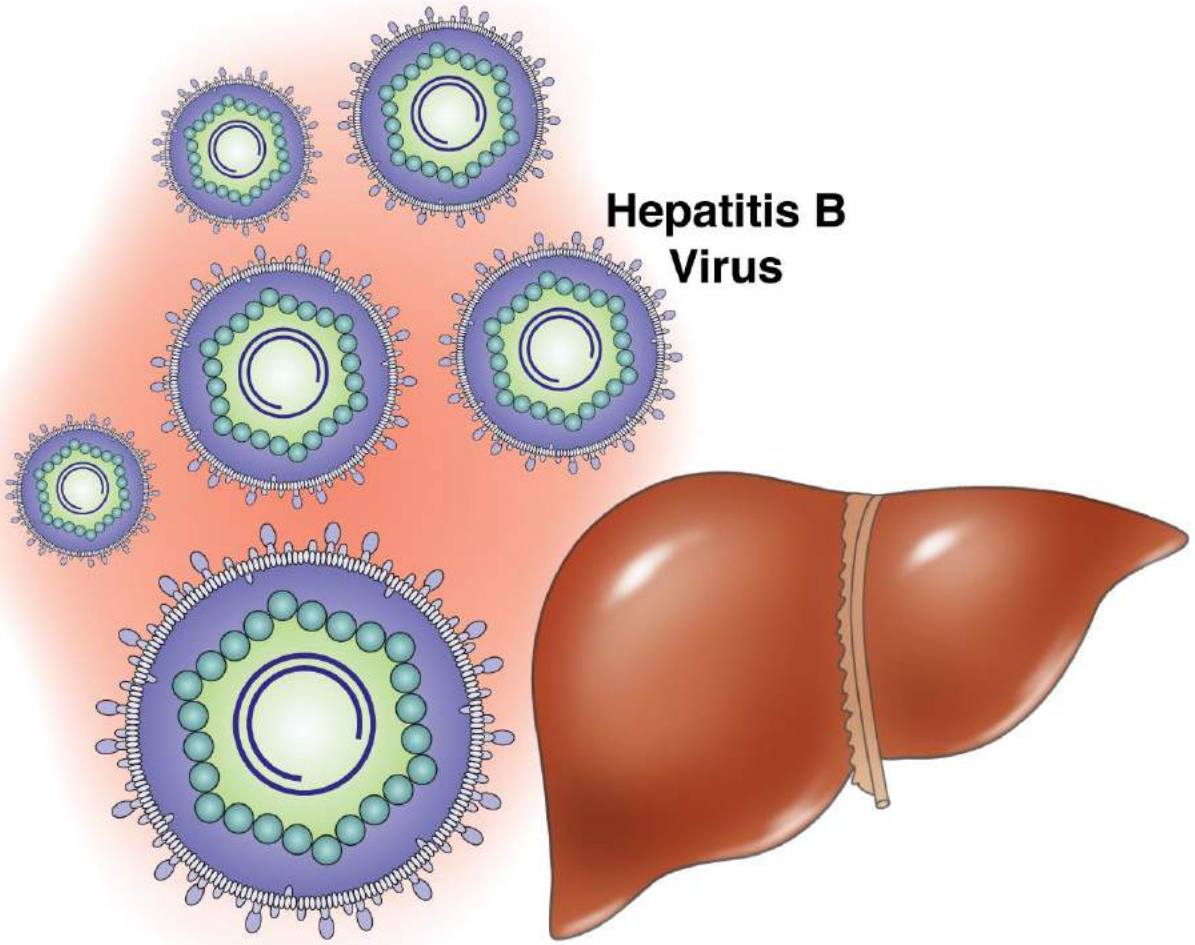
The Patient Journey



Hepatitis B virus (HBV)



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Introduction & Background

- Hepatitis B is a viral infection that attacks the liver and can cause both acute and chronic disease.
- The virus is transmitted through contact with the blood or other body fluids of an infected person.
- 350m – 400m million people are living with HBV infection (defined as Hep B surface antigen positive).
  - Almost 1m deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma).
- Prevalence in East Africa is at 5-8%
  - Rwanda prevalence around 3.5% vs HCV 3%
- HBV a big occupational hazard for health workers.
- Prevented by vaccination – safe and effective.

http://www.who.int/news-room/fact-sheets/detail/hepatitis-b

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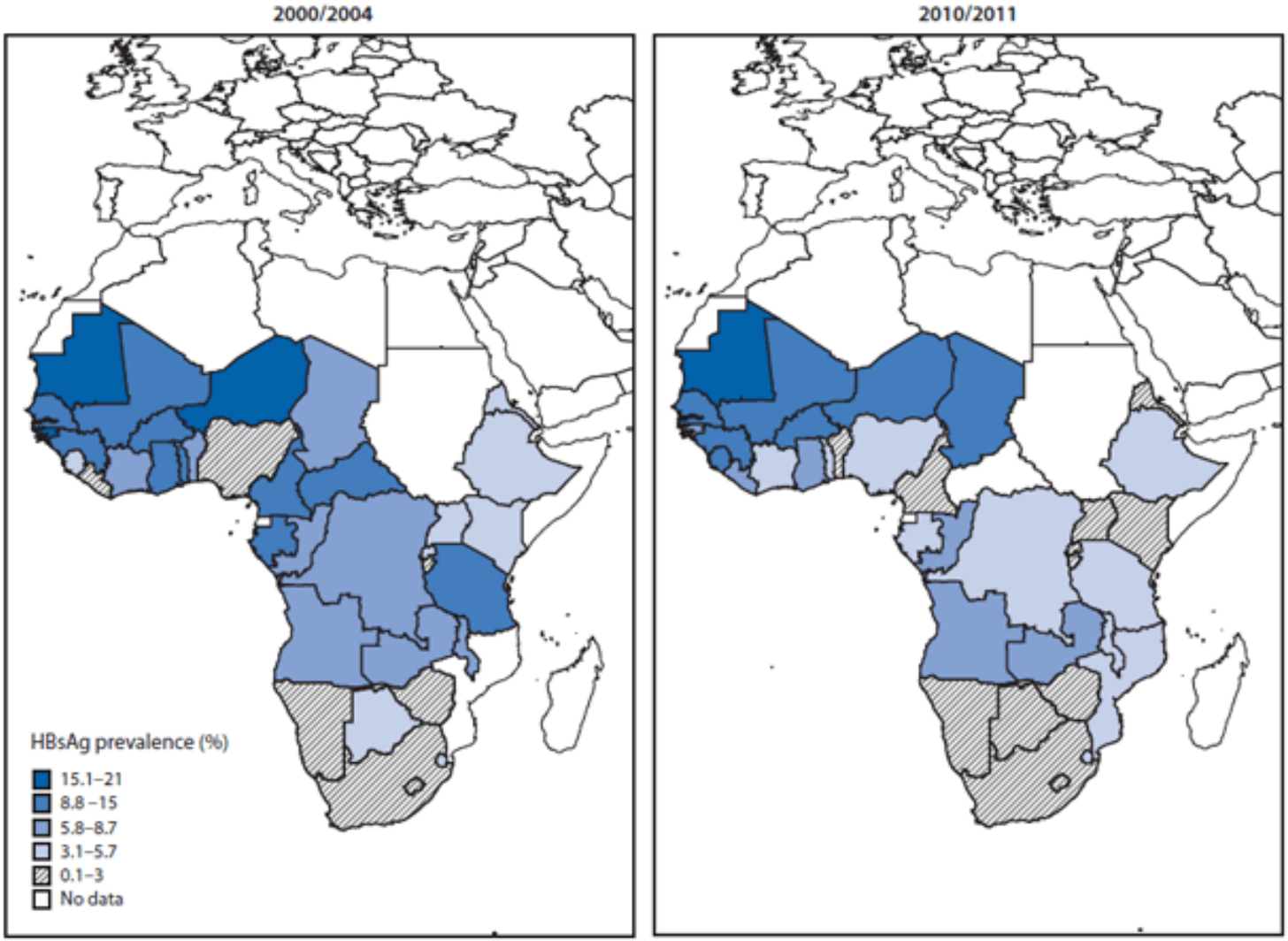
Hepatitis B prevalence



https://www.cdc.gov/MMWr/preview/mmwrhtml/mm6329a2.htm

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Exceptional progress in Rwanda

- Achievements by Rwanda Biomedical Centre:
  - awareness among the general population
  - capacity building for health care professionals
  - capacity building of labs nationwide to diagnose hepatitis B
  - access to medication, by negotiating with manufacturers
  - health insurance cover for diagnosis and treatment costs
  - enhanced screening & management of PLHIV

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VIRAL HEPATITIS SERVICES AVAILABILITY IN RWANDA

Facility level	Number of Facilities in Rwanda	Package of Services to be Offered
Health centres	More than 430	• Hepatitis B Vaccination • Education on Hepatitis B and Hepatitis C • Treatment of Hepatitis B
District Hospitals	39	• Diagnosis • Hepatitis B Vaccination • Education on Hepatitis B and Hepatitis C • Treatment of Hepatitis B
Referral Hospitals	• Rwanda Military Hospital • King Faisal Hospital • CHUK • CHUB • Ruhengeri RH • Kibungo RH • Kibuye RH	• Diagnosis • Vaccination • Education on Hepatitis B and Hepatitis C • Treatment for Hepatitis B and C
Provincial hospitals	• Rwamagana PH • Bushenge PH • Ruhango PH • Kinihira PH	• Diagnosis • Vaccination • Education on Hepatitis B and Hepatitis C • Treatment for Hepatitis B • Treatment for Hepatitis C planned

https://www.newtimes.co.rw/section/advertorial/826

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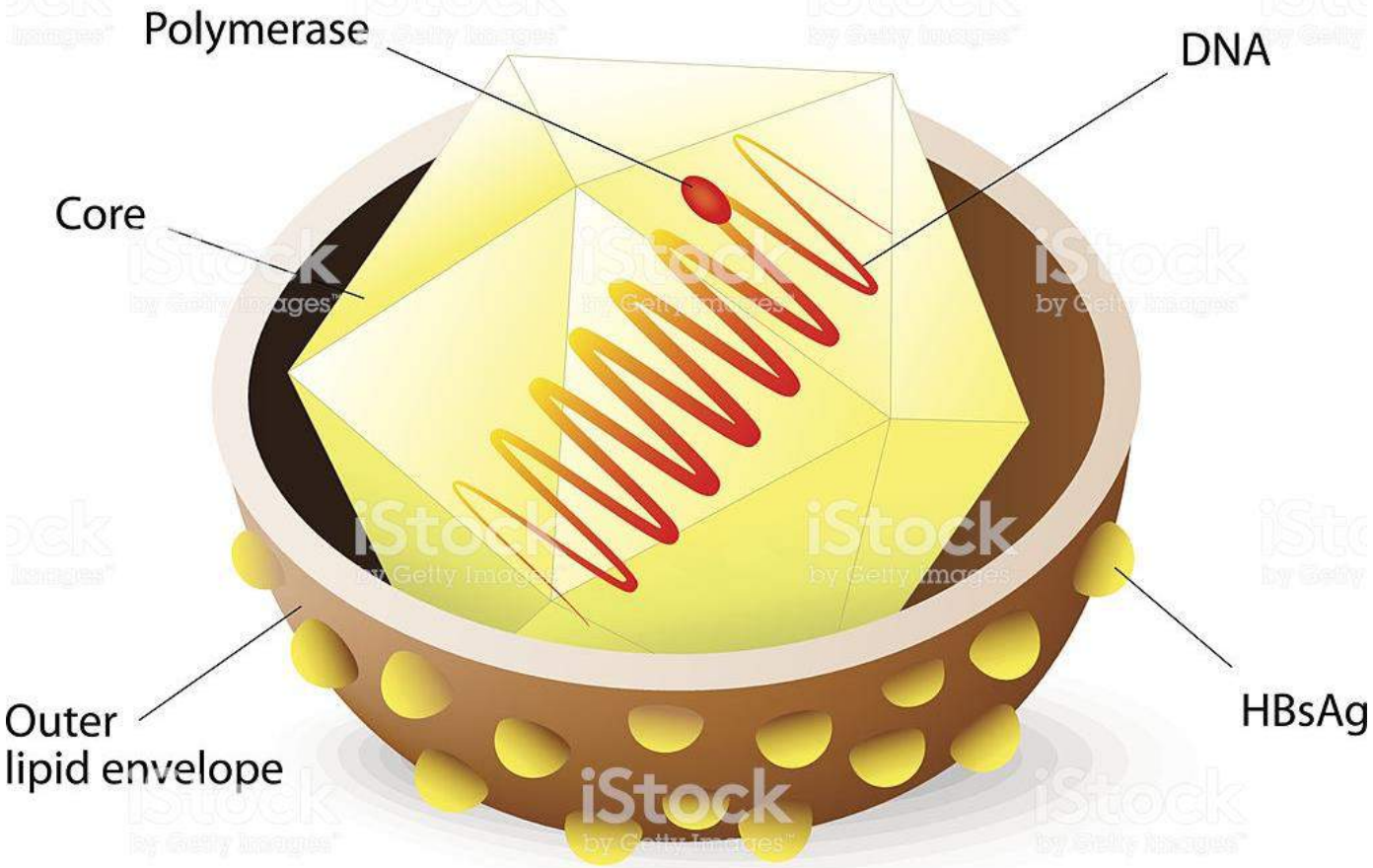
About HBV

- Member of hepadnavirus family
- Virus particle consists of
  - an outer lipid envelope
  - an icosahedral nucleocapsid core encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity
- Virus is hepatotropic

About HBV



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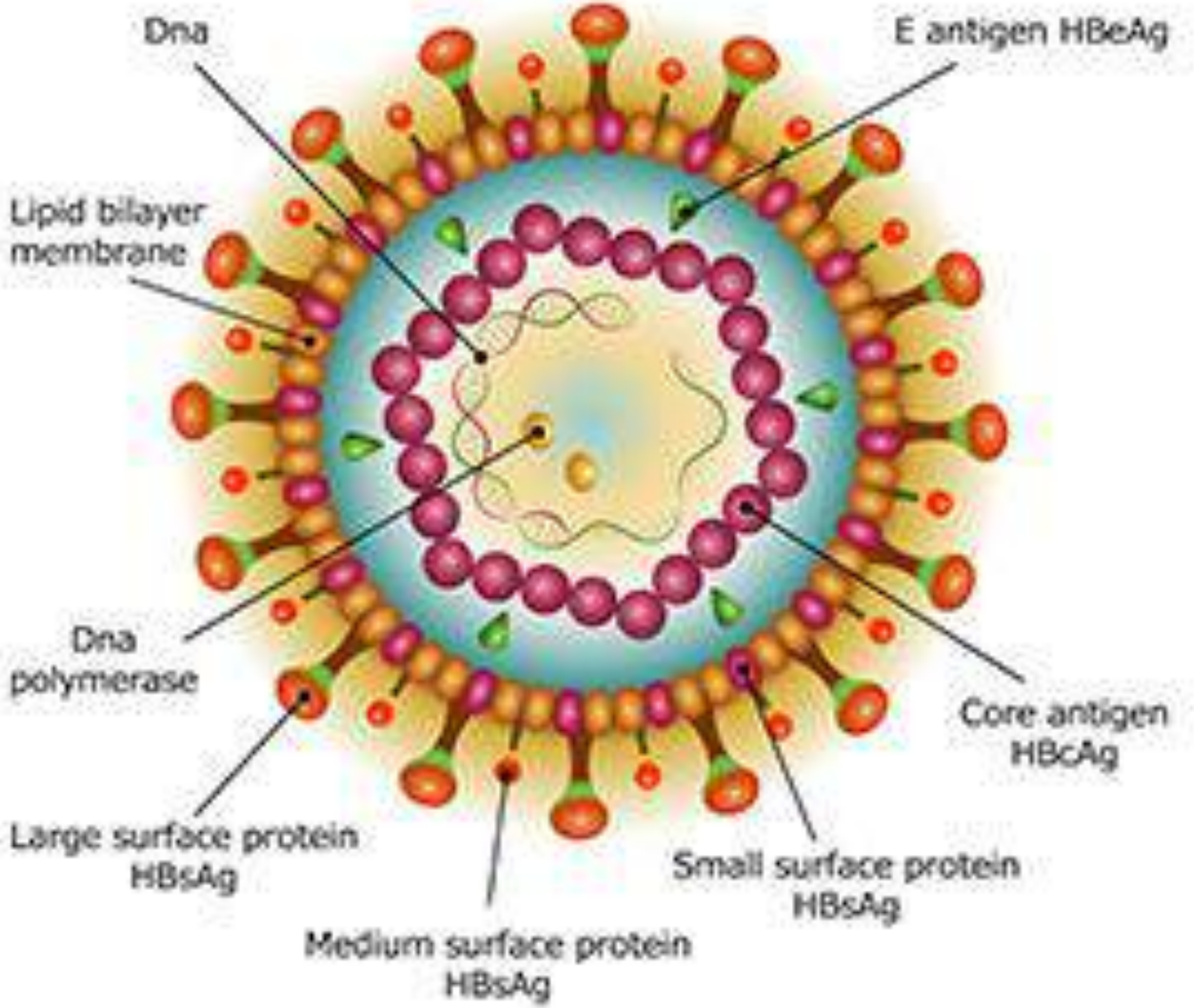

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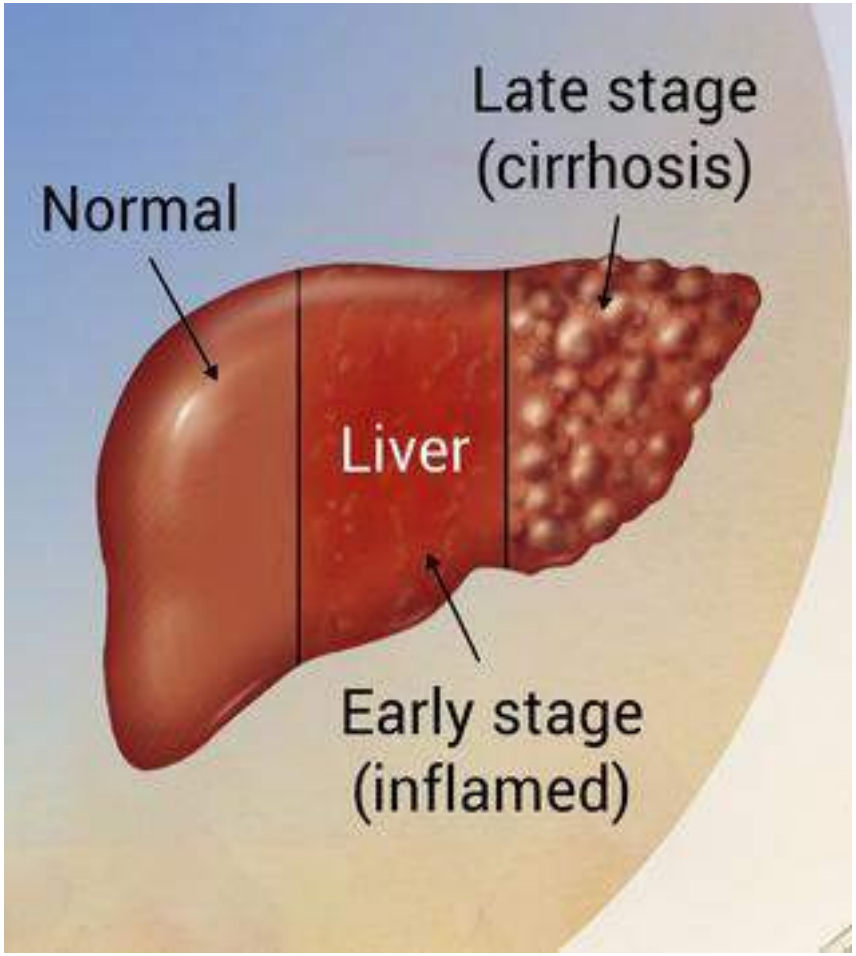
Transmission

- Exposure to infected blood or body fluids containing blood including from sexual contact, blood transfusion & MCT at birth
  - But not spread through usual kissing & contacts
- x50 to x100 times more infectious than HIV
- HBsAg+ mother has a 20% risk of passing the infection to her offspring at the time of birth, the risk is as high as 90% if the mother is HBeAg+

Clinical presentation



- Acute Phase
  - Incubation period 1-6 months
  - Mostly asymptomatic (anicteric) but have risk of chronic disease
  - Those with icteric presentation may have non-specific or specific
  - Fulminant hepatitis does occur
- Chronic Phase
  - Risk depends on age of infection
  - At birth >90%, U5 50%, Adults <5%
  - May be symptomatic (active hepatitis) or asymptomatic (inactive / persistent infection)
  - Complications (cirrhosis, HCC, GN)

Infection versus Disease (Hepatitis / Complication)???

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Serological markers of HBV

- **HBsAg, hepatitis B surface antigen**
- anti-HBs, antibody to hepatitis B surface (antigen)
- **HBcAg, hepatitis B core antigen**
- anti-HBc & IgM anti-HBc, antibody to HBc (antigen)
- **HBeAg, hepatitis B e antigen**
- anti-HBe, antibody to hepatitis B e (antigen)
- **HBV DNA in serum**

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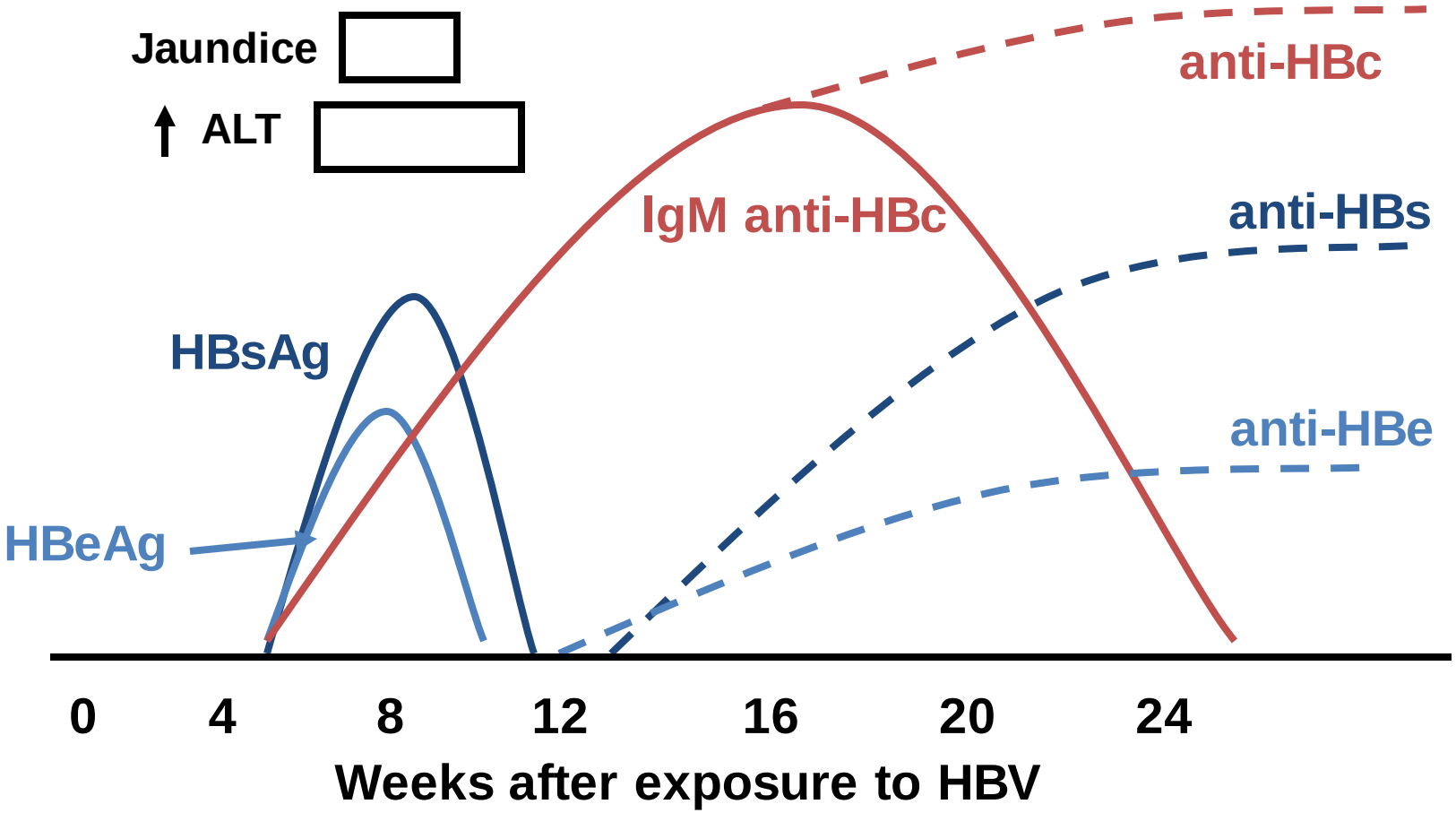
TYPICAL ACUTE HEPATITIS B



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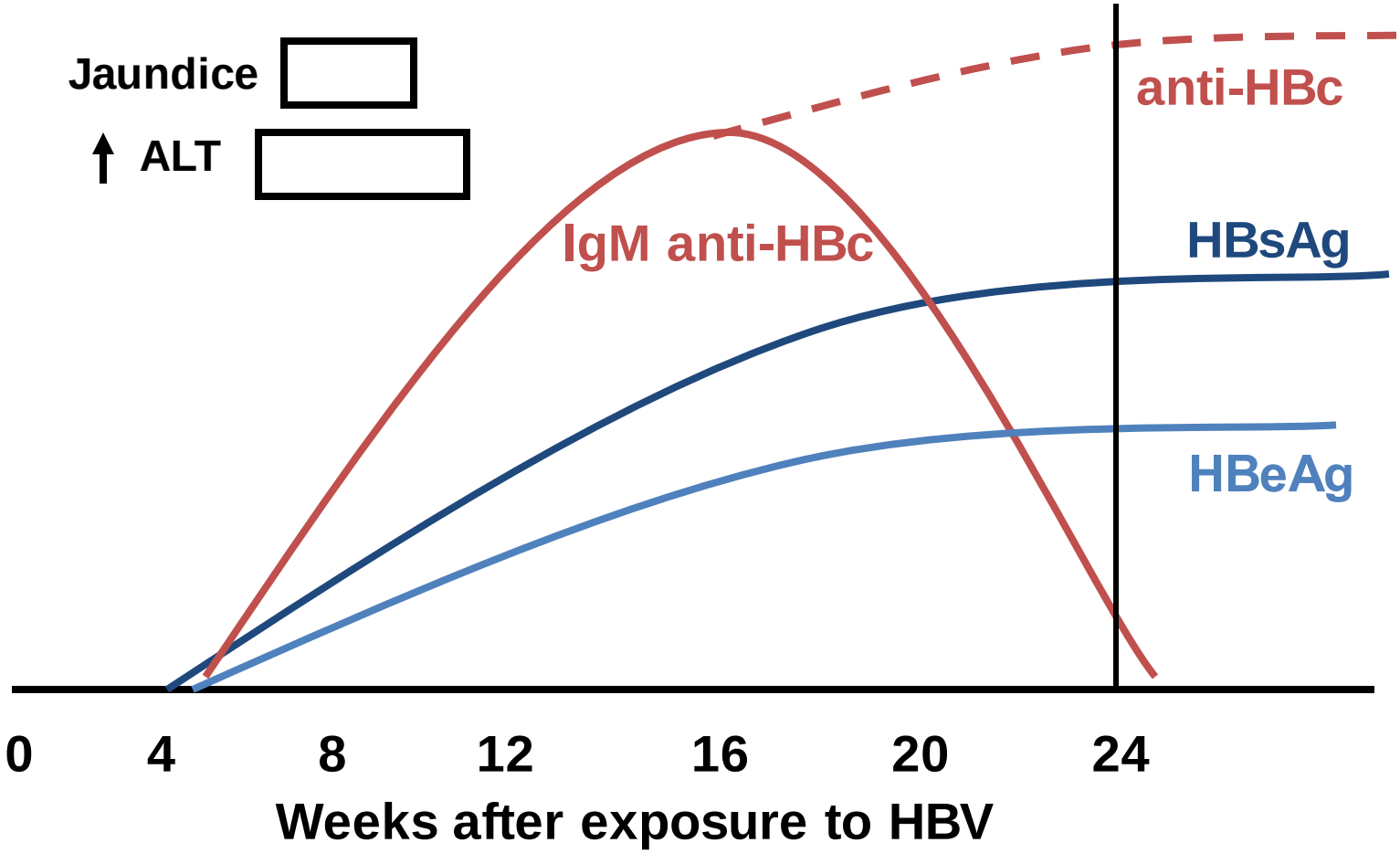
Progression of acute hepatitis B to chronicity



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Diagnosis of Hepatitis B

- **Combinations of serological markers (diagnosis of phase of infection)**

- **Requires knowledge of natural history**

- **Acute HBV infection:**

  IgM anti-HBc (+) with (or even without) HBsAg (+)

- **Past HBV infection:**

  HBsAg (-), anti-HBc (+) (IgM anti-HBc -), anti-HBs (+)

- **HBV vaccination:**

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

- **Chronic HBV infection**

  HBsAg (+) for >6 months or

  HBsAg (+) and IgM anti-HBc (-)

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Diagnostic approach of chronic Hepatitis B in clinical practice

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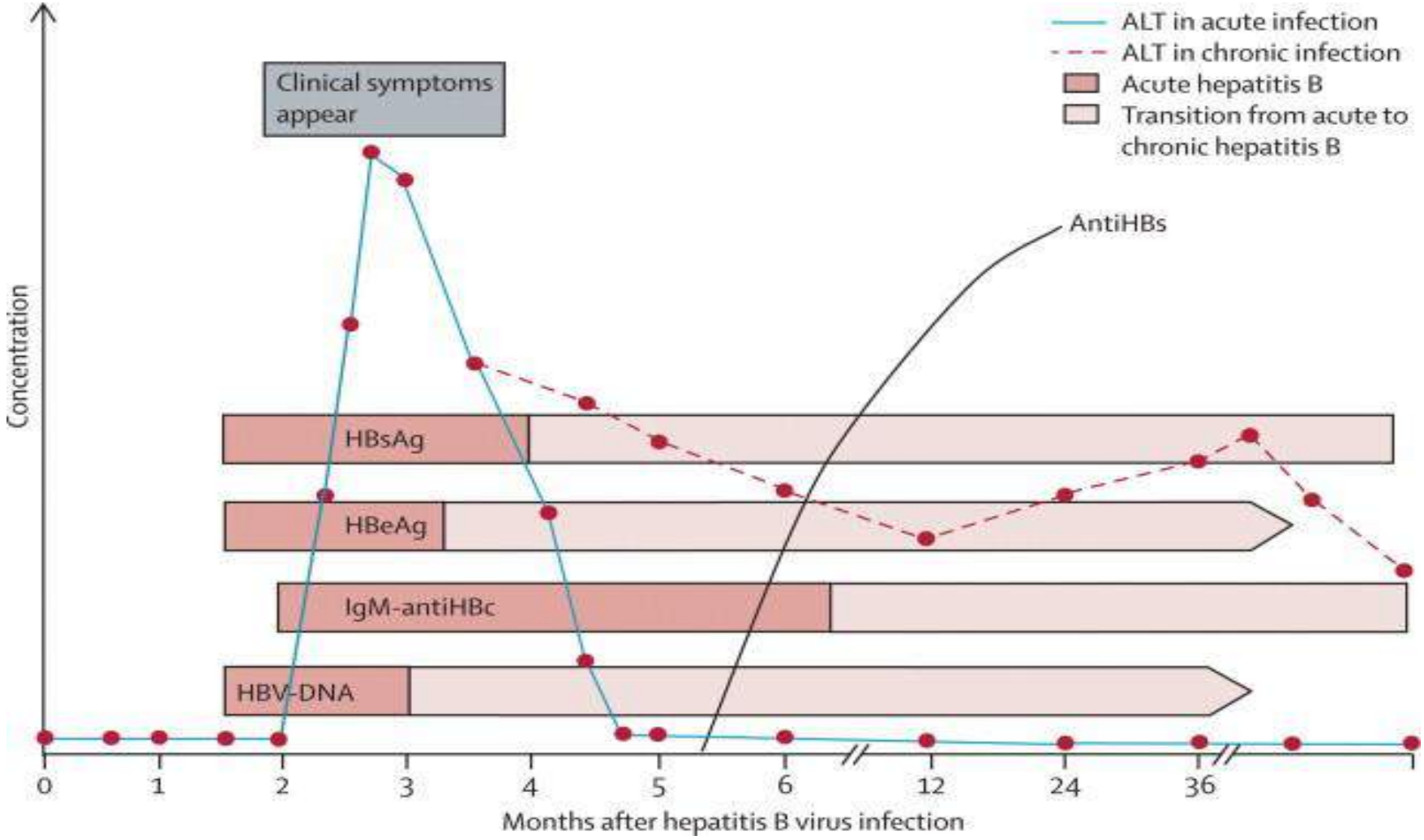

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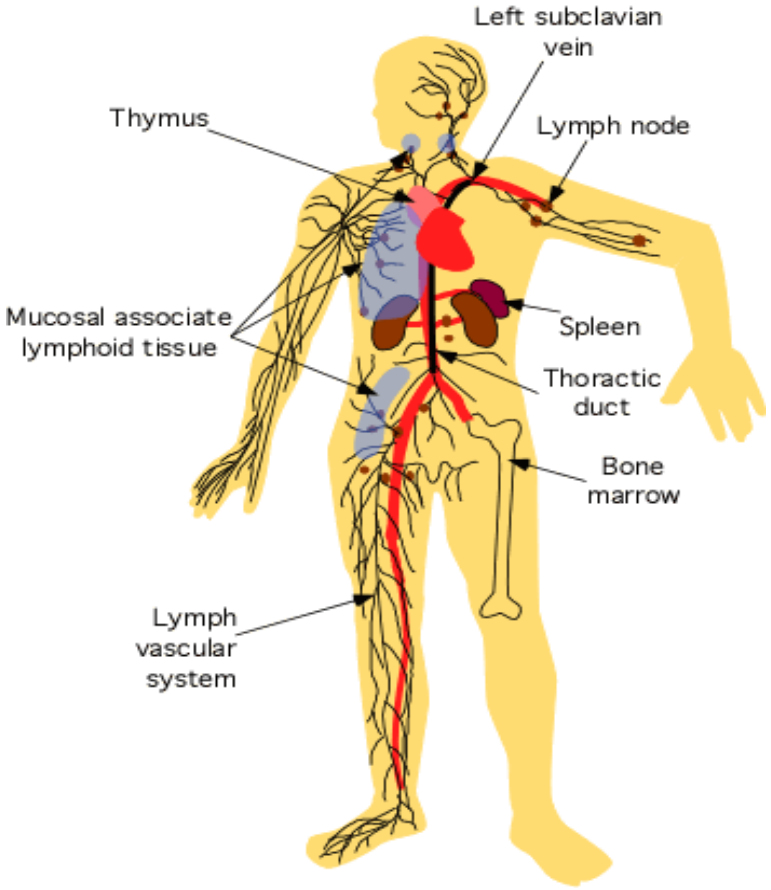
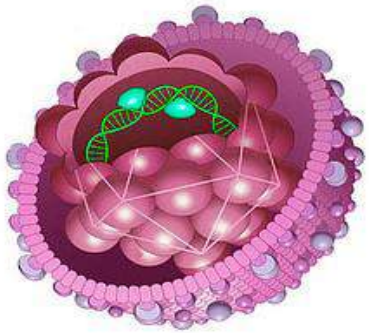
CHB INFECTION: HOST VS VIRUS



Host immune status
(Age, Sex, Drugs, Diseases)

VS



Replication, Mutations

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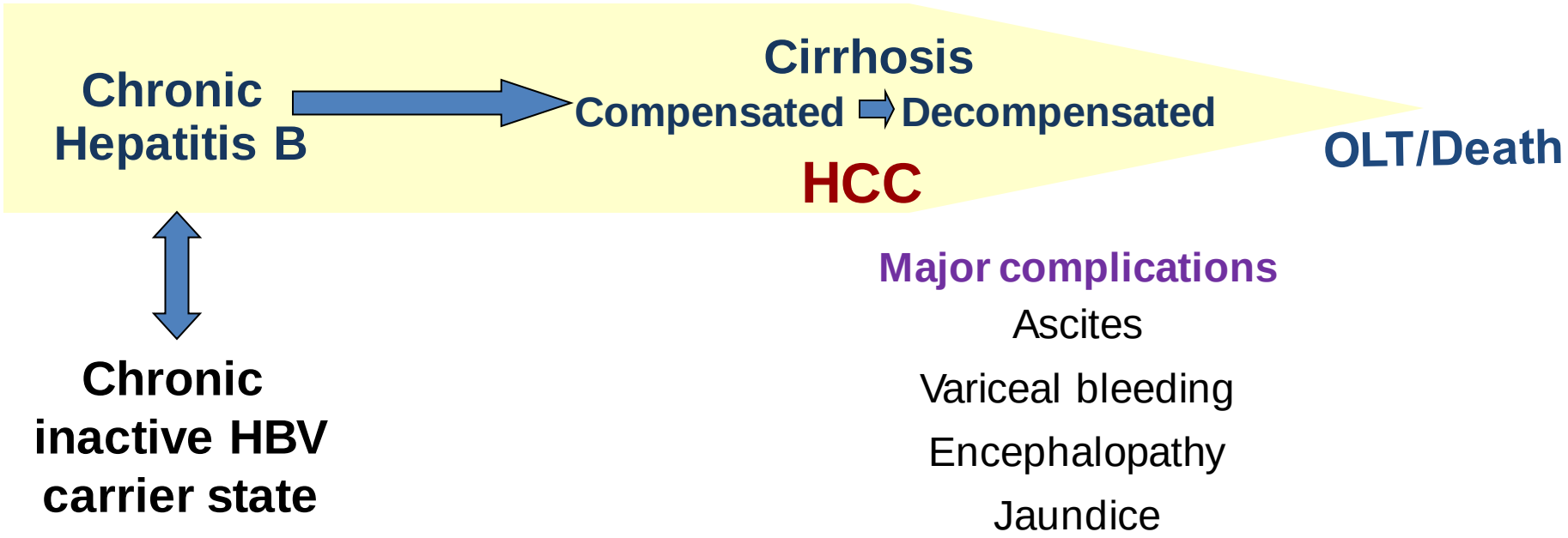
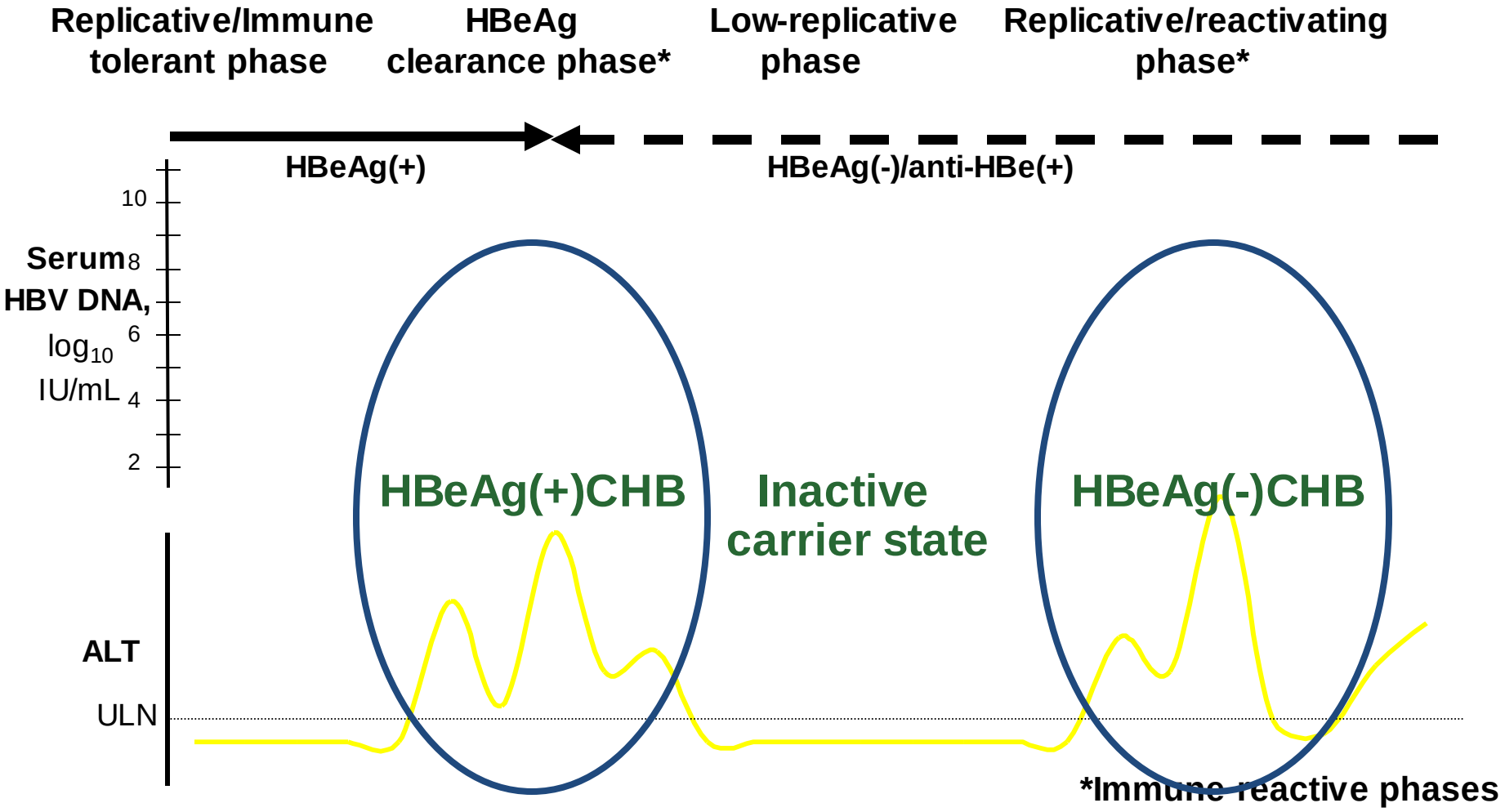
NATURAL HISTORY OF CHRONIC HBV(CHB) INFECTION



Natural History of Chronic HBV Infection



Papatheodoridis et al. Lancet Infect Dis 2008; 8: 167-178

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Phases of chronic HBV infection

	HBeAg positive		HBeAg negative	
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B
HBsAg levels	High	High/ intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg-negative chronic hepatitis

*HBV DNA levels can be between 2,000 and 20,000 IU/mL; **Persistently or intermittently.

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EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

Atypical serological patterns of chronic HBV infection

- Positive HBsAg & anti-HBs

  Forget anti-HBs

<u>Occult infection</u>

- Negative HBsAg with
  - positive only anti-HBc
  - positive anti-HBc, anti-HBs

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Positive anti-HBc with negative HBsAg & anti-HBs

- False positive anti-HBc
- False negative HBsAg or anti-HBs
- Recent acute HBV infection (window phase)
- Very old self-limited acute HBV infection
- Occult HBV infection

Recommendations

- Repeat HBsAg, anti-HBc, anti-HBs
- Check for IgM anti-HBc
- One dose of HBV vaccine
- Test for serum HBV DNA

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Treatment

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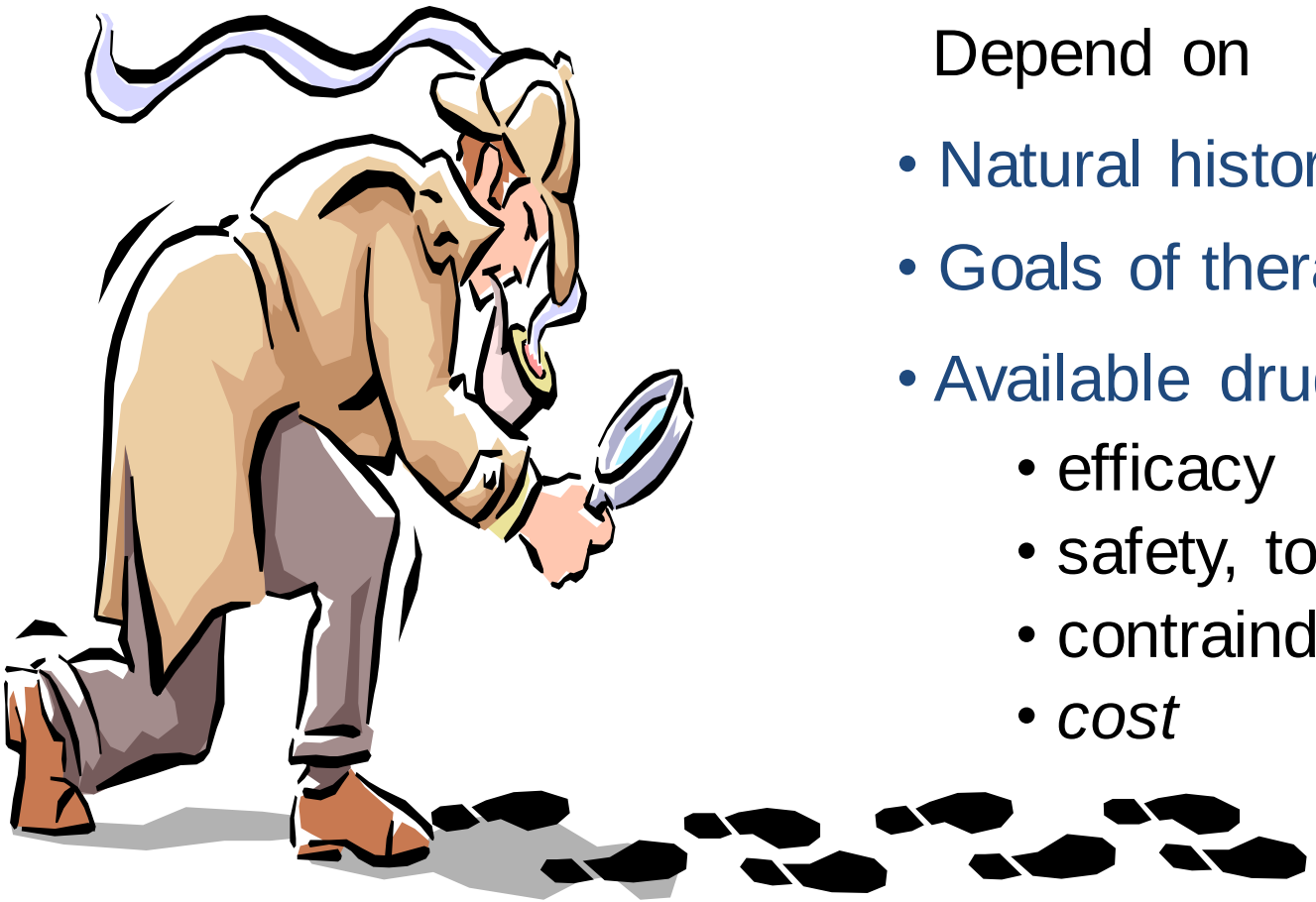
Who and when to treat (indications for treatment) in patients with chronic HBV infection



Depend on

- Natural history of disease
- Goals of therapy
- Available drugs
  - efficacy
  - safety, tolerability
  - contraindications
  - *cost*

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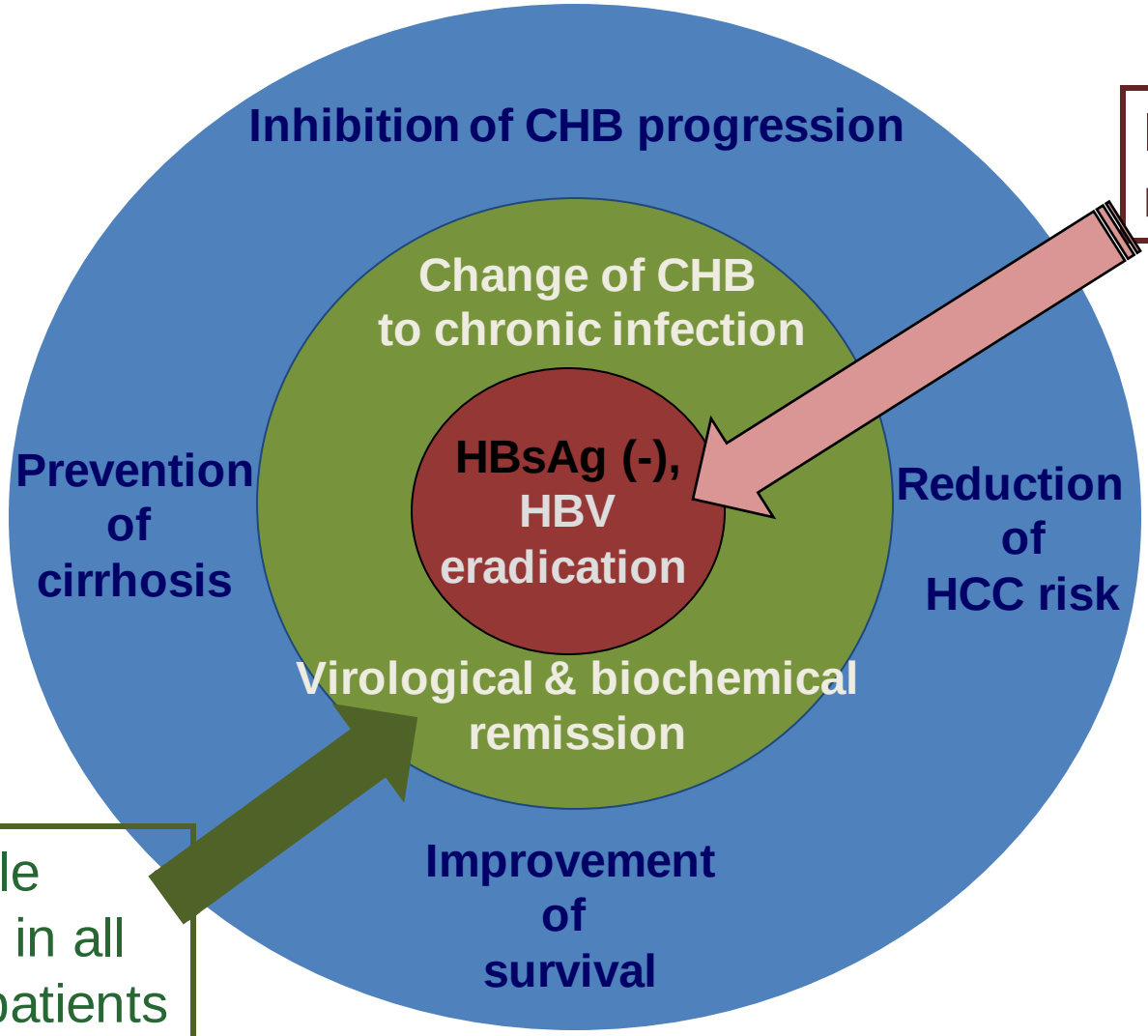
Treatment options

- Suppress the virus with antiviral therapy (ART) usingnucloes(t)ide analogues (Nas), and immunotherapy using interferons
- Currently the first-line agents in the treatment of hepatitis B disease include:
  - Pegylated interferon alfa (PEG-IFN-a)
  - Entecavir (ETV)
  - Tenofovir disoproxil fumarate (TDF)
- The NAs recommended based on barrier to drug resistance and toxicity

Therapeutic goals in CHB



Ideal but not realistic

Feasible practically in all compliant patients

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General indications for treatment

All patients with HBeAg-positive or -negative chronic hepatitis B, defined by

- HBV DNA >2,000 IU/ml
- ALT >ULN and/or
- at least moderate liver necroinflammation or fibrosis,

should be treated.

(Evidence level I, grade of recommendation 1)

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EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

Liver stiffness measurements in the management of chronic hepatitis B patients

- Liver stiffness >9 kPa if ALT ≤ULN

  or >12 kPa if ALT >ULN (<5xULN):

  severe fibrosis or cirrhosis in chronic HBV

EASL-ALEH CPGs. J Hepatol 2015; 63: 237–64

- If the above liver stiffness criteria fulfilled

& HBV DNA >2000 IU/mL:

indication for HBV treatment regardless of ALT

EASL HBV CPGs 2017. J Hepatol 2017;67:370-398.

Additional indications for treatment

1) Patients with compensated or decompensated **cirrhosis need treatment**, with any **detectable HBV DNA** level and regardless of ALT levels

(Evidence level I, grade of recommendation 1)

2) Patients with **HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of fibrosis severity** *(Evidence level II-2, grade of recommendation 1)*

3) Patients with **HBeAg-positive chronic HBV infection** (persistently normal ALT and high HBV DNA) **may be treated** if they are **older than 30 years** regardless of the severity of liver histology *(Evidence level III, grade of recommendation 2)*

4) Patients with HBeAg-positive or HBeAg-negative **chronic HBV infection** and **family history of HCC or cirrhosis** and **extrahepatic manifestations** **can be treated** even if typical indications are not fulfilled

(Evidence level III, grade of recommendation 2)

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EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

Monitoring of patients currently not treated

1) Patients with **HBeAg-positive chronic HBV infection who are younger than 30 years** and do not fulfill any of the above treatment indications should be followed **at least every 3–6 months**

(Evidence level II-2, grade of recommendation 1)

2) Patients with **HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml** who do not fulfill any of the above treatment indications should be followed **every 6–12 months**

(Evidence level II-2, grade of recommendation 1)

3) Patients with **HBeAg-negative chronic HBV infection and serum HBV DNA ≥2,000 IU/ml** who do not fulfill any of the above treatment indications should be followed **every 3 months for the first year and every 6 months thereafter** *(Evidence level III, grade of recommendation 1)*

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Additional indications of treatment/prophylaxis for chronic HBV patients

- **Liver transplantation**
- **HBV-HIV co-infection**
- **HDV-HBV co-infection with ongoing HBV replication**
- **HBV-HCV co-infection during and for 12 weeks after DAAs**
- **Last trimester of pregnancy and up to 12 weeks after delivery if HBV DNA >200,000 IU/ml or HBsAg >4 $\log_{10}$ IU/ml**
- **During and for 12 months after immunosuppressive therapy or chemotherapy**
- **Healthcare workers performing exposure prone procedures with serum HBV DNA >200 IU/ml**
- **Extrahepatic manifestations and replicative HBV infection**

Patients with decompensated cirrhosis

1) Patients with decompensated cirrhosis **should be** immediately treated with a NA with high barrier to resistance, irrespective of the level of HBV replication, and should be assessed for liver transplantation (Evidence level II-1, grade of recommendation 1)

2) **PegIFNa is contraindicated** in patients with decompensated cirrhosis (Evidence level II-1, grade of recommendation 1)

3) Patients should be **closely monitored** **for tolerability** of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction

4) (Evidence level II-2, grade of recommendation 1)

Patients with acute hepatitis B

1) More than 95% of adults with acute HBV hepatitis **do not require specific treatment**, because they will fully recover spontaneously (Evidence level II-2, grade of recommendation 1)
2) Only patients with **severe acute hepatitis B**, characterized by coagulopathy or protracted course, should be **treated with NA** and considered for liver transplantation (Evidence level II-2, grade of recommendation 1)

Severe acute hepatitis: INR >1.5 or protracted course *(i.e. persistent symptoms or marked jaundice for >4 weeks)* or signs of acute liver failure

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EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

HBV-HIV coinfected patients

1. **All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count**

(Evidence level II-2, grade of recommendation 1)

2. **HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen**

(Evidence level I for TDF, II-1 for TAF, grade of recommendation 1)

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EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

HBV-HDV coinfected patients

1. Peg-IFNa, for at least 48 weeks, is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (Evidence level I, grade of recommendation 1)

2. In HDV-HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered (Evidence level II-2, grade of recommendation 1)

3. Peg-IFNa treatment can be continued until week 48 irrespective of on-treatment response pattern if well tolerated (Evidence level II-2, grade of recommendation 2)

EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

HBV-HCV coinfected patients

1. Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment (Evidence level II, grade of recommendation 1)

2. HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA, and monitored closely (Evidence level II-2, grade of recommendation 2)

3. HBsAg-negative, anti-HBc positive patients undergoing DAA should be monitored and tested for HBV reactivation in case of ALT elevation (Evidence level II, grade of recommendation 1)

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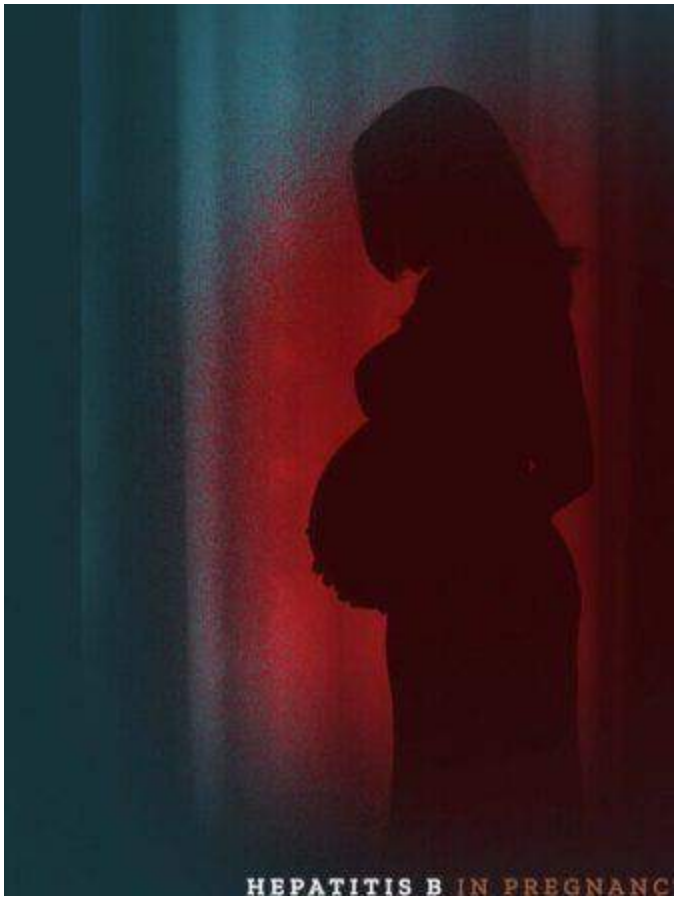
EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

HBV & Pregnancy

Importance of HBV infection in pregnancy

- Globally, >50% of the chronically HBV infected patients acquire the infection vertically
- High rate of chronicity (70-90%)
- High liver related mortality



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Screening in pregnancy

- **Screening for HBsAg** in the **first trimester** of pregnancy is strongly recommended

  (Evidence level 1, grade of recommendation 1)

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Is there a risk of HBV exacerbation during pregnancy? Need for therapy

- **No worsening of chronic liver disease in most pregnant women – Very often ALT normalization**

  Terrault NA et al. Semin Liver Dis 2007;(Suppl. 1):18-24

- **Isolated case reports with severe exacerbations and fulminant liver failure in HBsAg+ pregnant women**

  Rawal BK et al. Lancet 1991;337:364. Yang YB et al. World J Gastroenterol 2004;10: 2305-6. Mahtab MA et al. Hepatobiliary Pancreat Dis Int 2008;7:161-4.

- **Biochem. exacerbations (ALT>3xULN) within 6 mos after delivery:**

  - 36% (9/25) of HBsAg+ pregnant women without treatment

  - 62% (8/13) of pregnant women under LAM during last trimester

  ter Borg MJ et al. J Viral Hepat 2008;15:37-41

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When and how often can HBV be transmitted during pregnancy?

- **Transmission in uterus: rare (<10%)** – in high HBV DNA

  Wang Z et al. J Med Virol 2003;71:360-6

- **Transmission at amnioparacentesis: Exceptionally rare?**

  - Lack of data – No transmission in 2 cases

  Alexander JM et al. Infect Dis Obstet Gynecol 1999;7:283-6

  Towers CV et al. Am J Obstet Gynecol 2001;184:1514-8

- **During delivery! (without any prophylaxis)**

  - **HBeAg(+) mothers: 85% - HBeAg(-) mothers: 31%**

  Beasley RP et al. Am J Epidemiol 1977;105:94-98

- **Type of delivery: no effect on HBV transmission under prophylaxis**

  Wang J et al. Chin Med J 2002;115:1510-2

- **Elective caesarian: possible reduction of HBV transmission without prophylaxis**

  Yang J et al. Virol J 2008;5:100

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PREVENTION OF HBV VERTICAL TRANSMISSION

A. **Check serum HBV DNA ±HBsAg levels in HBsAg+ pregnant women at the 3rd trimester**

B. **If high serum HBV DNA >200,000 IU/mL** or **HBsAg levels >4 $\log_{10}$ IU/ml:** start prophylaxis with **TDF** at week 24–28 of gestation and continue for up to 12 weeks after delivery (Evidence level 1, grade of recommendation 1)

C. **HBIG + HBV vaccination to the newborn**

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Breast-feeding in HBsAg+ mothers

- **HBV can de detected in breast milk**

  Linnemann CC et al. Lancet 1974;2:155

- **Breast-feeding is allowed for neonates after HBIG+HBV vaccination**

  Hill JB et al. Obstet Gynecol 2002;99:1049-52. Cornberg M et al. J Viral Hepat 2008;15:1-21

Breast feeding is not contraindicated in HBsAg positive untreated women or on **TDF**-based treatment or prophylaxis (Evidence level Ⅲ, grade of recommendation 2)EASL HBV CPGs 2017. J Hepatol 2017; 67: 370-398.

- **Safety of NAs during lactation: unknown**
- **NAs can be detected in breast milk**

  Johnson MA et al. Clin Pharmacokinet 1999;36:41-66

  (tenofovir: limited oral bioavailability)

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Children with HBV

1) In children, the **course of the disease is generally mild**, and most of the children do not meet standard treatment indications. Thus, **treatment should be considered with caution**

   (Evidence level II-3, grade of recommendation 1)

2) In children or adolescents who meet treatment criteria, **ETV, TDF, TAF, and PegIFNa can be used** in this population

   (Evidence level II-2, grade of recommendation 2)

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Healthcare workers with HBV

1) **HBV infection alone should not disqualify infected persons** from the practice or study of surgery, dentistry, medicine, or allied health fields

   (Evidence level III, grade of recommendation 1)

2) Healthcare workers **performing exposure prone procedures with serum HBV DNA >200 IU/ml** may be treated with **NA to reduce transmission risk**

   (Evidence level II-2, grade of recommendation 2)

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