Unit-3 Viral diseases

I) HIV Human immunodeficiency virus / Acquired Immunodeficiency Syndrome (AIDS)

Acquired immune deficiency syndrome or **acquired immunodeficiency syndrome** (**AIDS**) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). The illness interferes with the immune system making people with AIDS much more likely to get infections, including opportunistic infections and tumors .

- **Discovery**

AIDS was first clinically observed between late 1980 and early 1981. Injection drug users and gay men with no known cause of impaired immunity showed symptoms of *Pneumocystis carinii* pneumonia (PCP), a rare opportunistic infection that was known to present itself in people with much compromised immune systems. Soon thereafter, additional gay men developed a previously-rare skin cancer called Kaposi's sarcoma

In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a novel retrovirus may have been infecting AIDS patients. Gallo claimed that a virus his group had isolated from an AIDS patient was strikingly similar in shape to other human T-lymphotropic viruses (HTLVs) his group had been the first to isolate. Gallo's group called their newly isolated virus HTLV-III.

At the same time, Montagnier's group isolated a virus from a patient presenting lymphadenopathy (swelling of the lymph nodes) of the neck and physical weakness. Montagnier's group named their isolated virus lymphadenopathy-associated virus (LAV). HIV was chosen as a compromise between the two claims (LAV and HTLV-III).

HIV is a member of the genus *Lentivirus*, part of the family of Retroviridae. Lentiviruses are responsible for long-duration illnesses with a long incubation period. Two types of HIV have been characterized: HIV-1 and HIV-2.

Comparison of HIV species				
Species	**Virulence**	**Infectivity**	**Prevalence**	**Inferred origin**
HIV-1	High	High	Global	Common Chimpanzee
HIV-2	Lower	Low	West Africa	Sooty Mangabey

- **Origin of HIV**

HIV is thought to have originated in non-human primates in sub-Saharan Africa and was transferred to humans late in the 19th or early in the 20th century. Both HIV-1 and HIV-2 are believed to have originated in West-Central Africa and to have jumped species (a process known as zoonosis) from non-human primates to humans.

HIV-1 appears to have originated in southern Cameroon through the evolution of SIV(cpz), a simian immunodeficiency virus (SIV) that infects wild chimpanzees (HIV-1 descends from the SIVcpz endemic in the chimpanzee subspecies *Pan troglodytes troglodytes*).

The closest relative of HIV-2 is SIV (smm), a virus of the sooty mangabey (*Cercocebus atys atys*), an Old World monkey living in litoral West Africa (from southern Senegal to western Ivory Coast). New World monkeys such as the owl monkey are resistant to HIV-1 infection, possibly because of a genomic fusion of two viral resistance genes. HIV-1 is thought to have jumped the species barrier on at least three separate occasions, giving rise to the three groups of the virus, M, N, and O.

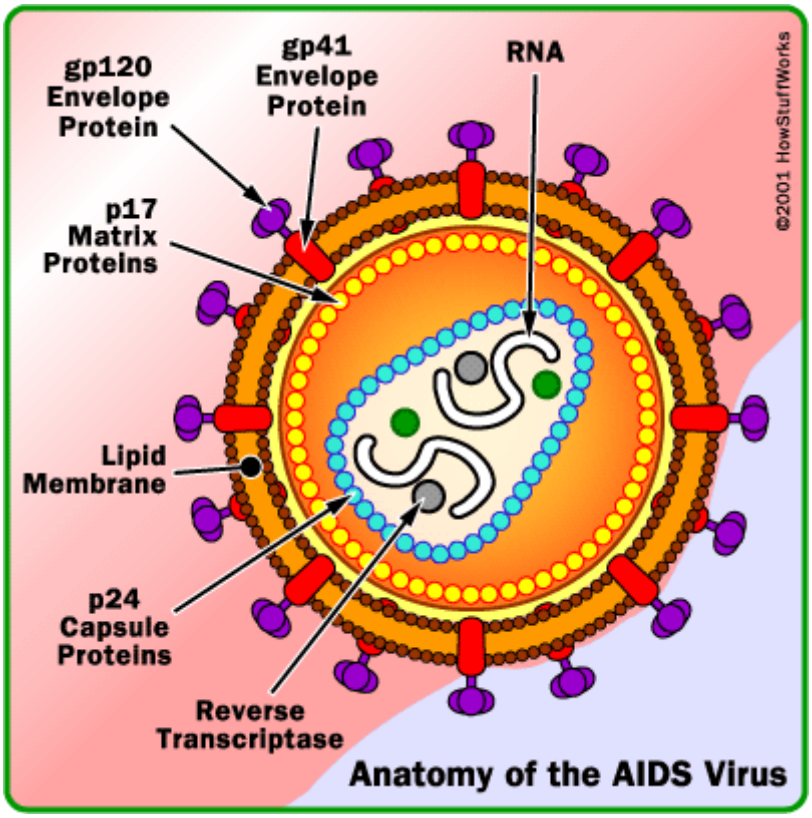
There is evidence that humans who participate in bushmeat activities, either as hunters or as bushmeat vendors, commonly acquire SIV.[181] However, SIV is a weak virus, it is typically suppressed by the human immune system within weeks of infection. It is thought that several transmissions of the virus from individual to individual in quick succession are necessary to allow it enough time to mutate into HIV.

- **Structure of HIV**

HIV is different in structure from other retroviruses. It is roughly spherical with a diameter of about 120 nm. It is composed of two copies of

positive single-stranded RNA that codes for the virus's nine genes enclosed by a conical capsid composed of 2,000 copies of the viral protein p24. The single-stranded RNA is tightly bound to nucleocapsid proteins, p7, and enzymes needed for the development of the virion such as reverse transcriptase, proteases, ribonuclease and integrase. A matrix composed of the viral protein p17 surrounds the capsid ensuring the integrity of the virion particle.

This is, in turn, surrounded by the viral envelope that is composed of two layers of fatty molecules called phospholipids taken from the membrane of a human cell when a newly formed virus particle buds from the cell. Embedded in the viral envelope are proteins from the host cell and about 70 copies of a complex HIV protein that protrudes through the surface of the virus particle. This protein, known as Env, consists of a cap made of three molecules called glycoprotein (gp) 120, and a stem consisting of three gp41 molecules that anchor the structure into the viral envelope. This glycoprotein complex enables the virus to attach to and fuse with target cells to initiate the infectious cycle. Both these surface proteins, especially gp120, have been considered as targets of future treatments or vaccines against HIV.[



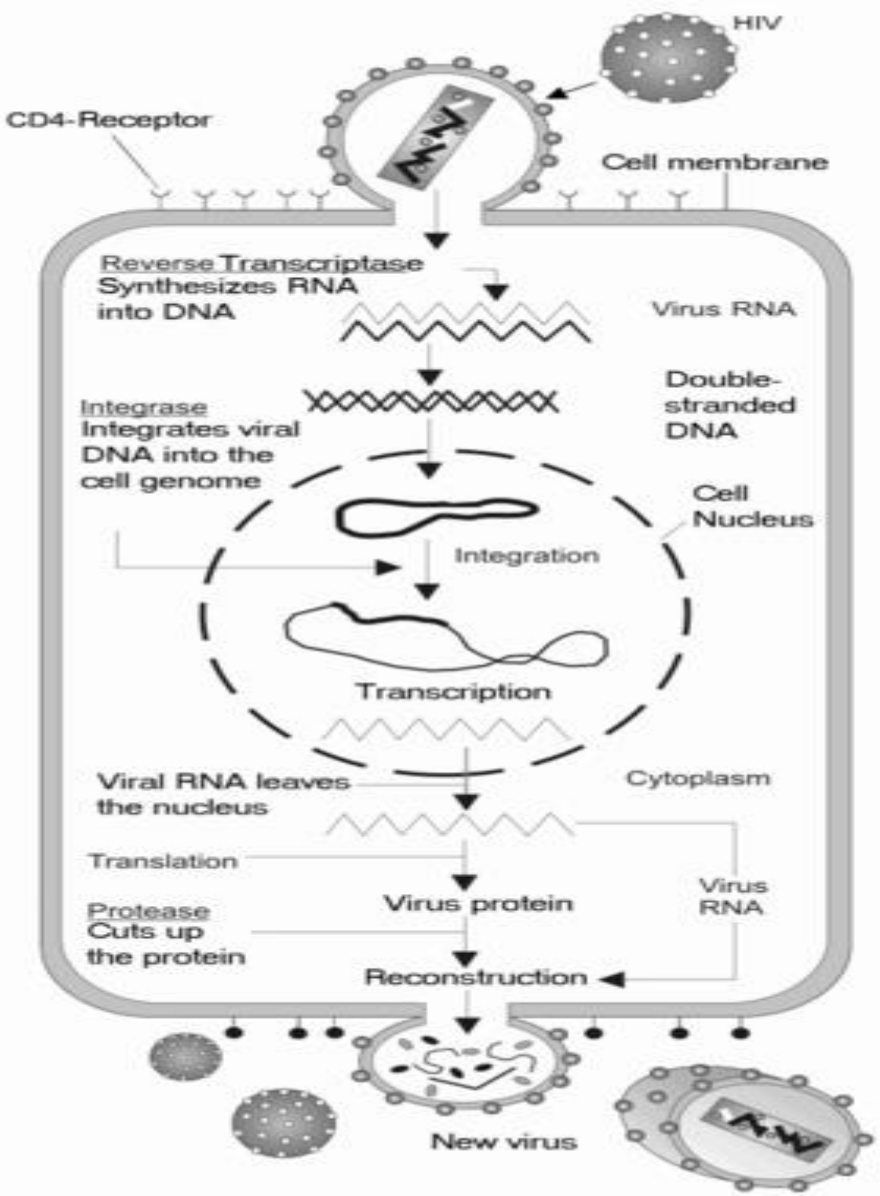
- **Replication cycle**

Entry to the cell

HIV enters macrophages and $CD4^+$ T cells by the adsorption of glycoproteins on its surface to receptors on the target cell followed by fusion of the viral envelope with the cell membrane and the release of the HIV capsid into the cell.

The first step in fusion involves the high-affinity attachment of the CD4 binding domains of gp120 to CD4. Once gp120 is bound with the CD4 protein, the envelope complex undergoes a structural change, exposing the chemokine binding domains of gp120 and allowing them to interact with the target chemokine receptor.

After HIV has bound to the target cell, the HIV RNA and various enzymes, including reverse transcriptase, integrase, ribonuclease, and protease, are injected into the cell. During the microtubule-based transport to the nucleus, the viral single-strand RNA genome is transcribed into double-strand DNA, which is then integrated into a host chromosome.



Replication and transcription

Shortly after the viral capsid enters the cell, an enzyme called *reverse transcriptase* liberates the single-stranded (+)RNA genome from the attached viral proteins and copies it into a complementary DNA (cDNA) molecule.

Together, the cDNA and its complement form a double-stranded viral DNA that is then transported into the cell nucleus. The integration of the viral DNA into the host cell's genome is carried out by another viral enzyme called *integrase*. This integrated viral DNA may then lie dormant, in the latent stage of HIV infection.

During viral replication, the integrated DNA provirus is transcribed into mRNA, which is then spliced into smaller pieces. These small pieces are

exported from the nucleus into the cytoplasm, where they are translated into the regulatory proteins. At this stage, the structural proteins Gag and Env are produced from the full-length mRNA. The full-length RNA is actually the virus genome; it binds to the Gag protein and is packaged into new virus particles.

Assembly and release

The final step of the viral cycle, assembly of new HIV-1 virons, begins at the plasma membrane of the host cell. The Env polyprotein (gp160) goes through the endoplasmic reticulum and is transported to the Golgi complex where it is cleaved by protease and processed into the two HIV envelope glycoproteins gp41 and gp120. These are transported to the plasma membrane of the host cell where gp41 anchors the gp120 to the membrane of the infected cell. The Gag (p55) and Gag-Pol (p160) polyproteins also associate with the inner surface of the plasma membrane along with the HIV genomic RNA as the forming virion begins to bud from the host cell. The various structural components then assemble to produce a mature HIV virion.

- **Genetic variability of HIV**

HIV differs from many viruses in that it has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of about 10^{10} virions every day, coupled with a high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle of replication and recombinogenic properties of reverse transcriptase.

This complex scenario leads to the generation of many variants of HIV in a single infected patient in the course of one day. Three groups of HIV-1 have been identified on the basis of differences in the envelope (*env*) region: M, N, and O.

Group M is the most prevalent and is subdivided into eight subtypes (or clades), based on the whole genome, which are geographically distinct. The most prevalent are subtypes B (found mainly in North America and Europe), A and D (found mainly in Africa), and C (found mainly in Africa and Asia).

- **Signs and symptoms**

Infection with HIV-1 is associated with a progressive decrease of the $CD4^+$ T cell count and an increase in viral load, the level of HIV in the blood. The symptoms of AIDS are primarily the result of conditions that do not normally develop in individuals with healthy immune systems. Most of these

conditions are infections caused by bacteria, viruses, fungi and parasites that are normally controlled by the elements of the immune system that HIV damages.

Opportunistic infections are common in people with AIDS. These infections affect nearly every organ system.

People with AIDS also have an increased risk of developing various cancers such as Kaposi's sarcoma, cervical cancer and cancers of the immune system known as lymphomas. Additionally, people with AIDS often have systemic symptoms of infection like fevers, sweats (particularly at night), swollen glands, chills, weakness, and weight loss.

Pulmonary infections

i. Pneumocystis pneumonia common among HIV-infected individuals. It is caused by *Pneumocystis jirovecii*.
ii. Tuberculosis (TB) is unique among infections associated with HIV because it is transmissible to immunocompetent people via the respiratory route, and is not easily treatable once identified. In advanced HIV infection, TB often presents atypically with extrapulmonary (systemic) disease a common feature. Symptoms are usually constitutional and are not localized to one particular site, often affecting bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system.

Gastrointestinal

i. Esophagitis is an inflammation of the lining of the lower end of the esophagus (gullet or swallowing tube leading to the stomach). In HIV-infected individuals, this is normally due to fungal (candidiasis) or viral (herpes simplex-1 or cytomegalovirus) infections.
ii. Unexplained chronic diarrhea in HIV infection is due to many possible causes, including common bacterial (*Salmonella*, *Shigella*, *Listeria* or *Campylobacter*) and parasitic infections; and uncommon opportunistic infections.

Neurological and psychiatric

i. HIV infection may lead to a variety of neuropsychiatric sequelae, either by infection of the now susceptible nervous system by organisms, or as a direct consequence of the illness itself.

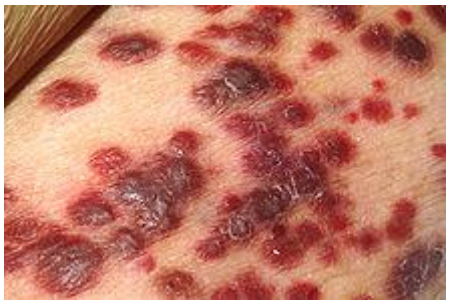
ii. Toxoplasmosis is a disease caused by the single-celled parasite called *Toxoplasma gondii*; it usually infects the brain, causing toxoplasma encephalitis, but it can also infect and cause disease in the eyes and lungs.

iii. Cryptococcal meningitis is an infection of the meninx (the membrane covering the brain and spinal cord) by the fungus *Cryptococcus neoformans*. It can cause fevers, headache, fatigue, nausea, and vomiting. Patients may also develop seizures and confusion; left untreated, it can be lethal.

iv. Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease, in which the gradual destruction of the myelin sheath covering the axons of nerve cells impairs the transmission of nerve impulses. It is caused by a virus called JC virus.

v. AIDS dementia complex (ADC) is a metabolic encephalopathy induced by HIV infection and fueled by immune activation of HIV infected brain macrophages and microglia. These cells are productively infected by HIV and secrete neurotoxins of both host and viral origin. Specific neurological impairments are manifested by cognitive, behavioral, and motor abnormalities that occur after years of HIV infection and are associated with low $CD4^+$ T cell levels and high plasma viral loads.

Tumors



Kaposi's sarcoma

Patients with HIV infection have substantially increased incidence of several cancers. This is primarily due to co-infection with an oncogenic DNA virus. Kaposi's sarcoma (KS) is the most common tumor in HIV-infected patients.

Invasive cervical cancer in HIV-infected women is also considered AIDS-defining, it is caused by human papillomavirus (HPV).

Other infections

AIDS patients often develop opportunistic infections that present with non-specific symptoms, especially low-grade fevers and weight loss. These include opportunistic infection with *Mycobacterium avium-intracellulare* and cytomegalovirus (CMV). CMV can cause colitis, as described above, and CMV retinitis can cause blindness.

Penicilliosis due to *Penicillium marneffei* is now the third most common opportunistic infection.

The rate of clinical disease progression varies widely between individuals, from two weeks up to 20 years. Many factors affect the rate of progression. These include factors that influence the body's ability to defend against HIV such as the infected person's general immune function. Older people have weaker immune systems, and therefore have a greater risk of rapid disease progression than younger people.

The stage of infection can be determined by measuring the patient's $CD4^+$ T cell count and viral load. The stages of HIV infection are

1. Aacute infection (also known as primary infection),
2. Latency
3. AIDS.

1. Acute infection (also known as primary infection)

Infection with HIV generally occurs by introduction of bodily fluids from an infected person into the body of an uninfected person. A period of rapid viral replication ensues, leading to an abundance of virus in the peripheral blood. During primary infection, the level of HIV may reach several million virus particles per milliliter of blood.

Cells affected

The virus, entering through which ever route, acts primarily on the following cells:

- Lymphoreticular system:
  - CD_4+ T-Helper cells
  - Macrophages
  - Monocytes
  - B-lymphocytes
- Certain endothelial cells
- Central nervous system:
  - Microglia of the nervous system
  - Astrocytes
  - Oligodendrocytes
  - Neurones – indirectly by the action of cytokines and the gp-120

During this period (usually 2–4 weeks post-exposure) many individuals develop an influenza or mononucleosis-like illness called acute HIV infection, the most common symptoms of which may include fever, lymphadenopathy, pharyngitis, rash, myalgia, malaise, mouth and esophageal sores, and may also include, but less commonly, headache, nausea and vomiting, enlarged liver/spleen, weight loss, thrush, and neurological symptoms. Infected individuals may experience all, some, or none of these symptoms. The duration of symptoms varies, averaging 28 days and usually lasting at least a week.

2. Chronic infection / Latency / Secondary infection

A strong immune defense reduces the number of viral particles in the blood stream, marking the start of secondary or chronic HIV infection. The secondary stage of HIV infection can vary between two weeks and 20 years. During this phase of infection, HIV is active within lymph nodes, which typically become persistently swollen, in response to large amounts of virus that become trapped in the follicular dendritic cells (FDC) network. The surrounding tissues that are rich in $CD4^+$ T cells may also become infected, and viral particles accumulate both in infected cells and as free virus. Individuals who are in this phase are still infectious.

3. AIDS

When $CD4^+$ T cell numbers decline below a critical level of 200 cells per μL, cell-mediated immunity is lost, and infections with a variety of opportunistic microbes appear. The first symptoms often include moderate and unexplained weight loss, recurring respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis), prostatitis, skin rashes, and oral ulcerations.

Common opportunistic infections and tumors, most of which are normally controlled by robust $CD4^+$ T cell-mediated immunity then start to affect the patient. Typically, resistance is lost early on to oral Candida species and to *Mycobacterium tuberculosis*, which leads to an increased susceptibility to oral candidiasis (thrush) and tuberculosis. Later, reactivation of latent herpes viruses may cause worsening recurrences of herpes simplex eruptions, shingles, Epstein-Barr virus-induced B-cell lymphomas, or Kaposi's sarcoma.

Pneumonia caused by the fungus *Pneumocystis jirovecii* is common and often fatal. In the final stages of AIDS, infection with cytomegalovirus (another herpes virus) or Mycobacterium avium complex is more prominent. Not all patients with AIDS get all these infections or tumors, and there are other tumors and infections that are less prominent but still significant.

- **Transmission of HIV**

HIV is transmitted in many ways, such as anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, and breastfeeding. It can be transmitted by any contact of a mucous membrane or the bloodstream with a bodily fluid that has the virus in it, such as the blood, semen, vaginal fluid, preseminal fluid, or breast milk from an infected person.

Sexual transmission

Sexual transmission occurs with the contact between sexual secretions of one person with the rectal, genital or oral mucous membranes of another. Unprotected sexual acts are riskier for the receptive partner than for the insertive partner,.Other sexually transmitted infections (STI) increase the risk of HIV transmission and infection, because they cause the disruption of the normal epithelial barrier by genital ulceration and/or microulceration; and by

accumulation of pools of HIV-susceptible or HIV-infected cells (lymphocytes and macrophages) in semen and vaginal secretions.

Blood products

This transmission route is particularly relevant to intravenous drug users, hemophiliacs and recipients of blood transfusions and blood products. Sharing and reusing syringes contaminated with HIV-infected blood represents a major risk for infection with HIV.

Needle sharing is the cause of one third of all new HIV-infections in North America, China, and Eastern Europe. This route can also affect people who give and receive tattoos and piercings.

The risk of transmitting HIV to blood transfusion recipients is extremely low in developed countries where improved donor selection and HIV screening is performed.

Perinatal transmission

The transmission of the virus from the mother to the child can occur *in utero* during the last weeks of pregnancy and at childbirth. In the absence of treatment, the transmission rate between a mother and her child during pregnancy, labor and delivery is 25%.

However, when the mother takes antiretroviral therapy and gives birth by caesarean section, the rate of transmission is just 1%. The risk of infection is influenced by the viral load of the mother at birth, with the higher the viral load, the higher the risk. Breastfeeding also increases the risk of transmission by about 4 %.

- **Epidemiology**

The AIDS pandemic can also be seen as several epidemics of separate subtypes; the major factors in its spread are sexual transmission and vertical transmission from mother to child at birth and through breast milk. Globally, an estimated 33.2 million people lived with HIV in 2007.

Sub-Saharan Africa remains by far the worst affected region. In 2007 it contained an estimated 68% of all people living with AIDS and 76% of all AIDS deaths.

South Africa has the largest population of HIV patients in the world, followed by Nigeria and India. South & South East Asia are second worst affected.

- **Lab diagnosis**

HIV tests are usually performed on venous blood. Many laboratories use *fourth generation* screening tests which detect anti-HIV antibody (IgG and IgM) and the HIV p24 antigen.

The detection of HIV antibody or antigen in a patient previously known to be negative is evidence of HIV infection. Individuals whose first specimen indicates evidence of HIV infection will have a repeat test on a second blood sample to confirm the results.

The window period (the time between initial infection and the development of detectable antibodies against the infection) can vary since it can take 3–6 months to seroconvert and to test positive. Detection of the virus using polymerase chain reaction (PCR) during the window period is possible, and evidence suggests that an infection may often be detected earlier than when using a fourth generation EIA screening test.

Positive results obtained by PCR are confirmed by antibody tests

- **Prevention of AIDS**

The three main transmission routes of HIV are sexual contact, exposure to infected body fluids or tissues, and from mother to fetus or child during the perinatal period. It is possible to find HIV in the saliva, tears, and urine of infected individuals, but there are no recorded cases of infection by these secretions, and the risk of infection is negligible. Anti-retroviral treatment of infected patients also significantly reduces their ability to transmit HIV to others, by reducing the amount of virus in their bodily fluids to undetectable levels.

Sexual contact

The majority of HIV infections are acquired through unprotected sexual relations between partners, one of whom has HIV. During a sexual act, only male or female condoms can reduce the risk of infection with HIV and other STDs.

Body fluid exposure

Health care workers can reduce exposure to HIV by employing precautions to reduce the risk of exposure to contaminated blood. These precautions include barriers such as gloves, masks, protective eyeware or shields, and gowns or aprons which prevent exposure of the skin or mucous membranes to blood borne pathogens. Frequent and thorough washing of the skin immediately after being contaminated with blood or other bodily fluids can reduce the chance of infection. Finally, sharp objects like needles, scalpels and glass, are carefully disposed of to prevent needle stick injuries with contaminated items.

Mother-to-child

HIV-infected mothers should avoid breast-feeding their infant.]

Education

One way to change risky behavior is health education. Several studies have shown the positive impact of education and health literacy on cautious sex behavior. Education works only if it leads to higher health literacy and general cognitive ability. This ability is relevant to understand the relationship between own risky behavior and possible outcomes like HIV-transmission.

There was a need for actual implementation of sex-education programmes (such as teacher training, access to related services through schools and the community, or parental attitudes to HIV and AIDS education) and more longitudinal studies on the deeper complexities of the relationship between education and HIV.

Management

There is currently no publicly available HIV vaccine or cure for HIV or AIDS. The only known methods of prevention are based on avoiding exposure

to the virus or, failing that, an antiretroviral treatment directly after a highly significant exposure, called post-exposure prophylaxis (PEP).

Antiviral therapy/ Treatment

There is currently no cure for HIV infection. Treatment consists of Highly Active Antiretroviral Therapy, or HAART. This has been highly beneficial to many HIV-infected individuals since its introduction in 1996, when the protease inhibitor-based HAART initially became available. Current HAART options are combinations (or "cocktails") consisting of at least three drugs belonging to at least two types, or "classes," of antiretroviral agents. Typically, these classes are two nucleoside analogue reverse transcriptase inhibitors (NARTIs or NRTIs) plus either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Specific treatment with antiretroviral drugs is the mainstay in the management of HIV infection. A number of effective drugs have become available in recent years these include nucleoside analogues like zidovudine (Azidothmidine, AZT), Dianosine, Zalcitabine, lamivudine and protease inhibitors like saquinavir, Ritonavir, Indinavir, which have been used as monotherapy or in various combinations.

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II) Hepatitis

Hepatitis means inflammation of the liver. Many illnesses and conditions can cause inflammation of the liver, for example, drugs, alcohol, chemicals, and autoimmune diseases. Many viruses, for example, the virus of mononucleosis and the cytomegalovirus can inflame the liver. Most viruses, however, do not primarily attack the liver; the liver is just one of several organs that the viruses affect. When doctors speak of viral hepatitis, they usually are referring to hepatitis caused by a few specific viruses that primarily attack the liver. There are several hepatitis viruses; they have been named types A, B, C, D, E, F (not confirmed), and G. As our knowledge of hepatitis viruses grows, it is likely that this alphabetical list will become longer. The most common hepatitis viruses are types A, B, and C.

When the liver is inflamed, it does not perform these functions well, which brings about many of the symptoms, signs, and problems associated with hepatitis.

Common types of viral hepatitis

Hepatitis A

Viral hepatitis A (HAV) accounts for about 150,000 of the 500,000-600,000 new cases of viral hepatitis that occur each year in the United States. The hepatitis caused by HAV is an acute illness (acute viral hepatitis) that never becomes chronic. At one time, hepatitis A was referred to as "infectious hepatitis" because it could be spread from person to person like other viral infections. Infection with hepatitis A virus can be spread through the ingestion of food or water, especially where unsanitary conditions allow water or food to become contaminated by human waste containing hepatitis A (the fecal-oral mode of transmission). Hepatitis A typically is spread among household members and close contacts through the passage of oral secretions (intimate kissing) or stool (poor hand washing). It also is common to have infection spread to customers in restaurants and among children and workers in day care centers if hand washing and sanitary precautions are not observed.

Hepatitis B

There are 200,000-300,000 new cases of viral hepatitis B (HBV) infection each year in the United States. Type B hepatitis was at one time referred to as "serum hepatitis," because it was thought that the only way hepatitis B virus (HBV) could spread was through blood or serum (the liquid portion of blood) containing the virus. It is now known that hepatitis B can spread by sexual contact, the transfer of blood or serum through shared needles in drug abusers, accidental needle sticks with needles contaminated with infected blood, blood transfusions, hemodialysis, and by infected mothers to their newborns. The infection also can be spread by tattooing, body piercing, and sharing razors and toothbrushes (if there is contamination with infected blood). About 6-10% of patients with hepatitis B develop chronic HBV infection (infection lasting at least six months and often years to decades) and can infect others as long as they remain infected. Patients with chronic hepatitis B infection also are at risk of developing cirrhosis, liver failure and liver cancer. It is estimated that there are 1.2 million people in the United States and 200-300 million people world-wide who suffer with chronic hepatitis B infection. article.

Hepatitis C

There are about 150,000 new cases of hepatitis C each year. Type C hepatitis was previously referred to as "non-A, non-B hepatitis," because the

causative virus had not been identified, but it was known to be neither hepatitis A nor hepatitis B. The hepatitis C virus (HCV) usually is spread by shared needles among drug abusers, blood transfusion, hemodialysis, and needle sticks. Approximately 90% of transfusion-associated hepatitis is caused by hepatitis C. Transmission of the virus by sexual contact has been reported, but is considered rare. An estimated 50-70% of patients with acute hepatitis C infection develop chronic HCV infection. Patients with chronic hepatitis C infection can continue to infect others. Patients with chronic hepatitis C infection are at risk for developing cirrhosis, liver failure, and liver cancer. It is estimated that there are about 3.5 million people with chronic hepatitis C infection in the United States. For more, please see the Hepatitis C article.

Types D, E, F, and G Hepatitis

There also are viral hepatitis types D, E, F (not confirmed yet), and G. The most important of these at present is the hepatitis D virus (HDV), also known as the delta virus or agent. It is a small virus that requires concomitant infection with hepatitis B to survive. HDV cannot survive on its own because it requires a protein that the hepatitis B virus makes (the envelope protein, also called surface antigen) to enable it to infect liver cells. The ways in which hepatitis D is spread are by shared needles among drug abusers, contaminated blood, and by sexual contact, essentially the same ways as for hepatitis B.

Patients who already have chronic hepatitis B infection can acquire delta virus infection at the same time as they acquire the hepatitis B infection or, alternatively, on top of a chronic hepatitis B infection. Patients with chronic hepatitis due to hepatitis B and hepatitis D viruses develop cirrhosis (severe liver scarring) rapidly. Moreover, the combination of delta and B virus infection is very difficult to treat.

People who are most at risk for developing viral hepatitis are workers in the health care professions, people with multiple sexual partners, intravenous drug users, and hemophiliacs who receive blood clotting factors. Blood transfusion, once a common means of spreading viral hepatitis, now is a rare cause of hepatitis. Viral hepatitis is generally thought to be as much as ten times more common among lower socioeconomic and poorly educated individuals. About one third of all cases of hepatitis come from an unknown or unidentifiable source.

Symptoms and signs of viral hepatitis

The period of time between exposure to hepatitis and the onset of the illness is called the incubation period. The incubation period varies depending on the specific hepatitis virus. Hepatitis A has an incubation period of about 15-45 days; hepatitis B from 45-160 days, and hepatitis C from 2 weeks to 6 months.

Many patients infected with hepatitis A, B, and C have few or no symptoms of illness. For those who do develop symptoms of viral hepatitis, the most common are flu- like symptoms including:

- loss of appetite
- nausea
- vomiting
- fever
- weakness
- tiredness
- aching in the abdomen

Less common symptoms include:

- dark urine
- light-colored stools
- fever
- jaundice (a yellow appearance to the skin and white portion of the eyes)

Chronic viral hepatitis

Patients infected with hepatitis B and hepatitis C can develop chronic hepatitis. Doctors define chronic hepatitis as hepatitis that lasts longer than 6 months. In chronic hepatitis, the viruses live and multiply in the liver for years or decades. For unknown reasons, these patients' immune systems are unable to eradicate the viruses. The viruses cause chronic inflammation of the liver. Chronic hepatitis can lead to the development over time of extensive liver scarring (cirrhosis), liver failure, and liver cancer. Liver failure from chronic hepatitis C infection is the most common reason for liver transplantation in the United States. Patients with chronic viral hepatitis can transmit the infection to others.

Diagnosis of Hepatitis

- Diagnosis of viral hepatitis is based on symptoms, physical findings as well as blood tests for liver enzymes, viral antibodies, and viral genetic materials.
- Diagnosis of acute viral hepatitis often is easy, but diagnosis of chronic hepatitis can be difficult. When a patient reports symptoms of fatigue, nausea, abdominal pain, darkening of urine, and then develops jaundice, the diagnosis of acute viral hepatitis is likely and can be confirmed by blood tests. On the other hand, patients with chronic hepatitis due to hepatitis B and hepatitis C often have no symptoms or only mild nonspecific symptoms such as chronic fatigue. Typically, these patients do not have jaundice until the liver damage is far advanced. Therefore, these patients can remain undiagnosed for years to decades.

Blood tests

- There are three types of blood tests for evaluating patients with hepatitis: liver enzymes, antibodies to the hepatitis viruses, and viral proteins or genetic material (viral DNA or RNA).
- **Liver enzymes.** Among the most sensitive and widely used blood tests for evaluating patients with hepatitis are the liver enzymes, called aminotransferases. They include aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT). These enzymes normally are contained within liver cells. If the liver is injured (as in viral hepatitis), the liver cells spill the enzymes into the blood, raising the enzyme levels in the blood and signaling that the liver is damaged.
- **Viral antibodies.** Antibodies are proteins produced by white blood cells that attack invaders such as bacteria and viruses. Antibodies against the hepatitis A, B, and C viruses usually can be detected in the blood within weeks of infection, and the antibodies remain detectable in the blood for decades thereafter. Blood tests for the antibodies can be helpful in diagnosing both acute and chronic viral hepatitis.

Examples of tests for viral antibodies are:

- anti-HAV (hepatitis A antibody)
- antibody to hepatitis B core, an antibody directed against the inner core (nucleus) of the virus (core antigen)
- antibody to hepatitis B surface, an antibody directed against the outer surface envelope of the virus (surface antigen)

- antibody to hepatitis B e, an antibody directed against the genetic material of the virus (e antigen)
- hepatitis C antibody-antibody against the C virus

Viral proteins and genetic material.

Examples of tests for viral proteins and genetic material are:

- hepatitis B surface antigen
- hepatitis B DNA
- hepatitis B e antigen
- hepatitis C RNA

Other tests.

Obstruction of the bile ducts, from either gallstones or cancer, occasionally can mimic acute viral hepatitis. Ultrasound testing can be used to exclude the possibility of gallstones or cancer. For more information, please read the Ultrasound article.

Treatment

Treatment of acute viral hepatitis and chronic viral hepatitis are different. Treatment of acute viral hepatitis involves relieving symptoms and maintaining adequate intake of fluids. Treatment of chronic viral hepatitis involves medications to eradicate the virus and taking measures to prevent further liver damage.

Acute hepatitis

In patients with acute viral hepatitis, the initial treatment consists of relieving the symptoms of nausea, vomiting, and abdominal pain. Careful attention should be given to medications which can have adverse effects in patients with abnormal liver function. Only those medications that are considered necessary should be administered since the impaired liver is not able to eliminate drugs normally, and drugs may accumulate in the blood and reach toxic levels. In addition, sedatives and "tranquilizers" are avoided because they may accentuate the effects of liver failure on the brain and cause lethargy and coma. The patient must abstain from drinking alcohol since alcohol is toxic to the liver. It occasionally is necessary to provide intravenous fluids to prevent dehydration caused by vomiting. Patients with severe nausea and/or vomiting may need to be hospitalized for treatment and intravenous fluids.

Chronic hepatitis

Treatment of chronic infection with hepatitis B and hepatitis C usually involves medication or combinations of medications to eradicate the virus. Doctors believe that in properly selected patients, successful eradication of the viruses can stop progressive damage to the liver and prevent the development of cirrhosis, liver failure, and liver cancer. Alcohol aggravates liver damage in chronic hepatitis, and can cause more rapid progression to cirrhosis. Therefore, patients with chronic hepatitis should stop drinking alcohol. Smoking cigarettes also can aggravate liver disease and should be stopped.

Medications for chronic hepatitis B infection include:

- injectable interferon
- oral lamivudine (Epivir)
- oral adefovir (Hepsera)
- oral entecavir (Baraclude)
- Prevention of hepatitis involves measures to avoid exposure to the viruses, using immunoglobulin in the event of exposure, and vaccines. Administration of immunoglobulin is called passive protection because antibodies from patients who have had viral hepatitis are given to the patient. Vaccination is called active protection because killed viruses or noninfective components of viruses are given to stimulate the body to produce its own antibodies.

Avoidance of exposure to viruses

- Prevention of viral hepatitis, like any other illness, is preferable to reliance upon treatment. Taking precautions to prevent exposure to another individual's blood (exposure to dirty needles), semen (unprotected sex), and other bodily waste (stool) will help prevent the spread of these viruses.
- **Use of immunoglobulins**
- Immune serum globulin (ISG) is human serum that contains antibodies to hepatitis A. ISG can be administered to prevent infection in individuals who have been exposed to hepatitis A. ISG works immediately upon administration, and the duration of protection is several months. ISG usually is given to travelers to regions of the world where there are high rates of hepatitis A infection and to close or household contacts of patients with hepatitis A. ISG is safe with few side effects.

- Hepatitis B immune globulin or HBIG (BayHep B), is human serum that contains antibodies to hepatitis B. HBIG is made from plasma (a blood product) that is known to contain a high concentration of antibodies to the hepatitis B surface antigen. If given within 10 days of exposure to the virus, HBIG almost always is successful in preventing infection. Even if given a bit later, however, HBIG may lessen the severity of HBV infection. The protection against hepatitis B lasts for about three weeks after the HBIG is given. HBIG also is given at birth to infants born to mothers known to have hepatitis B infection. In addition, HBIG is given to individuals exposed to HBV because of sexual contact or to healthcare workers accidentally stuck by a needle known to be contaminated with blood from an infected person.

Vaccination

Hepatitis A.

Two hepatitis A vaccines are available in the US, Havrix and Vaqta. Both contain inactive (killed) hepatitis A virus. For adults, two doses of the vaccine are recommended. After the first dose, protective antibodies develop in 70% of vaccine recipients in 2 weeks and more than 95% of recipients in 4 weeks. After two doses of the hepatitis A vaccine, immunity against hepatitis A infection is believed to last for many years.

Individuals at increased risk for acquiring hepatitis A and individuals with chronic liver disease (e.g., cirrhosis or chronic hepatitis C) should be vaccinated. Although individuals with chronic liver disease are not at increased risk for acquiring hepatitis A, they can develop serious (sometimes fatal) liver failure if infected with hepatitis A and, thus, they should be vaccinated.

Hepatitis B

For active vaccination, a harmless hepatitis B antigen is given to stimulate the body's immune system to produce protective antibodies against the surface antigen of hepatitis B. Vaccines that are currently available in the United States are made (synthesized) using recombinant DNA technology (joining DNA segments). These recombinant hepatitis B vaccines (Energix-B and Recombivax-HB) are constructed to contain only that part of the surface antigen that is very potent in stimulating the immune system to produce antibodies. The vaccine contains no viral component other than the surface

antigen and is not infectious. Hepatitis B vaccines should be given in three doses with the second dose 1-2 months after the first dose, and the third dose 4-6 months after the first dose. For the best results, the vaccinations should be given in the deltoid (shoulder) muscles and not in the buttocks.

Hepatitis B vaccines are 95% effective. Five percent of vaccinated individuals will fail to develop the necessary antibodies for immunity after the three doses. Patients with weakened immunity (such as HIV infection), elderly patients, and patients undergoing kidney hemodialysis are more likely to fail to respond to the vaccines.

Hepatitis B vaccine is recommended for:

- All infants
- Adolescents under 18 years of age who did not receive hepatitis B vaccine as infants
- People occupationally exposed to blood or body fluids
- Residents and staff of institutions for the developmentally disabled
- Patients receiving kidney hemodialysis
- Hemophiliacs and other patients receiving clotting factor concentrates
- Household contacts and sexual partners of patients infected with hepatitis B chronically
- Travelers who will spend more than 6 months in regions with high rates of hepatitis B infection
- Injection drug users and their sexual partners
- **Hepatitis C**
- There is currently no vaccine for hepatitis C.

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Oncogenic viruses (Cancer causing)

An **oncovirus** is a virus that can cause cancer. It now refers to any virus with a DNA or RNA genome causing cancer and is synonymous with "tumor virus" or "cancer virus".

Worldwide, the WHO International Agency for Research on Cancer estimated that in 2002 17.8% of human cancers were caused by infection, with 11.9% being caused by one of seven different viruses. The importance of this is that these cancers might be easily prevented through vaccination (e.g., papillomavirus vaccines), diagnosed with simple blood tests, and treated with less-toxic antiviral compounds.

Generally, tumor viruses cause little or no disease after infection in their hosts, or cause non-neoplastic diseases such as acute hepatitis for hepatitis B virus or mononucleosis for Epstein-Barr virus.

Tumor viruses come in a variety of forms: viruses with a DNA genome, such as adenovirus, and viruses with an RNA genome, like the Hepatitis C virus (HCV) can cause cancers, as can retroviruses having both DNA and RNA genomes (Human T-lymphotropic virus and hepatitis B virus, which normally replicates as a mixed double and single-stranded DNA virus but also has a retroviral replication component). In many cases, tumor viruses do not cause cancer in their native hosts but only in dead-end species.

A direct oncogenic viral mechanism involves either insertion of additional viral oncogenic genes into the host cell or to enhance already existing oncogenic genes (proto-oncogenes) in the genome.

Indirect viral oncogenicity involves chronic nonspecific inflammation occurring over decades of infection, as is the case for HCV-induced liver cancer. These two mechanisms differ in their biology and epidemiology: direct tumor viruses must have at least one virus copy in every tumor cell expressing at least one protein or RNA that is causing the cell to become cancerous. Chronic indirect tumor viruses, on the other hand, can be lost (at least theoretically) from a mature tumor that has accumulated sufficient mutations and growth conditions (hyperplasia) from the chronic inflammation of viral infection.

- **Classification**

DNA viruses

Genes have also been found in DNA tumor viruses that induce a malignant transformation of the host cell. These are genuine viral genes that have presumably developed independently of one another over a much longer evolutionary period. They code for viral regulator proteins, which are among the so-called early proteins. They are produced early in the viral replication cycle and assume essential functions in viral DNA replication. Their oncogenic potential derives among other things from the fact that they bind to the products of tumor suppressor genes such as p53, Rb (antioncogenes, "antitransformation proteins") and can thus inhibit their functions.

i. **Human papilloma virus (HPV),** a DNA virus, causes transformation in cells through interfering with tumor suppressor proteins such as p53. Interfering with the action of p53 allows a cell infected with the virus to move into a different stage of the cell cycle, enabling the virus genome to be replicated. Forcing the cell into the S phase of the cell cycle could cause the cell to become transformed. Some types of HPV increase the risk of, e.g., cervical cancer.
ii. **Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8)** is associated with Kaposi's sarcoma, a type of skin cancer.
iii. **Epstein-Barr virus (EBV or HHV-4)** is associated with four types of cancers
iv. **Merkel cell polyomavirus** – a polyoma virus – is associated with the development of Merkel cell carcinoma.
v. **Human cytomegalovirus (CMV or HHV-5)** is associated with mucoepidermoid carcinoma and possibly other malignancies.

RNA tumor viruses

Not all oncoviruses are DNA viruses. Some RNA viruses have also been associated such as the hepatitis C virus as well as human T-lymphotropic virus (HTLV-1).

The genomes of all oncoviruses possess gag (group-specific antigen), pol (enzymatic activities: polymerase complex with reverse transcriptase, integrase, and protease), and env (envelope glycoproteins) genes. These coding regions are flanked by two control sequences important for regulatory functions called

LTR (= long terminal repeats). These sequences have a promoter/enhancer function and are responsible for both reverse transcription and insertion of the viral genome into the cell DNA. Certain oncoviruses possess a so-called “onc gene” instead of the pol region (onc gene = oncogene, refers to a cellular gene segment acquired by recombination, see below). These viruses also often have incomplete gag and/or env regions. Such viruses are defective and require a helper virus to replicate (complementation).

Overview table of RNA tumor viruses

Virus	Percent of cancers	Associated cancer types
Hepatitis viruses, including hepatitis B (HBV) and hepatitis C (HCV)	4.9	Hepatocellular carcinoma (liver cancer).[27][28]
Human T-lymphotropic virus (HTLV)	0.03	Tropical spastic paraparesis and adult T-cell leukemia[29]
Human papillomaviruses (HPV)	5.2	Cancers of cervix,[30] anus,[30] penis,[30] vulva/vagina,[1] and some cancers of the head and neck.[1]
Kaposi’s sarcoma-associated herpesvirus	0.9	Kaposi’s sarcoma, multicentric Castleman's disease and primary effusion lymphoma
Merkel cell polyomavirus	NA	Merkel cell carcinoma
Epstein–Barr virus (EBV)	NA	Burkitt’s lymphoma, Hodgkin’s lymphoma, post-transplantation lymphoproliferative disease and Nasopharyngeal carcinoma.[31]

Pathogenesis

Transmission: Viruses can be transmitted horizontally (within a group of individuals or vertically (from mother to offspring). Vertical infection is either transovarial or by infection of the virus in utero (ascending or diaplacental). Connatal infection is the term used when offspring are born infected.

Portal of entry: The most important portals of entry for viruses are the mucosa of the respiratory and gastrointestinal tracts or mechanical inoculation (e.g., bloodsucking arthropods).

Local infection: In this form of infection, the viruses spread only from cell to cell. The infection and manifest disease are thus restricted to the tissues in the immediate vicinity of the portal of entry.

Generalized infection: In this type, the viruses usually replicate to some extent at the portal of entry and are then disseminated via the lymph ducts or bloodstream and reach their target organ either directly or after infecting a further organ. When the target organ is reached, viral replication and the resulting cell destruction become so widespread that clinical symptoms develop.

Tumor Transformation

Infections by a number of viruses do not result in eventual host cell death, but rather cause tumor transformation of the cell. This means the cell is altered in many ways, e.g., in its growth properties, morphology, and metabolism. Following an infection with DNA tumor viruses, the type of host cell infected determines whether the cell reaction will be a tumor transformation, viral replication or lytic cycle.

Defense Mechanisms:

The mechanisms available to the human organism for defense against viral infection can be classified in two groups. The nonspecific immune defenses, in which interferons play a very important part, come first. Besides their effects on cell growth, immune response, and immunoregulation, these substances can build up a temporary resistance to a viral infection. Interferons do not affect viruses directly, but rather induce cellular resistance mechanisms (synthesis of “antiviral proteins”) that interfere with specific steps in viral

replication. The specific immune defenses include the humoral immune system, consisting mainly of antibodies, and the cellular immune system, represented mainly by the T lymphocytes. In most cases, cellular immunity is more important than humoral immunity. The cellular system is capable of recognizing and destroying virus-infected cells on the surfaces of which viral antigens are expressed. The humoral system can eliminate only extracellular viruses.

Interferons (IFN)

Interferons (IFN) are cell-coded proteins with a molecularweight of about 20 kDa. Three types are differentiated (leukocyte interferon = IFNa, fibroblast interferon = IFNb, and immune interferon = IFNc) of which the amino acid sequences are known and which, thanks to genetic engineering, can now be produced in practically unlimited amounts. Whereas the principal biological effects of interferons on both normal and malignant cells are antiviral and antimitotic, these substances also show immunomodulatory effects. Their clinical applications are designed accordingly. In keeping with the scope of this section, the following description of their antiviral activity will be restricted to the salient virological aspects.

A number of substances can induce the production of interferon in a cell, for example double-stranded RNA, synthetic or natural polynucleotides, bacteria, various low-molecular compounds and, above all, viruses. All of these substances have the same effect: they derepress the cellular interferon gene, inducing the cell to begin producing interferon precursors.

Laboratory Diagnosis

The following methods can be used to obtain a virological laboratory diagnosis:

Virus isolation by growing the pathogen in a compatible host; usually done in cell cultures, rarely in experimental animals or hen embryos.

Direct virus detection. The methods of serology, molecular biology, and electron microscopy are used to identify viruses or virus components directly, i.e., without preculturing, in diagnostic specimens. Electron microscopy, EIA, IF, hybridization, PCR

Serodiagnostics involving assay of antiviral antibodies of the IgG or IgM classes in patient serum. EIA, IF, etc.

Prevention

The most important prophylactic measures in the face of potential viral infections are active vaccines. Vaccines containing inactivated viruses generally provide shorter-lived and weaker protection than live vaccines. Passive immunization with human immunoglobulin is only used in a small number of cases, usually as postexposure prophylaxis.

Chemotherapy

Inhibitors of certain steps in viral replication can be used as chemotherapeutic agents to treat viral infections.

Chemotherapeutic agent	Effect/indication
1. Adamantanamin (amantadine)	Inhibition of uncoating viruses
2. Acycloguanosine (acyclovir, Zovirax)	Inhibition of DNA synthesis
3. Dihydropropoxymethylguanosine (DHPG, ganciclovir, Cymevene)	Inhibition of DNA synthesis
4. Ribavirin	Inhibition of mRNA synthesis
5. Phosphonoformate (foscarnet)	Inhibition of DNA synthesis
6. Interferons	