



Hepatitis B

Part II

Mode of transmission and the serology



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قَالَ تَعَالَى: ﴿ وَمِنْهُمْ مَّنْ يَقُولُ رَبَّنَا آئِنَا فِي الدُّنْيَا حَسَنَةً وَفِي

الْآخِرَةِ حَسَنَةً وَقِنَا عَذَابَ النَّارِ ﴾ البقرة ٢٠١



"Our Lord, give us in this world [that which is] good and in the Hereafter [that which is] good and protect us from the punishment of the Fire."



اللهم إن أبي في ذمتك، وحبل جوارك، فقه من فتنة القبر وعذاب النار، وأنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم

O Allah, surely my father is under Your protection, and in the rope of Your security, so save him from the trial of the grave and from the punishment of the Fire. You fulfill promises and grant rights, so forgive him and have mercy on him. Surely You are Most Forgiving, Most Merciful.

Mode of HBV transmission

Mode of HBV transmission

- HBV is ubiquitous in body fluids → blood, saliva, sweat, breast milk, tears, urine, vaginal secretions, semen, and menstrual blood.
- **Transfusion:**
 - **1960s:** 50% developed post transfusion hepatitis and 60% were HBsAg positive.
 - **Nowadays:** rare event due to new serology techniques and NAT.
- **Percutaneous:**
 - **Inoculation** of body fluids and blood.
 - **Needle** sharing with IV drug abusers, tattooing, acupuncture, ear/body piercing.

Mode of HBV transmission

■ Sexual transmission:

- More common with men who have sex with men (MSM), heterosexuals with multiple sex partners.
- Safe sex is needed for these persons.

■ Hemodialysis:

- **Risk factors:** blood transfusions, contamination of dialysis machines or equipment, as well as interpersonal horizontal transmission in the dialysis units.
- **Infection control and vaccinations** are mandatory.

Mode of HBV transmission

- **Mother-to-child (vertical or perinatal transmission):**
 - Common in **high endemic** areas as Asia.
 - **Risk factors** → **replicating virus**: ↑ HBV DNA, HBeAg status (+ve HBeAg > -ve HBeAg mothers → 90 vs. 30%).
 - **Time of transmission:**
 - **Intrauterine** or amniocentesis is **rarely seen**.
 - **Time of delivery**: maternal–fetal transfusion or exposure to maternal blood during passage through the birth canal.
 - **Cesarean section** does not decrease the risk.
 - **Immediate post-natal HBV vaccination and hepatitis B immune globulin (HBIG)**: dramatically abolished the risk of transmission.
 - **Post-natal**: intimate mother–baby contact.
 - **Breast feeding is not contraindicated** though HBs Ag is detected in the milk.

Mode of HBV transmission

■ Organ transplantation:

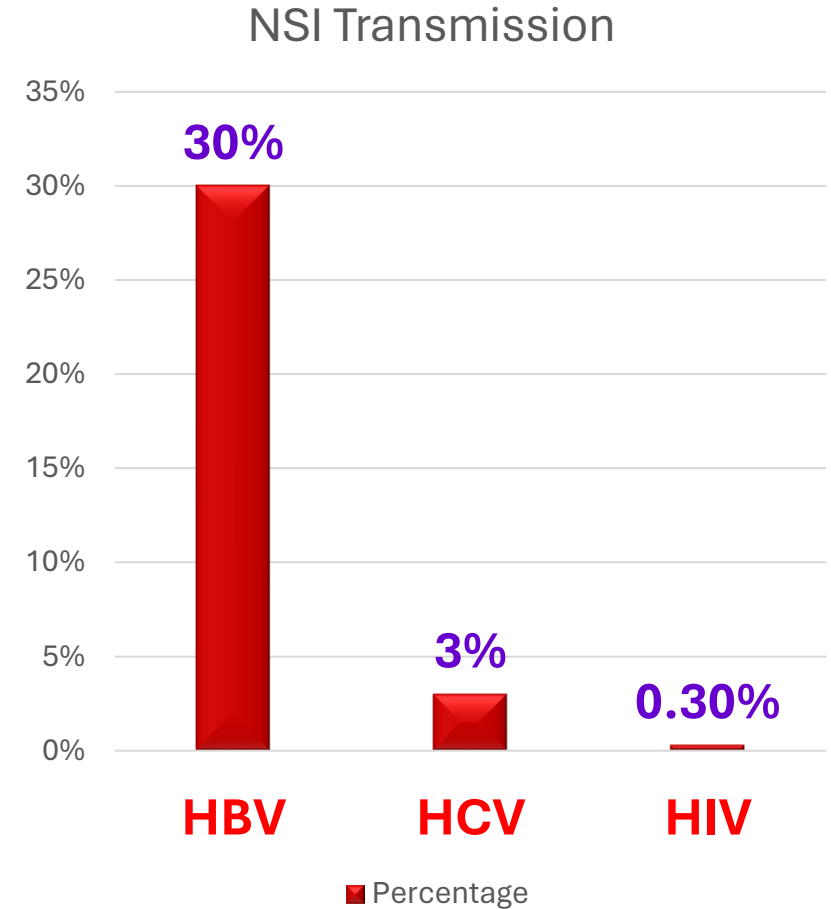
- HBV transmission was documented with **cornea transplantation**.
- **Isolated anti HBc IgG donors** transmitted infection to **negative recipients**.
- **Screening, vaccination and treatment** are mandatory.

■ Health care environment:

- **Replicating virus** is a risk factor.
- **Patient to patient.**
- **Patient to health care worker (HCW):** needle stick injuries.
 - **Small inoculum is sufficient**, especially if blood DNA 10^9 to 10^{13} /ml
 - HBeAg -ve (6%) , HBeAg +ve (30%), unvaccinated HCW.
- **Health care worker to patient:** rare but guidelines set HBV DNA cutoffs.
- **Vaccinations** are **mandatory**.

Needle stick injury (NSI).

- 20 bloodborne pathogens can be transmitted from contaminated needles
- Hollow needle NSI of HBV, HCV, HIV → see graph.
- Visible contaminated needle > invisible.
- IV > subcutaneous.
- **Apply infection control policies once injured.**



Mode of HBV transmission

- **Horizontal transmission (close person-to-person contact):**
 - **Children in endemic areas** → minor skin breaks, sores, open cuts and mucous membranes.
 - **Not transmitted by oral sections or feces** → kissing and lavatories are safe.
 - **HBV Virus Viability in dry secretions:**
 - **7-14 days** → contaminated environmental surfaces and daily articles such as toothbrushes, razors, eating utensils or even toys may also be possible.

HBV Vaccination

High risk groups that need vaccination

- **Persons** born in regions of high or intermediate HBV endemicity (HBsAg prevalence of $\geq 2\%$).
- U.S.-born persons not vaccinated as an infant whose parents were born in regions with high HBV endemicity ($\geq 8\%$)^a
- Persons who have ever **injected drugs**^a
- Men who have **sex with men**^a
- Persons needing **immunosuppressive therapy**, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders.
- Individuals with **elevated ALT or AST of unknown etiology**^a
- Donors of **blood, plasma, organs, tissues, or semen**
- Persons with **end-stage renal disease**, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients^a
- All **pregnant** women
- Infants born to **HBsAg-positive mothers**^a
- Persons with **chronic liver disease**, e.g., HCV^a
- Persons with **HIV**^a
- **Household, needle-sharing, and sexual contacts of HBsAg-positive persons**^a
- Persons who are not in a long-term, mutually monogamous relationship (e.g., >1 sex partner during the previous 6 months)^a
- Persons seeking evaluation or treatment for a **sexually transmitted disease**^a
- **Health care and public safety workers** at risk for occupational exposure to blood or blood-contaminated body fluids^a
- **Residents and staff** of facilities for developmentally **disabled persons**^a
- **Travelers to countries** with intermediate or high prevalence of HBV infection^a
- **Persons who are the source of blood or body fluid exposures** that might require postexposure prophylaxis
- **Inmates** of correctional facilities^a
- **Unvaccinated persons with diabetes** who are aged 19 through 59 years (discretion of clinician for unvaccinated adults with diabetes who are aged ≥ 60 years)^a
- A → vaccinate if seronegative.

HBV vaccines

- **Current recombinant:**

- **HBV small S protein (HBsAg)** produced by yeast or mammalian cells.

- **Regimens:**

- **Usual regimen:** 0, 1, 6 months ^{AASLD}.
 - **Rapid schedule:** 0, day 7 and day 21 to 30 days with a **booster** dose at **12 months** can be used for the combination hepatitis A and B vaccine (Twinrix[®]) for adults ^{AASLD}.
 - **HEPLISAV-B[®]:** 2-dose series given at 0 and 1 months ^{AASLD}.
 - **Combination vaccine (HAV and HBV):** day 0; 1 month; 6 months is considered for travelers who may be exposed to both organisms and patients with liver cirrhosis.

HBV Vaccine Dose

- **Newborn of HBeAg +ve mothers:**
 - Combined HBIG 0.5ml and vaccine must be given **within 12h of delivery** ^{AASLD}.
 - **Measure HBsAb titers after** 9-15months of age ^{AASLD}.
- **Hemodialysis:**
 - Double doses are used to induce response (40 µg of Recombivax HB or Engerix-B) and strict follow up is needed with booster doses.
 - Annual screening for HBsAb titers because they wane rapidly ^{AASLD}.
- **Booster doses and strict follow up are needed for high-risk groups.**
- **Pregnancy:** it is safe vaccine and safe during pregnancy.

Hepatitis B Vaccines and Dosage Recommendations				
Vaccine brand	Age gr (y)	Dose (ug)	Volume (ml)	Doses N
Engerix-B	0–19	10 (half strength)	0.5	3
	≥20	20 (full strength)	1.0	3
Recombivax HB	0–19	5	0.5	3
	≥20	10	1.0	3
(Optional 2 doses)	11–15	10	1.0	2
For hemodialysis patients, recommended dose is 40 µg with each dose (Engerix-B 40 µg/2.0 mL and Recombivax HB dialysis formulation 40 µg/1.0 mL).				

HBV vaccine

■ Efficacy:

- The **vaccine is usually effective**, and the **aim** is **HBs Ab titer ≥ 10 IU/L**.
- **Time of routine HBsAb titers:** 1-2months after the last dose ^{AASLD}.
- **Booster dose indication:** HBs Ab titer < 10 IU/L in HCWs, hemodialysis patients, immunocompromised patients, infants born to +ve HBV mothers ^{AASLD}.

■ Durability of the vaccine:

- Patients with **HBs Ab titer ≥ 10 IU/L** are protected for up to 15 years (30-66%).
- **90%** of patients show **anamnestic response** after booster vaccination.
- **Antibodies titers decrease with time**, but protection clinically is present and there.
 - **No consensus on the need for booster vaccination.**
 - **Booster dose** may be used for **high-risk groups**.

HBV vaccine nonresponse

■ Management:

- Be sure that the patient is not HBs Ag +ve.
- Repeat the 3-dose vaccination and use double dose in immunocompromised patients and cirrhosis^{AASLD}.
- Vaccine adjuvants and granulocyte macrophage colony stimulating factor GM-CSF.

Factors associated with hepatitis B vaccine failure

- Hepatitis B viral factors for failure in infants:
 - Maternal hepatitis B e-antigen positivity^a
 - Maternal high hepatitis B viral load^a
 - Vaccine escape mutant (such exposure may not be protected by vaccination in infants and adults)
- Host factors for failure in infants and adults
 - Preterm or low birth weight infants^a
 - Alcoholism^b
 - End-stage renal disease^b
 - Status of immune suppression^b
 - Diabetes mellitus^b
 - Drug abuse^b
 - Genetic variants (HLA loci)^b
- Inappropriate passive-active immunization^a

“a” infants, “b” adult.

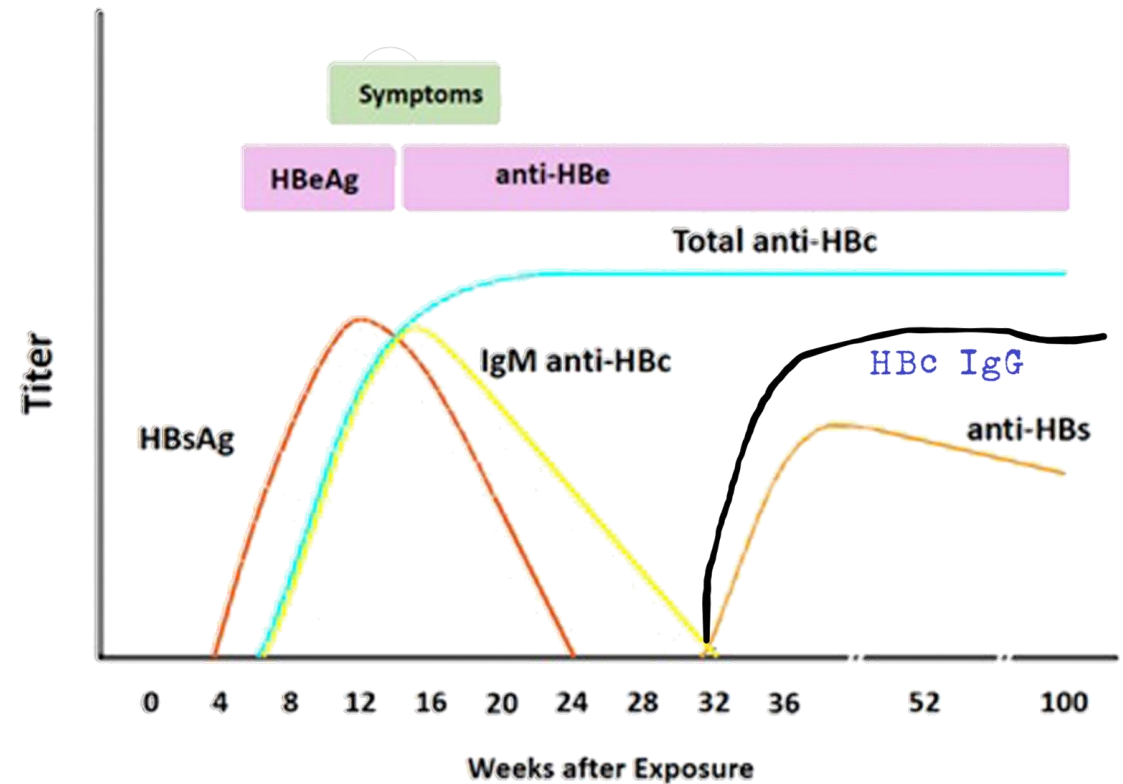
Post exposure prophylaxis for individuals exposed to hepatitis B virus

- If unvaccinated previously → give HBIG and vaccine.
- Previously vaccinated:
 - Known vaccine responder → no treatment.
 - Known vaccine non-responder → give HBIG and vaccine.

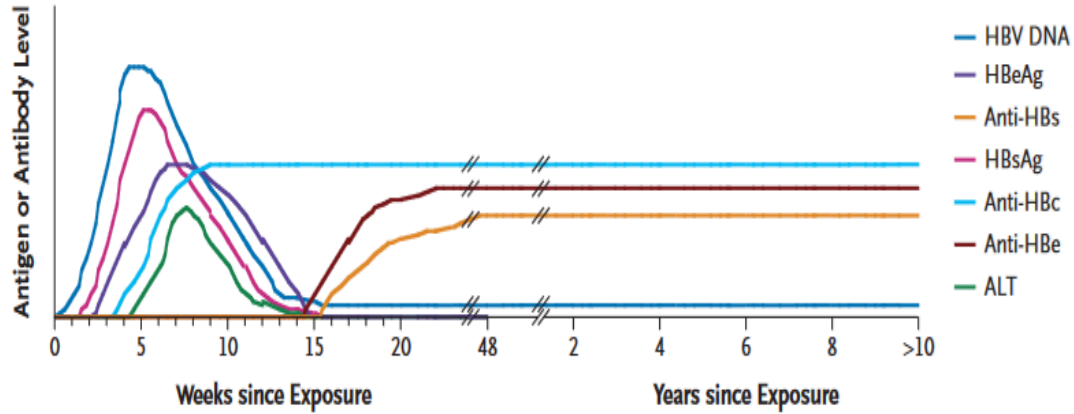
HBV serology

HBV serology

Acute HBV with Recovery



A Acute Self-Limited HBV Infection



B Chronic HBV Infection

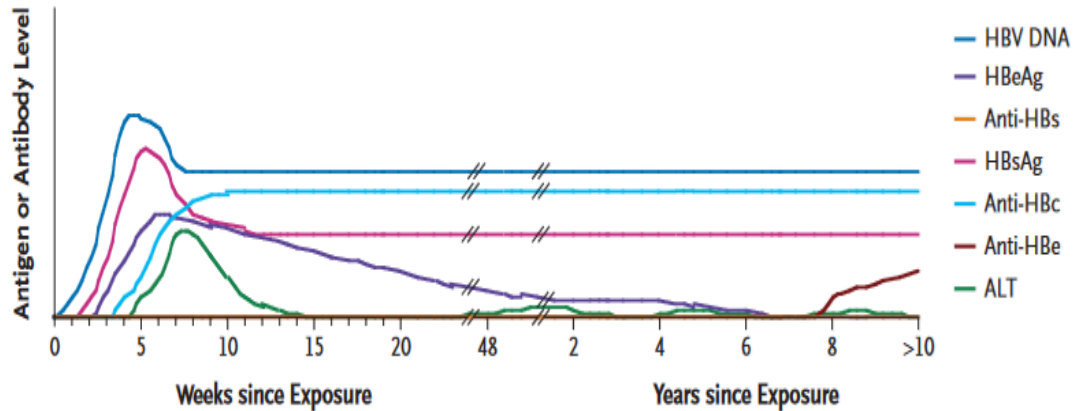
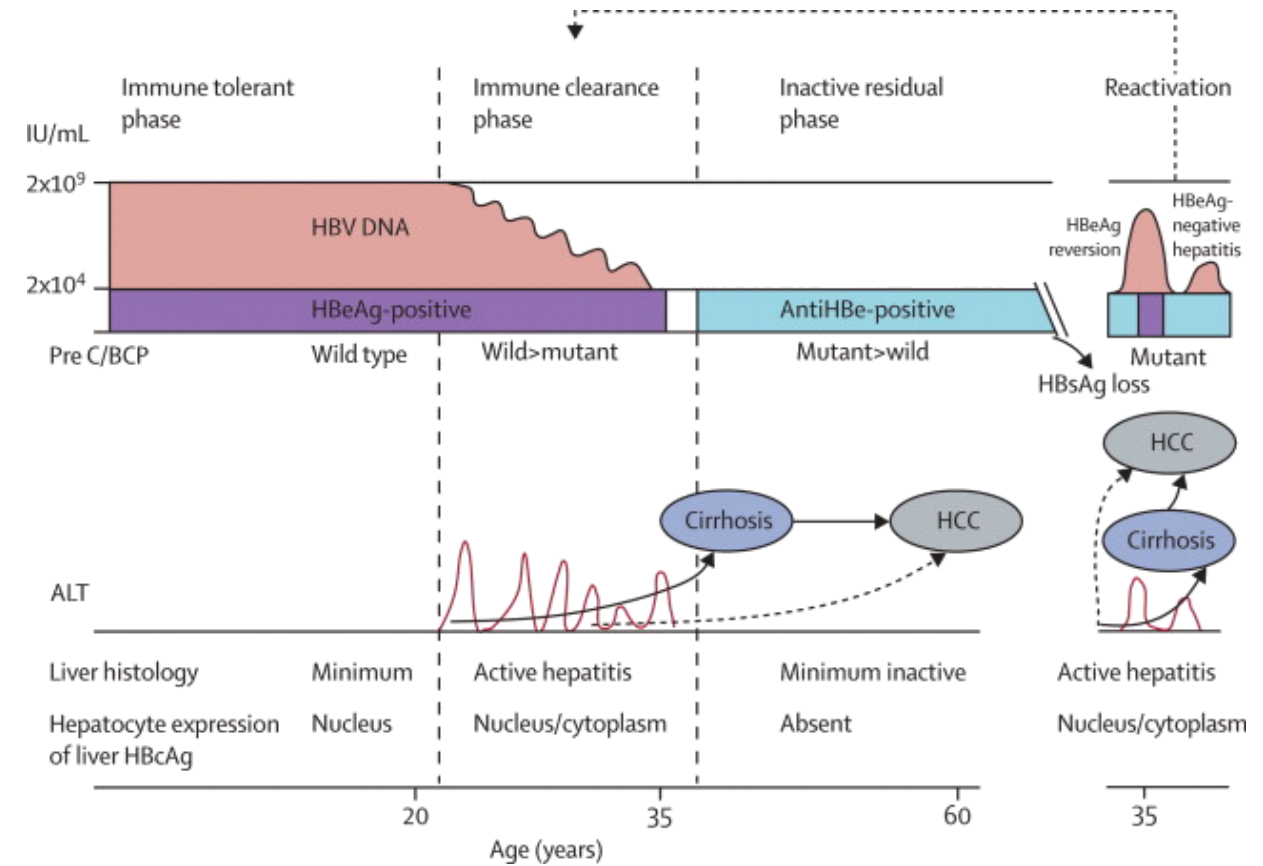
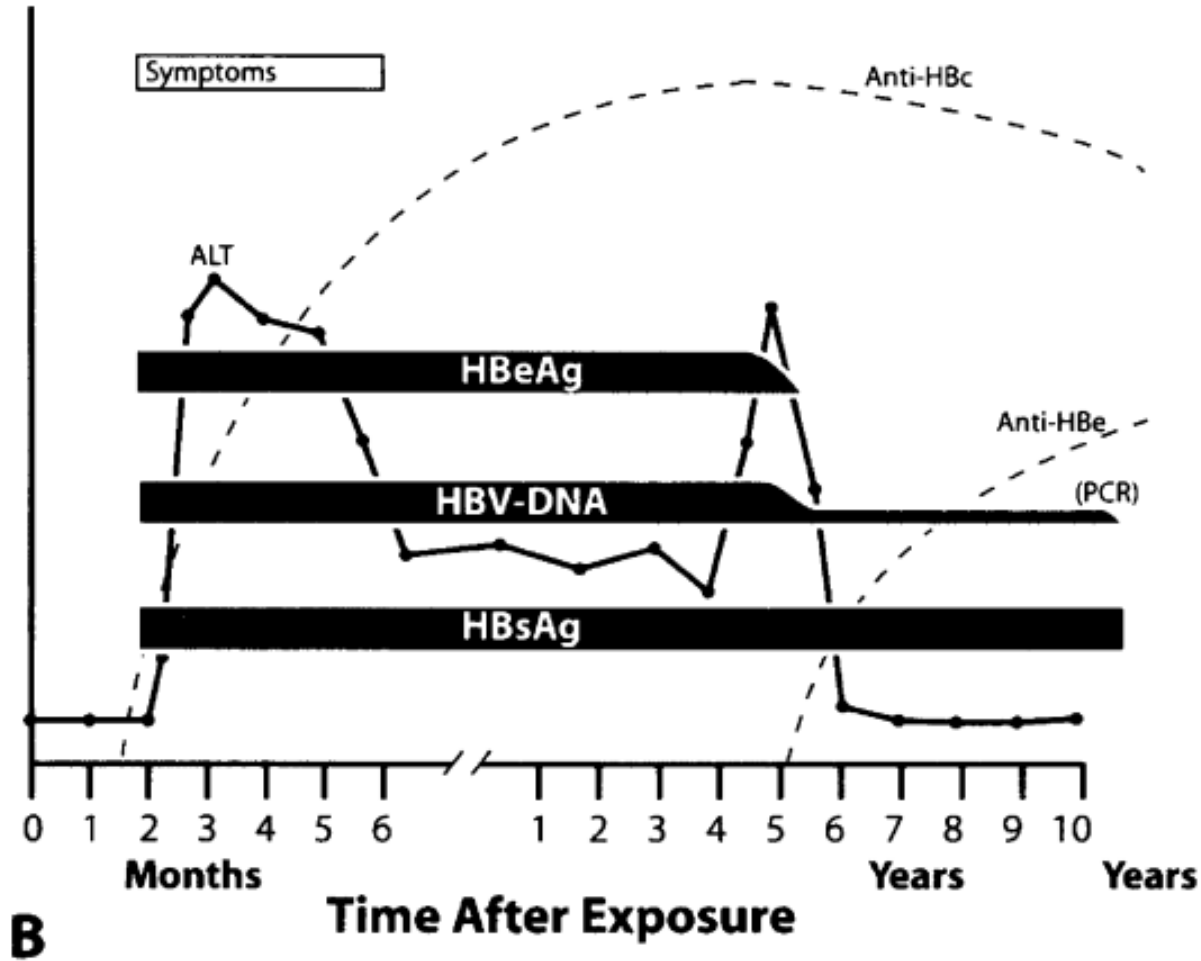


Figure 4. Patterns of Serologic and Molecular Markers in HBV Infection.

Typical levels of alanine aminotransferase (ALT), HBV DNA, hepatitis B s and e antigens (HBsAg and HBeAg), and anti-HBc, anti-HBe, and anti-HBs antibodies are shown in acute self-limited HBV infection (Panel A) and in infections that become chronic (Panel B). The intensity of the responses, as a function of time after infection, is indicated schematically. HBV DNA may persist for many years after the resolution of acute self-limited infection.⁴²



HBV serology

- **HBsAg positivity (hallmark):**
 - Active **replicating virus** → **acute or chronic** HBV.
- **HBsAb:**
 - It develops after HBV **recovery** (HBsAg disappearance) **OR** **vaccination**.
- **HBcAg:**
 - **Not detected in the serum.**
 - **HBc IgM** = active **replicating virus**.
 - **HBc IgG** (long-life and weak) = develop after **HBV recovery** **OR** **chronic hepatitis**.
- **HBeAg:**
 - **Replicating** infective **virus** → **correlate** with **DNA**.
- **HBeAb:**
 - It develops after **HBV recovery** **OR** **chronic hepatitis**.

HBsAg

- HBsAg is the hallmark for HBV diagnosis.
- Acute hepatitis: detected after 1-10 weeks.
- Chronic hepatitis: persistent HBsAg > 6 months.
- Qualitative HBsAg (qHBsAg):
 - Reflection of HBV replication, HBV DNA and cccDNA.
 - HBV carrier: qHBsAg <1000 IU/mL and HBV DNA ≤2000 IU/mL.
 - Increasing qHBsAg: ↑ risk of cirrhosis and HCC.
 - Guide to the IFN therapy^{EASL}.
 - If qHBsAg <1000 IU/mL in HBeAg -ve patients → impending HBsAg clearance.
 - AASLD: not recommended for routine testing and follow up of patients.

HBsAb (anti-HBsAg)

- It is usually **appearing with disappearance of HBsAg** → sign of recovery.
- **HBV vaccination:** normal vaccinated subjects → only +ve HBsAb.
- **A epitope mutations:**
 - HBsAg has **general epitope "a"** and other **sub epitopes** like "d", "y", "w" or "r" constituting the four major serotypes—"adr", "ayr", "adw", and "ayw".
 - **A epitope mutations** → **virus escape from antibodies** → inactive vaccine and HBIG.

HBcAg

- It is **only detected in the liver.**

HBc Ig M & G (anti-HBc Ab)

- **Total anti-HBc Ab** = IgM + IgG.
- **HBc IgM** is a marker of **replicating virus** (acute infection, exacerbation, reactivation).
- **Window phase**: it is the **time from disappearance of HBsAg and appearance of HBsAb** where the only clue for infection is positive anti HBc IgM.
- **HBc IgG**: a marker of acute hepatitis recovery **OR** chronic hepatitis **OR** occult HBV.
- **Routine HBc IgG assay** is **not recommended** ^{AASLD}.

Isolated core antibodies

- **Definition:** HBc IgG +ve, HBsAg –ve and HBsAb –ve.
- **Prevalence:** 10% in endemic areas.
- **Explanation (scenarios):**
 - **Normal subject:** false positive test in low endemic areas.
 - **Resolved acute HBV in infancy** and by the time the HBsAb titer waned → ↓ HCC risk.
 - **Resolved long standing chronic hepatitis** → ↑ HCC risk.
 - **Window phase** of acute hepatitis B but you measured total anti-HBc Ab.
 - **Mutated HBsAg** → false assay negative HBsAg despite chronic infection.
 - **Co-infection:** HCV and HIV → suppress HBV replication.

Isolated core antibodies

- Indication of assay:

- Against routine assay^{AASLD}.
- Before blood donation and liver transplantation.
- Before HCV, HIV treatment or starting immunosuppressive drugs or chemotherapy → high risk of HBV reactivation.

- Indication of HBV vaccination:

- Low endemic areas → start vaccination.
- High endemic areas → against vaccination.

- Isolated anti-HBc

- No risk of sexual or close contact transmission.

HBeAg

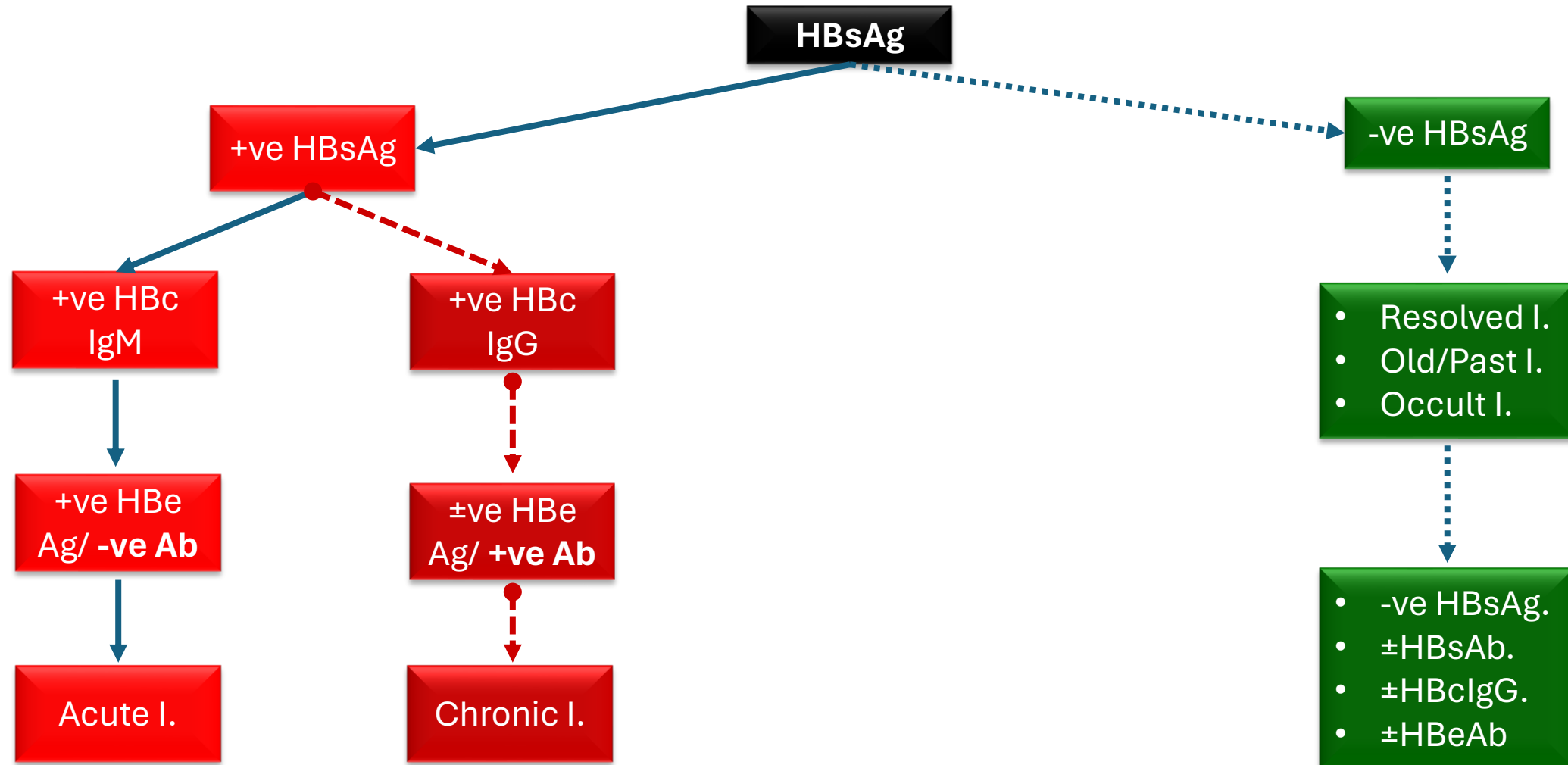
- HBeAg is a marker of replication and infectivity.
- HBeAg correlate with the HBV DNA.
- HBeAg marks chronic hepatitis B.

HBeAb

- HBeAb marks:
 - Recovery from acute infection (seroconversion from HBeAg +ve to HBeAb +ve).
 - It may persist for years.

Test Your self

HBV serology



HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA	
-	-	-	-	-	-	-	Naïve → vaccinate

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA	
-	-	-	-	+	-	-	Vaccinated

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA
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+	+	+		-		+
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Early phase AH

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA
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-	-	+		-	+	±
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Window phase AH

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA
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-	-	-	+	+	+	-
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Recovery of AH

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA
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+	+	-	+	-	-	+
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HBeAg +ve hepatitis

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA
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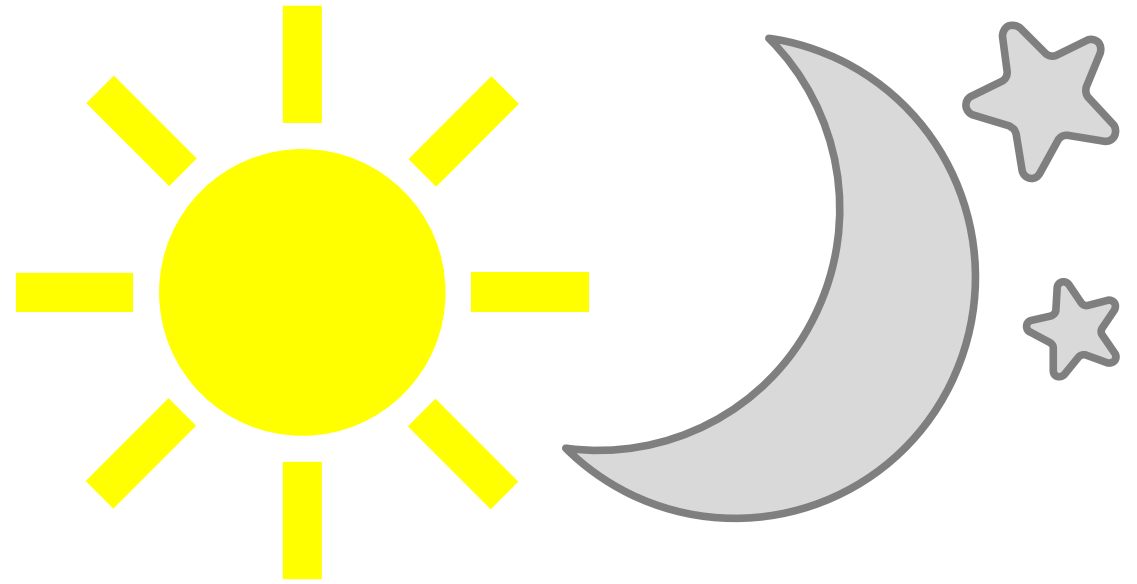
+	-	-	+	-	+	-
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Carrier

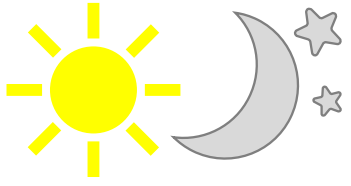
HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA	
+	-	-	+	-	+	+	HBeAg -ve hepatitis

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA	
+	±	±	+	-	±	±	Exacerbation

HBsAg	HBeAg	HBc IgM	HBc IgG	HBsAb	HBeAb	DNA	
-	-	-	-	-	-	-	Naïve → vaccinate
-	-	-	-	+	-	-	Vaccinated
+	+	+	-	-	-	+	Early phase AH
-	-	+	-	-	+	±	Window phase AH
-	-	-	+	+	+	-	Recovery of AH
+	+	-	+	-	-	+	HBeAg +ve hepatitis
+	-	-	+	-	+	-	Carrier
+	-	-	+	-	+	+	HBeAg -ve hepatitis
+	±	±	+	-	±	±	Exacerbation

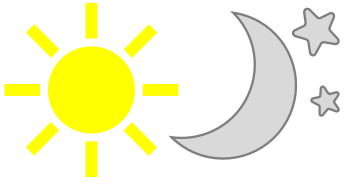


Discordant serologic profiles



HBsAg Positive and Anti-HBs Positive

- **Incidence:** 2.8-5.8%.
- **Effect:**
 - **Controversial** → ↑ risk of fibrosis, cirrhosis ±HCC.
- **Mechanism of discordance:**
 - **Unknown.**
 - **Immune escape mutations** in “a” determinant region (pre-S/S gene) → allow viral replication → escape the neutralizing effect of anti-HBs.
 - Heterologous serotype specific anti-HBs → **do not target the circulating HBsAg proteins.**
 - **Reinfection or superinfection** with the **inability of preexisting antibodies to neutralize a newly encountered strain of the virus.**
 - **New assay** is **against false positivity.**



HBsAg Negative and DNA Positive

- Occult HBV infection (OBI):

- -ve HBsAg + low-level HBV DNA replication + +ve anti-HBcAg ± anti-HBsAg.

- Incidence:

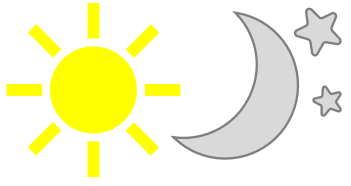
- 1-3% of blood donors.
 - ↑ association with HCC, cirrhosis, HBV coinfections.

- Clinical effect:

- Controversial ↑ fibrosis, cirrhosis, and HCC.
 - ↑ risk of HBV reactivation.

- Mechanism of discordance:

- **Assay sensitivity:** 50% of -ve HBsAg with standard lower limit of detection are positive with decreasing the cutoff of assay.
 - **Mutations in the HBV S genes and a determinant region in HBV S gene** → altered HBsAg not measured with routine assay (vaccine escape mutants).



HBeAg Positive and Anti-HBe Positive

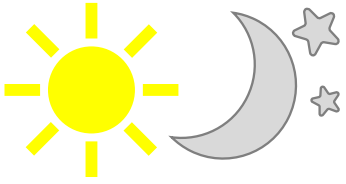
- **Normally:**

- **Loss of** circulating HBeAg by precore (PC) and/or basal core promotor (BCP) mutations → **emergence** of HBe antibodies (anti-HBe).
- **Normally** HBeAg is formed in huge quantities and few antibodies are formed that unit with antigen → assay detect antigen only.

- **Incidence:** rare.

- **Mechanism of discordance:**

- ↓ **cccDNA transcription without precore mutation** → ↓ antigen level \leq antibody level.
- **Flip floppers:** HBeAg and anti-HBe flip-flop back and forth for time then HBeAg loss and anti-HBe development (transition to HBeAg-negative disease).
- **Decreased affinity** between HBeAg and anti-HBe.



HBsAg Positive and Anti-HBc Negative

- **Chronic HBV** = +ve HBsAg and +ve HBc IgG (for life).
- **Incidence:** rare.
- **Mechanism of discordance:**
 - **Immunodeficiency syndrome and malignancies** → affect B and plasma cells, T cell exhaustion → ↓ **antibody formation**.
 - **Patient cleared HBsAg (recovery)** → positive HBcIgG → **neo-immunodeficiency** → HBV reactivation → +ve HBsAg and -ve HBcIgG.
 - **B-cell-depleting therapies** (rituximab).
 - **HBcAg/anti-HBc immune complexes due to excess serum HBcAg** → **undetectable levels** with commercially available tests.
 - **Vertical transmission:**
 - HBeAg can traverse the placenta from mother to fetus, leading to tolerance in the infant to HBeAg → **antigenically very similar to HBcAg** → initial failure to produce antibodies to HBcAg.
 - With maturation of the infant immune system during early infancy, however, the typical profile (HBsAg-positive/anti-HBc-positive) usually emerges.
 - **Nucleotide sequence deletions in the core gene** have been shown **to affect antigen recognition by immune cells**.

Key characteristics of discordant serologic profiles observed during hepatitis B virus infection

HBsAg – and HBV DNA +	<ul style="list-style-type: none"> 0.1%–3% of HBsAg – /anti-HBc + individuals 	<ul style="list-style-type: none"> Occult hepatitis S gene mutations Low assay sensitivity 	<ul style="list-style-type: none"> Antiviral therapy not recommended except to prevent HBV reactivation with potent immunosuppression
HBsAg + and anti-HBs +	<ul style="list-style-type: none"> 2.8%–5.8% of HBsAg-positive individuals 	<ul style="list-style-type: none"> Immune escape S gene mutations Heterologous HBsAg serotypes HBV superinfection 	<ul style="list-style-type: none"> Dual positivity does not affect disease course or management. Monitored and treated as per standard for chronic HBV infection
HBeAg+ and anti-HBe +	<ul style="list-style-type: none"> Common but transient 	<ul style="list-style-type: none"> precore (PC) and/or basal core promotor (BCP) mutations Transitional phase to HBeAg negative state Low assay sensitivity 	<ul style="list-style-type: none"> Management determined by disease phase, levels of viral replication, and liver histology
HBsAg + and anti-HBc –	<ul style="list-style-type: none"> 0.1% of HBsAg-positive individuals 	<ul style="list-style-type: none"> Immunodeficiency of B-cell/T-cell response Vertical transmission (transient) Core gene deletions 	<ul style="list-style-type: none"> May be indicative of immunodeficiency, but unlikely to affect disease course or alter management

Thanks

