MICROBIOLOGY HONS.

PAPER CC13

UNIT- 4

VIRAL DISEASES

1. DENGUE

Dengue fever is a mosquito-borne tropical disease caused by the dengue virus. Dengue is common in more than 120 countries. Infections are most commonly acquired in the urban environment. In recent decades, the expansion of villages, towns and cities in the areas in which it is common, and the increased mobility of people has increased the number of epidemics and circulating viruses.

Rates of dengue increased 30 fold between 1960 and 2010. This increase is believed to be due to a combination of urbanization, population growth, increased international travel, and global warming.

Symptoms typically begin three to fourteen days after infection. These may include a high fever, headache, vomiting, muscle and joint pains, and a characteristic skin rash. Recovery generally takes two to seven days. In a small proportion of cases, the disease develops into severe dengue, also known as dengue hemorrhagic fever, resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome, where dangerously low blood pressure occurs.

Most people with dengue recover without any ongoing problems. The risk of death among those with severe dengue is 0.8% to 2.5%, and with adequate treatment this is less than 1%. However, those who develop significantly low blood pressure may have a fatality rate of up to 26%. The risk of death among children less than five years old is four times greater than among those over the age of 10. Elderly people are also at higher risk of a poor outcome.

SYMPTOMS

Typically, people infected with dengue virus are asymptomatic (80%) or have only mild symptoms such as an uncomplicated fever. Others have more severe illness (5%), and in a small proportion it is life-threatening. The incubation period (time between exposure and onset of symptoms) ranges from 3 to 14 days, but most often it is 4 to 7 days. Therefore, travelers returning from endemic areas are unlikely to have dengue fever if symptoms start more than 14 days after arriving home. Children often experience symptoms similar to those of the common cold and gastroenteritis (vomiting and diarrhea) and have a greater risk of severe complications, though initial symptoms are generally mild but include high fever.

Clinical course

The characteristic symptoms of dengue are sudden-onset fever, headache (typically located behind the eyes), muscle and joint pains, and a rash. An alternative name for dengue, "breakbone fever", comes from the associated muscle and joint pains. The course of infection is divided into three phases: febrile, critical, and recovery.

The febrile phase involves high fever, potentially over 40 °C (104 °F), and is associated with generalized pain and a headache; this usually lasts two to seven days. Nausea and vomiting may also occur. A rash occurs in 50–80% of those with symptoms in the first or second day of symptoms as flushed skin, or later in the course of illness (days 4–7), as a measles-like rash. A rash described as "islands of white in a sea of red" has also been observed. Some petechiae (small red spots that do not disappear when the skin is pressed, which are caused by broken capillaries) can appear at this point, as may some mild bleeding from the mucous membranes of the mouth and nose. The fever itself is classically biphasic or saddleback in nature, breaking and then returning for one or two days.

In some people, the disease proceeds to a critical phase as fever resolves. During this period, there is leakage of plasma from the blood vessels, typically lasting one to two days. This may result in fluid accumulation in the chest and abdominal cavity as well as depletion of fluid from the circulation and decreased blood supply to vital organs. There may also be organ dysfunction and severe bleeding, typically from the gastrointestinal tract. Shock (dengue shock syndrome) and hemorrhage (dengue hemorrhagic fever) occur in less than 5% of all cases of dengue; however, those who have previously been infected with other serotypes of dengue virus ("secondary infection") are at an increased risk. This critical phase, while rare, occurs relatively more commonly in children and young adults.

Associated problems

Dengue can occasionally affect several other body systems, either in isolation or along with the classic dengue symptoms. A decreased level of consciousness occurs in 0.5–6% of severe cases, which is attributable either to inflammation of the brain by the virus or indirectly as a result of impairment of vital organs, for example, the liver.

Other neurological disorders have been reported in the context of dengue, such as transverse myelitis and Guillain–Barré syndrome. Infection of the heart and acute liver failure are among the rarer complications.

A pregnant woman who develops dengue is at higher risk of miscarriage, low birth weight birth, and premature birth.

ORGANISM

Dengue fever virus (DENV) is an RNA virus of the family *Flaviviridae*; genus *Flavivirus*. The dengue virus genome (genetic material) contains about 11,000 nucleotide bases, which code for the three different types of protein molecules (C, prM and E) that form the virus particle and seven other non-structural protein molecules (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) that are found in infected host cells only and are required for replication of the virus. There are fivestrains of the virus, called serotypes, of which the first four are referred to as DENV-1, DENV-2, DENV-3 and DENV-4. The fifth type was

announced in 2013. The distinctions between the serotypes are based on their antigenicity.

Dengue virus is primarily transmitted by *Aedes* mosquitos, particularly *A. aegypti*. These mosquitos usually live between the latitudes of 35° North and 35° South below an elevation of 1,000 metres (3,300 ft). They typically bite during the early morning and in the evening, but they may bite and thus spread infection at any time of day. Other *Aedes* species that transmit the disease include *A. albopictus*, *A. polynesiensis* and *A. scutellaris*. Humans are the primary host of the virus, but it also circulates in nonhuman primates. An infection can be acquired via a single bite. A female mosquito that takes a blood meal from a person infected with dengue fever, during the initial 2- to 10-day febrile period, becomes itself infected with the virus in the cells lining its gut. About 8–10 days later, the virus spreads to other tissues including the mosquito's salivary glands and is subsequently released into its saliva. The virus seems to have no detrimental effect on the mosquito, which remains infected for life. *Aedes aegypti* is particularly involved, as it prefers to lay its eggs in artificial water containers, to live in close proximity to humans, and to feed on people rather than other vertebrates.

Severe disease is more common in babies and young children, and in contrast to many other infections, it is more common in children who are relatively well nourished. Polymorphisms (normal variations) in particular genes have been linked with an increased risk of severe dengue complications

PATHOGENESIS

When a mosquito carrying dengue virus bites a person, the virus enters the skin together with the mosquito's saliva. It binds to and enters white blood cells, and reproduces inside the cells while they move throughout the body. The white blood cells respond by producing several signaling proteins, such as cytokines and interferons, which are responsible for many of the symptoms, such as the fever, the flu-like symptoms, and the severe pains. In severe infection, the virus production inside the body is greatly increased, and many more organs (such as the liver and the bone marrow) can be affected. Fluid from the bloodstream leaks through the wall of small blood vessels into body cavities due to capillary permeability. As a result, less blood circulates in the blood vessels, and the blood pressure becomes so low that it cannot supply sufficient blood to vital organs. Furthermore, dysfunction of the bone marrow due to infection of the stromal cells leads to reduced numbers of platelets, which are necessary for effective blood clotting; this increases the risk of bleeding, the other major complication of dengue fever.

Viral replication

Once inside the skin, dengue virus binds to Langerhans cells (a population of dendritic cells in the skin that identifies pathogens). The virus enters the cells through binding between viral proteins and membrane proteins on the Langerhans cell, specifically, the C-type lectins called DC-SIGN, mannose receptor and CLEC5A. DC-SIGN, a non-specific receptor for foreign material on dendritic cells, seems to be the main point of entry. The dendritic cell moves to the nearest lymph node. Meanwhile, the virus genome

is translated in membrane-bound vesicles on the cell's endoplasmic reticulum, where the cell's protein synthesis apparatus produces new viral proteins that replicate the viral RNA and begin to form viral particles. Immature virus particles are transported to the Golgi apparatus, the part of the cell where some of the proteins receive necessary sugar chains (glycoproteins). The now mature new viruses are released by exocytosis. They are then able to enter other white blood cells, such as monocytes and macrophages.

The initial reaction of infected cells is to produce interferon, a cytokine that raises many defenses against viral infection through the innate immune system by augmenting the production of a large group of proteins mediated by the JAK-STAT pathway. Some serotypes of the dengue virus appear to have mechanisms to slow down this process. Interferon also activates the adaptive immune system, which leads to the generation of antibodies against the virus as well as T cells that directly attack any cell infected with the virus. Various antibodies are generated; some bind closely to the viral proteins and target them for phagocytosis (ingestion by specialized cells and destruction), but some bind the virus less well and appear instead to deliver the virus into a part of the phagocytes where it is not destroyed but can replicate further.

Severe disease

It is not entirely clear why secondary infection with a different strain of dengue virus places people at risk of dengue hemorrhagic fever and dengue shock syndrome. Severe disease is marked by the problems of capillary permeability (an allowance of fluid and protein normally contained within the blood to pass) and disordered blood clotting. These changes appear associated with a disordered state of the endothelial glycocalyx, which acts as a molecular filter of blood components. Leaky capillaries (and the critical phase) are thought to be caused by an immune system response. Other processes of interest include infected cells that become necrotic—which affect both coagulation and fibrinolysis (the opposing systems of blood clotting and clot degradation)—and low platelets in the blood, also a factor in normal clotting.

DIAGNOSIS

The diagnosis of dengue is typically made clinically, on the basis of reported symptoms and physical examination; this applies especially in endemic areas. However, early disease can be difficult to differentiate from other viral infections. A probable diagnosis is based on the findings of fever plus two of the following: nausea and vomiting, rash, generalized pains, low white blood cell count, positive tourniquet test, or any warning sign (see table) in someone who lives in an endemic area. Warning signs typically occur before the onset of severe dengue. The tourniquet test, which is particularly useful in settings where no laboratory investigations are readily available, involves the application of a blood pressure cuff at between the diastolic and systolic pressure for five minutes, followed by the counting of any petechial hemorrhages. The earliest change detectable on laboratory investigations is a low white blood cell count, which may then be followed by low platelets and metabolic acidosis.

The diagnosis of dengue fever may be confirmed by microbiological laboratory testing. This can be done by virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection (such as for NS1) or specific antibodies (serology). Virus isolation and nucleic acid detection are more accurate than antigen detection, but these tests are not widely available due to their greater cost. Detection of NS1 during the febrile phase of a primary infection may be greater than 90% sensitive however is only 60–80% in subsequent infections. All tests may be negative in the early stages of the disease. PCR and viral antigen detection are more accurate in the first seven days.

These laboratory tests are only of diagnostic value during the acute phase of the illness with the exception of serology. Tests for dengue virus-specific antibodies, types IgG and IgM, can be useful in confirming a diagnosis in the later stages of the infection. Both IgG and IgM are produced after 5–7 days. The highest levels (titres) of IgM are detected following a primary infection, but IgM is also produced in reinfection. IgM becomes undetectable 30–90 days after a primary infection, but earlier following re-infections. IgG, by contrast, remains detectable for over 60 years and, in the absence of symptoms, is a useful indicator of past infection. After a primary infection, IgG reaches peak levels in the blood after 14–21 days. In subsequent re-infections, levels peak earlier and the titres are usually higher. Both IgG and IgM provide protective immunity to the infecting serotype of the virus. In testing for IgG and IgM antibodies there may be cross-reactivity with other flaviviruses which may result in a false positive after recent infections or vaccinations with yellow fever virus or Japanese encephalitis. The detection of IgG alone is not considered diagnostic unless blood samples are collected 14 days apart and a greater than fourfold increase in levels of specific IgG is detected. In a person with symptoms, the detection of IgM is considered diagnostic.

PREVENTION

Prevention depends on control of and protection from the bites of the mosquito that transmits it. The World Health Organization recommends an Integrated Vector Control program consisting of five elements:

1. Advocacy, social mobilization and legislation to ensure that public health bodies and communities are strengthened;
2. Collaboration between the health and other sectors (public and private);
3. An integrated approach to disease control to maximize the use of resources;
4. Evidence-based decision making to ensure any interventions are targeted appropriately; and
5. Capacity-building to ensure an adequate response to the local situation.

The primary method of controlling *A. aegypti* is by eliminating its habitats. This is done by getting rid of open sources of water, or if this is not possible, by adding insecticides or biological control agents to these areas. Generalized spraying with organophosphate or pyrethroid insecticides, while sometimes done, is not thought to be effective. Reducing open collections of water through environmental modification is the preferred method of control, given the concerns of negative health effects from

insecticides and greater logistical difficulties with control agents. People can prevent mosquito bites by wearing clothing that fully covers the skin, using mosquito netting while resting, and/or the application of insect repellent (DEET being the most effective). While these measures can be an effective means of reducing an individual's risk of exposure, they do little in terms of mitigating the frequency of outbreaks, which appear to be on the rise in some areas, probably due to urbanization increasing the habitat of *A. aegypti.* The range of the disease also appears to be expanding possibly due to climate change.

Vaccine

The vaccine is only recommended in individuals who have had a prior dengue infection or in populations where most (>80%) of people have been infected by age 9. In those who have not had a prior infection there is evidence it may worsen subsequent infections.

Studies of the vaccine found it was 66% effective and prevented more than 80 to 90% of severe cases.

TREATMENT

There are no specific antiviral drugs for dengue; however, maintaining proper fluid balance is important. Treatment depends on the symptoms. Those who can drink, are passing urine, have no "warning signs" and are otherwise healthy can be managed at home with daily follow-up and oral rehydration therapy. Those who have other health problems, have "warning signs", or cannot manage regular follow-up should be cared for in hospital. Intravenous hydration, if required, is typically only needed for one or two days. In children with shock due to dengue a rapid dose of 20 mL/kg is reasonable. Invasive medical procedures such as nasogastric intubation, intramuscular injections and arterial punctures are avoided, in view of the bleeding risk. Paracetamol (acetaminophen) is used for fever and discomfort while NSAIDs such as ibuprofen and aspirin are avoided as they might aggravate the risk of bleeding. Blood transfusion is initiated early in people presenting with unstable vital signs in the face of a *decreasing hematocrit*, rather than waiting for the hemoglobin concentration to decrease to some predetermined "transfusion trigger" level. Packed red blood cells or whole blood are recommended, while platelets and fresh frozen plasma are usually not.

During the recovery phase intravenous fluids are discontinued to prevent a state of fluid overload. If fluid overload occurs and vital signs are stable, stopping further fluid may be all that is needed.

2. RABIES

Rabies is a viral disease that causes inflammation of the brain in humans and other mammals. Early symptoms can include fever and tingling at the site of exposure. These symptoms are followed by one or more of the following symptoms: violent movements, uncontrolled excitement, fear of water, an inability to move parts of the body, confusion, and loss of consciousness. Once symptoms appear, the result is nearly always death.[1] The time period between contracting the disease and the start of symptoms is usually one to three months, but can vary from less than one week to more than one year.[1] The time depends on the distance the virus must travel along peripheral nerves to reach the central nervous system. Rabies caused about 17,400 human deaths worldwide in 2015. More than 95% of human deaths from rabies occur in Africa and Asia. Fear of water Hydrophobia ("fear of water") is the historic name for rabies. It refers to a set of symptoms in the later stages of an infection in which the person has difficulty swallowing, shows panic when presented with liquids to drink, and cannot quench their thirst. Any mammal infected with the virus may demonstrate hydrophobia. Saliva production is greatly increased, and attempts to drink, or even the intention or suggestion of drinking, may cause excruciatingly painful spasms of the muscles in the throat and larynx. This can be attributed to the fact that the virus multiplies and assimilates in the salivary glands of the infected animal with the effect of further transmission through biting. The ability to transmit the virus would decrease significantly if the infected individual could swallow saliva and water. Hydrophobia is commonly associated with furious rabies, which affects 80% of rabies-infected people. The remaining 20% may experience a paralytic form of rabies that is marked by muscle weakness, loss of sensation, and paralysis; this form of rabies does not usually cause fear of water.

CAUSES

The rabies virus is the type species of the Lyssavirus genus, in the family Rhabdoviridae, order Mononegavirales. Lyssavirions have helical symmetry, with a length of about 180 nm and a cross-section of about 75 nm. These virions are enveloped and have a single-stranded RNA genome with negative sense. The genetic information is packed as a ribonucleoprotein complex in which RNA is tightly bound by the viral nucleoprotein. The RNA genome of the virus encodes five genes whose order is highly conserved: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and the viral RNA polymerase (L).

To enter cells, trimeric spikes on the exterior of the membrane of the virus interact with a specific cell receptor, the most likely one being the acetylcholine receptor. The cellular membrane pinches in a procession known as pinocytosis and allows entry of the virus into the cell by way of an endosome. The virus then uses the acidic environment, which is necessary, of that endosome and binds to its membrane simultaneously, releasing its five proteins and single strand RNA into the cytoplasm. Once within a muscle or nerve cell, the virus undergoes replication. The L protein then transcribes five mRNA strands and a positive strand of RNA all from the original negative strand RNA using free nucleotides in the cytoplasm. These five mRNA strands are then translated into their

corresponding proteins (P, L, N, G and M proteins) at free ribosomes in the cytoplasm. Some proteins require post-translative modifications. For example, the G protein travels through the rough endoplasmic reticulum, where it undergoes further folding, and is then transported to the Golgi apparatus, where a sugar group is added to it (glycosylation). When there are enough viral proteins, the viral polymerase will begin to synthesize new negative strands of RNA from the template of the positive strand RNA. These negative strands will then form complexes with the N, P, L and M proteins and then travel to the inner membrane of the cell, where a G protein has embedded itself in the membrane. The G protein then coils around the N-P-L-M complex of proteins taking some of the host cell membrane with it, which will form the new outer envelope of the virus particle. The virus then buds from the cell. From the point of entry, the virus is neurotropic, traveling along the neural pathways into the central nervous system. The virus usually first infects muscle cells close to the site of infection, where they are able to replicate without being 'noticed' by the host's immune system. Once enough virus has been replicated, they begin to bind to acetylcholine receptors at the neuromuscular junction. The virus then travels through the nerve cell axon via retrograde transport, as its P protein interacts with dynein, a protein present in the cytoplasm of nerve cells. Once the virus reaches the cell body it travels rapidly to the central nervous system (CNS), replicating in motor neurons and eventually reaching the brain. After the brain is infected, the virus travels centrifugally to the peripheral and autonomic nervous systems, eventually migrating to the salivary glands, where it is ready to be transmitted to the next host.

Transmission

All warm-blooded species, including humans, may become infected with the rabies virus and develop symptoms.

Most animals can be infected by the virus and can transmit the disease to humans. Infected bats, monkeys, raccoons, foxes, skunks, cattle, wolves, coyotes, dogs, cats, and mongooses present the greatest risk to humans. The virus is usually present in the nerves and saliva of a symptomatic rabid animal. The route of infection is usually, but not always, by a bite. In many cases, the infected animal is exceptionally aggressive, may attack without provocation, and exhibits otherwise uncharacteristic behavior. This is an example of a viral pathogen modifying the behavior of its host to facilitate its transmission to other hosts. Transmission between humans is extremely rare. A few cases have been recorded through transplant surgery. After a typical human infection by bite, the virus enters the peripheral nervous system. It then travels along the afferent nerves toward the central nervous system. During this phase, the virus cannot be easily detected within the host, and vaccination may still confer cell-mediated immunity to prevent symptomatic rabies. When the virus reaches the brain, it rapidly causes encephalitis, the prodromal phase, which is the beginning of the symptoms. Once the patient becomes symptomatic, treatment is almost never effective and mortality is over 99%. Rabies may also inflame the spinal cord, producing transverse myelitis.

Symptoms

The first symptoms of rabies may be very similar to those of the flu and may last for days.

Later signs and symptoms may include:

- Fever
- Headache
- Nausea
- Vomiting
- Agitation
- Anxiety
- Confusion
- Hyperactivity
- Difficulty swallowing
- Excessive salivation
- Fear brought on by attempts to drink fluids because of difficulty swallowing water
- Hallucinations
- Insomnia
- Partial paralysis

The period between infection and the first symptoms (incubation period) is typically 1–3 months in humans. This period may be as short as four days or longer than six years, depending on the location and severity of the wound and the amount of virus introduced. Initial symptoms of rabies are often nonspecific such as fever and headache. As rabies progresses and causes inflammation of the brain and meninges, symptoms can include slight or partial paralysis, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, and hallucinations. The person may also have fear of water. The symptoms eventually progress to delirium, and coma. Death usually occurs 2 to 10 days after first symptoms. Survival is almost unknown once symptoms have presented, even with intensive care.

DIAGNOSIS

Rabies can be difficult to diagnose because, in the early stages, it is easily confused with other diseases or with aggressiveness. The reference method for diagnosing rabies is the fluorescent antibody test (FAT), an immunohistochemistry procedure, which relies on the ability of a detector molecule (usually fluorescein isothiocyanate) coupled with a rabies-specific antibody, forming a conjugate, to bind to and allow the visualisation of rabies antigen using fluorescent microscopy techniques. The PCR assays proved to be a sensitive and specific tool for routine diagnostic purposes, particularly in decomposed samples.

PREVENTION

Although all human cases of rabies were fatal until a vaccine was developed in 1885 by Louis Pasteur and Émile Roux. Their original vaccine was harvested from infected rabbits, from which the virus in the nerve tissue was weakened by allowing it to dry for five to ten days. Similar nerve tissue-derived vaccines are still used in some countries.

28 September is World Rabies Day, which promotes the information, prevention, and elimination of the disease. Vaccinating other animals In Asia and in parts of the Americas and Africa, dogs remain the principal host. Mandatory vaccination of animals is less effective in rural areas. Most deaths now result from bat bites, which may go unnoticed by the victim and hence untreated.

TREATMENT

After exposure Treatment after exposure can prevent the disease if given within 10 days. The rabies vaccine is 100% effective if given early, and still has a chance of success if delivery is delayed. Intramuscular vaccination should be given into the deltoid, not the gluteal area, which has been associated with vaccination failure due to injection into fat rather than muscle. Thoroughly washing the wound as soon as possible with soap and water for approximately five minutes is effective in reducing the number of viral particles. Povidone-iodine or alcohol is then recommended to reduce the virus further.

Rabies is a deadly virus spread to people from the saliva of infected animals. The rabies virus is usually transmitted through a bite.

Animals most likely to transmit rabies in the United States include bats, coyotes, foxes, raccoons and skunks. In developing countries of Africa and Southeast Asia, stray dogs are the most likely to spread rabies to people.

Once a person begins showing signs and symptoms of rabies, the disease nearly always causes death. For this reason, anyone who may have a risk of contracting rabies should receive rabies vaccinations for protection.

Prevention

To reduce your risk of coming in contact with rabid animals:

 Vaccinate your pets. Cats, dogs and ferrets can be vaccinated against rabies. Ask your veterinarian how often your pets should be vaccinated.

 Keep your pets confined. Keep your pets inside and supervise them when outside. This will help keep your pets from coming in contact with wild animals.

 Protect small pets from predators. Keep rabbits and other small pets, such as guinea pigs, inside or in protected cages so that they are safe from wild animals. These small pets can't be vaccinated against rabies.

 Report stray animals to local authorities.

 Don't approach wild animals. Wild animals with rabies may seem unafraid of people. It's not normal for a wild animal to be friendly with people, so stay away from any animal that seems unafraid.

 Keep bats out of your home. Seal any cracks and gaps where bats can enter your home. If you know you have bats in your home, work with a local expert to find ways to keep bats out.

 Consider the rabies vaccine if you're traveling. If you're traveling to a country where rabies is common and you'll be there for an extended period of time, ask your doctor whether you should receive the rabies vaccine.

3. AIDS

HIV/AIDS is a global pandemic. Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). AIDS was first clinically reported on June 5, 1981, with five cases in the United States.

Following initial infection a person may not notice any symptoms, or may experience a brief period of influenza-like illness. Typically, this is followed by a prolonged period with no symptoms.[5] If the infection progresses, it interferes more with the immune system, increasing the risk of developing common infections such as tuberculosis, as well as other opportunistic infections, and tumors which are otherwise rare in people who have normal immune function. These late symptoms of infection are referred to as acquired immunodeficiency syndrome (AIDS). This stage is often also associated with unintended weight loss.

HIV is spread primarily by unprotected sex , contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva, sweat and tears, do not transmit the virus.

HIV/AIDS has had a large impact on society, both as an illness and as a source of discrimination. The disease also has large economic impacts. There are many misconceptions about HIV/AIDS, such as the belief that it can be transmitted by casual non-sexual contact.

Origins

Both HIV-1 and HIV-2 are believed to have originated in non-human primates in West-central Africa and were transferred to humans in the early 20th century. 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 coastal West Africa 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.

The SIV is a weak virus which 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. Furthermore, due to its relatively low person-to-person transmission rate, SIV can only spread throughout the population in the presence of one or more high-risk transmission channels, which are thought to have been absent in Africa before the 20th century.

Specific proposed high-risk transmission channels, allowing the virus to adapt to humans and spread throughout the society, depend on the proposed timing of the animal-to-human crossing. Genetic studies of the virus suggest that the most recent common ancestor of the HIV-1 M group dates back to c. 1910. Proponents of this dating link the HIV epidemic with the emergence of colonialism and growth of large colonial African cities, leading to social changes, including a higher degree of sexual promiscuity, the spread of prostitution, and the accompanying high frequency of genital ulcer diseases (such as syphilis) in nascent colonial cities. While transmission rates of HIV during vaginal intercourse are low under regular circumstances, they are increased manyfold if one of the partners suffers from a sexually transmitted infection causing genital ulcers.

An alternative view holds that unsafe medical practices in Africa after World War II, such as unsterile reuse of single-use syringes during mass vaccination, antibiotic and anti-malaria treatment campaigns, were the initial vector that allowed the virus to adapt to humans and spread.

SYMPTOMS

There are three main stages of HIV infection: acute infection, clinical latency, and AIDS.

Acute infection

The initial period following the contraction of HIV is called acute HIV, primary HIV or acute retroviral syndrome. Many individuals develop an influenza-like illness or a mononucleosis-like illness 2–4 weeks after exposure while others have no significant symptoms. Symptoms occur in 40–90% of cases and most commonly include fever, large tender lymph nodes, throat inflammation, a rash, headache, tiredness, and/or sores of the mouth and genitals. The rash, which occurs in 20–50% of

cases, presents itself on the trunk and is maculopapular, classically. Some people also develop opportunistic infections at this stage. Gastrointestinal symptoms, such as vomiting or diarrhea may occur. Neurological symptoms of peripheral neuropathy also occur. The duration of the symptoms varies, but is usually one or two weeks.

Owing to their nonspecific character, these symptoms are not often recognized as signs of HIV infection. Even cases that do get seen by a family doctor or a hospital are often misdiagnosed as one of the many common infectious diseases with overlapping symptoms. Thus, it is recommended that HIV be considered in people presenting with an unexplained fever who may have risk factors for the infection.

Clinical latency

The initial symptoms are followed by a stage called clinical latency, asymptomatic HIV, or chronic HIV. Without treatment, this second stage of the natural history of HIV infection can last from about three years to over 20 years (on average, about eight years). While typically there are few or no symptoms at first, near the end of this stage many people experience fever, weight loss, gastrointestinal problems and muscle pains. Between 50% and 70% of people also develop persistent generalized lymphadenopathy, characterized by unexplained, non-painful enlargement of more than one group of lymph nodes (other than in the groin) for over three to six months.

Although most HIV-1 infected individuals have a detectable viral load and in the absence of treatment will eventually progress to AIDS, a small proportion (about 5%) retain high levels of $CD4^+$ T cells (T helper cells) without antiretroviral therapy for more than five years. These individuals are classified as "HIV controllers" or long-term nonprogressors (LTNP). Another group consists of those who maintain a low or undetectable viral load without anti-retroviral treatment, known as "elite controllers" or "elite suppressors". They represent approximately 1 in 300 infected persons.

Acquired immunodeficiency syndrome

Acquired immunodeficiency syndrome (AIDS) is defined as an HIV infection with either a $CD4^+$ T cell count below 200 cells per μL or the occurrence of specific diseases associated with HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that alert to the presence of AIDS are pneumocystis pneumonia (40%), cachexia in the form of HIV wasting syndrome (20%), and esophageal candidiasis. Other common signs include recurrent respiratory tract infections.

Opportunistic infections may be caused by bacteria, viruses, fungi, and parasites that are normally controlled by the immune system. Which infections occur depends partly on what organisms are common in the person's environment. These infections may affect nearly every organ system.

People with AIDS have an increased risk of developing various viral-induced cancers.

Additionally, people with AIDS frequently have systemic symptoms such as prolonged fevers, sweats (particularly at night), swollen lymph nodes, chills, weakness, and unintended weight loss. Diarrhea is another common symptom, present in about

90% of people with AIDS. They can also be affected by diverse psychiatric and neurological symptoms independent of opportunistic infections and cancers.

EPIDEMIOLOGY

HIV is spread by three main routes: sexual contact, significant exposure to infected body fluids or tissues and from mother to child during pregnancy, delivery, or breastfeeding (known as vertical transmission). There is no risk of acquiring HIV if exposed to feces, nasal secretions, saliva, sputum, sweat, tears, urine, or vomit unless these are contaminated with blood. It is also possible to be co-infected by more than one strain of HIV—a condition known as HIV superinfection.

Sexual

The most frequent mode of transmission of HIV is through sexual contact with an infected person. However, an HIV-positive person who has an undetectable viral load as a result of long-term treatment has effectively no risk of transmitting HIV sexually.

The viral load of an infected person is an important risk factor in both sexual and mother-to-child transmission. During the first 2.5 months of an HIV infection a person's infectiousness is twelve times higher due to the high viral load associated with acute HIV. If the person is in the late stages of infection, rates of transmission are approximately eightfold greater.

Body fluids

The second-most frequent mode of HIV transmission is via blood and blood products. Blood-borne transmission can be through needle-sharing during intravenous drug use, needle-stick injury, transfusion of contaminated blood or blood product, or medical injections with unsterilized equipment.

HIV is transmitted in about 93% of blood transfusions using infected blood.

Unsafe medical injections play a role in HIV. In 2007, People giving or receiving tattoos, piercings, and scarification are theoretically at risk of infection but no confirmed cases have been documented. It is not possible for mosquitoes or other insects to transmit HIV.

Mother-to-child

HIV can be transmitted from mother to child during pregnancy, during delivery, or through breast milk, resulting in the baby also contracting HIV. In the absence of treatment, the risk of transmission before or during birth is around 20%, and in those who also breastfeed 35%. Treatment decreases this risk to less than 5%.

Antiretrovirals when taken by either the mother or the baby decrease the risk of transmission in those who do breastfeed.

VIROLOGY

HIV is the cause of the spectrum of disease known as HIV/AIDS. HIV is a retrovirus that primarily infects components of the human immune system such as $CD4^+$ T cells, macrophages and dendritic cells. It directly and indirectly destroys $CD4^+$ T cells.

HIV is a member of the genus *Lentivirus*, part of the family *Retroviridae*. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses. Upon entry into the target cell, the viral RNA genome is converted (reverse transcribed) into double-stranded DNA by a virally encoded reverse transcriptase that is transported along with the viral genome in the virus particle. The resulting viral DNA is then imported into the cell nucleus and integrated into the cellular DNA by a virally encoded integrase and host co-factors. Once integrated, the virus may become latent, allowing the virus and its host cell to avoid detection by the immune system. Alternatively, the virus may be transcribed, producing new RNA genomes and viral proteins that are packaged and released from the cell as new virus particles that begin the replication cycle anew.

HIV is now known to spread between $CD4^+$ T cells by two parallel routes: cell-free spread and cell-to-cell spread.

Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was originally discovered (and initially referred to also as LAV or HTLV-III). It is more virulent, more infective, and is the cause of the majority of HIV infections globally. The lower infectivity of HIV-2 as compared with HIV-1 implies that fewer people exposed to HIV-2 will be infected per exposure. Because of its relatively poor capacity for transmission, HIV-2 is largely confined to West Africa.

PATHOGENESIS

After the virus enters the body there is a period of rapid viral replication, 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. This response is accompanied by a marked drop in the number of circulating $CD4^+$ T cells. The acute viremia is almost invariably associated with activation of $CD8^+$ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The $CD8^+$ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the $CD4^+$ T cell counts recover. A good $CD8^+$ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.

Ultimately, HIV causes AIDS by depleting $CD4^+$ T cells. This weakens the immune system and allows opportunistic infections. T cells are essential to the immune response and without them, the body cannot fight infections or kill cancerous cells. The mechanism of $CD4^+$ T cell depletion differs in the acute and chronic phases. During the acute phase, HIV-induced cell lysis and killing of infected cells by $CD8^+$ T cells accounts for $CD4^+$ T cell depletion, although apoptosis may also be a factor. During the chronic phase, the consequences of generalized immune activation coupled with the gradual loss of the ability of the immune system to generate new T cells appear to account for the slow decline in $CD4^+$ T cell numbers.

Although the symptoms of immune deficiency characteristic of AIDS do not appear for years after a person is infected, the bulk of $CD4^+$ T cell loss occurs during the first weeks of infection, especially in the intestinal mucosa, which harbors the majority of the lymphocytes found in the body. The reason for the preferential loss of mucosal $CD4^+$ T cells is that the majority of mucosal $CD4^+$ T cells express the CCR5 protein which HIV uses as a co-receptor to gain access to the cells, whereas only a small fraction of $CD4^+$ T cells in the bloodstream do so. A specific genetic change that alters the CCR5 protein when present in both chromosomes very effectively prevents HIV-1 infection.

HIV seeks out and destroys CCR5 expressing $CD4^+$ T cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. $CD4^+$ T cells in mucosal tissues remain particularly affected. Continuous HIV replication causes a state of generalized immune activation persisting throughout the chronic phase. Immune activation, which is reflected by the increased activation state of immune cells and release of pro-inflammatory cytokines, results from the activity of several HIV gene products and the immune response to ongoing HIV replication.

DIAGNOSIS

HIV/AIDS is diagnosed via laboratory testing and then staged based on the presence of certain signs or symptoms.

Most people infected with HIV develop specific antibodies (i.e. seroconvert) within three to twelve weeks after the initial infection. Diagnosis of primary HIV before seroconversion is done by measuring HIV-RNA or p24 antigen. Positive results obtained by antibody or PCR testing are confirmed either by a different antibody or by PCR. Antibody tests in children younger than 18 months are typically inaccurate, due to the continued presence of maternal antibodies. Thus HIV infection can only be diagnosed by PCR testing for HIV RNA or DNA, or via testing for the p24 antigen.

PREVENTION

Sexual contact

Universal precautions within the health care environment are believed to be effective in decreasing the risk of HIV. Safe sex reduces the risk of HIV transmission by approximately 80% over the long term.

Pre-exposure

Antiretroviral treatment among people with HIV whose CD4 count ≤ 550 cells/μL is a very effective way to prevent HIV infection of their partner (a strategy known as treatment as prevention, or TASP). TASP is associated with a 10- to 20-fold reduction in transmission risk. Pre-exposure prophylaxis (PrEP) with a daily dose of the medications tenofovir, with or without emtricitabine, is effective in people at high risk.

Post-exposure

A course of antiretrovirals administered within 48 to 72 hours after exposure to HIV-positive blood or genital secretions is referred to as post-exposure prophylaxis (PEP). The use of the single agent zidovudine reduces the risk of a HIV infection five-fold following a needle-stick injury. As of 2013, the prevention regimen recommended in the United States consists of three medications—tenofovir, emtricitabine and raltegravir—as this may reduce the risk further.

Mother-to-child

Programs to prevent the vertical transmission of HIV (from mothers to children) can reduce rates of transmission by 92–99%. This primarily involves the use of a combination of antiviral medications during pregnancy and after birth in the infant, and potentially includes bottle feeding rather than breastfeeding.

Vaccination Currently there is no licensed vaccine for HIV or AIDS. The most effective vaccine trial to date, RV 144, was published in 2009; it found a partial reduction in the risk of transmission of roughly 30%, stimulating some hope in the research community of developing a truly effective vaccine.

TREATMENT

There is currently no cure, nor an effective HIV vaccine. Treatment consists of highly active antiretroviral therapy (HAART) which slows progression of the disease.

Antiviral therapy

Current HAART options are combinations (or "cocktails") consisting of at least three medications belonging to at least two types, or "classes", of antiretroviral agents. Initially, treatment is typically a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus two nucleoside analog reverse transcriptase inhibitors (NRTIs). Typical NRTIs include: zidovudine (AZT) or tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC). As of 2019, dolutegravir/lamivudine/tenofovir is listed by the World Health Organization as the first-line treatment for adults, with tenofovir/lamivudine/efavirenz as an alternative. Combinations of agents that include protease inhibitors (PI) are used if the above regimen loses effectiveness.

Benefits of treatment include a decreased risk of progression to AIDS and a decreased risk of death. In the developing world, treatment also improves physical and mental health. Treatment recommendations for children are somewhat different from those for adults. The World Health Organization recommends treating all children less than 5 years of age; children above 5 are treated like adults.

Opportunistic infections

Measures to prevent opportunistic infections are effective in many people with HIV/AIDS. In addition to improving current disease, treatment with antiretrovirals reduces the risk of developing additional opportunistic infections. Adults and adolescents who are living with HIV (even on anti-retroviral therapy) with no evidence of active tuberculosis in settings with high tuberculosis burden should receive isoniazid preventive therapy (IPT); the tuberculin skin test can be used to help decide if IPT is needed. Vaccination against hepatitis A and B is advised for all people at risk of HIV before they become infected; however, it may also be given after infection. Trimethoprim/sulfamethoxazole prophylaxis between four and six weeks of age, and ceasing breastfeeding of infants born to HIV-positive mothers, is recommended in resource-limited settings.

PROGONOSIS

HIV/AIDS has become a chronic rather than an acutely fatal disease in many areas of the world. Prognosis varies between people, and both the CD4 count and viral load are useful for predicted outcomes.[] Without treatment, average survival time after infection with HIV is estimated to be 9 to 11 years, depending on the HIV subtype. After the diagnosis of AIDS, if treatment is not available, survival ranges between 6 and 19 months. If treatment is started late in the infection, prognosis is not as good: for example, if treatment is begun following the diagnosis of AIDS, life expectancy is ~10–40 years.

The primary causes of death from HIV/AIDS are opportunistic infections and cancer, both of which are frequently the result of the progressive failure of the immune system. Risk of cancer appears to increase once the CD4 count is below 500/μL.

SOCIALSTIGMA

AIDS stigma exists around the world in a variety of ways, including ostracism, rejection, discrimination and avoidance of HIV-infected people; compulsory HIV testing without prior consent or protection of confidentiality; violence against HIV-infected individuals or people who are perceived to be infected with HIV; and the quarantine of HIV-infected individuals. Stigma-related violence or the fear of violence prevents many people from seeking HIV testing, returning for their results, or securing treatment, possibly turning what could be a manageable chronic illness into a death sentence and perpetuating the spread of HIV.