**XV Lecture: Hepatitis viruses. HİV (human immune deficiency virus). Oncogenic viruses.**

**The purpose of the lecture.** To inform students about the characteristics of human immunodeficiency viruses and hepatitis viruses, the diseases they cause, the principles of microbiological diagnosis, treatment and prevention. Oncogenic viruses and mechanism of oncogenesis.

**Lecture plan:**

1. Hepatitis viruses.

- A hepatitis virus. Features of the virion. Microbiological diagnosis. Specific prevention problems.

- Hepatitis B virus. The structure of the virion. Antigens - HBs, HBs, HBe. Microbiological diagnosis. Specific prevention.

- Hepatitis C virus, characteristics, genotypes, ways of infection, pathogenesis. Microbiological diagnosis. Specific prevention problems.

- Hepatitis D virus. Structure of the virion, pathogenetic features of the disease.

2. Retroviruses. Human immunodeficiency viruses, classification. Virion structure. Microbiological diagnosis of AIDS. The problem of prevention and treatment.

3. Oncogenic viruses.The role of viruses in the etiology of malignant tumors. Specific prevention problems. Modern theory of cancerogenesis. Oncogenic viruses that cause tumors in humans.

DNA-containing oncogenic viruses:

1. Herpesviridae family (type 2 herpes simplex virus (SHV2), Epstein-Barr virus (Berkitt lymphoma), human herpes virus type 8 (Kaposh sarcoma).

2. Hepadnaviridae family (hepatitis B virus (BHV)).

3. Papillomaviruses, general features, the diseases they cause.

RNA-containing oncogenic viruses:

1. Retroviridae family (HIV-1, HIV-2).

2. Human T-lymphotropic viruses.

Lecture equipment: Computer, projector, electronic slides.

Literature: p.1

**HEPATİTİS**

Many viruses cause hepatitis. Of these, five medically important viruses are commonly described as "hepatitis viruses" because their main site of infection is the liver. These five are hepatitis A virus (HAV), hepatitis B virus

(HBV), hepatitis C virus (HCV), hepatitis D virus (HDV, delta virus), and hepatitis E virus (HEV)

Other viruses, such as Epstein- Barr virus (the cause of infectious mononucleosis), cytomegalovirus, and yellow fever virus, infect the liver but also infect other sites in the body and therefore are not exclusively hepatitis viruses.They are discussed elsewhere.

**HEPATITIS A VIRUS (HAV)**

HAV causes hepatitis A.

I***mportant Properties***

HAV is a typical enterovirus classified in the picornavirus family. It has a single-stranded RNA genome and a nonen-veloped icosahedral nucleocapsid and replicates in the cytoplasm of the cell. It is also known as enterovirus 72. It has one serotype, and there is no antigenic relationship to HBV or other hepatitis viruses.

***Transmission & Epidemiology***

HAV is transmitted by the fecal-oral route. Humans are the reservoir for HAV. Virus appears in the feces roughly 2 weeks before the appearance of symptoms, so quarantine of patients is ineffective. Children are the most frequently infected group, and outbreaks occur in special living situations such as summer camps and boarding schools. Common-source outbreaks arise from fecally contaminated water or food such as oysters grown in polluted water and eaten raw.Unlike HBV, HAV is rarely transmitted via the blood, because the level of viremia is low and chronic infection does not occur. About 50% to 75% of adults in the United States have been infected, as evidenced IgG antibody.

 ***Pathogenesis & Immunity***

The pathogenesis of HAV infection is not completely understood. The virus probably replicates in the gastrointestinal tract and spreads to the liver via the blood. Hepato-cytes are infected, but the mechanism by which cell damage occurs is unclear. HAV infection of cultured cells produces no cytopathic effect. It is likely that attack by cytotoxic T cells causes the damage to the hepatocytes. The infection is cleared, the damage is repaired, and no chronic infection ensues. Hepatitis caused by the different viruses cannot be distinguished pathologically.The immune response consists initially of IgM antibody, which is detectable at the time jaundice appears. It is therefore important in the laboratory diagnosis of hepatitis A. The appearance of IgM is followed 1 to 3 weeks later by the production of IgG antibody, which provides lifelong protection.

***Clinical Findings***

The clinical manifestations of hepatitis are virtually the same, regardless of which hepatitis virus is the cause (Table 41-3). Fever, anorexia, nausea, vomiting, and jaundice are typical. Dark urine, pale feces, and elevated trans-aminase levels are seen. Most cases resolve spontaneously in 2 to 4 weeks. Hepatitis A has a short incubation period

(3-4 weeks) in contrast to that of hepatitis B, which is 10 to weeks. Most HAV infections are asymptomatic and are detected solely by the presence of IgG antibody. No chronic hepatitis or chronic carrier state occurs, and there is no predisposition to hepatocellular carcinoma.

***Laboratory Diagnosis***

The detection of IgM antibody is the most important test. A fourfold rise in IgG antibody titer can also be used. Isolation of the virus in cell culture is possible but not available in the clinical laboratory.

***Treatment & Prevention***

No antiviral therapy is available. Active immunization with a vaccine containing inactivated HAV is available. The virus is grown in human cell culture and inactivated with formalin. Two doses, an initial dose followed by a booster 6 to 12 months later, should be given. No subsequent booster dose is recommended. The vaccine is recommended for travelers to developing countries, for children ages 2 to 18 years, and for men who have sex with men. If an unimmunized person must travel to an endemic area within 4 weeks, then passive immunization (see later) should be given to provide immediate protection and the vaccine given to provide long-term protection. This is an example of passive-active immunization.Passive immunization with immune serum globulin prior to infection or within 14 days after exposure can prevent or mitigate the disease. Observation of proper hygiene (e.g., sewage disposal and handwashing after bowel move-ments) is of prime importance.

**HEPATITIS B VIRUS (HBV**)

HBV causes hepatitis B.

***Important Properties***

HBV is a member of the hepadnavirus family. It is a 42-nm enveloped virion,' with an icosahedral nucleocapsid core containing a partially double-stranded circular DNA genome

The envelope contains a protein called the surface antigen (HBsAg), which is important for laboratory diagnosis and immunization. In addition to HBsAg, there are two other important antigens both located in the core of the virus: the core antigen (HBcAg) and the e antigen (HBeAg). The core anti-gen, as the name implies, is located on the nucleocapsid protein that forms the core of the virion, whereas the e antigen is soluble and is released from infected cells into the blood. The e antigen is an important indicator of transmissibility. The specificity of HBV for liver cells is based on two properties: virus-specific receptors located on the hepato-cyte cell membrane (facilitate entry) and transcription factors found only in the hepatocyte that enhance viral mRNA synthesis (act post-entry).After entry of the virion into the cell and its uncoating, the nucleocapsid moves to the nucleus. In the nucleus, the virion DNA polymerase synthesizes the missing portion of DNA, and a double-stranded circular DNA is formed. This DNA serves as a template for mRNA synthesis by cellular RNA polymerase. After the individual mRNAs are made, a full-length positive-strand RNA is made, which is the template for the minus strand of the progeny DNA. The minus strand then serves as the template for the plus strand of the genome DNA. This RNA-dependent DNA synthesis catalyzed by reverse transcriptase encoded by HBV takes place within the newly assembled virion nucleocapsid core in the cytoplasm. The RNA-dependent DNA synthesis that produces the genome and the DNA-dependent DNA synthesis that fills in the missing portion of DNA soon after infection of the next cell are carried out by the same enzyme (i.e., the HBV genome encodes only one polymerase). Progeny HBV with its HBsAg-containing envelope are released from the cell by budding through the cell membrane. Hepadnaviruses are the only viruses that produce genome DNA by reverse transcription with viral RNA as the template. (Note that this type of RNA-dependent DNA synthesis is similar to but different from the process in retroviruses, in which the genome RNA is transcribed into a DNA intermediate.)

***Transmission & Epidemiology***

The three main modes of transmission are via blood, during sexual intercourse, and perinatally from mother to newborn. The observation that needle-stick injuries can transmit the virus indicates that only very small amounts of blood are necessary. HBV infection is especially prevalent in addicts who use intravenous drugs. Screening of blood for the presence of HBsAg has greatly decreased the number of transfusion-associated cases of hepatitis B.However, because blood transfusion is a modern proce-dure, there must be another, natural route of transmission. HBV is found in semen and vaginal fluids, so it is likely that sexual transmission is important. Transmission from mother to child during birth is another important natural route. Transplacental transmission, if it occurs, is rare. There is no evidence that transmission of HBV occurs during breast feeding. Hepatitis B is found worldwide but is particularly prevalent in Asia. Globally, more than 300 million people are chronically infected with HBV, and about 75% of them are Asian. There is a high incidence of hepatocellular carcinoma (hepatoma) in many Asian countries-a finding that indicates that HBV is a human tumor virus . Immunization against HBV has significantly reduced the incidence of hepatoma in children. It appears that the HBV vaccine is the first vaccine to prevent a human cancer.

***Pathogenesis & Immunity***

After entering the blood, the virus infects hepatocytes, and viral antigens are displayed on the surface of the cells. Cytotoxic T cells mediate an immune attack against the viral antigens, and inflammation and necrosis occur. Immune attack against viral antigens on infected hepatocytes is mediated by cytotoxic T cells. The pathogenesis of hepatitis B is probably the result of this cell-mediated immune injury,

About 5% of adult patients with HBV infection become chronic carriers. In contrast, 90% of infected newborns become chronic carriers (see later. A chronic carrier is someone who has HBAg persisting in their blood for 6 months or longer. The chronic carrier state is attributed to a persistent infection of the hepatoctes, which results in the prolonged presence of HBV and HBsAg in the blood. The main determinant of whether a person clears the infection or becomes a chronic carrier is the adequacy of the cytotoxic T-cell response. HBV DNA exists primarily as an episome in the nucleus of persistently infected cells; a small number of copies of HBV DNA are integrated into cell DNA.

A high rate of hepatocellular carcinoma (HCC) occurs in chronic carriers. The HBx gene may be an oncogene because the HBx protein inactivates the p53 tumor suppressor protein (see Chapter 43). In addition, HCC may be the result of persistent cellular regeneration that attempts to replace the dead hepatocytes. Alternatively, malignant transformation could be the result of insertional mutagen-esis, which could occur when the HBV DNA integrates into the hepatocyte DNA. Integration of the HBV DNA could activate a cellular oncogene, leading to a loss of growth control. Almost all HCC cells have HBV DNA integrated into the cell DNA.

Chronic carriage is more likely to occur when infection occurs in a newborn than in an adult, probably because a newborn's immune system is less competent than that of an adults. Approximately 90% of infected neonates become chronic carriers. Chronic carriage resulting from neonatal infection is associated with a high risk of HCC.

***Clinical Findings***

Many HBV infections are asymptomatic and are detected only by the presence of antibody to HBsAg. The mean incubation period for hepatitis B is 10 to 12 weeks, which is much longer than that of hepatitis A (3-4 weeks). The clinical appearance of acute hepatitis B is similar to that of hepatitis A. However, with hepatitis B, symptoms tend to be more severe, and life-threatening hepatitis can occur. Most chronic carriers are asymptomatic, but some have chronic active hepatitis, which can lead to cirrhosis and death.

Patients confected with both HBV and human immunodeficiency virus (HIV) may have increased hepatic damage if HIV is treated prior to treating HBV. This occurs because the "immune reconstitution" that results when HIV is treated successfully leads to increased damage to the hepatocytes by the restored, competent cytotoxic T cells. For this reason, it is suggested that HBV be treated prior to treating HIV.

***Laboratory Diagnosis***

The two most important serologic tests for the diagnosis of early hepatitis B are the tests for HBsAg and for IgM antibody to the core antigen. Both appear in the serum early in the disease. HBsAg appears during the incubation period and is detectable in most patients during the pro-drome and acute disease (Figure 41-4). It falls to undetectable levels during convalescence in most cases; its prolonged presence (at least 6 months) indicates the carrier state and the risk of chronic hepatitis and hepatic car-cinoma. As described in Table 41-4, HBsAb is not detectable in the chronic carrier state. Note that HBsAb is, in fact, being made but is not detectable in the laboratory tests because it is bound to the large amount of HBAg present in the blood. HBsAb is also being made during the acute disease but is similarly undetectable because it is bound in antigen-antibody complexes.Note that there is a period The detection of viral DNA (viral load) in the serum is strong evidence that infectious virions are present. Reduction of the viral load in patients with chronic hepatitis B is used to monitor the success of drug therapy.

***Treatment***

No antiviral therapy is typically used in acute hepatitis B. For chronic hepatitis B, entecavir (Baraclude) or tenofovir (Viread) are the drugs of choice. They are nucleoside analogues that inhibit the reverse transcriptase of HBV. Interferon in the form of peginterferon alfa-2a (Pegasys) is also used. Other nucleoside analogues such as lamivudine (Epivir-HBV), adefovir (Hepsera), and telbivudine (Tyzeka) are used less frequently. A combination of tenofovir and emtricitabine (Emtriva) is also used.These drugs reduce hepatic inflammation and lower the viral load of HBV in patients with chronic active hepatitis. Neither interferon nor the nucleoside analogues cure theHBV infection. In most patients when the drug is stopped, HBV replication resumes.

***Prevention***

Prevention involves the use of either the vaccine or hyper-immune globulin or both. (1) The vaccine (e.g., Recombivax) contains HBsAg produced in yeasts by recombinant DNA techniques. The vaccine is highly effective in preventing hepatitis B and has few side effects. The seroconversion rate is approximately 95% in healthy adults. It is indicated for people who are frequently exposed to blood or blood products, such as certain health care personnel (e.g., medical students, sur-geons, and dentists), patients receiving multiple transfusions or dialysis, patients with frequent sexually transmitted disease, and abusers of illicit intravenous drugs. Travelers who plan a long stay in areas of endemic infection, such as many countries in Asia and Africa, should receive the vac-cine. The U.S. Public Health Service recommends that all newborns and adolescents receive the vaccine. At present, booster doses after the initial three-dose regimen are not recommended. However, if antibody titers have declined in immunized patients who are at high risk, such as dialysis patients, then a booster dose should be considered. Widespread immunization with the HBV vaccine has significantly reduced the incidence of hepatocellular carcinoma in children. A vaccine called Twinrix that contains both HBAg and inactivated HAV provides protection against both hepatitis B and hepatitis A. (2) Hepatitis B immune globulin (HBIG) contains a high titer of HBsAb. It is used to provide immediate, passive protection to individuals known to be exposed to HBsAg-positive blood (e.g., after an accidental needle-stick injury). Precise recommendations for use of the vaccine and HBIG are beyond the scope of this book. However, the recommendation regarding one common concern of medical students, the needle-stick injury from a patient with HBsAg-positive blood, is that both the vaccine and HBIG be given (at separate sites). This is true even if the patient's blood is HBeAb positive. Both the vaccine and HBIG should also be given to a newborn whose mother is HBsAg-positive. This regimen is very effective in reducing the infection rate of newborns whose mothers are chronic carriers. The regimen of vaccine plus HBIG in those with needle-stick injuries and in neonates is a good example of passive-active immuniza-tion, in which both immediate protection and long-term protection are provided.

**HEPATITIS C VIRUS (HCV)**

HCV causes hepatitis C.

***Important Properties***

HCV is a member of the flavivirus family. It is an enveloped virion containing a genome of single-stranded, positive-polarity RNA. It has no virion polymerase.HCV has at least six genotypes and multiple subgeno-types based on differences in the genes that encode one of its two envelope glycoproteins. This genetic variation results in a "hypervariable" region in the envelope glyco-protein. The genetic variability is due to the high mutation rate in the envelope gene coupled with the absence of a proofreading function in the virion-encoded RNA poly-merase. As a result, multiple subspecies (quasispecies) often occur in the blood of an infected individual at the same time. Genotype 1 causes approximately 75% of infections in the United States.

Summary of Replicative Cycle

The replication of HCV is uncertain because it has not been grown in cell culture. Other flaviviruses replicate in the cytoplasm and translate their genome RNA into large poly-proteins, from which functional viral proteins are cleaved by a virion-encoded protease. This protease is the target of potent anti-HCV therapy (see treatment section). In addi-tion, HCV genome RNA encodes a protein called NS5A that cooperates with the RNA polymerase of the virus to synthesize progeny genome RNA's. The NS5A protein is also the target of potent anti-HCV therapy (see treatment section). The replication of HCV in the liver is enhanced by a liver-specific micro-RNA called miR-122. This micro-RNA acts by increasing the synthesis of HCV mRNA. (Micro-RNAs are known to enhance cellular mRNA synthesis in many tissues.) In 2013, a clinical trial of an antisense nucleotide that bound to and blocked the activity of miR-122 showed prolonged reduction in HCV RNA levels in infected patients.

***Transmission & Epidemiology***

Humans are the reservoir for HCV. It is transmitted primarily via blood. At present, injection drug use accounts for almost all new HCV infections. Transmission from mother to child during birth is another very common mode of transmission. Transmission via blood transfusion rarely occurs because donated blood containing antibody to HCV is discarded. Transmission via needle-stick injury occurs, but the risk is lower than for HBV.Sexual transmission is uncommon, and there is no evidence for transmission across the placenta or during breast feeding.HCV is the most prevalent blood-borne pathogen in the United States. (In the nationally reported incidence data, HCV ranks below HIV and HBV as a blood-borne pathogen, but it is estimated that HCV is more prevalent.)

***Pathogenesis & Immunity***

HCV infects hepatocytes primarily, but there is no evidence for a virus-induced cytopathic effect on the liver cells. Rather, death of the hepatocytes is probably caused by immune attack by cytotoxic T cells. HCV infection strongly predisposes to hepatocellular carcinoma, but there is no evidence for an oncogene in the viral genome or for insertion of a copy of the viral genome into the DNA of the cancer cells.Alcoholism greatly enhances the rate of hepatocellular carcinoma in HCV-infected individuals. This supports the idea that the cancer is caused by prolonged liver damage and the consequent rapid growth rate of hepatocytes as the cells attempt to regenerate rather than by a direct onco-genic effect of HCV. Added support for this idea is the observation that patients with cirrhosis of any origin, not just alcoholic cirrhosis, have an increased risk of hepatocel-lular carcinoma.

***Clinical Findings***

The acute infection is often asymptomatic. If symptoms, such as malaise, nausea, and right upper quadrant pain do occur, they are milder than occur with infection by the other hepatitis viruses. Fever, anorexia, nausea, vomiting, and jaundice are common. Dark urine, pale feces, and elevated transaminase levels are seen.Hepatitis C resembles hepatitis B as far as the ensuing chronic liver disease, cirrhosis, and the predisposition to hepatocellular carcinoma are concerned. Note that a chronic carrier state occurs more often with HCV infection than with HBV. Liver biopsy is often done in patients with chronic infection to evaluate the extent of liver damage and to guide treatment decisions. Many infections with HCV, including both acute and chronic infections, are asymptomatic and are detected only by the presence of antibody. The mean incubation period is 8 weeks. Cirrhosis resulting from chronic HCV infection is the most common indication for liver transplantation. HCV infection also leads to significant autoimmune reactions, including vasculitis, arthralgias, purpura, and membranoproliferative glomerulonephritis. HCV is the main cause of essential mixed cryoglobulinemia. Cryo-globulins are defined by their ability to precipitate at cold temperature (cryo = cold). The cryoprecipitates are immune complexes composed of HCV antigens and antibodies.

***Laboratory Diagnosis***

HCV infection is diagnosed by detecting antibodies to HCV in an enzyme-linked immunosorbent assay (ELISA). The antigen in the assay is a recombinant protein formed from three immunologically stable HCV proteins and does not include the highly variable envelope proteins. The test does not distinguish between IgM and IgG and does not distinguish between an acute, chronic, or resolved infection.If the result of ELISA antibody test is positive, a polymerase chain reaction-based test that detects the presence of viral RNA (viral load) in the serum should be performed to determine whether active disease exists. Reduction of the viral load in patients with hepatitis C is used to monitor the success of drug therapy. Isolation of the virus from patient specimens is not done. A chronic infection is characterized by elevated transaminase levels, a positive ELISA antibody test, and detectable viral RNA for at least 6 months.

***Treatment***

Treatment of acute hepatitis C with peginterferon alfa significantly decreases the number of patients who become chronic carriers.The treatment of choice for chronic hepatitis C is a combination of drugs from three classes: RNA polymerase inhibi-tors, NS5A inhibitors, and protease inhibitors.These drugs are administered orally which is an improvement over the drugs in previous regimens that often included pegylated interferon-alpha which is administered parenter-ally and has significant adverse effects. One currently available combination is Harvoni which is a combination of sofosbuvir (RNA polymerase inhibitor) and ledipasvir (NS5A inhibitor). Another is Viekera which is a four-drug combina-tion: dasabuvir (RNA polymerase inhibitor), ombitsavir (NS5A inhibitor), paritaprevir (protease inhibitor) and rito-navir .These drug combinations are very effective against genotype 1, the most common type in the United States. Daklinza, a combination of sofosbuvir (RNA polymerase inhibitor) and daclatasvir (NS5A inhibitor) is effective against genotype 3 HCV. These various drug combinations offer the prospect of a "cure" for chronic hepatitis C.

***Prevention***

There is no vaccine and hyperimmune globulins are not available. Pooled immune serum globulins are not useful

Patients with chronic HCV infection should be advised to reduce or eliminate their consumption of alcoholic beverages to reduce the risk of hepatocellular carcinoma and cirrhosis. Patients with chronic HCV infection and cirrhosis should be monitored with alpha-fetoprotein tests and liver sonograms to detect carcinoma at an early stage.

Patients with liver failure due to HCV infection can receive a liver transplant, but infection of the graft with HCV typically occurs.

Patients confected with HCV and HIV should be prescribed highly active antiretroviral therapy (HAART) with caution because recovery of cell-mediated immunity can result in an exacerbation of hepatitis (immune reconstitution syndrome, IRIS). Consideration should be given to treat the HCV infection prior to starting HAART

**HEPATITIS D VIRUS (HDV, DELTA VIRUS**

HDV causes hepatitis D (hepatitis delta).

Important Properties & Replicative Cycle

HDV is unusual in that it is a defective virus (i.e., it cannot replicate by itself because it does not have the genes for its envelope protein). HDV can replicate only in cells also infected with HBV because HDV uses the surface antigen of HBV (HBsAg) as its envelope protein. HBV is therefore the helper virus for HDV.

HDV is an enveloped virus with an RNA genome that is a single-stranded, negative-polarity, covalently closed circle. The RNA genome of HDV is very small and encodes only one protein, the internal core protein called delta antigen. HDV genome RNA has no sequence homology to HBV genome DNA. HDV has no virion polymerase; the genome RNA is replicated and transcribed by the host cell RNA polymerase. HDV genome RNA is a "ribozyme" (ie., it has the ability to self-cleave and self-ligate-properties that are employed during replication of the genome). HDV replicates in the nucleus, but the specifics of the replicative cycle are complex and beyond the scope of this book.

***Transmission & Epidemiology***

HDV is transmitted by the same means as is HBV (i.e., sexually, by blood, and perinatally). In the United States, most HDV infections occur in intravenous drug users who share needles. HDV infections occur worldwide, with a similar distribution to that of HBV infections.

***Pathogenesis & Immunity***

It seems likely that the pathogenesis of hepatitis caused by

HDV and HBV is the same (i.e., the virus-infected hepa-tocytes are damaged by cytotoxic T cells). There is some evidence that delta antigen is cytopathic for hepatocytes.IgG antibody against delta antigen is not detected for long periods after infection; it is therefore uncertain whether long-term immunity to HDV exists.

***Clinical Findings***

Because HDV can replicate only in cells also infected with

HBV, hepatitis delta can occur only in a person infected with HBV. A person can either be infected with both HDV and HBV at the same time (i.e., be "confected") or be previously infected with HBV and then "superinfected" with HDV.

Hepatitis in patients confected with HDV and HBV is more severe than in those infected with HBV alone, but the incidence of chronic hepatitis is about the same in patients infected with HBV alone. However, hepatitis in chronic carriers of HBV who become superinfected with HDV is much more severe, and the incidence of fulminant, life-threatening hepatitis, chronic hepatitis, and liver failure is significantly higher.

***Laboratory Diagnosis***

The diagnosis of HDV infection in the laboratory is made by detecting either delta antigen or IgM antibody to delta antigen in the patients serum.

***Treatment & Prevention***

Peginterferon alfa can mitigate some of the effects of the chronic hepatitis caused by HD but does not eradicate the chronic carrier state. There is no specific antiviral therapy against HDV. There is no vaccine against HDV, but a person immunized against HBV will not be infected by HDV because HDV cannot replicate unless HBV infection also occurs.

**HEPATITIS E VIRUS (HEV)**

HEV is a major cause of hepatitis transmitted by the fecal-oral route. It is thought to be more common than HAV in many developing countries. It is a common cause of waterborne epidemics of hepatitis in Asia, Africa, India, and Mexico but is uncommon in the United States. HEV is a nonenveloped, single-stranded RNA virus classified as a member of the hepevirus family.

Clinically the disease resembles hepatitis A, with the exception of a high mortality rate in pregnant women.

Chronic infection resulting in chronic hepatitis and cirrhosis but not hepatocellular carcinoma, occurs in immuno-compromised individuals such as HIV-infected patients, those who are receiving cancer chemotherapy, and patients who are receiving immunosuppressive drugs to prevent reiection of solid-organ transplants.

The diagnosis is typically made by detecting IgM antibody to HEV. A PCR assay that detects HEV RNA in patient specimens is available. There is no antiviral drug available for acute infection in immunocompetent patients.

In immunocompromised patients, ribavirin cleared HEV viremia in solid organ transplant recipients. There is no

**HEPATITIS G VIRUS (HGV)**

In 1996, hepatitis G virus (HGV) was isolated from patients with posttransfusion hepatitis. HGV is a member of the flavivirus family, as is HCV. However, unlike HCV, which is clearly the cause of both acute hepatitis and chronic active hepatitis and predisposes to hepatocellular carcinoma, HGV has not been documented to cause any of these clinical findings. The role of HGV in the causation of liver disease has yet to be established, but it can cause a chronic infection lasting for decades. Approximately 60% to 70% of those infected clear the virus and develop antibodies.

HG V is transmitted via sexual intercourse and blood. It is carried in the blood of millions of people worldwide. In the United States, it is found in the blood of approximately 2% of random blood donors, 15% of those infected with HCV, and 35% of those infected with HIV. Patients coin-fected with HIV and HGV have a lower mortality rate and have less HIV in their blood than those infected with HIV alone. It is hypothesized that HGV may interfere with the replication of HIV. (HGV is also known as GB virus C.)

**HİV- human immune deficiency virus**

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS).

Both HIV-1 and HIV-2 cause AIDS, but HIV-1 is found worldwide, whereas HIV-2 is found primarily in West Africa. This chapter refers to HIV-1 unless otherwise noted.

***Important Properties***

HIV is one of the two important human T-cell lympho-tropic retroviruses (human T-cell leukemia virus is the other). HIV preferentially infects and kills helper (CD4) T lymphocytes, resulting in the loss of cell-mediated immunity and a high probability that the host will develop opportunistic infections. Other cells (e.g., macrophages and monocytes) that have CD4 proteins on their surfaces can be infected also.The natural host range of HIV is limited to humans, although certain primates can be infected in the laboratory.

HIV is not an endogenous virus of humans (i.e., no HIV sequences are found in normal human cell DNA). The origin of HIV and how it entered the human population remains uncertain. There is evidence that chimpanzees living in West Africa were the source of HIV-1. If chimpanzees are the source of HIV in humans, it would be a good example of a virus "jumping the species barrier.In addition to HIV-1, two other similar retroviruses are worthy of comment:Human immunodeficiency virus type 2 (HIV-2) was isolated from AIDS patients in West Africa in 1986. The proteins of HIV-2 are only about 40% identical to those of the original HIV isolates. HIV-2 remains localized primarily to West Africa and is much less transmissible than HIV-1. Simian immunodeficiency virus (SIV) was isolated from monkeys with an AIDS-like illness. Antibodies in some African women cross-react with SIV. The proteins of SIV resemble those of HIV-2 more closely than they resemble those of the original HIV isolates.

Summary of Replicative Cycle

In general, the replication of HIV follows the typical retro-viral cycle (Figure 45-4). The initial step in the entry of HIV into the cell is the binding of the virion gp120 envelope protein to the CD4 protein on the cell surface. The virion gp120 protein then interacts with a second protein on the cell surface, one of the chemokine receptors. Next, the virion gp41 protein mediates fusion of the viral envelope with the cell membrane, and the virion core containing the nucleocapsid, RNA genome, and reverse transcriptase enters the cytoplasm.

Chemokine receptors, such as CXCR4 and CCR5 pro-teins, are required for the entry of HIV into CD4-positive cells. The T cell-tropic strains of HIV bind to CXCR4,whereas the macrophage-tropic strains bind to CCR5.

Mutations in the gene encoding CCR5 endow the individual with protection from infection with HIV. People who are homozygotes are completely resistant to infection, and heterozygotes progress to disease more slowly. Approximately 1% of people of Western European ancestry have homozygous mutations in this gene, and about 10% to 15% are heterozygotes. One of the best-characterized mutations is the delta-32 mutation, in which 32 base pairs are deleted from the CCR5 gene.

In the cytoplasm, reverse transcriptase transcribes the genome RNA into double-stranded DNA, which migrates to the nucleus, where it integrates into the host cell DNA.The viral DNA can integrate at different sites in the host cell DNA, and multiple copies of viral DNA can integrate.

Integration is mediated by a virus-encoded endonuclease (integrase). Viral mRNA is transcribed from the integrated (proviral) DNA by host cell RNA polymerase (augmented by virus-encoded Tat protein) and translated into several large polyproteins. The Gag and Pol polyproteins are cleaved by the viral protease, whereas the Env polyprotein is cleaved by a cellular protease.

The Gag polyprotein is cleaved to form the main core protein (p24), the matrix protein (p17), and several smaller

proteins. The Pol polyprotein is cleaved to form the reverse transcriptase, integrase, and protease. The immature virion containing the precursor polyproteins forms in the cyto-plasm, and cleavage by the viral protease occurs as the immature virion buds from the cell membrane. It is this cleavage process that results in the mature, infectious virion.

***Transmission & Epidemiology***

Transmission of HIV occurs primarily by sexual contact and by transfer of infected blood. Perinatal transmission from infected mother to neonate also occurs, either across the placenta, at birth, or via breast milk. It is estimated that more than 50% of neonatal infections occur at the time of

delivery and that the remainder is split roughly equally between transplacental transmission and transmission via breast feeding. There is no evidence for airborne, water-borne, or insect transmission of HIV.

Infection occurs by the transfer of 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 and tears), there is no evidence that they play a role in infection. In general, transmission of HIV follows the pattern of hepatitis B virus (HBV), 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 sexually transmitted dis-eases, especially those with ulcerative lesions such as syphi-lis, chancroid, and herpes genitalis, have a significantly higher risk of acquiring HIV. Uncircumcised males have a higher risk of acquiring HIV than do circumcised males.

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.

***Pathogenesis & Immunity***

HIV infects helper T cells (CD4-positive cells) and kills them, resulting in suppression of cell-mediated immu-nity. This predisposes the host to various opportunistic infections and certain cancers such as Kaposi's sarcoma and lymphoma. HIV does not directly cause these tumors because HIV genes are not found in these cancer cells. The initial infection of the genital tract occurs in dendritic cells that line the mucosa (Langerhans' cells), after which the local CD4-positive helper T cells become infected. HIV is first found in the blood 4 to 11 davs after infection.HIV infection also targets a subset of CD4-positive cells called Th17 cells. These cells are an important mediator of mucosal immunity, especially in the gastrointestinal tract.Many mucosal Th17 cells are killed early in HIV infection.Th17 cells produce interleukin-17 (IL-17), which attracts neutrophils to the site of bacterial infection. The loss of'Th17 cells predisposes HIV-infected individuals to bloodstream infections by bacteria in the normal flora of the colon, such as Escherichia coli.HIV also infects brain monocytes and macrophages, producing multinucleated giant cells and significant central nervous system symptoms. The fusion of HIV-infected cells in the brain and elsewhere mediated by gp41 is one of the main pathologic findings. The cells recruited into the syncytia ultimately die.

***Clinical Findings***

The clinical picture of HIV infection can be divided into three stages: an early, acute stage; a middle, latent stage; and a late, immunodeficiency stage ). In the acute stage, which usually begins 2 to 4 weeks after infection, a mononucleosis-like picture of fever, lethargy, sore throat, and generalized lymphadenopathy occurs. A maculopapu-lar rash on the trunk, arms, and legs (but sparing the palms and soles) is also seen. Leukopenia occurs, but the number of CD4 cells is usually normal. A high-level viremia typically occurs, and the infection is readily transmissible during this acute stage. This acute stage typically resolves spontaneously in about 2 weeks. Resolution of the acute stage is usually accompanied by a lower level of viremia and a rise in the number of CD8-positive (cytotoxic) T cells directed against HIV. Antibodies to HIV typically appear 10 to 14 days after infection, and most patients will have seroconverted by 3 to 4 weeks after infection. Note that 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). 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 polymerase chain reaction (PCR)-based assay for viral RNA in the plasma should be done.Of those who become seropositive during the acute infection, approximately 87% are symptomatic (i.e., about 13% experience an asymptomatic initial infection).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) and 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 each day. This 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 and the prognosis.

***Laboratory Diagnosis***

The presumptive diagnosis of HIV infection is often made by the detection of antibodies in the patient's serum to the p24 protein of HIV using the enzyme-linked immunosor-bent assay (ELISA) test. Because there are some false-positive results with this test, the definitive diagnosis is made by Western blot (also known as Immunoblot) analysis, in which the viral proteins are displayed by acryl-amide gel electrophoresis, transferred to nitrocellulose paper (the blot), and reacted with the patient's serum. If antibodies are present in the patient's serum, they will bind to the viral proteins (predominantly to the gp41 or p24 protein). Enzymatically labeled antibody to human IgG is then added. A color reaction reveals the presence of the HIV antibody in the infected patient's serum. Figure 64-9 depicts a Western blot (Immunoblot) test used to diagnoseHIV infection. OraQuick is a rapid, screening immunoassay for HIV antibody that uses an oral swab sample in an ELISA-type test that can be done at home. Results are available in 20 minutes. Positive results for HIV antibody require confirmation by a Western blot test. The PCR test is a very sensitive and specific technique that can be used to detect HIV DNA within infected cells.

***Treatment***

The treatment of HIV infection has resulted in a remarkable reduction in mortality and improvement in the quality of life of infected individuals. The two specific goals of treatment are (1) to restore immunologic function by increasing the CD4 count, which reduces opportunistic infections and certain malignancies, and (2) to reduce viral load, which reduces the chance of transmission to others.There is evidence that starting drug therapy as soon as possible after making the diagnosis of HIV infection is the best way to achieve these goals.

Unfortunately, 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, and large amounts of infectious virus reappear.Treatment of HIV infection typically involves multiple antiretroviral drugs. The use of a single drug (monother-apv) for treatment is not done because of the high rate of mutation to drug resistance.The choice of drugs is complex and depends on several factors (e.g., whether it is an initial infection or an estab-ished infection, the number of CD4 cells, the viral load, the resistance pattern of the virus, and whether the patient is pregnant or is confected with HBV or hepatitis C virus

***Prevention***

No vaccine is available. Multiple trials of a variety of experimental vaccines have failed to induce protective antibodies, protective cytotoxic T cells, or mucosal immu-nity. Prevention consists of taking measures to avoid exposure to the virus (e.g., using condoms, not sharing needles, and discarding donated blood that is contaminated with HIV).

Postexposure prophylaxis (PEP), such as that given after a needle-stick injury or a high-risk nonoccupational exposure, employs three drugs: the preferred regimen consists of the combination of tenofovir and emtricitabine (given as Truvada) plus raltegravir. Three alternative drug regimens are available. PEP should be given as soon as possible after exposure and continued for 28 days. Truvada can also be used for preexposure prophylaxis (PrEP) in individuals at high risk of infection, such as men who have sex with men. Two steps can be taken to reduce the number of cases of HIV infection in children: antiretroviral therapy should be given to HIV-infected mothers and neonates, and HIV-infected mothers should not breast feed. The choice of antiretroviral drugs is dependent on several factors, so current guidelines should be consulted. In addition, the risk of neonatal HIV infection is lower if delivery is accomplished by cesarean section rather than by vaginal delivery. Circumcision reduces HIV infection.Several drugs are commonly taken by patients in the advanced stages of AIDS to prevent certain opportunistic infections . Some examples are trimethoprim-sulfamethoxazole to prevent Pneumocystis pneumonia, flu-conazole to prevent recurrences of cryptococcal meningitis,ganciclovir to prevent recurrences of retinitis caused by cytomegalovirus, and oral preparations of antifungal drugs, such as clotrimazole, to prevent thrush caused by C. albicans.