CHAPTER IV: VIRAL DISEASES

1.0 INTRODUCTION TO VIRUSES

In 1898, Friedrich Loeffler and Paul Frosch found evidence that the cause of foot-and-mouth disease in livestock was an infectious particle smaller than any bacteria. This was the first clue to the nature of viruses, genetic entities that lie somewhere in the grey area between living and non-living states.

Viruses depend on the host cells that they infect to reproduce. When found outside of host cells, viruses exist as a protein coat or **capsid**, sometimes enclosed within a membrane. The capsid encloses either DNA or RNA which codes for the virus elements. While in this form outside the cell, the virus is metabolically **inert**.When it comes into contact with a host cell, a virus can insert its genetic material into its host, literally taking over the host's functions. An infected cell produces more viral protein and genetic material instead of its usual products. Some viruses may remain dormant inside host cells for long periods, causing no obvious change in their host cells (a stage known as the **lysogenic** phase). But when a dormant virus is stimulated, it enters the **lytic** phase: new viruses are formed, self-assemble, and burst out of the host cell, killing the cell and going on to infect other cells.

The origin of viruses

There are two theories of viral origin:

1- Viruses may be derived from DNA or RNA or from both nucleic acid components of host cells that became able to replicate autonomously and evolve independently.

2- Viruses may be degenerate forms of intracellular parasites.

The Classification of virus

In 1995, the international committee on taxonomy of viruses had organized more than 4000 animal and plant viruses into 71 families, 11 subfamilies, and 164 genera, with hundreds of viruses still unassigned. Currently 24 families contain viruses that infect humans and animals. **According to the type of nucleic acid viruses are classified into DNA and RNA viruses.**

DNA VIRUSES

A- Parvoviruses

B- Polyomaviuses – Formerly part of Papovaviridae family before it splits into 2 families.

C- Papillomaviruses - Formerly part of Papovaviridae family before it splits into 2 families.

D- Adenoviruses

E- Herpesviruses

F- Poxviruses

G- Hepadnaviruses

RNA VIRUSES

A- Picornaviruses

B- Flaviviruses

C– Togaviruses

D- Coronaviruses

E- Caliciviruses

F- Retroviruses

G- Astrovirses

H- Reoviruses

I- Arboviruses

J- Arenaviruses

K- Bunyaviruses

L- Orthomyxoviruses

M- Paramyxoviruses

N- Rhabdoviruses

O- Bornaviruses

P- Filoviruses

Q- Other viruses

R- Viroids

S- Prions

PATHOGENESIS AND CONTROL OF VIRAL DISEASES

More than 300 viruses are known to infect humans and to cause as many as 50 different syndromes.

Steps in Viral Pathogenesis

A- Viral entry and primary replication.

B- Viral Spread and Cell Tropism.

C- Cell Injury and Clinical Illness.

D- Recovery From Infection.

E- Virus Shedding.

Host Immune Response

1- Both humeral and cellular immunity are involved in control of viral infection.

2- Cytotoxic T lymphocytes lyse virus infected cells.

3- Secretory IgA antibody is important against viral infections of the respiratory or gastrointestinal tract.

Viruses have a variety of ways that serve to suppress or evade the host immune response and thus avoid eradication:

1- Oftentimes the viral proteins involved in modulating the host response are not essential for the growth of the virus.

2- Some viruses infect cells of the immune system and abrogate their function(AIDS).

3- They may infect neurons that express little or no class 1 MHC(herpesviruses).

4- Form proteins that inhibit MHC function(adenoviruses).

5- Viruses may mutate and change the antigenic sites on virionproteins(influenza virus).

6- Regulate the level of viral surface proteins (herpesvirus).

PREVENTION AND TREATMENT OF VIRAL DISEASES

Viruses are obligate intracellular parasites, antiviral drugs must have to be of selectively inhibiting viral functions without damaging the host. Furthermore an ideal drug would reduce disease symptoms without modifying the viral infection so much as to prevent an immune

response in the host. There is a need for antiviral drugs active against viruses for which vaccines are not available or not highly effective.

RESISTANCE TO VIRAL DISEASES (REVIEW OF HUMAN IMMUNE SYSTEM)

IMMUNITY; is a biological term that describes a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion.
Immunity involves both **specific** and **non specific** immunity

Non -specific immunity; act either as **barriers** or as **eliminators** of wide range of pathogens irrespective of antigenic specificity (no antigen-antibody reaction]
e.g ***skin barriers and mucosal immunity;** the skin cannot be penetrated by most organisms unless it already has an opening such as a scratch or a cut
Mechanically, pathogens are expelled from the lungs by ciliary action, coughing and sneezing eject both living and non living things from the respiratory system, tears, saliva and urine also force out pathogens
Sticky mucus in respiratory tract traps many microorganisms
Acid Ph<7.0 of skin secretions inhibits bacterial growth
Hair follicles secrete sebum that contains **lactic acid** and **fatty acids** both of which inhibit the growth of some pathogenic bacteria and fungi. This is the reason why areas of the skin not covered with hair, such as the palms and soles of the feet, are most susceptible to fungal infections e.g **athlete foot.**
Saliva, tears, nasal secretions and perspiration contain **lysozyme** , an enzyme that destroys gram positive bacterial cell walls causing cell lysis
Spermine and **zinc** in semen destroy some pathogens
Lactoperoxidase is a powerful enzyme found in mother's milk.
Specific immunity; There is antigen-antibody reaction.

CLASSIFICATION OF IMMUNITY

A. **Passive immunity;**

Passive immunity is the transfer of active immunity in the form of readymade antibodies, from one individual to another. It can occur;

-**Naturally**; when maternal antibodies are transferred to the fetus through the placenta

-**Artificially**; when high levels of human antibodies specific for a pathogen or toxin are transferred to non-immune individuals

Passive immunization is used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce the symptoms of ongoing or immunosuppressive diseases.

Passive immunity provides **immediate protection**, but the body doesn't develop **memory**, therefore the patient is at risk of being infected by the same pathogen later.

- **Naturally acquired passive immunity**

Maternal antibodies are passed through the placenta to the fetus by a receptor on placental cells. Thus occurs around the third month of gestation.**IgG**is the only antibody that can pass through the placenta.

This immunity can also be provided through the transfer of **IgA** antibodies found in breast milk that are transferred to the gut of the infant, protecting against bacterial infections until the new borne can synthesize its own antibodies.

- **Artificially acquired passive immunity**

It is a short term immunization induced by the transfer of antibodies, which can be administered in several forms, as human or animal blood plasma for intravenous or intramuscular use. Passive transfer is used prophylactically in immunodeficiency diseases, in the treatment of acute infections.

The artificial induction of passive immunity has been used for over a century to treat infectious disease, and prior to the advent of antibiotics, was often the only specific treatment for certain infections e.g immunoglobulin therapy in the treatment of severe respiratory diseases.

B. Active immunity

Active immunity is induced in the host itself by an antigen.

Due to the formation of immunological memory , re-infection at later time points leads to a rapid increase in antibody production.

When B cells and T cells are activated by a pathogen, memory B-cells and T-cells develop. These memory cells will remember each specific pathogen encountered, and be able to mount a strong response if the pathogen is detected again.

- **Naturally acquired active immunity**

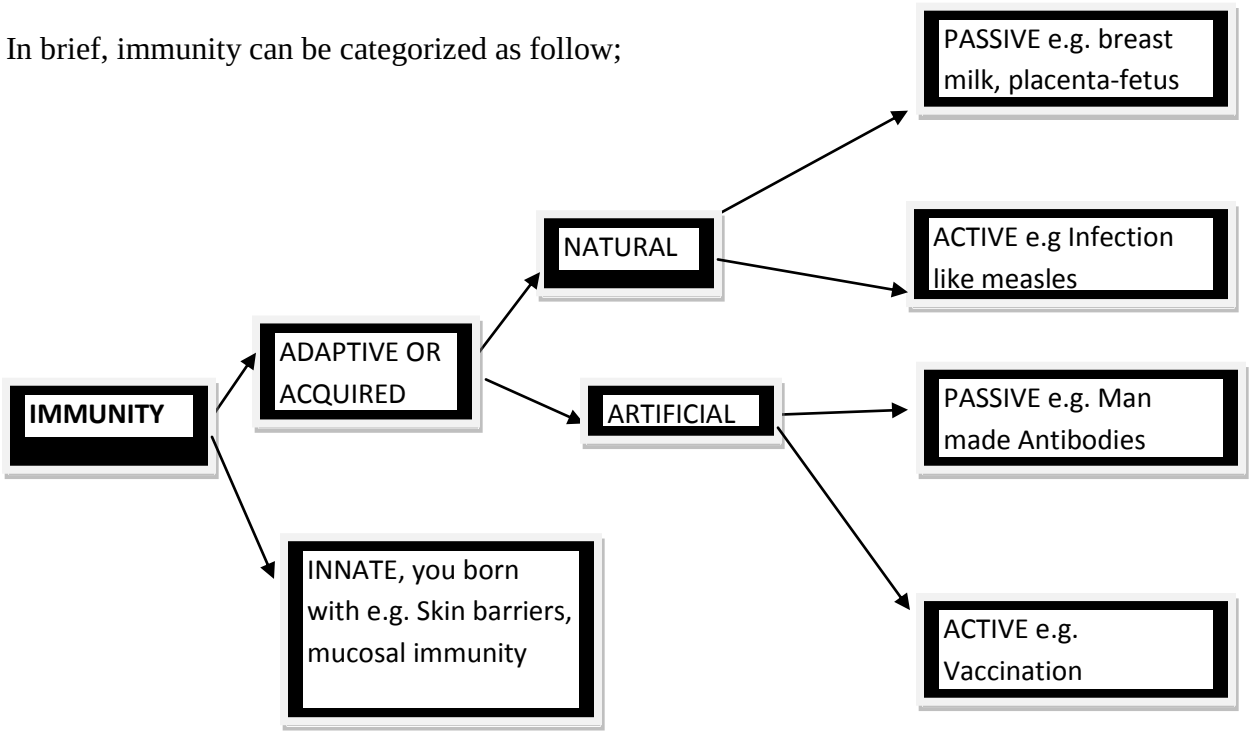
It occurs when a person is exposed to a live pathogen, and develops a primary immune response, which leads to immunological memory. This type of immunity is natural because it is not induced by man.

- **Artificially acquired active immunity**

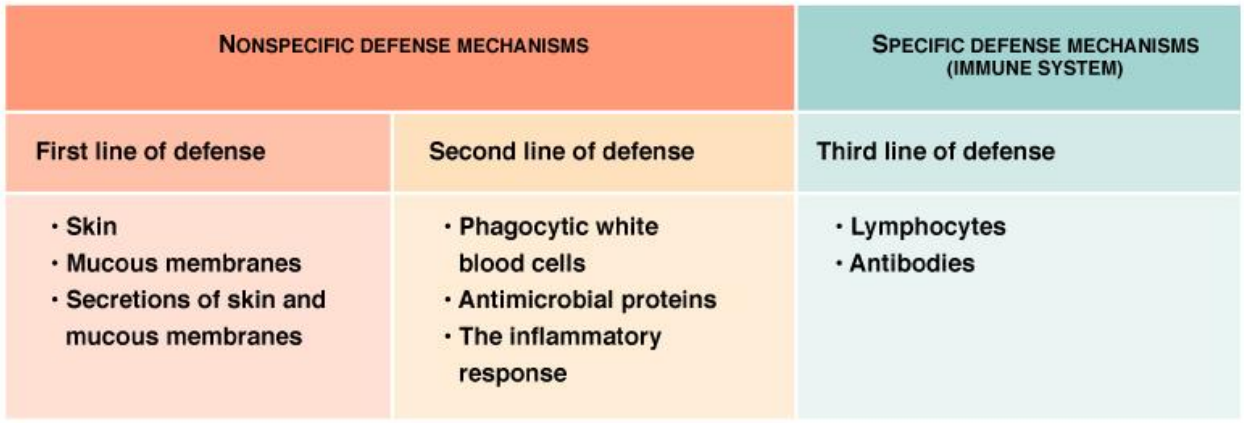
It can be induced by a vaccine or a substance that contains antigen

A vaccine stimulates a primary response against an antigen without causing symptoms of the disease.

In brief, immunity can be categorized as follow;



Human defense mechanisms



Duality of human immune response

The division of lymphocyte white blood cells into two classes of cells, types B and T to fight against invaders. Type B cells develop **humoral immunities**, while type T cells are active in **cellular immunity**.

Difference between humoral and cell mediated immunity

Humoral immunity (HI) or antibody-mediated immunity(AMI)	**Cell mediated immunity(CMI)**
Mediated by secreted antibodies produced in the cell of B lymphocytes: >B lymphocytes with co-stimulation from dendritic cells result in proliferation and terminal differentiation (transform) into plasma cells which secrete antibodies in response to an antigen. >Secreted antibodies bind to antigens on the	>Does not involve antibodies, thus it is mediated by certain types of T-lymphocytes >T- lymphocytes recognize foreign material by means of surface receptors >T- lymphocytes attack and destroy foreign material directly or through release of soluble mediators i.e. cytokines. >CMI is directed primarily to microbes that

surfaces of invading microbes	survive in phagocytes and microbes that infect non phagocystic cells. > It is most effective in removing virus-infected cells, but also participates in defending against fungi, protozoans, cancers, and intracellular bacteria. >It plays also a major role in transplant rejection.

1.1 HIV/AIDS

1.1.1 DEFINITION

HIVstands for Human Immunodeficiency Virus

AIDS stands for Acquired Immunodefiency Syndrome. It is a disease of the human immune system caused by the human immunodeficiency virus (HIV)

1.1.2 CAUSE

There are two **types** of HIV: HIV-1 and HIV-2. Both types are transmitted by sexual contact, through blood, and from mother to child, and they appear to cause clinically indistinguishable AIDS. However, it seems that HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2. Worldwide, the predominant virus is HIV-1, and generally when people refer to HIV without specifying the type of virus they will be referring to HIV-1. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere.

1.1.3 ORIGIN OF HIV /AIDS AND THE FIRST CASES

The first recognized cases of AIDS occurred in the USA in the early 1980s. A number of gay men in New York and California suddenly began to develop rare opportunistic infections and cancers that seemed stubbornly resistant to any treatment. At this time, AIDS did not yet have a name, but it quickly became obvious that all the men were suffering from a common syndrome.

The discovery of HIV, the Human Immunodeficiency Virus, was made soon after. While some were initially resistant to acknowledge the connection (and indeed some remain so today), there is now clear evidence to prove that HIV causes AIDS. So, in order to find the source of AIDS, it is necessary to look for the origin of HIV, and find out ***how, when and where*** HIV first began to cause disease in humans.

HOW?

HIV is a lentivirus, and like all viruses of this type, it attacks the immune system. Lentiviruses are in turn part of a larger group of viruses known as retroviruses. The name 'lentivirus' literally means 'slow virus' because they take such a long time to produce any adverse effects in the body. They have been found in a number of different animals, including cats, sheep, horses and cattle. However, the most interesting lentivirus in terms of the investigation into the origins of HIV is the Simian Immunodeficiency Virus (SIV) that affects monkeys, which is believed to be at least 32,000 years old.

It is now generally accepted that HIV is a descendant of a Simian Immunodeficiency Virus because certain strains of SIVs bear a very close resemblance to HIV-1 and HIV-2, the two types of HIV.

HIV-2 for example corresponds to *SIVsm*, a strain of the Simian Immunodeficiency Virus found in the sooty mangabey (also known as the White-collared monkey), which is indigenous to western Africa.

The more virulent, pandemic strain of HIV, namely HIV-1, was until recently more difficult to place. Until 1999, the closest counterpart that had been identified was *SIVcpz*, the SIV found in chimpanzees. However, this virus still had certain significant differences from HIV.

WHEN?

In February 1999 a group of researchers from the University of Alabama announced that they had found a type of SIVcpz that was almost identical to HIV-1. This particular strain was identified in a frozen sample taken from a captive member of the sub-group of chimpanzees known as Pan troglodytestroglodytes (*P. t. troglodytes*), which were once common in west-central Africa.

The researchers (led by Paul Sharp of Nottingham University and Beatrice Hahn of the University of Alabama) made the discovery during the course of a 10-year long study into the origins of the virus. They claimed that this sample proved that chimpanzees were the source of HIV-1, and that the virus had at some point crossed species from chimps to humans.

Their final findings were published two years later in *Nature* magazine . In this article, they concluded that wild chimps had been infected simultaneously with two different simian immunodeficiency viruses which had "viral sex" to form a third virus that could be passed on to other chimps and, more significantly, was capable of infecting humans and causing AIDS.

These two different viruses were traced back to a SIV that infected red-capped mangabeys and one found in greater spot-nosed monkeys. They believe that the hybridisation took place inside chimps that had become infected with both strains of SIV after they hunted and killed the two smaller species of monkey.

They also concluded that all three 'groups' of HIV-1 - namely Group M, N and O- came from the SIV found in *P. t. troglodytes*, and that each group represented a separate crossover 'event' from chimps to humans.

HOW?

It has been known for a long time that certain viruses can pass between species. Indeed, the very fact that chimpanzees obtained SIV from two other species of primate shows just how easily this crossover can occur. As animals ourselves, we are just as susceptible. When a viral transfer between animals and humans takes place, it is known as **zoonosis**.

Below are some of the most common theories about how this '**zoonosis**' took place, and how SIV became HIV in humans:

The 'hunter' theory

The most commonly accepted theory is that of the 'hunter'. In this scenario, SIVcpz was transferred to humans as a result of chimps being killed and eaten or their blood getting into cuts or wounds on the hunter. Normally the hunter's body would have fought off SIV, but on a few occasions it adapted itself within its new human host and became HIV-1. The fact that there were several different early strains of HIV, each with a slightly different genetic make-up (the most common of which was HIV-1 group M), would support this theory: every time it passed from a chimpanzee to a man, it would have developed in a slightly different way within his body, and thus produced a slightly different strain.

An article published in The Lancet in 2004 , also shows how retroviral transfer from primates to hunters is still occurring even today. In a sample of 1099 individuals in Cameroon, they discovered ten (1%) were infected with SFV (Simian Foamy Virus), an illness which, like SIV, was previously thought only to infect primates. All these infections were believed to have been acquired through the butchering and consumption of monkey and ape meat. Discoveries such as this have led to calls for an outright ban on bush meat hunting to prevent simian viruses being passed to humans.

The oral polio vaccine (OPV) theory

Some other rather controversial theories have contended that HIV was transferred iatrogenically (i.e. via medical interventions). One particularly well-publicised idea is that polio vaccines played a role in the transfer.

In his book, *The River*, the journalist Edward Hooper suggests that HIV can be traced to the testing of an oral polio vaccine called Chat, given to about a million people in the Belgian Congo, Ruanda and Urundi in the late 1950s. To be reproduced, live polio vaccine needs to be cultivated in living tissue, and Hooper's belief is that Chat was grown in kidney cells taken from local chimps infected with SIVcmz. This, he claims, would have resulted in the contamination of the vaccine with chimp SIV, and a large number of people subsequently becoming infected with HIV-1.

Many people have contested Hooper's theories and insist that local chimps were not infected with a strain of SIVcmz that is closely linked to HIV. Furthermore, the oral administration of the vaccine would seem insufficient to cause infection in most people (SIV/HIV needs to get directly into the bloodstream to cause infection - the lining of the mouth and throat generally act as good barriers to the virus).

In February 2000 the Wistar Institute in Philadelphia (one of the original manufacturers of the Chat vaccine) announced that it had discovered in its stores a phial of polio vaccine that had been used as part of the program. The vaccine was subsequently analysed and in April 2001 it was announced that no trace had been found of either HIV or chimpanzee SIV. A second analysis confirmed that only macaque monkey kidney cells, which cannot be infected with SIV or HIV, were used to make Chat. While this is just one phial of many, it means that the OPV theory remains unproven.

The fact that the OPV theory accounts for just one (group M) of several different groups of HIV also suggests that transferral must have happened in other ways too, as does the fact that HIV seems to have existed in humans before the vaccine trials were ever carried out. More about when HIV came into being can be found below.

The contaminated needle theory

This is an extension of the original 'hunter' theory. In the 1950s, the use of disposable plastic syringes became commonplace around the world as a cheap, sterile way to administer medicines. However, to African healthcare professionals working on inoculation and other medical programmes, the huge quantities of syringes needed would have been very costly. It is therefore likely that one single syringe would have been used to inject multiple patients without any sterilisation in between. This would rapidly have transferred any viral particles (within a hunter's blood for example) from one person to another, creating huge potential for the virus to mutate and replicate in each new individual it entered, even if the SIV within the original person infected had not yet converted to HIV.

The colonialism theory

The colonialism or **'Heart of Darkness'** theory is one of the more recent theories to have entered into the debate. It is again based on the basic 'hunter' premise, but more thoroughly explains how this original infection could have led to an epidemic. It was first proposed in 2000 by Jim Moore, an American specialist in primate behavior, who published his findings in the journal AIDS Research and Human Retroviruses.

During the late 19th and early 20th century, much of Africa was ruled by colonial forces. In areas such as French Equatorial Africa and the Belgian Congo, colonial rule was particularly harsh and many Africans were forced into labour camps where sanitation was poor, food was scarce and physical demands were extreme. These factors alone would have been sufficient to create poor health in anyone, so SIV could easily have infiltrated the labor force and taken advantage of their weakened immune systems to become HIV. A stray and perhaps sick chimpanzee with SIV would have made a welcome extra source of food for the workers.

The conspiracy theory

Some say that HIV is a 'conspiracy theory' or that it is ***'man-made'***. A recent survey carried out in the US for example, identified a significant number of African Americans who believe HIV was manufactured as part of a biological warfare programme, designed to wipe out large numbers of black and homosexual people. Many say this was done under the auspices of the US federal 'Special Cancer Virus Program' (SCVP). Linked into this theory is the belief that the virus was spread (either deliberately or inadvertently) to thousands of people all over the world through the smallpox inoculation programme, or to gay men through Hepatitis B vaccine trials. While none of these theories can be definitively disproved, the evidence given to back them up is usually based upon supposition and speculation, and ignores the clear link between SIV and HIV or the fact that the virus has been identified in people as far back as 1959.

WHEN

Studying the subtype of virus of some of the earliest known instances of HIV infection can help to provide clues about the time it first appeared in humans and its subsequent evolution.

Four of the earliest known instances of HIV infection are as follows:

1. A plasma sample taken in 1959 from an adult male living in what is now the Democratic Republic of the Congo.
2. A lymph node sample taken in 1960 from an adult female, also from the Democratic Republic of the Congo.
3. HIV found in tissue samples from an American teenager who died in St. Louis in 1969.
4. HIV found in tissue samples from a Norwegian sailor who died around 1976.

A 1998 analysis of the plasma sample from 1959 suggested that HIV-1 was introduced into humans around the 1940s or the early 1950s

In January 2000, the results of a new study suggested that the first case of HIV-1 infection occurred around 1931 in West Africa. However, a study in 2008dated the origin of HIV to between 1884 and 1924, much earlier than previous estimates. The researchers compared the viral sequence from 1959 (the oldest known HIV-1 specimen) to the newly discovered sequence from 1960. They found a significant genetic difference between them, demonstrating diversification of HIV-1 occurred long before the AIDS pandemic was recognised.

The authors suggest a long history of the virus in Africa and call Kinshasa the "*epicentre of the HIV/AIDS pandemic*" in West Africa. They propose the early spread of HIV was concurrent with the development of colonial cities, in which crowding of people increased opportunities for HIV transmission. If accurate, these findings imply that HIV existed before many scenarios (such as the OPV and conspiracy theories) suggest.

What about HIV-2? When did that get passed to humans?

Until recently, the origins of the HIV-2 virus had remained relatively unexplored. HIV-2 is thought to come from the SIV in Sooty Mangabeys rather than chimpanzees, but the crossover to humans is believed to have happened in a similar way (i.e. through the butchering and consumption of monkey meat). It is far rarer, significantly less infectious and progresses more slowly to AIDS than HIV-1. As a result, it infects far fewer people, and is mainly confined to a few countries in West Africa. By analysing samples of the two different subtypes of HIV-2 (A and B) taken from infected individuals and SIV samples taken from sooty mangabeys, DrVandamme concluded that subtype A had passed into humans around 1940 and subtype B in 1945 (plus or minus 16 years or so). Her team of researchers also discovered that the virus had originated in Guinea-Bissau and that its spread was most likely precipitated by the independence

war that took place in the country between 1963 and 1974 (Guinea-Bissau is a former Portuguese colony).

It is likely that we will never know who the first person was to be infected with HIV, or exactly how it spread from that initial person.

1.1.3 TRANSMISSION

HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid, and breast milk.

This transmission can involve anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above bodily fluids.

Sexual transmission

Sexual transmission occurs with the contact between sexual secretions of one person with the rectal, genital or oral mucous membranes of another. Unprotected sexual acts are riskier for the receptive partner than for the insertive partner, and the risk for transmitting HIV through unprotected anal intercourse is greater than the risk from vaginal intercourse or oral sex. Other sexually transmitted infections (STI) increase the risk of HIV transmission and infection, because they cause the disruption of the normal epithelial barrier by genital ulceration and/or microulceration; and by accumulation of pools of HIV-susceptible or HIV-infected cells (lymphocytes and macrophages) in semen and vaginal secretions.Women are more susceptible to HIV-1 infection due to hormonal changes, vaginal microbial ecology and physiology, and a higher prevalence of sexually transmitted diseases. People who have been infected with one strain of HIV can still be infected later on in their lives by other, more virulent strains.

Exposure to blood-borne pathogens

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

The risk of transmitting HIV to blood transfusion recipients is extremely low in developed countries where improved donor selection and HIV screening is performed. However, according to the WHO, the overwhelming majority of the world's population does not have access to safe blood and between 5% and 10% of the world's HIV infections come from transfusion of infected blood and blood products.

Perinatal transmission

The transmission of the virus from the mother to the child can occur *in utero* during pregnancy and at childbirth. In the absence of treatment, the transmission rate between a mother and her child during pregnancy, labor and delivery is 25%. However, when the mother takes antiretroviral therapy and gives birth by caesarean section, the rate of transmission is just 1%. The risk of infection is influenced by the viral load of the mother at birth, with the higher the viral load, the higher the risk. Breastfeeding also increases the risk of transmission by about 4 %.

1.1.4 PATHOPHYSIOLOGY

The Pathophysiology of AIDS is complex and not well clear, as is the case with all syndromes. Ultimately, HIV causes AIDS by depleting $CD4^+$ T helper lymphocytes. This weakens the immune system and allows opportunistic infections. T lymphocytes 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 cytotoxic 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 a majority of mucosal

$CD4^+$ T cells express the CCR5 co receptor, whereas a small fraction of $CD4^+$ T cells in the bloodstream do so.

HIV seeks out and destroys CCR5 expressing $CD4^+$ cells during acute infection. A vigorous immune response eventually controls the infection and initiates the clinically latent phase. However, $CD4^+$ T cells in mucosal tissues remain depleted throughout the infection, although enough remain to initially ward off life-threatening infections.

Continuous HIV replication results in 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. Another cause is the breakdown of the immune surveillance system of the mucosal barrier caused by the depletion of mucosal $CD4^+$ T cells during the acute phase of disease.

This results in the systemic exposure of the immune system to microbial components of the gut's normal flora, which in a healthy person is kept in check by the mucosal immune system. The activation and proliferation of T cells that results from immune activation provides fresh targets for HIV infection. However, direct killing by HIV alone cannot account for the observed depletion of $CD4^+$ T cells since only 0.01–0.10% of $CD4^+$ T cells in the blood are infected.

A major cause of $CD4^+$ T cell loss appears to result from their heightened susceptibility to apoptosis when the immune system remains activated. Although new T cells are continuously produced by the thymus to replace the ones lost, the regenerative capacity of the thymus is slowly destroyed by direct infection of its thymocytes by HIV. Eventually, the minimal number of $CD4^+$ T cells necessary to maintain a sufficient immune response is lost, leading to AIDS

Cells affected

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

- Lymphoreticular system:
    - CD_4+ T-Helper cells

    - Macrophages
    - Monocytes
    - B-lymphocytes
- Certain endothelial cells
- Central nervous system:
    - Microglia of the nervous system
    - Astrocytes
    - Oligodendrocytes
    - Neurons – indirectly by the action of cytokines and the gp-120

The effect

The virus has cytopathic effects but how it does it is **still not quite clear.** It can remain inactive in these cells for long periods, though. This effect is hypothesized to be due to the CD_4-gp120 interaction.

- The most prominent effect of HIV is its T-helper cell suppression and lysis. The cell is simply killed off or disturbed to the point of being function-less (they do not respond to foreign antigens) so the infected B-cells cannot produce enough antibodies. Thus the immune system collapses leading to the familiar AIDS complications, like infections and neoplasm.
- Infection of the cells of the CNS causes acute aseptic meningitis, subacuteencephalitis, vacuolar myelopathy and peripheral neuropathy. Later it leads to even AIDS dementia complex.
- The CD_4-gp120 interaction (see above) is also permissive to other viruses like Cytomegalovirus, Hepatitis virus, Herpes simplex virus, etc. These viruses lead to further cell damage i.e. cytopathy.

1.1.5 SYMPTOMS

The symptoms of AIDS are primarily the result of conditions that do not normally develop in individuals with healthy immune systems. Most of these conditions are infections caused by

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

People with AIDS also have an increased risk of developing various cancers such as Kaposi's sarcoma, cervical cancer and cancers of the immune system known as lymphomas. Additionally, people with AIDS often have systemic symptoms of infection like fevers, sweats (particularly at night), swollen glands, chills, weakness, and weight loss. The specific opportunistic infections that AIDS patients develop depend in part on the prevalence of these infections in the geographic area in which the patient lives.

Pulmonary infections

Pneumocystis pneumonia (originally known as *Pneumocystis carinii* pneumonia, and still abbreviated as PCP, which now stands for **P**neumo**c**ystis **p**neumonia) is relatively rare in healthy, immunocompetent people, but common among HIV-infected individuals. It is caused by *Pneumocystis jirovecii*.

Tuberculosis (TB) is unique among infections associated with HIV because it is transmissible to immunocompetent people via the respiratory route, is not easily treatable once identified due to its multidrug resistance which is a serious problem. Tuberculosis with HIV co-infection (TB/HIV) is a major world health problem according to the WHO, in 2007, 456,000 deaths among incident TB cases were HIV-positive, a third of all TB deaths and nearly a quarter of the estimated 2 million HIV died in that year.

Even though its incidence has declined because of the use of directly observed therapy and other improved practices in Western countries, this is not the case in developing countries where HIV is most prevalent. In advanced HIV infection, TB often presents atypically with extra pulmonary (systemic) disease a common feature. Symptoms are usually constitutional and are not localized to one particular site, often affecting bone marrow, bone, urinary and gastrointestinal tracts, liver, regional lymph nodes, and the central nervous system.

Gastrointestinal infections

Esophagitis is an inflammation of the lining of the lower end of the esophagus (gullet or swallowing tube leading to the stomach). In HIV infected individuals, this is normally due to fungal (candidiasis) or viral (herpes simplex-1 or cytomegalovirus) infections. In rare cases, it could be due to mycobacteria.

Unexplained chronic diarrhea in HIV infection is due to many possible causes, including common bacterial (*Salmonella*, *Shigella*, *Listeria* or *Campylobacter*) and parasitic infections; and uncommon opportunistic infections such as cryptosporidiosis, microsporidiosis, *Mycobacterium avium* complex (MAC) and viruses, astrovirus, adenovirus, rotavirus and cytomegalovirus, (the latter as a course of colitis).

In some cases, diarrhea may be a side effect of several drugs used to treat HIV, or it may simply accompany HIV infection, particularly during primary HIV infection. It may also be a side effect of antibiotics used to treat bacterial causes of diarrhea (common for *Clostridium difficile*). In the later stages of HIV infection, diarrhea is thought to be a reflection of changes in the way the intestinal tract absorbs nutrients, and may be an important component of HIV-related wasting.

Neurological and psychiatric involvement

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

Toxoplasmosis is a disease caused by the single-celled parasite called *Toxoplasma gondii*; it usually infects the brain, causing toxoplasma encephalitis, but it can also infect and cause disease in the eyes and lungs. Cryptococcal meningitis is an infection of the meninx (the membrane covering the brain and spinal cord) by the fungus *Cryptococcus neoformans*. It can cause fevers, headache, fatigue, nausea, and vomiting. Patients may also develop seizures and confusion; left untreated, it can be lethal.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease, in which the gradual destruction of the myelin sheath covering the axons of nerve cells impairs the transmission of nerve impulses. It is caused by a virus called JC virus which occurs in 70% of the population in latent form, causing disease only when the immune system has been severely

weakened, as is the case for AIDS patients. It progresses rapidly, usually causing death within months of diagnosis.

AIDS dementia complex (ADC) is a metabolic encephalopathy induced by HIV infection and fueled by immune activation of HIV infected brain macrophages and microglia. These cells are productively infected by HIV and secrete neurotoxins of both host and viral origin. Specific neurological impairments are manifested by cognitive, behavioral, and motor abnormalities that occur after years of HIV infection and are associated with low $CD4^+$ T cell levels and high plasma viral loads. AIDS related mania is sometimes seen in patients with advanced HIV illness; it presents with more irritability and cognitive impairment and less euphoria than a manic episode associated with true bipolar disorder. Unlike the latter condition, it may have a more chronic course. This syndrome is less often seen with the advent of multi-drug therapy.

Tumors and malignancies

Kaposi's sarcoma

As HIV is thought to be cytotoxic and even oncogenic, patients with HIV infection have substantially increased incidence of several cancers, which is primarily due to co-infection with an oncogenic DNA virus, especially Epstein-Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV) (also known as human herpesvirus-8 [HHV-8]), and human papillomavirus (HPV).

Caused by a gammaherpes virus called Kaposi's sarcoma-associated herpes virus (KSHV), it often appears as purplish nodules on the skin, but can affect other organs, especially the mouth, gastrointestinal tract, and lungs. High-grade B cell lymphomas such as Burkitt's lymphoma, Burkitt's-like lymphoma, diffuse large B-cell lymphoma (DLBCL), and primary central nervous system lymphoma present more often in HIV-infected patients. These particular cancers often foreshadow a poor prognosis. Epstein-Barr virus (EBV) or KSHV cause many of these lymphomas. In HIV-infected patients, lymphoma often arises in extra nodal sites such as the gastrointestinal tract. When they occur in an HIV-infected patient, KS and aggressive B cell lymphomas confer a diagnosis of AIDS. Invasive cervical cancer in HIV-infected women is also considered AIDS-defining. It is caused by human papillomavirus (HPV).

In addition to the AIDS-defining tumors listed above, HIV-infected patients are at increased risk of certain other tumors, notably Hodgkin's disease, anal and rectal carcinomas, hepatocellular carcinomas, head and neck cancers, and lung cancer. Some of these are causes by viruses, such as Hodgkin's disease (EBV), anal/rectal cancers (HPV), head and neck cancers (HPV), and hepatocellular carcinoma (hepatitis B or C). Other contributing factors include exposure to carcinogens (cigarette smoke for lung cancer), or living for years with subtle immune defects.

Interestingly, the incidence of many common tumors, such as breast cancer or colon cancer, does not increase in HIV-infected patients. In areas where HAART is extensively used to treat AIDS, the incidence of many AIDS-related malignancies has decreased, but at the same time malignant cancers overall have become the most common cause of death of HIV-infected patients. In recent years, an increasing proportion of these deaths have been from non-AIDS-defining cancers.

Other infections

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

Penicilliosis due to *Penicilliummarneffei* is now the third most common opportunistic infection (after extrapulmonary tuberculosis and cryptococcosis) in HIV-positive individuals within the endemic area of Southeast Asia.

An infection that often goes unrecognized in AIDS patients is Parvovirus B19. Its main consequence is anemia, which is difficult to distinguish from the effects of antiretroviral drugs used to treat AIDS itself

1.1.5 DIAGNOSIS

The diagnosis of AIDS in a person infected with HIV is based on the presence of certain signs or symptoms. Since June 5, 1981, many definitions have been developed for epidemiological surveillance such as the Bangui definition and the 1994 expanded World Health Organization

AIDS case definition. However, clinical staging of patients was not an intended use for these systems as they are neither sensitive, nor specific. In developing countries, the World Health Organization staging system for HIV infection and disease, using clinical and laboratory data, is used and in developed countries, the Centers for Disease Control (CDC) Classification System is used.

CDC Classification System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count (Table 1) and on previously diagnosed HIV-related conditions (Tables 2 and 3). For example, if a patient had a condition that once met the criteria for Category B but now is asymptomatic, the patient would remain in Category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

CDC Classification System for HIV-Infected Adults and Adolescents

Key to abbreviations: CDC = Centers for Disease Control and Prevention; PGL = persistent generalized lymphadenopathy.

	Clinical Categories		
CD4 Cell Categories	**A** **Asymptomatic, HIV, or PGL**	**B** **Acute Symptomatic Conditions,#* not A or C**	**C** **AIDS-Indicator Conditions***
(1)≥500 cells/µL	A1	B1	C1
(2)200-499 cells/µL	A2	B2	C2
(3)<200 cells/µL	A3	B3	C3

CDC Classification System: Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meets at least 1 of the following criteria:

a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity.

b) They are considered to have a clinical course or management that is complicated by HIV infection.

Examples include, but are not limited to, the following:

- Bacillary angiomatosis
- Oropharyngeal candidiasis (thrush)
- Vulvovaginal candidiasis, persistent or resistant
- Pelvic inflammatory disease (PID)
- Cervical dysplasia (moderate or severe)/cervical carcinoma in situ
- Hairy leukoplakia, oral
- Idiopathic thrombocytopenic purpura
- Constitutional symptoms, such as fever (>38.5°C) or diarrhea lasting >1 month
- Peripheral neuropathy
- Herpes zoster (shingles), involving ≥2 episodes or ≥1 dermatome

CDC Classification System: Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥2 episodes in 12 months)
- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1-month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)

- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1-month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex (MAC) or *M kansasii* , disseminated or extrapulmonary
- *Mycobacterium tuberculosis* , pulmonary or extrapulmonary
- *Mycobacterium* , other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jiroveci* (formerly *carinii*) pneumonia (PCP)
- Progressive multifocal leukoencephalopathy (PML)
- *Salmonella* septicemia, recurrent (nontyphoid)
- Toxoplasmosis of brain
- Wasting syndrome due to HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day ≥1 month) or chronic weakness and documented fever ≥1 month

WHO Clinical Staging of HIV/AIDS and Case Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2007. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many countries to determine eligibility for antiretroviral therapy, particularly in settings in which CD4 testing is not available. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (Table 4). These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥15 years.

WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- Persistent generalized lymphadenopathy

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for >1 month
- Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (hemoglobin <8 g/dL)

- Neutropenia (neutrophils <500 cells/µL)
- Chronic thrombocytopenia (platelets <50,000 cells/µL)

Clinical Stage 4

- HIV wasting syndrome, as defined by the CDC (see Table 3, above)
- *Pneumocystis* pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- Central nervous system toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis*Mycobacteria* infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent non typhoidal*Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

1.1.6 HIV TEST

HIV test

Many people are unaware that they are infected with HIV. Less than 1% of the sexually active urban population in Africa has been tested, and this proportion is even lower in rural populations. Furthermore, only 0.5% of pregnant women attending urban health facilities are counseled, tested or receive their test results. Again, this proportion is even lower in rural health facilities. Therefore, donor blood and blood products used in medicine and medical research are screened for HIV.

HIV tests are usually performed on venous blood. Many laboratories use *fourth generation* screening tests which detect anti-HIV antibody (IgG and IgM) and the HIV p24 antigen. The detection of HIV antibody or antigen in a patient previously known to be negative is evidence of HIV infection. Individuals whose first specimen indicates evidence of HIV infection will have a repeat test on a second blood sample to confirm the results.

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

Positive results obtained by PCR are confirmed by **antibody tests**. Routinely used HIV tests for infection in neonates and infants (i.e., patients younger than 2 years), born to HIV-positive mothers, have no value because of the presence of maternal antibody to HIV in the child's blood. HIV infection can only be diagnosed by PCR, testing for HIV pro-viral DNA in the children's lymphocytes.

1.1.7 PREVENTION

Sexual contact

- ✓ **The abstinence, faithfulness among couples; one sexual partner.**

- ✓ The male latex condom, if used correctly without oil-based lubricants, is the single most effective available technology to reduce the sexual transmission of HIV and other sexually transmitted infections. Female condoms have been shown to be an important HIV prevention strategy by preliminary studies which suggest that overall protected sexual acts increase relative to unprotected sexual acts where female condoms are available. At present, availability of female condoms is very low and the price remains prohibitive for many women.
- ✓ Randomized controlled trials have shown that male circumcision lowers the risk of HIV infection among heterosexual men by up to 60%. It is expected that this procedure will be actively promoted in many of the countries affected by HIV, although doing so will involve confronting a number of practical, cultural and attitudinal issues.

Exposure to infected body fluids

Health care workers can reduce exposure to HIV by employing precautions to reduce the risk of exposure to contaminated blood. These precautions include barriers such as gloves, masks, protective eyewear or shields, and gowns or aprons which prevent exposure of the skin or mucous membranes to blood borne pathogens. Frequent and thorough washing of the skin immediately after being contaminated with blood or other bodily fluids can reduce the chance of infection. Finally, sharp objects like needles, scalpels and glass, are carefully disposed of to prevent needles tick injuries with contaminated items. Since intravenous drug use is an important factor in HIV transmission in developed countries, harm reduction strategies such as needle-exchange programmes are used in attempts to reduce the infections caused by drug abuse.

Mother-to-child transmission (MTCT)

Current recommendations state that when replacement feeding is acceptable, feasible, affordable, sustainable and safe, HIV-infected mothers should avoid breast-feeding their infant. However, if this is not the case, exclusive breast-feeding is recommended during the first months of life and discontinued as soon as possible. It should be noted that women can breastfeed children who are not their own; see wet nurse.

Education, health literacy and cognitive ability

The most important way to change risky behavior is health education. Several studies have shown the positive impact of education and health literacy on cautious sex behavior. Education itself does not work, only if it leads to higher health literacy and general cognitive ability. This ability is relevant to understand the relationship between own risky behavior and possible outcomes like HIV-transmission.

1.1.8 HIV AND SEX EDUCATION

DEFINITION

Sex education, which is sometimes called sexuality education or sex and relationships education, is the process of acquiring information and forming attitudes and beliefs about sex, sexual identity, relationships and intimacy. Sex education is also about developing young people's skills so that they make informed choices about their behaviour, and feel confident and competent about acting on these choices

AIM

Sex education aims to reduce the risks of potentially negative outcomes from sexual behaviour, such as unwanted or unplanned pregnancies and infection with sexually transmitted diseases including HIV. It also aims to contribute to young people’s positive experience of their sexuality by enhancing the quality of their relationships and their ability to make informed decisions over their lifetime.

SKILLS THAT SEX EDUCATION SHOULD DEVELOP

The skills young people develop as part of sex education are linked to more general life-skills. Being able to communicate, listen, negotiate with others, ask for and identify sources of help and advice, are useful life-skills which can be applied to sexual relationships. Effective sex education develops young people's skills in negotiation, decision-making, assertion and listening. Other important skills include being able to recognise pressures from other people and to resist them, dealing with and challenging prejudice and being able to seek help from adults - including

parents, careers and professionals - through the family, community and health and welfare services.

Sex education that works also helps equip young people with the skills to be able to differentiate between accurate and inaccurate information, and to discuss a range of moral and social issues and perspectives on sex and sexuality, including different cultural attitudes and sensitive issues like sexuality, abortion and contraception.
Effective sex education also provides young people with an opportunity to explore the reasons why people have sex, and to think about how it involves emotions, respect for one self and other people and their feelings, decisions and bodies. Young people should have the chance to explore gender differences and how ethnicity and sexuality can influence people's feelings and options. They should be able to decide for themselves what the positive qualities of relationships are. It is important that they understand how bullying, stereotyping, abuse and exploitation can negatively influence relationships.

RELEVANT INFORMATION TO YOUNG PEOPLE

Young people need to have information on all the following topics:

Sexual development & reproduction - the physical and emotional changes associated with puberty and sexual reproduction, including fertilization and conception, as well as sexually transmitted diseases and HIV.
Contraception & birth control - what contraceptives there are, how they work, how people use them, how they decide what to use or not, and how they can be obtained.
Relationships - what kinds of relationships there are, love and commitment, marriage and partnership and the law relating to sexual behavior and relationships as well as the range of religious and cultural views on sex and sexuality and sexual diversity.

In addition, young people should be provided with information about abortion, sexuality, and confidentiality, as well as about the range of sources of advice and support that is available in the community and nationally.

1.1.9 IMPACT OF HIV

Introduction

AIDS has caused immense human suffering in the continent. The most obvious effect of this crisis has been illness and death, but the impact of the epidemic has certainly not been confined to the health sector; households, schools, workplaces and economies have also been badly affected. Although access to antiretroviral treatment is starting to lessen the toll of AIDS, fewer than half of Africans who need treatment are receiving it. The impact of AIDS will remain severe for many years to come.

Impact on health sector

In all heavily affected countries the AIDS epidemic is adding additional pressure on the health sector. As the epidemic matures, the demand for care for those living with HIV rises, as does the toll of AIDS on health workers.

The effect on hospitals

HIV-positive patients stay in hospital longer than other patients. Hospitals are struggling to cope, especially in poorer African countries where there are often too few beds available. This shortage results in people being admitted only in the later stages of illness, reducing their chances of recovery.

Health care workers

While AIDS is causing an increased demand for health services, large numbers of healthcare professionals are being directly affected by the epidemic. There is increased demand of health care workers.

Impact on household

In many cases, the presence of AIDS causes the household to dissolve, as parents die and children are sent to relatives for care and upbringing. The AIDS epidemic adds to food insecurity in many areas, as agricultural work is neglected or abandoned due to household illness. Taking care of a person sick with AIDS is not only an emotional strain for household members, but also a major strain on household resources. Loss of income, additional care-related expenses, the

reduced ability of caregivers to work, and mounting medical fees push affected households deeper into poverty. It is estimated that, on average, HIV-related care can absorb one-third of a household's monthly income. The financial burden of death can also be considerable, Aside from the financial burden, providing home based care can impose demands on the physical, mental and general health of carers – usually family and friends of the sick person.

Impact on education sector

There are numerous ways in which AIDS can affect education, but equally there are many ways in which education can help the fight against AIDS.

A decline in school enrolment is one of the most visible effects of the epidemic. This in itself will have an effect on HIV prevention, as a good, basic education ranks among the most effective and cost-effective means of preventing HIV. There are numerous barriers to school attendance in Africa. Children may be removed from school to care for parents or family members, or they may themselves be living with HIV. Many are unable to afford school fees and other such expenses – this is particularly a problem among children who have lost their parents to AIDS, who often struggle to generate income. HIV and AIDS are having a devastating effect on the already inadequate supply of teachers in African countries; Those with sick families may also take time off to attend funerals or to care for sick or dying relatives, and further absenteeism may result from the psychological effects of the epidemic. When a teacher falls ill, the class may be taken on by another teacher, may be combined with another class, or may be left untaught. Even when there is a sufficient supply of teachers to replace losses, there can be a significant impact on the students. The illness or death of teachers is especially devastating in rural areas where schools depend heavily on one or two teachers. Moreover, skilled teachers are not easily replaced.

The impact on enterprises and workplaces

AIDS damages businesses by squeezing productivity, adding costs, diverting productive resources, and depleting skills. Company costs for health-care, funeral benefits and pension fund commitments are likely to rise as the number of people taking early retirement or dying increases. Also, as the impact of the epidemic on households grows more severe, market demand for products and services can fall. The epidemic hits productivity through increased absenteeism.

The impact on life expectancy

The impact that AIDS has had on average life expectancy is partly attributed to child mortality, as increasing numbers of babies are born with HIV infections acquired from their mothers. The biggest increase in deaths, however, has been among adults aged between 20 and 49 years. This group now accounts for 60% of all deaths in sub-Saharan Africa, compared to 20% between 1985 and 1990, when the epidemic was in its early stages.

The economic impact

One way in which AIDS affects the economy is by reducing the labor supply through increased mortality and illness. Amongst those who are able to work, productivity is likely to decline as a result of HIV-related illness. Government income also declines, as tax revenues fall and governments are pressured to increase their spending to deal with the expanding HIV epidemic. The abilities of African countries to diversify their industrial base, expand exports and attract foreign investment are integral to economic progress in the region. By making labor more expensive and reducing profits, **AIDS limits the ability of African countries to attract industries** that depend on low-cost labour and makes investments in African businesses less desirable.

The future impact of HIV/AIDS

The access to treatment is slowly expanded throughout the continent of Africa, millions of lives are being extended and hope is being given to people who previously had none. Unfortunately, the majority of people in need of treatment are still not receiving it, and campaigns to prevent new infections (which must remain the central focus of the fight against AIDS) are lacking in many areas.

Impact of aids on Africa

HIV and AIDS are having a widespread impact on many parts of African society such as
The effect on life expectancy: In many countries of sub-Saharan Africa, AIDS has erased decades of progress made in extending life expectancy.

The effect on households. The effect of the AIDS epidemic on households can be very severe, especially when families lose their income earners. In other cases, people have to provide home based care for sick relatives, reducing their capacity to earn money for their family. Many of those dying from AIDS have surviving partners who are themselves infected and in need of care. They leave behind orphans, who are often cared for by members of the extended family.

The effect on healthcare. In all affected countries, the epidemic is putting strain on the health sector. As the epidemic develops, the demand for care for those living with HIV rises, as does the number of health care workers affected.

The effect on schools. Schools are heavily affected by AIDS. This a major concern, because schools can play a vital role in reducing the impact of the epidemic, through HIV education and support.

The effect on productivity. The HIV and AIDS epidemic has dramatically affected labour, which in turn slows down economic activity and social progress.

The effect on economic growth and development. The HIV and AIDS epidemic has already significantly affected Africa's economic development, and in turn, has affected Africa's ability to cope with the epidemic.

1.1.10 HIV AIDS ASSOCIATED STIGMA AND DESCRIMINATION

Definition

AIDS-related stigma and discrimination refers to prejudice, negative attitudes, abuse and maltreatment directed at people living with HIV and AIDS. They can result in being shunned by family, peers and the wider community; poor treatment in healthcare and education settings; an erosion of rights; psychological damage; and can negatively affect the success of HIV testing and treatment

AIDS stigma and discrimination exist worldwide, although they manifest themselves differently across countries, communities, religious groups and individuals

Why is there stigma related to HIV and aids

Fear of contagion coupled with negative, value-based assumptions about people who are infected leads to high levels of stigma surrounding HIV and AIDS

Factors that contribute to HIV/AIDS-related stigma include:

- HIV/AIDS is a life-threatening disease, and therefore people react to it in strong ways.
- HIV infection is associated with behaviors (such as homosexuality, drug addiction, prostitution or promiscuity) that are already stigmatized in many societies.
- Most people become infected with HIV through sex which often carries moral baggage.
- There is a lot of inaccurate information about how HIV is transmitted, creating irrational behavior and misperceptions of personal rise.
- HIV infection is often thought to be the result of personal irresponsibility.
- Religious or moral beliefs lead some people to believe that being infected with HIV is the result of moral fault (such as promiscuity or 'deviant sex') that deserves to be punished.

From early in the AIDS epidemic a series of powerful images were used that reinforced and legitimized stigmatization.

- HIV/AIDS as punishment (e.g. for immoral behavior)
- HIV/AIDS as a crime (e.g. in relation to innocent and guilty victims)
- HIV/AIDS as war (e.g. in relation to a virus which must be fought)
- HIV/AIDS as horror (e.g. in which infected people are demonized and feared)
- HIV/AIDS as otherness (in which the disease is an affliction of those set apart)

Consequences of HIV related stigma

Research by the International Centre for Research on Women (ICRW) found the possible consequences of HIV-related stigma to be:

- Loss of income/livelihood
- Loss of marriage & childbearing options
- Poor care within the health sector
- Withdrawal of caregiving in the home
- Loss of hope & feelings of worthlessness
- Loss of reputation

Some of these consequences refer to ‘internal stigma’ or ‘self-stigma’. Internal stigma refers to how people living with HIV regard themselves, as well as how they see public perception of people living with HIV. Stigmatizing beliefs and actions may be imposed by people living with HIV themselves:

Types of HIV/AIDS-related stigma and discrimination

AIDS-related stigma can lead to discrimination such as negative treatment and denied opportunities on the basis of their HIV status. This discrimination can affect all aspects of a person's daily life, for example, when they wish to travel, use healthcare facilities or seek employment.

Government

A country’s laws, rules and policies regarding HIV can have a significant effect on the lives of people living with the virus. Discriminatory practices can alienate and exclude people living with HIV, reinforcing the stigma surrounding HIV and AIDS.

There are many ways that governments can actively discriminate against people or communities with (or suspected of having) HIV/AIDS. Many of these laws have been justified on the grounds that HIV/AIDS poses a public health risk. Below are some examples of government level stigma and discrimination against people living with HIV/AIDS?

- President Museveni of Uganda supports the national policy of dismissing or not promoting members of the armed forces who test HIV positive(Tumushabe, 2006)
- The Chinese government advocates compulsory HIV testing for any Chinese citizen who has been living outside of the country for more than a year
- The UK legal system can prosecute individuals who pass the virus to somebody else, even if they did so without intent

Healthcare

In healthcare settings people with HIV can experience stigma and discrimination such as being refused medicines or access to facilities, receiving HIV testing without consent, and a lack of confidentiality.

Employment

In the workplace, people living with HIV may suffer stigma from their co-workers and employers, such as social isolation and ridicule, or experience discriminatory practices, such as termination or refusal of employment. Fear of an employer's reaction can cause a person living with HIV anxiety:

Restrictions on travel and stay

Many countries have laws that restrict the entry, stay and residence of people living with HIV.

Community

A community's reaction to somebody living with HIV can have a huge effect on that person's life. If the reaction is hostile a person may be discriminated against and may be forced to leave their home, or change their daily activities such as shopping, socializing or schooling. It can manifest as ostracism, rejection and verbal and physical abuse. It has even extended to murder.

Family

HIV positive members of the family can find themselves stigmatized and discriminated against within the home. There is concern that women and non-heterosexual family members are more likely than children and men to be mistreated.

1.1.11 HIV/AIDS TREATMENT AND APPROACH IN RWANDA

A. Definitions

What is HIV antiretroviral drug treatment?

This is the main type of treatment for HIV or AIDS. It is not a cure, but it can stop people from becoming ill for many years. The treatment consists of drugs that have to be taken every day for the rest of a person's life.

The aim of antiretroviral treatment is to keep the amount of HIV in the body at a low level. This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already.

The drugs are often referred to as:

Antiretrovirals
ARVs
Anti-HIV or anti-AIDS drugs

What is combination therapy?

Taking two or more antiretroviral drugs at a time is called combination therapy. Taking a combination of three or more anti-HIV drugs is sometimes referred to as **Highly Active Antiretroviral Therapy (HAART).**

Taking 2 or more HIV drugs combined into one pill refers to **fixed dose combination**.

Why do people need to take more than one drug at a time?

If only one drug was taken, HIV would quickly become resistant to it and the drug would stop working. Taking two or more antiretrovirals at the same time vastly reduces the rate at which resistance would develop, making treatment more effective in the long term.

How many HIV and AIDS drugs are there?

There are more than 20 approved antiretroviral drugs but not all are licensed or available in every country.

First and second line therapy

At the beginning of treatment, the combination of drugs that a person is given is called first line therapy. If after a while HIV becomes resistant to this combination, or if side effects are particularly bad, then a change to second line therapy is usually recommended.

Adherence

The term adherence means taking the drugs exactly as described. This includes taking all of the medication at the right time and exactly as the directions state. It also means ensuring that there will be no interactions with other drugs being taken.

Viral load

Viral load refers to the amount of HIV in the blood. If the viral load is high, T-helper cells tend to be destroyed more quickly. Therefore, the aim of antiretroviral treatment is to keep the viral load as low as possible.

Structured Treatment Interruptions (STIs)

A Structured Treatment Interruption (STI) or 'drug holiday' is when someone stops taking antiretroviral treatment temporarily.

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is a syndrome that occurs for a small number of patients soon after ARV treatment is started. It is caused by an excessive response by the recovering immune system to opportunistic infections that were already present, but were previously dormant and not producing symptoms. Although the symptoms of IRIS are often mild, occasionally they can be life threatening. Generally those who have a severely damaged immune system before starting antiretroviral treatment are more at risk of developing IRIS. IRIS does not indicate that treatment is failing. Usually the best response to IRIS is to continue treatment; the symptoms normally disappear within a few weeks

Switching treatment

A change of treatment is needed when the antiretrovirals fail to slow down the replication of the virus in the body. This can occur as a result of drug resistance, poor adherence, poor drug

absorption or a weak combination of drugs. **Substitution** refers to replacement of some ARVS but not all the entire regimen.

Salvage treatment

Salvage therapy is the term often used to describe the treatment for those who are resistant to drugs in the three original drug classes. In this situation it may be difficult to find a drug regimen that suppresses the viral load to undetectable.

B.HOLISTIC MANAGEMENT OF PERSONS LIVING WITH HIV/AIDS

Definition

Holistic Management (HM) is the medical, psychological and social care that takes into consideration all of the problems of the patient so as to be able to lead him/her towards a normal family, social and professional life (TRAC, 2009).

Its aims:

- ✓ Ensuring an adequate level of care to the concerned patient
- ✓ Reducing the mortality and morbidity related to HIV/AIDS
- ✓ Increasing the quality of life of the concerned patients
- ✓ Promoting prevention through increasing access to screening

Principles of holistic management

HM is a product of team work among many different professionals who must work together in a complementary and synergistic manner so as to meet the different needs of every patient.

The work of the different providers must be carried out with the highest degree of confidentiality.

HM must ensure a continuum of care within the health facility as well as beyond the boundaries of that structure.

Why psychosocial care in the holistic management of persons living with HIV/AIDS?

Three **reasons** justify the provision of psychosocial care:

1. HIV/AIDS affects different aspects of person‘s life.

2. Handling problems related to stigma and discrimination related to HIV/AIDS.

3. Ensuring adequate adherence to antiretroviral treatment and other drugs.

Therefore its **objectives** are:

- ✓ Provide support to the affected person regarding stress and psychosocial disturbances.
- ✓ Assist the affected person to adopt safe behavior for prevention and control of infection.
- ✓ Give correct information on HIV infection.
- ✓ Sensitize the community of the affected person to avoid stigmatization.
- ✓ Contribute to the prevention of HIV infection by making the patient responsible for its control.
- ✓ Educate the patient’s neighbors and family to support the adherence to ARVs

Activities of psychosocial care include:

- ✓ Psychosocial consultation
- ✓ Education and treatment initiation sessions
- ✓ Individual follow up
- ✓ Group counseling or support groups
- ✓ The pharmacy and distribution of drug
- ✓ Data entry and filling
- ✓ Follow up at home
- ✓ Providing care to multidisciplinary team.

C. PROTOCOL ON PROPHYLAXIS FOR OPPORTUNISTIC INFECTIONS

- ✓ **Introduction**

Regarding cotrimoxazole (CTZ) prophylaxis, the Rwanda national protocol recommends universal access. That is **systematically put all HIV- infected patients(adults or infants) on cotrimoxazole without taking into account the CD4 Count** (TRAC, 2009). Thus CTZ prophylaxis is maintained among patients on ARVs regardless of the trend in CD4 count level.

- ✓ **General prevention measures**

Every patient who has been diagnosed with an OI must have health education on the following facts:

- ✓ Information on the mode of transmission for HIV/AIDS
- ✓ Hygiene especially to avoid the diseases transmitted by oral-fecal route
- ✓ The environment: the work environment can constitute a risk especially the risk for TB
- ✓ Nutrition: boiled water and a balanced diet are recommended for all immunosuppressed patients. the consumption of alcohol and cigarette is discouraged
- ✓ Antiretroviral drugs and good adherence

Specific preventive measures

CTZ (cotrimoxazole or bactrim): protects against infections by toxoplasmosis, pneumocystis pneumonia, isospora belli and nocardia infections. The dosage is 960mg once a day orally. In case of allergy Dapsone 100 mg once a day PO is given.

IHN (izoniazide): currently systematic IHN is not recommended in Rwanda and should only be used in the reference hospital for selected cases where active TB has been excluded.

Azithromycin: 1200mg PO once a week for protection against mycobacterium avium complex (MAC). It should be stopped if the CD4 count is above 200 for more than 6 months and there are no signs suggestive of MAC. It should particularly be considered for patients that have IRIS.

Ganciclovir: 1000mg TID PO. For patient with cytomegalovirus (CMV) retinitis

Albendazole: 400MG once a year PO for intestinal helminthes

Fluconazole: 200 mg once a day PO in case of prevention against fungal infection such as Cryptococcus neoformans, oral and esophageal candidiasis.

- ✓ **Vaccination**

Vaccination should be postponed until CD4 Increases otherwise there may be insufficient immunological response. The live attenuated vaccines is contraindicated in symptomatic HIV patients and all persons whose CD4 Count is below 200.Pneumococcal , hepatitis B ,tetanus and diphtheria vaccines are recommended.

D. THE PRINCIPLES OF ANTIRETROVIRAL TREATMENT

- ✓ **Introduction**

ARV treatment is an essential element of the care for Person living with HIV/AIDS(PLWHA) and it changes the natural evolution of HIV infection. It results in reduced morbidity and mortality.

- ✓ **Keys factors in treatment**

There 3 factors that will influence the treatment success;

- The virus which may be more or less aggressive
- The patient who will determine the success of the treatment
- The ARV which should be ideally efficacious over a long time with minimum side effects.

- ✓ **Mechanism of action of ARVs: the multiplication cycle of HIV**

HIV is a RNA virus that must penetrate a CD4 cell in order to replicate inside the cell it undergoes a series of transformation to give rise to new viruses. Therefore the ARVs act by blocking one of the stages during the replication cycle of HIV within the CD4 cell.

The key stages of the replication cycle are:

1. Entry and fusion: entry through the membrane of the CD4 cell by fusion with the aid of co-receptors for eg.CCR5 or CXCR4.

2. Transcription: transformation of viral RNA into DNA carried out by enzyme r**everse transcriptase**

3. Integration of DNA formed above into foci of DNA within the CD4 nucleus under the action of an enzyme named **integrase enzyme**

4. Replication: manufacture of viral RNA from DNA. Formation of new viruses from that RNA and synthesized proteins in the CD4 cell under the influence of the protease enzyme.

5. Release of reconstituted particles.

The main ARVs currently in use in Rwanda block the action of the two enzymes: reverse transcriptase and protease. Drugs able to block entry of the virus into CD4 cells(coreceptor antagonists) and integrase inhibitors are newly available in other countries.

The aims of the ARV treatment are:

- ✓ Suppress the viral load to undetectable
- ✓ Increase the number of CD4 cells so as to improve the immune reconstitution
- ✓ Reduce the transmission of HIV
- ✓ Minimize the risk of cross resistance
- ✓ Minimize long term toxicity
- ✓ Improve the clinical status of the patient
- ✓ Improve the quality of life of the patient
- ✓ Minimize the cost of care

Hence to meet those aims, the quality of a good treatment regimen that can result in good adherence, is one that combine drugs that are:

- ✓ **Potent (powerful):** capable of adequately blocking replication of HIV.
- ✓ **With prolonged action**: the association must block the replication of HIV as long as possible.

Supporting a patient on ART

- Adequately prepare the patient before initiation of treatment.
- Prescribe to the patient the drugs that are most suited to him/her mode of life.
- Adequately inform the patient on how he needs to take his/her drugs and any possible side effects.
- Ensure the patient has people around to support throughout the treatment

E. ANTIRETROVIRAL TREATMENT

Background

More than 1.3 million receiving ARV in dev. Countries that represents 20% of people in need (WHO, 2006).

Without treatment, the infected persons can produce 10.000.000.000 new viruses every day.

14000 new cases of HIV per day; 12000 adults(50% women) and 2000 children. However,

90% do not know they are infected.

HIV in Rwanda

- Prevalence 3% (3.6% women and 2.3% men) to be reduced to less than 1% from 2008-2012(EDPRS)
- More than 200,000 PLWHA(RBC,2009)
- Patient on ARV 31,379 ad.&2,757 children(dec,2006), 56,153 people on ARV in 2008 and 72,539 in 2009(igihe .com from cnls report). Currently 76,726 people on ARVs (CNLS report,2011)
- Future estimate of 300,000 in a population of 10 million plus.

Evolution

Reflecting on 100 patients on treatment:

- 60% remain on treatment
- 15% die
- 25% lost **(TRAC ,2008)**

Definitions

HIV drug therapy

Treatment of HIV/AIDS

Is not a cure

Reduce the severity of the disease

Referred to:

- ✓ ARVS
- ✓ Anti HIV drugs
- ✓ Anti AIDS drugs
- ✓ Antiretrovirals

Combination therapy

Taking 2 or more ARV drugs at a time

Taking 3 or more is referred as highly active antiretroviral therapy **(HAART)**

Why combination therapy?

Avoid resistance.

Making the treatment more effective.

Fixed dose combination

HIV drugs combined into one pill.

Reduce the nnumber of pills to be taken each day.

Adherence

Taking drugs exactly as prescribed, on time following any dietary restrictions.

Salvage treatment

Is the term often used to describe the treatment for those who are resistant to drugs in the three original drug classes?

Switching treatment

A change of treatment is needed when the antiretrovirals fail to slow down the replication of the virus in the body.

Substitution refers to replacement of some ARVS but not all the entire regimen.

Structured Treatment Interruptions (STIs)

Or **'drug holiday'** is when someone stops taking antiretroviral treatment temporarily**.**

HISTORICAL ADVANCES OF ARV THERAPY

- 1983: discovery of HIV& its link to AIDS by institute Louis Pasteur de France
- 1985 :approval of 1st HIV antibody test
- 1987: 1st ARV: ZIDOVIDINE (AZT)

LATEX CONDOMS

- 1991-1993: Introduction of transcriptase inhibitors
- 1995-1996: protease inhibitors were approved
- 2003: approval of fusion or entry inhibitors
- 2007: discovery of integrase inhibitors

In Rwanda: 1st case was discovered in 1983 at CHK

HIV LIFE CYCLE

Binding and Fusion: HIV begins its life cycle when it binds to a **CD4 receptor** and one of two **co-receptors** on the surface of a CD4+ **T- lymphocyte**. The virus then fuses with the host cell. After fusion, the virus releases RNA, its genetic material, into the host cell.

Reverse Transcription: An HIV enzyme called reverse transcriptase converts the single-stranded HIV RNA to double-stranded HIV DNA.

Integration: The newly formed HIV DNA enters the host cell's nucleus, where an HIV enzyme called integrase "hides" the HIV DNA within the host cell's own DNA. The integrated HIV DNA is called provirus. The provirus may remain inactive for several years, producing few or no new copies of HIV.

Assembly: An HIV enzyme called protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins come together with copies of HIV's RNA genetic material, a new virus particle is assembled.

Budding: The newly assembled virus pushes out ("buds") from the host cell. During budding, the new virus steals part of the cell's outer envelope. This envelope, which acts as a covering, is studded with protein/sugar combinations called HIV glycoproteins. These HIV glycoproteins are necessary for the virus to bind CD4 and co- receptors. The new copies of HIV can now move on to infect other cells.

ARVS, CLASS & MECHANISM OF ACTION

CLASS	APPROVAL	EXAMPLES	MECHANISM
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS(NRTI)	1987	Zidovidine(azt),lamividine(3tc),stavidine(d4t),ddi,abc,ftc	Interfere with reverse transcriptase
NON nucleoside REVERSE TRANSCRIPTASE INHIBITORS(NnRTI)	1997	Nevirapine(nvp) Efavirenz(efv) Delavirdine(dlv)	Interfere with reverse transcriptase by stopping from replication within cell
PROTEASE INHIBITORS(PI)	1995	Lop/rit(kaletra) Nelfinavir(nfv) Indinavir,ritonavir	Interfere with protease
FUSION/ENTRY INHIBITORS	2003	Enfivirtine T20(fuseon)	Prevent from binding/entry
INTEGRASE INHIBITORS	2007		Interfere with integrase

KEY FACTORS IN HIV TREATMENT

There are three key factors:

- The virus which may be more or less aggressive
- The patient who will determine the success of the treatment
- The ARV which should be ideally efficacious over a long time with minimum side effects.

TREAMENT OUTCOMES

- ✓ Suppress the viral load to undetectable
- ✓ Increase the number of CD4 cells so as to improve the immune reconstitution
- ✓ Reduce the transmission of HIV
- ✓ Minimize the risk of cross resistance

- ✓ Minimize long term toxicity
- ✓ Improve the clinical status of the patient
- ✓ Improve the quality of life of the patient
- ✓ Minimize the cost of care

PRINCIPLES FOR SELECTION OF REGIMEN

It is necessary to block

- either block replication at several levels: combination of NRTI and PI
- Or block at the same level but through different but complementary mechanisms: NRTI with NNRTI

MAIN ASSOCIATIONS

- 2NRTIs+1NNRT(**1st line regimen**)
- 2NRTIs+1PI(**2nd line regimen**)

The association of 3 NRTIs is possible in extreme necessity or after expert opinion.

INITIATE HIV TREATMENT IN ADULT

Initial assessment:

- Full clinical examination
- Exclusion of active Tuberculosis
- CD4,FBC,ALAT &CREATININE

Eligibility criteria

Criteria for clinical & immunological eligibility

HIV+ and one or two of the following criteria:

- Any patient with WHO clinical stage 4,regargless of CD4 count
- Any patient WHO clinical stage 1,2 or 3 whose CD4 count <350/mm3

Social criteria

- Having disclosed HIV to one member in the family
- Accept to be visited at home
- Accept medication over the whole lifetime
- Have fixed residence within Rwanda
- Accept to make financial contribution
- Commit having protected sex intercourse

RECOMMENDED FIRST LINE TREATMENT

1.TDF(TENOFOVIR)+3TC/FTC(LAMIVIDINE)OREMITRICITABINE+ NVP(NEVIRAPINE)
2. TDF(TENOFOVIR)+3TC/FTC(LAMIVIDINE)OR EMITRICITABINE+ EFV(EFAVIRENZ)
3. ABC(ABACAVIR)+3TC (LAMIVIDINE) + EFV(EFAVIRENZ)
4. ABC(ABACAVIR)+3TC (LAMIVIDINE) + NVP(NEVIRAPINE)

First regimen:

1. TDF +3TC +NVP/EFV,
2. ABC +3TC +NVP/EFV

Second regimen:

1. TDF+3 TC+ Kaletra
2. ABC+3 TC+ Kaletra
3. AZT+3 TC+ Kaletra

NB:

1. Give EFV in case of allergy to NVP or patient on TB drugs, or patient with less than 9gr/dl of hemoglobin. **In HIV-tuberculosis co-infection, the first line treatment**

   Can be for e.g.: TDF (TENOFOVIR)+3TC/FTC(LAMIVIDINE) or EMITRICITABINE$_+$ EFAVIRENZ ~~NVP(NEVIRAPINE~~) plus *ANTI-TB*

2. Give ABC in case where TDF is CI (renal failure)

3. Give ABC instead of TDF when initiating ART in pregnant women

PRINCIPLE SIDE EFFECTS

SIDE EFFECTS	ARV
LIPODISTROPHY	**D4T,DDI,AZT , D4T+TDF or ABC**
ANEMIA	**AZT**
PANCREATITIS	**DDI+D4T also WITH AZT**

SIDE EFFECTS DUE TO NON NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTS)

NEVIRAPINE INDUCED DERMATOLOGIC TOXICITY

GRADE 1	GRADE 2	GRADE 3	GRADE 4
Erythema,	Widespread macula papular eruptions of dry	Appearance of blisters or humid	Affection of the mucosa,

Pruritis	desquamation	desquamation or ulceration or association with fever or pain.	Steven Johnson syndrome Multiform erytherma, necrosis

NEVIRAPINE INDUCED HEPATOTOXICITY

	NORMAL	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ALAT(SGPT) UI/L	<40	50-100	100-200	200-400	>400

EFAVIRENZ

- Skin rash 15-25% of patients
- CNS side effects 50% of patients: nightmares, vertigo, and insomnia.

PROTEASE INHIBITORS

- Insulin resistance
- Hyperlipidemia(increases glycerol &triglycelides)
- Lipodistrophy
- Hepatotoxicity. **Side effect common to all ARVs**

HIV-TUBERCULOSIS COINFECTION

Consequences of HIV on TB control

- Increases the number of Tuberculosis linked to HIV
- Late diagnosis: due to fear of the stigma attached to both TB-HIV
- Difficult in treating a 1 patient with two diseases at the same time in two separate clinics
- Difficult in diagnosis due to different clinical presentation of TB linked to HIV increases EXTRAPULMONARY TB
- High rate of relapse
- Risk of nosocomial infection/transmission
- Heavy workload in the TB and HIV clinics

NB: The treatment of TB is a priority and must be supervised (DOTS)

TREATMENT OF TB IN HIV/AIDS PATIENTS

SITUATION	RECOMMENDATION
Pulmonary TB&CD4<500/mm3 or Extra Pulmonary TB	Start anti-TB 2-8 weeks after the start of anti-TB, start one of the following regimen: TDF+3TC/FTC+EFV ABC+3TC+EFV For pregnant women in 1st trim.:AZT/D4T+3TC+ABC 2nd trim: ABC/AZT+3TC+EFV

Pulmonary TB &CD4 >500/mm3	Anti-TB treatment Do CD4 Test after 2months of anti TB treatment. If >500/mm3, continue anti-TB only <500/mm3, start ARV treatment

CLINICAL AND BIOLOGICAL FOLLOW UP OF PATIENT ON TREATMENT

DATE	CLINICAL	LABORATORY
Pre ARV	+	CD4,FBC,CREAT,GPT,X-RAY if clinical indication
D15	+adherence	None
M1	+adherence	None
M2	+adherence	None

M3	+adherence	FBC IF AZT, CREAT IF TDF,GPT if indicated
M4	+adherence	None
M5 M6	+adherence +adherence	None CD4,FBC,CREAT,if on TDF,GPT if indicated
Monthly for 1 year +adherence		❖ CD4 every 6 months ❖ VL every 12 months ❖ FBC ❖ Creatinine if on TDF ❖ GPT if clinically indicated

TREATMENT FAILURE

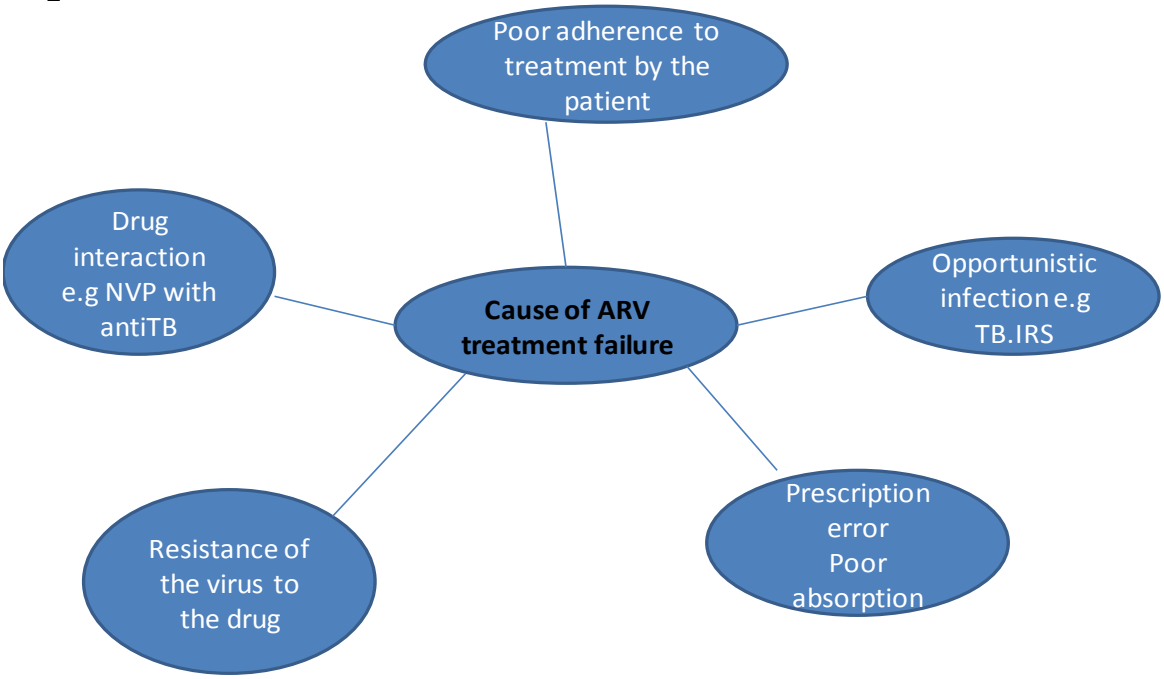
Clinical failure: occurrence of new OI, or malignancy reveals progession of disease to next stage (new WHO stage 4 condition).reocurence of previous OI.

Immunological failure: return of CD4 to pretreatment baseline or below (in absence of any concomitant infection that is liable to cause transient reduction of CD4),a fall >50%

Virological failure: detectable VL (40 copies/ml) after 12 months on treatments

Causes of treatment failure

-



IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

Inflammatory response in first 1-2 months following initiation of ARV among patient with latent TB(non active TB) which becomes active.

It is due to decreased CD4 and exagerated host response to ARVS

Its features are fever, adenopathy, pulmonaly and neurologic disorders

Common in infection with Mycobacterium tuberculosis

When it appears, don't stop ARVs **BUT** adjust.

POST EXPOSURE PROPHYLAXIS (PEP)

Accidental exposure to bloody /body fluids or rape (sex violence)

It has shown that initiating the prophylaxis early diminishes the risk of HIV infection by about 80%.

Criteria for prophylactic ARV treatment

- ✓ The severity of the exposure(r/t to depth of the wound and the type of wound).
- ✓ Venapuncture needle type.
- ✓ Less with skin contact than with blood being higher than other body secretions.

Treatment

Always clean the area immediately with clean water, rince with antiseptic: dakin, povidone,70% alcohol at least 5 minutes.

ARVs depends on HIV serostatus of the source and degree of exposure

Evaluation of degree of exposure

- **Massive exposure**: deep penetration with intravenous devices(IV)
- **Moderate exposure**: cut with a lancet through gloves superficial with IV OR IAN
- **Minimum exposure**: superficial bruise with a plain needle(suture) or a small caliber needle(SC/IM),contact with mucosa or skin

Maximum delay in implementing prophylaxis

- Given within 6 hours following the exposure without following the lab results of the source

- A limit of 48 hours is reasonable in seeking maximum efficacy.

Treatment duration

4 WEEKS (28 DAYS)

Choice of drugs

- TDF+3TC/FTC+KALETRA
- TDF+3TC/FTC+EFV

If no TDF or a Contraindication: AZT+3TC+KALETRA

Follow up

Person should be informed of

- Side effects
- Adherence
- Need for prevention

1.2 ACUTE CORYZA=COMMON COLD=COLD=NASOPHARYNGITIS=ACUTE VIRAL RHINOPHARYNGITIS

1.2.1 DEFINITION

It is the **common cold** (also known as **nasopharyngitis**, **acute viral rhinopharyngitis**, **acute coryza**, or **a cold**) (Latin: *rhinitis acuta catarrhalis*) is a viral infectious disease of the upper respiratory system, caused primarily by rhinoviruses and coronaviruses.

1.2.2 ETIOLOGY

The most commonly implicated virus is a rhinovirus (30–50%), a type of picornavirus with 99 known serotypes.Others include: coronavirus (10–15%), influenza (5–15%), humanparainfluenza viruses, human respiratory syncytial virus, adenoviruses, enteroviruses, and metapneumovirus.

1.2.3 TRANSMISSION

The common cold virus is transmitted mainly from contact with saliva or nasal secretions of an infected person, either directly, when a healthy person breathes in the virus-laden aerosol generated when an infected person coughs or sneezes, or by touching a contaminated surface and then touching the nose or eyes.

1.2.4 PATHOGENESIS

The major entry point for the virus is normally the nose, but can also be the eyes (in this case drainage into the nasopharynx would occur through the nasolacrimal duct). From there, it is transported to the back of the nose and the adenoid area. The virus then attaches to a receptor, ICAM-1, which is located on the surface of cells of the lining of the nasopharynx. The receptor fits into a docking port on the surface of the virus. Large amounts of virus receptor are present on cells of the adenoid. After attachment to the receptor, virus is taken into the cell, where it starts an infection, and increases ICAM-1 production, which in turn helps the immune response against the virus. Rhinovirus colds do not generally cause damage to the nasal epithelium.

Macrophages trigger the production of cytokines which, together with bradykinin, plays a major role in causing the local symptoms such as sore throat and nasal irritation.

The common cold is self-limiting, and the host's immune system effectively deals with the infection, specific antibodies, and leukocytes destroy the virus through phagocytosis and destroy infected cells to prevent further viral replication. In healthy, immunocompetent individuals, the common cold resolves in seven days on average.

1.2.4 SIGNS AND SYMPTOMS

Symptoms are cough, sore throat, runny nose, and nasal congestion; sometimes this may be accompanied by conjunctivitis (pink eye), muscle aches, fatigue, headaches, shivering, and loss of appetite. Fever is often present thus creating a symptom picture which overlaps with influenza.The symptoms of influenza however are usually more severe.

Those suffering from colds often report a sensation of chilliness even though the cold is not generally accompanied by fever, and although chills are generally associated with fever, the sensation may not always be caused by actual fever. In one study, 60% of those suffering from a sore throat and upper respiratory tract infection reported headaches,often due to nasal congestion. In the acute stage, the principal lesions are swollen face, watery eyes, rhinitis, nasal exudates that become crusty on the beak around nostrils and cheesy in nostrils and sinuses. Eyelids stick together by the exudate or an accumulation of cheesy exudate in the conjunctival sac. Early exudates are copious, grayish-yellowish, thick and sticky. Other lesions include tracheitis, bronchitis and on occasion air sacculitis. The exudates in the trachea produce raffling (rales)

1.2.5 PROGNOSIS

The common cold is generally mild and self-limiting. Pneumonia is a possible severe complication

1.2.6 COMPLICATIONS

There are numerous complications such as

Acute sinusitis

Acute laryngitis

Acute tonsillitis

Acute bronchitis

Pneumonia

Acute otitis

Sacculitis

1.2.7 DIAGNOSTIC

A presumptive diagnosis can be rendered ***on the history, progress of the disease and the lesions***. The organism can be demonstrated in a ***gram-stained smear*** of the nasal exudates. ***Cultures*** should be made from nostrils, eye, cleft and trachea plus lung or air sacs if lesions are present. Treatment should be started based on presumptive diagnosis

1.2.8 MANAGEMENT

There are currently no medications or herbal remedies which have been conclusively demonstrated to shorten the duration of infection in all people with cold symptoms.Treatment comprises symptomatic support usually via analgesics for fever, headache, sore muscles, and sore throat.

Symptomatic

Treatments that help alleviate symptoms include simple analgesics and antipyretics such as **ibuprofen** and **acetaminophen / paracetamol**

Symptoms of a runny nose can be reduced by a first **generation antihistamine**

Getting plenty of rest, drinking fluids to maintain hydration, and gargling with warm salt water, are reasonable conservative measures. Saline nasal drops may help alleviate nasal congestion.

Zinc supplements

Zinc may inhibit rhinovirus replication and reduce inflammation.

Vitamin C supplements

It may reduce the duration of illness.

Antibiotics and antiviral

The antibiotics should be used when suspecting surinfection especially after 7 days of unimprovement.

1.2.9 PREVENTION

The best prevention for the common cold is isolation. Regular hand washing is recommended to reduce transmission of cold viruses and other pathogens via direct contact.

Cleaning contaminated surfaces such as coffee cup handles with a mixed alcohol/phenol disinfectant has been shown to almost halve the chance of transmission via direct contact

Avoid the exposure to cold temperatures and wet weather has been found to facilitate viral infection, explaining why colds and flu are more prevalent in winter outside of tropical areas.

Common colds are produced by a large variety of rapidly mutating viruses; successful creation of a broadly effective vaccine is highly improbable.

1.3 INFLUENZA OR FLU

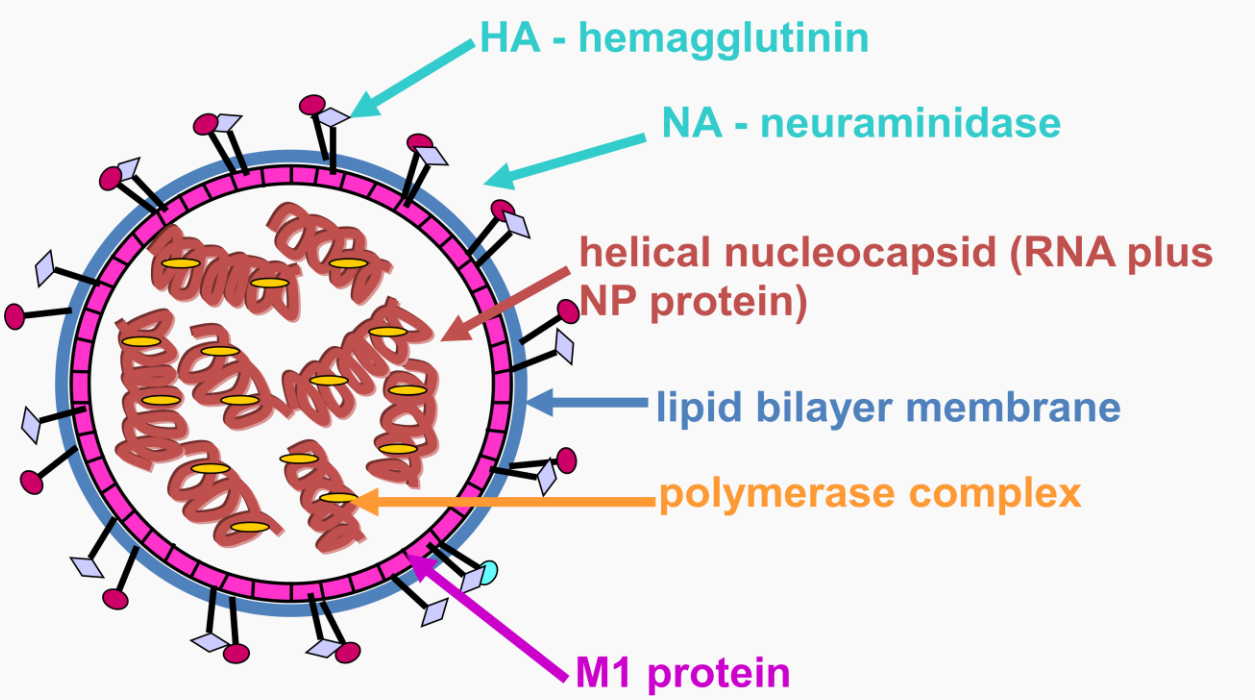
1.2.1. DEFINITION

Influenza, commonly referred to as the **flu**, is an infectious disease caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses), that affects the respiratory tract of many birds and mammals. The flu (or common flu) is a very contagious viral infection which is raised as epidemic.The disease is generally benign but it can become serious at the old person or debility

1.2.2 ETIOLOGY

The flu or Influenza is caused by the virus of the family the Orthomyxoviridae: myxovirus ABC (influenza virus A, B, and C)

Structure of the influenza



The hemagglutinin (HA) and neuraminidase (NA) proteins are shown on the surface of the particle.

In virus classification influenza viruses are RNA viruses that make up three of the five genera of the family Orthomyxoviridae:

- Influenzavirus A
- Influenzavirus B
- Influenzavirus C

Influenzavirus A: This genus has one species, influenza A virus. The type A viruses are the most virulent human pathogens among the three influenza types and cause the most severe disease. The influenza A virus can be subdivided into different serotypes based on the antibody response to these viruses. The serotypes that have been confirmed in humans, ordered by the number of known human pandemic deaths, are:

- H1N1, which caused Spanish Flu in 1918, and Swine Flu in 2009
- H2N2, which caused Asian Flu in 1957
- H3N2, which caused Hong Kong Flu in 1968

- H5N1, which caused Bird Flu in 2004
- H7N7, which has unusual zoonotic potential
- H1N2, endemic in humans, pigs and birds
- H9N2
- H7N2
- H7N3
- H10N7

Influenzavirus B: It has one species, influenza B virus and almost exclusively infects humans and is less common than influenza A

Influenzavirus C: it has one species, influenza C virus, which infects humans, dogs and pigs, sometimes causing both severe illness and local epidemics.

1.2.3 TRANSMISSION

Influenza can be spread by:

Direct transmission (when an infected person sneezes mucus directly into the eyes, nose or mouth of another person);

Through hand-to-eye, hand-to-nose, or hand-to-mouth transmission, either from contaminated surfaces or from direct personal contact such as a hand-shake.

Avian influenza viruses can survive indefinitely when frozen. They are inactivated by heating to 56 °C (133 °F) for a minimum of 60 minutes, as well as by acids (at pH <2).

1.2.4 PATHOGENESIS

Essentially related to the viral hemagglutinin protein which is responsible for determining both which species a strain can infect and where in the human respiratory tract a strain of influenza will bind. Strains that are easily transmitted between people have hemagglutinin proteins that bind to receptors in the upper part of the respiratory tract, such as in the nose, throat and mouth. In contrast, the highly lethal H5N1 strain binds to receptors that are mostly found deep in the lungs. This difference in the site of infection may be part of the reason why the H5N1 strain

causes severe viral pneumonia in the lungs, but is not easily transmitted by people coughing and sneezing.Common symptoms of the flu such as fever, headaches, and fatigue are the result of the huge amounts of proinflammatory cytokines and chemokines (such as interferon or tumor necrosis factor) produced from influenza-infected cells. In contrast to the rhinovirus that causes the common cold, influenza does cause tissue damage, so symptoms are not entirely due to the inflammatory response. This massive immune response might produce a life-threatening cytokine storm. This effect has been proposed to be the cause of the unusual lethality of both the H5N1 avian influenza, and the 1918 pandemic strain. However, another possibility is that these large amounts of cytokines are just a result of the massive levels of viral replication produced by these strains, and the immune response does not itself contribute to the disease.

1.2.5 SIGNS AND SYMPTOMS

The influenza is a very polymorphic affection. The most usual form is the respiratory form. The disease is usually most severe in very young children (under 5 years of age) and the elderly. Young children often lack antibodies to the influenza virus because of no prior exposure. In addition, the small diameter of components of the respiratory tract in the very young also means that inflammation and swelling can lead to blockage of parts of respiratory tract, sinus system or Eustachian tubes. In the elderly, influenza is often severe because of an underlying decreased effectiveness of the immune system and/or chronic obstructive pulmonary disease or chronic cardiac disease.

- **Incubation**: is two to five days
- **Invasion**: The beginning is brutal with temperature of 40^0cwith shills and aches in a few hours
- **Phase of state**: Once declared, the influenza is characterized by the association of the ache, fever and catarrh of the respiratory tracts. The fever is generally raised, often the thermal curve drops to 3 or 4^{th} days, to begin again then thus drawing the V of the flu.
- It is accompanied by the general signs of the infection particularly of asthma.
    - The severe headache diffuses, irradiated to the frontal sinuses and jawbones.
    - It is accompanied by the various aches, rachialgia, myalgia, etc…

- The oculo-nasal catarrh is intense, throat is red, fitfull(quinteuse) cough and the raucousness of the voice testify the Laryngo-Tracheal attack.

Nausea, vomiting, and diarrhea can sometimes accompany influenza infection.

Novel H1N1 infections cause more nausea, vomiting, and diarrhea than the conventional (seasonal) flu viruses.

1.2.6 DIAGNOSTIC

It is based on the history, physical examination and, in some instances, laboratory testing before treatment is initiated. However, it is very difficult to distinguish influenza from viral and bacterial causes of respiratory illness on the basis of symptoms alone.

The table below shows the distinction from influenza and common cold

TABLE: **Comparison of Influenza and the Common Cold**

Features	***Influenza***	***Common cold***
Onset*	Abrupt	More gradual
Fever*	Common: 37.7°C to 40.0°C (100°F to 104°F)	Uncommon or only 0.5°C (1°F) increase
Myalgia*	Severe, common	Uncommon
Arthralgia	Severe, common	Uncommon
Anorexia	Common	Uncommon
Headache	Severe, common	Mild, uncommon
Cough (dry)*	Common, severe	Mild to moderate
Malaise	Severe	Mild
Fatigue, weakness	More common than with the common cold; lasts 2 to 3 weeks	Very mild, short lasting
Chest discomfort	Common, severe	Mild to moderate
Stuffy nose	Occasional	Common

Features	*Influenza*	*Common cold*
Sneezing	Occasional	Common
Sore throat	Occasional	Common

*—*Clusters of more severe or common features may be more likely to predict influenza*

Virus Isolation – Throat and nose swabs, It is reported that nasal washings are the best specimens for virus isolation. Tissue culture or eggs

Rapid Diagnosis by Immunofluorescence - cells from pathological specimens may be examined for the presence of influenza A and B antigens by indirect immunofluorescence.

PCR assays for the detection of influenza RNA have also been developed but their usefulness in a clinical setting is highly questionable.

Serology - Virus cannot be isolated from all cases of suspected infection.

1.2.7 EVOLUTION

It is of short duration in few days, the symptoms attenuate, cough becomes loose and is accompanied by a purulent expectoration. At the end of the influenza, the patient remains asthenic and convalescence is often long.

1.2.8 PROGNOSIS

Influenza's effects are much more severe and last longer than those of the common cold. Most people will recover completely in about one to two weeks, but others will develop life-threatening complications (such as pneumonia). Influenza, thus, can be deadly, especially for the weakimmune system, young and old, or chronically ill.

Below are the major causes of influenza virus- associated death

- Bacterial pneumonia
- Cardiac failure

- 90% of deaths in those over 65 years of age

1.2.9 CLINICAL FORMS

Respiratory or thoracic form

Gastro-intestinal form with vomiting and diarrhea,

Nervous form pseudo-meningitis which is malignant form resulting in death in a few days. It is a major form of deep toxi-infection.

1.2.10 COMPLICATIONS

Pulmonary complications

- Upper respiratory tract infection (URTI)
  - otitis media
  - sinusitis
- Lower respiratory tract infection (LRTI)
  - exacerbation of asthma/chronic obstructive pulmonary disease (COPD)
  - croup, bronchiolitis or Acute laryngotracheobronchitis in young children :symptoms include cough (like a barking seal), difficulty breathing, stridor (crowing sound during inspiration)
  - primary viral pneumonia (rare*)
  - secondary bacterial pneumonia: This often involves *Streptococcus pneumoniae, Staphylococcus aureus, Hemophilusinfluenzae* (surinfection).The buildup of fluids and lack of mucociliary clearance in the respiratory tract provide a good environment for bacterial growth.

Complications often occur in patients with underlying chronic obstructive pulmonary or heart disease. The underlying problems may not have been recognized prior to the influenza infection.

Non-pulmonary complications of influenza

- myositis (rare, > in children, > with type B)
- cardiac complications:pericardiatis,myocarditis
- recent studies report encephalopathy
  - studies of patients <21 yrs in Michigan 8 cases seen last season
- liver and CNS
  - Reye syndrome : even if its origin is unclear ,it seems to be due to the fatty deposits in the liver and edema in the brain. It includes vomiting, lethargy and may result in coma. The risk factors include youth, certain viral infections (influenza, chicken pox) and the treatment use of aspirin(risk factor in the development Reye's syndrome).
- Peripheral nervous system
  - Guillian-Barré syndrome (acute idiopathic polyneuritis) :The cause of this syndrome in the central nervous system is mysterious. It is an autoimmune disease that can follow a viral or bacterial infection.

Others influenza related complications

Decompensation of chronic diseases

- pulmonary disease
- heart disease
- renal insufficiency
- metabolic disease
- Gastrointestinal bleeding – in children
- Decompensation of pre-existing pathology
- Excess mortality
- Possible association with prenatal exposure and schizophrenia

Influenza complications in children

- Higher fever than in adults>convulsions & dehydration
- Higher incidence of coryza, otitis media and gastrointestinal manifestations
- Influenza may present as croup or bronchiolitis
- Higher incidence of drowsiness and delirium
- Complications like myositis and pneumonia are more frequent

Influenza complicatios in pregnancy : Increased vulnerability during the second and third trimester, possible consequences are :

- Severe pulmonary complications and death for pregnant woman
- Foetalloss and abortion
- Otherrisks
  - foetal complications (growth, weight, etc.)
  - brain damage
  - neural tube defects

1.2.11 GROUPS AT HIGHER RISK OF COMPLICATIONS

- Elderly (> 60 years of age), especially in residential care units
- Children and teenagers (6 months–18 years of age) receiving long-term aspirin therapy
- Pregnant women belonging to high-risk groups
- Patients with:
  - chronic respiratory disease, e.g. asthma, chronic obstructive pulmonary disease(COPD)
  - chronic heart disease
  - chronic metabolic disease, e.g. diabetes mellitus
  - immunosuppression due to treatment or disease, e.g. HIV
  - haematological disorders
  - chronic renal failure

1.2.12. TREATMENT

People with the flu are advised to get plenty of rest, drink plenty of liquids, avoid using alcohol and tobacco and, if necessary, take medications such as acetaminophen (paracetamol) to relieve the fever and muscle aches associated with the flu. Children and teenagers with flu symptoms should avoid taking aspirin during an influenza infection (especially influenza type B), because doing so can lead to Reye's syndrome. Since influenza is caused by a virus, antibiotics have no effect on the infection; unless prescribed for secondary infections such as bacterial pneumonia.

Neuraminidase inhibitors

Antiviral drugs such as Tamiflu) and zanamivir (trade name Relenza) are neuraminidase inhibitors that are designed to halt the spread of the virus in the body. These drugs are often effective against both influenza A and B and therefore were concluded that they reduce symptoms and complications.

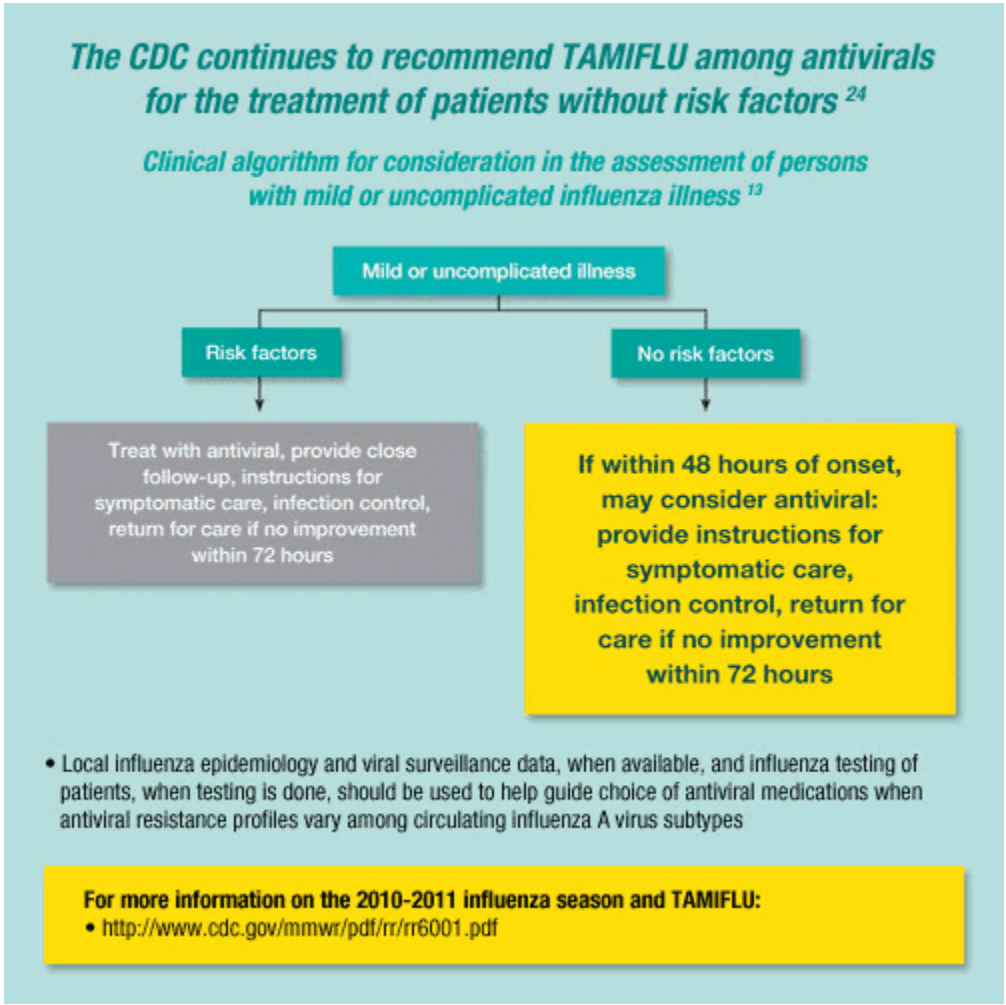
Managing Influenza with Tamiflu

According to the CDC, antiviral medications can also be effective at treating and preventing influenza.

Treatment	Prevention
Antiviral treatment should be started within 48 hours of influenza illness onset Treatment should not be delayed while the results of diagnostic testing are awaited	As an adjunct to vaccination, antivirals are 68% to 89% effective in preventing influenza Post exposure chemoprophylaxis is typically administered for a total of no more than 10 days after the most recent known exposure

Antiviral treatment also can be considered for any previously healthy, non-high-risk, symptomatic outpatient with confirmed or suspected influenza based upon clinical judgment, if treatment can be initiated within 48 hours of illness onset	Generally, post exposure chemoprophylaxis for persons should be only used when antivirals can be started within 48 hours of the most recent exposure

2011 Flu Treatment Guidelines from the Centers for Disease Control and Prevention



Indications and Limitations of Use

TAMIFLU is indicated in patients 1 year and older for the treatment of uncomplicated influenza caused by viruses types A and B who have been symptomatic for no more than 2 days and for the prophylaxis of influenza

Vaccination

Vaccination against influenza with an influenza vaccine is often recommended for high-risk groups, such as children and the elderly, or in people who have asthma, diabetes, heart disease, or are immuno-compromised.

Infection control

Good personal health and hygiene habits such as: not touching your eyes, nose or mouth; frequent hand washing (with soap and water, or with alcohol-based hand rubs); covering coughs and sneezes; avoiding close contact with sick people; and staying home yourself if you are sick. Avoiding spitting is also recommended.

1.3 CHICHEN POX

1.3.1 DEFINITION

Chickenpox or **chicken pox** is a highly contagious illness caused by primary infection with varicella zoster virus (VZV). It usually starts with vesicular skin rash mainly on the body and head rather than at the periphery and becomes itchy, raw pockmarks, which mostly heal without scarring.

1.3.2 ETIOLOGY

Chickenpox is caused by the varicella-zoster virus (VZV), also known as human herpes virus 3 (HHV-3), one of the eight herpes viruses known to affect humans.

1.3.3 TRANSMISSION

Chickenpox is an airborne disease spread easily through coughing or sneezing of ill individuals or through direct contact with secretions from the rash. A person with chickenpox is infectious one to two days before the rash appears. The contagious period continues for 4 to 5 days after the

appearance of the rash, or until all lesions have crusted over. Immuno-compromised patients are probably contagious during the entire period new lesions keep appearing. Crusted lesions are not contagious.

1.3.4 EPIDEMILOGY

Primary varicella is a disease that is endemic to all countries worldwide. In temperate countries, **chickenpox** is primarily a disease of children, with most cases occurring during the winter and spring, most likely due to school contact. It is one of the classic diseases of childhood, with the highest prevalence in the 4–10 year old age group. Like rubella, it is uncommon in preschool children. Varicella is highly communicable, with an infection rate of 90% in close contacts. In temperate countries, most people become infected before adulthood but 10% of young adults remain susceptible. In the tropics, chickenpox often occurs in older people and may cause more serious disease. In adults the pock marks are darker and the scars more prominent than in children.

1.3.5 PATHOGENESIS

Exposure to VZV in a healthy child initiates the production of antibodies that can persist for life and confer immunity. Cell-mediated immune responses are also important in limiting the scope and the duration of primary varicella infection. After primary infection, VZV is hypothesized to spread from mucosal and epidermal lesions to local sensory nerves. VZV then remains latent in the dorsal ganglion cells of the sensory nerves. Reactivation of VZV results in the clinically distinct syndrome of herpes zoster (i.e., *shingles*), and sometimes Ramsay Hunt syndrome type II. In pregnant women, antibodies produced as a result of immunization or previous infections are transferred via the placenta to the fetus. Women who are immune to chickenpox cannot become infected and do not need to be concerned about it for themselves or their infant during pregnancy.Varicella infection in pregnant women could lead to viraltransmission via the placenta and infection of the fetus. If infection occurs during the first 28 weeks of gestation, this can lead to fetal varicella syndrome (also known as *congenital varicella syndrome*). While a late infection in gestation or immediately following birth is referred to as "*neonatal varicella*. Effects on the fetus can range in severity from underdeveloped toes and fingers to severe anal and bladder malformation

1.3.6 SIGNS AND SYMPTOMS

It takes from 10 to 21 days after contact with an infected person for someone to develop chickenpox. The contagious period continues for 4 to 5 days after the appearance of the rash, or until all lesions have crusted over. Immunocompromised patients are probably contagious during the entire period new lesions keep appearing. Crusted lesions are not contagious. The onset of illness with chickenpox is often characterized by symptoms including myalgia, nausea, fever, headache, sore throat, pain in both ears, complaints of pressure in head or swollen face, and malaise in adolescents and adults. In children, the first symptom is usually the development of a papular rash, followed by development of malaise, fever (a body temperature of 38 °C (100 °F), but may be as high as 42 °C (108 °F) in rare cases), and anorexia. Typically, the disease is more severe in adults. Chickenpox is rarely fatal, although it is generally more severe in adult males than in adult females or children. Non-immune pregnant women and those with a suppressed immune system are at highest risk of serious complications. Chickenpox is believed to be the cause of one third of stroke cases in children. The most common late complication of chickenpox is shingles, caused by reactivation of the **varicella zoster** virus decades after the initial episode of chickenpox. Note also that Chickenpox has been observed in other primates, including chimpanzees and gorillas.

1.3.7 COMPLICATIONS

In adults, the disease is more severe, though the incidence is much less common. Infection in adults is associated with greater morbidity and mortality due to pneumonia, hepatitis, and encephalitis.Inflammation of the brain, or encephalitis, can occur in immunocompromised individuals, although the risk is higher with herpes zoster. Necrotizing fasciitis is also a rare complication.Varicella is a particular problem in hospitals, especially when there are patients with immune systems weakened by drugs (e.g., high-dose steroids) or HIV. Secondary bacterial infection of skin lesions, manifesting as impetigo, cellulitis, and erysipelas, is the most common complication in healthy children. Disseminated primary varicella infection usually seen in the immunocompromised may have high morbidity. Rarer complications of disseminated chickenpox also include myocarditis, hepatitis, and glomerulonephritis. Hemorrhagic complications are more common in the immunocompromised or immunosuppressed populations,

although healthy children and adults have been affected. Malignant chickenpox with purpura is a grave clinical condition that has a mortality rate of greater than 70%. The etiology of these hemorrhagic chickenpox syndromes is not known.

Note that the immune system keeps the virus at bay, but later in life, usually as an adult, it can be reactivated and cause a different form of the viral infection called shingles (scientifically known as **herpes zoster**).

If infection occurs during the first 28 weeks of gestation, this can lead to fetal varicella syndrome (also known as *congenital varicella syndrome*). Effects on the fetus can range in severity from underdeveloped toes and fingers to severe anal and bladder malformation. Possible problems include:

- **Damage to brain:**encephalitis, microcephaly, hydrocephaly, aplasia of brain
- **Damage to the eye**: optic stalk, optic cup, and lens vesicles, microphthalmia, cataracts, chorioretinitis, optic atrophy
- **Other neurological disorder**: damage to cervical and lumbosacral spinal cord, motor/sensory deficits, absent deep tendon reflexes, anisocoria/Horner's syndrome
- **Damage to body**: hypoplasia of upper/lower extremities, anal and bladder sphincter dysfunction
- **Skin disorders**: (cicatricial) skin lesions, hypopigmentation
- ***Neonatal varicella***
- Newborns who develop symptoms are at a high risk of pneumonia and other serious complications of the disease.

1.3.8 DIAGNOSIS

The diagnosis of varicella is primarily clinical, with typical early "prodromal" symptoms, and then the characteristic rash. Confirmation of the diagnosis can be sought through either examination of the fluid within the vesicles of the rash, or by testing blood for evidence of an acute immunologic response. Vesicular fluid can be examined with a Tsanck smear, or better with examination for direct fluorescent antibody. The fluid can also be "cultured", whereby attempts are made to grow the virus from a fluid sample. Blood tests can be used to identify a

response to acute infection (IgM) or previous infection and subsequent immunity (IgG). Prenatal diagnosis of fetal varicella infection can be performed using ultrasound, though a delay of 5 weeks following primary maternal infection is advised. A PCR (DNA) test of the mother's amniotic fluid can also be performed, though the risk of spontaneous abortion due to the amniocentesis procedure is higher than the risk of the baby developing foetal varicella syndrome

1.3.9 TREATMENT

Local antiseptic, antibiotherapy when cutaneous surinfection , antihistamine and acyclovir are recommended . Some treatments are however available for relieving the symptoms while the immune system clears the virus from the body. It is important to maintain good hygiene and daily cleaning of skin with warm water to avoid secondary bacterial infection. To relieve the symptoms of chicken pox, people commonly use anti-itching creams and lotions. Treatment with antiviral drugs (e.g. **acyclovir or valacyclovir**) is generally advised.

1.3.10 PREVENTION

Hygiene measures

The spread of chicken pox can be prevented by isolating affected individuals. The chicken pox virus (VZV) is susceptible to disinfectants, notably chlorine bleach (i.e., sodium hypochlorite). Also, like all enveloped viruses, VZV is sensitive to desiccation, heat and detergents. Therefore these viruses are relatively easy to kill.

Vaccine

Some countries require the varicella vaccination or an exemption before entering elementary school. The chickenpox vaccine is not part of the routine childhood vaccination schedule in the Rwanda

1.4 SHINGLES /ZONA/ZOSTER/HERPES ZOSTER

1.4.1 DEFINITION

Herpes zoster (or simply **zoster**), commonly known as **shingles** and also known as **zona**, is a viral disease characterized by a painful skin rash with blisters in a limited area on one side of the body, often in a stripe.

1.4.2 ETIOLOGY

The causative agent for herpes zoster is varicella zoster virus (VZV), a double-stranded DNA virus related to the Herpes simplex virus group .The same varicella-zoster virus causes chickenpox

1.4.3 TRANSMISSION /REACTIVATION

Varicella zoster virus (VZV) has a high level of infectivity and has a worldwide prevalence. Herpes zoster is a re-activation of latent VZV infection: this means that zoster can only occur in someone who has previously had chickenpox (varicella). It has a strong relationship with increasing age. Another important risk factor is immunocompromised: HIV is an important example of immune compromise. Other risk factors include psychological stress. Other potential risk factors include mechanical trauma, and exposure to immunotoxins.

1.4.4 PATHOGENESIS

Herpes zoster occurs only in people who have had chickenpox, and although it can occur at any age, the majority of sufferers are more than 50 years old. Most people are infected with this virus as children, and suffer from an episode of chickenpox. The immune system eventually eliminates the virus from most locations, but it remains dormant (or latent) in the ganglia adjacent to the spinal cord (called the dorsal root ganglion) or the ganglion semilunare (ganglion Gasseri) in the

base of the skull. Repeated attacks of herpes zoster are rare, and it is extremely rare for patients to suffer more than three recurrences. The disease results from the virus reactivating in a single sensory ganglion. Unless the immune system is compromised, it suppresses reactivation of the virus and prevents herpes zoster. It is more likely to occur in people whose immune system is impaired due to aging, immunosuppressive therapy, psychological stress, or other factors. Upon reactivation, the virus replicates in the nerve cells, and virions are shed from the cells and carried down the axons to the area of skin served by that ganglion. In the skin, the virus causes local inflammation and blisters. The short- and long-term pain caused by herpes zoster comes from the widespread growth of the virus in the infected nerves, which causes inflammation.

As with chickenpox and/or other forms of herpes, direct contact with an active rash can spread VZV to a person who has no immunity to the virus. This newly infected individual may then develop chickenpox, but will not immediately develop shingles. Until the rash has developed crusts, a person is extremely contagious. A person is also not infectious before blisters appear, or during postherpetic neuralgia (pain after the rash is gone)

1.4.5 SIGNS AND SYMPTOMS

The first symptom is usually one-sided pain, tingling, or burning. The pain and burning may be severe and is usually present before any rash appears.

Red patches on the skin, followed by small blisters, form in most people.

- The blisters break, forming small ulcers that begin to dry and form crusts. The crusts fall off in 2 to 3 weeks. Scarring is rare.
- The rash usually involves a narrow area from the spine around to the front of the belly area or chest.
- The rash may involve face, eyes, mouth, and ears.

Additional symptoms may include:

- Abdominal pain
- Chills

- Difficulty moving some of the muscles in the face
- Drooping eyelid (ptosis)
- Fever and chills
- General ill-feeling
- Genital lesions
- Headache
- Hearing loss
- Joint pain
- Loss of eye motion
- Swollen glands (lymph nodes)
- Taste problems
- Vision problems

Patient may also have pain, muscle weakness, and a rash involving different parts of your face if shingles affects a nerve in your face.

Zoster sine herpete ("zoster without herpes") describes a patient who has all of the symptoms of herpes zoster except this characteristic rash. Later the rash becomes vesicular, forming small blisters filled with a serous exudate, as the fever and general malaise continue. The painful vesicles eventually become cloudy or darkened as they fill with blood, crust over within seven to ten days; usually the crusts fall off and the skin heals, but sometimes, after severe blistering, scarring and discolored skin remain

Herpes zoster may have additional symptoms, depending on the dermatome involved. *Herpes zoster ophthalmicus* involves the orbit of the eye and occurs in approximately 10–25% of cases. It is caused by the virus reactivating in the ophthalmic division of the trigeminal nerve. In a few patients, symptoms may include conjunctivitis, keratitis, uveitis, and optic nervepalsies that can sometimes cause chronic ocular inflammation, loss of vision, and debilitating pain. *Herpes zoster oticus*, also known as Ramsay Hunt syndrome type II, involves the ear. It is thought to result from the virus spreading from the facial nerve to the vestibulocochlear nerve. Symptoms include hearing loss and vertigo (rotational dizziness)

1.4.6 COMPLICATIONS

About one in five patients develops a painful condition called postherpetic neuralgia, which is often difficult to manage. In some patients, herpes zoster can reactivate presenting as *zoster sine herpete*: pain radiating along the path of a single spinal nerve (a *dermatomal distribution*), but without an accompanying rash. This condition may involve complications that affect several levels of the nervous system and cause multiple cranialneuropathies, polyneuritis, myelitis, or aseptic meningitis. Other serious effects that may occur in some cases include partial facial paralysis (usually temporary), ear damage, or encephalitis. During pregnancy, first infections with VZV, causing chickenpox, may lead to infection of the fetus and complications in the newborn, but chronic infection or reactivation in shingles are not associated with fetal infection. There is a slightly increased risk of developing cancer after a herpes zoster infection. Although herpes zoster typically resolves within 2 weeks, certain complications may arise:

- Secondary bacterial infection
- Motor involvement - including weakness especially in "motor herpes zoster"
- Eye involvement - trigeminal nerve involvement (as seen in herpes ophthalmicus) should be treated early and aggressively as it may lead to blindness. Involvement of the tip of the nose in the zoster rash is a strong predictor of herpes ophthalmicus.
- Postherpetic neuralgia - a condition of chronic pain following herpes zoster

Other complications may include:

- Another attack of shingles
- Deafness
- Infection, including encephalitis or sepsis (blood infection) in persons with weakened immune systems
- Ramsay Hunt syndrome if shingles affected the nerves in the face

1.4.7 DIAGNOSIS

It is made by looking clinical features and medical history taking. If the rash has appeared, identifying this disease only requires a visual examination, since very few diseases produce a

rash in a dermatomalpattern . The Tsanck smear is helpful for diagnosing acute infection with a herpes virus, but does not distinguish between HSV and VZV. The most popular test detects VZV-specific IgM antibody in blood; this only appears during chickenpox or herpes zoster and not while the virus is dormant. In larger laboratories, lymph collected from a blister is tested by polymerase chain reaction for VZV DNA, or examined with an electron microscope for virus particles.

1.4.8 TREATMENT

The aims of treatment are to limit the severity and duration of pain, shorten the duration of a shingles episode, and reduce complications. Symptomatic treatment is often needed for the complication of postherpetic neuralgia.

Strong anti-inflammatory medicines called corticosteroids, such as prednisone, may be used to reduce swelling and the risk of continued pain. These drugs do not work in all patients. Other medicines may include:

- Antihistamines to reduce itching (taken by mouth or applied to the skin)
- Pain medicines
- Zostrix, a cream containing capsaicin (an extract of pepper) that may reduce the risk of post herpetic neuralgia

Cool wet compresses can be used to reduce pain. Soothing baths and lotions may help to relieve itching and discomfort. Resting in bed until the fever goes down is recommended. The skin should be kept clean, and contaminated items should not be reused. Nondisposable items should be washed in boiling water or otherwise disinfected before reuse. The person may need to be isolated while lesions are oozing to prevent infecting other people who have never had chickenpox especially pregnant women.

1.4.9 PREVENTION

Avoid touching the rash and blisters of persons with shingles or chickenpox if you have never had chickenpox or the chickenpox vaccine. A herpes zoster vaccine is available. Older adults who receive the herpes zoster vaccine are less likely to have complications from shingles.

1.4.10 PROGNOSIS (EXPECTATION)

The rash and pain usually subside within three to five weeks, but about one in five patients develops a painful condition called **postherpetic neuralgia**, which is often difficult to manage. In some patients, herpes zoster can reactivate presenting as *zoster sine herpete*: pain radiating along the path of a single spinal nerve (a *dermatomal distribution*), but without an accompanying rash. This condition may involve complications that affect several levels of the nervous system and cause multiple cranial neuropathies, polyneuritis, myelitis, or aseptic meningitis .

1.5 VIRAL HEMORRHAGIC FEVERS

The **viralhemorrhagicfevers** (**VHFs**) are a diverse group of animal and human illnesses that are caused by four distinct families of RNA viruses: the Arenaviridae, Filoviridae, Bunyaviridae, and Flaviviridae. All types of VHF are characterized by fever and bleeding disorders and all can progress to high fever, shock and death in extreme cases.

Etiologic agents

- The Arenaviridae include the viruses responsible for Lassa fever and Argentine, Bolivian, Brazilian and Venezuelan hemorrhagic fevers.
- The Bunyaviridae include the members of the *Hantavirus* genus that cause hemorrhagic fever with renal syndrome (HFRS), the Crimean-Congo hemorrhagic fever (CCHF) virus from the *Nairovirus* genus, and the Rift Valley fever (RVF) virus from the *Phlebovirus* genus.
- The Filoviridae include Ebola and Marburg viruses.
- Finally, the Flaviviridae include dengue, yellow fever, and two viruses in the tick-borne encephalitis group that cause VHF: Omsk hemorrhagic fever virus and Kyasanur Forest disease virus.

The most recently recognized virus capable of causing hemorrhagic fever is Lujo virus, a new member of the arenaviruses described in 2009 and found in South Africa.

Pathophysiology

The diversity of clinical features seen among the VHF infections probably originates from varying mechanisms of pathogenesis. An immunopathogenic mechanism, for example, has been identified for dengue hemorrhagic fever, which usually occurs among patients previously infected with a heterologous dengue serotype. An influential theory explaining this phenomenon is called "antibody-dependent enhancement." In contrast, disseminated intravascular coagulation (DIC) is thought to underlie the hemorrhagic features of Rift Valley, Marburg and Ebola fevers. In most VHFs, however, the etiology of the coagulopathy is most likely multifactorial (e.g., hepatic damage, consumptive coagulopathy, primary marrow dysfunction, etc).

The reasons for variation among patients infected with the same virus are unknown but stem from a complex system of virus-host interactions. Moreover, why some infected persons develop full-blown VHF while others do not also remains an unresolved issue. Virulence of the infecting agent clearly plays an important role. The "VHF syndrome" (capillary leak, bleeding diathesis and hemodynamic compromise leading to shock) occurs in a majority of patients manifesting disease from filoviruses, CCHF and the South American hemorrhagic fever viruses, while it occurs in a small minority of patients with dengue, RVF and Lassa fever.

Transmission

Bats drop partially eaten fruits and pulp, terrestrial mammals such as gorillas and duikers feed on these fallen fruits. This chain of events forms a possible indirect means of transmission from the natural host to animal populations, which have led to research towards viral shedding in the saliva of bats. Fruit production, animal behavior, and other factors vary at different times and places which may trigger outbreaks among animal populations Transmission between natural reservoirs and humans rare, and outbreaks are usually traceable to a single index case where an individual has handled the carcass of gorilla, chimpanzee, or duiker. The virus then spreads person-to-person, especially within families, hospitals, and during some mortuary rituals where contact among individuals becomes more likely.

The virus has been confirmed to be transmitted through body fluids. Transmission through oral exposure and through conjunctiva exposure is likely, which have been confirmed in non-human primates. Filoviruses are not naturally transmitted by aerosol. They are, however, highly infectious as breathable 0.8-1.2 micron droplets in laboratory conditions; because of this potential route of infection, these viruses have been classified as Category A biological weapons.

All epidemics of Ebola have occurred in sub-optimal hospital conditions, where practices of basic hygiene and sanitation are often either luxuries or unknown to caretakers and where disposable needles and autoclaves are unavailable or too expensive. In modern hospitals with disposable needles and knowledge of basic hygiene and barrier nursing techniques, Ebola has never spread on a large scale. In isolated settings such as a quarantined hospital or a remote village, most victims are infected shortly after the first case of infection is present. The quick onset of symptoms from the time the disease becomes contagious in an individual makes it easy to identify sick individuals and limits an individual's ability to spread the disease by traveling. Because bodies of the deceased are still infectious, some doctors had to take measures to properly dispose dead bodies in a safe manner despite local traditional burial rituals.

EBOLA

Ebola is the virus Ebolavirus (EBOV), a viral genus, and the disease is Ebola hemorrhagic fever (EHF), a viral hemorrhagic fever (VHF).

SIGNS AND SYMPTOMS

The incubation period ranges from 2–21 days, although it is generally 5–18 days. Illness is characterized by the rapid onset of fever, malaise, muscle pain, headache, and the inflammation of the pharynx. Six days following vomiting and bloody diarrhea, individuals may develop maculopapular rash with bleeding at needle sites and bodily orifices.

Reston ebolavirus is non-pathogenic to humans and individuals often do not show any symptoms, although it is fatal in monkeys. There is only one known case of Ivory Coast ebolavirus. There has been only one outbreak of Bundibugyoebolavirus Zaire virus, then Sudan ebolavirus, is the most common. Symptoms include: abdominal pain, fever, headache, bloody

vomit, Maculopapular rash, malaise, joint and muscle pain, inflammation of the pharynx , blood fails to clot , chest pain , CNS involvement (rare), dry and sore throat , hemorrhagic diathesis (71%-78%), hiccups , non-bloody diarrhea (81%), vomiting (59%). Purpura, petechia, sclerotic arterioles, and low blood-pressure are characteristic as the disease progresses.

DIAGNOSIS

Before outbreaks are confirmed in areas of weak surveillance on the local or regional levels ebola is often mistaken for malaria, typhoid fever, dysentery, influenza, or various bacterial infections which may be endemic to the region. Learning from the failure response such as the 2000 Uganda outbreak, public health measures such as the WHO's Global Outbreak and Response Network were instituted in areas at high risk. Field laboratories were established in order to confirm cases as to shipping samples to South Africa.

Methods of diagnosis of Ebola include testing saliva and urine samples. Ebola is diagnosed with an Enzyme-Linked ImmunoSorbent Assay (ELISA) test.

PREVENTION

In the early stages, Ebola may not be highly contagious. Contact with someone in early stages may not even transmit the disease. As the illness progresses, bodily fluids from diarrhea, vomiting, and bleeding represent a hazard. In such conditions, immediately cease all needle-sharing or use without adequate sterilization procedures, isolate patients, and observe strict barrier nursing procedures with the use of a medical rated disposable face mask, gloves, goggles, and a gown at all times. This should be strictly enforced for all medical personnel and visitors.

TREATMENT

There is no standard treatment for Ebola hemorrhagic fever. Treatment is primarily supportive and includes minimizing invasive procedures, balancing electrolytes, and, since patients are frequently dehydrated, replacing lost coagulation factors to help stop bleeding, maintaining oxygen and blood levels, and treating any complicating infections.

PROGNOSIS

Ebola hemorrhagic fever is potentially lethal and encompasses a range of symptoms including fever, vomiting, diarrhea, generalized pain or malaise, and sometimes internal and external bleeding. The span of time from onset of symptoms to death is usually between 2 and 21 days.

MARBURG VIRUS

Marburg virus or simply Marburg is the common name for the genus of viruses *Marburgvirus*, which contains one species, *Lake Victoria marburgvirus*. The virus causes the disease Marburg Hemorrhagic Fever (MHF), also referred to as *Marburg Virus Disease*, and previously also known as *green monkey disease* due to its primate origin. Marburg originated in Central and East Africa, and infects both human and nonhuman primates. The Marburg Virus is in the same taxonomic family as Ebola, and both are identical structurally although they elicit different antibodies.

TRANSMISSION

The disease is spread through bodily fluids, including blood, excrement, saliva, and vomit. Early symptoms are often non-specific, and usually include fever, headache and myalgia after an incubation period of three to nine days. After five days, a maculopapularrash is often present on the torso. Later-stage Marburg infection is acute and can include jaundice, pancreatitis, weight loss, delirium and neuropsychiatric symptoms, haemorrhaging, hypovolemic shock and multi-organ dysfunction, with liver failure most common. Accounts of external haemorrhaging from bodily orifices are pervasive in popular references to the disease but are in fact rare. Time course varies but symptoms usually last for one to three weeks until the disease either resolves or kills the infected host. The fatality rate is from 23% to over 90%.

SYMPTOMS

Many of the symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases, such as malaria or typhoid, but are most similar to those of Ebola strains.

DIAGNOSIS

Diagnosis of Marburg is similar to Ebola using the Enzyme-Linked ImmunoSorbent Assay (ELISA) test.

PROGNOSIS

If a patient survives, recovery is usually prompt and complete, though it may be prolonged in some cases, with inflammation or secondary infection of various organs, including: orchitis(testicles), hepatitis (liver), transverse myelitis (spinal cord), uveitis (eyes), and parotitis (salivary glands). Recovered patients often have little or no memory of being sick, though only 10-40% survives.

TREATMENT

There is no specific antiviral therapy indicated for treating Marburg, and hospital care is usually supportive in nature. Hypotension and shock may require early administration of vasopressors and hemodynamic monitoring with attention to fluid and electrolyte balance, circulatory volume, and blood pressure. Viral hemorrhagic fever (VHF) patients tend to respond poorly to fluid infusions and may develop pulmonary edema.

PREVENTION

Caregivers require barrier infection control measures including double gloves, impermeable gowns, face shields, eye protection, and leg and shoe coverings. Marburg thus requiring the highest level of precautions.

LASSA FEVER

Lassa fever is an acute viralhemorrhagic fever first described in 1969 in the town of Lassa, in Borno State, Nigeria located in the Yedseram river valley at the south end of Lake Chad.

PATHOGENESIS

Lassa virus will infect almost every tissue in the human body. It starts with the mucosa, intestine, lungs and urinary system, and then progresses to the vascular system.

EPIDEMIOLOGY

Vectors

Lassa virus is zoonotic (transmitted from animals), in that it spreads to man from rodents, specifically multi-mammate rats (*Mastomysnatalensis*).

SYMPTOMS

In 80% of cases the disease is inapparent, but in the remaining 20% it takes a complicated course. It is estimated that the virus is responsible for about 5,000 deaths annually. The fever accounts for up to one third of deaths in hospitals within the affected regions and 10 to 16% of total cases.

After an incubation period of six to twenty-one days, an acute illness with multiorgan involvement develops. Non-specific symptoms include fever, facial swelling, and muscle fatigue, as well as conjunctivitis and mucosal bleeding. The other symptoms arising from the affected organs are:

- Gastrointestinal tract
  - Nausea
  - Vomiting (bloody)
  - Diarrhea (bloody)

    - Stomach ache
    - Constipation
    - Dysphagia (difficulty swallowing)
    - Hepatitis
- Cardiovascular system
    - Pericarditis
    - Hypertension
    - Hypotension
    - Tachycardia (abnormally high heart rate)
- Respiratory tract
    - Cough
    - Chest pain
    - Dyspnoea
    - Pharyngitis
    - Pleuritis
- Nervous system
    - Encephalitis
    - Meningitis
    - Unilateral or bilateral hearing deficit
    - Seizures

Clinically, Lassa fever infections are difficult to distinguish from other viral hemorrhagic fevers such as Ebola and Marburg, and from more common febrile illnesses such as malaria. The virus is excreted in urine for three to nine weeks and in semen for three months.

DIAGNOSIS

There is a range of laboratory investigations that are performed to diagnose the disease and assess its course and complications. ELISA test for antigen and IgM antibodies gives 88% sensitivity and 90% specificity for the presence of the infection. Other laboratory findings in

Lassa fever include lymphopenia (low white blood cell count), thrombocytopenia (low platelets), and elevated aspartate aminotransferase (AST) levels in the blood.

PROGNOSIS

About 15%-20% of hospitalized Lassa fever patients will die from the illness. It is estimated that the overall mortality rate is 1%, however during epidemics mortality can climb as high as 50%. The mortality rate is greater than 80% when it occurs in pregnant women during their third trimester; fetal death also occurs in nearly all those cases. Abortion decreases the risk of death to the mother.

TREATMENT

All persons suspected of Lassa fever infection should be admitted to isolation facilities and their body fluids and excreta properly disposed of. Ribavirin is a drug which appears to interfere with viral replication by inhibiting RNA-dependent nucleic acid synthesis, although the precise mechanism of action is disputed.

PREVENTION

Control of the *Mastomys* rodent population is impractical, so measures are limited to keeping rodents out of homes and food supplies, as well as maintaining effective personal hygiene. Gloves, masks, laboratory coats, and goggles are advised while in contact with an infected person.

1.6YELLOW FEVER

1.6.1 DEFINITION

Yellow fever is an acute viral hemorrhagic disease.

1.6.2 CAUSE

Yellow fever is caused by the yellow fever virus of the Flaviviridae family.

1.6.3 TRANSMISSION

The yellow fever virus is mainly transmitted through the bite of the yellow fever mosquito ***Aedesaegypti***, but other mosquitos such as the " tiger mosquito" (*Aedesalbopictus*) can also serve as a vector for the virus. Like other Arboviruses which are transmitted via mosquitos, the yellow fever virus is taken up by a female mosquito which sucks the blood of an infected person.

1.6.4 PATHOGENESIS

After transmission of the virus from a mosquito the viruses replicate in the lymph nodes and infect dendritic cells in particular. From there they reach the liver and infect hepatocytes (probably indirectly via Kupffer cells), which leads to eosinophilic degradation of these cells and to the release of cytokines. Necrotic masses (Councilman bodies) appear in the cytoplasm of hepatocytes. When the disease takes a deadly course, a cardiovascular shock and multi organ failure with strongly increased cytokine levels (cytokine storm) follow.

1.6.5 SIGNS AND SYMPTOMS

Yellow fever begins after an incubation period of three to six days. Most cases only cause a mild infection with fever, headache, chills, back pain, loss of appetite, nausea and vomiting. In these cases the infection lasts only three to four days. 15% of cases enter a second, toxic phase of the disease with recurring fever, this time accompanied by jaundice due to liver damageas well as abdominal pain. Bleeding in the mouth, the eyes and in the gastrointestinal tract can cause vomitus containing blood (giving the name "vómitonegro"). The toxic phase is fatal in approximately 20% of cases. Surviving the infection causes life-long immunity and normally there is no remaining organ damage.

1.6.6 DIAGNOSIS

Yellow fever is a clinically diagnosed, which often relies on the whereabouts of the diseased person during the incubation time. A direct confirmation can be obtained by Reverse transcription polymerase chain reaction where the genome of the virus is amplified. Another

direct approach is the isolation of the virus and its growth in cell culture using blood plasma; this can take one to four weeks.

Serologically an enzyme linked immunosorbent assay during the acute phase of the disease using specific IgM against yellow fever or an increase in specific IgG-titer (compared to an earlier sample) can confirm yellow fever.

In a differential diagnosis, infections with yellow fever have to be distinguished from other feverish illnesses like malaria.Other viral hemorrhagic fever.such as Ebola virus, Lassa virus, Marburg virus or Junin virus have to be excluded as cause.

1.6.7 PREVENTION

Personal prevention of yellow fever includes vaccination as well as avoidance of mosquito bites in areas where yellow fever is endemic. Institutional measures for prevention of yellow fever include vaccination programmes and measures of controlling mosquitos.

1.6.8 TREATMENT

For yellow fever there is, like for all diseases caused by Flaviviruses, no causative cure. Hospitalization is advisable and intensive care may be necessary because of rapid deterioration in some cases. Different methods for acute treatment of the disease have been shown to not be very successful; passive immunisation after emergence of symptoms is probably without effect. Ribavirin and other antiviral drugs as well as treatment with interferons do not have a positive effect in patients. A symptomatic treatment includes rehydration and pain relief with drugs like paracetamol. Acetylsalicylic acid (for example *Aspirin*) should not be given because of its haemodiluting effect, which can be devastating in the case of inner bleeding that can occur with yellow fever.

1.7HERPES

1.7.1 DEFINITION AND ETIOLOGY

Herpes simplex (herpes, lit. "Creeping") is a viral disease caused by both herpes simplex virustype 1 (HSV-1) and type 2 (HSV-2).

1.7.2 TRANSMISSION

Herpes simplex is most easily transmitted by direct contact with a lesion or the body fluid of an infected individual. Transmission may also occur through skin-to-skin contact during periods of asymptomatic shedding.

1.7.3 CLASSIFICATION

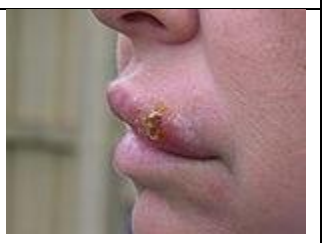
Herpes simplex is divided into two types HSV type 1 and HSV type 2. HSV1 primarily causes mouth, throat, face, eye, and central nervous system infections while HSV2 primarily causes anogenital infections. However each may cause infections in all areas.

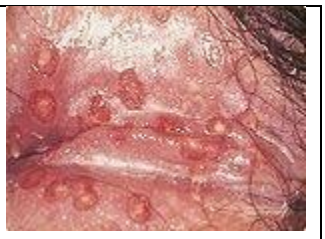
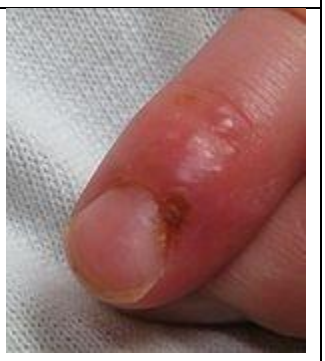
1.7.4 SIGNS AND SYMPTOMS

HSV infection causes several distinct medical disorders. Common infection of the skin or mucosa may affect the face and mouth (orofacial herpes), genitalia (genital herpes), or hands (herpes whitlow). More serious disorders occur when the virus infects and damages the eye (herpes keratitis), or invades the central nervous system, damaging the brain (herpes encephalitis). Patients with immature or suppressed immune systems, such as newborns, transplant recipients, or AIDS patients are prone to severe complications from HSV infections. HSV infection has also been associated with cognitive deficits of bipolar disorder, and Alzheimer's disease, although this is often dependent on the genetics of the .infected person.

1.7.5 PATHOGENESIS

In all cases HSV is never removed from the body by the immune system. Following a primary infection, the virus enters the nerves at the site of primary infection, migrates to the cell body of the neuron, and becomes latent in the ganglion. As a result of primary infection, the body produces antibodies to the particular type of HSV involved, preventing a subsequent infection of that type at a different site. In HSV-1 infected individuals, seroconversion after an oral infection will prevent additional HSV-1 infections such as whitlow, genital herpes, and keratitis. Prior HSV-1 seroconversion seems to reduce the symptoms of a later HSV-2 infection, although HSV-2 can still be contracted. Most indications are that an HSV-2 infection contracted prior to HSV-1 seroconversion will also immunize that person against HSV-1 infection. Many people infected with HSV-2 display no physical symptoms—individuals with no symptoms are described as asymptomatic or as having subclinical herpes.

CONDITION	**DESCRIPTION**	**ILLUSTRATIONS**
Oral herpes: herpetic gingistomatitis	is often the initial presentation during the first herpes infection. It is of greater severity than herpes labials. The severity of the disease varies from trivial cases to extensive ulceration of the mouth, tongue, gums and fauces.. The patient experiences pain and bleeding of the gums.	
Oral herpes: herpetic labials	Infection occurs when the virus comes into contact with oral mucosa or abraded skin.	

Herpes genitals	When symptomatic, the typical manifestation of a primary HSV-1 or HSV-2 genital infection is clusters of inflamed papules and vesicles on the outer surface of the genitals resembling cold sores.	
Herpetic whitlow	is a painful infection that typically affects the fingers or thumbs. Occasionally infection occurs on the toes or on the nail cuticle.	
Herpes gladiatorum	Individuals that participate in contact sports sometimes acquire a condition caused by HSV-1 known as herpesgladiatorum,which presents as skin ulceration on the face, ears, and neck. Symptoms include fever, headache, sore throat and swollen glands. It occasionally affects the eyes or eyelid	
Herpetic keratoconjuctivitis	Primary infection as swelling of the conjunctiva and eyelids (blepharoconjunctivitis), accompanied by small white itchy lesions on the surface of the cornea.	
Herpes viral encephalitis	herpetic infection of the brain that is thought to be caused by the retrograde transmission of virus from a peripheral	

	site on the face following HSV-1 reactivation, along the trigeminal nerveaxon, to the brain. HSV is the most common cause of viral encephalitis. When infecting the brain, the virus shows a preference for the temporal lobe.	
Herpes viral meningitis	HSV-2 is the most common cause of Mollaret's meningitis, a type of recurrent viral meningitis.	
Neonatal Herpes simplex	Neonatal HSV infection is a rare but serious condition, usually caused by vertical transmission of HSV (type 1 or 2) from mother to newborn.	
During Immunodeficiency	Patients with a weakened immune system, herpes simplex can cause unusual lesions in the skin. One of the most striking is the appearance of clean linear erosions in skin with the appearance of a knife cut.	
Herpetic sycosis	Is a recurrent or initial herpes simplex infection affecting primarily the hair follicle.	
Herpes esophagitis	Symptoms may include painful swallowing (odynophagia) and difficulty swallowing (dysphagia). It is often associated with impaired immune	

	function (e.g. HIV/AIDS, immunosuppression in solid organ transplants).	

Bell's palsy

Although the exact cause of Bell's palsy, a type of facial paralysis, is unknown it may be related to reactivation of herpes simplex virus type 1. This theory has been contested, however since HSV is detected in large numbers of individuals who never experienced facial paralysis, and higher levels of antibodies for HSV are not found in HSV-infected individuals with Bell's palsy compared to those without. Regardless antivirals have been found to not improve outcomes.

Alzheimer's disease

HSV-1 has been proposed as a possible cause of Alzheimer's disease. In the presence of a certain gene variation (APOE-epsilon4 allele carriers), HSV-1 appears to be particularly damaging to the nervous system and increases one's risk of developing Alzheimer's disease. The virus interacts with the components and receptors of lipoproteins, which may lead to the development of Alzheimer's disease. Without the presence of the gene allele, HSV type 1 does not appear to cause any neurological damage and thus increase the risk of Alzheimer's. Herpes simplex virus type 1 DNA is localized within the beta-amyloid plaques that characterize Alzheimer's disease. It suggests that this virus is a major cause of the plaques and hence probably a significant aetiological factor in Alzheimer's disease.

1.7.6 DIAGNOSIS

Essentially clinical. Laboratory tests include: culture of the virus, direct fluorescent antibody (DFA) studies to detect virus, skin biopsy, and polymerase chain reaction (PCR) to test for presence of viral DNA. Although these procedures produce highly sensitive and specific diagnoses, their high costs and time constraints discourage their regular use in clinical practice. Until recently, serological tests for antibodies to HSV were rarely useful to diagnosis and not routinely used in clinical practice.

1.7.7 PREVENTION

Barrier methods

The use of condoms or dental dams also limits the transmission of herpes from the genitals of one partner to the mouth of the other (or vice versa) during oral sex. When one partner has a herpes simplex infection and the other does not, the use of antiviral medication, such as valaciclovir, in conjunction with a condom, further decreases the chances of transmission to the uninfected partner

Pregnancy

To prevent neonatal infections, seronegative women are recommended to avoid unprotected oral-genital contact with an HSV-1 seropositive partner and conventional sex with a partner having a genital infection during the last trimester of pregnancy. Women that are seropositive for only one type of HSV are only half as likely to transmit HSV as infected seronegative mothers. Mothers infected with HSV are advised to avoid procedures that would cause trauma to the infant during birth (e.g., fetal scalp electrodes, forceps, and vacuum extractors) and, should lesions be present, to elect caesarean section to reduce exposure of the child to infected secretions in the birth canal. The use of antiviral treatments, such as acyclovir, given from the 36th week of pregnancy, limits HSV recurrence and shedding during childbirth, thereby reducing the need for caesarean section.

1.7.8 TREATMENT

There is no method to eradicate herpes virus from the body, but antiviral medications can reduce the frequency, duration, and severity of outbreaks. Analgesics such as ibuprofen and acetaminophen can reduce pain and fever. Topical anesthetic treatments such as prilocaine, lidocaine, benzocaine or tetracaine can also relieve itching and pain.

Antiviral

There are several antivirals that are effective for treating herpes including:acyclovir,valacyclovir, famciclovir, and penciclovir.

Evidence supports the use of acyclovir and valacyclovir in the treatment of herpes labialis as well as herpes infections in people with cancer. The evidence to support the use of acyclovir in primary herpetic gingivostomatitis is less strong.

Topical

A number of topical antivirals are effective for herpes labialis including acyclovir, penciclovir, and docosanol. Docosanol can be purchased over the counter in Canada and the USA.

1.7.9 PROGNOSIS

Many HSV-infected people experience recurrence within the first year of infection. The causes of reactivation are uncertain.

1.8 RABIES

1.8.1 DEFINITION

Rabies is an acute viral disease in the group of rabdovirus that causes acute encephalitis (inflammation of the brain)

1.8.2 ETIOLOGY

The virus of rabies is in the group of rhabdovirus. This virus is fragile and is quickly destroyed by the soap, the ether, the ammonium derives. It is sensitive to heat, the light and the desiccation

1.8.3 TRANSMISSION

It is zoonotic , most commonly by a bite from an infected animal but occasionally by other forms of contact. The main route of transmission is the bites of rabid dogs. The disease is transmitted to domestic animals and humans through exposure to infected saliva. Humans also become infected with rabies the bite of infected cats, wild carnivorous species like foxes, raccoons, skunks, jackals and wolves. Cattle, horses, deer and other herbivores can become infected with rabies.

People at risk

- Poor people, especially children, are at highest risk of dog rabies. Children often play with animals and are less likely to report bites or scratches.
- In areas known for rabies, professionals with frequent exposure to animals (e.g. veterinarians), or who spend a lot of time outdoors (e.g. wildlife specialists or researchers), particularly in rural areas, should be vaccinated preventively.

Virulence depends

- Depends on severity of bites
- If treatment is given and when
- Once the disease manifests in CNS: ultimate death

Vehicle of transmission

- Saliva
- Mucous membranes
- Aerosol transmission
- Corneal transplantations

1.8.4 PATHOGENESIS

Begins when infected saliva of host is passed to uninfected animal by Scratches or bites. Virus replicated in muscle cells near site of bite for most of incubation time. Incubation time 30-90 days. Latency up to 7 years. Then ascends along motor and sensory axons at rate of 12-100mm/day and has predilection for brainstem and medulla. It enters salivary glands after replication in CNS where it undergoes the perivascular infiltration throughout entire central nervous system that causes cytoplasmic eosinophilic inclusion bodies (Negri bodies) in neuronal cells which will be defined by encephalitis and myelitis Several factors may affect outcome of rabies exposure; rabies variant, dose, route, location of exposure and Individual host factors.

1.8.5 SIGNS AND SYMPTOMS.

Incubation: The incubation period of the disease is usually a few months in humans, depending on the distance the virus must travel to reach the central nervous system.

Invasion: Once the rabies virus reaches the central nervous system and symptoms begin to show: The first symptoms of rabies are flu-like, including fever, headache and fatigue, and then progress to state phase which involves the respiratory, gastrointestinal and/or central nervous systems.

State phase: Two clinical form which are critical stages are possible translating the encephalitis:

- ***The furious rabies or spastic or encephalitic*** : there are signs of hyperactivity (psychomotor excitation) with hallucination and convulsions, pain, violent movements, uncontrolled excitement, depression, and hydrophobia very characteristic of the human rabies, and finally, the patient may experience periods of mania and lethargy, eventually leading to coma.Vitals abnormal: tachycardia, tachypnea, fever

  Hydrophobia**:** Patient can't swallow because violent jerky contraction of diaphragm and accessory muscles of inspiration when patient attempts to swallow liquids. Patients will be terrified during this reaction and may even experience this at the sight of water or if water touch es their face.

Aerophobia**:** an extreme fear of air in motion can be elicited from some patients. This can also cause violent muscle spasms in the neck and pharynx.

- ***Paralytic rabies or dumb rabies****:* it is less frequent. It carries out (realizes) an ascending paralytic syndrome (reach of lower limb then sphincters and after cranial nerves).
  - In both furious and dumb rabies, some paralysis eventually progresses to complete paralysis, followed by coma and death in all cases, usually due to respiratory failure. Without intensive care, death occurs during the first seven days of illness

1.8.6 DIAGNOSIS

Essentially done by assessing patient history and clinical features.

Saliva can be tested by virus isolation or reverse transcription by polymerase chain reaction (RT-PCR). Serum and spinal fluid are tested for antibodies to rabies virus. Skin biopsy specimens are examined for rabies antigen in the cutaneous nerves at the base of hair follicles.

It is possible to make the diagnosis by viral culture of saliva, urine and cerebrospinal fluid samples, Inclusion bodies called Negri bodies are of certain diagnostic(100%) for rabies infection, but are found in only about 80% of cases.

1.8.7. TREATMENT

TREATMENT AFTER EXPOSURE

- ✓ To check if the anti-rabid vaccination is update

- ✓ Wound cleansing and immunizations, done as soon as possible after suspect contact with an animal and following WHO recommendations, can prevent the onset of rabies in virtually 100% of exposures. Recommended treatment to prevent rabies depends on the category of the contact:

- Category I: touching or feeding suspect animals, but skin is intact
- Category II: minor scratches without bleeding from contact, or licks on broken skin
- Category III: one or more bites, scratches, licks on broken skin, or other contact that breaks the skin; or exposure to bats

- ✓ Post-exposure care to prevent rabies includes cleaning and disinfecting a wound, or point of contact, and then administering anti-rabies immunizations as soon as possible.

    - Anti-rabies vaccine is given for **Category II and III exposures**.
    - Anti-rabies immunoglobin, or antibody, should be given for Category III contact, or to people with weaker immune systems.

- They give one dose of *human rabies* immunoglobulin (HRIG) and four doses of rabies vaccine over a fourteen day period.
- The immunoglobulin dose should not exceed 20 units per kilogram body weight.
- As much as possible of this dose should be infiltrated around the bites and other is given by deep intramuscular injection at a site distant from the vaccination site.
- The first dose of rabies vaccine is given as soon as possible after exposure, with additional doses on days three, seven and fourteen after the first. Patients who have previously received pre-exposure vaccination do not receive the immunoglobulin, only the post-exposure vaccinations on day 0 and 2.

✓ When humans are exposed to suspect animals, attempts to identify, capture or humanely sacrifice the animal involved should be undertaken immediately. Post-exposure treatment should start right away and only be stopped if the animal is a dog or cat and remains healthy after 15 days.

✓ Once the signs and symptoms of rabies start to appear, there is no treatment and the disease is almost always fatal.

1.8.8 PREVENTION

Eliminating rabies in dogs through animal vaccinations.

Anti-rabic vaccination for human *uses the inactivated vaccine* in subcutaneous or in intra muscular according to the protocols below:

- **WHO Protocol**: injection on day 0, 3, 7, 14, 30 and day 90
- **Short Protocol**; injection with on day 0, 7, and 21

1.9 POLIOMYELITIS

1.9.1 DEFINITION

Poliomyelitis, often called **polio** or **infantile paralysis**, is an acute viral infectious disease spread from person to person, primarily via the fecal-oral route

1.9.2 ETIOLOGY

Three serotypes of poliovirus have been identified—poliovirus type 1 (PV1), type 2 (PV2), and type 3 (PV3)—each with a slightly different capsid protein. All three are extremely virulent and produce the same disease symptoms. PV1 is the most commonly encountered form, and the one most closely associated with paralysis.

1.9.3 TRANSMISSION

Poliomyelitis is highly contagious via the oral-oral (oropharyngeal source) and fecal-oral (intestinal source) routes. In endemic areas, wild polioviruses can infect virtually the entire human population

The disease is transmitted primarily via the fecal-oral route, by ingesting contaminated food or water. It is occasionally transmitted via the oral-oral route, a mode especially visible in areas with good sanitation and hygiene. Polio is most infectious between 7–10 days before and 7–10 days after the appearance of symptoms, but transmission is possible as long as the virus remains in the saliva or feces.

Factors that increase the risk of polio infection or affect the severity of the disease include immune deficiency, malnutrition, tonsillectomy, physical activity immediately following the onset of paralysis, skeletal muscle injury due to injection of vaccines or therapeutic agents and pregnancy. Although the virus can cross the placenta during pregnancy, the fetus does not appear to be affected by either maternal infection or polio vaccination.

1.9.4 PATHOGENESIS

Poliovirus enters the body through the mouth, infecting the first cells it comes in contact with—the pharynx (throat) and intestinal mucosa. It gains entry by binding to an immunoglobulin-like receptor, known as the poliovirus receptor or CD155, on the cell membrane. The virus then hijacks the host cell's own machinery, and begins to replicate. Poliovirus divides within gastrointestinal cells for about a week, from where it spreads to the tonsils (specifically the

follicular residing within the tonsilar germinal centers), the intestinal lymphoid tissue including the M cells of Peyer's patches, and the deep cervical and mesenteric lymph nodes, where it multiplies abundantly. The virus is subsequently absorbed into the bloodstream.

Known as viremia, the presence of virus in the bloodstream enables it to be widely distributed throughout the body. Poliovirus can survive and multiply within the blood and lymphatics for long periods of time, sometimes as long as 17 weeks. In a small percentage of cases, it can spread and replicate in other sites such as brown fat, the reticuloendothelial tissues, and muscle. This sustained replication causes a major viremia, and leads to the development of minor influenza-like symptoms. Rarely, this may progress and the virus may invade the central nervous system, provoking a local inflammatory response. In most cases this causes a self-limiting inflammation of the meninges, the layers of tissue surrounding the brain, which is known as *non-paralytic aseptic meningitis*. Penetration of the CNS provides no known benefit to the virus, and is quite possibly an incidental deviation of a normal gastrointestinal infection. The mechanisms by which poliovirus spreads to the CNS are poorly understood, but it appears to be primarily a chance event—largely independent of the age, gender, or socioeconomic position of the individual

1.9.5 CLASSIFICATION

Two basic patterns of polio infection are described: a **minor illness** which does not involve the central nervous system (CNS), sometimes called ***abortive poliomyelitis***, and a major illness involving the CNS, which may be **paralytic or non-paralytic.** In most people with a normal immune system, a poliovirus infection is asymptomatic. Rarely the infection produces minor symptoms; these may include upper respiratory tract infection (sore throat and fever), gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhea), and influenza-like illness.

The virus enters the central nervous system in about 3% of infections. Most patients with CNS involvement develop non-paralytic aseptic meningitis, with symptoms of headache, neck, back, abdominal and extremity pain, fever, vomiting, lethargy and irritability. Approximately 1 in 1000 to 1 in 200 cases progress to paralytic disease, in which the muscles become weak, floppy and poorly controlled, and finally completely paralyzed; this condition is known as acute flaccid paralysis.

Depending on the site of paralysis, paralytic poliomyelitis is classified as *spinal*, *bulbar*, or *bulbospinal*. Encephalitis, an infection of the brain tissue itself, can occur in rare cases and is usually restricted to infants. It is characterized by confusion, changes in mental status, headaches, fever, and less commonly seizures and spastic paralysis.

Paralytic polio

In around 1% of infections, poliovirus spreads along certain nerve fiber pathways, preferentially replicating in and destroying motor neurons within the spinal cord, brain stem, or motor cortex. This leads to the development of paralytic poliomyelitis, the various forms of which (spinal, bulbar, and bulbo spinal) vary only with the amount of neuronal damage and inflammation that occurs, and the region of the CNS that is affected.

The destruction of neuronal cells produces lesions within the spinal ganglia; these may also occur in the reticular formation, vestibular nuclei, cerebellar vermis, and deep cerebellar nuclei. Inflammation associated with nerve cell destruction often alters the color and appearance of the gray matter in the spinal column, causing it to appear reddish and swollen. Other destructive changes associated with paralytic disease occur in the forebrain region, specifically the hypothalamus and thalamus.

The molecular mechanisms by which poliovirus **causes paralytic diseases are poorly understood.**

Early symptoms of paralytic polio include high fever, headache, stiffness in the back and neck, asymmetrical weakness of various muscles, sensitivity to touch, difficulty swallowing, muscle pain, loss of superficial and deep reflexes, paresthesia (pins and needles), irritability, constipation, or difficulty urinating. Paralysis generally develops one to ten days after early symptoms begin, progresses for two to three days, and is usually complete by the time the fever breaks.

In children under five years of age, paralysis of one leg is most common; in adults, extensive paralysis of the chest and abdomen also affecting all four limbs (**quadriplegia)** is more likely. Paralysis rates also vary depending on the serotype of the infecting poliovirus; the highest rates of paralysis (1 in 200) are associated with poliovirus type 1, the lowest rates (1 in 2,000) are associated with type 2.

Spinal polio (The location of motor neurons in the anterior horn cells of the spinal column). Spinal polio is the most common form of paralytic poliomyelitis; it results from viral invasion of the motor neurons of the anterior horn cells, or the ventral (front)gray matter section in the spinal column, which are responsible for movement of the muscles, including those of the trunk, limbs and the intercostal muscles. Virus invasion causes inflammation of the nerve cells, leading to damage or destruction of motor neuron ganglia. When spinal neurons die,Wallerian degeneration takes place, leading to weakness of those muscles formerly innervated by the now dead neurons. With the destruction of nerve cells, the muscles no longer receive signals from the brain or spinal cord; without nerve stimulation, the **muscles atrophy, becoming weak, floppy and poorly controlled, and finally completely paralyzed**. Progression to maximum paralysis is rapid (two to four days), and is usually associated with fever and muscle pain. Deep tendon reflexes are also affected, and are usually absent or diminished; sensation (the ability to feel) in the paralyzed limbs, however, is not affected. The extent of spinal paralysis depends on the region of the cord affected, which may be cervical, thoracic, or lumbar. The virus may affect muscles on both sides of the body, but more often the paralysis is asymmetrical. Any limb or combination of limbs may be affected one leg, one arm, or both legs and both arms. Paralysis is often more severe proximally (where the limb joins the body) than distally (the fingertips and toes).

Bulbar polio (The location and anatomy of the bulbar region)

Making up about 2% of cases of paralytic polio, bulbar polio occurs when poliovirus invades and destroys nerves within the bulbar region of the brain stem. The bulbar region is a white matter pathway that connects the cerebral cortex to the brain stem.

The destruction of these nerves weakens the muscles supplied by the cranial nerves, producing symptoms of encephalitis, and causes difficulty breathing, speaking and swallowing. Critical nerves affected are the glosso pharyngeal nerve, which partially controls swallowing and functions in the throat, tongue movement and taste; the vagus nerve, which sends signals to the heart, intestines, and lungs; and the accessory nerve, which controls upper neck movement. Due to the effect on swallowing, secretions of mucus may build up in the airway causing suffocation. Other signs and symptoms include facial weakness, caused by destruction of

the trigeminal nerve and facial nerve, which innervate the cheeks, tear ducts, gums, and muscles of the face, among other structures; double vision; difficulty in chewing; and abnormal respiratory rate, depth, and rhythm, which may lead to respiratory arrest. Pulmonary edema and shock are also possible, and may be fatal.

Bulbospinal polio

Approximately 19% of all paralytic polio cases have both bulbar and spinal symptoms; this subtype is called *respiratory polio* or *bulbospinal polio*. Here, the virus affects the upper part of the cervical spinal cord (C3 through C5), and paralysis of the diaphragm occurs. The critical nerves affected are the phrenic nerve, which drives the diaphragm to inflate the lungs, and those that drive the muscles needed for swallowing. By destroying these nerves this form of polio affects breathing, making it difficult or impossible for the patient to breathe without the support of a ventilator. It can lead to paralysis of the arms and legs and may also affect swallowing and heart functions.

1.9.6 DIAGNOSIS

Paralytic poliomyelitis may be clinically suspected in individuals experiencing acute onset of flaccid paralysis in one or more limbs with decreased or absent tendon reflexes in the affected limbs that cannot be attributed to another apparent cause, and without sensory or cognitive loss.

A laboratory diagnosis is usually made based on recovery of poliovirus from a stool sample or a swab of the pharynx. Antibodies to poliovirus can be diagnostic, and are generally detected in the blood of infected patients early in the course of infection. Analysis of the patient's cerebrospinal fluid (CSF), which is collected by a lumbar puncture ("spinal tap"), reveals an increased number of white blood cells (primarily lymphocytes) and a mildly elevated protein level. Detection of virus in the CSF is diagnostic of paralytic polio, but rarely occurs.

1.9.7 PROGNOSIS

Patients with abortive polio infections recover completely. In those that develop only aseptic meningitis, the symptoms can be expected to persist for two to ten days, followed by complete recovery. In cases of spinal polio, if the affected nerve cells are completely destroyed, paralysis

will be permanent. The degree of both acute paralysis and residual paralysis is likely to be proportional to the degree of viremia, and inversely proportional to the degree of immunity. Spinal polio is rarely fatal.

1.9.8 COMPLICATIONS

Muscle paresis and paralysis can sometimes result in **skeletal deformities**, tightening of the joints and movement disability. Once the muscles in the limb become flaccid, they may interfere with the function of other muscles. A typical manifestation of this problem is equinus foot (similar to club foot). Polio victims that develop equinus foot cannot walk properly because they cannot put their heel on the ground. A similar situation can develop if the arms become paralyzed. . In some cases the growth of an affected leg is slowed by polio, while the other leg continues to grow normally thus one leg is shorter than the other and the person limps and leans to one side, in turn leading to deformities of the spine (such as **scoliosis**). **Osteoporosis** and increased likelihood of **bone fractures** may occur. Extended use of braces or wheelchairs may cause **compression neuropathy**, as well as a loss of proper function of the veins in the legs, due to pooling of blood in paralyzed lower limbs. Complications from prolonged immobility involving the lungs, kidneys and heart include **pulmonary edema, aspiration pneumonia, urinary tract infections, kidney stones, paralytic ileus, myocarditis and corpulmonale**.

Post-polio syndrome

Between 25% and 50% of individuals who survive paralytic polio in childhood develop additional symptoms, notably new muscle weakness and extreme fatigue. This condition is known as post-polio syndrome (PPS) or post-polio sequelae. The symptoms of PPS are thought to involve a failure of the over-sized motor units created during recovery from paralytic disease. Factors that increase the risk of PPS include the length of time since acute poliovirus

infection. Post-polio syndrome is not an infectious process, and persons experiencing the syndrome do not shed poliovirus

1.9.9 TREATMENT

There is no cure for polio. The focus of modern treatment has been on providing relief of symptoms, speeding recovery and preventing complications. Supportive measures include antibiotics to prevent infections in weakened muscles, analgesics for pain, moderate exercise and a nutritious diet. Treatment of polio often requires long-term rehabilitation, including physical therapy, brace, corrective shoes and, in some cases, orthopedic surgery. Portable ventilators may be required to support breathing.

1.9.10 PREVENTION

Vaccine

Oral polio vaccine (OPV) is inexpensive, easy to administer, and produces excellent immunity in the intestine. It has been the vaccine of choice for controlling poliomyelitis in many countries.

1.10 INFECTIOUS MONONUCLEOSIS/EPSTEIN-BARR VIRUS INFECTION/ *"THE KISSING DISEASE"*

1.10.1 DEFINITION

Infectious Mononucleosis, a disease caused by the Epstein-Barr virus (EBV). It is often called simply mono or "the kissing disease" because the virus is usually transmitted in saliva.

1.10.2 ETIOLOGY

The disease is caused by Epstein Barr Virus (EBV) in 90% of Herpes Family

- Two subtypes

  EBV-1 (type A): Western countries

  EBV-2(type B): less virulence

- In immunocompromised persons : co-infection both type 1 and type 2 strains
- No one subtype is responsible for specific lymphoproliferative diseases (geographic differences)
- Other Herpesviruses :
  - Cytomegalovirus (CMV)
  - herpes simplex 1 and simplex 2
  - human herpesvirus 6
- Other viruses :
  - adenovirus
  - hepatitis A, hepatitis B, or hepatitis C
  - rubella
  - primary human immunodeficiency virus in adolescents or young adults.

1.10.3 TRANSMISSION

Kissing is only one means of transmission; sneezing, coughing, or drinking from a glass used by an infected person can also spread it. This disease is sometimes known as glandular fever because fever and swollen lymph nodes are among its symptoms.

1.10.4 PATHOGENESIS

In a normal host, both cellular and humoral immunity develops in response to EBV infection. However in 2-7 weeks after exposure, up to 20% of circulating B lymphocytes become infected during primary EBV infection. In acute stage, proliferating EBV-infected B cells are controlled principally by host antibodies, adequate for control and sequestration of EBV-infected cells.After T-cell response, number of EBV-infected B cells falls dramatically. Primary EBV infection, like herpes viruses, is able to persist in a latent state in a human host throughout that person's lifetime. This ability indicates that EBV exerts some influence on the immune response to prevent its complete eradication.

In cellular immune deficiency: there is an excess EBV-associated B-cell production. However, life-threatening EBV infections include strong virus-induced T-cell proliferation that cause autoaggressive activity producing hypogammaglobulinemia or other major organ dysfunctions that are multifactorial : mixture of virology genetic environmental factorsthe virus causes the most common form of non-Hodgkin lymphoma (NHL), Burkitt lymphoma, which consists of sheets of small noncleaved cells that are histologically uniform.

1.10.5 SIGNS AND SYMPTOMS

- In children and infants the time of onset is usually vague and the duration of prodromal symptoms is difficult to determine.
- Anorexia, sometimes accompanied by nausea and vomiting, is a common and non-specific early symptom of this infection.
- The most important and most characteristic symptom of IM is a sore throat. This usually develops a few days after the onset of the illness, increases in severity during the first week, and then rapidly subsides during the next five to seven days.
- In many young adults sore throat is the first indication of sickness and in some it is the only major symptom throughout the entire illness.
- Although anorexia may persist for as long as there is fever, its intensity and duration are more directly related to the severity of sore throat and dysphagia.

- Gross tonsillar and pharyngeal edema may cause virtually complete pharyngeal obstruction with harsh-sounding breathing and complete inability to swallow either food or fluids.
- In some patients the soreness of the throat is so severe that swallowing even a few sips of water is extremely painful.
- The headaches of early IM are often retro-orbital in location but have no characteristic features. They may be moderately severe for one or two days but usually they are mild and rarely last for more than three or four days.
- Ocular symptoms may be in the form of photophobia, ocular muscle aching or the awareness of puffiness
- Lymphadenopathy, disease of the lymph nodes, is sometimes accidentally discovered or detected during self-examination following the development of systemic symptoms.
- In about 3 percent of all cases of IM, the gross cervical lymphadenopathy imparts a "bull neck" appearance. Enlargement of lymph nodes usually begins two or three days after the onset of the first symptoms and, by the end of the week, palpable lymphadenopathy is present in 70-80 percent of all patients.
- Jaundice is a moderately important symptom of infectious mono as 8-10 percent of patients eventually become visibly jaundiced. In most instances, however, it is not noticed since it consists of only a transient icteric tint to the sclerae and mucous membranes, lasting for a few days.

1.10.6 COMPLICATIONS

- Meningitis/Encephalitis (<1%)
- Hepatitis : > 90% of patients
- Hemolytic anemia
- Upper airway obstruction
    - 0.1-1%,due to hypertrophy of tonsils and other lymph nodes of Waldeyer ring
    - treatment with corticosteroids may be beneficial
- Splenic rupture : 0.1-0.2%

- Hematologic complications
  - hemophagocytic syndrome.
  - Immune thrombocytopenic purpura occurs and may evolve to aplastic anemia.
  - Accelerate hemolytic anemia in congenital spherocytosis or hereditary elliptocytosis.
  - Disseminated intravascular coagulation associated with hepatic necrosis has occurred
- Neurologic complications : < 1%
  - During the first 2 weeks.
  - Negative for the heterophile antibody.
  - Severe (fatal),complete recovery
  - Aseptic meningitis, acute viral encephalitis, coma, meningitis, and meningoencephalopathy.
  - Hypoglossal nerve palsy, Bell palsy, hearing loss, brachial plexus neuropathy, multiple cranial nerve palsies, Guillain-Barré syndrome, autonomic neuropathy, gastrointestinal dysfunction secondary to selective cholinergic dysautonomia, acute cerebellar ataxia, transverse myelitis.
- Cardiac and pulmonary complications
  - rare
  - Chronic interstitial pneumonitis.
  - Myocarditis and pericarditis
- Autoimmune complications
  - Autoimmune diseases and Reye syndrome have been associated with EBV infection.

- Infectious mononucleosis stimulates production of many antibodies not directed against EBV. These include autoantibodies, anti-I antibodies, cold hemolysins, antinuclear antibodies, rheumatoid factors, cryoglobulins, and circulating immune complexes. These antibodies may precipitate autoimmune syndromes.

- Miscellaneous complications
  - Renal disorders: immune deposit nephritis, renal failure, paroxysmal nocturnal hemoglobinuria.
  - After cardiac bypass or transfusion, an infectious mononucleosis–like syndrome : primary CMV infection> EBV.
  - A syndrome of chronic fatigue, myalgias, sore throat, and mild cognitive dysfunction occurring primarily in young adult females initially was attributed to EBV. Current data suggest that EBV is not the etiologic agent.

Diagnosis

The 3 classic criteria for laboratory confirmation

1) lymphocytosis

2) the presence of at least 10% atypical lymphocytes on peripheral smear

3) a positive serologic test for Epstein-Barr virus (EBV).

Prognosis

- Immunocompetent: full recovery in several months.
- The common hematologic and hepatic complications resolve in 2-3 months.
- Neurologic complications
  - Children :resolve quickly
  - Adults : neurological deficits
- All individuals develop latent infection: asymptomatic.

1.10.7 TREATMENT

Medical Care:

- Self-limited illness: not require specific therapy.
- Inpatient therapy of medical and surgical complications may be required.
- Acyclovir (10 mg/kg/dose IV every 8h for 7-10 d)
- Short-course corticosteroids : prednisolone (1 mg/kg/d, max 60 mg/d for 7 days

and tapered over another 7 for

  - Marked tonsillar inflammation with impending airway obstruction
  - Massive splenomegaly
  - Myocarditis
  - Hemolytic anemia
  - Hemophagocytic syndrome
  - Seizure and meningitis

Surgical Carefor splenic rupture.

Activity:

- Depends on severity of the patient's symptoms.
- Extreme fatigue: bed rest for 1-2 weeks.
- Malaise may persist for 2-3 months.
- Patients should not participate in contact sports or heavy lifting for at least 2-3 weeks
- Some authors recommend avoiding activities that may cause splenic trauma for 2 months.

1.10.8 PREVENTION

- Isolation is not required: low transmission.

- Avoid contact with saliva.
- Do not kiss children on the mouth.
- Maintain clean conditions: day care, avoid sharing toys.
- EBV can be transmitted by blood transfusion and by bone marrow transplantation.
- Vaccine development is proceeding, although the role of a vaccine is unclear.

1.11 CYTOMEGALOVIRUS

1.11.1 DEFINITION

Cytomegalovirus (from the Greek*cyto-*, "cell", and *-megalo-*, "large") is a herpes viralgenus of the Herpesviruses group: in humans it is commonly known as HCMV or Human Herpesvirus 5 (HHV-5). CMV belongs to the *Betaherpesvirinae* subfamily of *Herpesviridae*, which also includes Roseolovirus. Other herpesviruses fall into the subfamilies of *Alphaherpesvirinae* (including HSV 1 and 2 and varicella) or *Gammaherpesvirinae* (including Epstein-Barr virus). All herpesviruses share a characteristic ability to remain latent within the body over long periods.

1.11.2 TRANSMISSION

Transmission of HCMV occurs from person to person through bodily fluids. Infection requires close, intimate contact with a person excreting the virus in their saliva, urine, or other bodily fluids. CMV can be sexually transmitted and can also be transmitted via breast milk, transplanted organs, and rarely from blood transfusions.

1.11.3 PATHOGENESIS

Infection requires close, intimate contact with a person excreting the virus in their saliva, urine, or other bodily fluids. After infection, the virus remains latent in the body for the rest of the person's life. Overt disease rarely occurs unless immunity is suppressed either by drugs, infection or old-age. Initial HCMV infection, which often is asymptomatic is followed by a prolonged, inapparent infection during which the virus resides in T - cells without causing detectable damage or clinical illness. Major areas of risk of infection include pre-natal or postnatal infants and immunocompromised individuals, such as organ transplant recipients, persons with leukemia, or those infected with human immunodeficiency virus (HIV). In HIV infected persons, HCMV is considered an *AIDS-defining infection*, indicating that the T-cellcount has dropped to low levels. Lytically replicating virus disrupts the cytoskeleton, causing massive cell enlargement, which is the source of the virus' **name**.

CMV diseases

The most common types of infections by CMV can be grouped as follows:

- Fetus/Infant:
    - Congenital CMV infection
    - Perinatal CMV infection
- Immunocompetent patient:
    - CMV mononucleosis
    - Post-transfusion CMV - similar to CMV mononucleosis
- Immunocompromised patient:
    - CMV pneumonitis
    - CMV GI disease
    - CMV retinitis
    - Polyradiculopathy, transverse myelitis, and subacute encephalitis

Pregnancy and congenital infection

HCMV is one of the **TORCH** infections that lead to congenital abnormalities. These are: **To**xoplasmosis, **R**ubella, **H**erpes simplex, and **C**ytomegalovirus. Congenital HCMV infection occurs when the mother suffers a primary infection (or reactivation) during pregnancy. Due to the lower seroprevalence of HCMV in industrialized countries and higher socioeconomic groups, congenital infections are actually more common in poorer communities, where more women of child-bearing age are already seropositive. The incidence of primary CMV infection in pregnant women in the United States varies from 1% to 3%. Healthy pregnant women are not at special risk for disease from CMV infection. When infected with CMV, most women have no symptoms and very few have a disease resembling infectious mononucleosis. It is their developing fetuses that may be at risk for congenital CMV disease. CMV remains the most important cause of congenital viral infection in the United States. HCMV is the most common cause of congenital infection in humans and intrauterine primary infections are second only to Down's syndrome as a known cause of mental retardation.

For infants who are infected by their mothers before birth, two potential adverse scenarios exist:

- Generalized infection may occur in the infant, and can cause complications such as low birth weight, microcephaly, seizures, petechial rash similar to the "blueberry muffin" rash of congenital rubella syndrome, and moderate hepatosplenomegaly (with jaundice). Though severe cases can be fatal, with supportive treatment most infants with CMV disease will survive. However, from 80% to 90% will have complications within the first few years of life that may include hearing loss, vision impairment, and varying degrees of mental retardation.
- Another 5% to 10% of infants who are infected but without symptoms at birth will subsequently have varying degrees of hearing and mental or coordination problems.

During a pregnancy when a woman who has never had CMV infection becomes infected with CMV, there is a potential risk that after birth the infant may have CMV-related complications, the most common of which are associated with hearing loss, visual impairment, or diminished mental and motor capabilities. On the other hand, infants and children who acquire CMV after birth have few, if any, symptoms or complications.

Recommendations for pregnant women with regard to CMV infection:

- Throughout the pregnancy, practice good personal hygiene, especially hand washing with soap and water, after contact with diapers or oral secretions (particularly with a child who is in day care).
- Women who develop a mononucleosis-like illness during pregnancy should be evaluated for CMV infection and counseled about the possible risks to the unborn child.
- Laboratory testing for antibody to CMV can be performed to determine if a woman has already had CMV infection.
- Recovery of CMV from the cervix or urine of women at or before the time of delivery does not warrant a cesarean section.
- The demonstrated benefits of breast-feeding outweigh the minimal risk of acquiring CMV from the breast-feeding mother.

Recommendations for individuals providing care for infants and children:

- Employees should be educated concerning CMV, its transmission, and hygienic practices, such as hand washing, which minimize the risk of infection.
- Susceptible non pregnant women working with infants and children should not routinely be transferred to other work situations.
- Pregnant women working with infants and children should be informed of the risk of acquiring CMV infection and the possible effects on the unborn child.

Immunocompromised patients

CMV hepatitis may cause fulminant liver failure. Specific disease entities recognised in those people are cytomegalovirus retinitis (inflammation of the retina, characterised by a "pizza pie appearance" on ophthalmoscopy) and cytomegalovirus colitis (inflammation of the large bowel).

Exposing immunosuppressed patients to outside sources of CMV should be minimized to avoid the risk of serious infection. Whenever possible, patients without CMV infection should be given organs and/or blood products that are free of the virus.

Patients without CMV infection who are given organ transplants from CMV-infected donors should be given prophylactic treatment with valganciclovir (ideally) or ganciclovir and require regular serological monitoring to detect a rising CMV titre, which should be treated early to prevent a potentially life-threatening infection becoming established.

Potential role in vascular disease and hypertension

CMV infection may be linked to the development of arterial hypertension. CMV infection stimulated cytokines – IL6, TNF, and MCP1 – in the infected mice indicating that the infection led to an inflammatory response in vessels and other tissues. Further, renin and angiotensin II release were increased in these animals as additional factors to lead to hypertension. In humans CMV infection has been demonstrated in the aortic smooth muscle cells from patients with abdominal aortic aneurysms suggesting that CMV infection contributes to vascular disease.

1.11.4 DIAGNOSIS

Most infections with CMV are not diagnosed because the virus usually produces few, if any, symptoms and tends to reactivate intermittently without symptoms. Laboratory tests that detect CMV antibodies have been developed. In addition, the virus can be cultured from specimens obtained from urine, throat swabs, bronchial lavages and tissue samples to detect active infection. Both qualitative and quantitative polymerase chain reaction (PCR) testing for CMV are available as well, allowing physicians to monitor the viral load of CMV-infected patients. A virus culture can be performed at any time the patient is symptomatic. Laboratory testing for antibody to CMV can be performed to determine if a woman has already had CMV infection. ELISA is the most commonly available serologic test for measuring antibody to CMV.

1.11.5 TREATMENT

Cytomegalovirus Immune Globulin Intravenous (Human) (CMV-IGIV) is an immunoglobulin G (IgG) containing a standardized amount of antibody to Cytomegalovirus (CMV). It may be used for the prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart.

Alone or in combination with an antiviral agent, it has been shown to:

- Reduce the risk of CMV-related disease and death in some of the highest-risk transplant patients
- Provide a measurable long-term survival benefit
- Produce minimal treatment-related side effects and adverse events.

Ganciclovir (Cytovene®) treatment is used for patients with depressed immunity who have either sight-related or life-threatening illnesses. Valganciclovir (Valcyte®) is an antiviral drug that is also effective and is given orally.

1.11.6PREVENTION

Vaccine

Cytomegalovirus vaccines are still in the research and development stage.