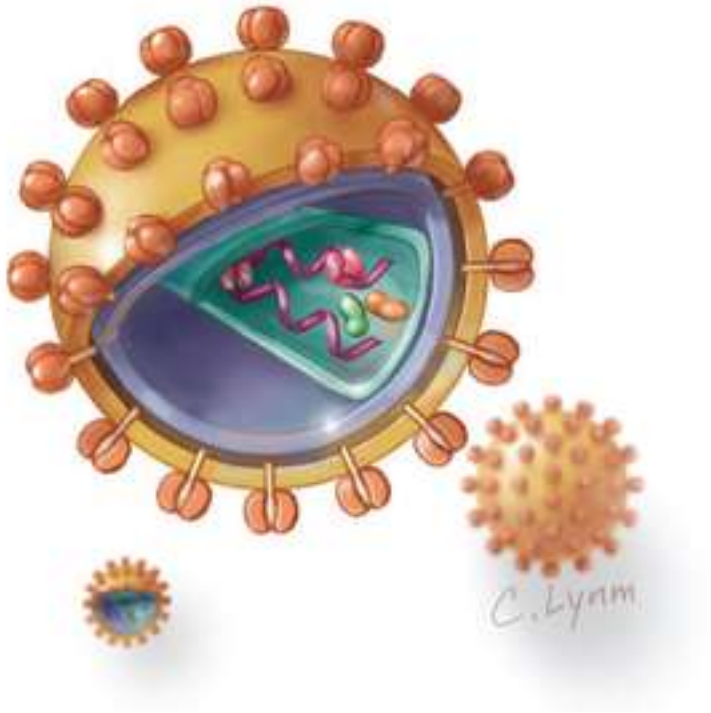


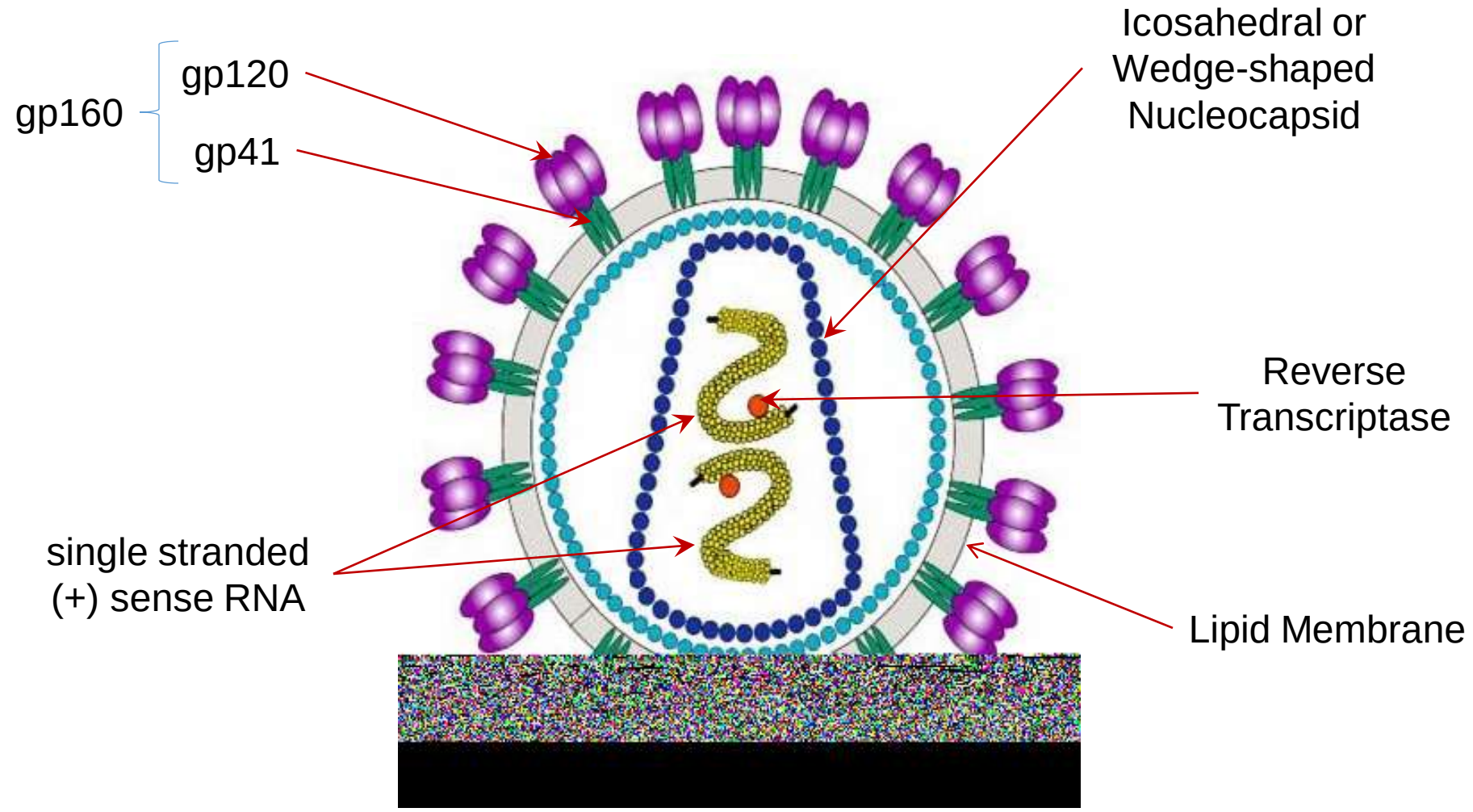
Human Immunodeficiency Virus (HIV)

Introduction

- HIV is a viral infection that destroy helper T cells of the immune system
- HIV is a lentivirus
- Genus of the retroviridae family
- Produce multi-organ diseases
- Characterized by long incubation periods and persistent infection
- Infect a wide range of prime hosts, as well as some non-primate mammals

Morphology

- Icosahedral (20 sided)
- Retroviruses transcribe RNA to DNA
- Two viral strands of RNA found in core surrounded by protein outer coat.
- Enveloped virus
- Outer envelope contains a lipid matrix within which specific viral glycoproteins are imbedded.
- These knob-like structures responsible for binding to target cell.


gp160
gp120
gp41
Icosahedral or
Wedge-shaped
Nucleocapsid
Reverse
Transcriptase
single stranded
(+) sense RNA
Lipid Membrane

(NIH, 2005)

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}

History

- 1926-1946 - Scientists believe HIV first spread from monkeys to humans
- 1959 - First proven AIDS death
- 1978 - Gay men in US and Sweden begin showing signs of what is now known as AIDS
- 1981 - CDC notices increase in cases of Kaposi's sarcoma and Pneumocystis carinii pneumonia
- 1982 - The term AIDS (acquired immune deficiency syndrome) is used for the 1st time
- 1983 - Institute Pasteur isolates HIV-1 CDC issues warning to blood banks about potential problem
- 1984 - Dr. Robert Gallo claims discovery of HIV

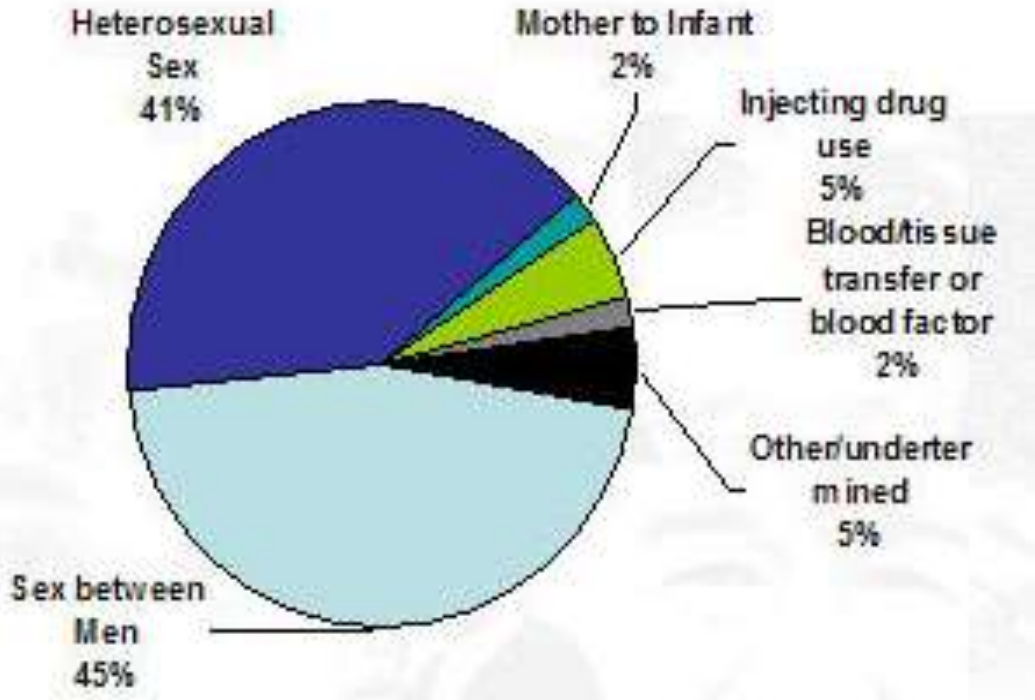
Epidemiology

- The virus was first successfully identified and classified in 1981.
- At end of 2003 in the U.S. 1,039,000 - 1,185,000 persons infected with HIV/AIDS
- Global (2006 statistics): 39.5 million infected with HIV/AIDS
- 4.3 million new infections in 2006; 2.8 million (65%) of these were in sub-Saharan Africa
- Increases in Eastern Europe and Central Asia, where there may have been a more than 50% rise in infection rates since 2004
- In 2006, 2.9 million deaths due to AIDS-related illnesses.
- Global (2026 statistics): 39.5 million infected with HIV/AIDS, ~1.3 million new infections/year, ~600,000 deaths/year (mainly from AIDS-related illnesses).

Transmission

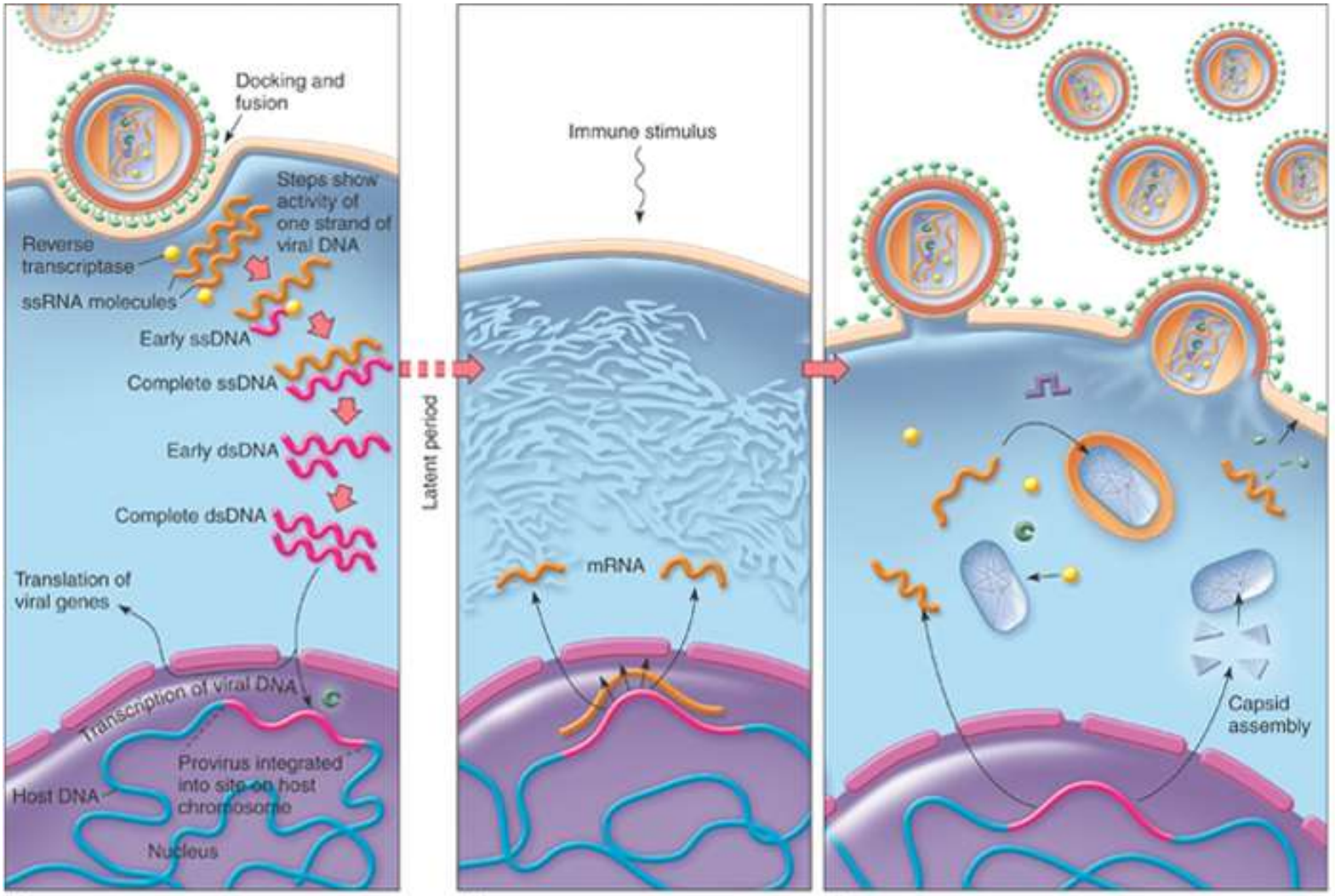
- Sharing of infected drug injection needles/syringes
- Accidental needle stick (healthcare professionals)
- Unprotected sex with infected individual
- Blood transfusions/Organ transplants
- Transmission from infected mother-to-fetus during pregnancy or delivery
- Transmission from breast milk of infected mother to her baby

Route of Transmission of HIV Infection, infections before 2006



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 CD4 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 CD4 lymphocytes allows for opportunistic infections and malignancies.

Clinical Manifestations

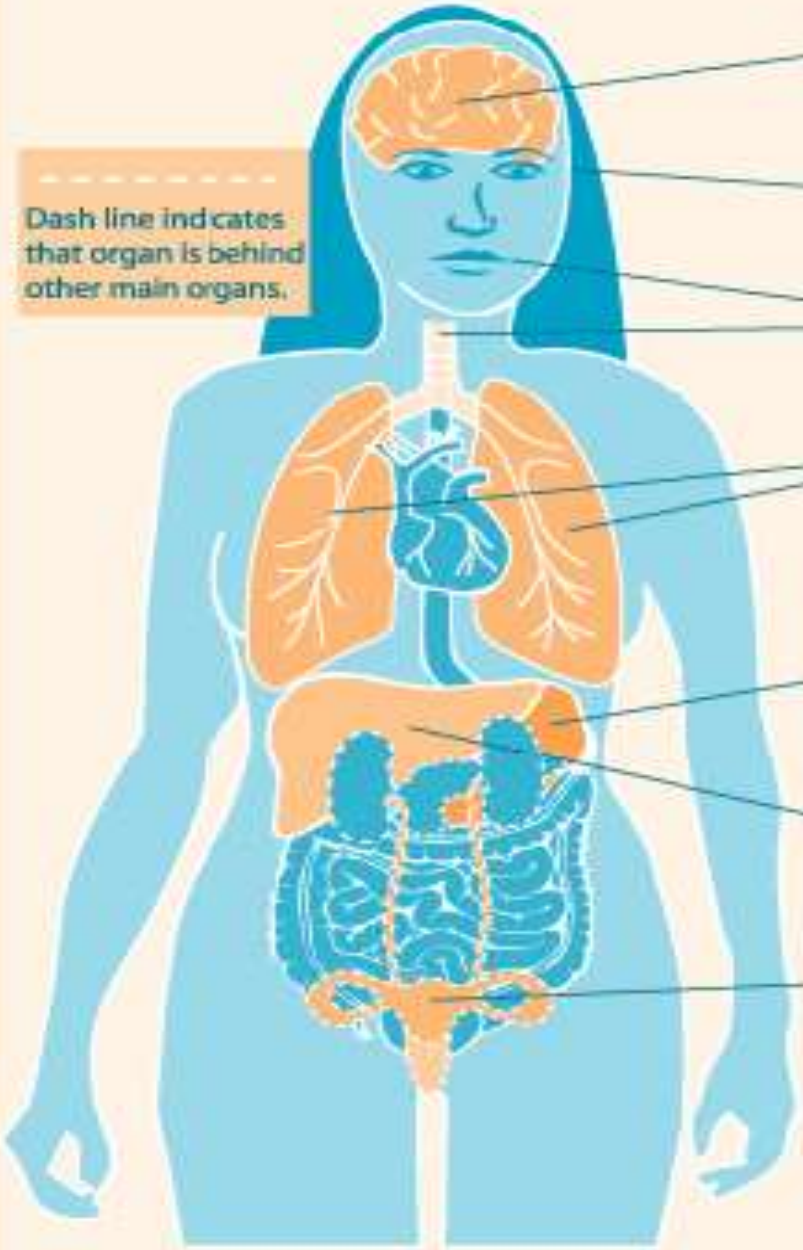
- Human Immunodeficiency Virus (HIV) has an incubation period of about 10 years and eventually leads to Acquired Immunodeficiency Syndrome (AIDS), resulting in the impairment of the immune system.

- 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) ★

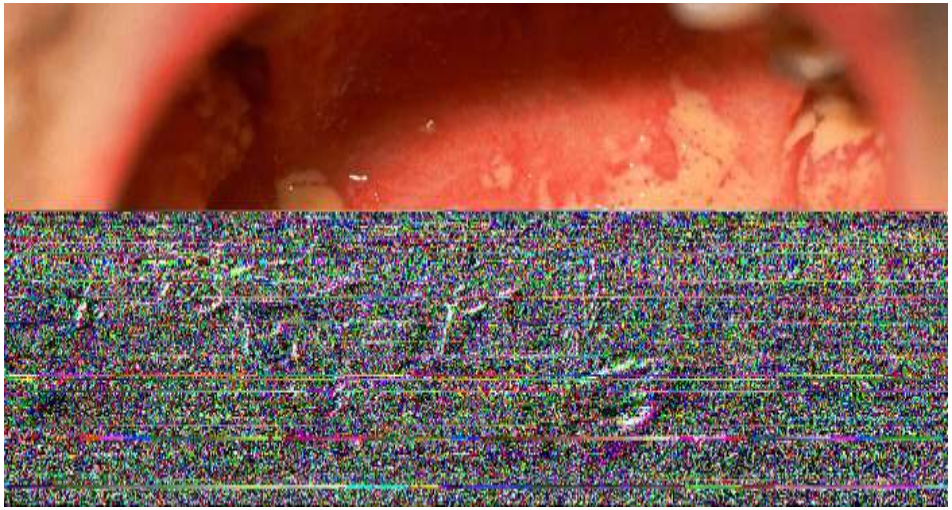
Lungs
PCP (pneumocystis carinii pneumonia) ★
Histoplasmosis
TB (tuberculosis)

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

- Methods utilized to detect:
  - Antibody
  - Antigen
  - Viral nucleic acid
  - Virus in culture

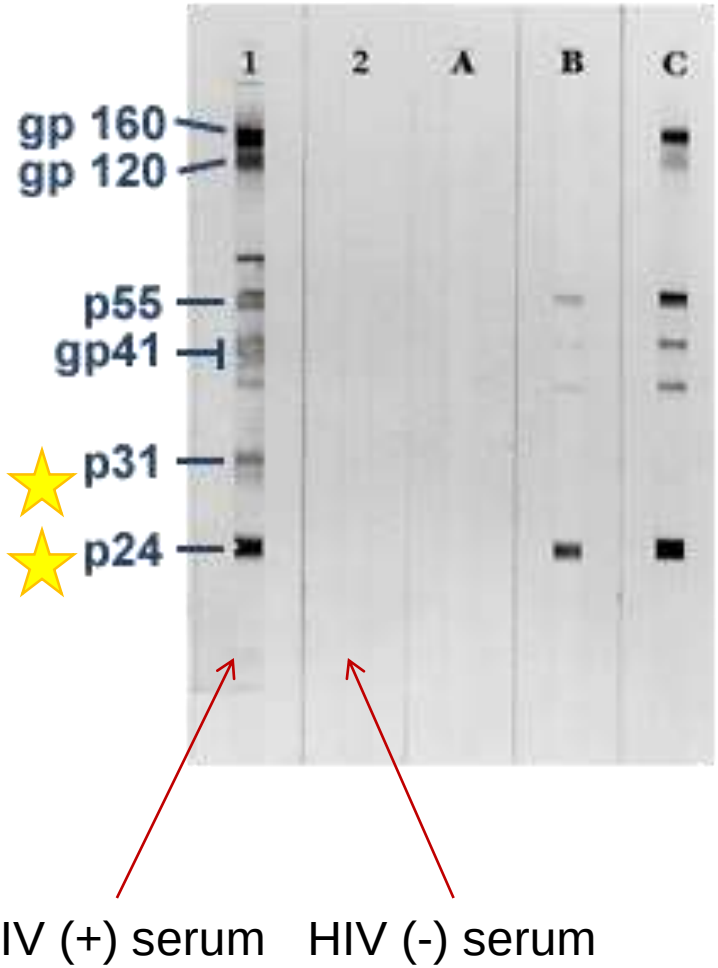
ELISA Testing

- First serological test developed to detect HIV infection.
- Antibodies detected in ELISA include those directed against: p24, gp120, gp160 and gp41, detected first in infection and appear in most individuals
- ELISA tests useful for:
  - Screening blood products.
  - Diagnosing and monitoring patients.
  - Determining prevalence of infection.
  - Research investigations.

Western Blot

- Most popular confirmatory test.
- Utilizes a lysate prepared from HIV virus.
- The lysate is electrophoresed to separate out the HIV proteins (antigens).
- The paper is cut into strips and reacted with test sera.
- After incubation and washing anti-antibody tagged with radioisotope or enzyme is added.
- Specific bands form where antibody has reacted with different antigens.
- Most critical reagent of test is purest quality HIV antigen.

HIV – Western Blot Results



gp160 = viral envelope precursor

gp120 = viral envelope protein binds to CD4

p31 = reverse transcriptase

p24 = viral core protein

Indirect immunofluorescence

- Can be used to detect both virus and antibody to it.
- Antibody detected by testing patient serum against antigen applied to a slide, incubated, washed and a fluorescent antibody added.
- Virus is detected by fixing patient cells to slide, incubating with antibody.

Detection of p24 HIV antigen

- The p24-antigen screening assay is an EIA performed on serum or plasma.
- P24 antigen only present for short time, disappears when antibody to p24 appears.
- Test not recommended for routine screening as appearance and rate of rise are unpredictable.
- Sensitivity lower than ELISA.

Polymerase Chain Reaction (PCR)

- Looks for HIV DNA in the WBCs of a person.
- PCR amplifies tiny quantities of the HIV DNA present, each cycle of PCR results in doubling of the DNA sequences present.
- The DNA is detected by using radioactive or biotinylated probes.
- Once DNA is amplified it is placed on nitrocellulose paper and allowed to react with a radiolabeled probe, a single stranded DNA fragment unique to HIV, which will hybridize with the patient's HIV DNA if present.
- Radioactivity is determined.

Virus isolation

- Virus isolation can be used to definitively diagnose HIV.
- Best sample is peripheral blood, but can use CSF, saliva, cervical secretions, semen, tears or material from organ biopsy.
- Cell growth in culture is stimulated, amplifies number of cells releasing virus.
- Cultures incubated one month, infection confirmed by detecting reverse transcriptase or p24 antigen in supernatant.

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

Methods for Prevention

- Intravaginal lime or lemon juice to kill the HIV virus before entry
- Intravaginal estrogen: Karotinizing the vagina with estrogen
- Post-coital penile hygiene: Wiping the penis immediately after intercourse with lime or lemon juice or vinegar should kill the virus before it has had a chance to infect.
- Male circumcision: Removal of the inner foreskin removes the main site of HIV entry into the penis, resulting in a sevenfold reduction in susceptibility to infection
- Use condoms.

Treatment

- Anti-viral agents
- Nucleoside Reverse Transcriptase inhibitors
  - AZT (Zidovudine)
- Non-Nucleoside Transcriptase inhibitors
  - Viramune (Nevirapine)
- Protease inhibitors
  - Norvir (Ritonavir)

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