LECTURE XV

Hepatitis viruses. HIV (human immunodeficiency virus) infections, oncogen viruses

Types of Hepatitis

- Hepatitis A – Infectious hepatitis
- Hepatitis B – Serum hepatitis
- Hepatitis C – Non-A non-B or Post transfusion hepatitis
- Hepatitis D – with Hep B
- Hepatitis E - Epidemic hepatitis

Viral hepatitis

By ways of transmission

Hepatitis A

Hepatitis E

Enteral rout of transmission

Hepatitis B

Hepatitis C

Hepatitis D

Parenteral rout of transmission

Hepatitis A

- CLASSIFICATION:

  Group: Group IV ((+) ssRNA)

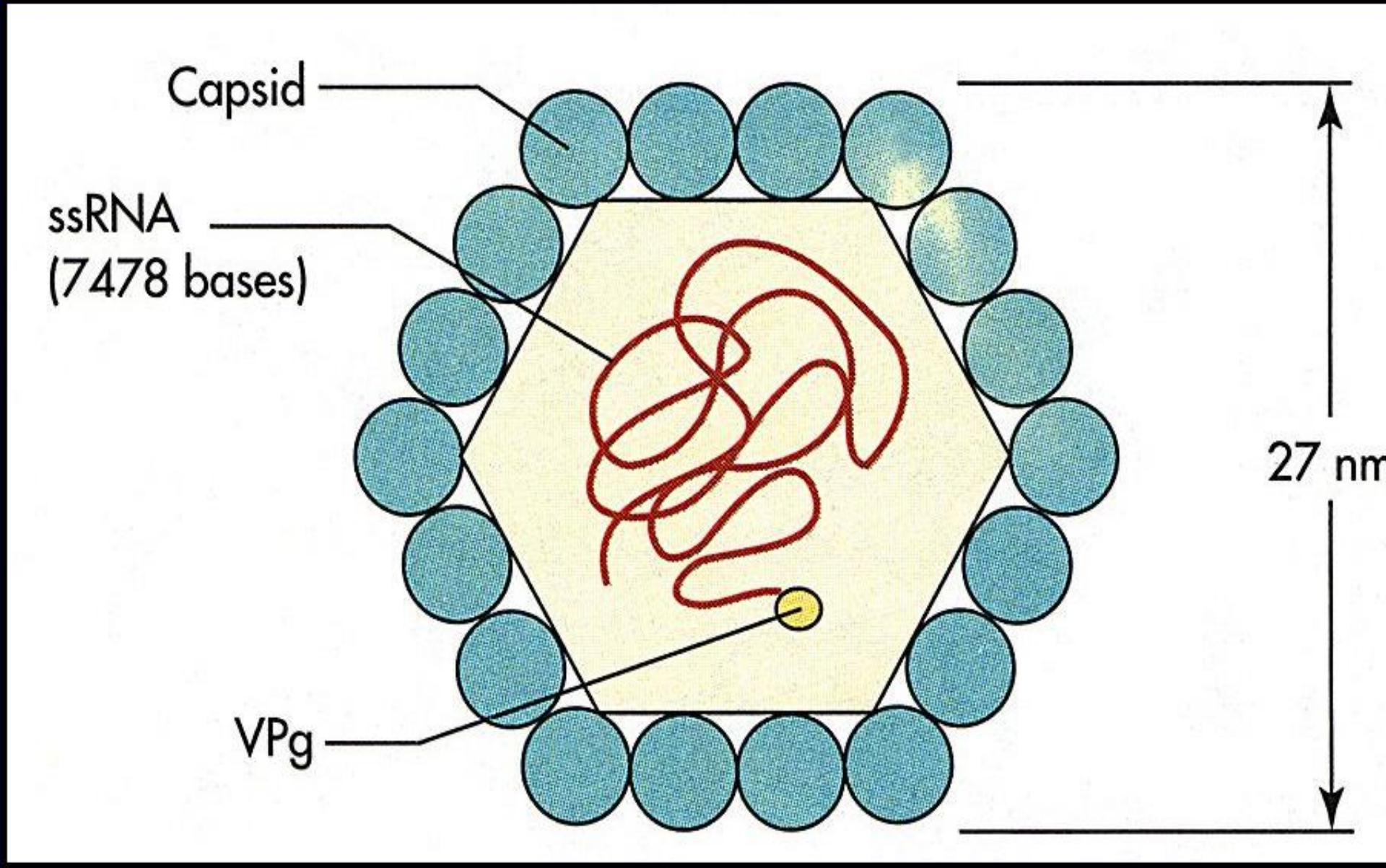
  Family: Picornaviridae

  Genus: Hepatovirus

  Specie: Hepatitis A virus

- Hepatitis A infection does not cause chronic liver disease and is rarely fatal, but it can cause debilitating symptoms.

Hepatitis A Structure



Epidemiology

- Most common Viral Hepatitis
- Source of Infection: **patients**.
- Route of spread : Faeco-oral
- Patient remains infectious 2 weeks prior to & for upto 1 week after onset of illness
- Overcrowding & Poor Sanitation
- No carrier state

CLINICAL FEATURES

- Incubation period 15 – 45 days
- Asymtomatic (90%):
  - Clinically silent
  - Nonspecific: Anorexia
    Nausea
    Vomiting
- Symptomatic (10%):

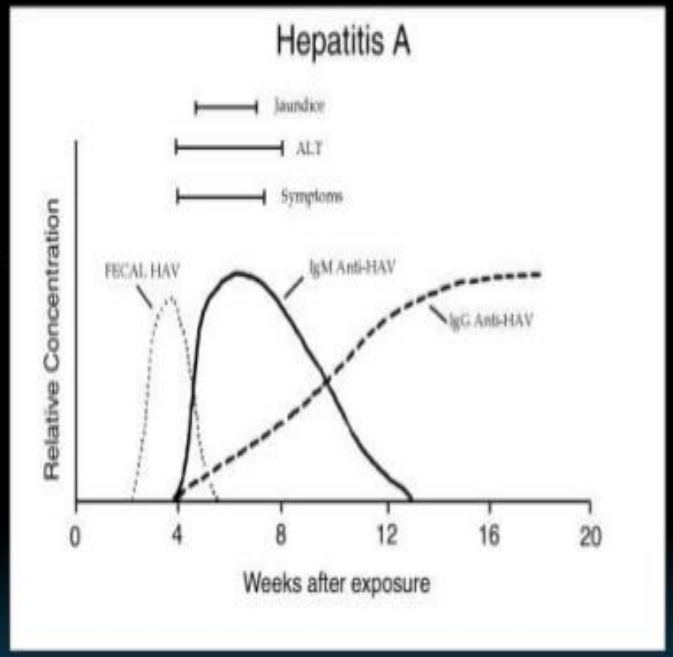
  Jaundice, Dark urine & Pale stools

DIAGNOSIS

- Anti HAV IgM +ve: Acute infection

  Disappears within

  3 months of recovery.



- Anti HAV IgG is of no diagnostic value

  as it persists years after infection.

Prevention

- Vaccine - Formalin inactivated
- 2 doses 0, 6 -12 months
- IM deltoid or gluteal
- Protection period 25 yrs in adult & 15 – 20 yrs in children

HEPATITIS B

DNA virus

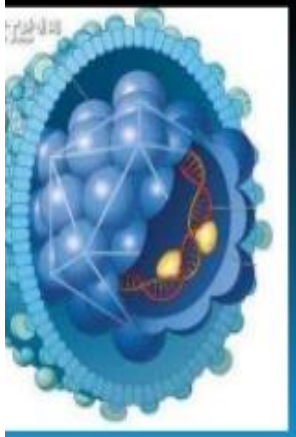
Family- Hepadnaviridae

Genus – Orthohepadnavirus

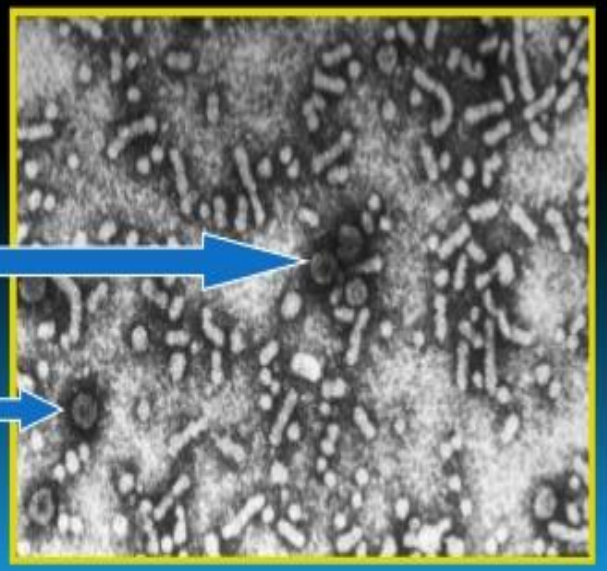
Hepatitis B virus is 30-42 nm in diameter.

Hepatitis B virus (HBV)

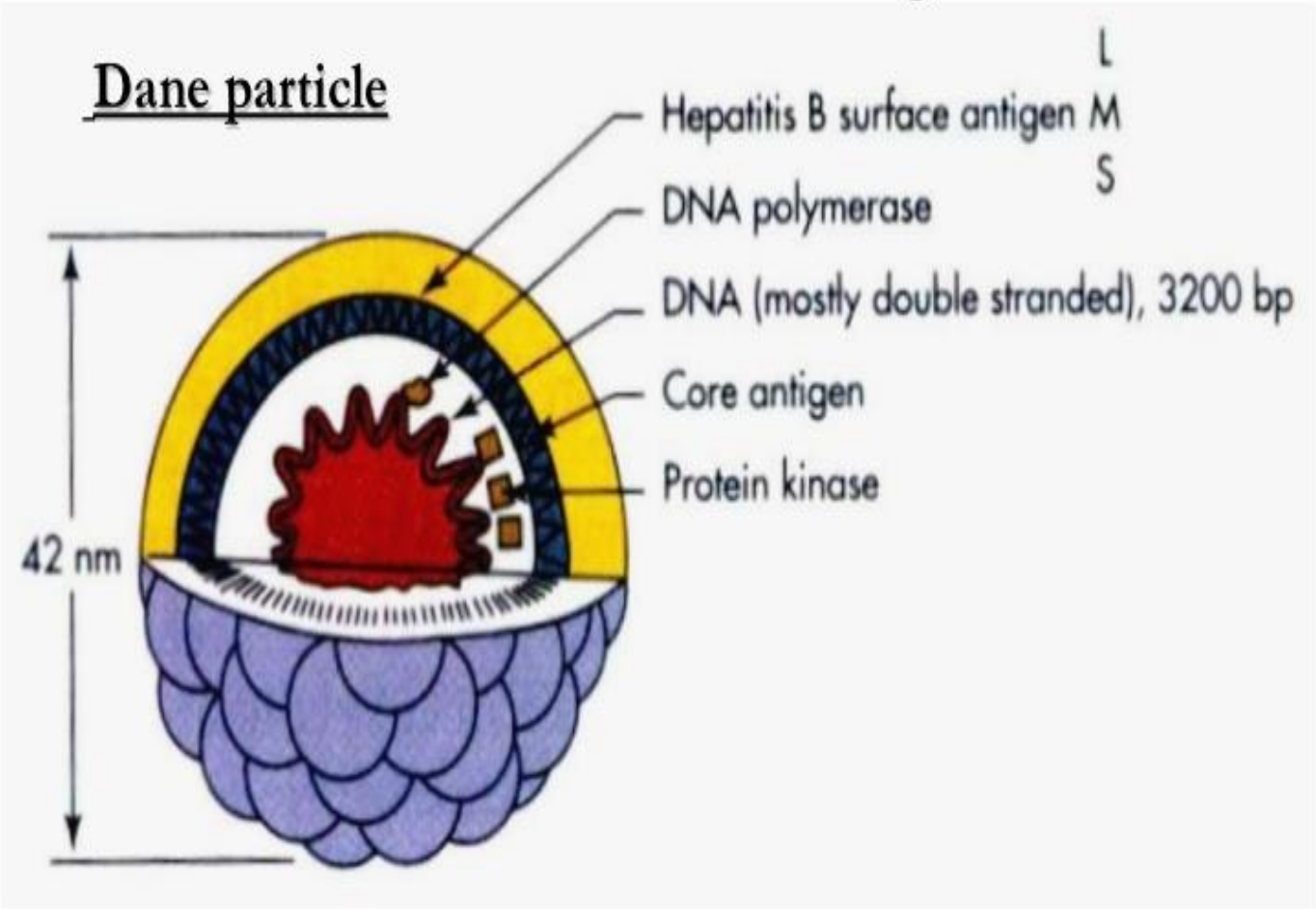
- DNA virus (hepadnavirus).
- Complete virus particle is named Dane-particle,
- Genome is composed of incomplete double-stranded DNA.



Dane's particle



HBV Structure & Antigens



HBsAg = surface (coat) protein (**4 phenotypes : adw, adr, ayw and ayr)**

HBcAg = inner core protein (**a single serotype)**

HBeAg = secreted protein; function unknown

Route of transmission

Body fluids contain viral particles

- Semen
- vaginal secretions
- Blood
- Saliva

Route of transmission

- HORIZONTAL TRANSMISSION
  - Parenteral: Blood & blood products

    Injections

    Acupuncture needles
  - Sexual
- VERTICAL TRANSMISSION
  - Hbs Ag – positive mothers

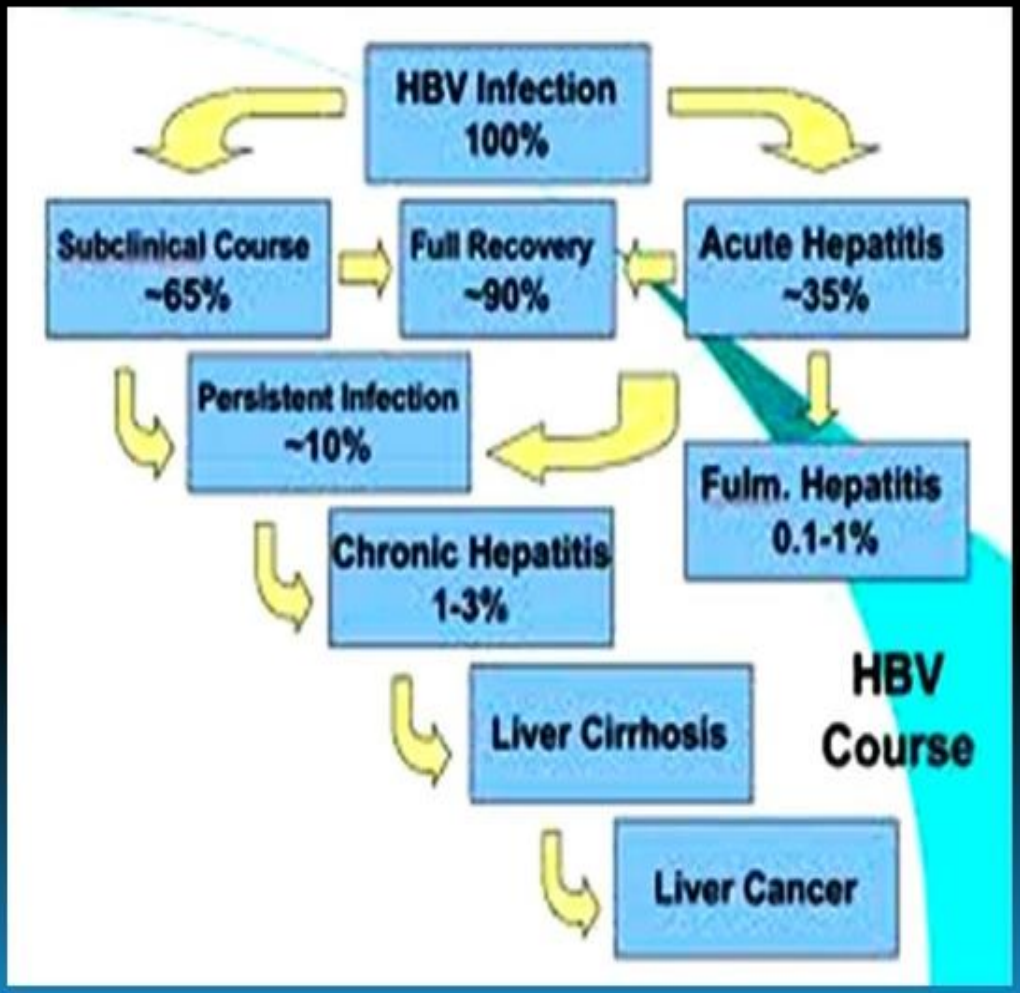
Risk Groups

- Multiple sex partners
- IV drug abusers
- Hemodialysis patients
- Patients requiring repeated blood transfusions
  - Hemophilia
  - Thalassemia
- Health care workers

Factors associated with the severity of hepatitis

- Infecting dose
  - Higher the dose of HBV, shorter is incubation period and more severe hepatitis.
- Age
  - Young age: mild initial hepatitis & more chance of chronicity.
- Immunological status
  - Immunological impaired hosts: Milder initial disease.

CLINICAL COURSE



ACUTE ICTERIC HEPATITIS

- Incubation period - 70 days (30 - 180 days);

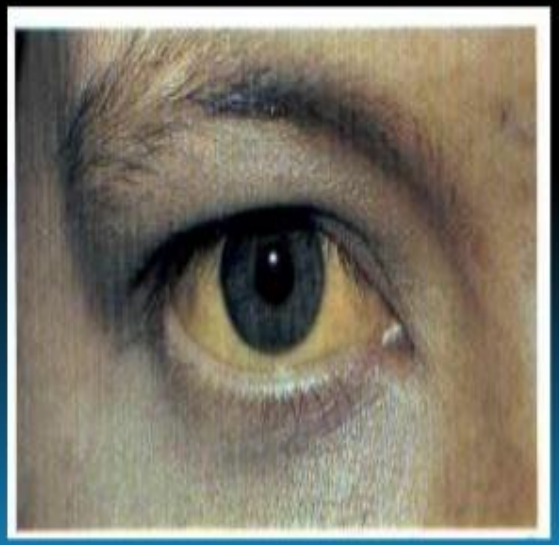
- Four clinical stages:
  - incubation period,
  - prodromal phase (pre-icteric phase),
  - icteric phase
  - convalescence.

Pre-icteric phase

- Symptoms are nonspecific;
  - Moderate fever
  - Headache
  - Malaise and weakness
  - Anorexia, nausea, vomiting
  - A vague, dull, right upper quadrant pain.

Icteric phase

- Clinical features of icteric phase:
  - Symptoms of pre-icteric phase being mild;
  - Jaundice (dark urine, skin and scleral icterus);
  - Stool light or clay colored;
  - Hepatomegaly
  - Liver function abnormalities
    - ALT and AST ⇧
    - Bilirubin (direct & indirect) ⇧



Acute anicteric hepatitis

---No jaundice otherwise similar to acute icteric hepatitis,.

---The symptoms are less severe than that in acute icteric hepatitis.

COMPLICATIONS

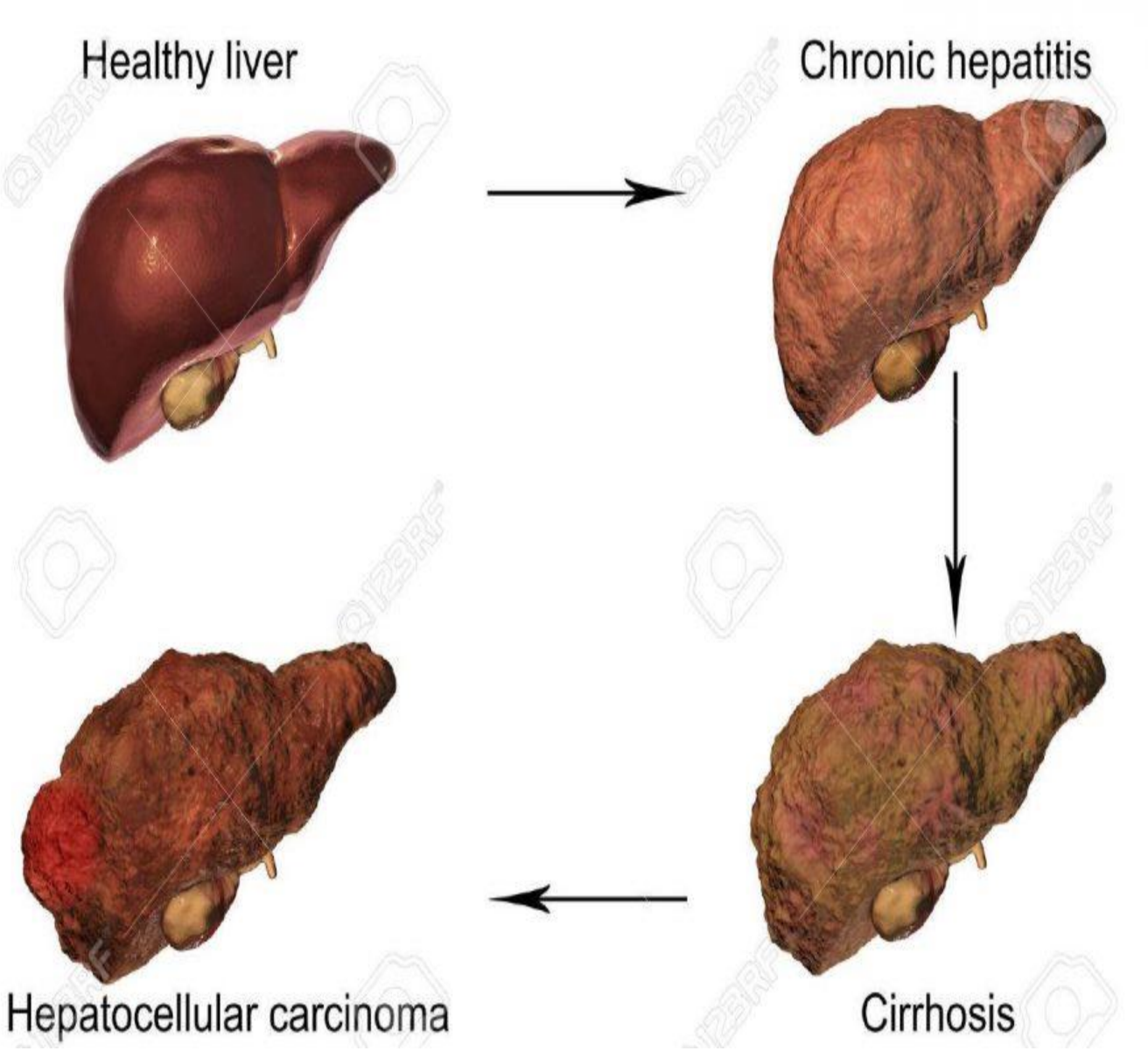
- Fulminant Hepatitis
- Chronic Hepatitis
- Rare complications:
  - Pancreatitis,
  - Myocarditis
  - Atypical pneumonia
  - Aplastic anemia
  - Transverse Myelitis

CHRONIC HEPATITIS

- Chronic viral hepatitis: Inflammatory disease of the liver > 6 months.

CLINICAL FEATURES

- Fatigue, anorexia, abdominal distension, diarrhea are common, but they are fluctuant.
- Hepatomegaly, splenomegaly, hepatic facies, liver palms, spider angioma can be seen.


Healthy liver
Chronic hepatitis
Cirrhosis
Hepatocellular carcinoma

DIAGNOSIS

SEROLOGY

- HBsAg
- Anti HBcAg IgM
- HBV DNA by PCR is most sensitive test

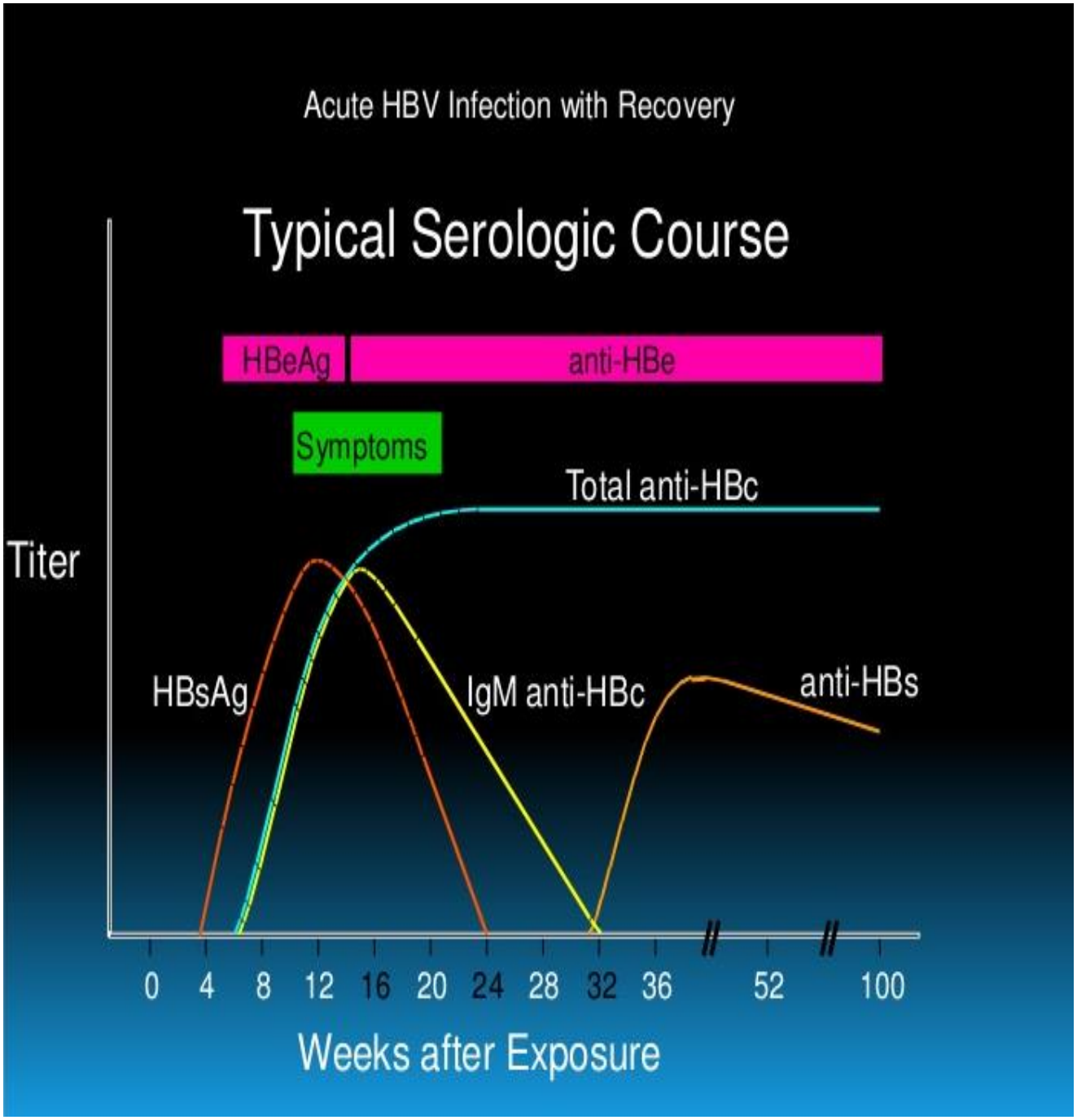
DIAGNOSIS

SEROLOGY

- HBsAg positive > 6 months
- Anti-HBc IgG in blood
- Serum HBV DNA > 10^5 copies/ml (20,000 IU/ml)
- HBeAg or Anti HBeAg may be present

Serological Markers of HBV

- **HBsAg**: Marker of infectivity
- **Anti-HBs**: Marker of immunity
- **HBcAg**: No commercial test available.
- **Anti-HBc**: Marker of past or current infection.
  - **IgM anti-HBc:** Recent infection.
  - **IgG anti-HBc**: Older infection.
- **HBeAg**: Marker of high degree of infectivity.
- **Anti-HBe**: May be present in infected or immune person.


Acute HBV Infection with Recovery
Typical Serologic Course
HBeAg
anti-HBe
Symptoms
Total anti-HBc
Titer
HBsAg
IgM anti-HBc
anti-HBs
0
4
8
12
16
20
24
28
32
36
52
100
Weeks after Exposure

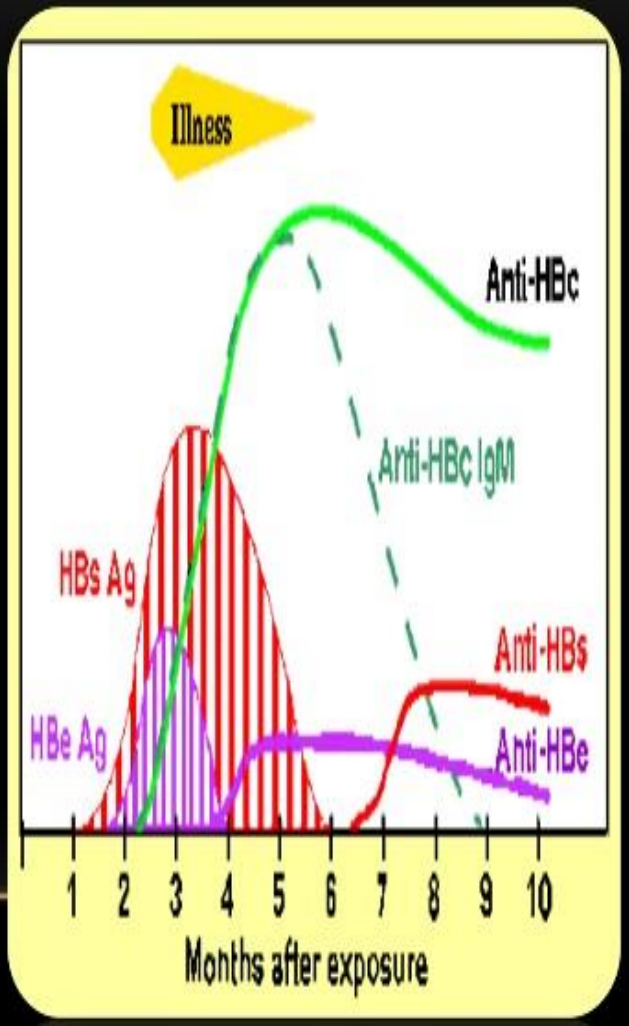
HBV Markers in different Stages:

Stage of infection	HBV DNA	HBsAg	HBeAg	Anti-HBc Ig M	Anti-HBc Total	Anti-HBe	Anti-HBs
Susceptible	–	–	–	–	–	–	–
Early incubation	+	–	–	–	–	–	–
Late incubation	+	+	+/–	–	–	–	–
Acute infection	+	+	+	+	–	–	–
Recent infection	–/+	–	–	+	+	+	+++

Stage of infection	HBV DNA	HBsAg	HBeAg	Anti-HBc Ig M	Anti-HBc Total	Anti-HBe	Anti-HBs
Remote infection	_ or very low	–	–	–	+	+/_	+
HBsAg-ve Acute infect	_	–	–	+	+	–	–
HBsAg variant infect.	_/+	–	_/+	+/_	+	–	–
Immune active carrier	++	+	_/+	_/+	+++	–	–
Healthy HBsAg carrier	_	+	–	–	+	+	–
Vaccination response	_	–	–	–	–	–	+

HBV – SEROLOGY INTERPRETATION

- **Acute infection**
  - HBsAg positive and anti-HBcAg IGM
  - Rarely, IgM anti-HBc only marker
    - Usually seen in acute fulminate Hep B
- **Chronic infection**
  - HBsAg positive and anti-HBcAg
- **Previous Infection**
  - HBsAg negative
  - anti-HBs positive
  - IgG anti-HBc positive



Treatment of Chronic Hepatitis B

- **DRUGS :** No specific therapy available
  - Interferon-alfa
    - IFN α → 6 month in Hbe +ve
    - Peg IFN α → 12 months in Hbe - ve
  - Lamivudine :100mg OD 48 weeks
  - Adefovir : 10 mg OD 48 weeks
  - Entecavir
  - Telbivudine
- **Liver Transplantation**

PREVENTION

- HBV Vaccine
  - DNA Recombinant vaccine
  - IM (deltoid but not gluteal)
  - 3 doses 0, 1, 6
  - Duration of protection – 5 to 10 yrs

❖ POST-EXPOSURE PROPHYLAXIS

- Combination of HBIG & HB vaccine (24 hrs)

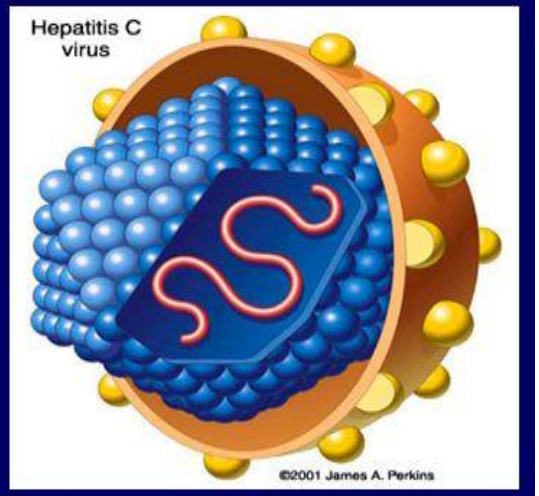
❖ PERINATAL PROPHYLAXIS OF INFANTS

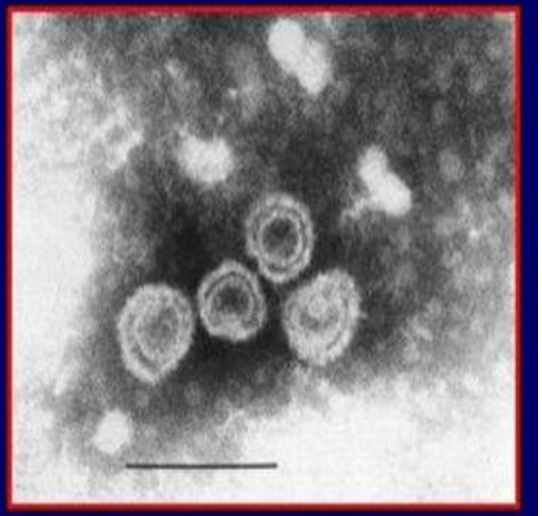
- HBIG 0.5ml IM in thigh immediately after birth
- Full course of HB vaccine started within 12 hrs of birth

Hepatitis C

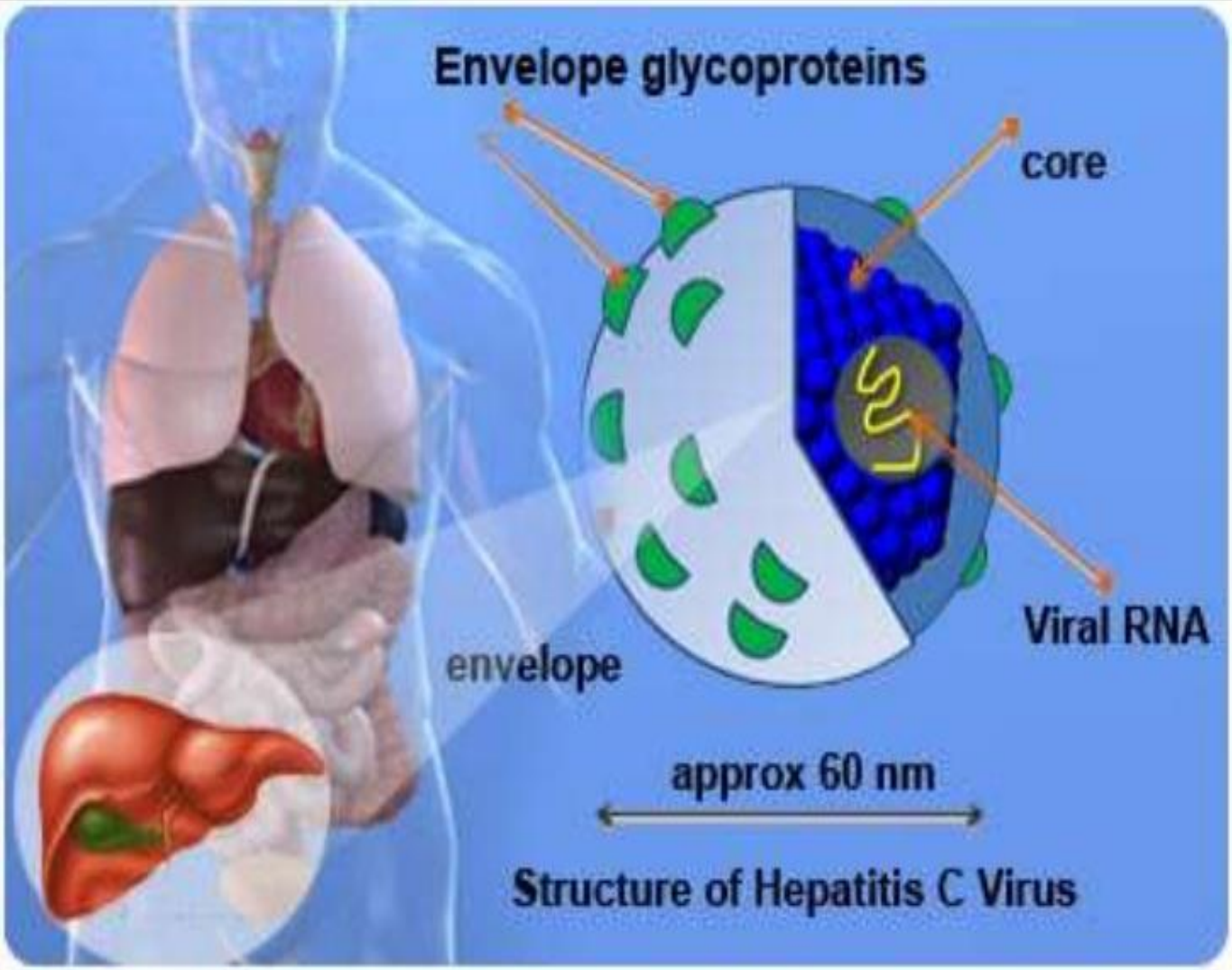
Hepatitis C virus: Classification & structure

- Family: *Flaviviridae.*
- Genus: *hepacivirus.*
- The virus is small, 60 – 80 nm in diameter.
- Consists of an outer envelope, icosahedral core and linear positive polarity ss-RNA gemone.
- There are 6 major genotypes (1 – 6), genotype 4 is the dominant in Saudi patients.

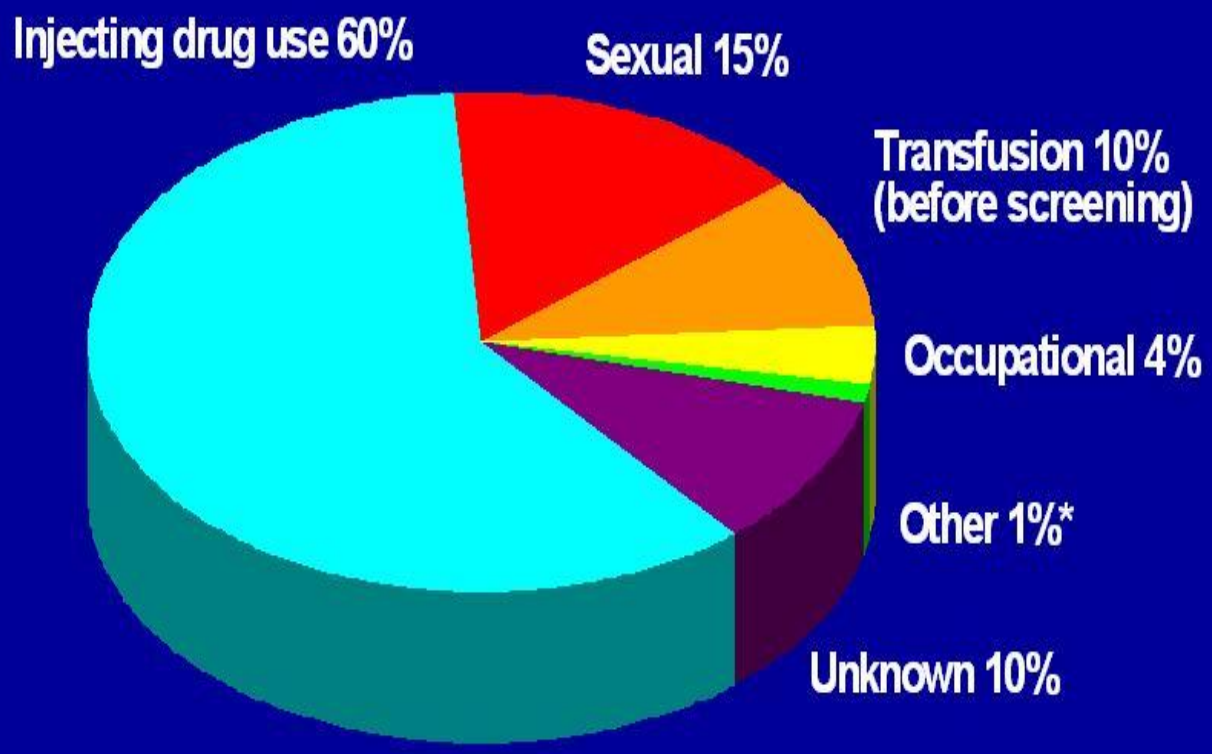




STRUCTURE OF HEPATITIS C



Routes of Transmission



* Nosocomial; iatrogenic; perinatal

CLINICAL FEATURES

- Incubation period: 50 days (15 – 150 days)
- 90% : Asymptomatic
- 10%: Mild flu like illness with jaundice & raised serum amino transferrases
- Extrahepatic Manifestation : Arthritis

  Glomerulonephritis

Clinical Course

- 85% : Chronic liver disease
- 15 – 20% : Cirrhosis in 10 – 30 yrs
- 7 – 15% of cirrhosis patient: Hepatocellular carcinoma

DIAGNOSIS

- HCV RNA detected in 1 – 2 weeks after infection
- Anti HCV is + ve 6 weeks after infection

Treatment for Chronic HC

- For CHC: IFN-α + Ribavirin 6 - 12 months

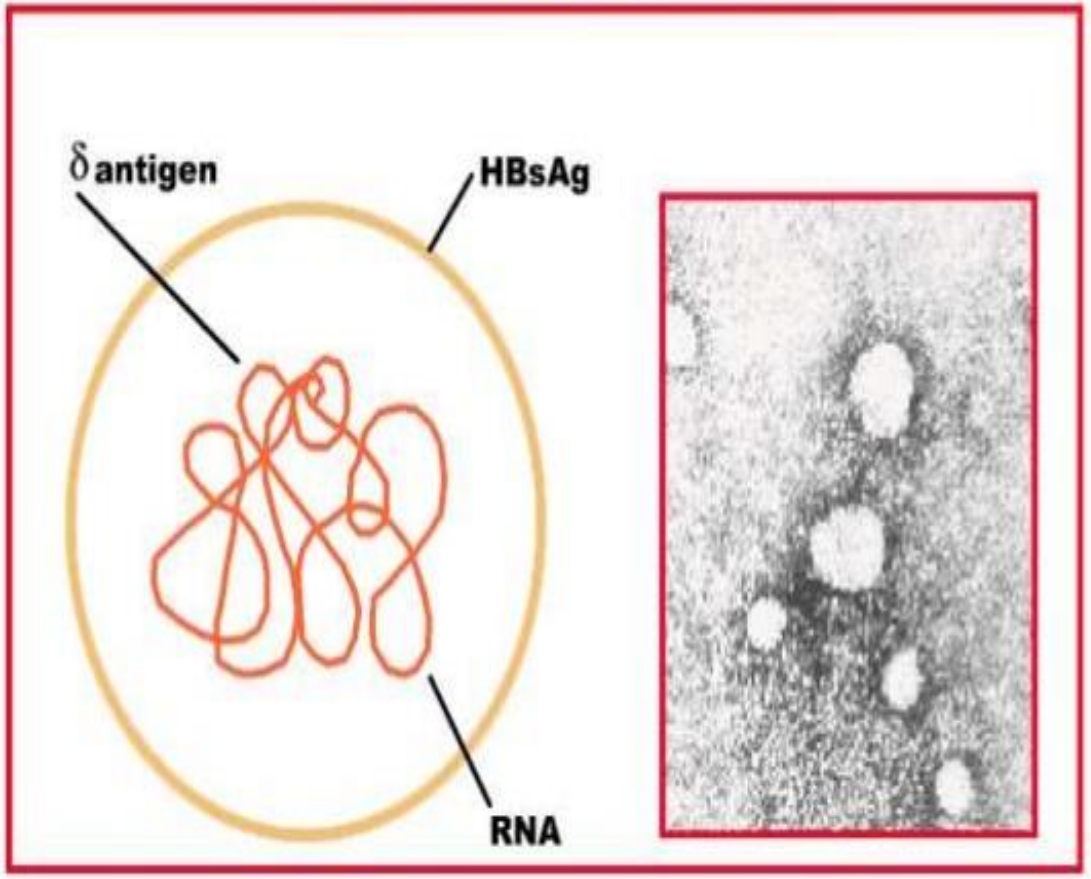
  Side Effects

  - Ribavirin: Hemolytic anemia
  - Interferon: Flu like symptoms

- Liver Tranplantation in Cirrhosis

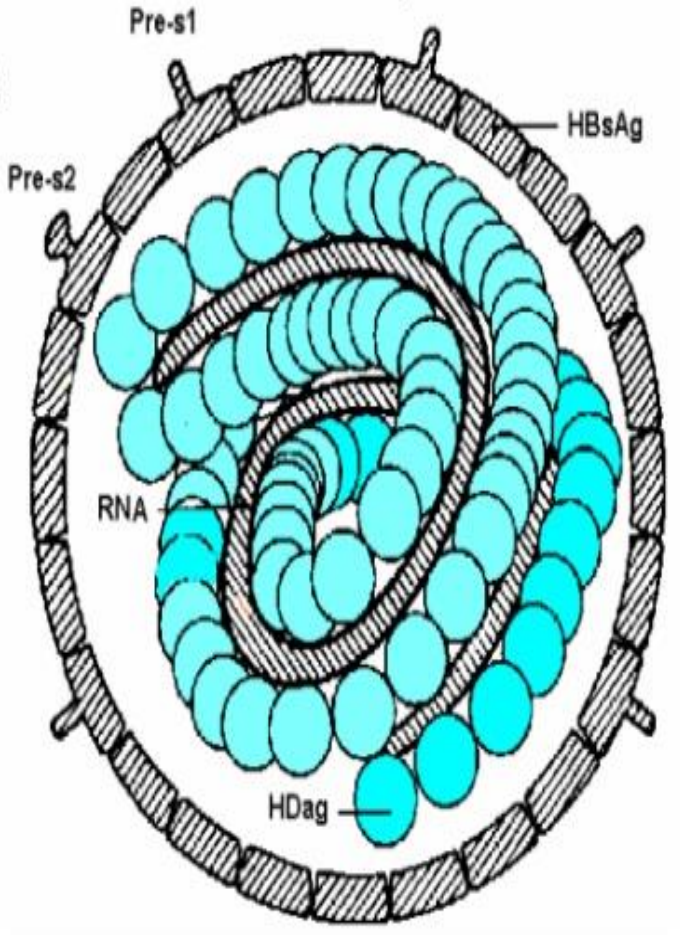
HDV STRUCTURE

Hepatitis D (Delta) Virus



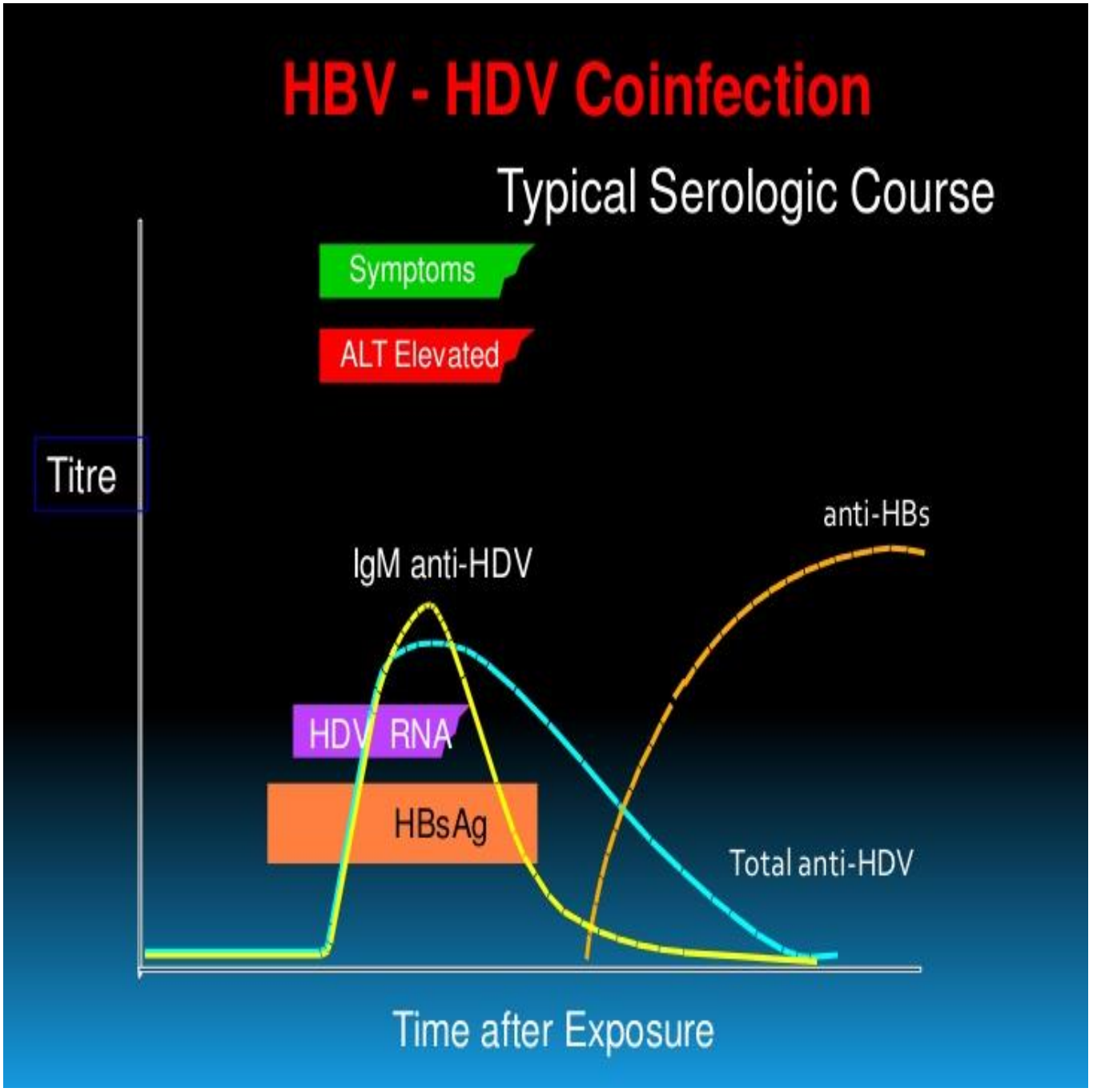
HEPATITIS D VIRUS (HDV, DELTA AGENT)

VIRION: spherical, 36-38 nm,
HBV capsid, HDV nucleoprotein
NUCLEIC ACID: (-) ss RNA, circular
Satellite virus : replicates only
in the presence of HBV

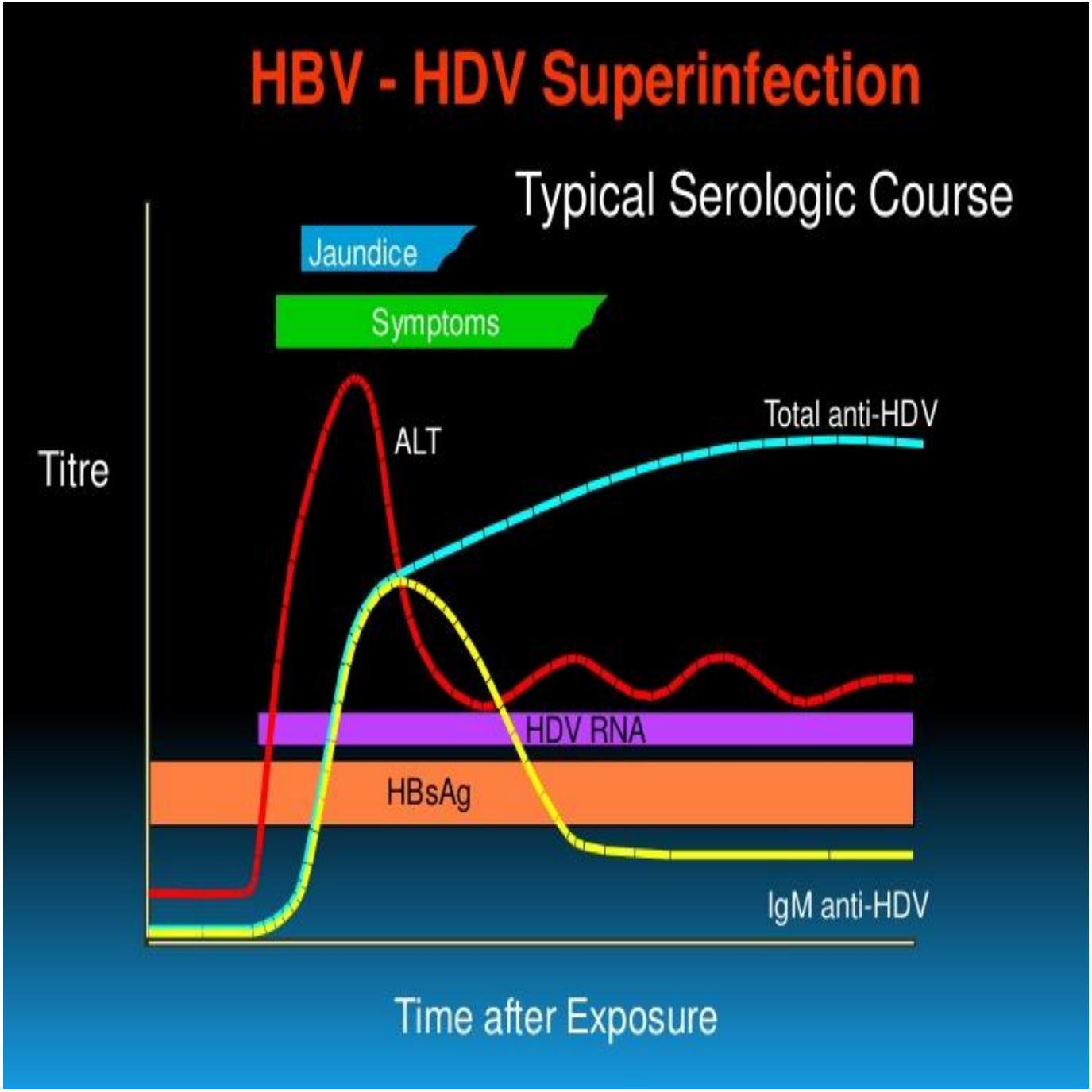


Hepatitis D virus (HDV)

- Delta virus
- Incomplete defective RNA virus.
- Requires coating of hepatitis B surface antigen (HBsAg) for entry into and exit from the hepatocyte.
- HDV- antigen and Anti-HDV in serum
- Route of transmission: Similar to HBV


HBV - HDV Coinfection
Typical Serologic Course
Symptoms
ALT Elevated
Titre
anti-HBs
IgM anti-HDV
HDV RNA
HBsAg
Total anti-HDV
Time after Exposure

HBV - HDV Superinfection



Hepatitis D Prevention

- Hepatitis D can be prevented by vaccinating susceptible persons with Hepatitis B vaccine

Hepatitis E virus (HEV)

- Single-stranded RNA,
- At least four Genotypes.
- Enterically trasmitted by contaminated water
- "Enterically Transmitted Non A Non B Hepatitis"
- Symptoms similar to Hepatitis A
- Self Limiting & no progression to chronic liver disease
- Incubation period: 40 days (15 – 60 days)

DIAGNOSIS

- ELISA for IgM & IgG anti HEV
- HEV RNA in serum or stools

PREVENTION

No vaccine available

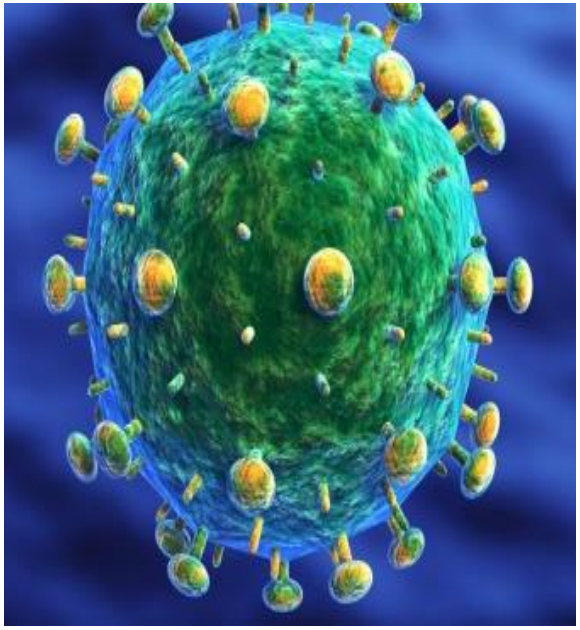
Retroviridae family (retroviruses)

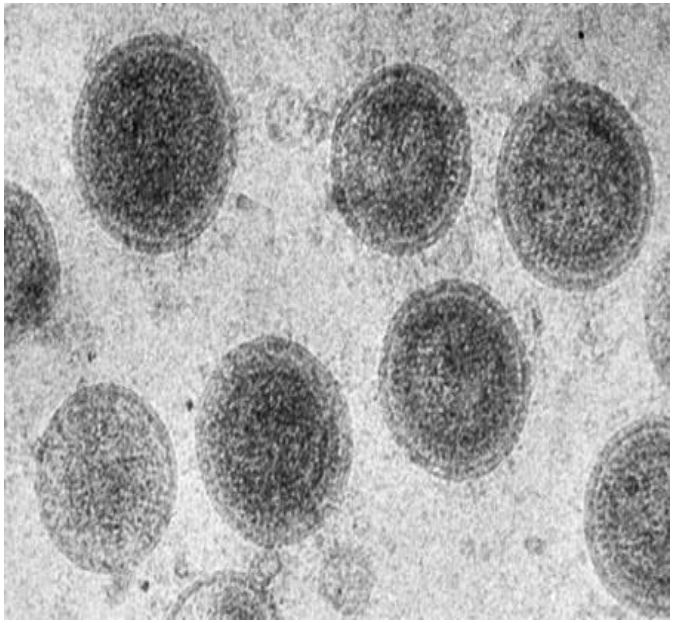
- The retroviridae family consists of single-stranded RNA viruses. The family is named after an enzyme that enables the synthesis of DNA from RNA in virions (RNA-dependent DNA polymerase, or reverse transcriptase).
- Retroviruses are spherical in shape and measure 80-110 nm. The core of the virion consists of a helical nucleoprotein surrounded by an icosahedral capsid, surrounded on the outside by a lipid-like membrane. There are glycoprotein spikes on the surface of the outer membrane.
- At the center of the central part is the presence of the viral genome and the complex reverse transcriptase associated with it.
- The genome consists of two identical positive-stranded, linear RNAs

Classification of retroviruses

- The Retroviridae family consists of 7 genera with many representatives. Most of them cause malignant tumors (cancer, sarcoma, leukemia, etc.) in various animals.
- Human immunodeficiency virus (IIV-1, IIV-2) and human T-lymphotropic viruses (HTLV-1 and HTLV-2) are more important in human pathology.

Human immunodeficiency virus





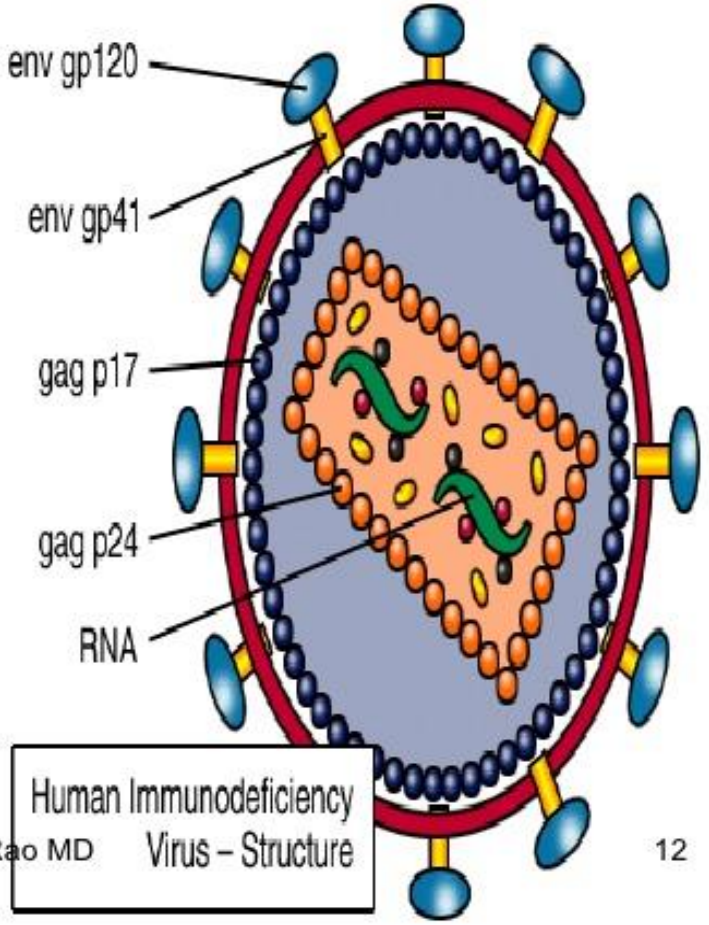
Introduction

- HIV was first Identified in 1981 in USA among homosexuals
- In 1983, French investigator named Lymphadenopathy associated virus (LAV).
- In 1984 virus was isolated by Gallo and co-workers from national institute of health in United States.

They named Human T-cell Lymphotropic virus III (HTLV-III).

Family : Retroviridae
Subfamily : Lentivirus

- RNA virus, 120nm in diameter
- Envelope gp160; gp120 & gp41
- Icosahedral symmetry
- Nucelocapsid
  - Outer matrix protein (p17)
  - Major capsid protein (p24)
  - Nuclear protein (p7)
- Diploid RNA with several copies of reverse transcriptase



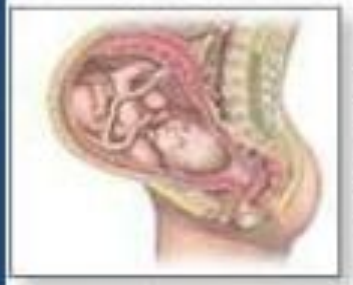
Human Immunodeficiency Virus – Structure

HIV Modes of Transmission

Unprotected sex with an infected partner

Sharing needles with infected person

Almost eliminated as risk factors for HIV transmission are:



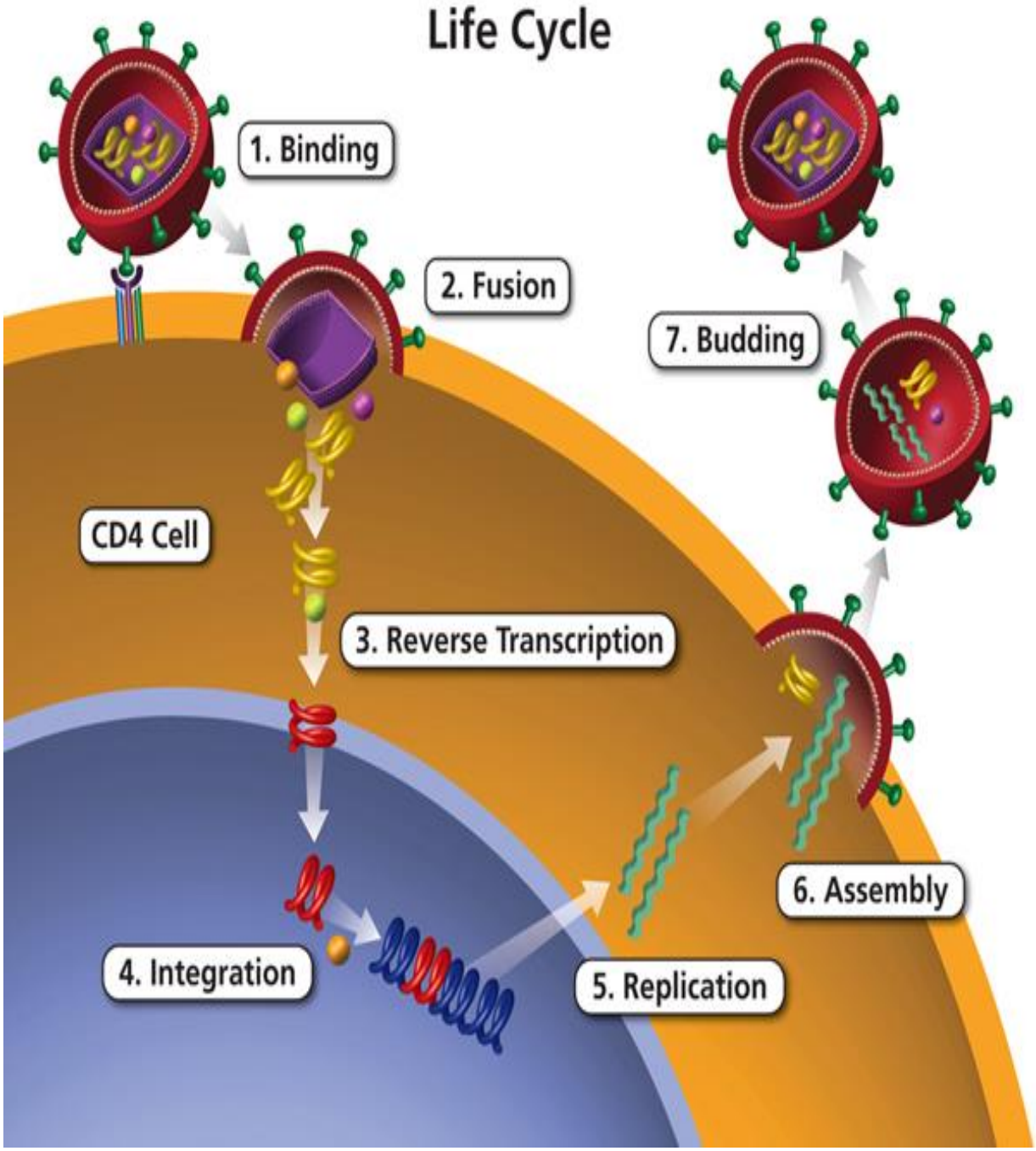
Transmission from infected mother to fetus

Infection from blood products

- vertical transmission of HIV from mother to child is the main route by which childhood HIV infection is acquired
- the risk of perinatal acquisition is 25-40% without intervention

- *The body fluids have been proven to spread HIV:*

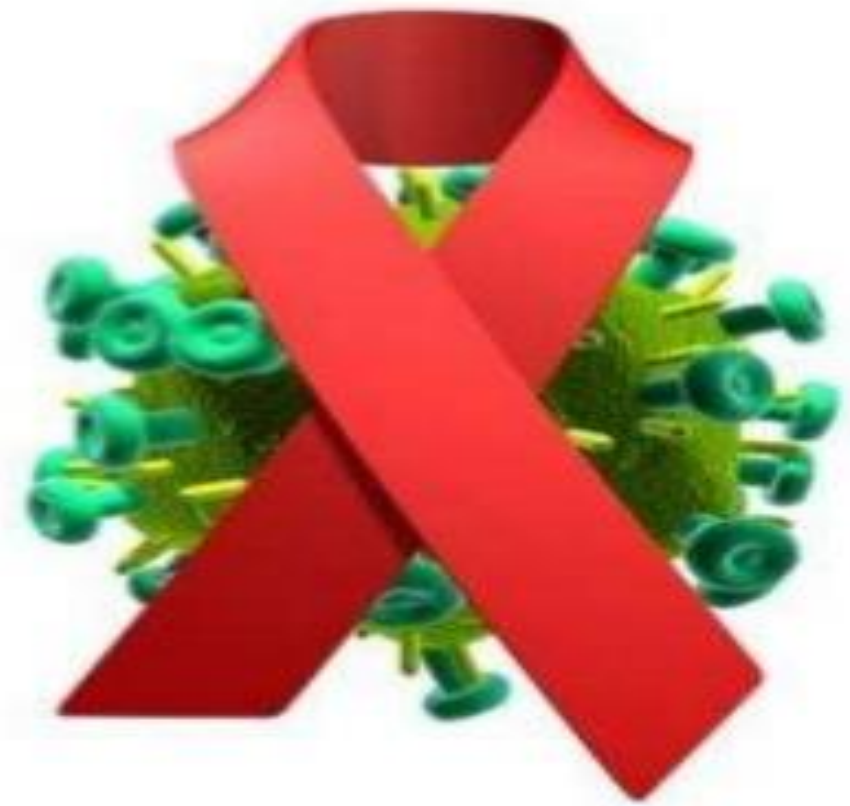
- *blood*
- *semen*
- *vaginal fluid*
- *breast milk*
- *other body fluids containing blood*
- *cerebrospinal fluid surrounding the brain and the spinal cord*
- *synovial fluid surrounding bone joints*


Life Cycle
1. Binding
2. Fusion
7. Budding
CD4 Cell
3. Reverse Transcription
6. Assembly
4. Integration
5. Replication

PATHOGENESIS :

- *Attachment of virus at the CD4 receptor and chemokine co-receptors .*
- *viral fusion and uncoating*
- *Reverse transcriptase .*
- *Migration to nucleus*
- *Integration of the viral DNA into cellular DNA by the enzyme integrase*
- *Transcription and RNA processing*
- *Protein synthesis.*
- *protease cleaves polypeptides into functional HIV proteins and the virion assembles*
- *virion budding*
- *Virion maturation*

FOUR STAGES OF HIV



STAGE 1 – PRIMARY :

- *flu like illness - occurs two to six weeks after infection or there may be*
- *no symptoms at all*
- *Infected person can infect other people*

Stage 2 - Asymptomatic

- *This stage is free from symptoms*
- *There may be swollen glands.*
- *HIV antibodies are detectable in the blood*
- *This stage is last for about ten years*

STAGE 3 – SYMPTOMATIC :

The person starts showing symptoms like fever, skin disease.

The immune system deteriorates emergence of opportunistic infections and cancers

STAGE 4 - HIV ⇨ AIDS :

- *The immune system weakens*
- *The illnesses become more severe leading to AIDS*
- *The illnesses become more severe leading to emergence of opportunistic infections and cancers*

SYMPTOMS :

The symptoms of this :

- *diarrhea*
- *fatigue or weakness*
- *fever*
- *headache*
- *joint pain*
- *night sweats*
- *rash*
- *swollen glands*
- *weight loss*
- *yeast infections (of the mouth or vagina) that last a long time or occur frequently*

Diagnostic Tests for HIV Infection

- Serological methods for detection of antibody
  - Rapid tests
  - ELISA
  - Western blot
- Antigen detection methods
  - P24 antigen capture test
  - Polymerase Chain Reaction (also known as PCR or viral load)

HIGHLY ACTIVE ANTIRETROVIRAL DRUGS

- NUCLEOSIDE REVERSE TRANSCRIPTASE
  - *Zidovudine*
  - *Stavudine*
- NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR
  - *Efavirenz*
  - *Nevirapine*
- PROTEASE INHIBITOR
  - *Atazanavir*
  - *Darunavir*

PREVENTION

There's no vaccine to prevent HIV infection and no cure for AIDS. But it's possible to protect yourself and others from infection. That means educating yourself about HIV and avoiding any behavior that allows HIV-infected fluids — blood, semen, vaginal secretions and breast milk — into your body.

ONCOGENIC VIRUS

Introduction

- **Oncogenesis** -An abnormal growth of tissue resulting from uncontrolled, progressive multiplication of cells and serving no physiological function. Result of genetic changes that alter the expression or function of proteins that play critical roles in the control of cell growth and division.
- **Proto-oncogenes** - normal gene,present in normal cells, conserved in their genomes, code for proteins which regulate cell growth and differentiation.
- **Oncogenes** - mutated versions of proto-oncogenes that contribute to cancer development by disrupting a cell's ability to control its own growth.

ONCOGENIC VIRUSES

- Viruses that produce tumours in their natural host/experimental animals or which induce malignant transformation of cells on culture.

TYPES:

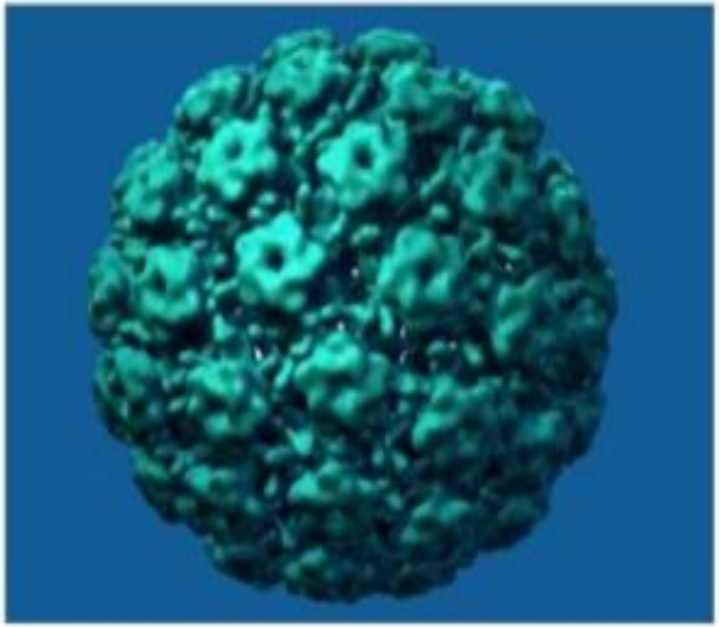
- Oncogenic RNA Viruses

  Retroviruses are divided into oncoviruses, lentiviruses, and spumaviruses.

- Oncogenic DNA Viruses

  Oncogenic human DNA viruses include hepatitis B viruses, herpesviruses, and papillomaviruses.

Human Papillomavirus (HPV)



Double-stranded DNA virus

Infects human epithelial cells

>200 different strains of the virus

- 30-40 anogenital
- 15-20 oncogenic

Genital warts, cervical dysplasia not-reportable, so prevalence data incomplete

Considered the most common sexually transmitted infection in the United States

HPV

- Small
- Non-enveloped
- Virion –Icosahedral
- Genome – double stranded ,circular DNA (8000bp)
- 16 genera (5 – human infections)

Epidemiology:

- HPV induced cervical cancer is 2nd most common cancer worldwide
- 16% of all female cancers are linked to HPV
- Papilloma virus is found in 90% of women with cervical cancers

HPV DISEASES

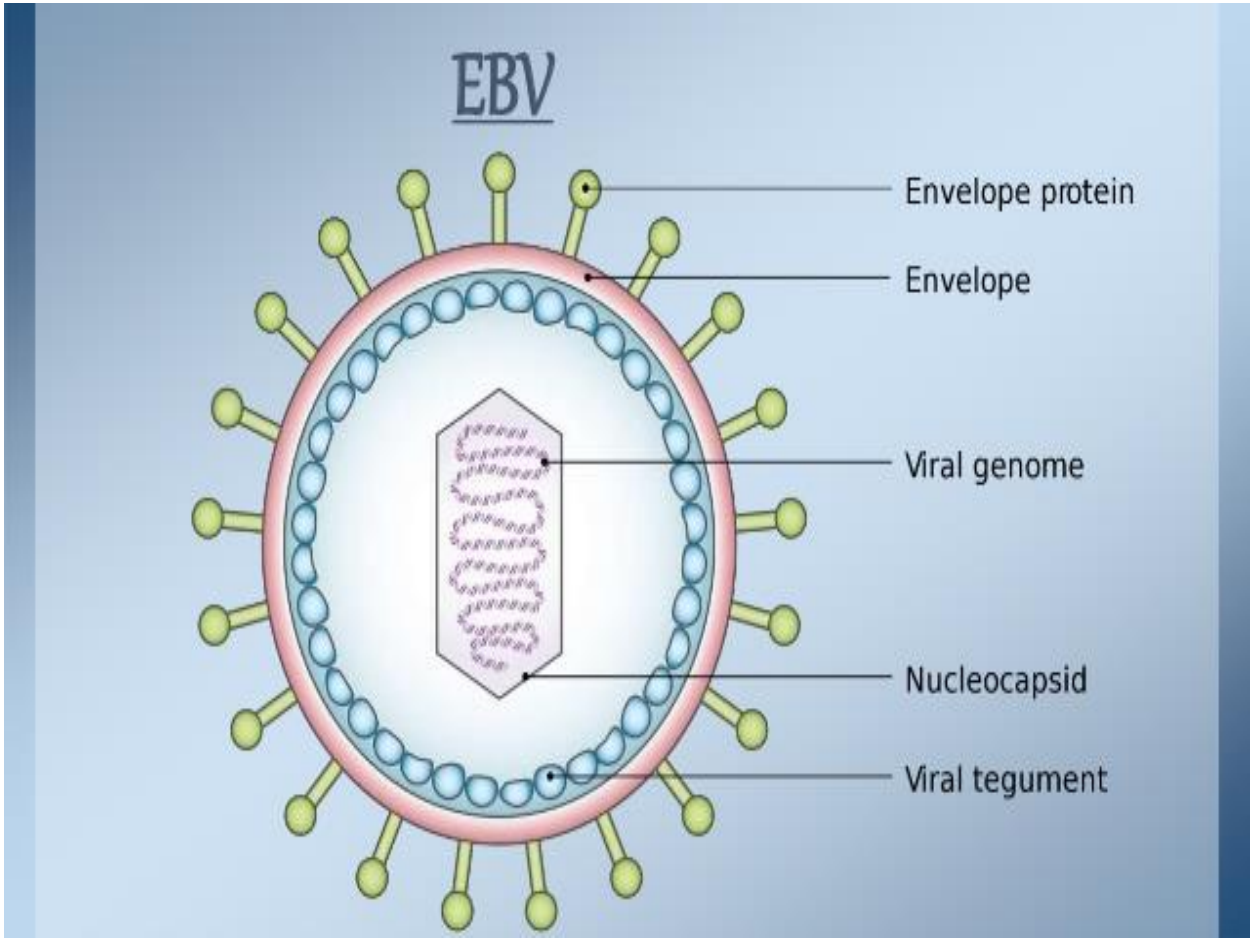
- Genital HPV is a very common sexually transmitted infection which usually causes no symptoms and goes away by itself, but can sometimes cause serious illness. HPV is responsible for:
- almost all cases of genital warts and cervical cancer
- 90% of anal cancers
- 65% of vaginal cancers
- 50% of vulva cancers
- 35% of penile cancers
- 60% of oropharyngeal cancers (cancers of the back of the throat, including the base of the tongue and tonsils).
- Four out of five people have at least one type of HPV at some time in their lives. It is sometimes called the 'common cold' of sexual activity. HPV infects both men and women.

Diagnosis

- The **Pap test** can find abnormal cells on the cervix so that they can be removed before cancer develops. Abnormal cells often become normal over time, but can sometimes turn into cancer. These cells can usually be treated, depending on their severity and on the woman's age, past medical history, and other test results.
- An **HPV DNA test**, which can find certain HPV types on a woman's cervix, may also be used with a Pap test in certain cases (called co-testing). Even women who were vaccinated when they were younger need regular cervical cancer screening because the vaccines do not protect against all cervical cancers.

Treating HPV

- **HPV vaccination** could prevent most cancers and other diseases caused by HPV. There is **no treatment** for the virus itself, but there are treatments for the problems that HPV can cause.
- ✓ In most cases the immune system clears HPV from the body naturally over time and has no long-lasting effects. Most people with HPV have **no symptoms** and will never know they have it.
- ✓ For women, having regular **Pap tests** once they become sexually active is the only way to detect abnormal cells on the cervix caused by HPV.
- ✓ **Genital warts** can be treated by doctors or at sexual health clinics.
- ✓ **Recurrent Respiratory Papillomatosis (RRP)**, a rare condition in which warts grow in the throat, can be treated with surgery or medicines.


EBV
Envelope protein
Envelope
Viral genome
Nucleocapsid
Viral tegument

EBV

- Infectious mononucleosis
- Burkitt's lymphoma
- Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a member of the herpes virus family. It is one of the most common human viruses. EBV is found all over the world.
- **Epidemiology**
  - Ubiquitous
  - Burkitt's lymphoma – children in Central Africa
  - Nasopharyngeal carcinoma – Cantonese China , Alaskan eskimos.
- Malaria - cofactor

Symptoms

- Once you're infected with EBV, symptoms can take 4 to 6 weeks to show up. When they do, they're often mild, especially in young children. Kids' symptoms may be more like those of a cold or flu. Teens often have more obvious symptoms of mononucleosis. If you do get symptoms, most likely you'll have:

- Fatigue
- Fever
- Lack of appetite
- Rash
- Sore throat
- Swollen glands in the neck
- Weakness and sore muscles

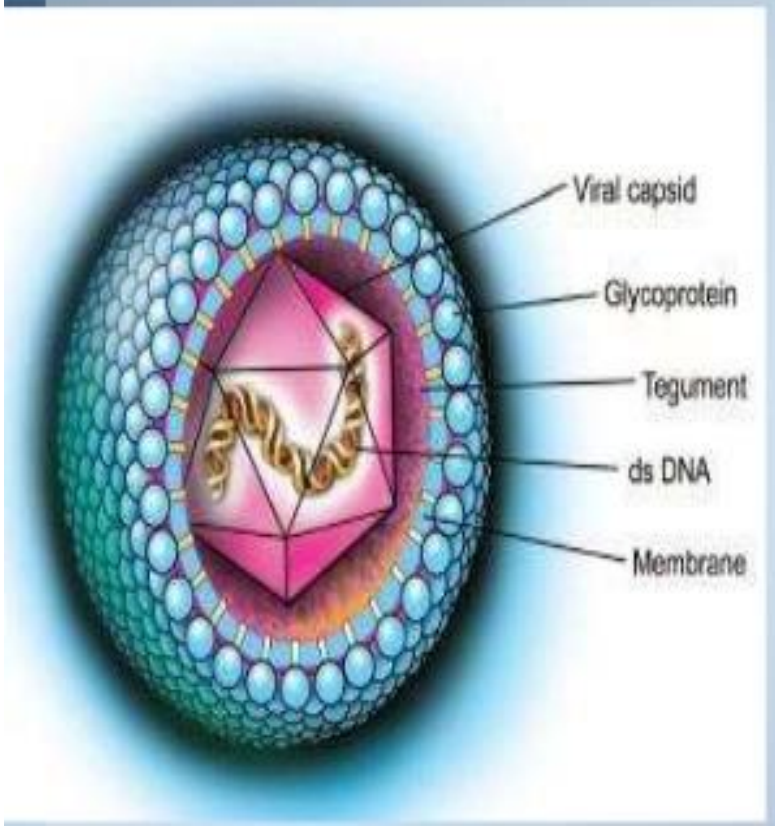
Symptoms of Burkitt's Lumphoma

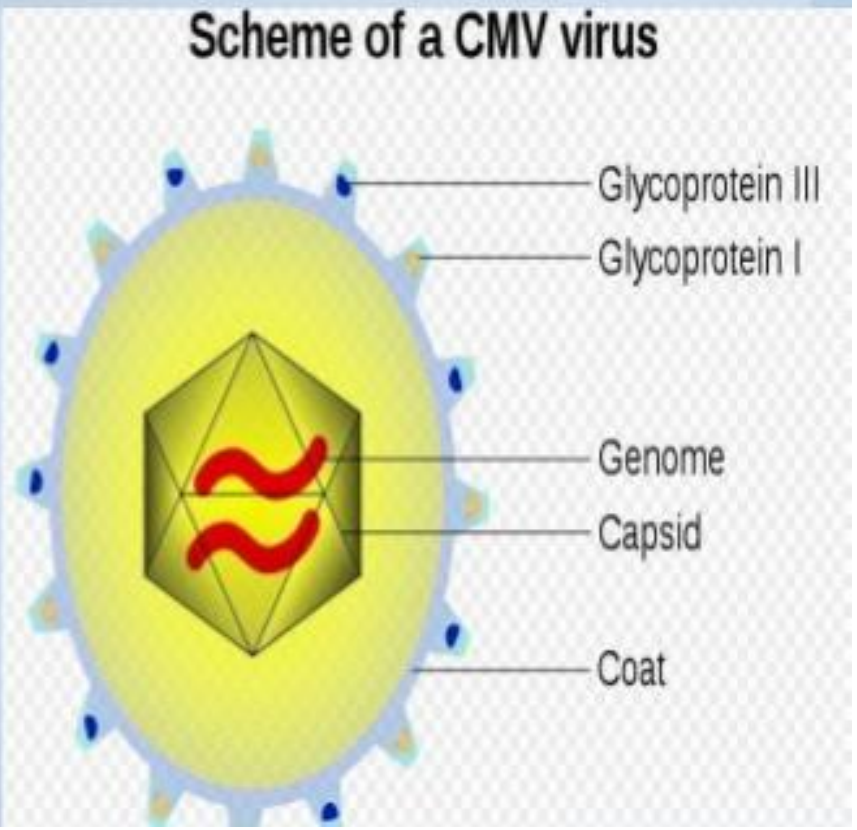
- The symptoms depend on the type.
- The endemic (African) variant usually starts as tumors of the jaw or other facial bones. It also can affect the gastrointestinal tract, ovaries, and breasts and can spread to the central nervous system, causing nerve damage, weakness, and paralysis.
- The sporadic and immunodeficiency-associated types usually start in the bowel and form a bulky tumor mass in the abdomen, often with massive involvement of the liver, spleen, and bone marrow. These variants also can start in the ovaries, testes, or other organs, and spread to the brain and spinal fluid.

TREATMENT

- Treatments for Burkitt lymphoma may include intensive chemotherapy in combination with:
- **Rituximab (Rituxan),** a monoclonal antibody that sticks to proteins on cancer cells and stimulates the immune system to attack cancer cells
- **Autologous stem cell transplantation**, in which the patient's stem cells are removed, stored, and returned to the body
- Radiation therapy
- Steroid therapy
- In some cases, surgery may be needed to remove parts of the intestine that are blocked, bleeding, or have ruptured

CMV


Viral capsid
Glycoprotein
Tegument
ds DNA
Membrane


Scheme of a CMV virus
Glycoprotein III
Glycoprotein I
Genome
Capsid
Coat

CMV

- Cytomegalovirus or CMV, is a common virus that infects people of all ages. In the United States, nearly one in three children are already infected with CMV by age 5 years. Over half of adults by age 40 have been infected with CMV. Once CMV is in a person's body, it stays there for life and can reactivate. A person can also be reinfected with a different strain of the virus.
- Most people infected with CMV show no signs or symptoms. That's because a healthy person's immune system usually keeps the virus from causing illness. However, CMV infection can cause serious health problems for people with weakened immune systems, as well as babies infected with the virus before they are born (Congenital CMV).

Signs & Symptoms

- Most people with CMV infection have no symptoms and aren't aware that they have been infected. In some cases, infection in healthy people can cause mild illness that may include

•Fever,

•Sore throat,

•Fatigue, and

•Swollen glands.

•Occasionally, CMV can cause mononucleosis or hepatitis

- People with weakened immune systems who get CMV can have more serious symptoms affecting the eyes, lungs, liver, esophagus, stomach, and intestines. Babies born with CMV can have brain, liver, spleen, lung, and growth problems. Hearing loss is the most common health problem in babies born with congenital CMV infection.

Diagnosis

- **Blood tests** can be used to diagnose CMV infections in people who have symptoms.
- A person who has been infected with cytomegalovirus (CMV) will develop **antibodies** to the virus that will stay in the body for the rest of that person's life. A blood test for these antibodies can tell whether a person has ever been infected with CMV.
- Tests that can indicate when a person was infected are **not** widely available commercially.
- If the virus is detected in the blood, saliva, urine or other body tissues, it means that the person has an active infection.

Treatment

- Healthy people who are infected with CMV usually **do not** require medical treatment.
- **Medications** are available to treat CMV infection in people who have weakened immune systems and babies who show symptoms of congenital CMV infection.
- If treatment is needed, it's most often in the form of **antiviral drugs**. Antiviral drugs slow the virus reproduction, but can't cure it.
- The antiviral medications against CMV include the following:
  - Ganciclovir (Cytovene)
  - Valganciclovir (Valcyte)
  - Foscarnet (Foscavir)
  - Cidofovir (Vistide)