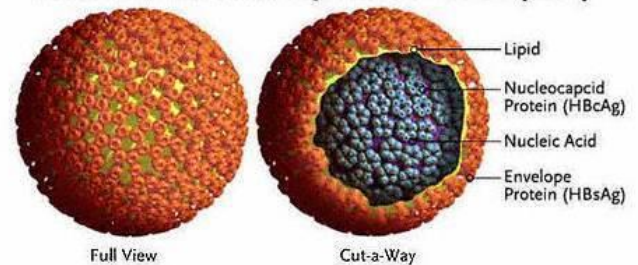


## HEPATITIS B VIRUS

**Partial dsDNA and Enveloped** : within the envelope we have (HBsAg) on the surface .

Also we have Nucleic Acid inside (which is partial ds DNA) and the Nucleocapsid protein –which is the core of the virus- and two antigens in the core : (HBcAg) associated with it (HBeAg)

Model of Human Hepatitis B Virus (HBV)



## PROPERTIES OF HBV

- Member of the Hepadnavirus : the nomenclature is came from its present in the Hepatocyte DNA and it's a DNA Virus !
- Enveloped, **partially double-stranded DNA viruses**, smallest DNA virus as a GENOME!
- Replication involves a **reverse transcriptase**
- **Endemic** in the human population and **Hyperendemic** in many parts of the world. ( 1/3 from the population had been infected with the virus and now we have more than 400 millions living with CHRONIC infection !! )
- **8 genotypes (A-H)**, **type D** in middle east ( this variation occurs at the genome level and there is 8% difference between genotype and the other , Genotype D is more prevalent in our World /**Jordan** )
- **4 serotypes** these four serotypes differ in there (HBsAg)
- **CAN NOT Be grown in CELL Culture !**

## HBV : STRUCTURE

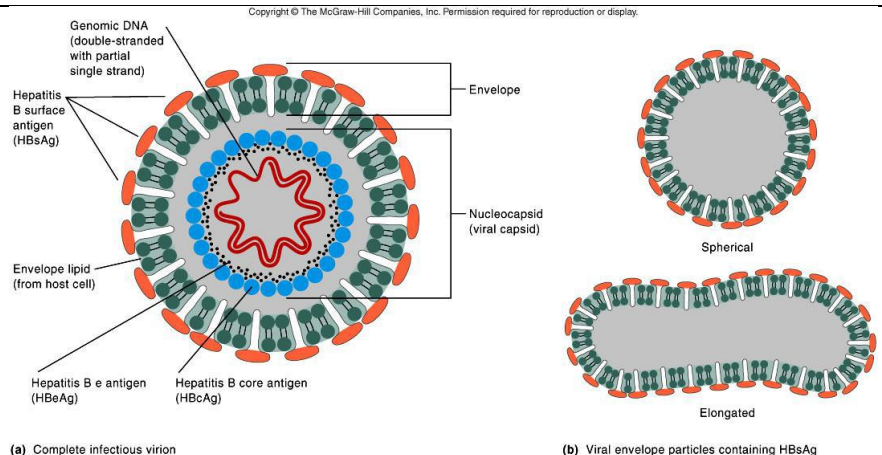
We have two structures here !

### A) Complete infectious Virion

-called the DANE particle

### B) Viral Envelope particle containing HBsAg

-which don't have the core or the Nucleocapsid , only have the surface Ag .  
- Two shapes : spheres and filaments  
-also this form present in the excess of the DANE particles!



- ✓ For the genome we have complete one and Partial strand, the **complete** one is the negative sense strand and the **partial** one is the positive sense strand!

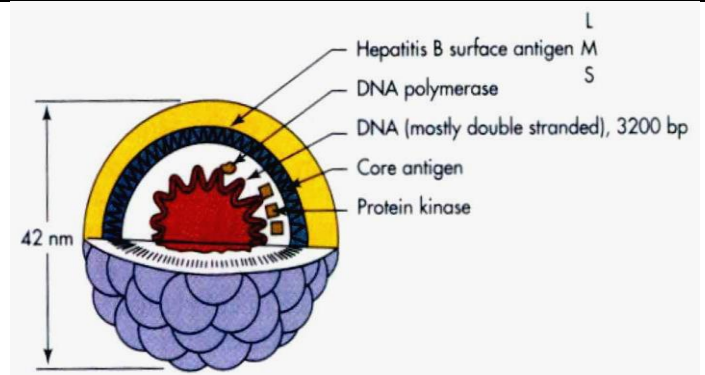
- ✓ Within the nucleocapsid we have the (**polymerase-gene: P-gene**): RNase H for reverse transcriptase , RNA-dependent DNA polymerase and DNA-dependent DNA polymerase, this (P-gene) is one of the reading frames derived from the +ve partial strand!

The core-Ag associated with the e-Ag.

Core antigens located in the center (nucleocapsid)

- \* Core antigen (HBcAg)
- \* e antigen (HBeAg)- an **indicator of transmissibility** (minor component of the core- antigenically distinct from HBcAg)

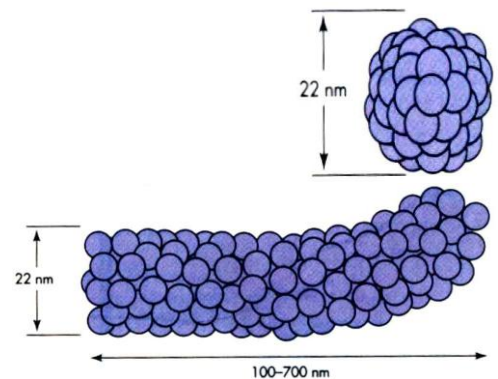
We have the (HBsAg) : it has three initiation codons!  
And you might see them as ( small – medium – Large )



- ✓ **HBsAg** = surface (coat) protein ( **4 phenotypes** : adw, adr, ayw and ayr)
- HBcAg** = inner core protein (a **single serotype**)
- HBeAg** = secreted protein; function unknown

### Decoy particles

- 1- HBsAg-containing particles are released into the serum of infected people and outnumber the actual virions.
- 2- They are immunogenic and were processed into the first commercial vaccine against HBV.
- 3- **spheres and filaments** other forms- **no DNA** in these forms so they are **not infectious** (composed of surface antigen)- these forms outnumber the actual virions



There are **4 open reading frames** derived from the same strand (the incomplete + strand)

- ✚ **S** - the **3 polypeptides of the surface antigen (preS1, preS2 and S** - produced from alternative translation start sites , and these forms the **small , medium and large** HBSAg ! also plays role in the attachment of the virus to receptors on the target cell .
- ✚ **C** - **Core protein**: HBcAg, HBeAg: **glycoprotein** secreted from infected cells.
- ✚ **P** - **The polymerase**: RNase H, RNA-dependent DNA polymerase and DNA-dependent DNA polymerase.
- ✚ **X** - **A transactivator** of viral transcription (and cellular genes). HBx is conserved in all mammalian (but not avian) hepadnaviruses. Though not essential in transfected cells, it is required for infection in vivo, *the function of this transactivator is not clearly known but it's associated with cancers in the LIVER!*

Pls check slide 8 :D

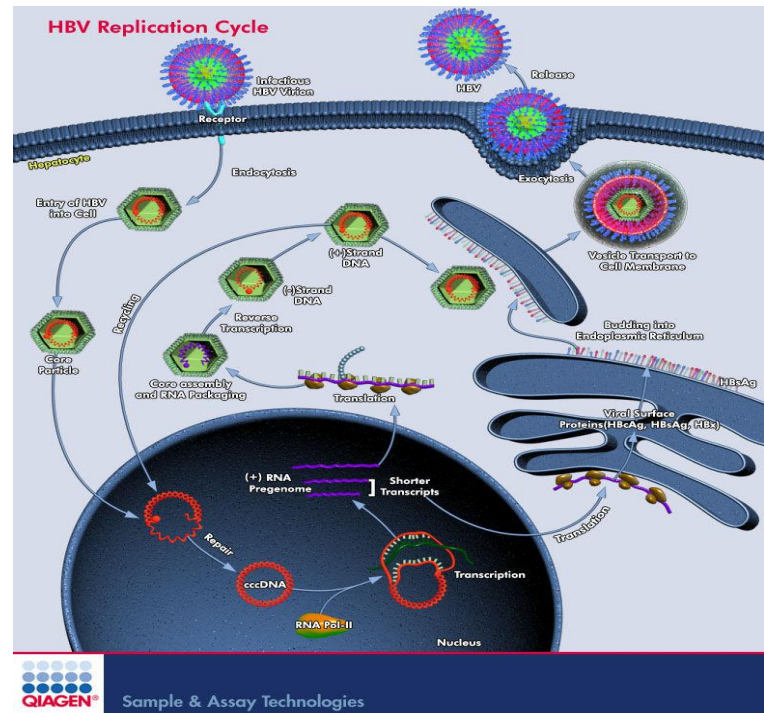
## HBV: REPLICATION

Sum:

Attachment of the surface antigen of the virus to receptors on the target cell, then it enters by a mechanism called **Receptor Mediated Endocytosis**, then it is released into the cytoplasm and uncoated, then the partial dsDNA enters into the nucleus.

The completion of the partial dsDNA into Covalently Closed Circular DNA (cccDNA) occurs via **the DNA-dependant DNA-Pol.** of the virus, followed by **RNA Pol.II of the host cell** which transcribes the cccDNA! That will give us m-RNA( +ve sense), then it will go to cytoplasm to ribosome (translation) and gives us **INDIVIDUAL** proteins, these proteins give us the **early** proteins: enzymes which is necessary for the replication of the virus and **Late** proteins later!

The **Reverse Transcriptase** will convert the m-RNA (which is the +ve sense RNA) into **-ve strand DNA** (complete one). After that the m-RNA (which still bound to the -ssDNA) will dissociate, destroyed by the RNase H and after that the **DNA-dependant DNA Pol.** binds to -ve strand and forms the +ve partial strand (which will be with the complete one now).



After that **assembly** occurs in ER and Golgi, **acquires a membrane from the ER**, and then exit the cell by **EXOCYTOSIS**. **All the Replication steps occur inside the nucleus.**

In **general** the integration does not occur but in cases of Hepatocellular Carcinoma you may see integration while the replication cycle is occurring!

## EPIDEMIOLOGY

350,000,000 carriers worldwide - the carrier rate can exceed 10% (at least know that there is Chronic Carrier)

The infectivity of HBV is 50-100 times more than that of HIV (Highly Infectious)

15 to 25% of chronically infected patients will die from chronic liver disease (cirrhosis or HepatoCellular Carcinoma-HCC)

If the mother is Hepatitis B active then the percentage of transmitting the infection to the fetus is 90-95%!

## HBV: MODES OF TRANSMISSION

- ❖ Parenteral - IV drug abusers, health workers are at increased risk.
- ❖ Sexual (50%)- sex workers and homosexuals are particular at risk.
- ❖ Perinatal (**Vertical**) – mother → infant. Does not cross placenta / it can occur due to presence of the virus in the body secretion! 1-2% occurs through PLACENTAL route! and 98-99% during Delivery)

**HCC** associated with high virus load and integrated viral infections; activate cellular oncogene, know that the major affinity for the HBV for the Hepatocyte!



Concentration of Hepatitis B Virus →  
in Various Body Fluids

**High** – blood , serum , wound exudates

**Moderate** – semen , vaginal fluid , Saliva

**Low**- urine, feces ,sweat ,tears ,Breast milk

After birth the infected baby might be Asymptomatic but after a while, they will have all the consequences of the chronic carrier of HBV!

### High-risk groups for HBV infection

- People from endemic regions
- Babies of mothers with chronic HBV
- Intravenous drug abusers
- People with multiple sex partners
- Hemophiliacs and other patients requiring blood and blood product treatments
- Health care personnel who have contact with blood
- Residents and staff members of institutions for the mentally retarded

## PATHOGENESIS & IMMUNITY

- Virus enters hepatocytes via **blood** (Mostly) – **Albumin** carries the virus into Hepatocytes or chaperones !
- **HBsAg** found in blood, semen and cervical fluid
- **1ul** of infectious blood has produced infection (the infectious dose is small)
- Serum sickness-like **rash** and **arthritis** may precede symptoms ( due to the deposition of the Ag-Ab complexes in joints) ; immune complexes and complement activation
- **Immune response (cytotoxic T cell)** to viral antigens expressed on hepatocyte cell surface responsible for clinical syndrome ( Ag of the HBV will going to bind MHC type I , they're going to be presented on the surface of the infected cell , they are going to be recognized by the CD8 , the CD8 will lead to lysis and death of the infected cell ! )
- 5-10% becomes chronic carriers (**HBsAg last for longer than 6 months**: that means if we do serological test after 6 months and see that HBsAg still +ve that means the Pt now is a chronic Carrier)
- Higher rate of hepatocellular carcinoma chronic carriers, especially those who are “e” antigen positive
- **Hepatitis B surface antibody** likely confers lifelong immunity (**anti-HBs Ag : recovery** )
- **Hepatitis B e Ab** indicates low transmissibility(no longer replication of the virus and there is a clearance of the virus)

SUM :

In chronic infection , there is rounds of damage to the liver cells as a result of Cytotoxic T cells as a result of Inflammation this will lead to Necrosis and as result will lead to Fibrosis and with those cycles being continued , Cirrheses of the liver might occur and might get into liver failure or Carcinoma !

- ✓ Incubation period from two to three months

- ✓ 90-95% of Adults would clear the virus spontaneously ( that mean will recover completely) onlt 5-10 % may develop into Chronic carrier ( Except for newborn : 90-95% will be chronic carriers)

## CLINICAL FEATURES

- ✓ Gradual onset of fatigue, loss of appetite, nausea, pain and fullness in the right upper abdominal quadrant (non specific symptoms)
- ✓ Early in the disease the pt. might have joint pain and rash ( due to Ag-Ab complexes)
- ✓ Liver damage associated with cholestasis, and hence clay-colored stool, dark urine and jaundice. Symptoms may persist for months before resolving
- ✓ Anicteric disease and asymptomatic infection may occur
- ✓ Infection to disease ratio 3:1 ( for every three infected one with symptoms)

CHECK SLIDE 18 pls

## DIAGNOSIS

A battery of serological tests are used for the diagnosis of acute and chronic hepatitis B infection. Also PCR

- ✓ **HBsAg** - used as a general marker of **infection ( can be acute or chronic)**
- ✓ **HBsAb** - used to document recovery and/or immunity to HBV infection. ( Past infection)
- ✓ **anti-HBc IgM** - marker of acute infection.
- ✓ **anti-HBcIgG** - past or chronic infection.
- ✓ **HBeAg** - indicates active replication of virus and therefore infectiveness.
- ✓ **Anti-HBe** - virus no longer replicating. However, the patient can still be positive for HBsAg which is made by integrated HBV.
- ✓ **HBV-DNA** - indicates active replication of virus, **more accurate than HBeAg** especially in cases of escape mutants. Used mainly for monitoring response to therapy.

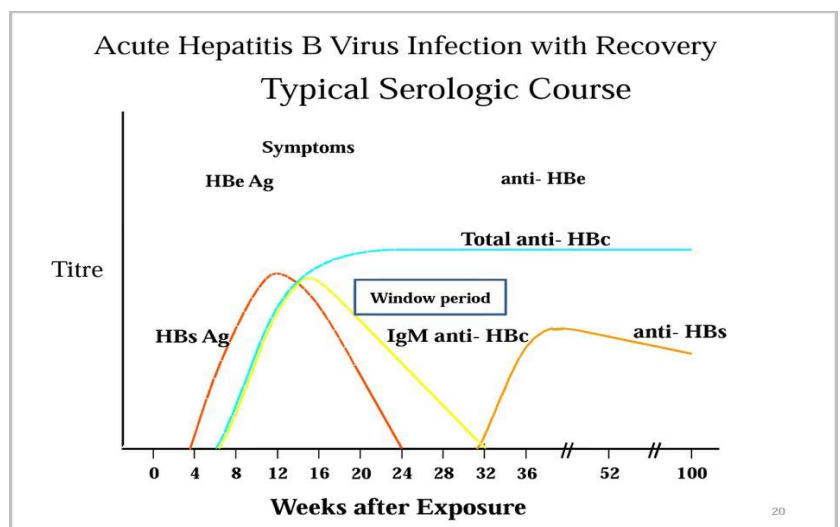
The **First** marker to emerge is HBsAg  
**After** that we have Anti-HBc

### Window Period :

HBsAg –ve

Anti-HBs –ve

Anti-Core IgM +ve ( the only positive)





**We have here scenarios :**

<ul style="list-style-type: none"> <li>❖ HBsAg –ve</li> <li>❖ Anti-HBc –ve</li> <li>❖ Anti-HBs –ve</li> </ul> <p><i>No Infection and the Pt is susceptible to HBV infection</i></p>	<ul style="list-style-type: none"> <li>❖ HBsAg +ve</li> <li>❖ Anti-HBc +ve (IgM)</li> <li>❖ Anti-HBs –ve</li> </ul> <p><i>Acute Infection</i></p>
<ul style="list-style-type: none"> <li>❖ HBsAg –ve</li> <li>❖ Anti-HBc +ve (Total)</li> <li>❖ Anti-HBs +ve</li> </ul> <p><i>Immunity (cuz of Anti-HBs ) ; immunity due to previous infection (Natural)</i></p>	<ul style="list-style-type: none"> <li>❖ HBsAg +ve</li> <li>❖ Anti-HBc +ve (IgG)</li> <li>❖ IgM HBc –ve</li> <li>❖ Anti-HBs –ve</li> </ul> <p><i>Chronic Infection, <u>Anti-HBs –ve still there is replication of the virus !</u></i></p>
<ul style="list-style-type: none"> <li>❖ HBsAg –ve</li> <li>❖ Anti-HBc –ve</li> <li>❖ Anti-HBs +ve</li> </ul> <p><i>Immunity ; acquired the immunity from Vaccination , the vaccine only surface Ag :P</i></p>	<ul style="list-style-type: none"> <li>❖ HBsAg –ve</li> <li>❖ Anti-HBc +ve (IgM)</li> <li>❖ Anti-HBs –ve</li> </ul> <p><i>WINDOW Period</i></p>

**Note :** HBsAg if it is Positive and the Anti-HBs negative then we look at the Anti-HBc , now if the IgM HBc is negative then its is Chronic Infection ( then IgG Present) and if it is Positive then it is Acute Infection . ( I hope tkoon clear! hay el 5al6at el se7reyyeh :P )

## TREATMENT

- I. **Interferon** - for HBeAg +ve carriers with chronic active hepatitis. Response rate is 30 to 40%.
  - alpha-interferon 2b (original)
  - alpha-interferon 2a (**newer**, claims to be more efficacious and efficient)

Pegylated interferons are modified interferons to make pts life much easier since it's given once a week instead of once daily or 3-4 times a week
- II. **Lamivudine** - a nucleoside analogue reverse transcriptase inhibitor
- III. **Adefovir**
- IV. **Entecavir**

Successful response to treatment will result in the disappearance of HBsAg, HBV-DNA, and seroconversion to anti-HBeAg and anti HBsAg.( The way we see how is the Pt getting better or not by monitoring these things)

## PREVENTION

- 🚦 **Vaccination : Recombinant vaccine** , Vaccine can be given to those who are at increased risk of HBV infection such as health care workers. It is also given routinely to neonates as universal vaccination in many countries.

✚ **Hepatitis B Immunoglobulin** - HBIG may be used to protect persons who are exposed to hepatitis B. It is particularly efficacious within 48 hours of the incident.

**Who need to be given Ig** : who exposed to HBV ( health worker ) , you give him Ig immediately then check anti HBsAg level to determine whether it's protective or not , if not, then he has to take the vaccine in addition to Ig ! , also Newborns of mothers with Active Hepatitis B you give Igs then start vaccination !

**In developed countries HBV vaccination starts directly after birth (first dose)**

✚ **Other measures** - screening of blood donors, blood and body fluid precautions.

In Jordan (National Vaccination for HBV)

❖ **Infant 3-4-5 Months!**

**Adults are given the vaccine at 0, 1, 6 months (first dose then after 1 month a second dose then after 5 months a third dose)**

Vaccine recommended in :

- ❖ All those aged 0-18
- ❖ Those at high risk

## HEPATITIS D (DELTA) VIRUS

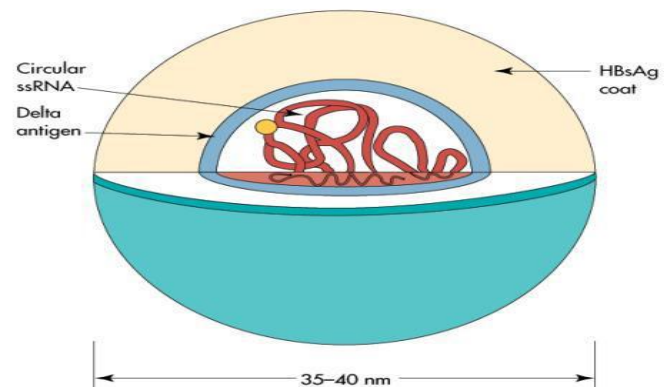
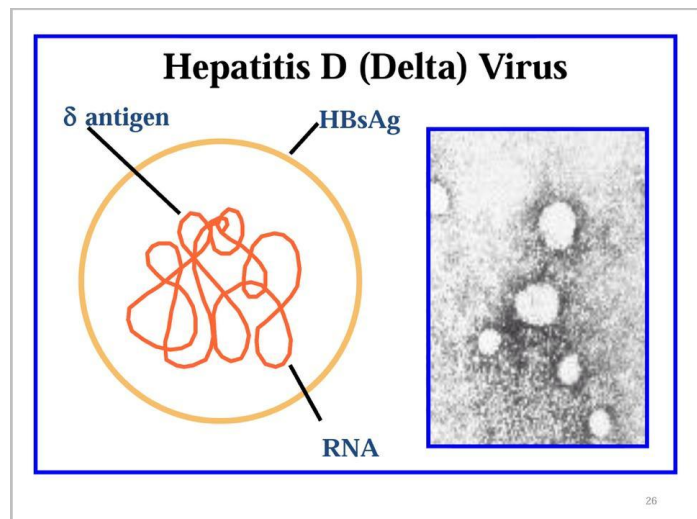
**VIRION**: spherical, 36-38 nm, HBV capsid, HDV nucleoprotein

**Satellite virus** : replicates *only* in the presence of HBV (It's incapable of replicating without HBV as Co-infection or super Infection! It's very Important for the Assembly , It will not occur without Hepatitis B Antigens )

**NUCLEIC ACID**: **(-) ss RNA**, circular

## PROPERTIES OF HDV

- ✓ The delta agent is a defective virus which shows similarities with the **viroids** in plants.
- ✓ The agent consists of a particle 35 nm in diameter consisting of the delta antigen surrounded by an outer coat of HBsAg.
- ✓ The genome of the virus is very small and consists of a single-stranded RNA
- ✓ HDV genome is not capable of encoding an RNA polymerase ( **Unique Feature** ) (although its RNA virus but it's not encoding its own RNA Pol. it requires the RNA Pol. of the cell – which in normal



works on DNA template but here it works in RNA template of the HDV – that's it :P )

- ✓ Replicates in the nucleus using the cellular machinery

## HEPATITIS D VIRUS REPLICATION

- ✓ Lacks RNA polymerase; uses cellular RNA polymerase II to synthesis mRNA and RNA genome in the nucleus
- ✓ It is unique for an RNA virus to replicate in the nucleus without encoding its own RNA polymerase
- ✓ The extensive base-pairing in some regions of the HDV genome allows the cellular RNA polymerase to bind the base-paired RNA sequences, as RNA polymerase binds to DNA sequences, and to transcribe HDV mRNA.

“The genome of the virus contain **extensive base pairing**, the RNA Pol. of the cell can detect these base pairing and start the transcription from there.”

- ✓ The RNA genome further forms a ribozyme structure that allows self-cleaving of the RNA genome to generate mRNA
- ✓ The delta capsid antigens are synthesized and associate with HDV circular RNA genomes followed by acquiring an envelope from endoplasmic reticulum or Golgi apparatus containing HBsAg
- ✓ The presence of HBsAg is essential for assembly of HDV virions

## Modes of Transmission Like HBV

- ✓ Percutaneous exposures
- ✓ Injecting drug use
- ✓ Per mucosal exposures sex contact
- ✓ Vertical transmission can also occur
- ✓

## Hepatitis D - Clinical Features

### Co infection

–Severe acute disease indistinguishable from acute hepatitis A and B, but may manifest as second rise in liver enzymes (AST, ALT). “When HD presents it increases the severity of HB symptoms and associated with a higher level of chronicity”

Dear colleagues :

regarding this point the Dr contradicted his OWN slides during the lecture (he said that a co –infection is associated with a higher level of chronicity while in the slides it's written that it's associated with low risk of chronic infection so in order to stay in the safe side we asked him to clarify this point to us during the next lecture >> if we found that what's written here is wrong we'll correct the information in the next sheet ! فصبراً جميلاً والله المستعان !





### **Super infection**

- Relapse of jaundice (new symptoms)
- Usually develop chronic HDV infection.
- High risk of severe chronic liver disease with 20% mortality.

## **Treatment and Prevention**

Interferon and anti-HBV drugs are not active against hepatitis D

### ❖ **HBV-HDV Co infection**

Pre or post exposure prophylaxis to prevent HBV infection.

### ❖ **HBV-HDV Super infection**

Education to reduce risk behaviors among persons with chronic HBV infection:

- Blood, organ and tissue donation prohibited
- Safe sex
- decrease use of contaminated needles and use of needle safety devices by health care workers

Sorrerrrry for Any Mistake!

Actually everything here u don't need to check the slide except three I mentioned two and the last one is slide No. 35 ! the doctor didn't say anything about it I think its not that important <bas bedde abra2 men 5a6eyyetko >

THANK YOU ALL : D

GooD LucK ;)

*"You can't start the next chapter! If you keep Re-Reading the Last one!!"*