MEDICAL VIROLOGY
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General Properties of Viruses

• In contrast to bacteria, fungi and parasites, viruses are not cells.
• They do not have a nucleus.
• They do not have organelles such as ribosomes, mitochondria or lysosomes.
• They are the smallest infectious agents known, range from 20 to 300 nm in diameter.
General Properties of Viruses

• They can infect man, animals, insects, plants and bacteria.
• They contain one kind of nucleic acid (RNA or DNA) as their genome.
• They are metabolically inert as they do not possess ribosomes or protein synthesizing apparatus.
• They are obligate intracelluar parasites i.e. can only replicate inside living cells.
• They can not be grown on artificial culture media.
Structure of viruses

- Each virus particle or virion is composed of a protein coat or capsid and a nucleic acid core.
- The capsid with its enclosed nucleic acid is called nucleocapsid.
- Many viruses are naked but some viruses are enveloped.
Genetic Material
Viruses can have one of two kinds of genetic material, DNA or RNA. The latter are named retroviruses.

Membrane Envelope and Capsid
a layer of fatty acids coats many viruses. It is usually derived from the membrane of the host cell.

Ligands
proteins that stick out of the surface of the virus. They act as a key to recognize the cell to be infected and invade it.
Viral capsid:

- It surrounds viral nucleic acid and is made up of subunits called capsomers.

- Each capsomer is consisting of one or several proteins.
Functions of the capsid

- It protects the viral genome against inactivation by nuclease enzymes.

- The arrangement of capsomers gives the virus structure its geometrical symmetry.
Viruses show three types of symmetry:

- **1-Icosahedral symmetry:**
  - the capsomers are arranged in 20 triangles that form a symmetric figure (an icosahedron) with the approximate outline of a sphere.
1-Icosahedral symmetry

A

T=1

T=3

T=4

T=7

B

Poliovirus
T=1

Hepatitis B Virus
T=3

Bovine Papilloma virus
T=7

Herpes Simplex
T=16

HK-97 prohead

HK-97 head II
T=7
The capsomers are arranged in a hollow coil that appears rod-shaped.
3-Complex symmetry:
- They are regular structures, but the nature of symmetry is not understood.

- It participates in adsorption of virions to susceptible cells.

- It determines the antigenicity of the virion.
Viral Symmetry

Nidoviruses

CORONAVIRUS

TOROVIRUS

Bafinivirus

ARTERIVIRUS

RONIVIRUS

Ronivirus
Viral Nucleic Acid (genome):

- Virus possesses one type only of nucleic acid, either DNA or RNA.
- It may be single or double stranded, linear or circular.
- It is the infectious part of the virus, coreless particles are non-infectious.
- Lipoprotein in nature.
- Lipid fraction is derived from the host cell membranes and protein fraction is virus specific.
• There are frequently **glycoproteins** in the form of spike like projections on the surface which attach to the host cell receptors during the entry of the virus into the cell.

-Surface glycoproteins are also antigenic and determinants of virus specificity.
Virus Replication

- Viruses have **no metabolic activity** of their own.
- They depend on living cells for providing energy for the synthesis of **viral nucleic acid** and proteins.
The sequence of events for virus replication

1-Adsorption:
- It is the attachment of the virus on the host cell.
- It needs specific molecular structures on the viral surface and specific receptors on the host cells.
2-Penetration

• It is the passage of the virion from the surface of the cell, across the cell membrane and into the cytoplasm.

• In non enveloped viruses penetration occurs by crossing the plasma membrane directly or by receptor mediated endocytosis.

• In enveloped viruses penetration occurs by fusion of viral envelope with cell membrane or with membrane of endosome at the cell surface.
It is the release of viral nucleic acid by cellular enzymes. Uncoating renders viral nucleic acid accessible for transcription and replication.
Viral gene expression (transcription) and protein synthesis (translation)
• **Transcription** is the synthesis of mRNA from viral nucleic acid.
• It is carried out by cellular enzymes or by viral enzymes.
• The mRNA transcription varies depending on the nucleic acid type.
• Single stranded (ss) RNA viruses may be of (+) polarity or (-) polarity:
• In ss RNA of (+) polarity, the genomic viral RNA acts directly as mRNA → translation → viral proteins.

• In ss RNA viruses of (-) polarity, the genomic viral RNA must be transcribed to mRNA → translation → viral proteins.
Viral structure: Nucleic acid

RNA Virus Genomes

+ssRNA: If the single-stranded RNA molecules combine with ribosomes of host cells and serve directly as messenger RNA (mRNA) then the viral RNA molecule is considered to be of positive polarity.
• **Assembly:**
  Assembly of viral nucleic acid and protein coats to form mature virus particles occurs in the cytoplasm e.g. polivirus or in the nucleus e.g. herpesvirus.

• **Release:**
  Virus particles are released from the cell by either of two processes: one is the rupture of the cell membrane and release of the mature particles, this usually occurs with unenveloped viruses. The other, which occurs with enveloped viruses, is the release of viruses by budding through the outer cell membrane.
Laboratory diagnosis of viral infection
• There are 3 approaches to the diagnosis of viral infections

• **1-Direct detection:**
  • Detection of virus particles by electron microscope.
  • Detection of viral inclusion bodies (intra-cytoplasmic or intranuclear) by light microscope.
  • Detection of viral antigens in different clinical specimens by ELISA, RIA and IF tests
  • Detection of viral nucleic acid by nucleic acid hybridization and by polymerase chain reaction (PCR).
ELECTRON MICROSCOPE

LIGHT MICROSCOPE

PCR MACHINE

MICROTITRATION PLATE OF ELISA
2-Virus isolation

- Viruses are **obligate intracellular parasites** and can be isolated by:
  - **A) Tissue culture:**
    - Pieces of animal or human tissues are trypsinized to get separate cells
    - Cells are grown in media containing amino acids, vitamins, calf serum and antibiotics
    - A monolayer or sheet of cells is formed on the flat side of the container within few days. Viruses are inoculated on the monolayer.
Types of tissue culture
1. Primary cell lines

- Obtained from organ fragments e.g. monkey kidney.
- Can divide only for 4-6 passages.
- Susceptible to a wide range of viruses.
2. **Human diploid cell lines (semi continuous cell line)**

- They are fibroblasts derived from human embryo tissues e.g. human embryonic lung.
- Can be sub cultured for about 30-40 passages.
- Susceptible to a wide range of viruses.
3. Continuous cell lines

- Derived from tumor cell e.g. HELA cells derived from human cervical cancer.
- Can divide indefinitely (300 passage).
- Susceptible to fewer viruses than other types.
Detection of viral replication in cell cultures
• **Cytopathic effects (CPE):**
• These are changes in cells that can be observed microscopically.

• They may be in the form of:
• 1-Cell death and detachment from the glass surface *e.g.* polivirus
• 2-Rounding and grape like cluster formation (e.g. adenovirus).

• 3-Syncytium or multinucleated giant cell formation e.g. measles and mumps viruses.
If the virus does not produce a CPE, its presence can be detected by:
1. **Haemadsorption**: attachment of erythrocytes to the surface of virus infected cells e.g. in mumps, parainfluenza and influenza viruses.

2. Interference with the formation of a CPE by a second virus.

3. A decrease in acid production by infected, dying cells.

4. A definitive identification of the virus growth in cell culture by CF, HI, NT, CPE, IF, RIA and ELISA tests.
B) Embryonated eggs

- Chorioallantoic membrane inoculation is used in pox and herpes viruses.
- The influenza virus can readily grow in the amniotic sac and in the respiratory cells of the embryo.
- The age of embryo used and the site of inoculation vary according to the virus inoculated.
C) Animal inoculation

- Animal inoculation was used in the past when tissue culture methods were not known.
- It is still used for studying viral oncogenesis, pathogenesis of viral diseases.
- Viral growth is detected by death of animal, cytopathic effect or serologically by neutralization.
III- Serologic detection of antiviral antibodies

- By any serological test like ELISA, RIA, IF.
- Diagnosis of recent infection depends on:
  - Rising titer (at least 4 fold antibody titer (IgG) higher in convalescent phase than in acute phase).
  - Detection of IgM in a single serum sample e.g. detection of IgM to core antigen indicates HBV infection.
Effects of viral infection on the host cell
The response of a host cell to infection by a virus can range from:

1. **Lytic infection:**

Viral infections resulting in host cell death and production of progeny virus.
• **2- Abortive infections:**

- Virus infections in which no progeny virus are produced. An abortive response to infection is commonly due to:
  - 1) a normal virus infecting non permissive cells.
  - 2) infection by a defective virus of a cell normally supports viral replication.
3- **Persistent infections:**

-Viral infections where the host cell may be altered antigenically but is not killed, although progeny virus are released.
4- *Latent infections:*

- Viral infections that result in a latent viral state in the host cell:
- In latent state the viral genome is present inside a host cell with no production of progeny virus.
- Such latent viruses can be reactivated months or years in the future, leading to a productive infection.
Classification of viruses
DNA VIRUSES

- Double stranded
  - Enveloped
    - Herpesviridae
    - Hepadnaviridae
  - Non-enveloped
    - Papovaviridae
    - Adenoviridae

- Single stranded
  - Enveloped
    - Parvoviridae
  - Non-enveloped
    - Poxviridae
- Complex

Linear

Circular
RNA VIRUSES

- Single strand positive
  - Enveloped: Togaviridae, Coronaviridae, Retroviridae
  - Non-enveloped: Picornaviridae, Calciviridae

- Single strand negative
  - Enveloped: Orthomyxoviridae, Paramyxoviridae, Rhabdoviridae, Bunyaviridae, Arenaviridae, Filoviridae
  - Non-enveloped: Reoviridae

- Double strand
Prevention and Treatment of Viral Diseases
• **Prevention:**
  - Vaccination and public health measures.

• **Treatment:**
  - Antiviral drugs are medicines that cure or control virus infections. Unlike antibacterial drugs, which may cover a wide range of pathogens, antiviral agents tend to be narrow in spectrum, and have limited efficacy.
Antiviral drugs

• Since viruses are obligate intracellular parasites it is difficult to find antiviral drug that selectively inhibits the virus without affecting the cell.

• They act by stopping virus attachment, penetration, uncoating or intracellular synthesis.
EXAMPLES OF ANTIVIRAL DRUGS
• 1-Inhibitors of Herpes viruses:

• Nucleoside analogue: inhibits virus specific DNA polymerase e.g. Acyclovir, Ganciclovir and Vidarabine.
• **2-Inhibitors of retroviruses:**
  
  • **Nucleoside analogue:** inhibits reverse transcriptase enzyme of HIV. *e.g.* Azidothymidine (AZT), dideoxyinosine and stavudine.
  
  • **Inhibitors of protease encoded by HIV** *e.g.* Squinavir and Indinavir.
• 3-Inhibitors of other viruses:
  • Amantadine: inhibits Influenza A virus uncoating.
  • Ribavirin: inhibits both DNA and RNA polymerase enzymes. Used for treatment of HBV, HCV infections and RSV pneumonitis.
4-Interferon
Interferon:

- Infection of cells with viruses induces the production of proteins that are known as interferons because they were found to interfere with viral replication in previously uninfected tissue culture cells.

- Interferons are believed to have a similar role in vivo, blocking the spread of viruses to uninfected cells.

- There are 3 types of interferons, called interferon-α (IFN-α) and IFN-β, are quite distinct from interferon-γ (IFN-γ).
• IFN-α and IFN-β are secreted by the infected cell and then bind to a common cell-surface receptor, known as the interferon receptor, on both the infected cell and nearby cells.

• Interferon induces the synthesis of several host cell proteins that contribute to the inhibition of viral replication.
Viral Vaccines
1-Live attenuated Vaccines:

- Viruses whose virulence has been artificially reduced by *in vitro* culture under adverse conditions, such as reduced temperature.

- Most successful viral vaccines belong to this group which may be naturally occurring virus (e.g. *cowpox*) or artificially attenuated (*Sabine vaccine*).
*Advantages*

- The immune response is usually good. When the virus replicates in the host cells, both antibody as well as cell mediated immune responses are generated and immunity is generally long lived.
- Often, only a single dose is needed to induce long term immunity.
- It is cheap in preparation.
*Disadvantages*

- Unstable: biologically (live virus may die) and genetically (reversion to virulence). *Therefore, maintenance of the cold chain is very important.*
- Not easy to produce in all cases.
- Contamination by other living viruses is possible.
- Inappropriate for immunocompromised hosts e.g. rubella vaccine in pregnancy may lead to disease.
2-Inactivated Vaccines

- The organism is propagated in bulk, *in vitro*, and inactivated with either propinolactone or formaldehyde.

- Immunogenicity may be enhanced by the incorporation of *adjuvant* into the vaccine preparation.
*Advantages*

1. **Safe**: inactivated, therefore cannot replicate in the host and cause no disease even in immunocompromised hosts.

2. **Stable**: efficacy of the vaccine does not rely on the viability of the organisms. These vaccines tend to be able to withstand more adverse storage conditions.
*Disadvantages*

- Immune response is poor; only antibody (no mucosal immunity or IgA), no cell mediated immune response.
- It is short-lived and hence multiple doses are needed.
- Local reactions at the site of injection may occur.
- Denaturation may lead to loss of antigenicity, e.g. measles.
- Expensive to prepare.
- Not possible for all viruses.
3-Sub-unit Vaccines

- The newest type; completely safe, except for rare adverse reactions. Unfortunately, they also tend to be the least effective.

- **Problems:**
  - (Relatively) poor antigenicity (especially short peptides).
  - Difficult delivery (carriers/adjuvants are needed).
4-Recombinant proteins

- Immunogenic proteins of virulent organisms may be synthesized artificially by introducing the gene coding for the protein into an expression vector, such as *E. coli* or yeasts.
- The protein of interest can be extracted from lysates of the expression vector, then concentrated and purified for use as a vaccine.
- The only example of such a vaccine, in current use, is the hepatitis B vaccine.
Bacteriophages
Bacteriophages may be DNA viruses (double stranded or single-stranded) as well as RNA viruses (double or single-stranded).

Each phage can infect only a specific strain of bacteria e.g. there are more than 25 phages for different strains of *Staphylococcus aureus*. 

![Bacteriophage Structure](image)
Importance:

- **Industrial:** Phages of *Lactobacillus* are a serious problem for the dairy industry.
- **Medical:** Phage typing to trace sources of infection (e.g. *Staphylococci, Salmonella*). Also some investigators think of their use as antibacterial agents (not practical).
- **Recombinant DNA vectors:** Phages are used for cloning, expression, expansion of many useful genes producing enzymes, cytokines, hormones.
Virulent vs. Temperate Phages

• **Virulent:**
  • phages do not integrate their genetic material into the host cell chromosome and usually kill the host cells (lytic infection).

• **Temperate:**
  • phages may integrate into host DNA without killing it, causing lysogeny.
Lysogeny

- It means indefinite persistence of phage genomes within bacterial cells in the absence of a productive infection but with the potential to produce progeny phage under certain circumstances.
On infection with a temperate phage, vegetative replication (lysis) occurs in most cells, but a few become persistently infected due to integration of the phage genome.

These lysogenized cells are immune to superinfection by the same phage due to repression of transcription caused by the resident prophage.
The phage DNA inserts itself (as a prophage) into the bacterial chromosome. Phage is replicated along with the bacterial DNA prior to binary fission.
SYSTEMIC VIROLOGY
Herpesviruses

- Eight human herpesvirus species are known.
- All have the ability to enter a latent state following primary infection and to be reactivated at a later time.
Structure:

- **Virion**: Icosahedral

- **Genome**: Double stranded DNA, linear

- **Envelope**: Contains glycoprotein spikes
Classification of herpesviruses
The herpesviridae family has been divided into three subfamilies:

1- **Alphaherpesvirinae**:
   - Herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).
   - Varicella – Zoster virus (VZV or HHV-3).

2- **Beta herpesvirinae**:
   - Cytomegalovirus (HHV-5).
   - Human herpesviruses types 6 and 7 (HHV-6 and HHV-7).
• **3-Gammaherpesvirinae:**
  - Epstein – Barr virus (EBV or HHV-4)
  - Human herpesvirus 8 (HHV-8)
  - *Herpes simplex viruses*
  - There are 2 distinct herpes simplex viruses, type 1 and type 2. The two viruses cross-react serologically but some unique proteins exist for each type.
Transmission and pathogenesis
• HSV-1 is transmitted primarily in saliva, while HSV-2 is transmitted by sexual contact.

• Virus multiplies locally in mucous membrane or a braded skin causing vesicular lesion.
  • HSV-1: Mainly orofacial lesions
  • HSV-2: Genital lesions.

• However, both types of HSV can infect oral or genital mucosa depending on regions of contact.
Clinical syndromes

1-primary infection
1-HSV-1 Causes

- **Acute gingivostomatitis**: Occurs primarily in children and is characterized by fever, irritability and vesicular lesions in the mouth.

- **Herpes libialis (cold sores)**: characterized by crops of vesicles, usually at the mucocutaneous junction of the lips or nose.
• **Keratoconjunctivitis.**
• **Herptic whitlow:** is a pustular lesion of the skin of finger or hand of medical personnel.
• **Encephalitis.**
• **Disseminated infections**, such as esophagitis and pneumonia in immunocompromised patients.
2-HSV-2 causes the following

• **Genital herpes:** vesiculo-ulcerative lesions on the external genitalia as well as the cervix

• **Neonatal infection:**
  – Originates chiefly from contact with vesicular lesions within the birth canal.
  – Neonatal herpes varies from a severe generalized disease often involving the CNS, through milder local lesion to asymptomatic infection

**Aseptic meningitis**
Skin lesions of a newborn with HSV-2 infection
Mother with active herpes infection although active infection may not be apparent.

Blisters due to congenital herpes.
2- Latency
• After primary infection, the virus travels via the nerves from the site of infection to the related ganglia as following:
  • HSV-1 \rightarrow trigeminal ganglia
  • HSV-2 \rightarrow sacral ganglia
• Expression of HSV genes is shut off in latently infected cells, although characteristic, non translated RNA transcripts are present in some cells.
3- Reactivation
• Reactivation of virus occurs in response to various stimuli as common colds, hormonal changes and sunlight.
• Reactivation of HSV-1 may lead to:
  • a- Cold sores
  • b- Keratitis
• Reactivation of HSV-2 can occur more frequently, and is often asymptomatic but still results in viral shedding.
Diagnosis

- **Virus isolation from herpetic lesions.** CPE occurs in 1-3 days. Virus is identified by IF or ELISA.

- **Histological staining** (Giemsa stain) of scrapings or swabs from the base of skin lesions → the presence of multinucleated giant cells is suggestive.

- **Detection of viral particles** by electron microscopy, viral antigens by IF in vesicular fluid by and detection of HSV-1 DNA in CSF by PCR.

- **Serologic diagnosis**
Treatment:

• **Acyclovir** is the treatment of choice.

• The drug shortens the duration of the lesion and decreases shedding of the virus.

• No drug treatment prevents recurrences and drugs have no effect on the latent state.
Varicella-Zoster virus (VZV)

- VZV is structurally and morphologically identical to other herpesviruses but is antigenically different.

- The same virus causes both _varicella_ (primary disease) and _zoster_ (recurrent form).
1-Primary infection: Varicella or chiken pox
Transmission and pathogenesis:

- The virus is transmitted by droplets and by direct contact with the lesions.
- VZV infects the mucosa of upper respiratory then spreads via the blood to the skin → vesicular rash.
- I-P: 14-21 days.
**Clinical findings:**

– A mild febrile illness with a characteristic vesicular rash which starts on the trunk and spreads to the limbs and face.

– Vesicles appear in successive waves so that the lesions of different stages are present together.

– Complications are rare as encephalitis and pneumonia.
Chicken Pox

CH Clinical Practice Guidelines (www.rch.org.au/clinicalguide) / Kids Health Info
A-Neonatal varicella:

- Early in pregnancy fetal infection is uncommon, but can result in multiple developmental abnormalities (Scarring of the skin of the limbs, damage to the lens, retina and brain and microphthalmia).

- Near the time of birth: fetal infection is more common and may exhibit typical varicella at birth or shortly thereafter.

- The severity of the disease depends on whether the mother has begun to produce anti-VZV IgG by the time of delivery or not.
B- Latency

• Trigeminal and dorsal root ganglia being most common sites of latency.
C- Reactivation (Zoster or shingles)

- Zoster is a sporadic disease of adults or immunosuppressed patients.

- It results from reactivation of latent varicella virus acquired during childhood infection when immunity wanes.
• Painful vesicles along the course of a sensory nerve of the head or the trunk (a belt of roses from hell) is the usual picture. The pain can last for weeks and post-zoster neuralgia may exist.

• In immunocompromised, disseminated infection as pneumonia can occur.
Diagnosis

- Diagnosis is mainly clinically. However, laboratory diagnosis can be done as on the same line used for HSV.

- A rise in antibody titer can be used to diagnose varicella, but is less useful in diagnosis of zoster, since antibody is already present.
Prevention

- **Varicella-Zoster immunoglobulin (VZIG)**: Can be used to prevent varicella and disseminated zoster in immunocompromised people exposed to the virus.

- **VZV vaccine**: a live attenuated vaccine, one dose is recommended for children 1 to 12 years of age. It prevents varicella, but zoster still occur in those previously infected because the vaccine does not eliminate the latent state.
Treatment

• No antiviral therapy is necessary for chicken pox in normal.

• Systemic disease in immunocompromised patients can be treated with acyclovir.
Cytomegalovirus (CMV)

- **CMV** is structurally and morphologically identical to other herpesviruses but is antigenically different.

- Giant cells are formed, hence the name cytomegalo.
Transmission and pathogenesis

- Early in life, CMV is transmitted transplacentally, within the birth canal and commonly in breast milk.

- Later in life it is transmitted via saliva (most common route), sexually, by blood transfusion and organ transplants.

- Initial replication of the virus in the epithelial cells of the respiratory tract and gastrointestinal tract is followed by viremia and infection of all organs of the body.
Clinical significance:

**A-Primary infection:**

- In healthy individuals, primary CMV infection may cause:
  - **Asymptomatic infection** which may be associated with intermittent virus shedding in saliva and urine.
  - **Infectious mononucleosis like syndrome:** clinically similar to EBV infection. However, they are heterophile antibodies negative.
  - **Infection of immunodeficient patients:** hepatitis and pneumonia are common. In AIDS patients, diarrhea and retinitis may also occur.
Congenital infection:

- CMV is the most common intrauterine viral infection.
- In-utero it causes abortion, still birth or cytomegalic inclusion disease.
- The disease is characterized by congenital anomalies, e.g. mental retardation, microcephaly, blindness, and deafness.
- Perinatal infection from the birth canal or from the milk usually results in subclinical infection.
B- Latency and reactivation

• Latency is established in monocytes, macrophages and kidney.

• Repeated episodes of asymptomatic virus shedding over prolonged periods of times occur.
Laboratory Diagnosis

- **Virus isolation in cell culture**, CPE is slow usually taking 2-3 weeks. CPE in the form of typical swollen and translucent cells with intra nuclear inclusion bodies.

- **Fluorescent antibody and histological staining** of inclusion bodies in giant cells in urine and in tissue. The inclusion bodies are intranuclear and have an oval “owls eye” shape.
• **PCR for detection** of CMV nucleic acid in tissues or body fluids e.g. CSF.

• **Seroological test**, to detect rising IgG titer or IgM especially in congenitally infected infants is diagnostic.
Treatment

• **Ganciclovir** is effective for treatment of retinitis and pneumonia in AIDS patients.

• **Foscarnet** is also effective but more common side effects.

• CMV is largely resistant to acyclovir.
Epstein barr virus (EBV)

- **EBV** is structurally and morphologically identical to other herpesviruses but is genetically different.
Transmission and pathogenesis

- Transmission of EBV occurs by intimate contact with infected saliva.
- Viral replication occurs in the oropharyngeal epithelium, following which some of the progeny virus infect B lymphocytes \(\rightarrow\) polyclonal B cell proliferation and non-specific increase of IgM (heterophil antibodies that aggregate sheep and horse RBCs), IgG and IgA.
- Infected B cells are rejected by cytotoxic T cells which change in morphology and appear as atypical T lymphocytes in the peripheral blood.
Clinical significance

- Infectious mononucleosis (IM):
  - The disease is manifested by fever, headache, malaise, pharyngitis lymphadenopathy and increased levels of liver enzymes in the blood.
  - It lasts several weeks and complete recovery may take much longer.
• **EBV and malignancies:**

• **Burkitt’s lymphoma (BL):** It is a unique malignancy of jaw in African children. Malarial infection and HIV infection are risk factors for development of BL.

• **Nasopharyngeal carcinoma:** common among Chinese.

• **Oral hairy leukoplakia:** benign lesion of the tongue.
• **B-Latency and reactivation**:

• **EBV** remains latent in B cells, reactivation results in initiation of the viral lytic cycle → progeny EBVs infect permissive epithelial cells such as those of oropharynx.
Laboratory Diagnosis

- **Blood smear to detect lymphocytosis** and as many as 30% abnormal lymphocytes are seen on a smear (atypical lymphocytes, downy cells).

- **Detection of EBV** in patient’s peripheral lymphocytes by DNA hybridization is the most sensitive technique.

- **Detection of heterophile antibodies** which agglutinate sheep erythocytes (poul-Burnel test). It is non specific test.

- **Serum of the patient + sheep RBCs** → agglutination of RBCs.
• **Detection of EBV specific antibodies:** Abs to viral capsid antigen (VCA) or EBV nuclear antigen (EBNA) by ELISA test.

• **Virus isolation from saliva** by using cord blood lymphocytes but it is difficult and not readily available.
Treatment

- No drug available to treat EBV (due to absence of thymidine kinase enzyme encoded by the virus).

- EBV vaccine is being developed.
Human herpesviruses types 6 (HHV-6)

• **Pathogenesis:**
  • The viruses replicate into the salivary glands and are secreted into the saliva.
  • The viruses also infect peripheral blood lymphocytes and various organs including CNS.
Clinical significance

- **Exanthem subitum (roseola infantum)**: erythematous macular rash appears on the neck and trunk and spare face.

- **Acute febrile illness and febrile seizures in infants.**

- **Prolonged lymphoadenopathy, hepatitis and infectious mononucleosis like syndrome**: are relatively rare cases of primary infection of adults.
Recurrent infections

- Reactivation of latent HHV-6 together with HCMV following immunosupression → interstitial pneumonitis, fever, hepatitis and encephalitis.
HHV-6 and HIV:

- **HHV-6** is able to induce expression of **CD4** in cells not normally expressing it, this has consequence of extending the range of cells infectible by **HIV**.

- **HHV-6 transactivate transcription of HIV** → accelerate the rate of cell death in confected cells.
Laboratory diagnosis:

– PCR to detect HHV-6 DNA in the CSF of patients with neurological disorders and in serum of patients with recurrent infection.
Human herpesviruses types 7 (HHV-7)

- HHV-7 is immunologically distinct from HHV-6, though they have limited homology at the DNA level.

- The virus can be isolated from the saliva of most individuals.

- Any association of HHV-7 with disease remains to be established.
Human herpesviruses types 8 (HHV-8)

- HHV-8 is also called Kaposi's sarcoma-associated herpes virus (KSHV).

- It is lymphotropic and more closely related to EBV.
- It is believed to be the cause of Kaposi's sarcomas and some vascular tumors.
Adenoviruses are non-enveloped, double-stranded DNA viruses with icosahedral symmetry. The viral capsid is composed of 240 hexon proteins (shown in blue) and 12 penton base proteins (shown in green). The fiber spike associated with each penton base allows the virus to attach to human cells using the coxsackie-adenovirus receptor. There are 51 serotypes of human adenoviruses identified so far, three of which are currently in or soon to enter clinical trials as AIDS vaccine vectors (Ad5, Ad35, and Ad26). To circumvent pre-existing immunity to these vectors, Dan Barouch and colleagues have constructed a chimeric Ad5/Ad48 virus where the hexon proteins, the primary target of antibodies, are substituted with the corresponding proteins from Ad48.
Infection occurs by droplets, feco-oral or contact. Diseases caused by adenoviruses are:

- Respiratory disease e.g. acute febrile pharyngitis and pneumonia which is common in military recruits.
- Pharyngoconjunctival fever (Swimming pool conjunctivities).
- Eye infections, conjunctivities and keratoconjunctivities.
- Gastroenteritis and intussusception in infants.
- Acute hemorrhagic cystitis in children.
- Immunocompromized e.g. transplant or AIDS patients may suffer fatal adenovirus infections.
Laboratory Diagnosis

- **Virus isolation in a cell culture of human origin**: rounding and clustering of swollen cells indicate the presence of adenovirus.

- **Detection of adenovirus DNA** in tissue sample or body fluids by **PCR**.

- **Serology**: **CF** test to detect adenovirus group, **NT and HI tests** to detect adenovirus serotype.
No antiviral agent is available for treating adenovirus infections.

Live attenuated adenovirus vaccine capsules given orally was given for prevention of epidemic respiratory disease in military population.

The oncogenic capacity of the adenovirus in experimental animals has inhibited the use of vaccine on a wide scale.
Papilloma viruses

• There are more than 100 different types of HPV.
• Clinical significance:

  • Papillomaviruses cause papillomas which are benign tumors of sequamous cells e.g. warts on the skin, planter warts and genital warts (HPV types 1-4, 7, 10, 26-28).

  • Carcinoma of uterine cervix, penis and anus (HPV types 16, 18, 31).
Transmission:
It requires direct contact with infected individuals e.g. sexual contact or contaminated surfaces e.g. common bathroom floors.

Lab. Diagnosis:
Virus has not been isolated in cell line
Serologic tests rarely done (large number of serotypes)
PCR to detect virus DNA is available.
Poxviruses

- The poxvirus family includes 3 viruses of medical importance: Small pox virus, vaccinia virus, and molluscum contagiosum virus.

- **Structure:** poxviruses are brick shaped particles. Contain linear double stranded DNA and lipoprotein envelope.
Small poxvirus

• The only disease that has been eradicated from the face of the earth.

• Eradication is due to the vaccine.
Transmission and pathogenesis

- **Transmission** is via respiratory aerosol or by direct contact with virus either in skin lesions or on fomites such as bedding.

- The virus infects the upper respiratory tract and local lymph nodes → **blood (primary viremia).**

- **Internal organs are infected** → virus re-enters the blood → **secondary viremia** → skin.
Laboratory Diagnosis

- Detection of the virus by E/M
- Detection of viral antigen in vesicular fluid by IF.
- Virus isolation in cell culture or chick embryo.
- PCR for DNA detection
- Detection of serum Abs by Nt, IF or ELISA.
Vaccination

- Live attenuated vaccina virus vaccine.

- Vaccinia virus is prepared from vesicular lesions on shaved skin of calves or sheep or from virus grown on chick embryo, to which are added 40% glycerol and 0.4 % phenol.
Causes of successful eradication

- Man is the only host and there is no animal reservoir of infection.
- There is only one stable serotype of the virus.
- There are no chronic or asymptomatic carriers.
- Effective vaccine that is highly immunogenic and was used worldwide.
- A surveillance containment program was used by the WHO. Cases of smallpox were traced and all susceptible contacts were identified and vaccinated.
Although the disease has been eradicated, its description is important for following reasons:

- Differentiation from similar clinical conditions e.g. chickenpox, pustular acne, meningococcaemia and drug rash.
- The use of smallpox virus as a weapon in biological war.
Molluscum contagiosum virus

• It is a member of the poxvirus family.

• The virus causes small, pink, wart like benign tumors of the skin.
Hepatitis viruses

• Hepatitis means 'inflammation of the liver' .

• Among infectious causes Hepatitis viruses are the most common and the most important.

• Hepatitis B virus (HBV) was identified in the 1960's .
• Hepatitis A virus (HAV) was isolated in 1973.
• In 1990s Hepatitis C virus (HCV) was identified.

• Now, there are at least six viruses which specifically seem to infect and damage hepatocytes.
Hepatitis B Virus (HBV)

- HBV is a member of the family Hepadnaviridae, which has 2 subfamilies.
- About 350 million persons are chronically infected with HBV worldwide.

Geographic Distribution of Chronic HBV Infection

- HBsAg Prevalence:
  - 8% - High
  - 2.7% - Intermediate
  - <2% - Low
Morphology

• Virions are 42 nm in diameter and possess a nucleocapsid or “core”, surrounded by an outer coat is termed “surface antigen” or HBsAg.

• HBV has circular partially d/s DNA plus an RNA-dependent DNA polymerase (reverse transcriptase).

• The surface antigen is produced in vast excess, and is found in blood of infected individuals in the form of filamentous and spherical particles.
### Pathogenesis

- Infection is parenterally transmitted.
- The virus replicates in liver and virus particles, as well as excess viral surface protein, are shed in large amounts into the blood.
- Viraemia is prolonged and the blood of infected individuals is highly infectious.
- Incubation period: 2 - 5 months.

### How hepatitis is spread

<table>
<thead>
<tr>
<th>INFECTION SOURCE</th>
<th>TRANSMISSION PROBABILITIES</th>
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<td>Job exposure to blood</td>
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<td>Acupuncture/tattooing</td>
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<tr>
<td>Recreational cocaine</td>
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Laboratory diagnosis

• The serological diagnosis of HBV depends on detection of hepatitis markers.
Viral antigens Markers

• **Surface antigen (HBsAg):**
  • Its presence in serum indicates exposure to the virus.
  • It is the first Ag to appear and the last to disappear.
  • Chronic carriers are **HBsAg-positive**.
• **'e' antigen (HBeAg)**
  • Its presence in serum indicates a high level of viral replication.
  • It is a marker of severe illness and high infectivity.
Antibody Markers

- **Surface antibody (anti-HBs):**
  - It becomes detectable late in convalescence, and indicates immunity following infection.
  - It remains detectable for life and is not found in chronic carriers.
  - It is the antibody found in vaccinated persons and its presence may protect from new infections.
• “e” antibody (anti-HBe)
• It becomes detectable as viral replication falls.
• It indicates low infectivity in a carrier. Not found in vaccinated persons.
• **Core IgM** rises *early* in infection and indicates *recent* infection.

• **Core IgG** rises soon *after* IgM, and remains present for life in both chronic carriers as well as those who clear infection.

• Its presence indicates exposure to **HBV**.
• It is not present in vaccinated persons.
• **NB:**

• *The role of PCR in diagnosis of HBV infection should be limited to estimation of the virus load before, during and after treatment.*
HBV Vaccination: Active Immunization

• **Recombinant HBsAg:**
  - Recombinant HBsAg vaccines produced in yeast have been available since 1986 and are now widely used.
  - The administration of three doses induces protective levels of antibodies in 95% of vaccine recipients.
• Vaccine should be administered to people at high risk of infection with HBV as:
  – Health care workers
  – Sexual partners of chronic carriers
  – Infants of HBV carrier mothers.
  – Universal immunization of infants was introduced in Egypt since April 1995. Infants receive 3 doses at 0, 6, and 14 weeks of age.
Passive Immunization

• Hepatitis B immune globulin should be administered to non immune individuals following single episode exposure to HBV-infected blood e.g. needle stick injuries.
HBV antigens and antibodies in the blood

- **Infectious**
  - HBsAg
  - HBeAg
  - anti-HBc IgM

- **Immune**
  - anti-HBc Total
  - anti-HBs
  - anti-HBe

- Incubation period
- Symptoms
- Time

- Infection: 2 weeks to 3 months
- After 6 to 12 months
- >20 years
Treatment

• Combination therapy of both **IFN** and **Lamivudine** gives good results.
Markers of Acute HBV infection

- HBs Ag
- HBe Ag
- Anti-HBc
- Anti-HBc IgM
- Anti-HBs
- Anti-HBe

Months after exposure
Markers of Chronic HBV infection

- Anti-HBc IgM
- HBs Ag
- HBe Ag
- Anti-HBc
- Anti-HBe

ILLNESS often subclinical

1 2 3 4 Months
1 2 4 6 8 10 Years
Hepatitis A Virus (HAV)

- **HAV is a Picornavirus.** HAV is a small, non-enveloped icosahedral particle.

- **Size:** ~ 27 nm in diameter.

- **Genome:** ss RNA genome.
Transmission

- **Enteric**: HAV spreads via:
  - Case-to-case, via fecal-oral route.
  - Contamination of food or water with sewage.
  - Infected food handlers.
  - Shell fish grown in sewage-polluted water.
Clinical Features

- **Incubation period**: 3-5 weeks (mean 28 days)
- Milder disease than Hepatitis B.
- HAV infection is very variable with more than 90% of childhood infections asymptomatic.
- About 25-50% of adult infections are asymptomatic.
– Fever, loss of appetite and jaundice are main symptoms.

– 99% cases recover completely, a few cases experience permanent liver damage.

• Although convalescence may be prolonged, there is no chronic form of the disease.
Laboratory diagnosis

• Diagnosis depends mainly on the presence of HAV-specific IgM in the patient's blood.
Prevention and treatment

- Assurance of the patient and his family is essential.
- Health education to the family to avoid further spread of infection to other members of the family.
- Currently, two Hepatitis A vaccines are available; HAVRIX and VAQTA.
• Both vaccines are given intramuscularly and repeated in six to 12 months.

• A combined hepatitis A and B vaccine (Twinrix) is now licensed for use in persons aged 18 years.

• This consists of the antigenic components used in Havrix (HAV) and Engerix-B (HBV) vaccines.
Hepatitis C Virus (HCV)

• The major cause of parenterally transmitted none A non B hepatitis.

• In Egypt, most studies found that at least 12 - 15% of adult population have antibodies to HCV making it the most common viral infection and may be the most important health problem in Egypt.
HCV is a member of the Flaviviridae family. It is an enveloped virus with a linear, ss, +ve sense RNA genome. Isolates from all over the world have now been grouped into 6 main genotypes, each with several subtypes, based on sequence data. Genotype 4a is prevalent in Egypt.
Rasha El Naggar

Route of transmission

• The parenteral route of infection seems to be most prevalent, with high rates of infection seen in:
  • Intravenous drug abusers
  • Hemophiliacs and recipients of unscreened blood transfusions.
• Sexual transmission cannot be eliminated, but if it occurs, the risk seems to be very low.

Risk factors:

• people who share needles
• health workers who are exposed to infected blood

Possible symptoms:

• pain in the upper right quadrant of abdomen
• nausea and vomiting
• loss of appetite
• jaundice
• fatigue
• itching
• Vertical transmission of HCV seems to occur at a very low rate.

• Infection in utero seems to be rare.

• Breast feeding is not a significant risk factor.
Laboratory diagnosis: 1) Serology

- Reliable serological tests (ELISA) have become available including simple rapid tests.

- Positive sera in low-prevalence regions need confirmation by a more specific test like RIBA (Recombinant Immune Blotting Assay).

- In Egypt we do not need confirmation of ELISA by RIBA but instead we go to do PCR.
2) Viral genome detection

- **PCR** detects viral genome in patient's serum, in liver biopsy or in macrophages.

- It can be done both **quantitative and qualitative**.

- **Quantitative PCR** should be done before starting treatment and **12 weeks** after starting treatment and at the end of treatment.

- **Ab** indicates exposure and **PCR** positivity indicates presence of **viraemia**.

In Egypt HCV diagnosis should be thought in:

- Adult patients with more than 2-fold constant rise in serum transaminases.
- Adults with thrombocytopenia without any apparent cause.
- Spouses and children of HCV-positive patients.
- All blood or organ donors.
- Patients who are doing hemodialysis.
- IV drug abusers (if identified).
Treatment and prevention

• A combination of interferon-2b and ribavirin is the only currently recommended treatment of choice for patients considered to be at risk of disease progression.

• During treatment follow up is done by blood picture every 2 weeks and PCR after 12 weeks, 24 weeks then at the end of treatment.
• Until a vaccine is developed prevention of infection spread and health education are essential to minimize exposure of non infected persons to the virus.

• Health care workers and other people who may have contact with body fluids should learn the principals of infection control.

• (Any blood sample should be considered infectious even if proved otherwise).
Hepatitis D (delta) virus (HDV)

- HDV is a defective transmissible pathogen dependent on HBV for replication.
- The virus particle is 36 nm in diameter, encapsulated with HBsAg.
- Its genome is a covalently closed circular RNA molecule.
- HDV can be controlled by controlling HBV infection.
Hepatitis E virus (HEV)

- The cause of enterically-transmitted non-A, non-B hepatitis.

- The virion is a 30-32 nm non-enveloped particle containing an s/s (+) sense RNA genome.

- Genetic organization similar (not identical) to *Caliciviruses*.

- Similar to hepatitis A: virus replicates in the gut initially, before invading the liver, and virus is shed in the stool prior to the onset of symptoms.
• Viraemia is transient.
• Normal course of infection seems to be an acute but relatively benign illness, except in pregnant women where there is 15-30% mortality.
• *Diagnosis depends on detection of:*
  1) Calicivirus-like particles in the stool, by electron microscopy.
  2) Specific IgM in serum.
  3) PCR HEV-specific sequences in stool.
RNA Viruses

- Picornavirus
  - Genome: 22-30 nm
- Astrovirus
  - Capsid: 30-35 nm
- Calicivirus
  - C = 32 (holes): 35-39 nm
- Flavivirus
  - Icosahedral: 45-50 nm
- Togavirus
  - Icosahedral: 70 nm

- Coronavirus
  - Pleomorphic: 120-160 nm
- Retrovirus
  - Icosahedral: 90-120 nm
  - C = 132 segments: 60-80 nm

- Reovirus
  - 10-12 segments

- Bunyavirus
  - 90-120 nm
- Orthomyxovirus
  - Helical, Pleomorphic: 80-120 nm

- Arenavirus
  - Pleomorphic: 110-130 nm
- Filovirus
  - Helical: 80x800-2500 nm
- Rhabdovirus
  - Helical: 60x180 nm
- Paramyxovirus
  - Helical, Pleomorphic: 150-300 nm

DNA Viruses

- Circovirus
  - Icosahedral: 17-22 nm
- Parovirus
  - C = 12 segments: 18-26 nm
- Hepadnavirus
  - C = 180 Icosahedral: 40-48 nm
- Papovavirus
  - C = 72 Complex: 45/55 nm

- Adenovirus
  - Icosahedron: 75-80 nm
- Herpesvirus
  - C = 162 Complex: 150-200 nm
- Poxvirus
  - Complex: 240x300 nm
Picornaviridae

• 'Pico (Greek = very small) RNA Viruses'.
Classification

- The most recent revision of virus taxonomy has recognized nine genera within the family. The most important of them are:
  - *Enterovirus*: Poliovirus, Coxsackie, echo viruses
  - *Rhinovirus*: Human rhinovirus.
  - *Hepatovirus*: Hepatitis A virus.
  - *Cardiovirus*: Encephalomyocarditis virus
Enteroviruses

- Enterovirus infections are common in humans; seasonal peak in **autumn**; frequently undiagnosed.

- Human enteroviruses are small non-enveloped isometric viruses that multiply in the gut mucosa and are transmitted from person to person by the **fecal-oral route** (ingestion disease).
• They spread throughout the body via the blood stream.

• Most infections occur during childhood, and they are usually transient but produce life-long immunity.

• **Clinical syndromes** are generally mild, but occasional infections may cause serious disease e.g. paralytic poliomyelitis, meningitis, or myocarditis.
Poliovirus

- **Virus**: small (30nm) with an icosahedral capsid enclosing a (+) sense, single-stranded RNA genome.

- Relatively resistant to extremes of: pH and temperature, and to lipid solvents and detergents.

- Antigenically 3 types can be distinguished.
Pathogenesis of Poliomyelitis

• After ingestion of the virus, there is local multiplication in the oropharynx and associated lymph nodes.

• Local multiplication also takes place in the gut mucosa and regional lymph nodes.

• Thereafter a viraemia follows, and the patient may experience a fever about a week after exposure.

• Virus is produced and released into the gut (and throat initially) and can be isolated from the throat or stools for some weeks following the incubation period.
• Most infections are asymptomatic, although in some patients there is a minor transient febrile illness.

• Occasionally (between 1/100 and 1/1000 of cases) the viraemia may lead to CNS involvement and paralysis due to permanent damage to the anterior horn motor neurons of the spinal cord.

• About 1% of people infected with the most virulent strains experience paralysis.

• Death is usually due to respiratory failure by paralysis of the intercostal muscles and diaphragm.
Clinically

- Four forms are usually described:
  - 1-Abortive Poliomyelitis
  - 2-Nonparalytic Poliomyelitis (Aseptic Meningitis)
  - 3-Paralytic Poliomyelitis
  - 4-Progressive post poliomyelitis Muscle Atrophy.
Laboratory diagnosis

- **Direct detection:**
  - Virus may be recovered from feces or throat swabs.

- Cultures (on human or monkey cells) and recognition of *cytopathic effects* (after 3 – 6 days) with confirmation by *neutralization of infectivity* with specific antisera.
Serology

• **Antibodies** are not usually helpful in providing a positive diagnosis of poliomyelitis, but do give the immune status of an individual (does/does not need further vaccination).

• **CSF:** Polio virus is never found in the CSF but antibodies here mean either CNS infection or a leak from blood antibodies.
Poliovaccines

• Live attenuated virus (Sabin vaccine): Strains of poliovirus 1, 2, and 3 which have been attenuated by passage in unnatural conditions to lose neurovirulence.

• The 3 live strains mixed, given as oral drops on 3 occasions plus boosters.

• This vaccine is used in Egypt, USA and most other countries.
Rasha El Naggar

Advantages

• Given as oral drops (easy administration).
• Live vaccine that mimics natural infection with good immunity including IgA in the gut.
• It is also cheap to prepare and may spread to the community giving wider range of vaccination.

“Wellbee” says BE WELL! take ORAL POLIO VACCINE

• tastes good
• works fast
• prevents polio
Disadvantages

- Wild enteroviruses coincidentally present in the gut may also interfere, especially in the tropics.

- It is very important to maintain 'cold chain' when storing and distributing vaccine as it may lose potency.

- It can not be used in immunocompromized patients.
2. **Inactivated whole virus (Salk vaccine)**

- Polio 1, 2 and 3 inactivated with formalin.

- It is given as 3 injections at 3 to 6 months of age with later boosters.
• **Advantages**: Safe, stable and can be used in immunocompromized.

• **Disadvantages**: Much antigen is required which makes the vaccine expensive.

• Difficult to administer and gives no local immunity.
Coxsackie viruses

- Coxsackie viruses are classified into two groups, based on pathology in suckling mice:
  - **Group A**: Cause acute myositis with inflammation and necrosis. 24 serotypes.
  - **Group B**: Cause degenerative 'plaques' in brain, muscle and pancreas (model for induced diabetes in mice). 6 serotypes.
• In man, coxsackie viruses show a seasonal, epidemic pattern of infection (mostly sub-clinical), associated with meningitis, paralysis (less severe than acute poliomyelitis), and myocarditis.

• Coxsackie A16 causes the common childhood infection [link: hand-foot-mouth disease](http://example.com) (Not foot and mouth: hand-foot-mouth).
Echoviruses

- Enteric Cytopathic Human Orphan viruses; not linked to any human disease (hence 'orphan').

- 32 serotypes.

- Common cause of enteric infections.

- Associated with some cases of aseptic meningitis and some enteric infections.
Human Rhinoviruses (HRV)

- Small RNA viruses similar to other Picornaviruses.
- They cause 'the common cold' (but not the only one).
- About 105 serotypes are identified (hence repeated infections).
- They are relatively fragile viruses, with optimum growth temperature of 33°.
- An infected person is infectious in the first two days of coryza.
Symptoms of common cold are due to **damage to ciliated epithelium in the URT**.

Secondary bacterial infections (a major problem in infants and elderly as 5-10% of viral upper respiratory tract infections progress to bacterial sinusitis.).
Treatment

• No specific treatment or vaccines are available.
• However, numerous symptomatic treatments are available.
• Recently, a drug (Pleconaril) has been developed which has activity against enteroviruses and rhinoviruses.
• It inhibits viral replication by blocking viral uncoating, viral attachment to host cell receptors.
Aphthoviruses

• This is the group of viruses responsible for foot-and-mouth disease (FMD).
• One of the most contagious animal diseases, with important economic losses.
• Aphthoviruses are physically quite distinct from other Picornaviruses as it is acid-labile (inactivated by pH <6.0).
• Antigenically: 7 serotypes: A, O, C, SAT1, SAT2, SAT3 and Asia 1.
• Genome: Larger than other Picornaviruses, ~ 8.5kb.
Clinical Features

• Foot and mouth disease is a zoonosis, a disease transmissible to humans by contact or ingestion, but it crosses the species barrier with difficulty and with little effect.

• The type of virus most often isolated in humans is type O followed by type C and rarely A.

• The incubation period in humans is 2-6 days.
• Symptoms have mostly been mild and self limiting.

• Mainly uncomfortable tingling blisters on the hands but also fever, sore throat, and blisters on the feet and in the mouth, including the tongue.

• Patients have usually recovered a week after the last blister formation.
Laboratory diagnosis

- **Identification of the antigen:** by ELISA or CFT.
- **Virus isolation:** by culture on suitable cells.

- **Sero logical tests:** Detection of Ab in sera of infected animals by: ELISA or Virus neutralization test (Samples should be frozen to below -40°C immediately after collection).
Myxoviridae

• **Orthomyxoviridae**: containing the *influenza viruses* (*A*, *B*, and *C*).

• **Particle size**: 80-120 nm (highly pleomorphic).

• **Core diameter**: 9 nm.

• **Replication**: Nuclear.

• **Genome**: Segmented (-) sense RNA.
- **Paramyxoviridae**: containing the parainfluenza, mumps, measles and respiratory syncytium virus.

- **Particle size**: 125-250 nm (somewhat pleomorphic)

- **Core diameter**: 14-20 nm.

- **Replication**: Cytoplasmic.

- **Genome**: Non-segmented (-) sense RNA.
Influenza virus
Morphology:

- Influenza virus particles are highly pleomorphic, 80-120 nm in diameter.
- The outer surface of the particle consists of a lipid envelope from which project prominent glycoprotein spikes of two types:
  1. Haemagglutinin (HA),
  2. Neuraminidase (NA).
- The inner side of the envelope is lined by matrix protein (MP).
- The genome consists of s/s (–) sense RNA in 8 segments (7 in Influenza C).

Influenza Virus Anatomy:

- Nucleoprotein (RNA)
- Lipid Envelope
- Capsid
- Hemagglutinin
- Neuraminidase (Sialidase)

Figure 1
• **Classification** of virus strains is done on the basis of antigenicity of NP and MP into three main groups A, B and C.
• **Influenza is characterized by:**
  • fever, myalgia, headache and pharyngitis.
  • In addition there may be cough and in severe cases, prostration.
  • There is usually *no* coryza (runny nose) which characterizes common cold infections.
  • Infection may be very mild, even asymptomatic, moderate or very severe.
Influenza Virus

Influenza enters through the nose and settles in the respiratory tract.
Complications

- Tend to occur in the young, elderly, and persons with chronic cardio-pulmonary diseases.

- **Complications consist of:**
  - Pneumonia caused by influenza virus itself.
  - Pneumonia caused by bacteria: *Haemophilus influenza, Staphylococcus aureus* or *Streptococcus pneumoniae*.
  - Other viral super-infection, e.g. Adenovirus.
Epidemiology

- Influenza A virus is essentially an avian virus that has "recently" crossed into mammals.
- Birds have the greatest number and range of influenza strains.
- Avian haemagglutinins sometimes appear in pig, human and horse influenza strains (pig is the mixing pot).
- There is constant antigenic change down the years which means that new vaccines have to be made on a regular basis.
• Every now and then (10 - 15 years) a major new pandemic strain appears in man, with a totally new HA and sometimes a new NA as well (Antigenic Shift).

• This variant causes a major epidemic around the world (pandemic).

• Over the subsequent years this strain undergoes minor changes (Antigenic Drift) every two to three years, probably driven by selective antibody pressure in the populations of humans infected.
Laboratory diagnosis

- **Viral Isolation**: Samples:
- Respiratory secretions: obtained by direct aspirate, gargle or nasal washings used for:
  - Rapid examination of cells by IF.
  - Inoculation of cell cultures (or eggs).
- **Serology**: By detection of antibodies in the serum by haemagglutination inhibition.
Treatment

- Several anti-influenza drugs exist.

- **Amantadine** and **Rimantadine** are active against influenza A (but not B viruses).
Vaccines

• Formaline inactivated vaccine:
• Are produced by re-assortment of egg-adapted strains with strains with the required HA type.
• Large amounts of virus are then grown in embryonated eggs (cheap and efficient), purified and formalin inactivated.
• The vaccine is given subcutaneously, 2 doses.
Avian influenza is an infectious disease of birds caused by type A strains of the influenza virus. Highly pathogenic avian influenza is characterized by sudden onset, severe illness, and rapid death, with a mortality that can approach 100% of the infected birds.
• **Migratory waterfowl** — most notably wild ducks – are the natural reservoir of avian influenza viruses, and these birds are also the most resistant to infection.

• Domestic poultry, including chickens and turkeys, are particularly susceptible to epidemics of rapidly fatal influenza.
• Direct or indirect contact of domestic flocks with wild migratory waterfowl has been implicated as a frequent cause of epidemics.

• Live bird markets have also played an important role in the spread of epidemics.
Avian influenza in Humans

• **H5N1** variants from avian viruses demonstrated a capacity to directly infect humans in 1997 in Hong Kong and in Viet Nam in January 2004.

• In **Egypt** we had about 100 human cases with death rates above 30%.

• Infection is transmitted from birds to human but no Human to Human transmission is documented.
Swine Flu (H1N1)

What is it?
• It is a new strain of Influenza virus A/H1N1.

* There have been reporting of influenza-like illness (ILI) and severe pneumonia cases in Mexico and USA. Cases began to appear on 17 March 2009 in Mexico.

* Two cases in children were reported in Southern California in USA on 17 April, 2009.

* Neither child had contact with animals.

* Between 17 March and now, clusters of outbreaks have appeared in multiple locations in Mexico and USA.

* These clusters are consistent with human-to-human spread.
What are the characteristics of the virus?

- The virus causing this illness is being described in the USA as a new subtype of A/H1N1 not previously detected in swine or humans.
- Genetically, it is a reassortant of America-Eurasian swine influenza viruses.
Who are affected?

• Most of the cases in Mexico have been found in healthy young adults between the age of 4 and 45 years old.

• In the USA, the cases range in age from 7 years to 54 years.
How does it spread?

- It is believed to spread in the same way as seasonal influenza.
- That means through direct contact (being within one meter of an infected person) or indirect contact (touching a contaminated surface).
What are the clinical symptoms?

- Patients experience high fever, cough, and sore throat, symptoms similar to typical influenza, with some patients experiencing diarrhoea and vomiting.
- The cases can rapidly progress to severe and unusual pneumonia.
What medicines can be used for treatment of an infection by this new virus?

- This virus is susceptible to oseltamivir and zanamivir.
- The virus strain has been shown to be resistant to rimantadine and amantadine.

Skin Care
Method for using hand cream, soap and cleanser

Follow the steps shown:

1. Apply hand cream or soap/cleanser
2. Palm to palm
3. Palm to back, fingers overlaced
4. Palm to palm fingers interlaced
5. Fingers interlocked
6. Rubbing of each wrist
7. Rotational rubbing of fingertips in palm
8. Rotational rubbing of thumb in palm
9. Ensure shaded areas are not missed
Paramyxoviridae

• This sub-family contains parainfluenza viruses (1, 2, 3 and 4), measles virus, mumps virus and respiratory syncytium virus.
Morphology

- **Paramyxoviruses** are composed of:
  - One piece of single stranded RNA,
  - A helical nucleocapsid,
  - An outer lipoprotein envelope.

- The envelope is covered with spikes, which contain haemagglutinin, neuraminidase, and a fusion protein that causes cell fusion (form large multinucleate syncytia or giant cells) and, in some cases, haemolysis.
Primary infections

- Usually occur in (early) childhood, with some degree of protection against developing clinical disease later on in life.

- Re-infections do occur in adulthood, but disease is sub-clinical or very minor.
Spread

• The human paramyxoviruses are essentially diseases of man only.
• Spread by droplets from the nose and mouth to fairly close contacts.
• Many of them are highly infectious and go around the community in epidemics.
• Often seasonal (winter coughs and colds).
Para-Influenza Viruses 1 – 4

• Types 1, 2 and 3 may be associated with more severe lower respiratory tract disease in children called acute laryngo-tracheo-bronchitis. Para-influenza viruses have also been isolated from patients with pneumonia.

• Primary infections with Para-influenza viruses usually occur in the first year or years of life.

• Re-infection usually causes only minor infection of the URT (one of the causes of a common cold in children and adults).
• **Diagnosis**
  - In cell cultures, the Para-influenza viruses produce a recognizable cytopathic effect, and hemadsorption is also used to detect their presence.

• **Treatment**
  - No specific treatment is available.
  - Killed virus vaccines have been tried but are of limited value in an infection which is so widespread and usually of trivial significance.
Mumps Virus

- Mumps virus is spread by the respiratory route, and has a relatively long incubation of about 21 days.
- It causes a febrile illness and inflammation of the salivary glands, classically the parotid and submaxillary glands.
- The swelling of the glands may be asynchronous, and lasts about 1 week.
Complications

• Aseptic meningitis
• Mumps meningoencephalitis
• Orchitis
• **Diagnosis:**

• **Isolation of the virus** from saliva, CSF or urine by culture on monkey kidney cells.

• **Serologically:** Diagnosis can be confirmed by positive IgM antibodies by using CF, HI and ELISA tests.

• **Prevention:** live attenuated virus vaccine given in MMR vaccine.
Measles Virus

- Measles is one of the most infectious diseases known.
- Transmission and initial stages of disease are similar to mumps, but this virus can also infect via the eye and multiply in the conjunctivae.
Viraemia following primary local multiplication results in widespread distribution to many organs.

After a 10-12 day incubation period, dry cough, sore throat, conjunctivitis, followed a few days later by the characteristic red, maculopapular rash and Koplik's spots (raised red spots with white centers in the mouth).
complication

- Bronchopneumonia and otitis media.

- Encephalitis occurs in ~1:2000 cases.

- Subacute sclerosing pan encephalitis: It is a chronic infection in which the virus multiplies in the brain resulting in neurodegenerative disease.
• **Diagnosis:**
  Measles is easy to diagnose clinically. Laboratory diagnosis is rarely needed.

• **Treatment:**
  No specific drugs. Symptomatic treatment only.
Prevention

• Trivalent live attenuated vaccine (MMR) is usually given.

• All of these viruses best avoided during pregnancy.

• A single dose of the MMR vaccine gives around 90% protection against measles and mumps and 95-99% against rubella.

• The present WHO target for eradication of measles is the year 2015.
Respiratory Syncytial Virus (RSV)

- RSV resembles the other members of Paramyxoviruses morphologically, but it has no haemagglutinin or neuraminidase.

- Also, no hemolytic properties have been detected, and there is no antigenic similarity to other paramyxoviruses.

- RSV is highly infectious, transmission occurs by respiratory secretions.
• **RSV** is the prime cause of bronchiolitis.

• **RSV** may be linked to epidemics of asthma and has been identified as an exacerbating factor in nephrotic disease, cystic fibrosis, and opportunistic infections in the immunocompromized.
Diagnosis

• **Virus isolation:** On cell culture using human diploid fibroblasts (HDF).

• **Direct:** by IF on smears of respiratory epithelium.

*A rise of antibody titer of at least 4 folds is also diagnostic.*
Coronaviridae

• First isolated from chickens in 1937 but obtained major importance in 2003 when SARS appeared.
Morphology

- Particles are **irregularly-shaped**.
- **Size:** 60-220 nm in diameter,
- An outer envelope bearing distinctive, 'club-shaped' peplomers.
- This 'crown-like' appearance gives the family its name.
- The genome is **non-segmented, s/s, (+) sense RNA, 27-31 kb** (the longest of any RNA virus).
SARS

- **Severe Acute Respiratory Syndrome (SARS)** is a respiratory illness that has been reported in Asia, North America, and Europe. The disease spreads from person to person.

- It often begins with a high fever, headache and sore throat.
• Other possible symptoms include loss of appetite, confusion, rash and diarrhea (that is why it is called syndrome).

• Fatality reached 90%, although not everyone has reacted the same way.
There are more than 150 species in the family Reoviridae.

They are unified by their most unique feature - the composition of their genome double-stranded RNA.
General Characteristics

- **Size:** 70-85 nm in diameter, nearly spherical icosahedral particles.
- Non-enveloped, the capsid forms double shell of proteins.
- **Genome:** composed of 10-12 segments d/s RNA.
- **Replication:** occurs in cytoplasm; after incomplete uncoating of virions, which possess all the enzymes required for d/s RNA transcription.
Rotaviruses

- Rotavirus is the most important human pathogen.

- It is the major cause of **Infantile gastroenteritis**.
Morphology

- Double stranded RNA.
- Icosahedral.
- 60-80 nm particles having a *double layered* capsid.
- It is non-enveloped and difficult to grow in culture.
Pathogenesis

- **Incubation period**: 1-4 days.

- It is common in children between the age of 6 months and 2 years.

- The virus infects by **faeco-oral route**.
The virus multiplies in the villi of small intestine and damage their transport mechanisms.

Sodium and glucose absorption is impaired.

This causes watery non-bloody diarrhea and vomiting associated with fever and abdominal pain ending with dehydration, acidosis and shock.

If not treated, death may occur.
Diagnosis

- **Stools samples collected during the first few days of illness are examined as follows:**
  - Rapid diagnosis
  - Kits that detect the virus in stools by ELISA, latex agglutination or RIA.
  - Demonstration of the virus in stools by immunoelectron microscopy.
  - PCR.
  - A rising antibody titer can be detected by ELISA or CF in serum samples.
Treatment and control

- Replacement of fluids and restoration of electrolyte balance.
- There is neither antiviral therapy nor vaccine available.
Arboviruses

- They are a large group (more than 400) of enveloped RNA viruses.

- They are transmitted primarily by Arthropod vectors (mosquitoes, sand-flies, fleas, ticks, lice).

- They have complex life-cycles and replicate in both the primary hosts, secondary hosts (which may often be dead-ends) and the Arthropod vectors.
• Group I: (+) sense RNA Viruses:
  • Flaviviridae:
    • 1) Flavivirus: Yellow fever virus.
    • 2) Pestivirus: Bovine diarrhea virus.
    • 3) Hepacivirus: Hepatitis C virus.
  • Togaviridae:
    • 1) Alphavirus: Sindbis virus.
    • 2) Rubivirus: Rubella virus.
• **Group II: (-) sense RNA Viruses:**
  • *Arenaviridae:*
    • Arenavirus.
  
  • *Bunyaviridae:*
    • 1) Bunyavirus: Bunyamwera virus.
    • 2) Hantavirus: Hantaan virus.
General Characters

• Arboviruses are single-stranded enveloped RNA viruses with haemagglutinating properties.

• They grow in suckling mice and/or in cell cultures.
Diagnosis

• Isolation of the virus (usually done in a special P4 level laboratory).

• Detection of IgM and IgG antibodies by haemagglutination-inhibition, or ELISA.
Control

- Human disease control is limited to prevention by:
  - 1) Control of vector, e.g. mosquito control which can be very effective.
  - 2) Use of vaccines in a few types of infection, e.g. Yellow Fever.
  - 3) Surveillance.
Human diseases caused by Arboviruses

- There are 4 major clinical patterns of disease:
  - No clinical illness.
  - Febrile systemic illness.
  - Encephalitis
  - Hemorrhagic fever.
Hemorrhagic Fevers

• A number of arboviruses.

• (Togaviruses and Bunyaviruses) and some similar viruses (Arenaviruses and Filoviruses) may cause a non-specific flu-like illness which rapidly progresses to a severe disseminated illness with a marked bleeding tendency and multi-organ failure.
Examples

- Yellow Fever:
- It has 2 types:
  - 1-Jungle (sylvan) YF.
  - 2-Urban YF.
- Lassa Fever
- Hanta Fever
- Crimean Congo Hemorrhagic Fever
Yellow Fever

• It is the first identified disease caused by Flaviviruses (Latin 'flavus' = yellow).

• Transmitted by mosquitoes.
• **Jungle (sylvan) YF**: mainly in monkeys with sporadic cases in forest worker/visitor.

• **Urban YF**: from the jungle YF can be introduced into towns getting new cycle: man - mosquito – man.
Pathogenesis

• Transient viraemia.

• primary multiplication in lymph nodes.

• secondary multiplication occurs in liver (jaundice), spleen, kidneys, heart and bone marrow with much tissue damage.
• After an incubation period of 3 to 6 days, 5% to 50% of infected people develop disease.

• Beginning with a nonspecific 1- to 3-day febrile illness, followed by a brief remission.

• Then by a life-threatening "toxic" syndrome accompanied by epistaxis, other hemorrhagic phenomena, jaundice, and disseminated intravascular coagulation.

• Mortality rates for yellow fever are approximately 20%.
Laboratory Diagnosis

- Cultivation of the virus from blood (serum) or tissue.
- Antigen detection by IF or immunohistochemistry.
- RNA detection by RT-PCR, or by
- Specific antibody detection.
Vaccine

1) "17 D strain": live attenuated vaccine strain prepared in eggs, very effective.
- It is given in one SC injection.

2) "French Dakar Vaccine": live attenuated brain tissue-derived vaccine.
- Inoculated by skin scratch.
- More stable and cheap to administer.
  Occasionally causes CNS complications.
Rubella

- Characteristic pink, continuous maculopapular rash appears in 95% of adolescent patients 14-25 days (average: 18 days) after infection.
- Patient is infectious for most of this time.
- After early viraemia, virus multiplies in many organs, particularly lymph nodes (lymphadenopathy), including the placenta.
• **In children**, a mild febrile illness - less severe than measles.

• Other than pregnant women, symptoms in adults are rare.
RASHA ELNAGAR

Congenital Rubella

- Virus crosses placenta and multiplies in the fetus.
- Up to 85% of infants infected in the first trimester of pregnancy get congenital rubella syndrome (CRS) with low birth weight, deafness, CNS involvement and abortion.
- The earlier in pregnancy infection occurs, the worse the prognosis becomes.

Rubella syndrome

Microcephaly

PDA

Cataracts
• Fetus is persistently infected (presumably due to immature immune response) and continues to excrete virus after birth.

• (a risk to doctors, nurses and other patients).
Prevention/Control

- **MMR**: A live attenuated vaccine has been used effectively.

- For women infected during first trimester of pregnancy, therapeutic abortion may be recommended.
Filoviridae

- Name comes from the Latin: *filo* = 'thread-like'.

- Two outbreaks of unrecognized haemorrhagic fever; one in 1967 (Marburg) and the other in 1976 (Ebola) have been occurred.

*From these two outbreaks, 2 novel viruses (Marburg & Ebola) were isolated and placed in a new family, the Filoviridae.*
Morphology:

- Pleiomorphic (130-14,000 nm long).
- The filovirus genome is s/s.
- Unsegmented.
- (-) sense RNA.
- 19kb encoding 7 proteins.
Ebola Disease

- The clinical manifestations of Ebola virus infection are severe.
- The incubation period varies between four and sixteen days.
  - **The initial symptoms:**
  - Severe frontal and temporal headache.
  - Generalized aches.
  - Pains and malaise.
  - By the second day the victim will have a fever.
  - Later symptoms include watery diarrhea, abdominal pain, nausea, vomiting, a dry sore throat, and anorexia.
• Ebola causes lesions in almost every organ, although the liver and spleen are the most noticeably affected.
• Both are darkened and enlarged with signs of necrosis.
• The cause of death is normally shock, associated with fluid and blood loss into the tissues.
Treatment

• No vaccines or treatments are available for human use.
• The effects of various candidate vaccines have been evaluated in both rodents and nonhuman primates.

*Steroids may be useful in preventing the worse symptoms of Ebola infection.
Rhabdoviruses

- Rhabdo in Greek means 'rod-shaped'.

**Morphology:**
- Particles $180 \times 70$ nm with unique bullet-shaped appearance.
- They are enveloped with prominent spikes on surface (G protein haemagglutinates RBCs).
- Genome: \((\text{sense ss RNA ~11 kb})\)

![Diagram of Rhabdovirus morphology](image)
Rabies

How it spreads
ANIMAL BITE: The farther away from brain, the longer virus takes to spread

VIRUS: Spreads through central nervous system

Common carriers of rabies
Infected animals: Show no fear for humans; act very agitated
Bat, Fox, Cat, Skunk

Dog: Another common rabies source

Symptoms in humans
- Fever, depression
- Agitation
- Painful spasms followed by excessive saliva
- Death within a week without vaccine

Treatment: Hospitalization, immune globulin injections, anti-rabies vaccine

Foaming at mouth after drinking: Produced by spasms in throat

SOURCE: The World Book Medical Encyclopedia
Rasha ElNagar

• Primary replication occurs locally in muscle and connective tissue (no symptoms).

• Virus eventually infects peripheral nerves, and then travels along neuronal axons to CNS, where it produces severe and fatal encephalitis.

• Few cases escape these severe consequences.

• Incubation period varies from 3-8 weeks to 1 year depending on size and site of inoculation (e.g. head/face/neck vs. hands or feet).

NEGRI BODIES
Treatment and Vaccination

• In veterinary medicine rabies vaccines are used as a preventive measure.
• Vaccination of humans takes place mainly after exposure to a rabid animal.
• There is no effective drug treatment against rabies.
• Passive immunization is of value.

• In the case of severe exposure: vaccination is often accompanied by injection of rabies immunoglobulin (IG).
Three types of vaccine exist:

- **Inactivated**: Pioneered by Pasteur in the 1880's
  - used until the 1950's.
  - It contains material from infected animals containing up to 5% nervous tissue (provoked severe immune reactions in recipients, but saved lives).
• **Duck embryo vaccine:** This type of vaccine was then produced by growing the virus in embryonated duck eggs (better).
  • Still produced severe encephalitis in some recipients.
  • It is given in 21 injections.
• **HDC vaccine:** Inactivated vaccine is now produced by growing the virus in diploid human fibroblasts (effective and safe but expensive).
  • Duck egg-produced material still used in third world.
  • It is given in 6 injections.
• **Live attenuated:** It has been used to vaccinate domestic animals and livestock.

• Effective, but not considered sufficiently safe for human use.

• **Recombinant:** A recently developed recombinant vaccinia virus / G protein vaccine is being used to eradicate rabies in foxes in Europe.
Retroviruses

• Retroviruses have received much attention in recent years, but they have a long history (before being called Retroviruses, at that time it was considered as RNA oncogenic viruses).

• After discovery of the Reverse Transcriptase (RT) enzyme in these viruses the name Retroviruses was used.
Morphology

• Retroviruses have enveloped particles, about 100 nm diameters.

• The envelope carries a virus-encoded glycoprotein, which forms spikes in the membrane.

• Nucleocapsid protein: p24 protein.

• Inside the membrane is the matrix p17 (MA) protein.

• Viral genome (ss RNA in 2 parts), associated with reverse transcriptase (RT).
Retroviruses Classification
• **Oncovirinae**: Viruses contain an extra gene termed, ‘onc’.

• These genes are called oncogenes because their expression in the virus infected cell is associated with tumor production causing sarcomas and leukemias in animals.

• Rous Sarcoma Virus and Murine leukemia virus.

• HTLV is causing leukemia in human but through a different mechanism (*HTLVs do not possess an onc gene*).
• **Lentivirinae:** Viruses causing fusion and lysis of infected cells leading to progressive degenerative disorders.

• visnavirus of sheep and human immunodeficiency virus (HIV) causing AIDS.

• **Spumavirinae:** foamy viruses with no pathology known.
HTLV

- HTLV-I infection occurs with varying degrees of prevalence, in several regions of the world.

- Infection may lead to Adult T-Cell leukemia (ATL) or Tropical spastic paraparesis (TSP).

- The highest prevalence is in southwestern Japan, where the prevalence of anti-HTLV-1 antibodies in inhabitants of some areas ranges from 6 to 37 percent.

- In Egypt seropositivity of HTLV-I is 0.06%.
• The predominant modes of transmission of HTLV infection are by sexual contact, via contaminated blood or blood products, and from mother to child via breast milk.

• One unique characteristic of HTLV-1 infection is the extremely long incubation period.

• The incubation period for adult T-cell leukemia can range from years to decades and may be as long as 40 years; the incubation period for tropical spastic paraparesis is thought to be shorter but is still several years.
HIV-1 is the major cause of the AIDS pandemic. HIV-2 is of lower virulence and infection has largely remained confined to West Africa.
The most common methods of transmission of HIV are:

- 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
There no evidence that the virus is transmitted by:

- Insects.
- Casual contact direct or indirect including toilets or swimming pools.
- Saliva.
- Kissing.
- Sharing of eating and drinking utensils.
Pathogenesis

- HIV attacks CD4 T helper cells (attachment occurs between viral glycoprotein gp120 and CD4 receptors and other co-receptors on T helper cells).

- Death and fusion of cells (syncytial formation) → depletion of CD4 T helper cells → marked suppression of the immune response.
Macrophages and monocytes also express CD4 on their surfaces, and are required for their infection.

It is believed that the virus survives in these cells which transport it to other organs (e.g. brain, lungs).
Clinical Presentations
Primary (Acute) infection

- About 90% of patients develop a flu-like illness which coincides with sero-conversion, between 2 and 4 weeks post exposure.

- Symptoms include, fever, night sweats, sore throat, lympho-adenopathy and diarrhea.

- The illness is self limiting.

- It may be difficult to diagnose HIV infection at this stage due to lack of antibodies.
1-Asymptomatic phase

• Symptoms and signs of infection disappear for a variable duration (up to 10 years or more).

• Patients are clinically well, but infectious. Diagnosis may be done if a blood sample of those persons is examined for the antibodies against the HIV.
2-Prodromal phase

• This period starts by the insidious onset of a variety of prodromal disorders called ARC (AIDS Related Conditions).

• Including: weight loss, prolonged fever, persistent lympho-adenopathy, oral Candidiasis and persistent diarrhea.
AIDS Syndrome with the following features:

- Constitutional disease: fever, diarrhea, weight loss and skin rashes.
- Neurological disease: dementia, myelopathy and peripheral neuropathy.
- Immunodeficiency: increased susceptibility to opportunistic infections (fungal, protozoal, viral and bacterial) that need cellular immunity to clear.
- Rare malignancies: Kaposi sarcoma, oral hairy leukoplakia and lymphomas.
HIV Testing

• HIV testing should be done for each blood unit.

• In all hemodialysis patients.

• In all organ or tissue donors.
• **Serology:** Screening of blood for antibodies to HIV is first done by ELISA
• Very sensitive test (detecting all positive cases + few false positive).
• Positive results should be confirmed (before telling anyone) using more specific tests like Western Blot (WB) or immunofluorescence (IF) which will detect the true positive only.
• **Detection of p24 antigen:**

• **ELISA** test to detect the viral antigen p24 which is important to diagnose infection before seroconversion.
• **PCR:**
  - Used mainly for detection of viral genome in suspected seronegative samples.
  - For determination of the viral load before and during therapy.
Management:

• Treatment for AIDS or HIV infection is available but very expensive.
• AIDS needs both symptomatic treatment and specific treatments for HIV and also for other pathogens causing opportunistic infections.
• Anti HIV drugs include RT inhibitors, Protease inhibitors and the newly designed Integrase inhibitors.
• New treatments including gene therapy, cytokines and others are in clinical trials.
• **AIDS vaccine** have not been successful thus far.

• Anti viral drugs are extremely expensive, the only hope for worldwide control of HIV is to develop an effective cheap and safe vaccine.

• More importantly we have to raise the awareness of people to stop the spread of infection.
TUMOUR VIRUSES AND ONCOGENESIS

• It is proved that viruses cause cancer in animals.
• However, proving causal relationship between viruses and human cancer is difficult.
• The virus cannot be always isolated from the tumor.
• Many of the viruses isolated from human tumors do not produce tumors in experimental animals.
Viruses that induce tumors in human occur in several taxonomic groups
<table>
<thead>
<tr>
<th>Virus family</th>
<th>Type</th>
<th>Human type</th>
<th>Cofactors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenovirus</td>
<td>Type 2, 5, 12</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>Hepadnavirus</td>
<td>Hepatitis B virus (HBV)</td>
<td>Hepatocellular carcinoma</td>
<td>- AFLATOXIN. - ALCOHOL. - SMOKING.</td>
</tr>
<tr>
<td>Hepatotropic viruses (others)</td>
<td>Hepatitis C virus (HCV)</td>
<td>Hepatocellular carcinoma</td>
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<tr>
<td></td>
<td>HHV-8</td>
<td>Kaposi sarcoma Basal lymphoma Cattleman’s disease</td>
<td>HIV INFECTION</td>
</tr>
<tr>
<td>Papilloma viruses</td>
<td>HPV-16,18,33,39</td>
<td>Anogenital cancer.</td>
<td>- SMOKING.</td>
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<tr>
<td></td>
<td>HPV-5,8,17</td>
<td>Skin cancer.</td>
<td>- SUNLIGHT. - IMMUNOSUPPRESSION.</td>
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<td>Retroviruses</td>
<td>HTLV-1</td>
<td>Adult T-cell leukemia/ lymphoma.</td>
<td>Uncertain. 1/4/2011</td>
</tr>
<tr>
<td></td>
<td>HTLV-II</td>
<td>Hairy cell leukemia.</td>
<td>Uncertain.</td>
</tr>
</tbody>
</table>
Prions

- Prion is a self-replicating protein agent devoid of nucleic acid.

- They are usually a mutated form of a cellular protein.

*Mutated forms take the upper hand and can induce the same mutation in their normal counterparts.*
• **Some of the transmissible amyloidoses:**
  
  • can be explained by defined mutations in a protein causing a primary soluble glycoprotein to become insoluble.

• which in turn leads to the **pathognomonic accumulation** of amyloid fibers and plaques.
The fatal transmissible dementias in humans and other animals (Scrapie in sheep and goat; bovine spongiform encephalopathy in cattle, transmissible mink encephalopathy; Kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome in humans) are caused by prions. The pathology seems to be due to the accumulation of non-soluble amyloid fibrils in the central nervous systems.
Thank You