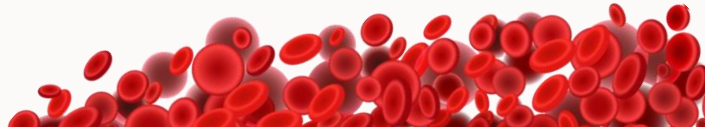
Lecture 1

intro to medical viro

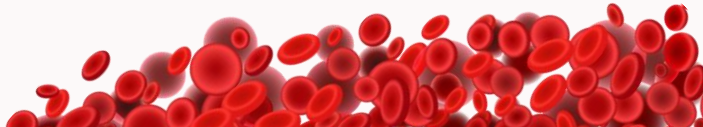


Introduction to Medical Virology

- What are viruses?
- Virus = Nucleic acid + Protein coat
- A virus is a microorganism consisting of genetic material (either DNA or RNA) enclosed within a protective protein coat known as a capsid.

- The virion is the complete infectious unit of a virus. It includes the viral nucleic acid (genome) enclosed within the capsid. Virions are the structures able to attach to susceptible host cells to initiate the infection process.

- The capsid is a protein shell that protects the viral nucleic acid. It plays an important role in the attachment to host cells and the release of the viral genome into the host cell during infection



- Viruses have the ability to infect a wide range of living cells, including those of humans , animals, plants, bacteria (phage/bacteriophage), and archaea. However, medical virology focuses on viruses that specifically infect humans and cause various infectious diseases (e.g.,influenza, AIDS, hepatitis B, hepatitis C, common cold, viral gastroenteritis, aseptic meningitis, measles, mumps, rubella, poliomyelitis, Ebola fever, rabies, etc.)

General features of viruses:

- **A. Single type of nucleic acid**: Virions contain either DNA or RNA, but never both.
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- **B. Variability in size, host range, and structure**: Viruses exhibit high variability, including size (5 to 300 nanometers for most viruses), host specificity (human, animal, plant, bacteria), genome type (DNA or RNA), and structural diversity (shape, presence of envelope, spike proteins, etc.)

- **C. Unknown origin**: The origin of viruses is still a subject of scientific debate and remains unknown.

- **D. Uncertain living status**: Viruses exist as inactive particles outside host cells and exhibit characteristics of life only when inside host cells during viral replication. Thus, “presently viruses do not find a place on the universal tree of life”

Variability in virus genome:

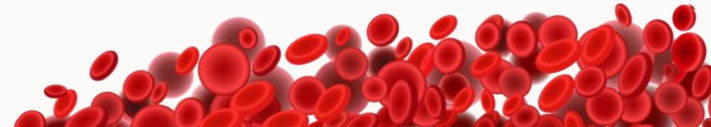
- **A. DNA viruses**: Some viruses have DNA genomes, which can be either single-stranded (one strand) or double-stranded (two strands).
- **B. RNA viruses**: Others possess RNA genomes, which can also be single-stranded or double-stranded.
- **C. Positive-sense RNA**: Single-stranded RNA viruses can be positive-sense, meaning their RNA can serve as a template for direct protein translation (acts like a messenger RNA).
- **D. Negative-sense RNA**: Some single-stranded RNA viruses are negative-sense, requiring conversion to positive-sense RNA before protein translation. This conversion occurs through the enzyme RNA-dependent RNA polymerase.
- **E. Ambisense RNA**: In certain cases, single-stranded RNA viruses have an ambisense genome, with both positive-sense and negative-sense regions within their RNA.

This is the only material required for the exam. No other source is needed

End of lecture 1

Lecture 2

Virus Classification , Replication & Pathogenesis



A. Classification of viruses can be based on shared features:

1. Virus family (the name ends in viridae).
Example: Coronaviruses are classified in the family Coronaviridae.

2. Virus sub-family (the name ends in viniae). Example: SARS coronavirus 2 is classified in the subfamily Orthocoronavirinae.

3. Virus genus (the name ends in virus). Example: monkeypox virus is classified in the Orthopoxvirus genus.

There are shared features among the members of the same family. Similarities increase among the members of the same subfamily. The features become very similar among the members of the same genus.

B. Virus Replication and Baltimore classification

1. **Attachment**: The virus recognizes a cell receptor and binds it. الارتباط بالخلية

2. **Penetration**: The virus enters the cell. اختراق الخلية

3. **Uncoating**: The virus genome is exposed.
إزالة غطاء الخلية لإعطاء الحمض النووي للفيروس الفرصة للتفاعل مع مكونات الخلية والبدأ بإنتاج بروتينات الفيروس

4. **Early transcription and early translation**: Production of the early mRNA and its translation into early virus proteins involved in virus replication.
البدء بإنتاج بروتينات الفيروس المسؤولة عن إنتاج نسخ من الحمض النووي

5. **Virus genome sunthesis.** صناعة عدد كبير من نسخ الحمض النووي للفيروس

B. Virus Replication and Baltimore classification

6. Late transcription and late translation: Production of the late mRNA and its translation into late virus proteins involved in virus structure.
البدء بإنتاج بروتينات الفيروس المسؤولة عن تكوين هيكل الفيروس الذي يحمي الحمض النووي

7. Virus assembly: The virus genome and capsid come together. تجميع مكونات الفيروس

8. Virus release from the infected cell. تحرر الفيروسات المصنعة من الخلية المصابة وانطلاقها لتصيب خلايا مجاورة

C. Baltimore classification of viruses depends on genome type:

ديفيد بلتيمور حائز على جائزة نوبل واقترح نظام التصنيف المسمى باسمه

A) DNA vs. RNA – B) double stranded vs. single stranded – C) reverse transcription

Note: transcription is the conversion of DNA into RNA. So, reverse transcription is the conversion of RNA into DNA.

Baltimore classification system

Group	Description
1	Double-stranded DNA
2	Single-stranded DNA
3	Double-stranded RNA
4	Positive-sense single-stranded RNA
5	Negative-sense single-stranded RNA
6	Positive-sense single-stranded RNA with reverse transcription
7	Double-stranded DNA with reverse transcription

D. Pathogenesis of virus infections: The processes of virus infection involving direct virus effect and host responses.

Pathogenic viruses cause disease. So, non-pathogenic viruses do not cause disease.
Virulent viruses cause more severe disease. شديدة الفتك

What are the possible outcomes of exposure to viruses ?

1. Exposure without virus attachment and without infection.
2. Virus infection but without obvious damage: Asymptomatic infection.(بدون أعراض)
3. Infection with cell damage (تخريب الخلايا) or cell transformation (تحويل الى خلايا سرطانية)
   Symptomatic disease. Sometimes this can lead to fatality (وفاة)

So, the possible clinical outcomes of acute virus infection can be:

A. Acute infection with complete virus clearance. شفاء بعد الإصابة

B. Acute infection followed by chronic infection. اصابة مزمنة

C. Acute infection followed by silent persistence and periodic reactivation.
بقاء الفيروس كامن بدون أعراض مع نشاط دوري للفيروس من فترة الى فترة

D. Acute infection followed by death.وفاة نتيجة الإصابة الحادة

How can viruses enter the body?

A. Direct: Skin contact. Respiratory aerosols رذاذ or droplets قطرات .Blood. Genital secretions. Saliva.

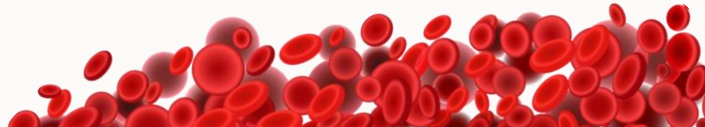
B. Indirect: Fomites المواد التي من المحتمل أن تنقل العدوى ، مثل الملابس وأدوات الطعام والأثاث. (non living objects) or Vector ناقل (e.g. insects)

Viruses are foreign entities. Upon entry into the body, the immune system will react. The immune response to virus infection can contribute to the disease process.

End of lecture 2

Lecture 3

Classification of viruses



A. How to diagnose virus infections?

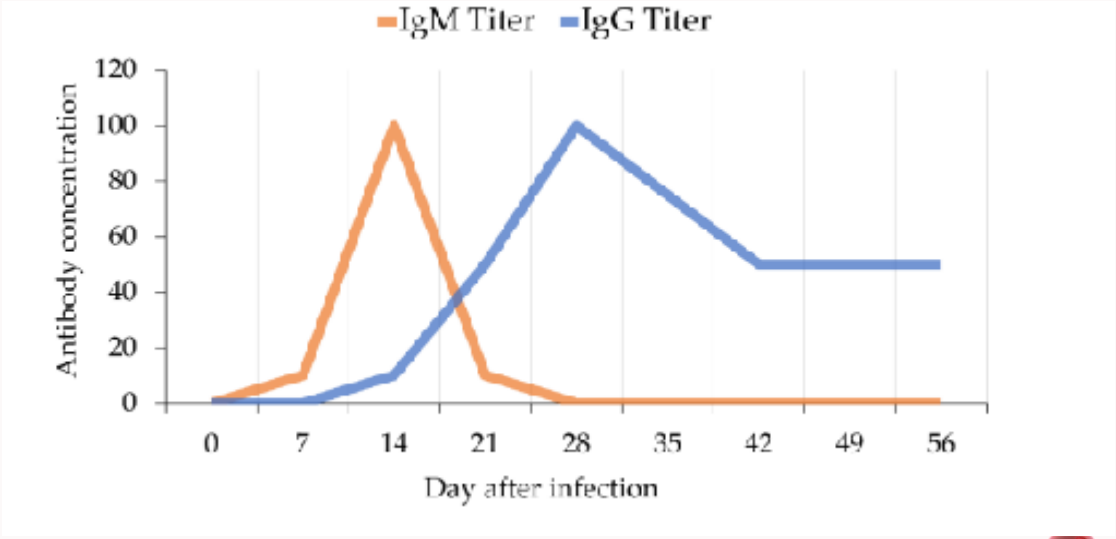
1. Virus culture: The gold-standard, reference method. However, it is not used routinely in clinical practice because:

A. Many viruses are difficult to grow in culture.
B. Virus culture is often difficult and complex process.
C. Slow.

2. Serology. The study of serum that contains antibodies. Blood is two parts (cells + fluid that have proteins). The fluid part is called serum. Antibodies are part of these serum proteins. Antibody is also called immunoglobulin (immuno=immunity, globulin=proteins that look like spheres) كروية الشكل
Specific virus infections will cause specific antibody production. So, if these specific antibodies are present, it means that the infection by that specific virus occurred.

For example, virus A will cause the production of antibody A, virus B will cause the production of antibody B and virus C will cause the production of antibody C.

Let’s assume that viruses A, B, and C cause influenza-like disease (fever, cough, fatigue). We want to reach a specific diagnosis. We take a blood sample. We separate the cells from serum. We take the serum. We test the serum for antibodies. We find antibody B. Then, we can reach a specific diagnosis. VIRUS B caused this influenza-like disease.



Antibodies are produced in the following order: immunoglobulin M (IgM) in the first 1-2 weeks. Immunoglobulin G (IgG) in the first two months. IgM will disappear in a few weeks. IgG will stay in the blood for long time. So, IgM=recent infection and IgG=past infection
Disadvantage of serology: the body will take 1-2 weeks for antibody production. So, serology is NOT helpful for very EARLY diagnosis.
The details of serology tests will be covered later on during the Immunology lectures.

3. Antigen detection. We look for the specific virus proteins. For example, virus A have antigen A, virus B have antigen B and virus C have antigen C.
Let's assume that viruses A, B, and C cause influenza-like disease (fever, cough, fatigue). We want to reach a specific diagnosis. We take a sample through the nose or throat. We test the sample for antigens. We find antigen C. Then, we can reach a specific diagnosis. VIRUS C caused this influenza-like disease.

4. Molecular detection. We look for specific DNA or RNA sequence in the virus genome. This can be done using different methods. The most common method used for molecular detection is Polymerase Chain Reaction (PCR).

5. Histopathologic examination of cells or tissue infected by the virus. Specific changes in the cells can give an idea about the virus that caused the infection.

6. Clinical diagnosis. Sometimes, certain signs and symptoms can help to reach the diagnosis of virus infection.

B. How to treat virus infections?

• Usually symptomatic treatment. Treat the symptoms. Fever → antipyretic. Pain → analgesic. Dehydration → fluids. Cough → antitussive.

• Antiviral drugs can be used for several virus infections.
• Antiviral drugs can reduce the severity of infection.
• Antiviral drugs can reduce the duration of symptoms.
• Antiviral drugs can help to control a few chronic infections.
• Antiviral drugs can help to cure hepatitis C chronic infection.
• Development of resistance, high cost and side effects are the major problems of antiviral drugs.
• Interferons have non-specific broad-spectrum antiviral activity and can be used.
• Antibiotics can NOT help to treat virus infections. المضادات الحيوية
• Antibodies CAN help to treat virus infections.الأجسام المضادة

Source: https://www.reuters.com/article/uk-health-coronavirus-usa-trump-treatmen-idUKKBN26N3CO

C. How to prevent virus infections?

1. Passive immunonization. تعطى أجسام مضادة جاهزة للمريض أو لمنع الإصابة

Mother to child through the placenta. Mother to child through breast milk. Specific antibodies taken from persons immune to the disease and given to a person at risk of infection.

2. Active immunization (Vaccination).

The Gold standard prevention method.

Several types:

A. Live attenuated
B. Inactivated
C. Subunit

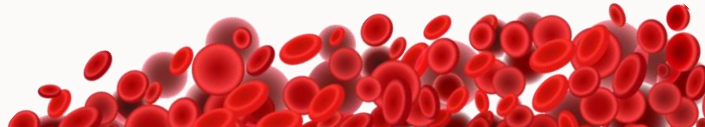
3. Behavioural changes and non-pharmaceutical interventions.

Examples:

A. Clean needles/syringes
B. Infection control measures in hospitals
C. Personal protective equipment (PPE) including face masks

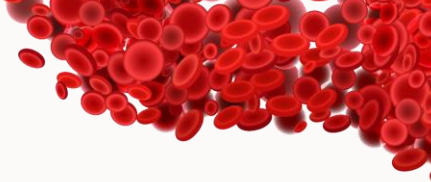
Lecture 4

retroviruses (retroviridae)



The virus family Retroviridae has four members that can cause human disease:

1. Human immunodeficiency virus type 1 (HIV-1)
2. Human immunodeficiency virus type 2 (HIV-2)
3. Human T cell lymphotropic virus type 1 (HTLV-1)
4. Human T cell lymphotropic virus type 2 (HTLV-2)



General features of retroviruses:

A. The genome is two copies (**diploid**) of **positive-sense single stranded RNA**

B. The three major gene regions are:

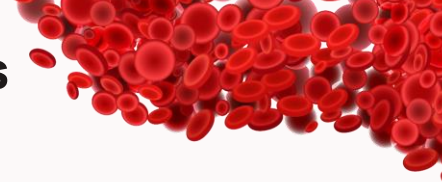
1. Gag (Group antigen): codes the capsid proteins
2. Pol: Polymerase gene region that codes reverse transcriptase, integrase and protease
3. Env: Envelope gene region that codes the envelope glycoproteins

C. Reverse transcriptase converts viral RNA into DNA which will be integrated in the host cell chromosomes by the viral enzyme called integrase. The integrated viral DNA is called “provirus”. Based on that, retroviruses are classified in Baltimore group 6

D. An envelope is present

E. They infect cells of the immune system (mainly CD4+ T helper cells, monocytes)

F. They remain in the body forever in the form of proviruses



HTLVs will be discussed briefly because these two viruses will be covered in details in the third year (hematolymphatic system).

The most important points about HTLVs:

1. More than 95% of all HTLV infections remain asymptomatic (will NOT cause any known disease).

2. Transmission through mother-to-child (vertical) route, injection drug use (استخدام الحقن الملوثة عند مدمني المخدرات) sexual route, and blood transfusion

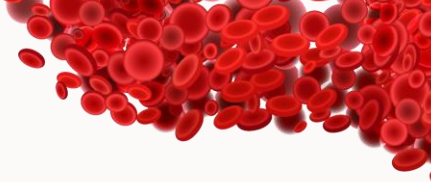
3. A recent estimate about HTLV-1 prevalence: 5–10 million had the virus

4. A recent estimate about HTLV-2 prevalence: Less than 1 million had the virus

5. In less than 5% of the infected persons, adult T-cell leukemia/lymphoma can Occur

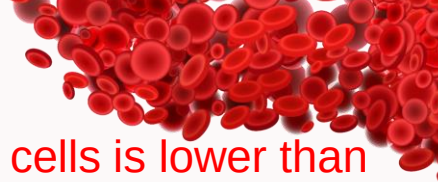
6. Diagnosis of infection is by serology or PCR

HIV/AIDS (acquired immune deficiency syndrome)



1. Tropism: CD4+ T cells, monocytes/macrophages, dendritic cells
2. Receptors: CD4 (present on CD4+ T cells, monocytes/macrophages and dendritic cells) and a coreceptor (CCR5 on monocytes/macrophages, dendritic cells) or (CXCR4 on CD4+ T cells). So, HIV strains that infect CD4+ T cells are called X4 viruses. HIV strains that infect monocytes/macrophages and dendritic cells are called R5 viruses. HIV strains that infect all these cells are called R5X4 viruses.
3. Epidemiology: In 2021, 40 million people were living with HIV infection. Mostly in sub-Saharan Africa.
4. Transmission:
A. Heterosexual and homosexual practices with infected persons (high-risk sexual behavior)
B. Mother to Child (vertical) من الأم لطفلها أثناء الحمل أو الولادة أو الرضاعة
C. Injection drug use by contaminated needles
D. Needle stick injuries (إصابات الوخز بالابر في المستشفيات والعيادات بشكل رئيسي
E. Blood/blood component transfusion.

Not every exposure will result in infection. For example, of all needle stick Injuries only 0.3% will result in HIV infection.
After transmission, the incubation period is variable (few weeks to few months).
This is followed by acute infection. Acute HIV infection can be symptomatic (influenzalike illness or sore throat, fever and lymphadenopathy). **Acute infection can also be totally asymptomatic.**
In acute HIV, the CD4+ T cells are killed and their numbers decrease significantly.
About 6 months after exposure, the immune system controls the viral replication and subsequently the viral load (number of viruses) in blood to a low level.
This low level of viral load is different from person to person based mainly on the genetics of the patient.
CD4+ T cells increase when the immune system controls the virus.
Viral load (number of viruses in the blood) after 6 months is called HIV set point.
After 6 months, the patient will be mostly asymptomatic but the virus remains in the body. This is called the clinical latency period. HIV escapes from immunity. During clinical latency, immunity tries to control HIV again. HIV escapes from immunity. Immunity tries to control HIV again and again. HIV escapes from immunity. Immunity tries to control HIV again, again and again.



Finally, the immune system becomes exhausted (منهك ومستنزِف) So, the virus takes over and the number of CD4+ T cells will be lower than 200 cells/mm3 (normal level is 500–1500 cells/mm3). When the CD4+ T cells is lower than 200 cells/mm3, the diagnosis of AIDS is reached.

In AIDS patients, cellular immunity is deficient (نقص في المناعة بسبب موت الخلايا التائية المساعدة) So, the patients will develop severe virus and fungal infections and cancers.

Time from acute infection to AIDS is called progression to AIDS.
Rapid progressors will have AIDS in 2–3 years. Long-term non-progressors can live for more than 20 years without AIDS. A majority of patients will have AIDS in 8-12 years.
Higher HIV set point is associated with shorter time of progression to AIDS. Lower HIV viral set point is associated with longer time of progression to AIDS. So, viral set point can be used as a PROGNOSTIC MARKER

5. Diagnosis:

A. Nucleic acid amplification to measure the viral load. This is done by real-time quantitative PCR

B. Serology (antibody testing).

C. Antigen detection. P24 antigen detection which is a viral protein present in the capsid.

6. Treatment: is based on combination of two or three drugs to prevent emergence of resistance. This is called highly active anti-retroviral therapy (HAART). Early treatment can slow progression to AIDS. Treat as early as possible. Drugs:

A. Reverse transcriptase inhibitor drugs.

B. Protease inhibitor drugs.

C. Integrase inhibitor drugs.

D. CCR5 receptor antagonists.

7. Prevention

A. Effective vaccines have not been developed so far. So, HIV/AIDS cannot be prevented by active immunization until now.

B. Drugs can be given before exposure in the high-risk groups (called pre-exposure prophylaxis الوقاية)

C. Drugs can be given after exposure (called post-exposure prophylaxis)

D. Behavioral (clean needles, condoms, or even better not engaging in high-risk sexual practices)

End of lecture 4