HIV/AIDS: A Life Threatening Disease

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Human Immune Deficiency Virus is a member of Retrovirus family, which causes AIDS. In 1984, a human retrovirus (HIV) was isolated and identified as the causes AIDS. AIDS was recognized for first time in USA in 1981, in 1986 the first case of HIV was identified in India. It is transmitted through unprotected sex, sharing of infected needle & syringe, from infected mother to her fetus and HIV infected blood transfusion. It is identified by testing antibodies to HIV within six month after infection. Mostly HIV test positive within three month. In rare case it takes six month for someone to test positive. Interval from HIV to diagnose AIDS ranges from about nine month to twenty years or longer, with a median of twelve years. There is no vaccine to prevent HIV infection and no cure for AIDS but life span after exposure is enhanced by the ART. There are different Holistic, Ayurvedic & Allopathic treatments are there but these treatment only increase the life span of patients, but are not responsible to kill the virus so AIDS could also be pronounced as “After Infection Death Sure”.

Keyword: Aldosterone, Marker of Heart Failure NT-ProBNP, Proinflammatory Cytokine Tnfα, Apoptosis Inducer Fas-Ligand, Enalapril, Candesartan, Chronic Pulmonary Heart Disease

1. Introduction

The word AIDS stand for Acquired Immuno Deficiency Syndrome. This mean deficiency of immune system, acquired during the lifetime of an individual indicating that it is not a congenital disease. This disease is mainly indicate by SYNDROME: this mean that "a group of symptom". AIDS was first reported in 1981 and in the last 25 years or so, it has spread all over the world killing more than 25 million persons.

AIDS is caused by Human Immuno Deficiency Virus (HIV), a member of a group of viruses called Retrovirus, which have an envelope enclosing the RNA genome. Transmission of HIV infection generally occurs by (a) sexual contact with infected person, (b) transfusion of contaminated blood, (c) by sharing the infected needles (d) from infected mother to her child[1].

Human immunodeficiency virus (HIV) is a Lentivirus (a member of the retrovirus family)[2][3].

1.1 Epidemiology:

In June 1981, five cases of Pneumocystis jiroveci i.e. pneumonia were described in homosexual men in USA. Reports of other unusual condition, such as Kaposi sarcoma, followed shortly. In each of these patients, there was found to be a marked impairment of cellular immune response, and so the term acquired immune deficiency syndrome, or aids, was coined. In 1984, a new human retrovirus, subsequently named HIV, was isolated and identified as the cause of AIDS.

In the UK, since 1999 the number of new HIV diagnoses has been higher in heterosexuals than in men who have sex with men, although more
recently this trend has been reversing, due to decline in diagnoses among people infected heterosexually abroad. The majority of heterosexual with HIV have acquired their infection in countries of high prevalence, whilst the majority of ongoing transmission within the UK is still amongst men who have sex with men. Additionally there is an increasing proportion of individual with HIV who are living in to older age. It is postulated that the ageing process is accelerated in the context of HIV infection, with a resultant increase in co-morbidities, such as cardiovascular disease, osteoporosis and osteopaenia, cancer, conegenitive impairment, and hepatic and renal dysfunction.

The impact of treatment advance on the incidence of AIDS related illness and mortality has been dramatic. However, the absolute number of new AIDS diagnoses and HIV related death in the UK has plateaued, largely due to late presentation and the failure to diagnose HIV infection amongst the asymptomatic population\(^4\).

1.2 History of AIDS in INDIA:
AIDS was recognized for the first time in the USA in 1981. In 1986, the first known case of HIV was diagnosed by Dr. Suniti Solmon amongst female sex workers in Chennai. Later that year, sex workers began showing signs of this deadly disease\(^5\).

At that time, foreigners in India were traveling in and out of the country. It is thought that these foreigners were the ones responsible for the first infections. By 1987, about 135 more cases came to light. Among these 14 had already progressed to AIDS. Prevalence in high risk groups reached above 5% by 1990. As per UNDP's 2010 report, India had 2.39 million (23.95 lakh) people living with HIV at the end of 2009, up from 2.27 million (22.7 lakh) in 2008. Adult prevalence also rose from 0.29% in 2008 to 0.31% in 2009. In 1986, HIV started its epidemic in India, attacking sex workers in Chennai, Tamil Nadu. Setting up HIV screening centers was the first step taken by the government to screen its citizens and the blood bank.

To control the spread of the virus, the Indian government set up the National AIDS Control Programme in 1987 to co-ordinate national responses such as blood screening and health education. In 1992, the government set up the National AIDS Control Organisation (NACO) to oversee policies and prevention and control programmes relating to HIV and AIDS and the National AIDS Control Programme (NACP) for HIV prevention. The State AIDS Control Societies (SACS) was set up in 25 societies and 7 union territories to improving blood safety.

In 1999, the second phase of the National AIDS Control Programme (NACP II) was introduced to decrease the reach of HIV by promoting behaviour change. The prevention of mother-to-child transmission programme (PMTCT) and the provision of antiretroviral treatment were materialized.

In 2007, the third phase of the National AIDS Control Programme (NACP III) targeted the high-risk groups, conducted outreach programmes, amongst others. It also decentralised the effort to local levels and non-governmental organisations (NGOs) to provide welfare services to the affected\(^6\).

1.3 Difference Between HIV & AIDS
Some people have a doubt between HIV and AIDS. So to differentiate them basic differences are given below:

HIV stands for Human Immunodeficiency Virus. It is the name of the virus which infects our immune system and damages it severely over a period of time.

Viruses, such as HIV, never go away. When a person becomes infected with HIV, that person becomes “HIV positive” and will always be HIV positive. Over time, HIV disease infects and kills white blood cells called CD4 lymphocytes (or “T cells”) and can leave the body unable to fight off certain kinds of infections and cancers.

AIDS stands for Acquired Immuno–Deficiency Syndrome. A healthy person usually has a CD4, (white blood cells) count of between 600 and 1,200. When the CD4 count drops below 200, a person's immune system is severely weakened,
and that person is then diagnosed with AIDS, even if he or she has not become sick from other infections. Once a person has been diagnosed with AIDS, she or he is always considered to have AIDS, even if that person's CD4 count goes up again and/or they recover from the disease that defined their AIDS diagnosis. After the diagnosis of AIDS is made, the current average survival time with antiretroviral therapy is estimated to be now more than 5 years, but because new treatments continue to be developed and because HIV continues to evolve resistance to treatments, estimates of survival time are likely to continue to change. Antiretroviral medication can prolong the time between HIV infection and the onset of AIDS. Without antiretroviral therapy, death normally occurs within a year. Most patients die from opportunistic infections or malignancies associated with the progressive failure of the immune system\[7\].

1.4 Transmission:

- HIV is primarily found in the blood, semen, or vaginal fluid of someone who is infected with the virus and is transmitted in four ways:
  - Having unprotected sex (anal, oral or vaginal) with someone infected with HIV.
  - Sharing needles and syringes with someone infected with HIV.
  - Being exposed to the virus as a fetus or infant before or during birth or through breastfeeding from an HIV-infected mother.
  - Receiving a transfusion of HIV-infected blood or blood products.

The following “bodily fluids” are NOT infectious:
- Saliva
- Tears
- Sweat
- Feces
- Urine\[8\]

1.5 Symptom:
Many people who are HIV-positive do not have symptoms of HIV infection. Often people only begin to feel sick when they progress toward AIDS (Acquired Immunodeficiency Syndrome). Sometimes people living with HIV go through periods of being sick and then feel fine. While the virus itself can sometimes cause people to feel sick, most of the severe symptoms and illnesses of HIV disease come from the opportunistic infections that attack a damaged immune system. It is important to remember that some symptoms of HIV infection are similar to symptoms of many other common illnesses, such as the flu, or respiratory or gastrointestinal infections.

As early as 2-4 weeks after exposure to HIV (but up to 3 months later), people can experience an acute illness, often described as “the worst flu ever.” This is called acute retroviral syndrome (ARS), or primary HIV infection, and it’s the body’s natural response to HIV infection. During primary HIV infection, there are higher levels of virus circulating in the blood, which means that people can more easily transmit the virus to others.

Symptoms can include:
- Fever
- Chills
- Rash
- Night sweats
- Muscle aches
- Sore throat
- Fatigue
- Swollen lymph nodes
- Ulcers in the mouth\[9\]

If you receive no treatment for your HIV infection, the disease typically progresses to AIDS in about 10 years. By the time AIDS develops, your immune system has been severely damaged, making you susceptible to opportunistic infections — diseases that wouldn't trouble a person with a healthy immune system. The signs and symptoms of some of these infections may include:
1.6 Symptoms of HIV/AIDS in Women
It's possible that a woman infected with HIV—the virus that causes AIDS, could display no symptoms, it's more typical that women infected with HIV will experience some subtle signs and symptoms of HIV that they may not perceive as warning signs of HIV infection. The three most common symptoms experienced by women after exposure to HIV are:

- Frequent or severe vaginal infections
- Abnormal Pap smears
- Pelvic infections such as PID that are difficult to treat

Other signs and symptoms of HIV infection include:
- Recurrent vaginal yeast infections
- Pelvic inflammatory disease or PID
- Pap smears that indicate abnormal changes or dysplasia
- Genital ulcers
- Genital warts
- Severe mucosal herpes infections[10].

1.7 Classification of HIV:
Two types of HIV infect humans:
A) HIV-1
B) HIV-2.
Both types are transmitted by sexual contact, through blood, and from mother to child. 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[12].

A) Classification of HIV 1:
The strains of HIV-1 can be classified into four groups: the "major" group M, the "outlier" group O and two new groups, N and P.

Group O appears to be restricted to west-central Africa and group N - a strain discovered in 1998 in Cameroon - is extremely rare. In 2009 a new strain closely relating to gorilla simian immunodeficiency virus was discovered in a Cameroonian woman. It was designated HIV-1 group P. More than 90 percent of HIV-1 infections belong to HIV-1 group M and, unless specified, the rest of this page will relate to HIV-1 group M only.

Within group M there are known to be at least nine genetically distinct subtypes (or clades) of HIV-1. These are subtypes A, B, C, D, F, G, H, J and K[13][14].

B) HIV 2:
HIV-2 was first described in 1985[15] and was isolated in 1986 in West Africa[16]. HIV-2 is associated with lower viral load levels and slower rates of CD4 decline and clinical progression compared with HIV-1.[17][18] 86% to 95% of people infected with HIV-2 are long-term nonprogressors[19][20].
Table: Distribution of HIV-1 Subtypes

<table>
<thead>
<tr>
<th>Group</th>
<th>Subtype</th>
<th>Distribution</th>
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<tbody>
<tr>
<td></td>
<td>A</td>
<td>East and Central Africa</td>
</tr>
<tr>
<td>M</td>
<td>B</td>
<td>North and South Africa, Europe, Asia, Oceania</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>South and East Africa, India, Brazil</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Central Africa</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Central Africa, Romania, Latin America</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Central Africa, Taiwan, Russia</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>Central Africa, Belgium</td>
</tr>
<tr>
<td></td>
<td>J</td>
<td>Congo, Gambia, Sweden</td>
</tr>
<tr>
<td></td>
<td>K</td>
<td>Cameroon</td>
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<tr>
<td>O</td>
<td></td>
<td>Cameroon, Gabon, France</td>
</tr>
<tr>
<td>N</td>
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<td>Cameroon</td>
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</tbody>
</table>

The most prevalent HIV-1 genotypes are subtypes C (47%), A (27.2%), B (12.3%), D (5.3%) and CRF01_AE (3.2%)[21].

1.8 Action of HIV in body:

1.8.1 Action:
In order for viruses to reproduce, they must infect a cell. Viruses are not technically alive: they are sort of like a brain with no body. In order to make new viruses, they must hi-jack a cell, and use it to make new viruses. Just as your body is constantly making new skin cells, or new blood cells, each cell often makes new proteins in order to stay alive and to reproduce itself. Viruses hide their own DNA in the DNA of the cell, and then, when the cell tries to make new proteins, it accidentally makes new viruses as well. HIV mostly infects cells in the immune system.

a. Infection: Several different kinds of cells have proteins on their surface that are called CD4 receptors. HIV searches for cells that have CD4 surface receptors, because this particular protein enables the virus to bind to the cell. Although HIV infects a variety of cells, its main target is the T4-lymphocyte (also called the "T-helper cell"), a kind of white blood cell that has lots of CD4 receptors. The T4-cell is responsible for warning your immune system that there are invaders in the system.

b. Replication: Once HIV binds to a cell, it hides HIV DNA inside the cell's DNA: this turns the cell into a sort of HIV factory.

c. DNA: DNA is like the "blueprint" for building living cells.

d. Enzymes: Enzymes are like the workers of a cell. They build new proteins, transport materials around the cell, and carry out other important cellular functions.

e. RNA: RNA is like the construction boss. Cells use RNA to tell enzymes how to build a specific part of a cell. To make a new protein, enzymes will copy a specific part of the DNA into a piece of RNA. This RNA is then used by other enzymes to build a new protein or enzyme.s

f. Proteins: The building blocks that are used to make living things.
**g. Nucleus:** A small package inside the cell where the genetic material is kept.

1.8.2 Steps include in action of hiv:

a. **Binding:**

Virus consists of an outer envelope of protein, fat, and sugar wrapped around a set of genes (in the case of HIV, genetic information is carried as RNA instead of DNA) and special enzymes. HIV has proteins on its envelope that are strongly attracted to the CD4+ surface receptor on the outside of the T4-cell. When HIV binds to a CD4+ surface receptor, it activates other proteins on the cell's surface, allowing the HIV envelope to fuse to the outside of the cell. Entry can be blocked by entry inhibitors.

b. **Reverse transcription:**

HIV's genes are carried in two strands of RNA, while the genetic material of human cells is found in DNA. In order for the virus to infect the cell, a process called "reverse transcription" makes a DNA copy of the virus's RNA. After the binding process, the viral capsid (the inside of the virus which contains the RNA and important enzymes) is released into the host cell. A viral enzyme called reverse transcriptase makes a DNA copy of the RNA. This new DNA is called "proviral DNA."

Reverse transcription can be blocked by: Nucleoside Reverse Transcriptase Inhibitors (NRTIs), and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs). In fig point 1 can represent the binding.

c. **Integration:**

The HIV DNA is then carried to the cell's nucleus (center), where the cell's DNA is kept. Then, another viral enzyme called integrase hides the proviral DNA into the cell's DNA. Then, when the cell tries to make new proteins, it can accidentally make new HIVs. Integration can be blocked by integrase inhibitors. Point 3 represent it.

d. **Transcription:**

Once HIV's genetic material is reach inside the cell's nucleus, it directs the cell to produce new HIV. The strands of viral DNA in the nucleus separate, and special enzymes create a complementary strand of genetic material called messenger RNA or mRNA (instructions for making new HIV). Transcription can be blocked by antisense antivirals or transcription inhibitors (TIs), new classes of drugs that are in the earliest stage of research.
The mRNA carries instructions for making new viral proteins from the nucleus to a kind of workshop in the cell. Each section of the mRNA corresponds to a protein building block for making a part of HIV. As each mRNA strand is processed, a corresponding string of proteins is made. This process continues until the mRNA strand has been transformed or "translated" into new viral proteins needed to make a new virus.

Maturation is the final step in the process and is required for the virus to become infectious. With viral assembly and maturation completed, the virus is able to infect new cells. Each infected cell can produce a lot of new viruses. Viral assembly can be blocked by Protease Inhibitors (PIs). Maturation, a new target of companies developing anti-HIV drugs, may be blocked using Maturation Inhibitors.

Viral assembly and maturation:
The final step begins with the assembly of new virus. Long strings of proteins are cut up by a viral enzyme called protease into smaller proteins. These proteins serve a variety of functions; some become structural elements of new HIV, while others become enzymes, such as reverse transcriptase.

Once the new viral particles are assembled, they bud off the host cell, and create a new virus. The virus then enters the maturation stage, which involves the processing of viral proteins.

Incubation period:
Most people who have HIV, the virus that can lead to AIDS, have no symptoms for several years. Some people do have flu symptoms within a couple months after getting infected, but many do not, and it is impossible to tell the difference between flu symptoms that are caused by normal flu and symptoms caused by HIV infection. Testing can detect antibodies to HIV within 6 months after infection. In fact, more than 98% of people who have HIV would test positive within 3 months. In very rare cases, it may take up to 6 months for someone to test positive. Testing is recommended 3 months and 6 months after possible exposure. It is very important to note that although symptoms may not appear for several years, and it may take months for someone to test positive, once someone is infected, they can transmit the virus to other people within a day or two.

Many people who have HIV can live long, healthy lives, because of improved treatments. Treatment can also increase the amount of time between diagnosis of HIV and diagnosis of AIDS. HIV kills CD4 cells, which help fight...
infections. AIDS is diagnosed when the CD4 count drops to 200 or below, and the immune system is severely damaged\cite{23}.

The interval from HIV infection to the diagnosis of AIDS ranges from about nine months to 20 years or longer, with a median of 12 years\cite{24}.

1.9 Stages of HIV:
HIV infection can be broken down in four different stages i.e.
1. primary infection
2. clinically asymptomatic stage
3. symptomatic HIV infection
4. progression from HIV to AIDS

**STAGE 1 : Primary HIV infection:**
- It is the first stage of infection and last for few weeks and symptom are flu like illness. During this stage there is a large amount of HIV in the peripheral blood and the immune system begins to respond to the virus by producing HIV antibodies and cytotoxic lymphocytes. This process is known as seroconversion.

**STAGE 2 : Clinically asymptomatic stage**
- This stage lasts for an average of ten years and, as its name suggests, is free from major symptoms, although there may be swollen glands. The level of HIV in the peripheral blood drops to very low levels but people remain infectious and HIV antibodies are detectable in the blood, so antibody tests will show a positive result.
- Research has shown that HIV is not dormant during this stage, but is very active in the lymph nodes. A test is available to measure the small amount of HIV that escapes the lymph nodes. This test which measures HIV RNA (HIV genetic material) is referred to as the viral load test, and it has an important role in the treatment of HIV infection.

**STAGE 3 : Symptomatic HIV infection**
- Over time the immune system becomes severely damaged by HIV. This is thought to happen for three main reasons:
- The lymph nodes and tissues become damaged or 'burnt out' because of the years of activity;
- HIV mutates and becomes more pathogenic, in other words stronger and more varied, leading to more T helper cell destruction;
- The body fails to keep up with replacing the T helper cells that are lost.
- Antiretroviral treatment is usually started when CD4 count (the number of T helper cells) drops to a low level. Treatment can stop HIV from damaging the immune system, therefore, HIV-infected individuals on treatment usually remain clinically asymptomatic.
- Symptomatic HIV infection is mainly caused by the emergence of certain opportunistic infections that the immune system would normally prevent. This stage of HIV infection is often characterised by multi-system disease and infections can occur in almost all body systems.

**STAGE 4 : Progression from HIV to AIDS**
- As the immune system becomes more and more damaged the individual may develop increasingly severe opportunistic infections and cancers, leading eventually to an AIDS diagnosis.
- A clinical criteria is used by WHO to diagnose the progression to AIDS, this differs slightly between adults and children under five. In adults and children (aged 5 or over) the progression to AIDS is diagnosed when any condition listed in clinical stage 4 is diagnosed and/or the CD4 count is less than 200 cells/mm3 or a CD4 percentage less than 15. In children younger than five, an AIDS diagnosis is based on having any stage 4 condition and/or a CD4 percentage less than 20 (children aged 12-35 months) and a CD4 percentage less than 25 (children less than 12 months). The criteria for diagnosing AIDS may differ depending on individual country guidelines.

1.10 WHO clinical staging of HIV disease in adults and adolescents

**Clinical Stage I:**
- Asymptomatic
- Persistent generalized lymphadenopathy
**Clinical Stage II:**
weight loss (under 10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruptions
Seborrhoeic dermatitis
Fungal nail infections

**Clinical Stage III:**
severe weight loss (over 10% of presumed or measured body weight)**
chronic diarrhoea for longer than one month
persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
anaemia (below 8 g/dl), neutropenia (below 0.5 billion/l) and/or chronic thrombocytopenia (below 50 billion/l)

**Clinical Stage IV:**
HIV wasting syndrome
Pneumocystis pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month’s duration or visceral at any site)
Oesophageal 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
Extrapulmonary cryptococcosis including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including non-typhoidal Salmonella)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis[25].

**1.11 Treatment for HIV:**
- There's no vaccine to prevent HIV infection and no cure for AIDS. But it's possible to protect yourself and others from infection. That means educating yourself about HIV and avoiding any behavior that allows HIV-infected fluids: blood, semen, vaginal secretions and breast milk - into your body.

There are the some protective measure which can be taken in account to prevent the HIV:

1. The best preventive measure is to completely abstain from having sex. Always follow safe sex practices such as use of condoms and avoiding any oral or anal intercourse. Sexual devices used by HIV positive individuals should not be shared with others. By this way, one can prevent the spread of this disease to others.

2. One should never shares needles, syringes, razors, toothbrushes or blades with others. These items can become a potential source of transmission.

3. An HIV-positive individual should never donate blood or organs. Any such donation can cause the disease to spread to other individuals.

4. If the partner with whom an HIV-positive individual had sex is pregnant, it is always better to share with her the fact about your condition. An early treatment can help in preventing the disease within the woman as well as the child[26].
1.12 Ayurvedic Herbal Treatment for HIV/AIDS
The following are some of the herbs, which are commonly used for the treatment of HIV/AIDS:

a. Amalaki (Emblica officinalis)
Amalaki or amla, or Indian gooseberry, is perhaps the richest known source of Vitamin C, which plays a very vital role in enhancing the immune system of the body. It has traditionally been used for curing number of diseases, such as inflammation, cancer, age-related renal disease, and diabetes. Nowadays, it is also used for the treatment of HIV.

c. Ashwagandha (Withania somnifera)
Ashwagandha or Indian ginseng, or Winter cherry has been traditionally used in Ayurveda, as a herb, which works to increase health and longevity. It is also considered to be a nontoxic herb that is said to normalize physiological function. Today, it is one of the most important components in HIV treatment.

d. Tulsi (Ocimum sanctum)
Tulsi extract has traditionally been used in Ayurveda, as a remedy for a number of ailments like common colds, headaches, stomach disorders, inflammation, heart disease, various forms of poisoning, and malaria. Its usage in Treatment of HIV has shown promising results, resulting in a number of patent right applications[27].

1.13 Ayurveda HIV Medicines:

a. Virus Killers- These type of medicine kills different viruses, including HIV Virus. Drugs like chathura, thriphala, sukshma thrifala etc, they directly act on virus and kill them in blood and lymph's. They will take time to act. They can avoid mutating HIV and even after mutation they surely find HIV in body. The Examples are- Sukshama Thriphala, Normal Thriphala, Etc

b. Immune Developers- These type of medicine develop immunity and CD4 cells as well as CD8 cells. Very useful as they increase immunity. More CD4 cells will be pumped in and human body will not face immunity deficiency there after. -Example- Chyavanprash, Ashwagandha Rasayana, Ajamamsa Rasayana, KannmadaRasayana, Shonitha Baskara Arishta. This give body a chance to fight HIV and evil effects.

c. Body Cleaners- These type of medicine clean the toxic after math of HIV and the deadly viral particles from body. These medicines are useful in clearing many other diseases as well. Examples are- Shonitha Baskara Arishta, nanary Arishta, Ksheera Bala.

d. Holistic HIV Medicines- This treatment is a holistic Medication with bio Magnetic HIV Medicines and immune enhancing herbal medicines. No side effects in this. This is purely ethical and most successful treatment in the history of HIV. Very easy to use -Even a 10 year old boy can use this. Bio Magnetic medicines will Inhibit HIV from entering in CD4 and within days HIV will be ousted from body- While herbals will enhance the immune system to fight with secondary infections. This will underline the success.

BM Tablets are potent HIV Medicines. HIV Medicines are useful for both curing HIV and regaining strength. HIV Medicines are very useful to check the enemy.

Holistic medicines are divine and pure. Never create any bad effects to body and soul. They do not kill anything but they block HIV from entering CD4 by creating a similar (negative) charge on CD4 cell's membrane which in due repel the HIV protein from settling on CD4 cell. And HIV will fail to attach to CD4 anymore. HIV will be ousted out of body and patient will come back to life.
1.14 Allopathic Hiv Medicines-
1. Nucleoside analog reverse transcriptase inhibitors- These drugs can block HIV's ability to copy a cell's DNA. Without complete DNA, HIV can't make new virus copies. These HIV medicines include the following

   **Zidovudine**, also known as AZT (brand name: Retrovir)
   **Didanosine**, also known as ddI (brand name: Videx)
   **Zalcitabine**, also known as ddC (brand name: Hivid)
   **Lamivudine**, also known as 3TC (brand name: Epivir)
   **Stavudine**, also known as d4T (brand name: Zerit)
   **Abacavir**, also known as ABC (brand name: Ziagen)

2. Non-nucleoside reverse transcriptase inhibitor-
   Also doing same function as above but better way and faster.
   These HIV medicines include the following

   **Delavirdine** (brand name: Rescriptor)
   **Nevirapine** (brand name: Viramune)
   **Efavirenz**, also known as EFV

3. Protease inhibitors-
   These medicine will prevent infected cells from releasing **HIV Medicine into** the body.
   Type of medicines are following-

   **Saquinavir** (brand name: Invirase)
   **Indinavir** (brand name: Crixivan)
   **Nelfinavir** (brand name: Viracept)
   **Ritonavir** (brand name: Norvir)
   **Amprenavir** (brand name: Agenerase)

4. Fusion inhibitors-
   Prevent HIV from entering into CD4 cells.
   Examples-
   **Enfuvirtide** (brand name: Fuzeon)[28].

1.15 Mechanism of action of allopathic drugs:
1.15.1. Nucleoside analog reverse transcriptase inhibitors:
   A nucleoside analog antiretroviral drug whose chemical structure constitutes a modified version of a natural nucleoside. These compounds suppress replication of retroviruses by interfering with the reverse transcriptase enzyme. The nucleoside analogs cause premature termination of the proviral (viral precursor) DNA chain. All NRTIs require phosphorylation in the host's cells prior to their incorporation into the viral DNA.

   **Action 1:**
   As nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) have a similar mechanism of
action, they are usually regarded as a single drug class.

When reverse transcription occurs in the presence of these drugs, they disrupt the construction of a new piece of proviral DNA. Instead of taking up a natural nucleotide from the supply in the cell, reverse transcriptase may use an NRTI or NtRTI triphosphate instead. Because these drugs have a slightly different structure than natural nucleotides, they cannot form the necessary chemical bonds, and natural nucleotides cannot be added on to continue the chain. Since HIV has no mechanism for correcting such mistakes, NRTIs and NtRTIs can interrupt reverse transcription and thereby halt HIV replication. NRTIs and NtRTIs can stop reverse transcription and interfere with workings of human cells. Because they resemble the natural building blocks of DNA, there is a risk that NRTI or NtRTI triphosphates may be taken up when host cells reproduce. Some researchers believe this is a not a major problem, since the equivalent human enzyme, called DNA polymerase, has a much lower affinity than reverse transcriptase for NRTI/NtRTI triphosphates. Moreover, human cells have mechanisms for recognising and correcting mistakes in DNA production.[29][30].

1.16 Mechanisms of HIV antiretroviral drug action and drug resistance

1.16.1 Mechanism of resistance

There are two ways in which NRTI resistance can be achieved:
1. Discrimination pathway
2. Excision pathway

1. Discrimination pathway

These resistance mutations are amino acid changes in the primary structure of reverse transcriptase that increase the selective ability of the enzyme to incorporate the natural nucleotide over the NRTI-triphosphate (eg. K65R, K70E, L74V, M184V and Q151M).

There are two ways in which discrimination can be achieved:
Decrease the binding affinity of the NRTI-triphosphate over the natural nucleotide in the reverse transcriptase active site (eg. M184V and V75T). In experiments with wild-type and mutant reverse transcriptase carrying the M184V mutation measuring the binding affinity for 3TC-triphosphate, the mutant reverse transcriptase was shown to bind the 3TC-triphosphate with a reduced affinity over the wild-type enzyme resulting in a 48.8 fold increase in resistance.

Decrease the rate of incorporation of the NRTI-triphosphate over the natural nucleotide (eg. K65R, K70E, L74V and Q151M). In experiments with wild-type and mutant reverse transcriptase carrying the K65R mutation measuring the polymerisation activity for 3TC-triphosphate, the mutant reverse transcriptase was shown to reduce the rate of incorporation of 3TC-triphosphate resulting in a 13.1 fold increase in resistance.

2. Excision pathway

These resistance mutations are amino acid changes in the primary structure of reverse transcriptase that facilitate the removal of the chain-terminators NRTI-triphosphate from the 3’ end of the DNA chain after it has been incorporated (eg. M41L, D67N, K70R, L210W, T215F/Y and K219Q).

The excision pathway is dependent on adenosine triphosphate (ATP) or pyrophosphate therefore mutations that increase the affinity of reverse transcriptase for ATP or increase the rate of removal of the analogue complex are favoured. Also changes in the translocation ability of the residues from the active site (N-site) to the post-translocation site (P-site) as well as the rate of dissociation of the template/primer from the enzyme can enhance the excision pathway.[31]
1.17 Action of NRTI[32]

1.17.1 Side effect of NRTI:
Nausea, stomach discomfort, headache, insomnia, muscle wasting, anemia, neutropenia (low white blood cell count). Medicine should be taken with food to reduce the stomach discomfort[33].

1.17.2 Non-Nucleoside Reverse Transcriptase Inhibitor-
NNRTIs inhibit reverse transcriptase (RT), an enzyme that controls the replication of the genetic material of HIV. [34] NNRTI bind directly to the reverse transcriptase enzyme and causes a structural change that disrupts the formation of the active site and leads to impaired polymerization activity[35].

1.17.3 Mechanism of action:-
these drugs bind to hiv reverse transcriptase at a site adjacent to active site including a conformational change that result in enzyme inhibition. they do not require activation by cellular enzyne. their major advantages is their lack of effect on the host blood forming element and their lack of cross resistance with NRTI. these drug however do have a common characteristics that include cross resistance with in the NNRTI class drug interaction and a high incidence of hypersensitivity reaction including rashes.[36]

Side effect:-
Rash, including Stevens-Johnson syndrome
  Hepatotoxicity (especially NVP)[37].

a. Protease inhibitor:
The third class of antiretroviral drugs developed against HIV were the protease inhibitors. These work far back in the life cycle of HIV, after host cell integration but before budding. These drugs affect the enzyme protease, which is used to cut up the HIV protein to be packaged into virions. When the cell produces HIV proteins, the raw material is in a long connected string. The enzyme protease acts as a “scissor” to cut up the string into the protein for each virion. Protease inhibitors prevent protease from doing this. They resemble pieces of the protein string that protease usually cuts. This disrupts the cutting process, which prevents the chain from being cut into small pieces, which prevents HIV from making copies of itself[38][39][40][41].

side effect:-
An increase in blood sugar.
Changes in the distribution of body fat.
Headaches.
Nausea, diarrhea, and vomiting.
Rash.
An increase in cholesterol and triglycerides.
Liver problems, especially if you have liver disease[42][43].

b. mechanism of PI:

After transcription in the nucleus, viral mRNA enters the cytoplasm and uses the host's cellular machinery to manufacture virus proteins. The viral components then gather at the cell membrane and immature viruses bud off the cell. Core proteins are produced as part of long polypeptides, which must be cut into smaller fragments by the enzyme protease in order to form mature, functional proteins. Protease inhibitors bind to the site where protein cutting occurs, and so prevent the enzyme from releasing the individual core proteins. In this way the new viral particles are unable to mature or become infectious[44].
c. Fusion Inhibitor:—fusion inhibitor also called the entry inhibitor, are a class of antiretroviral drugs, used in combination therapy for the treatment of HIV infection. This class of drugs interferes with the binding, fusion and entry of an HIV virion to a human cell. By blocking this step in HIV's replication cycle, such agents slow the progression from HIV infection to AIDS. When HIV invades your body, the virus attaches to the outside of a CD4+ cell (a type of white blood cell) where it joins (fuses) with the cell and then multiplies. Fusion and entry inhibitors prevent fusion between the virus and the cell from occurring and prevent the virus from entering the cell. So HIV is unable to infect the cell and multiply.

Side effect:-

a. Enfuvirtide
Common side effects of enfuvirtide include skin itchiness, swelling, and pain at the site of the injection. Other side effects may include fatigue, numbness in feet or legs, dizziness, and insomnia.

c. Maraviroc
Common side effects of maraviroc include a cough, fever, dizziness, headache, and nausea. Other side effects reported for maraviroc include an increased risk of some infections and also liver and heart problems.

b. Maraviroc
Common side effects of maraviroc include a cough, fever, dizziness, headache, and nausea. Other side effects reported for maraviroc include an increased risk of some infections and also liver and heart problems.

d. Integrase inhibitor
Integrase inhibitor bind to the integrase enzyme, thus blocking the integration of viral DNA in to host DNA. there is currently one licenced agent, Raltegravir.

1.17.4 Mechanism of action
IV integrase is one of three enzymes (reverse transcriptase, protease, and integrase) encoded by the virus, which are essential for HIV replication. After entry into CD4+ T cells, viral RNA is transcribed into DNA by HIV reverse transcriptase. Following this step, the integrase enzyme combines with viral DNA and other cellular cofactors to form the preintegration complex (PIC). Subsequently, the integrase enzyme removes a nucleotide from each 3’ DNA terminus, thereby exposing reactive hydroxyl groups. The PIC then enters the host cell nucleus where it binds to host cell DNA. Integrase nicks each strand of the host cell DNA and exposes the 5’ phosphate groups, enabling covalent bonding of host and viral DNA. After this strand transfer is complete, host cell enzymes repair gaps between the viral and host DNA. Raltegravir and elvitegravir both target the strand transfer step of viral DNA integration and are sometimes referred to as “INSTI” (integrase strand transfer inhibitor) drugs. These drugs prevent or inhibit the binding of the preintegration complex to host cell DNA, thus terminating the integration step of HIV replication.

Side effect:-

a. Enfuvirtide
Common side effects of enfuvirtide include skin itchiness, swelling, and pain at the site of the injection. Other side effects may include fatigue, numbness in feet or legs, dizziness, and insomnia.

b. Maraviroc
Common side effects of maraviroc include a cough, fever, dizziness, headache, and nausea. Other side effects reported for maraviroc include an increased risk of some infections and also liver and heart problems.

1.18 Toxicity of Antiretroviral Therapies:
1.18.1 Mitochondrial toxicity: mitochondrial toxicity is increasingly recognised in patient with prolong exposure to nucleoside analogue antiretrovirals, particularly stavudine, didanosine and, to a lesser extent, zidovudine, and is thought to explain such side effect as peripheral neuropathy, myopathy, pancreatitis and lactic acidosis. If these problem should arises, management is to switch the likely causative agent, if possible.
1.18.2 Rash and Hepatitis
These are the both recognised sideeffect of the NNRTI class, although the incidence and severity appear greatest with nevirpine, particularly in patient with a higher CD4 count.

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