

Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS).

Introduction

Human T-cell Lymphotropic Retroviruses

- HIV is the cause of AIDS.
- Human T-cell leukemia virus.

Important Properties

- HIV preferentially infects & kills
- Helper (CD₄) T lymphocytes, resulting in the loss of CMI & a high probability that the host will develop opportunistic infections.
- Other cells (e.g., macrophages & monocytes) that have CD₄ proteins on their surfaces can also be infected.

Genes & Proteins of HIV

Gene	Proteins Encoded by Gene	Function of Proteins
I. Structural genes found in all retroviruses		
<i>gag</i>	p24, p7	Nucleocapsid
	p17	Matrix
<i>pol</i>	Reverse transcriptase¹	Transcribes RNA genome into DNA
	Protease	Cleaves precursor polypeptides
	Integrase	Integrates viral DNA into host cell DNA
<i>env</i>	Gp120	Attachment to CD4 protein
	Gp41	Fusion with host cell

¹Reverse transcriptase also contains ribonuclease H activity, which degrades the genome RNA to allow the second strand of DNA to be made.

Genes & Proteins of HIV

Gene	Proteins Encoded by Gene	Function of Proteins
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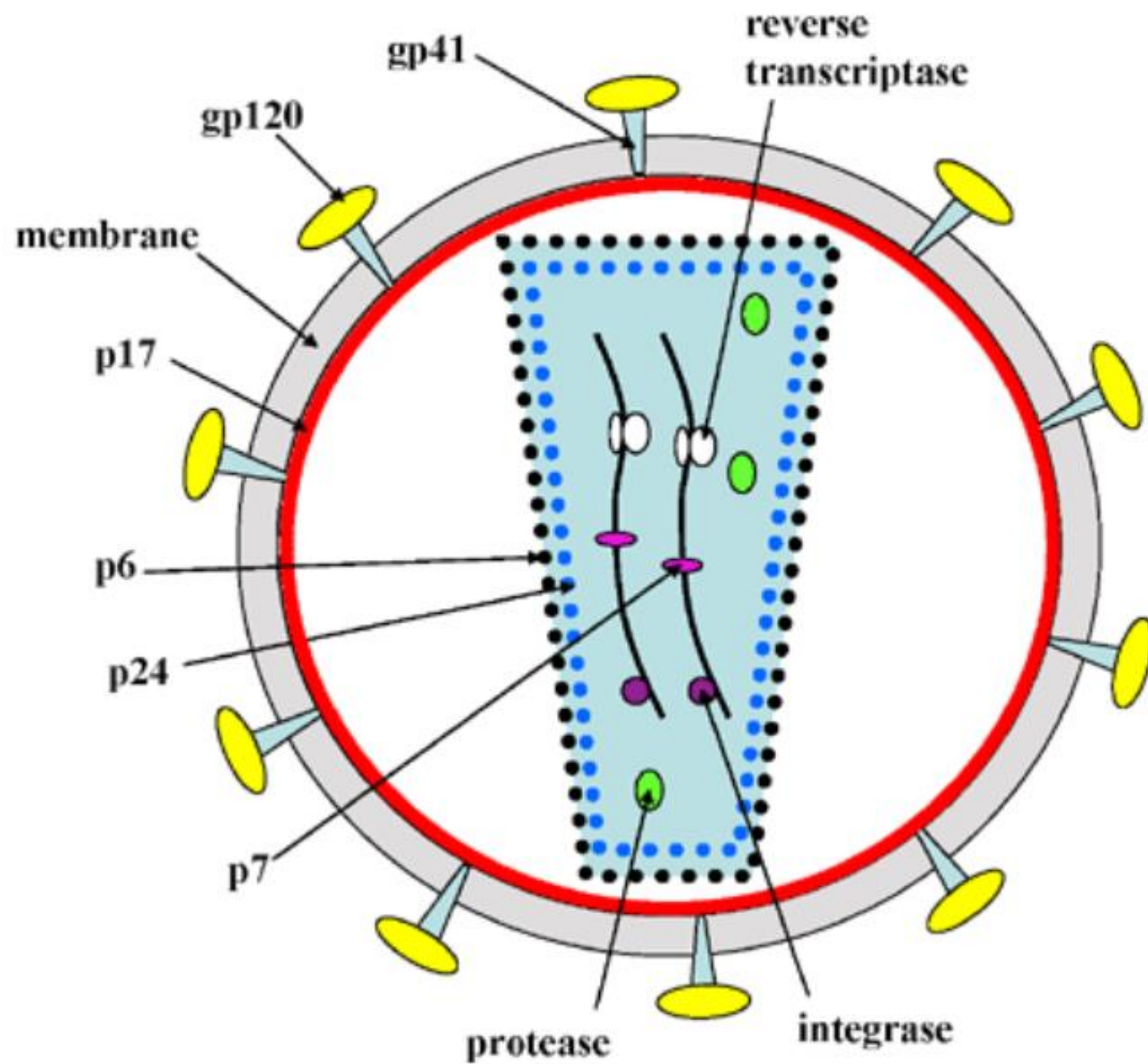
II. Regulatory genes found in HIV that are required for replication

<i>tat</i>	<i>Tat</i>	Activation of transcription of viral genes
<i>rev</i>	<i>Rev</i>	Transport of late mRNAs from nucleus to cytoplasm

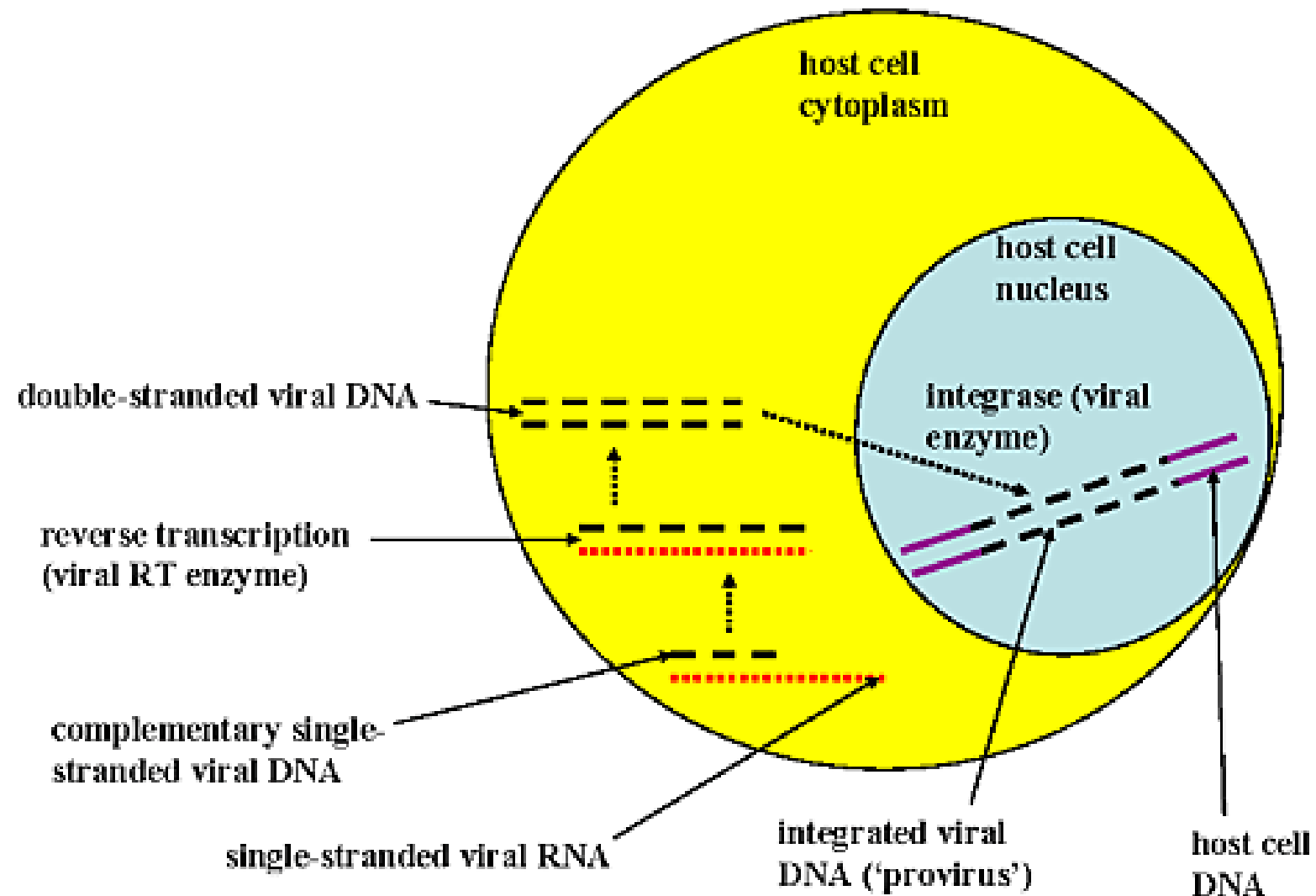
Genes & Proteins of HIV

Gene	Proteins Encoded by Gene	Function of Proteins
III. Regulatory genes found in HIV that are <i>not</i> required for replication (accessory genes)		
<i>nef</i>	<i>Nef</i>	Decreases CD4 proteins and class I MHC proteins on surface of infected cells; induces death of uninfected cytotoxic T cells; important for pathogenesis by SIV ²
<i>vif</i>	<i>Vif</i>	Enhances infectivity by inhibiting the action of APOBEC3G (an enzyme that causes hypermutation in retroviral DNA)
<i>vpr</i>	<i>Vpr</i>	Transports viral core from cytoplasm into nucleus in nondividing cells
<i>vpu</i>	<i>Vpu</i>	Enhances virion release from cell

²Mutants of the *nef* gene of simian immunodeficiency virus (SIV) do not cause AIDS in monkeys.



Box 1.2 Integration of HIV viral RNA into host-cell DNA (adapted from reference 6).



HIV

- Three enzymes are located within the nucleocapsid of the virion:
 1. Reverse transcriptase
 2. Integrase
 3. Protease

Important antigens of HIV

1. **gp120** is an envelope glycoprotein & protrudes from the surface & interacts with the CD4 receptor (& a second protein, a chemokine receptor) on the cell surface.
 - Antibody against gp120 neutralizes the infectivity of HIV, but the rapid appearance of gp120 variants will make production of an effective vaccine difficult.
2. **gp41** is an envelope glycoprotein & embedded in the envelope & mediates the fusion of the viral envelope with the cell membrane at the time of infection.

Important antigens of HIV

3. The group-specific antigen, p24, is located in the core & is not known to vary.
- Antibodies against **p24** do not neutralize HIV infectivity but serve as important serologic markers of infection.

Important antigens of HIV

- The gene encodes gp120 mutates rapidly, resulting in many antigenic variants.
- The most immunogenic region of gp120 is called the V₃ loop; it is one of the sites that varies antigenically to a significant degree.

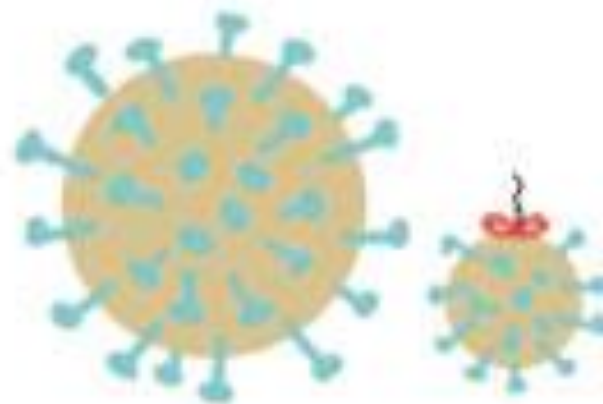
Host of HIV

- The natural host range of HIV is limited to humans, although certain primates can be infected in the laboratory.
- The origin of HIV & how it entered the human population remains uncertain.
- There is evidence that chimpanzees living in West Africa were the source of HIV-1.

HIV **ATTACKS** YOUR T-CELLS



AND USES THEM TO
MAKE COPIES
OF ITSELF



Transmission

- Transmission of HIV occurs primarily by
 - Sexual contact
 - Transfer of infected blood.
- Perinatal transmission from the infected mother to the neonate
 - across the placenta,
 - at birth, or
 - via breast milk.
- It is estimated that
 - more than 50% of neonatal infections occur at the time of birth
 - transplacental transmission 25%
 - transmission via breastfeeding 25%

Transmission

- Infection occurs by transferring either HIV-infected cells or free HIV (i.e., HIV that is not cell-associated).
- Although small amounts of virus have been found in other fluids, e.g., saliva & tears, there is no evidence that they play a role in infection.
- Transmission of HIV follows the pattern of hepatitis B virus, except that HIV infection is much less efficiently transferred, i.e.,
 - the dose of HIV required to cause infection is much higher than that of HBV.
- People with STDs, especially those with ulcerative lesions such as syphilis, chancroid, & herpes genitalis, have a significantly higher risk of both transmitting & acquiring HIV.
- Uncircumcised males have a higher risk of acquiring HIV than do circumcised males.

Transmission

- Transmission of HIV via blood transfusion has been greatly reduced by screening donated blood for the presence of antibody to HIV.
- However, there is a "window" period early in infection when the blood of an infected person can contain HIV but antibodies are not detectable.
- Blood banks now test for the presence of p24 antigen in an effort to detect blood that contains HIV.

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

Epidemiology

- Worldwide, it is estimated that approximately 40 million people are infected, two-thirds of whom live in sub-Saharan Africa.
- Three regions, Africa, Asia, & Latin America, have the highest rates of new infections.
- AIDS is the fourth leading cause of death worldwide.
 1. Ischemic heart disease,
 2. Cerebrovascular disease
 3. Acute lower respiratory disease
 4. AIDS

Clinical Findings

- The clinical picture of HIV infection can be divided into three stages:
- An early, acute stage
- A middle, latent stage
- A late, immunodeficiency stage.

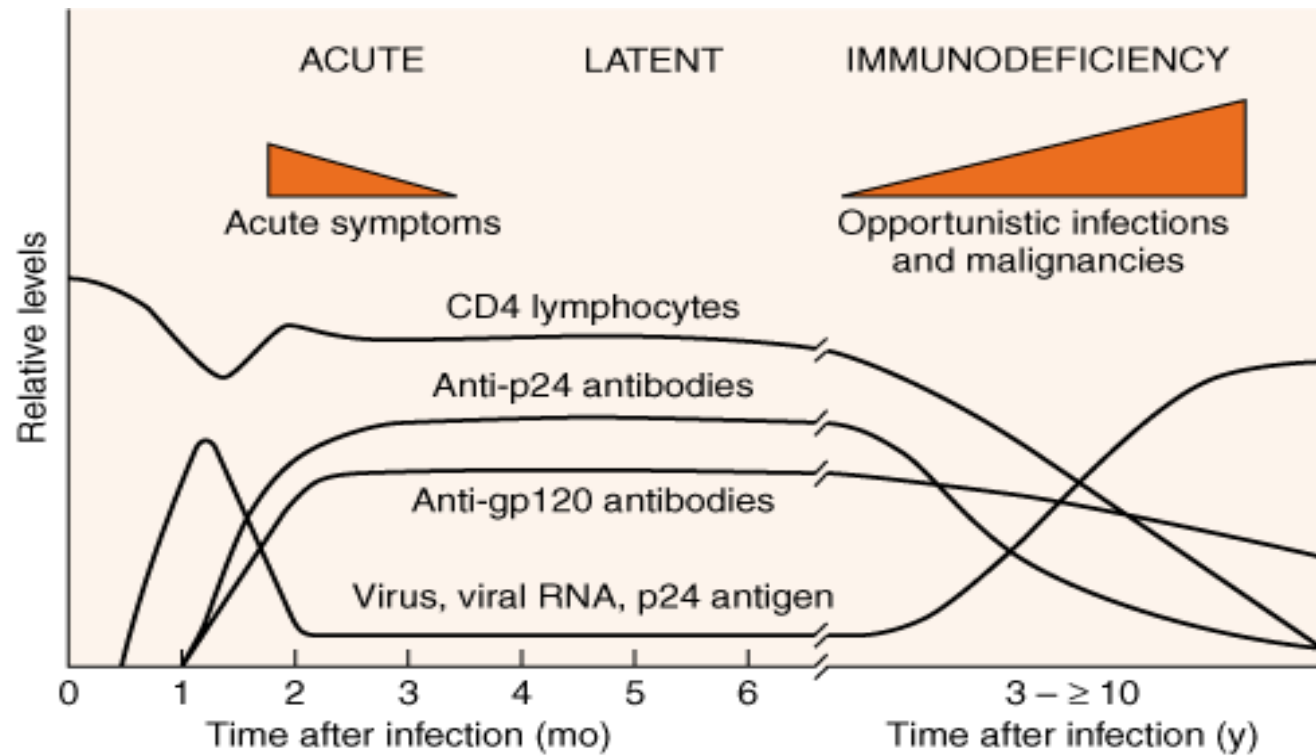
Clinical Findings Early Acute stage

- Usually begins 2 to 4 weeks after infection
- This acute stage typically resolves spontaneously in about 2 weeks.
- A mononucleosis-like picture of
- Fever, lethargy, sore throat, & generalized lymphadenopathy occurs.
- A maculopapular rash on
- The trunk, arms, & legs (but sparing the palms & soles) is also seen.

usually

Clinical Findings Early Acute stage

- Leukopenia occurs, but the number of CD4 cells is usually normal (500- 1500/mm³).
- A high-level viremia typically occurs, & the infection is readily transmissible during this acute stage.
- Resolution of the acute stage is usually accompanied by
 - lower level of viremia
 - rise in the number of CD8-positive (cytotoxic) T cells directed against HIV (normal 150- 1000/mm³).



Time course of HIV infection

The three main stages of HIV infection—acute, latent, and immunodeficiency—are shown in conjunction with several important laboratory findings.

Levels of virus & viral RNA (viral load) are high early in the infection, become low for several years, & then rise during the immunodeficiency stage.

Level of CD4 lymphocytes remains more or less normal for many years but then falls.

This results in the immunodeficiency stage, which is characterized by opportunistic infections & malignancies.

HIV antibodies

- **Antibodies to HIV typically appear 10 to 14 days after infection, & most will have seroconverted by 3 to 4 weeks after infection.**
- **The inability to detect antibodies prior to that time can result in "false-negative" serologic tests, i.e.,**
- **The person is infected, but antibodies are not detectable at the time of the test.**

HIV antibodies

- This has important implications because HIV can be transmitted to others during this period.
- If the antibody test is negative but HIV infection is still suspected, then a PCR-based assay for viral RNA in the plasma should be done.

HIV antibodies

- Of those who become seropositive during the acute infection, approximately:
- 87% are symptomatic, i.e.,
- 13% experience an initial asymptomatic infection.

HIV antibodies

- After the initial viremia, a viral set point occurs, which can differ from one person to another.
- The set point represents the amount of virus produced, i.e., the viral load, & tends to remain "set," or constant, for years.
- The higher the set point at the end of the initial infection, the more likely the individual is to progress to symptomatic AIDS.
- It is estimated that an infected person can produce up to 10 billion new virions daily.

HIV antibodies

- The viral load can be estimated by using an assay for viral RNA in the patient's plasma.
- (The assay detects the RNA in free virions in the plasma, not cell-associated virions.)
- The amount of viral RNA serves to guide treatment decisions & the prognosis.
- If a drug regimen fails to reduce the viral load, the drugs should be changed.

HIV antibodies & Prognosis

- As far as the prognosis is concerned,
- a patient with more than 10,000 copies of viral RNA/mL of plasma is significantly more likely to progress to AIDS than
- The frequency & severity of opportunistic infections significantly increases when the CD4 counts fall below 200/mm³.

HIV antibodies

- The number of CD4-positive T cells is another important measure that guides the management of infected patients. It is used to:
 - determine whether a patient needs chemoprophylaxis against opportunistic organisms
 - determine whether a patient needs anti-HIV therapy
 - determine the response to this therapy.
-
- In the middle stage, a long latent period, measured in years, usually ensues.

HIV antibodies

- In untreated patients, the latent period usually lasts for 7 to 11 years.
- The patient is asymptomatic during this period.
- Although the patient is asymptomatic & viremia is low or absent, a large amount of HIV is being produced by lymph node cells but remains sequestered within the lymph nodes.
- This indicates that during this period of clinical latency, the virus itself does not enter a latent state.

Clinical Findings A Middle Latent period of HIV

- A syndrome called AIDS-related complex (ARC) can occur during the latent period.
- The most frequent manifestations are:
 - persistent fevers
 - fatigue
 - weight loss
 - lymphadenopathy
- ARC often progresses to AIDS.

Clinical Findings

The late stage of HIV infection is

AIDS

- **Manifested by**
- **A decline in the number of CD₄ cells to below 400/L &**
- **An increase in the frequency & severity of opportunistic infections.**

Common Opportunistic Infections in AIDS Patients

Site of Infection	Disease or Symptom	Causative Organism
Lung	1. Pneumonia	<i>Pneumocystis carinii</i> , cytomegalovirus
	2. Tuberculosis	<i>Mycobacterium tuberculosis</i>
Mouth	1. Thrush	Candida albicans
	2. Hairy Leukoplakia	EBV
	3. Ulcerations	Herpes simplex virus-1, <i>Histoplasma capsulatum</i>
Esophagus	1. Thrush	Candida albicans
	2. Esophagitis	Cytomegalovirus, herpes simplex virus-1
Intestinal tract	Diarrhea	<i>Salmonella sp.</i> , <i>Shigella sp.</i> , cytomegalovirus, <i>Cryptosporidium parvum</i> , <i>Giardia lamblia</i>

Common Opportunistic Infections in AIDS Patients

Site of Infection	Disease or Symptom	Causative Organism
CNS	1. Meningitis	<i>Cryptococcus neoformans</i>
	2. Brain abscess	<i>Toxoplasma gondii</i>
	3. Progressive multifocal leukoencephalopathy	JC virus
Eye	Retinitis	Cytomegalovirus
Skin	1. Kaposi's sarcoma	Cytomegalovirus
	2. Zoster	VZV
	3. Subcutaneous nodules	<i>Cryptococcus neoformans</i>
Reticuloendothelial system	Lymphadenopathy or splenomegaly	<i>Mycobacterium avium</i> complex, Epstein-Barr virus

Manifestations of AIDS

- The two most characteristic manifestations of AIDS are
 1. *Pneumocystis pneumonia*
 2. Kaposi's sarcoma.

Other opportunistic infections of AIDS

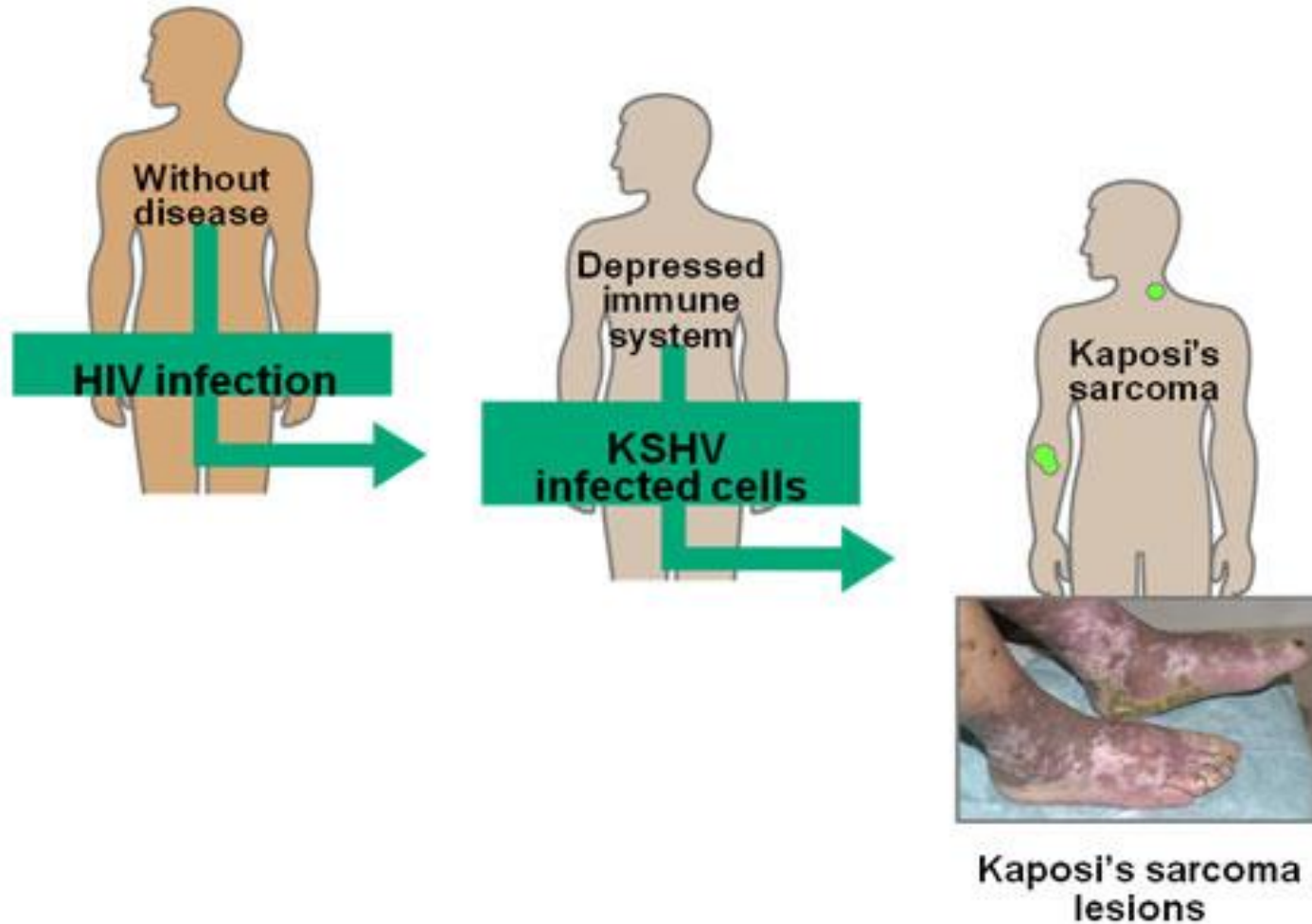
- Viral infections
 - Disseminated HSV
 - Herpes zoster
 - CMV infections
 - Progressive multifocal leukoencephalopathy
- Fungal infections
 - Thrush (caused by *Candida albicans*),
 - Cryptococcal meningitis,
 - Disseminated histoplasmosis
- Protozoal infections
 - Toxoplasmosis
 - Cryptosporidiosis

Other opportunistic infections of AIDS

- Disseminated bacterial infections
- *Mycobacterium avium-intracellulare*
- *Mycobacterium tuberculosis*.

- Many AIDS patients have severe neurologic problems, e.g.,
- dementia &
- neuropathy,
- which can be caused by either HIV infection of the brain or by many of these opportunistic organisms.

Other Viruses



KSHV: Kaposi's sarcoma-associated herpesvirus

Laboratory Diagnosis

Presumptive Diagnosis of HIV infection

- Is made by the detection of antibodies by **ELISA**.
- During the first month after infection, antibody tests may be negative.
- These false-negative tests are due to insufficient antibodies being made early in infection to be detected in the ELISA test.
- The average time for seroconversion is 10 to 14 days & most, but not all, will have seroconverted by 4 weeks.
- Because there are some false-positive results with this test.

Laboratory Diagnosis

- Definitive Diagnosis of HIV infection
- Is made by Western blot analysis
- OraQuick
- Is a rapid screening immunoassay for HIV antibody that uses a blood sample obtained by finger prick.
- Results are available in 20 minutes.
- Positive results require confirmation by a Western blot test.

Laboratory Diagnosis

- Culture
- HIV can be grown in culture from clinical specimens
- This procedure is available only at a few medical centers.
- The polymerase chain reaction (PCR), is a very sensitive & specific technique

Laboratory Diagnosis

- **Diagnosis of acute HIV infection**
- May not be able to be made using serologic tests.
- The presence of HIV can be detected best during acute infection by the plasma HIV RNA assay (viral load) as viremia is typically high at this early stage.
- The p24 antigen test or viral culture can also be used.

Treatment

- The treatment has resulted in a remarkable reduction in mortality & improvement in the quality of life of infected individuals.
- Specific goals of treatment are to:
- Restore immunologic function that reduces the incidence of both opportunistic infections & certain malignancies.
- Reduce viral load, which reduces the chance of transmission to others.
- No drug regimen results in a "cure," i.e., eradicates the virus from the body, but long-term suppression can be achieved.
- However if drugs are stopped, the virus resumes active replication & large amounts of infectious virus reappear.

Treatment

- Treatment of HIV infection typically involves multiple antiretroviral drugs.
- The use of a single drug (monotherapy) for treatment is not done because of the high mutation rate to drug resistance.
- The choice of drugs is complex & depends on several factors, e.g.,
 - whether it is an initial infection or an established infection,
 - the number of CD₄ cells,
 - the viral load,
 - the resistance pattern of the virus, &
 - whether the patient is pregnant or is co-infected with HBV or HCV.

Prevention

- No vaccine is available.

General Prevention

- Measures to avoid exposure to the virus, e.g.,
- using condoms
- not sharing needles
- discarding donated blood that is contaminated with HIV.

Prevention

- Steps were taken to reduce the number of cases of HIV infection in children:
 1. ZDV or nevirapine should be given perinatally to HIV-infected mothers & neonates.
 2. HIV-infected mothers should not breastfeed.
 3. The risk of neonatal HIV infection is lower if delivery is accomplished by cesarean section rather than by vaginal delivery.
- Circumcision reduces HIV infection.

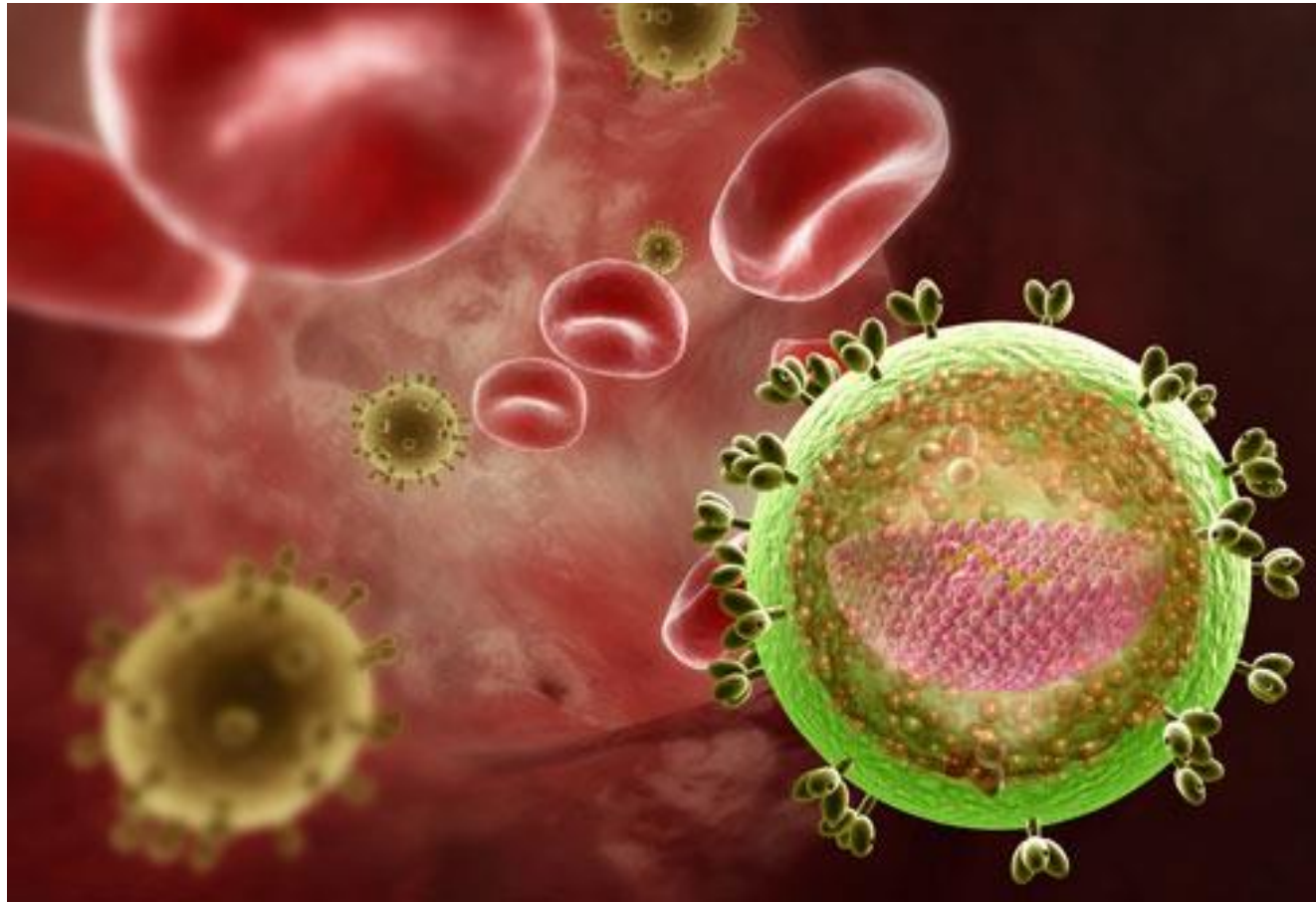
Prevention Post-exposure prophylaxis

- Post-exposure prophylaxis, such as that given after
- a needle-stick injury or
- a high-risk non-occupational exposure consists of two drugs, e.g.,
- For low-risk exposures
 1. lamivudine &
 2. zidovudine
- For high-risk exposures.
 1. lamivudine &
 2. zidovudine plus
 3. lopinavir/ritonavir
- Instead of lamivudine and zidovudine, a combination of tenofovir and emtricitabine can be given.

Prevention

Patients commonly take several drugs in the advanced stages of AIDS to prevent certain opportunistic infections. e.g

- Trimethoprim-sulfamethoxazole to prevent *Pneumocystis pneumonia*
- Fluconazole to prevent recurrences of cryptococcal meningitis
- Ganciclovir to prevent recurrences of retinitis caused by cytomegalovirus,
- Oral preparations of antifungal drugs, such as clotrimazole, to prevent thrush caused by *Candida albicans*.



Myth. HIV is a virus that destroys the body's CD4 immune cells, which help fight disease. With the right medications, you can have HIV for years or decades without HIV progressing to AIDS. AIDS is diagnosed when you have HIV, and certain opportunistic infections or your CD4 cell count drops below 200.



It's Difficult to Get HIV From Casual Contact

Fact. You can't catch or spread HIV by hugging someone, using the same towel, or sharing the same glass. It's very rare to get HIV from a blood transfusion -- the U.S. blood supply is carefully tested. However, you can spread the disease by having unprotected sex, sharing needles, or getting a tattoo from unsterilized equipment.



You Have Just a Few Years to Live

Myth. Everyone with HIV experiences it differently. Some people may develop AIDS within a few months as the virus quickly weakens their immune system. Many others can live for decades with HIV and have a normal life expectancy. You can help prevent HIV from progressing to AIDS by seeing your doctor regularly and following your doctor's recommendations.



You'll Know You Have HIV Because of Your Symptoms

Myth. Some people don't show any signs of HIV for years after being infected. Many can have some symptoms within 10 days to a few weeks after infection. These first symptoms are similar to the flu or mononucleosis and may include fever, fatigue, rash, and sore throat. They usually disappear after a few weeks and you may not have symptoms again for several years. The only way to tell you have HIV is to get tested.



HIV Can Be Cured

Myth. There is no cure for HIV, but treatment can keep virus levels low and help maintain your immune system. Some drugs interfere with proteins HIV needs to copy itself; others block the virus from entering or inserting its genetic material into your immune cells. Your doctor will consider your general health, the health of your immune system, and the amount of virus in your body to decide when to start treatment.



Anyone Can Get HIV

Fact. About 56,000 people in the U.S. get HIV each year, and 18,000 people with AIDS die each year. Anyone can get HIV -- men, women, and children, people who are gay or straight. Men who have sex with men make up more than half (53%) of new HIV infections each year. Women account for 27% of new infections, and children 13%. African-Americans make up almost half of all new HIV infections each year.



Sex Is Safe When Both Partners Have HIV

Myth. Just because you and your partner both have HIV, doesn't mean you should forget about protection when you have sex. Using a condom or other latex barrier can help protect you from other sexually transmitted diseases as well as other strains of HIV, which may be resistant to anti-HIV medication. Even if you are being treated and feel well you can still infect others.



You Can Have a Baby if You Are HIV-Positive

Fact. Infected mothers can indeed pass HIV to their babies during pregnancy or delivery. However, you can lower the risk by working with your doctor and getting the appropriate care and medication. Pregnant women with HIV can take medications to treat their infection and to protect their babies against the virus.



You Can't Avoid Other HIV-Related Infections

Myth. Due to weakened immune systems, people with HIV can be vulnerable to infections like pneumocystis pneumonia, tuberculosis, candidiasis, cytomegalovirus, and toxoplasmosis. The best way to reduce your risk is to take your HIV medications. Some infections can be prevented with drugs. You can lessen your exposure to some germs by avoiding undercooked meat, litter boxes, and water that may be contaminated.



Without Insurance You Can't Get Lifesaving Drugs

Myth. There are government programs, nonprofit groups, and some pharmaceutical companies that may help cover the cost of HIV/AIDS drugs. But be aware: These drug "cocktails" can cost \$15,000 a year. Talk to your local HIV/AIDS service organization to learn about financial help.