10- Human Immunodeficiency Virus (HIV)

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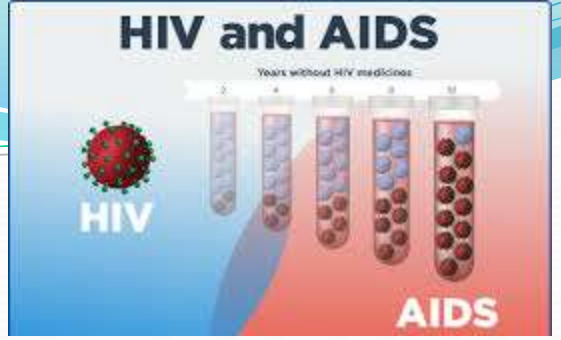
Objectives

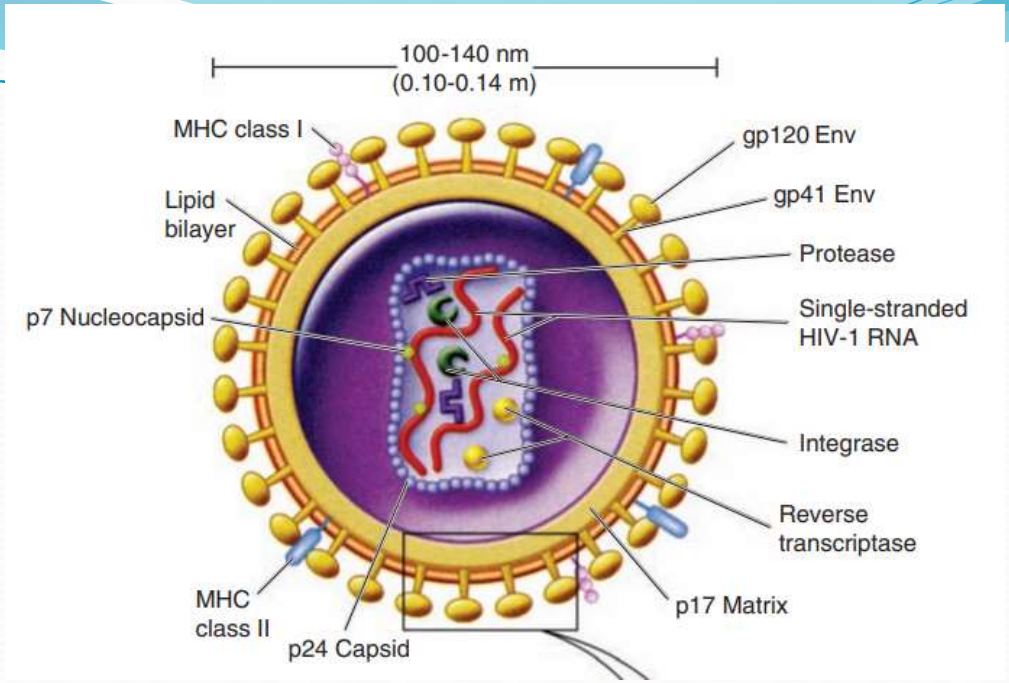
- Understand the morphology, epidemiology, pathogenesis, and clinical manifestations, laboratory diagnosis and treatment of HIV and AIDS



Introduction

- The etiologic agents of Acquired Immune Deficiency Syndrome (AIDS)
- The main targeted cell is the human T helper (CD4)
- HIV is a lentivirus
- Genus of the retroviridae family
- The illness was first described in 1981, and HIV-1 was isolated by the end of 1983
- AIDS has become a worldwide epidemic
- Characterized by long incubation periods, persistent infection, and development of opportunistic infections
- Once infected, individuals remain infected for life

Morphology



- Two viral strands of linear
- Positive sense RNA
- Retroviruses transcribe RNA to DNA
- Icosahedral (20 sided)
- Enveloped virus
- The outer envelope contains a lipid matrix within which specific viral glycoproteins (gp41 and gp120).
- These knob-like structures are responsible for binding to target cells.

Types of HIV

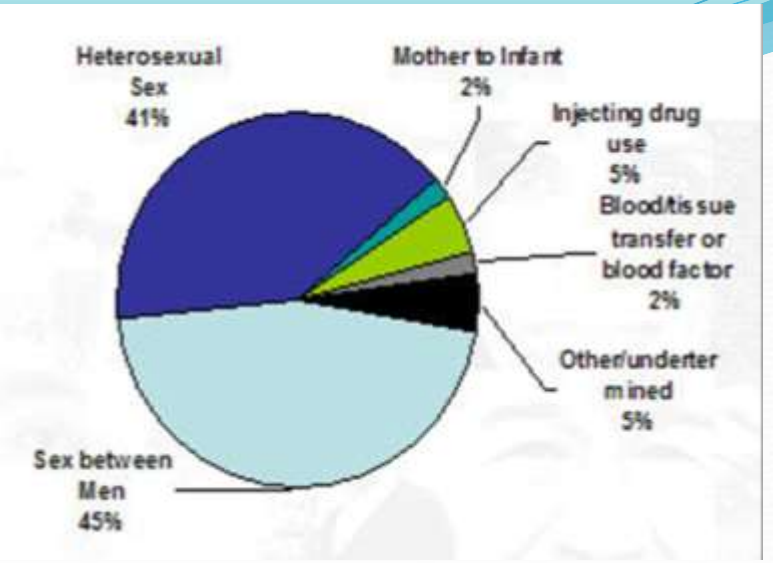
- Two species of HIV infect humans:
  1. HIV-1
     - More virulent, relatively easy to transmit
     - Majority of HIV infections globally
     - 3 types of HIV-1: (based on alterations in *env* gene)
  2. HIV-2
     - Less transmittable
     - Largely confined to West Africa

Origins of HIV

HIV-1 likely descended from SIV_{cpz}

HIV-2 likely descended from SIV_{sm}

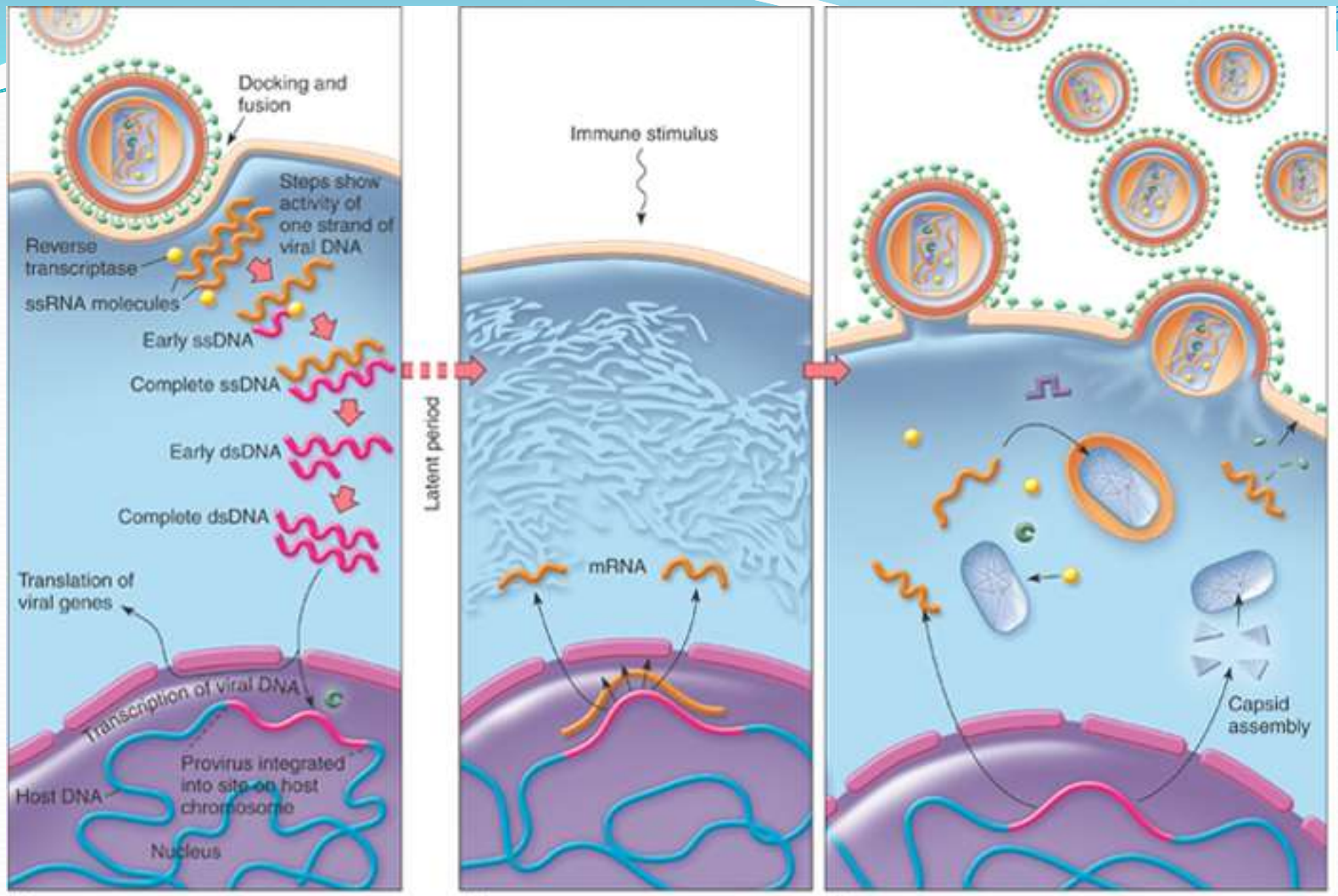
Epidemiology



- Global (2009 statistics):
  - 39.5 million infected with HIV/AIDS
  - 2.9 million deaths
  - 4.3 million new infections (65%) of these were in sub-Saharan Africa and increased in Eastern Europe and Central Asia
- Transmission
  - Unprotected sex with an infected individual (Homosexual)
  - Blood transfusions/Organ transplants
  - Sharing of infected drug injection needles/syringes and accidental needle sticks (healthcare professionals)
  - Transmission from infected mother-to-fetus during pregnancy or delivery
  - Transmission from breast milk of infected mother to her baby

Pathogenesis and Virulence Factors

- HIV enters through mucous membrane or skin and travels to dendritic phagocytes beneath the epithelium, multiplies and is shed.
- Virus is taken up and amplified by macrophages in the skin, lymph organs, bone marrow, and blood.
- HIV attaches to CD_4 and coreceptor; HIV fuses with cell membrane.
- Reverse transcriptase makes a DNA copy of RNA.
- Viral DNA is integrated into host chromosome
- Can produce a lytic infection or remain latent



The virus is adsorbed and endocytosed, and the twin RNAs are uncoated. Reverse transcriptase catalyzes the synthesis of a single complementary strand of DNA (ssDNA). This single strand serves as a template for synthesis of a double strand (ds) of DNA. In latency, dsDNA is inserted into the host chromosome as a provirus.

After a latent period, various immune activators stimulate the infected cell, causing reactivation of the provirus genes and production of viral mRNA.

HIV mRNA is translated by the cell's synthetic machinery into virus components (capsid, reverse transcriptase, spikes), and the viruses are assembled. Budding of mature viruses lyses the infected cell.

Primary effects of HIV infection:

- extreme leukopenia – lymphocytes in particular
- formation of giant T cells allowing the virus to spread directly from cell to cell
- Infected macrophages release the virus in central nervous system, with toxic effect, inflammation.

Secondary effects of HIV:

- Destruction on CD_4 lymphocytes allows for opportunistic infections and malignancies.

Clinical Manifestations

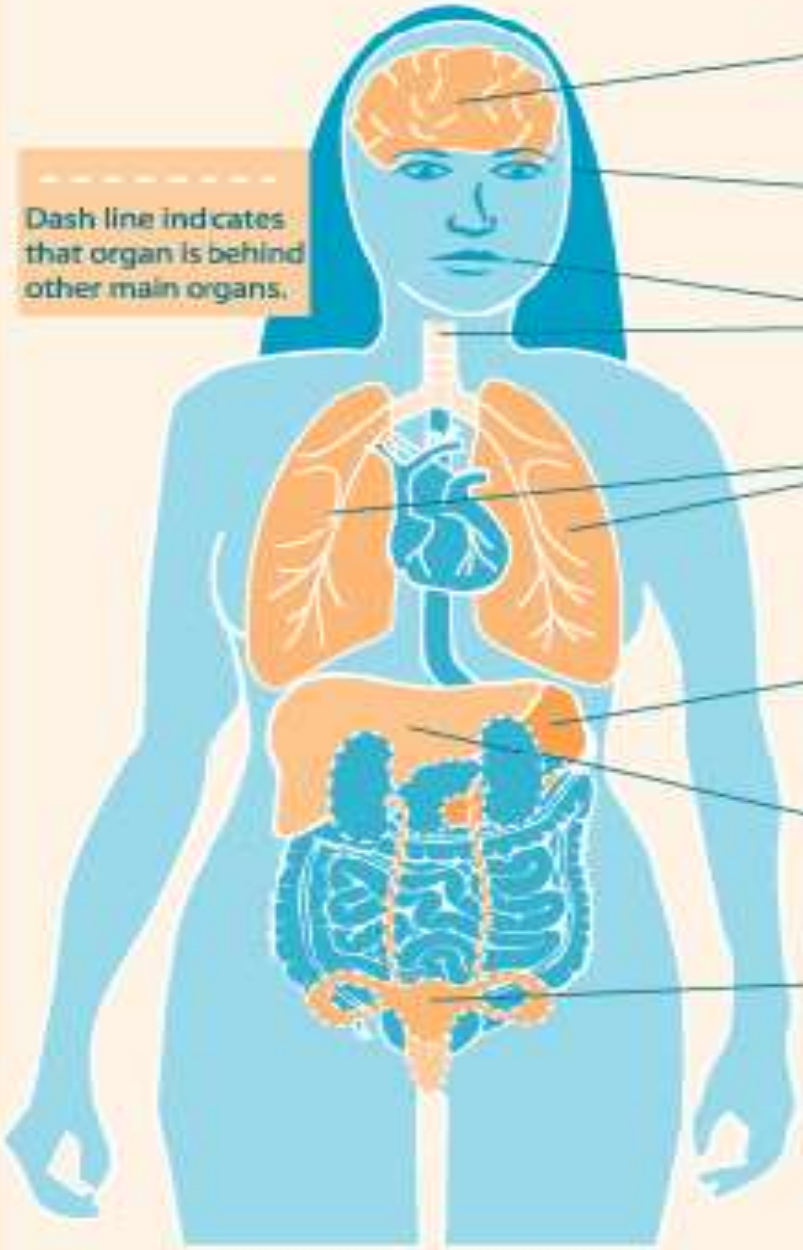
- Human Immunodeficiency Virus (HIV) has an incubation period of about 10 years and eventually leads to Acquired Immunodeficiency Syndrome (AIDS), resulting in the impairment of the immune system.

- This can lead to death from infections, secondary diseases from opportunistic bacteria and/or viruses that are usually harmless to people, or many different types of cancers.

- Common diseases associated with HIV infection:
  - Kaposi's sarcoma (KS)
  - Pneumocystis carinii pneumonia (PCP)
  - Mycobacterium avium complex (MAC)

- Early Symptoms:
  - Most don't exhibit symptoms when first infected
  - However, may have flu-like symptoms (fever, headache, tired, enlarged lymph nodes) 1-2 months after exposure
  - Very infectious during this period
- Later Symptoms:
  - More sever symptoms may not appear until after 10yrs, however this varies with each individual
  - Decline in number of $CD4^+$ T cells
  - The most advanced stage of AIDS is classified as having < 200 $CD4^+$ T cells/cubic millimeter of blood (in healthy adults $CD4^+$ T-cell counts = 1,000+)

Opportunistic Infections



Brain
Toxo (toxoplasmosis)
Cryptococcal meningitis

Eyes
CMV (cytomegalovirus)

Mouth and Throat
Candidiasis (thrush)

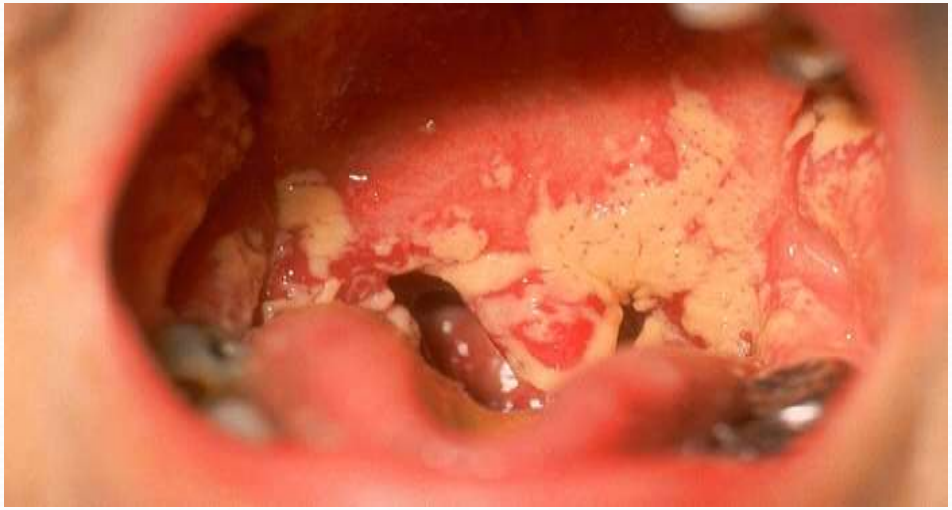
Lungs
PCP (pneumocystis carinii pneumonia)
Histoplasmosis
TB (tuberculosis)

Stomach
MAC (mycobacterium avium complex)
Crypto (cryptosporidiosis)
CMV (cytomegalovirus)

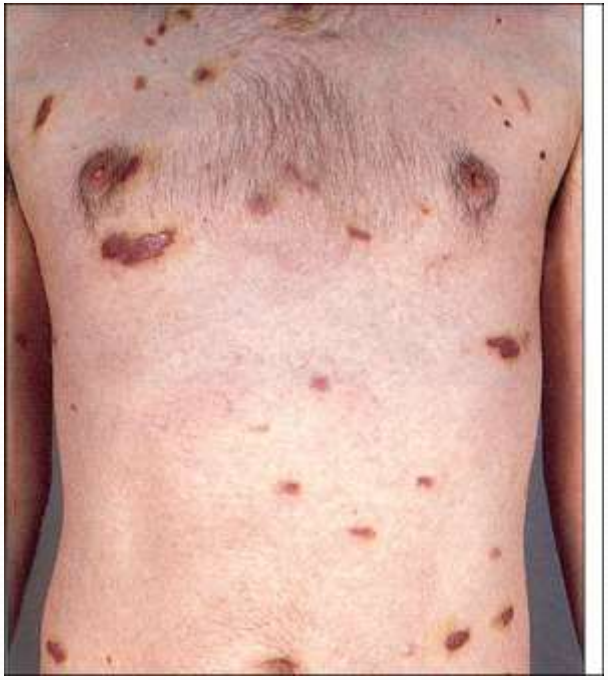
Liver
HCV (hepatitis C virus)

Reproductive System
HPV (human papillomavirus) and Cervical cancer
Menstrual problems
Vaginal candidiasis (yeast infection)
PID (pelvic inflammatory disease)
UTI (urinary tract infections)
Genital ulcers

Oral Candidiasis (thrush)

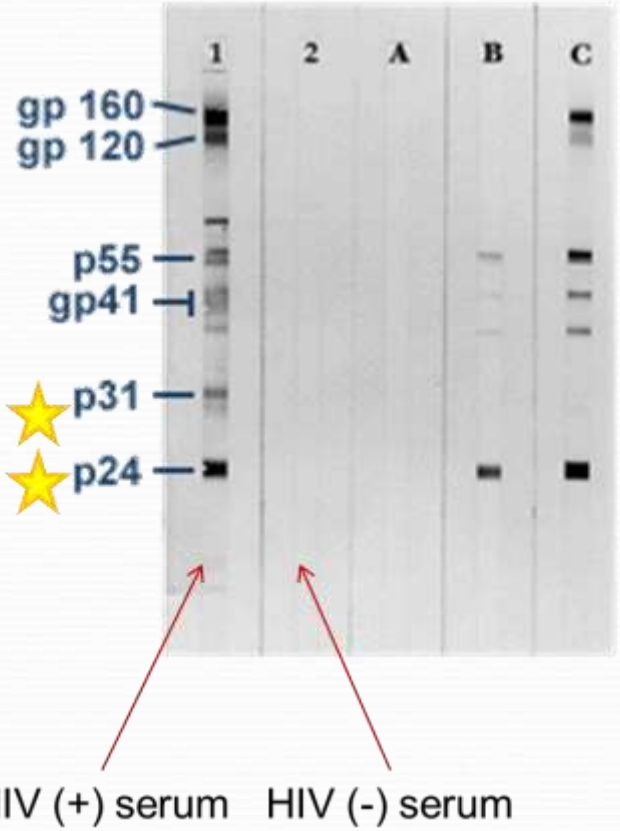


Kaposi's sarcoma (KS)



Laboratory Tests

- ELISA Testing for HIV antibodies including those directed against p24, gp120, gp160 and gp41 (screening)
- Detection of p24 HIV antigen
- Indirect immunofluorescence
- HIV – Western Blot
- Viral nucleic acid (PCR)
- Viral isolation and culture



Prevention

- Avoid sexual contact with infected individuals
  - Abstinence
  - Monogamous Relationship
  - Protected Sex
- Avoid sharing needles/syringes that could be contaminated with HIV
- Avoid any type of contact with the bodily fluid of an infected individual

Treatment

HAART

1. Nucleoside Reverse Transcriptase inhibitors: Zidovudine Non-Nucleoside Transcriptase inhibitors: Nevirapine
2. Protease inhibitors: Ritonavir
3. Fusion inhibitors: Enfuvirtide
4. Entry inhibitors: Maraviroc
5. Integrase inhibitors Dolutegravir

- Highly active antiretroviral therapy (HAART):
  - suppress viral replication and decrease viral load
  - recovery of immune responses to opportunistic pathogens
  - prolong patient survival
  - FAILED to cure HIV-1 infections

Vaccine

- Currently, no vaccines approved for use by the FDA
- Two types in development:
  - Therapeutic Vaccine - intended to boost the immune systems of those already infected
  - Preventive Vaccine – intended to generate an immune response in an uninfected person to prevent future infection