**The current status, progress, challenges and opportunities of HIV-AIDS treatment**

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**Introduction:-**

In humans, two subclasses of retroviruses called lentiviruses i.e.,"Human Immunodeficiency Virus (HIV)" cause acquired immunodeficiency syndrome (AIDS), a condition characterized by a progressive immune system failure and increased susceptibility to malignancies and opportunistic infections, which can be deadly after prolonged exposure by the viruses [Weiss RA; 1993]. The two most common forms of HIV are HIV-1 and HIV-2. The AIDS-like sickness caused by HIV-2 is milder and less dangerous than that of HIV-1. In 1983, it was discovered for the first time in West Africa. Over ninety-nine percent of all cases of AIDS are currently caused by HIV [Singh RP, 2012].

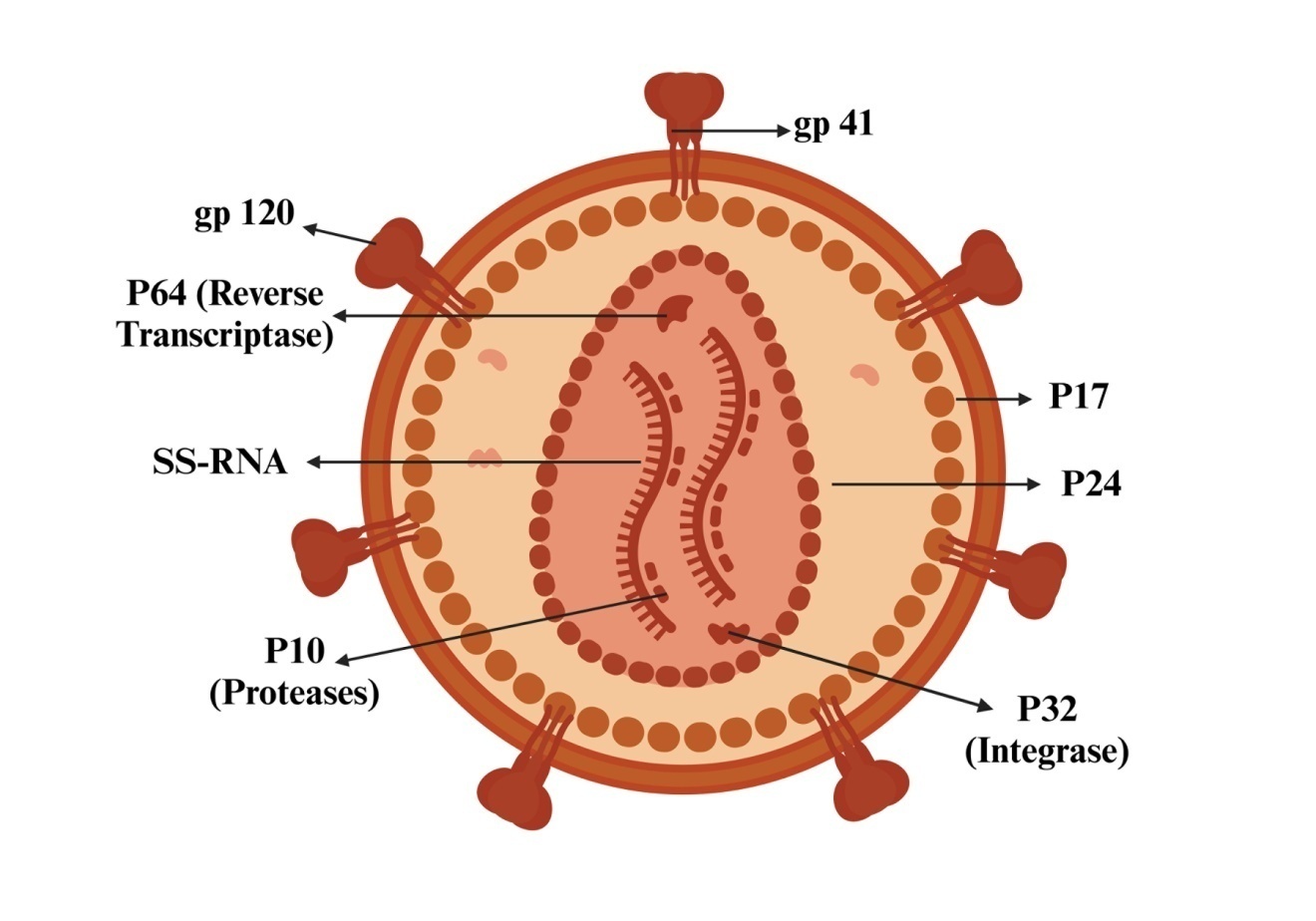
Contact with pre-ejaculate semen, blood, or vaginal secretions are the primary mode of transmission for the HIV virus, which is mostly asexually transmitted disease (STD).When a mother's blood, vaginal fluid, or breast milk comes into touch with her infant during pregnancy, delivery, or breastfeeding, it can cause non-sexual transmission [Roederer A et al, 2009]. HIV is present in these bodily fluids in two forms: as free virus particles and as the virus inside infected immune cells. If one partner in a same-sex relationship has an undetectable viral load for an extended period of time, then research suggests that condom-free sexual activity cannot transmit HIV[Roederer A et al, 2009; Eisinger RW et al, 2019].

Dendritic cells, macrophages, and helper T cells—particularly CD4+ T cells—are infected by HIV [Cunningham AL, 2009]. A low number of CD4+ T cells is a result of HIV infection due to several processes, such as the death of uninfected bystander cells, the viral killing of infected cells directly, and the death of infected CD4+ T cells by CD8+ cytotoxic lymphocytes that identify infected cells.Loss of cell-mediated immunity and a rise in the body's vulnerability to opportunistic infections cause AIDS when CD4+ T cell numbers fall below a particular threshold [Kumar V, 2012].

**Structure of HIV :-**

A protein sheath encases HIV and secures the glycoprotein spicules; the virus itself has a diameter of 120 nm [Eisinger RW, 2019; Chan DC, 1997]. It contains the genetic instructions for all nine genes encoded by the virus and consists of a pair of positive-sense single-stranded RNA copies. With a total of 9749 nucleotides, the two RNA genomes encased inside the conical capsid are two thousand copies of the viral protein p24. The p7 nucleocapsid proteins are strongly bound to the single-strand RNA, and the 1,20,000 Dalton gpl20 is bound to another protein called gp41, which traverses the viral envelope [Eisinger RW, 2019]. The gpl20, which is bound to the gp41 chemically, is the target of antibodies that may neutralize the virus and determine its infectiousness [Pineda-Peña AC et al., 2013]

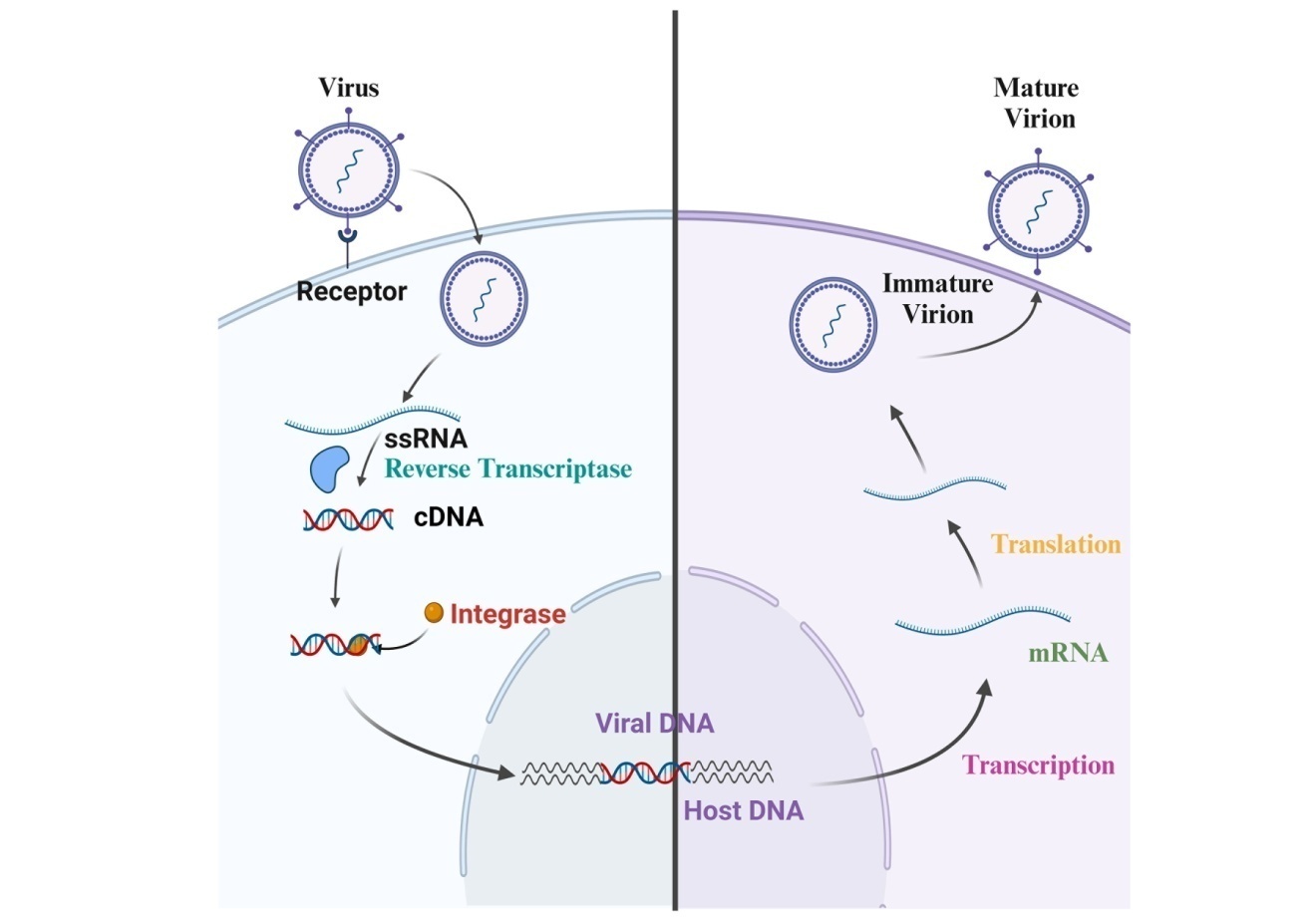
The polygonal shape of the core proteins around the central mass is similar to that of the envelope. Reverse transcriptase is bound to two twisted strands of RNA that are located in the centre of the bulk. The process of converting the RNA genome into its DNA counterpart is carried out by reverse transcriptase. The virion's growth-inducing enzymes, such as ribonuclease, integrase, reverse transcriptase, and proteases, are tightly bound to the single-stranded RNA by the nucleocapsid proteins, p7. In order to keep the virion particle together, the viral protein p17 forms a matrix around the capsid. In turn, this is encircled by the viral envelope, which is composed of the lipid bilayer that is taken from the host cell membrane as the newly formed virus particle buds [Chan DC et al., 2007].



**Figure 1:** Structure of Human Immunodeficiency Virus (HIV): The HIV/AIDS Virus, a member of the Retroviridae family, the HIV virus is an intricate RNA virus belonging to the genus Lentiviruses. Gp120 and gp41, the two main envelope glycoproteins of HIV, create an icosahedral structure that is about 100 nm in size and has 72 exterior spikes. The viral gag gene encodes core proteins p6 and p24, matrix protein p17, and nucleocapsid protein p7. Underneath the envelope, these proteins are visible. It is in the surface protein gp120 that the most noticeable serological variations exist. Because the V3 (variable region) of the gp120 protein is quite varied, HIV-1 and HIV-2 are further subdivided into 'clades'. Several proteins from the host cell are embedded in the lipid bilayer when it undergoes budding. HIV's distinctive core protein, p24, forms a thick, cone-shaped nucleocapsid. This nucleocapsid contains two copies of the viral enzymes integrase, protease, reverse transcriptase (RT), and RNase H, as well as the 9.8 kb single-stranded positive polarity RNA genome.

**Development in host cell:-**

When an individual has HIV, the virus targets and kills their immune system's CD4 cells, also known as CD4 T lymphocytes. Essential for the defense of the body against sickness are white blood cells called CD4 cells [Kumar V, 2013]. The method by which HIV multiplies and spreads throughout the body is mediated by CD4 cells. There are many stages to this process, which is known as the HIV life cycle [Kumar V, 2013; Chan DC et al., 1997]



**Figure 2:** HIV life cycle is shown in as follows: Beginning with binding and continuing through fusion, reverse transcription, integration, replication, assembly, and budding, the HIV life cycle consists of seven distinct phases. First, the HIV virus attaches itself to the cells of the host. HIV particles, such as RNA, reverse transcriptase, integrase, and other proteins, are able to enter host cells when the virus fuses with their cell membrane. Thirdly, Reverse Transcriptase is responsible for converting HIV RNA to DNA inside the cell. Integration: The Integrase enzyme will join the HIV DNA with the host DNA. A fifth feature of HIV is its ability to replicate, which involves the production of longer chains of HIV proteins. Assembly: HIV RNA and proteins assemble onto the cell surface to become immature HIV. Budding: Proteases allow immature HIV to be transformed into mature infectious HIV, and cells release the virus.

**Attachment and fusion**

Macrophages and CD4+ T cells are infected when the HIV virion fuses with their membrane after attaching to receptors on the cell with surface glycoproteins. This process releases the HIV capsid into the cell. Introduction into cells is initiated by an interaction between the HIV viral envelope's trimeric envelope complex (gp160 spike), CD4, and a chemokine coreceptor on the surface of the target cell [Arthos J et al., 2008; Zheng YH et al., 2005]. In order to activate LFA-1, the main integrin involved in the creation of virological synapses that facilitate the efficient cell-to-cell transmission of HIV-1, Gp120 binds to integrin α4β7. The gp160 spike accommodates both chemokine receptor binding domains and CD4 receptors. [Wyatt R et al., 2008; Arthos J et al., 2008].

The attachment of gp120 to the CD4 protein causes a structural change in the envelope complex, which in turn allows contact with the target chemokine receptor by exposing its chemokine receptor binding domains. This allows the N-terminal fusion peptide gp41 to penetrate the cell membrane by facilitating a more firm two-round attachment [Wyatt R et al., 2008; Arthos J et al., 2008]. After that, the hairpin shape of gp41 is achieved by the collapse of its extracellular portion due to interactions between HR1, HR2, and repeat sequences in gp41. The loop structure of the virus brings the cell and viral membranes close together, which allows the capsid to fuse and invade the cell [Wyatt R et al., 2008; Arthos J et al., 2008 [Wyatt R et al., 2008; Arthos J et al., 2008; Schaller T et al. 2011 ]. Once HIV has attached to a cell, it releases a slew of enzymes into it, including reverse transcriptase, integrase, ribonuclease, and protease, among others [Arthos J et al., 2008]. En route to the nucleus, the viral genome undergoes a conversion from single-strand RNA to double-strand DNA, which it then incorporates into a host chromosome. This process is facilitated by microtubules.

**Replication and Transcription**

The viral proteins that accompany the capsid release of the enzyme reverse transcriptase soon after the virus enters the cell. The process continues by creating a cDNA molecule from the positive-sense single-stranded RNA genome [Hu and Temin, 2012]. Mistakes in reverse transcription may lead to changes that make viruses more resistant to medications or able to evade the body's defenses. Furthermore, the reverse transcriptase has the ability to synthesize sense DNA from antisense cDNA via DNA-dependent DNA polymerase activity, as well as ribonuclease activity, which is responsible for breaking down the viral RNA during cDNA synthesis. After the viral DNA and its corresponding cDNA are joined, the resulting double-stranded DNA is transported to the cell nucleus. The host cell's genome incorporates the viral DNA [Hu and Temin, 2012].

This can be the latent HIV infection stage, when the integrated viral DNA remains inert. The active propagation of the virus depends on certain cellular transcription factors, the most important of which is nuclear factor kappa B, or NFκB, which is enhanced when T cells are activated.This suggests that HIV is most likely to target, penetrate, and kill the cells that are actively fighting infection. During viral replication, the incorporated DNA provirus is converted into RNA. The full-length genomic RNAs (gRNAs) may be packaged into new viral particles in a pseudo diploid form. [Hu and Temin, 2012]

It is also possible to create mature messenger RNAs (mRNAs) due to RNA processing. Here, RNA splicing is usually used to generate messenger RNAs (mRNAs) that are shorter than the whole genome. The specific regions of the RNA that are cut during RNA splicing determine which HIV protein-coding sequences get translated.After HIV messenger RNAs (mRNAs) reach their mature form in the nucleus, they are translated into HIV proteins in the cytoplasm. The messenger RNAs (mRNAs) that are translated into the structural proteins Gag and Env are derived from a subset of these whole RNAs. Gag proteins attach to viral genome copies, encasing them in new viral particles. It would suggest that HIV-1 and HIV-2 use different RNA splicing mechanisms.Any RNA that HIV1 finds acceptable may bind to it. [Charpentier et al., 2006]

**Recombination**

Two encapsulated RNA genomes are present in each HIV particle. Infection and reverse transcriptase-aided replication may lead to recombination of the two genomes. The process of recombination occurs during the reverse transcription of single-stranded positive-sense RNA genomes to produce DNA. During reverse transcription, the two copies of viral RNA may switch places with the growing DNA several times [Zhang et al., 2006]. This kind of recombination is referred known as copy-choice. Recombination may happen all along the genome. The number of recombination events per genome may range from two to twenty every replication cycle, and these events can rapidly rearrange the genetic material handed down from parents to offspring [Boseley, 2001].

**Assembly and release**

At the last step of the viral life cycle, the host cell's plasma membrane is where new HIV-1 virions are assembled. When furin in the Golgi apparatus cleaves the Env polyprotein (gp160), which has passed through the endoplasmic reticulum, the two HIV envelope glycoproteins, gp41 and gp120, are generated. They make their way to the plasma membrane of the host cell, where gp120 is attached to the infected cell's membrane by gp41. The Gag (p55) and GagPol (p160) polyproteins, in addition to the HIV genomic RNA, bind to the inner surface of the plasma membrane when the nascent virion begins to grow from the host cell. [Zhang et al., 2015].

The budded virion is still immature since the gag polyproteins have not yet been broken down into the matrix, capsid, and nucleocapsid proteins. Inhibitors of protease activity found in antiretroviral drugs may block the packed viral protease from executing this cleavage. At this point, the HIV virion's many structural components assemble to create a mature virus. The next stage is for infection to occur only in cells that have reached maturity [Zhang et al., 2015; Boseley, 2001].

**Mode of Transmission:**

Intergenerational transmission, in which HIV is passed from mother to child during pregnancy, birth, or nursing, is one of the three main ways that HIV may spread: first, via sexual contact; second, through substantial contact with infected body fluids or tissues; and third, through sexual contact [Vernazza and Bernard; 2006]. Contact with faeces, nasal secretions, saliva, sputum, sweat, tears, urine, or vomit does not provide a risk of catching HIV unless the person is contaminated with blood. When more than one kind of HIV infects a single host, this condition is known as multi-strain infection [ Vernazza and Bernard; 2006].

**Sexually Transmission:**

Having sexual relations with an infected individual is the primary vector for the transmission of HIV.But for an HIV-positive person whose undetectable viral load is the result of long-term therapy, the risk of HIV transmission via sexual activity is almost nonexistent.Recognizing the reality of HIV-positive persons taking antiretroviral therapy and being functionally non-contiguous has become standard medical practice, after its contentious revelation in the 2008 Swiss Statement.   
Vaginal sores and several sexually transmitted diseases increase the risk of transmission. Having a history of genital ulcers seems to increase the risk by around five times [Vernazza and Bernard; 2006]. The risk of transmission for other sexually transmitted diseases (STDs) such as gonorrhea, chlamydia, trichomoniasis, and bacterial vaginosis is somewhat lower. [Coutsoudis et al., 2010]. An individual's viral load is a major risk factor for passing the virus on to their kid or other people via sexual interaction. A person's infectiousness is twelve times greater during the first 2.5 months of HIV infection due to the high viral load associated with acute HIV.Transmission rates increase by almost eight times when an infected person reaches the latter stages of the disease.[ Vernazza and Bernard; 2006; Katano et al., 2007; Coutsoudis et al., 2010 ]

**Transmission via body fluids:**

The transmission of HIV may also occur via direct contact with infected blood. However, due to screening procedures, the risk of HIV transmission during blood transfusions is minimal [Baggaley et al., 2006]

**Mother to child (vertical transmission):**

Antiretroviral lessen the likelihood of transmission in mothers and their infants who prefer to breastfeed. Contamination of pre-chewn food with blood might lead to transmission.There is an estimated 17% probability that an untreated kid of a pregnant mother may get HIV/AIDS after two years of breastfeeding [Baggaley et al., 2006]. Due to the higher risk of mortality associated with not breastfeeding in many third world nations, the World Health Organization recommended either exclusive breastfeeding or the supply of safe formula.Lifelong antiretroviral drug treatment is recommended for all women diagnosed with HIV [Baggaley et al., 2006; Keosha and Gunn; 2016].

**Other:**

One typical route of transmission of the HIV virus is the sharing of needles, syringes, and other medical equipment amongst people who are HIV positive. Infections transmitted by patients to healthcare providers or healthcare providers to patients via accidental contact with contaminated needles or other medical equipment are quite rare [CDC's Role; 2018]

**Prophylaxis and Symptoms of HIV-AIDS**

**Prophylaxis:-**

Prevention after exposure (PEP) refers to the practice of taking HIV medicine to avoid contracting the virus within three days (or 72 hours) following a possible encounter. Only in extreme cases should PEP be administered. Anyone who might come into frequent contact with HIV should not use it routinely. There should be no substitution for pre-exposure prophylaxis (PrEP) as an HIV preventive method.It is essential to begin pre-exposure prophylaxis (PEP) within 72 hours after a possible HIV encounter. As soon as possible after a possible HIV exposure, PEP should be started. Time is of the essence. You will need to take your HIV medicine every day for 28 days if PEP is prescribed to you.   
One of the best ways to avoid contracting HIV is to take PEP as prescribed [Barré-Sinoussi et al. 1983].

**PEP: What is it?**

One such measure is PEP, or post-exposure prophylaxis. Preventing or controlling the spread of a sickness or infection is what "prophylaxis" is all about. Taking anti-HIV treatment no later than three days (or 72 hours) after a possible exposure is known as PEP.[28 ]PEP should only be used in extreme cases. Those who are at high risk of contracting HIV should not use it often. Pre-exposure prophylaxis (PrEP) should not be seen as a substitute for other standard HIV preventive measures, such as the frequent and proper use of condoms during sexual activity [HIV Classification; 2017]. In contrast to PEP, PrEP requires at-risk individuals to inject or take a particular HIV medicine every two months. Who could benefit from taking PEP?If you have not contracted HIV through intercourse, have used shared needles or injectable equipment, have been the victimof sexual assault, or are uncertain of your status, and if you have been in the past 72 hours, it is possible that you were exposed to HIV on the job, you may be recommended to take PEP. As soon as you suspect you may have been exposed to HIV, see your primary care physician or an emergency room physician for PEP.Quick action is required for any healthcare provider who suspects they may have been exposed to HIV. When should PEP start? [Sepkowitz, 2006].

Initiation of PEP must occur no later than three days subsequent to a possible HIV exposure. As soon as possible after a possible HIV exposure, PEP should be started. Time is of the essence. Start the PEP no later than 72 hours after exposure to HIV, and studies show that it will likely not prevent HIV infection.If PEP is prescribed, you must take your HIV medicine every day for duration of 28 days [Pietrangelo; 2009]. For PEP, which HIV medications are recommended?When it comes to pre-exposure prophylaxis (PEP), the CDC has guidelines about the recommended HIV drugs. Specific demographics, including children, adults, and teenagers, as well as expecting moms and those with renal illness, are addressed in the CDC recommendations. The most recent PEP guidelines may be found on the CDC's PEP resources website.Your ER doctor or primary care physician will work with you to determine which meds are best for PEP [Douek et al., 2009].

How well does PEP work? PEP should begin as soon as possible after a possible HIV exposure. Time is of the essence. Observational studies show that PEP may considerably reduce HIV risk—by up to 80%—although it is difficult to measure the exact effectiveness of PEP. To be successful, one must adhere to the treatment plan (take PEP daily for 28 days) and avoid other HIV exposures if the exposure was not occupational. It is quite likely that the efficacy of PEP will be far higher than 80% when taken correctly, regularly, and according to the instructions.Even when taking PEP, it is essential to keep up with other HIV prevention techniques, such as taking it consistently and appropriately. Is there a risk of side effects with PEP? During PEP, some people may take HIV drugs, which might have side effects. The negative effects are manageable and won't kill you. Talk to your doctor if you have any unwanted side effects from taking PEP that are bothersome or don't go away [Fineberg, 1998].

**Symptoms:-**

Indicators of HIV prevalence in its early stages. People usually seem and feel OK for a long time after getting an illness. It may take up to 10 years for HIV symptoms to appear, and that number might increase significantly for those who take treatment. Thus, it is essential to undergo regular HIV testing, especially if you have shared needles or had intercourse without protection. Treatment for HIV may help you stay healthy. Treatment may also lessen or eliminate the risk of HIV transmission during sexual encounters.It is common to feel ill, have pains and fevers in the two to four weeks after contracting HIV. These flu-like symptoms are your body's way of letting the HIV infection in. You currently have a high level of infection in your system [Andrew, 2018].

**The latter stages of HIV/AIDS:**

HIV destroys immune system cells called CD4 cells, which are also called T cells. In the absence of CD4 cells, the immune system struggles to ward against disease. Because of this, you are more likely to have dangerous infections that wouldn't normally hurt you. HIV slowly damages the immune system, leading to the gradual development of AIDS. Loss of a certain proportion of CD4 cells, certain types of cancer, or rare diseases called "opportunistic infections" may all lead to AIDS. This often happens after 10 years of being HIV positive, in the absence of therapy. Treatment may delay or even prevent the onset of AIDS. The symptoms of AIDS are: A thick, white coating that forms on the tongue or lips, known as thrush; Pain in the throat; Infections caused by yeast that are too severe   
Chronic pelvic inflammatory disease; Recurring painful infections   
The following symptoms may be present: headaches, lightheadedness, dizziness, excessive fatigue, rapid weight loss, more bruising than usual, persistent diarrhoea, fever, or night sweats, firm or enlarged glands in the groin, armpit, or throat, dry coughing fits that last for a long time, difficulty exhaling, and purplish growths inside or on the skin. Side effects may include: vaginal, anus, nasal, or oral bleeding; skin rashes; severe paralysis or numbness in the extremities; impaired reflexes and motor coordination; inability to move; and weaker muscles. There are a few hallmark signs of AIDS in women. The symptoms of AIDS in women are quite similar to those of AIDS in persons of either gender, as is the case with many sexually transmitted diseases.

Human immunodeficiency virus (AIDS) refers to the most advanced stage of HIV infection. Symptoms such as fever, headaches, sore muscles, and enlarged glands are common in the early stages of HIV infection. You could not have any symptoms for as long as 10 years. At that point, HIV begins to weaken your immune system, allowing you to get illnesses that normally wouldn't hurt you.HIV progresses to AIDS when the immune system declines to a certain point. Some symptoms of AIDS in women include: thrush, a yeast infection that may lead to a thick, white coating on the tongue or lips and, in rare cases, a painful throat. Yeast infections, either severe or recurrent, in the vagina; pelvic inflammation, either persistent or severe; infections, either severe or recurrent unusual and severe weariness, sometimes coupled with other symptoms including headaches, dizziness, or vertigo. Dropping more than 10 pounds quickly without cutting down on food or activity; more readily bruising than usual; protracted episodes of diarrhoea; Recurrent fevers and/or sweats at night; dyspnea; darkened or purplish growths inside the mouth or on the skin; Inexplicable bleeding from skin growths, orifices in the mouth, nose, anus, or vagina, or from any other bodily opening; extreme pain or numbness in your hands or feet, paralysis, a loss of muscular strength, or a loss of response and control over your muscles; bewilderment; personality changes, or a decline in mental capacity. There are a few hallmark signs of AIDS in males.   
The signs and symptoms of AIDS in males are quite similar to those of either gender, as is the case with many sexually transmitted diseases. Human immunodeficiency virus (AIDS) refers to the most advanced stage of HIV infection. Symptoms such as fever, headaches, sore muscles, or enlarged glands may appear in the early stages of HIV infection. You could not have any symptoms for as long as 10 years. Once HIV begins to weaken your immune system, it opens the door for you to get illnesses that would normally be harmless.When the immune system becomes significantly compromised, HIV transforms into AIDS. Signs and symptoms of male AIDS include: thrush, a yeast infection that may induce a painful throat and a thick, white coating to develop on the tongue or lips; Infections that are severe and return; Symptoms to look out for include; extreme and unexplained tiredness accompanied by headaches; lightheadedness or vertigo; rapid weight loss of over ten pounds without changing diet or exercising more; longer episodes of diarrhoea than normal; night sweats and fevers; enlarged or stiff glands in the groin; armpit; or throat; dyspnea; darkened or purple growths in the mouth or on the skin; unexplained bleeding from growths on the skin, from the nose, anus, or any opening in your body; unusual or frequent skin rashes   
; Disorientation, changes in personality, or a decrease in mental ability; Paralysis, inadequate muscular strength, or loss of reflex control; Severe pain or numbness in the hands or feet.

**PREVENTION OF HIV VIRUS ON HUMAN BODY**

AIDS is caused by the human immunodeficiency virus (HIV), which is sometimes called the lentivirus. HIV infects many different types of cells in the body. Babies born to moms with HIV are at increased risk of contracting the virus, as are other forms of blood and vaginal secretions. When an infection occurs, HIV communicates with more than only cells' CD4 molecule; it also uses other, more recently identified cellular receptors. After then, the HIV enters the cell and fuses with the cell. Several intracellular mechanisms decide whether an infection is latent or productive based on the relative expression of viral regulatory and auxiliary genes after infection. Chronic infection in other cells, such macrophages, may lead to reservoirs for the virus seen in many organs and tissues; syncytium development and cell death in CD4+ lymphocytes are possible outcomes of HIV replication. Different genetic sequences impact the wide range of biologic and serologic features seen in HIV strains [Fauci; 1998].

There is evidence linking these traits to pathogenic pathways and immune response resistance. With strong cellular immune responses and neutralizing antibodies, the host response to HIV may suppress the virus for years. The immune response, and specifically the modulation of CD8+ cell antiviral activity, seems to be crucial for the long-term survival of the virus, which suggests that a low-virulence strain is important. Many other types of treatment have been tried, and many more are being studied. Despite some promising outcomes from vaccine research, these findings underscore the enormous challenge of preventing HIV infection. Finding a cure for this devastating worldwide epidemic will need ongoing research. Various strategies are used to reduce the likelihood of catching the virus and to limit its transmission in the fight against HIV/AIDS.A overview of measures to prevent the transmission of HIV is provided below [Piot et al., 1988].

**1. INTELLIGENCE AND SENSITIVITY:** Efforts to educate the public about sexual health and the prevention of HIV via comprehensive sex education programs.   
False assumptions and misconceptions about HIV/AIDS may be dispelled via community education initiatives.

**2. CONDOM USE:** The consistent and proper use of condoms during oral, anal, and vaginal intercourse is being advocated with. Providing low- or no-cost condoms via community outreach programs, pharmacies, and healthcare facilities. [Walters; 1998]

**3. Testing and Counselling for HIV:** It is advised that at-risk individuals get regular HIV testing. This includes those who inject drugs, have several sexual partners, or are men who have intercourse with men. Confidential HIV counseling and support services are accessible to anyone who test positive or who are at risk. [. WHO AIDS series; 2002]

**4. Pretreatment with Prophylactic Agents:** Sex workers, injectable drug users, and members of serodiscordant marriages are among those at high risk of contracting HIV; hence, they should have access to PrEP medicine. A vigilant watch for adverse effects and education on proper PrEP usage. [Resnick et al., 1986].

**5. Syringe and Needle Program:** Drug injectors may reduce their risk of contracting HIV by participating in needle exchange programs that provide them with clean needles.   
  
 **6.The Treatment of Prevention**: Promoting the rapid initiation of antiretroviral therapy (ART) for HIV positive individuals to decrease viral loads and the likelihood of infection transmission to healthy individuals; urging patients to adhere to their ART regimens to maintain viral suppression and prevent the development of drug-resistant strains [Ng’uni, 2020].

**7. CIRCUMCISION OF MALE:** Promoting voluntary medical male circumcision as an additional protective measure against HIV, particularly in regions where the virus is prevalent but the practice is not widely practiced.

**8. Conquering Unfair Treatment and Stigma**: Individuals living with HIV/AIDS may benefit greatly from the establishment of more accepting communities via the implementation of stigma reduction programs. This will encourage more individuals to seek out testing, treatment, and support services without fear of discrimination. This comprehensive approach has the potential to significantly reduce the number of new HIV infections while simultaneously improving the health of those affected and their communities [Hsu and O’Connell; 2017].

**ROLE OF VACCINE ON HIV**

The HIV-1 epidemic has been going strong since the 1980s. While anti-retroviral medications have shown encouraging results, it is very unlikely that the virus will be entirely eliminated from populations where a vaccine is not yet available [Hemelaar; 2012]. Efforts to produce vaccines have been persistently impeded by the virus's fundamental biology, and the development time is almost comparable to the period of the pandemic itself [Ventura; 2020]. The HIV-1 retrovirus is fundamentally an error-prone reverse transcriptase, which results in a significant degree of viral variability [Rios; 2018]. Furthermore, infected cells may have HIV-1 DNA incorporated into their genomes. In addition, there is a lot of unexplored ground when it comes to the immune system and the reactions that are required to end an infection [Hemelaar; 2012]. Presence of HIV-1 on CD4+ cells is necessary for an effective HIV-1 vaccination to prevent infection [Excler; 2001; 2014; Rerks-Ngarm; 2009]. Although producing antibodies is a secondary goal in the development of HIV-1 vaccines, their effect is not neutralizing [Haynes et al., 2012]. So yet, only the RV144 clinical trial has shown effectiveness for the HIV-1 vaccine in phase III [Su et al., 2019]. According to this research, the presence of antibodies bound to the V1V2 loop in the encapsulated protein reduced the likelihood of infection by 31.2% [Su et al., 2019, Stefic; 2019]. A neutralizing agent that acts via alternative mechanisms, antibody-dependent cell mediated cytotoxicity (ADCC) was not effective against some antibodies [Stefic et al., 2019]. Many summaries of this research have sought to highlight the immune system's response to these many non-neutralizing actions [Hel, 2002]. The kind of virus and developing an appropriate sequence that is effective against several viral subtypes provide substantial challenges to the production of non-neutralizing antibodies, just as they do to the creation of bNAbs [Ostrowski et al., 2000]. Last but not least, we might strive to create immunological responses mediated by T cells. Although inducing CD8+ cytotoxic lymphocytes (CTLs) is the main goal of vaccine development, CD4+ T helper cells are essential for memory B-cell and CTL maturation [S­edlock; 2003; A­rends et al., 2019; Collier; 1998; McGovern 2002]. The envelope carries not only the other viral proteins like Pol and Nef, but also T-cell epitopes. Because of their roles in viral replication, all proteins are more conserved candidates for vaccine development than Env, which means they are subject to more selection pressure.

**Vaccine Manufacturing Process:**

In an ideal world, an HIV vaccine would be able to stop the virus from replicating [Fisher et al., 2007]. Potential vaccine targets in the HIV life cycle include the following stages: Stage one: unrestricted Step; Two: Affixation: Third Stage: Intrusion Stage; Four: De-coating Part; Stage Five: Making a Copy Stage Six: Collaboration; Stage Seven: Eliminating.

Therefore, the following is a list of possible HIV vaccination methods:   
Methods for physically, chemically, or biologically eliminating HIV virions from blood constitute Stage I editing. Strategies for virion extraction (I–III, VI, VII):   
1. HIV viral particle phagocytosis. Chemical and organic methods exist for capturing HIV virions, with the latter including the formation of a protective covering or additional membrane. 3. chemical or organic linkages to the virion. Ways to kill or damage the virion or any part of it (I through VI).

To "damage" virion in this sense is to diminish or eliminate its ability to process any of the Phase II VII. Here are a few different types of methods: A. Because of how the method is designed: Phases I through VII of the physical approach. Chemistry and biology-based procedures (Acts I–VI) B. By blocking the destination of the HIV virion structure [Foley et al, 2007; Malashkevich et al., 2008]. Through the damage of GP120 [Doll et al., 2013], a docking glycoprotein, in phase’s I–III, VI, and VII; Through the damage of GP41 [Facciola et al; 2019], a transmembranous glycoprotein, in phases I–III, VI, and VI.; Through the damage of the virion matrix, virion capsid, reverse transcriptase, and RNA, in phases I–VI. C. V. Disruption of Replication: Putting gp120-binding chemical or organic compounds into circulation. Parts of the CD4 cell membrane that contain the receptor might be the culprit. It is also possible to use any chemical or pharmacological receptor replacement that can bind gp120. Biological or chemical agents introduced to the bloodstream with the purpose of binding to CD4 cell receptors. D. Non-physical, chemical, or biological means of preventing the phase transition 1. Physical, chemical, or biological methods may be used to prevent adhesion, penetration, uncoating, integration, replication, assembly, and release. E. Reducing the functional capacity of infected cells (Phase VI–VII) to kill the diseased cells: first, blocking the metabolic processes of infected cells. 2. Blocking the energy exchange between the sick cells.

**NEW VENTURE CURE**

Modern approaches to vaccine creation have made use of nanotechnology, which defines groups of particles with sizes ranging from 1 nm to 999 nm [Bagasra et al., 2012]. Biological metals, polymers, macromolecules, and other components may make up nanovaccines, which are usually 1–100 nm in size. This spectrum encompasses a large number of infectious agents, mostly viruses. Nanoparticles are an excellent building block for vaccines because of their ability to interface with different immune systems, including phagocytic cells and B-cells [Perera and Arosh; 2012]. Nanovaccines most often employ antigens to coat their surfaces, allowing them to connect directly with B-cell receptors; however, some may also include immunostimulatory chemicals, antigens, or both inside their particles.

Further research on an HIV vaccine: Although GBV-C, the hepatitis G virus, has been associated with longer life durations for HIV patients, there may be other distinctions among these individuals. Using GBV-C might be useful for creating an HIV vaccine down the road [Arachchige et al; 2021].One example is a genetically modified variant of the HIV virus that can replicate by relying on an uncommon amino acid for proper protein translation rather than the typical sequence of three nucleotides. Since humans aren't used to this amino acid, the virus can't replicate. A new discovery suggests the use of universal CAR NK cells to fight HIV [Arachchige et al; 2021]. However, whereas live attenuated immunizations are very successful against polio, measles, and rotavirus, HIV has not been tested in humans. The possible safety risk of reversion to live virus is the reason why a live attenuated HIV-1 vaccine has not yet reached clinical testing. Innovative research is underway in the quest to create a live attenuated HIV-1 vaccine that is not harmful to humans.

**References :-**

1. Weiss RA; How does HIV cause AIDS?; Science: 1993; 260(5112):pp1273-1279.

2. Roederer M, Koup RA, and Douek DC; Developing Approaches in the Immunopathogenesis of HIV/AIDS; Annu Rev Med: 2009:60:pp471-484.

3. R.P. Singh; Microbiology: Kalyani Publishers, 2012: pp1- 886.

3.Eisinger RW, Dieffenbach CW, Fauci AS; HIV Viral Load and Transmissibility of HIV Infection: Undetectable Equals Untransmittable. JAMA; 2019;321(5):pp451-452.4

4.Cunningham AL, Donaghy H, Harman AN, Kim M, Turville SG; Manipulation of dendritic cell function by viruses; Curr Opin Microbiol; 2010 Aug;13(4):pp524-529.

5. Kumar V; Robbins Basic Pathology (9th ed.). Elsevier Health Sciences. 2012; p. 147. ISBN 978-1-4557-3787-1.

6. McGovern SL, Caselli E, Grigorieff N, Shoichet BK (2002). "A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening". Journal of Medicinal Chemistry; J Med Chem; 2002 Apr 11;45(8):pp1712-1722.

7. Chan DC, Fass D, Berger JM, Kim PS; Core structure of gp41 from the HIV envelope glycoprotein; Cell: 1997;89(2):263-73.

8. Pineda-Peña AC, Faria NR, Imbrechis, Libin P, Abecasis AB, Deforche K, Gomez-Lopez A, Camacho RJ, Oliveria TD, Vandamme AM; Automated subtyping of HIV-1 genetic sequences for clinical and surveillance purposes: performance evaluation of the new REGA version 3 and seven other tools; Infect Genet Evol; 2013:19:pp337-348.

9. Chan DC, Fass D, Berger JM, Kim PS; Core structure of gp41 from the HIV envelope glycoprotein; Cell; 1997;89(2):pp263-273.

10. Chan DC, Kim PS; HIV entry and its inhibition; Cell. 1998;93(5):pp681-684.

12. Wyatt R, Sodroski J; The HIV-1 envelope glycoproteins: fusogens, antigens, and immunogens; Science. 1998;280(5371):pp1884-1888.

11. Arthos J, Cicala C, Martinelli E, Macleod K, Van Ryk D, Wei D, Xiao Z, Veenstra TD, Conrad TP, Lempicki RA, McLaughlin S, Pascuccio M, Gopaul R, McNally J, Cruz CC, Censoplano N, Chung E, Reitano KN, Kottilil S, Goode DJ, Fauci AS; HIV-1 envelope protein binds to and signals through integrin alpha(4) beta(7), the gut mucosal homing receptor for peripheral T cells’ Nature Immunology; 2008;9(3):pp301-309.

12. Zheng YH, Lovsin N, Peterlin BM; Newly identified host factors modulate HIV replication". Immunology Letters; 2005; 97(2):pp225-34.

13. Schaller T, Ocwieja KE, Rasaiyaah J, Price AJ, Brady TL, Roth SL, Hué S, Fletcher AJ, Lee K, KewalRamani VN, Noursadeghi M, Jenner RG, James LC, Bushman FD, Towers GJ. HIV-1 capsid-cyclophilin interactions determine nuclear import pathway, integration targeting and replication efficiency; PLoS Pathog; 2011; 7(12):e1002439.

14. Hu WS, Temin HM; HIV-1 reverse transcription; Cold Spring Harb Perspect Med. 2012;2(10):a006882.

15.Charpentier C, Nora T, Tenaillon O, Clavel F, Hance AJ; Extensive recombination among human immunodeficiency virus type 1 quasispecies makes an important contribution to viral diversity in individual patients; J Virol; 2006;80(5):pp2472-2482.

16. Zhang C, Zhou S, Groppelli E, Pellegrino P, Williams I, Borrow P, Chain BM, Jolly C; Hybrid spreading mechanisms and T cell activation shape the dynamics of HIV-1 infection; PLoS Comput Biol; 2015;11(4):e1004179.

17. Boseley S; Embarrassed firms slash prices for AIDs drugs. N Z Med J. 2001 Oct 12; 114(1141):440.

18. Vernazza P, Bernard EJ; HIV is not transmitted under fully suppressive therapy: The Swiss Statement – eight years later; Swiss Med Wkly; 2016; 146:w14246.

19. Katano H, Sato Y, Hoshino S, Tachikawa N, Oka S, Morishita Y, Ishida T, Watanabe T, Rom WN, Mori S, Sata T, Weiden MD, Hoshino Y;  Integration of HIV-1 caused STAT3-associated B cell lymphoma in an AIDS patient; Microbes Infect; 2007;9pp14-15.

20. Coutsoudis A, Kwaan L, Thomson M; Prevention of vertical transmission of HIV-1 in resource-limited settings". Expert Review of Anti-Infective Therapy; Expert Rev Anti Infect Ther; 2010 Oct;8(10):pp1163-1175.

21. Baggaley RF, Boily MC, White RG, Alary M; Baggaley RF, Boily MC, White RG, Alary M;   Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. AIDS. 2006 Apr 4;20(6):805-12.

# 22. Keosha TB and Gunn AJ; Perceived Advantages and Disadvantages of Using Pre-Exposure Prophylaxis (PrEP) among Sexually Active Black Women; J Black Sex Relatsh. 2016 3(1): pp1–24.

# 23*.*CDC's Role in Global HIV Control". Centers for Disease Control and Prevention*.* Retrieved April 19, 2018.

# 24. HIV Classification: CDC and WHO Staging Systems". AIDS Education & Training Center Program. 2017.

25. Sepkowitz KA; AIDS – the first 20 years"; The New England Journal of Medicine; 2006; 344 (23): pp1764–1772.

# 26. Andrew DB; Human Immunodeficiency Virus; 2018.

# 27. Douek DC, Roederer M, Koup RA. [Emerging Concepts in the Immunopathogenesis of AIDS](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2716400).*Annual Review of Medicine*. 2009: 60: pp471–478

28. Cunningham AL, Donaghy H, Harman AN, Kim M, Turville SG (August 2010). "Manipulation of dendritic cell function by viruses". *Current Opinion in Microbiology*. 13 (4): pp524–529

29. Pietrangelo A, A Comprehensive Guide to HIV and AIDS; 2020; Edited: Yvette Brazier

.

30. Barré-Sinoussi F, Chermann JC, Rey F, Nugeyre MT, Chamaret S, Gruest J, Dauguet C, Axler-Blin C, Vézinet-Brun F, Rouzioux C, Rozenbaum W, Montagnier L. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science. 1983;220(4599):pp868-871.

31. Fineberg HV; Education to prevent AIDS .Prospects and obstacles; Science 1988; pp239:592.

32. Fauci A.S.: The human immunodeficiency virus: Infectivity and mechanism of pathogenesis. Science 1988; pp239:617.

33. Piot P, Plummer FA, Mhalu FS, Lamboray, JL; Chin J, Mann M; AIDS :An international perspective. Science. 1988; pp239:573.

34. Walters L; Ethical issues in the prevention and treatment of HIV infection and AIDS .Science. 1988; pp239:597

35. WHO AIDS series Booklets: Available from WHO/GPA, 1211 Geneva 27,Switzerland. 2012

36. Resnick L, Veren K, Salahuddin SZ, Tondreau S and Markham PD. Stability and inactivation of HTLV-III/LAV under clinical and laboratory environments; JAMA; 1986;255(14):pp1887-1891

37. Ng’uni T, C­asara C, Nd­lovu ZM. Major scientific ­urdles in HIV vaccine development: ­istorical perspective and future directions; Front Immunol. 2020;11:pp590780.

38. Hsu DC, O’Connell RJ, Progress in HIV vaccine development. Hum Vaccin Immunot­er. 2017;13(5):pp1018–1030.

39. Hemelaar J. T­e origin and diversity of t­e HIV-1 pandemic. Trends Mol Med. 2012;18(3):pp182–192

40. Ventura JD. Human immunodeficiency virus 1 (HIV-1): viral latency, t­e reservoir, and t­e cure. Yale J Biol Med. 2020;93(4):pp549–560.

41. Rios A. Fundamental c­allenges to t­e development of a preventive HIV vaccine. Curr Opin Virol. 2018;29:pp26–32

42. Excler JL, Ake J, Robb ML, et al. Nonneutralizing functional antibodies: a new “old” paradigm for HIV vaccines. Clin Vaccine Immunol. 2014;21(8):pp1023–1036.

43. Rerks-Ngarm S, Pitisuttit­um P, Nitayap­an S, et al. Vaccination wit­ ALVAC and AIDSVAX to prevent HIV-1 infection in T­ailand.; N Engl J Med. 2009;361(23):pp2209–2220.

44. Haynes BF, Gilbert PB, McElrat­ MJ, et al. Immune-correlates analysis of an HIV-1 vaccine efficacy trial. N Engl J Med. 2012;366 (14):pp1275–1286.

45. Su B, Dispinseri S, Iannone V, et al. Update on Fc-mediated antibody functions against HIV-1 beyond neutralization. Front Immunol. 2019;10:p2968.

46. Stefic K, Bouvin-Pley M, Braibant M, et al. Impact of HIV-1 diversity on its sensitivity to neutralization. Vaccines (Basel). 2019;7(3).

47. Hel Z, Nacsa J, Tryniszewska E, et al. Containment of simian immunodeficiency virus infection in vaccinated macaques: correlation with the magnitude of virus-specific pre- and postc­allenge CD4+ and CD8+ T cell responses. J Immunol. 2002;169 (9):pp4778–4787.

48. Ostrowski MA, Justement SJ, E­ler L, et al. T­e role of CD4+ T cell­elp and CD40 ligand in t­e in vitro expansion of HIV-1-specific memory cytotoxic CD8+ T cell responses. J Immunol. 2000;165 (11):pp6133–6141.

49. S­edlock DJ, S­en H. Requirement for CD4 T cell ­elp in generating functional CD8 T cell memory. Science. 2003;300 (5617):pp337–339.

50. A­rends T, Busselaar J, Severson TM, et al. CD4(+) T cell ­elp creates memory CD8(+) T cells with innate and ­elp-independent recall capacities. Nat Commun. 2019;10(1):pp5531.

51. Collier L, Balows A, Sussman M (1998). Mahy B, Collier L (eds.). Virology. Topley and Wilson's Microbiology and Microbial Infections. Vol. 1 (ninth ed.). Hodder Education Publishers. pp. 75–91. ISBN 978-0-340-66316-5.

52. McGovern SL, Caselli E, Grigorieff N, Shoichet BK; A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. Journal of Medicinal Chemistry. 2002: 45 (8): pp1712–1722.

53. Fisher, Bruce; Harvey, Richard P.; Champe, Pamela C. Lippincott's Illustrated Reviews: Microbiology (Lippincott's Illustrated Reviews Series). Hagerstown, MD: Lippincott Williams & Wilkins. 2007; ISBN 0-7817-8215-5. pp3

54. Foley B, Leitner T, Apetrei C, Hahn B, Mizrachi I, Mullins J, Rambaut A, Wolinsky S, Korber B. HIV Sequence Compendium (Report). Theoretical Biology and Biophysics Group, Los Alamos National Laboratory, 2007; NM, LA-UR 17-25240.

55. Malashkevich VN, Chan DC, Chutkowski CT, Kim PS. "Crystal structure of the simian immunodeficiency virus (SIV) gp41 core: conserved helical interactions underlie the broad inhibitory activity of gp41 peptides". Proceedings of the National Academy of Sciences of the United States of America. 2008; 95 (16): 9134–9.

56. Doll TA, Raman S, Dey R, et al. Nanoscale assemblies and t­eir biomedical applications. J R Soc Interface. 2013;10 (80):20120740.

57. Facciola A, Visalli G, Lagana P, et al. T­e new era of vaccines: t­e “nanovaccinology.” Eur Rev Med P­armacol Sci. 2019;23 (16):pp7163–7182.

58. Bagasra O, Bagasra AU, Sheraz M, Pace DG ; Potential utility of GB virus type C as a preventive vaccine for HIV-1". Expert Review of Vaccines. 2012: 11 (3): 335–47.

59. Arachchige PM, Arosh S; NK cell-based therapies for HIV infection: Investigating current advances and future possibilities. Journal of Leukocyte Biology. 2012; 111 (4): pp921–931.

60. Arachchige PM, Arosh S. Perera Molligoda; A universal CAR-NK cell approach for HIV eradication. AIMS Allergy and Immunology. 2021; 5 (3): pp192–194–194.