ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) – HIV VIRUS

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1. Introduction:

1.1 HIV History

Acquired Immune Deficiency Syndrome (AIDS) was first described as a new clinical entity in 1981. Initial reports were based on an unusual increase in the incidence of Kaposi sarcoma (KS) and Pneumocystis pneumonia (PCP), diseases that were considered at that time to occur rarely.

While both diseases are occasionally observed in different populations (e.g., KS in older men from the Mediterranean region or PCP in patients with leukemia after intensive chemotherapy), the occurrence of these diseases as indicators for severe immunodeficiency had not been observed before in otherwise healthy young individuals.

For example, the first two cases of HIV and AIDS in Nigeria were identified in 1985.

At the end of 2014, 14.9 million people were receiving ART worldwide; this represents 40% [37–45%] of the 36.9 million [34.3–41.4 million] people living with HIV.

Progress has also been made in preventing and eliminating mother-to-child transmission and keeping mothers alive. In 2014, a little over 7 out of 10
pregnant women living with HIV, or 1 070 000 women, received antiretrovirals (ARVs).

WHO has released a set of normative guidelines and provides support to countries in formulating and implementing policies and programmes to improve and scale up HIV prevention, treatment, care and support services for all people in need.

This fact file provides current data on the disease, and ways to prevent and treat it.)

### 1.2. Introduction of the virus

HIV is the abbreviation used for the Human Immunodeficiency Virus. HIV attacks the body's immune system. Normally, the immune system produces white blood cells and antibodies that attack viruses and bacteria. The infection fighting cells are called T-cell lymphocytes.

Months to years after a person is infected with HIV, the virus destroys all the T-cell lymphocytes. This disables the immune system to defend the body against diseases and tumors. Various infections will be able to develop, these opportunistic infections take advantage of the body's weakened immune system. These infection which normally won't cause severe or fatal health problems will eventually cause the death of the HIV patient.

Untreated HIV disease is a chronic progressive process that begins with infection, is often followed by a "primary HIV syndrome," and progresses in adults over a median period of more than 10 years to the late stage: AIDS. From the time of infection, the virus continuously and rapidly replicates, mutates, and as a result diversifies and evolves in response to selective pressure. Immune system damage also begins upon infection.
The burden of virus and the bulk of this process occurs in lymphoid tissue, and the immune system struggles to hold the process in check. Slowly, but relentlessly, the process destroys essential components of the host immune system. Progression is often accelerated in infants with prenatal HIV infection. Eventually the host becomes increasingly susceptible to and eventually dies as a result of complications of opportunistic infections and malignancies resulting from immune system dysfunction.

1.3 The Distribution

According to data published by the World Health Organization (WHO), roughly 35 million people were living with HIV, approximately 2.1 million people were newly infected with HIV.

HIV infection and AIDS are spreading rapidly among the world's children, especially among African-American and Hispanic children in the USA, and those in developing countries. Although recent research has identified several ways of preventing perinatal transmission of HIV, most of these methods are too expensive for widespread use in developing countries, where the epidemic is most severe.

1.4 The HIV Epidemic

CDC estimates that 1.2 million people in the United States are living with HIV – and nearly one in eight of those are not aware that they are infected.

GLOBAL STATISTICS

15.8 million People accessing antiretroviral therapy (June 2015)

36.9 million [34.3 million–41.4 million] people globally were living with HIV (end 2014)
2 million [1.9 million–2.2 million] people became newly infected with HIV (end 2014).

1.2 million [980 000–1.6 million] people died from AIDS-related illnesses (end 2014).

Approximately 50,000 people become newly infected each year.\(^2\) In addition to recognized risk behaviors, a range of social prevention efforts have helped keep the rate of new infections stable in recent years, but continued growth in the number of people living with HIV ultimately may lead to more new infections if prevention, care, and treatment efforts are not targeted to those at greatest risk and economic factors places some Americans at increased risk for HIV infection.
<table>
<thead>
<tr>
<th>Region</th>
<th>People living with HIV 2014</th>
<th>New HIV infections 2014</th>
<th>AIDS-related deaths 2014 (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>children</td>
<td>total</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>25.8 million [24.0 million–28.7 million]</td>
<td>2.3 million [2.2 million–2.5 million]</td>
<td>1.4 million [1.2 million–1.5 million]</td>
</tr>
<tr>
<td>Asia and the Pacific</td>
<td>5.0 million [4.5 million–5.6 million]</td>
<td>200 000 [180 000–230 000]</td>
<td>340 000 [240 000–480 000]</td>
</tr>
<tr>
<td>Latin America</td>
<td>1.7 million [1.4 million–2.0 million]</td>
<td>33 000 [20 000–40 000]</td>
<td>87 000 [70 000–100 000]</td>
</tr>
<tr>
<td>Middle East and North</td>
<td>240 000 [150 000–320 000]</td>
<td>13 000 [10 000–16 000]</td>
<td>22 000 [13 000–33 000]</td>
</tr>
</tbody>
</table>
3. HIV Classification

HIV is a member of the genus Lentivirus, part of the family Retroviridae. Two types of HIV have been characterized: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed both LAV and HTLV-III. It is more virulent, more infective, and is the cause of the majority of HIV infections globally.

4. HIV Structure

4.1. Shape

An HIV virus particle is spherical.

4.2. Size

Has a diameter of about 1/10,000 mm.

Like other viruses, HIV does not have a cell wall or a nucleus.

4.3. Nucleic acid

Single-stranded RNA genome

<table>
<thead>
<tr>
<th>Group</th>
<th>Group VI (ssRNA-RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>Unassigned</td>
</tr>
<tr>
<td>Family</td>
<td>Retroviridae</td>
</tr>
<tr>
<td>Subfamily</td>
<td>Orthoretrovirinae</td>
</tr>
<tr>
<td>Genus</td>
<td>Lentivirus</td>
</tr>
<tr>
<td>Species</td>
<td>Human immunodeficiency virus 1.</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus 2.</td>
</tr>
</tbody>
</table>
4.4 Envelope:

The outer coat of the virus, consists of two layers of lipids; different proteins are embedded in the viral envelope, forming "spikes" consisting of the outer glycoprotein (gp) 120 and the transmembrane gp41.

5. Proteins

5.1 Structural Proteins

A - The HIV matrix proteins:
(Consisting of the p17 protein), lie between the envelope and core.

B- Gag proteins:
The gag gene gives rise to the 55 kilodalton Gag precursor protein, also called p55, which is expressed from the unspliced viral mRNA.

D- Envelope proteins:
Env exists as a multimer, most likely a trimer, on the surface of the cell of the virion. Interactions between HIV and the virion receptor, CD4, are mediated through specific domains of gp120.
5. **2 Non-Structural Proteins**

A- **HIV-1 protease:**
The HIV-1 protease is an aspartyl protease that acts as a dimer. Protease activity is required precursors during virion maturation.

B- **Reverse transcriptase:**
During the process of reverse transcription, the polymerase makes a double stranded DNA copy of the dimer of single stranded genomic RNA present in the virion.

C- **Integrase:**
The integrase protein mediates the insertion of the HIV proviral DNA into the genomic DNA of an infected cell.

D- **Regulator proteins:**
- **Tat:**
  Tat is a transcriptional transactivator that is essential for HIV-1 replication.
- **Rev:**
  Rev is a 13-kD sequence-specific RNA binding protein. Rev acts to induce the transition from the early to the late phase of HIV gene expression.

E- **Accessory proteins**
- **Vpr:**
  Vpr can block cell division.
- **Vpu:**
  Vpu also increases the release of HIV from the surface of an infected cell.

6. **Transmission**
• **Sexual transmission**:  
  Having anal or vaginal sex with someone who has HIV without using a condom or taking medicines to prevent or treat HIV  

• **Injection drug use related HIV infection**:  
  Transmission of HIV among injection drug users occurs primarily through HIV infected blood contamination of injection paraphernalia  

• **Transmission of HIV by blood, blood products, tissue transplantation and artificial insemination**:  

• **Vertical Transmission**:  
  Perinatal transmission of human immunodeficiency virus accounts for virtually all new HIV infections in children  

7. **Penetration and the Target Organ**  
CD4+ T lymphocytes and macrophages are the primary cellular CD4+ T lymphocytes and macrophages are the cellular targets of HIV targets of HIVSite of Replication  

8. **Replication Cycle (the main site)**.  
   The site of replication process occurs inside the nucleus.  

1. **HIV entry**.  
   CD4 as a primary receptor for HIV embedded in the outer membrane of the HIV virion bind to receptors on the surface of target cells. T-cells (white blood cells) have CD4 and CCR5 receptors to which HIV can bind. Binding of the HIV envelope protein to CD4 and CCR5 allows the HIV-1 outer membrane to fuse with the cell’s outer membrane and the contents of the virus particle to enter the cell.  

2. **Reverse transcription**:  

The genetic material of the virus is in the form of RNA, or ribonucleic acid. There are two strands of RNA in each HIV-1 virus particle. An enzyme known as reverse transcriptase initiates the formation of one double-stranded molecule of viral DNA (deoxyribonucleic acid) by copying the sequence of the RNA strands contained in the virus particle.

- **Integration of the viral DNA into cellular genomic DNA:**

  The viral DNA enters the nucleus of the host and becomes integrated into the host’s DNA. An enzyme called integrase is key in this process. Once the viral DNA has integrated into the cell’s DNA, the cell is infected for the remainder of its life. The integrated viral DNA is now referred to as a provirus.

- **Transcription:**

  The provirus DNA serves as a template for the creation of new viral RNA via a process known as transcription. The host cell’s own machinery that is normally used for the transcription of human genes is used by the virus to create new viral RNA molecules. The newly formed viral RNA moves out of the infected cell’s nucleus.

- **Translation:**

  The viral RNA carries code for the synthesis of viral proteins and enzymes. The code is translated into long chains of amino-acids, known as a polypeptide chains, which fold to form the protein and enzyme components of new virus particles.
9. Assembly and Egression.

9.1 Assembly:
Components that are required to build new virus particles, namely viral proteins, enzymes and genetic material (viral RNA) move to the cell’s outer membrane where they accumulate and assemble in the form of a bud.

9.2 Release and Maturation:
Host-cell proteins cut the virus bud from the cell’s outer membrane, thereby releasing a new virus particle. During and after assembly and release, a viral enzyme called protease cuts the HIV polypeptide chains at several positions, in a process called maturation, to make the finished components of the new, infectious, virus particle. A single infected cell can release many new HIV particles which move on to infect other cells in various parts of the body, where the viral life cycle is repeated. The infected cells are eventually destroyed.

10. HIV/AIDS Symptoms

10.1 Early Symptoms:
In the first stages of HIV infection, most people will have very few, if any, symptoms. Within a month or two after infection, they may experience a flu-like illness, including:

1. Fever
2. Headache
3. Tiredness
4. Enlarged lymph nodes in the neck and groin area
These symptoms usually disappear within a week to a month and are often mistaken for another viral infection, such as flu. However, during this period people are highly infectious because HIV is present in large quantities in genital fluids and blood. Some people infected with HIV may have more severe symptoms at first or symptoms that last a long time, while others may have no symptoms for 12 years or more.

**10.2 Later Symptoms:**

During the late stages of HIV infection, the virus severely weakens the immune system, and people infected with the virus may have the following symptoms:

1. Rapid weight loss
2. Recurring fever or profuse night sweats
3. Extreme and unexplained tiredness
4. Prolonged swelling of the lymph glands in the armpits, groin, or neck
5. Diarrhea that lasts for more than a week
6. Sores of the mouth, anus, or genitals
7. Pneumonia
8. Red, brown, pink, or purplish blotches on or under the skin or inside the mouth, nose, or eyelids
9. Memory loss, depression, and other neurologic disorders.

**11. Diagnosis Of HIV Infection and Cytopathic effect.**

**11.1 HIV TESTING:**

Testing serum for antibodies to HIV with a standard ELISA (followed by a confirmatory Western Blot) is currently the most common, cost effective, and accurate method of screening for infection. Rapid serum HIV antibody tests, saliva- and urine-based antibody tests, and home HIV antibody testing kits
11.2. Cytopathic Effect Of HIV Infection

Direct cytopathic effect by HIV. The ability to directly lyse CD4+ T cells cause the reduction of these immune effector cells which leads to the clinical condition of AIDS.

In vitro, HIV causes two types of CPE – syncytia and single cell lysis. Syncytia are formed when Env expressed on an infected cell late in infection interacts with CD4 of a neighboring cell, triggering the fusion peptide of TM to fuse the two membranes.

12. Control the virus and Prevention:

There's no vaccine to prevent HIV infection and no cure for AIDS. But it's possible to protect yourself and others from infection. There are a number of ways you can protect yourself from HIV, including:

1. Avoiding sharing needles, syringes and other injecting equipment with anyone if you take drugs.

2. Taking HIV treatment if you are a new or expectant mother living with HIV, as this can dramatically reduce the risk of passing HIV to your baby during pregnancy, childbirth and breastfeeding.

3. Taking precautions if you are a healthcare worker, such as wearing protection (e.g. gloves, goggles), washing hands after contact with blood and other bodily fluids, and safely disposing of sharp equipment (like needles).

4. Asking your healthcare professional if the blood product you are receiving (blood transfusion, organ or tissue transplant) has been tested for HIV.

13. Treatment

A. Vaccines  no  Vaccines

B. Medication
Worryingly, many people think there is a 'cure' for HIV, the virus that causes AIDS. The only way to ensure that you avoid AIDS is to be aware of how HIV is transmitted and how to prevent HIV infection.

However, people can take antiretroviral treatment, which suppresses the HIV virus. This can prevent them from reaching a point where they are diagnosed with AIDS.

**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 the drugs are often referred to as: antiretrovirals, ARVs, anti-HIV or anti-AIDS drugs.

**What does combination therapy usually consist of?**

The leading recommendations for antiretroviral treatment were published by the World Health Organisation in 2013. 1 For adults and adolescents, they recommend starting on a first line therapy of two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI). The favoured recommendation is a fixed-dose combination (just one pill) of:

1. TDF (Tenofovir).
2. 3TC (Lamivudine) or FTC (Emtricitabine).
3. EFV (Efavirenz).

**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.

Second line therapy recommendations by WHO suggest two NRTIs and a ritonavir-boosted protease inhibitor.

14. Genetic

Proposed methods for the treatment of AIDS is: Viral vectors for gene therapy of HIV/AIDS which Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein.

1. Lentiviral vectors for gene therapy for HIV/AIDS
2. Using recombinant SV40-derived vectors to deliver anti-HIV-1 genetic therapy
3. Transgenes used to inhibit HIV-1
4. Combination genetic therapeutics to inhibit HIV-1
5. Transduction of CD34+ cells

15. Host Immune Defense

Humans are in continuous associations with microorganisms, including those that readily colonize the body surfaces (see The Bacterial Flora of Humans). It is relatively rare that these microorganisms cause damage to their host. In part, this is due to the effectiveness of the host defense mechanisms, which restrict invasion by normal flora (some of which may be potential pathogens), and which defend against non-indigenous microorganisms that are overt pathogens.

The outcome of an interaction between a human host and a microbe, whether it is a component of the normal flora or an exogenous pathogen, depends on specific properties inherent to both the host and the microbe. Sometimes, the host tolerates colonization by a parasite but restricts it to regions of the body where it can do no harm (e.g. Staphylococcus aureus on
the nasal membranes or Streptococcus pneumoniae in the upper respiratory tract). If the parasite invades (i.e., breaches an anatomical barrier or progresses beyond the point of colonization), an infection is said to have occurred. If, as a result of infection, pathological harm to the host becomes evident, this is called an infectious disease.

The healthy animal defends itself against pathogens different stages. The host defenses may be of such a degree that infection can be prevented entirely. Or, if infection does occur, the defenses may stop the process before disease is apparent. At other times, the defenses that are necessary to defeat a pathogen may not be effective until infectious disease is well into progress.

The host defense mechanisms are mediated by the immune system. For our purposes, the term immunity refers to the relative state of resistance of the host to infectious disease. Particularly as it relates to innate immunity and adaptive immunity.

The immune system is composed of two major subdivisions, the innate or nonspecific immune system and the adaptive or specific immune system. The innate immune system is a primary defense mechanism against invading organisms, while the adaptive immune system acts as a second line of defense. Both aspects of the immune system have cellular and humoral components by which they carry out their protective functions. In addition, there is interplay between these two systems, i.e., cells or components of the innate immune system influence the adaptive immune system and vice versa.

The innate and adaptive immune systems differ in several ways. The adaptive immune system requires some time to react to an invading organism, whereas the innate immune system includes defenses that, for the most part, are constitutively present and mobilized immediately upon
infection. Additionally, the adaptive immune system is antigen specific and reacts only with the organism that induced the response. The innate system is not antigen specific and reacts similarly to a variety of organisms. Finally, the adaptive immune system exhibits an immunological memory. It "remembers" that it has encountered an invading organism and reacts more rapidly on subsequent exposure to the same organism. The innate immune system does not exhibit a memory response.

Cellular defense. This term is used to distinguish whether an immune response is mediated by a particular type of cell, as opposed to a noncellular defense which does not involve a specifically programmed cell. As stated above, a variety of tissue cells are involved in innate and adaptive immunity, hence the term cellular defense. These include neutrophils and macrophages, which are involved in phagocytosis, basophils and mast cells, which are involved in inflammation, and B cells and T cells which account for antibody mediated immunity and cell mediated immunity, respectively.

All these cells have their origin in the bone marrow. Myeloid progenitor (stem) cells in the bone marrow give rise to neutrophils, eosinophils, basophils, monocytes and dendritic cells, while lymphoid progenitor (stem) cells give rise to T cells and B cells. Macrophages and dendritic cells, which play a key role in innate and adaptive immunity, are derived from monocytes; and mast cells, which are fixed in tissues, develop from the same precursor cell as circulating basophils. B cells are produced in bone marrow and released into the blood and lymphatic systems. B-cells can develop into plasma cells that secrete antibodies. Precursor T cells undergo differentiation in the thymus into two distinct types of T cells, CD4+ T helper cells, and the CD8+ cytotoxic T cells. Macrophages and dendritic cells function as one of several bridges between innate immunity and adaptive immunity, since they present antigens to immunocompetent T-cells, which initiates an immunological response.
Destruction following the action of toxic viral proteins (Apoptosis)

Apoptosis, or programmed cell death, is a physiological mechanism by which the cell «commits suicide» in a controlled way. Apoptosis-induced cell death.

Protein gp120 is probably the most important pro-apoptotic factor in HIV. It has been demonstrated that both the contact of viral particles and that of recombinant gp120 with the receptors of non-infected CD4 lymphocytes induce apoptosis by activating a series of metabolic routes which in turn induce the extrinsic and intrinsic pathways of apoptosis. In addition to gp120, it has been reported that three regulatory proteins, Tat, Vpr and Nef, have a pro-apoptotic effect by acting through different mechanisms. Tat activates the exogenous and endogenous pathway of apoptosis.

16. Recent studies

- The findings build on the success of several recent TSRI studies showing that, with prompting, the immune system can develop antibodies to neutralize many strains of HIV.
- In the new study, the researchers carried out a series of experiments involving virus modifications, protein and antibody engineering. They found that four antibodies targeted a single spot on HIV’s surface called the V2 apex. This was significant because the V2 apex could be recognized by these antibodies on about 90 percent of known HIV strains—and even related strains that infect other species. A vaccine targeting this region could protect against many forms of the virus. “This region helps stabilize the virus, so it’s an important area to target if you want to neutralize HIV,”

Investigating further, the researchers noticed that two of the four antibodies had an unusual feature that could prove important in vaccine design.
Unfortunately, the immune system seems to naturally produce only a small number of these HIV-neutralizing germline antibodies. To generate an immune response that would favor these antibodies, it was critical for the scientists to find the right proteins in HIV that the antibodies could recognize and bind to.

In the new study, the researchers succeeded in mimicking a structure on HIV called the native HIV coat protein. This let them design proteins that do indeed bind well to the germline antibodies and hopefully start a useful immune response. The next step will be to test the vaccine candidates in animal models.

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