Recent Innovative Advances in Treatment of Human Immunodeficiency Virus.

*Naïda Tabassum¹, Andleeb Bashir², Amreen Naqash³, Saima Rasool⁴, Mubashir H Masoodi⁵
Department of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar-190006. India.

Abstract:
Immunodeficiency disorders involve malfunction of the immune system, resulting in infections that develop and recur more frequently, are more severe, and last longer than usual. AIDS is an immunodeficiency disease caused by HIV (human immunodeficiency virus). People with HIV have what is called HIV infection. Most of these people will develop AIDS as a result of their HIV infection and symptoms they develop are known as AIDS defining condition. The latest statistics of the global HIV and AIDS epidemic, published by UNAIDS in 2008 reported that 31.1-35.8 million people were living with HIV/AIDS. Although newer advances have been introduced in the treatment of HIV, still research is going on. Several recent major developments in human immunodeficiency virus treatment, prevention, outcome, and social policy changes have taken place. Updated international guidelines endorse more aggressive treatment strategies, safer antiretroviral drugs and gene therapies in treatment of HIV syndrome. New antiretroviral options are being tested. Vaccines and microbicide gels are under trials, and additional trials in prevention, especially pre-exposure prophylaxis, are nearing completion. Insight into the role of the virus in the pathogenesis of diseases, traditionally thought to be unrelated to acquired immunodeficiency syndrome, has become a driving force for earlier and universal therapy.

Key words: AIDS; Antiretroviral therapy, HIV vaccine, Human immunodeficiency virus, Multitalented protein sheds.

Introduction:
Immunodeficiency (or immune deficiency) is a state in which the immune system’s ability to fight infectious disease is compromised or entirely absent. Most cases of immunodeficiency are acquired (“secondary”) but some people are born with defects in the immune system called primary immunodeficiency. Transplant patients take medications to suppress their immune system as an anti-rejection measure, as do some patients suffering from an over-active immune system. A person who has an immunodeficiency of any kind is said to be immune compromised. An immune compromised person may be particularly vulnerable to opportunistic infections, in addition to normal infections that could affect everyone [1,2].

Immunodeficiency is of two types.
1. Primary Immunodeficiency (PID)
A number of rare diseases feature a heightened susceptibility to infections from childhood onward. Many of these disorders are hereditary and are autosomal recessive or X-linked. There are over 80 recognized primary immunodeficiency syndromes; they are generally grouped on the basis of the immune system that is malfunctioning, such as lymphocytes or granulocytes. The treatment of PID depends on the nature of the defect and may involve antibody infusions, long-term antibiotics and stem cell transplantation. [3]

2. Acquired Immunodeficiency or Secondary Immunodeficiency (SID)
Immune deficiency may also be the result of particular external processes or diseases; the resultant state is called "secondary" or "acquired" immunodeficiency. Common causes are malnutrition, aging and medications like chemotherapy, disease-modifying antirheumatic drugs, immunosuppressive drugs after organ transplants and glucocorticoids etc.[4]

Many specific diseases directly or indirectly impair the immune system, which includes many types of cancers like leukemia, lymphoma, multiple myeloma, and certain chronic infections. Immunodeficiency is also the hallmark of acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV) which infects a small number of T helper cells, and also impairs other immune system responses indirectly it is a lentivirus (a member of the retrovirus family) that causes AIDS, a condition in humans in which the immune system begins to fail, leading to life-threatening opportunistic infections.

Screening of blood products for HIV has largely eliminated transmission through blood transfusions or infected blood products in the developed world. HIV has been found to be of two types; HIV-1 & HIV-2. Most untreated people infected with HIV-1 eventually develop AIDS. HIV progresses to AIDS at a variable rate affected by viral, host, and environmental factors. Most people will progress to AIDS within 10 years of HIV infection. Some will have progressed much sooner, and some will take much longer.[5]
Cells affected: Whichever route the virus follows for entering the body, it primarily acts on the following cells:

- Lymphoreticular system: CD8+ T-Helper cells, Macrophages, Monocytes, B-lymphocytes.
- Certain endothelial cells
- Central Nervous system: Microglia of the nervous system, Astrocytes, Oligodendrocytes, Neurons on which it acts indirectly by the action of cytokines and the glycoprotein-120.[6]

WHO Disease Staging System for HIV Infection and Disease:
In 1990, the World Health Organization (WHO) grouped these infections and conditions together by introducing a staging system for patients infected with HIV-1. Most of these conditions are opportunistic infections that are easily treatable in healthy people.

Stage I: HIV infection is asymptomatic and not categorized as AIDS
Stage II: It includes minor mucocutaneous manifestations and recurrent upper respiratory tract infections
Stage III: It includes unexplained chronic diarrhea for longer than a month, severe bacterial infections and pulmonary tuberculosis.
Stage IV: It includes toxoplasmosis of the brain, candidiasis of the esophagus, trachea, bronchi or lungs and Kaposi’s sarcoma. These diseases are indicators of AIDS.[7]

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)
AIDS is a disease of the human immune system caused by the HIV. This condition progressively reduces the effectiveness of the immune system and leaves individuals susceptible to opportunistic infections and tumors. HIV is transmitted through direct contact of a mucous membrane or the bloodstream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid and breast milk. This transmission can involve anal, vaginal or oral sex, blood transfusion, contaminated hypodermic needles, exchange between mother and baby during pregnancy, childbirth, breastfeeding or other exposure to one of the above bodily fluids.[8]

Symptoms and Signs:
AIDS is an advanced stage of HIV infection. Because the CD4 cells in the immune system have been largely destroyed, people with AIDS develop symptoms and signs of unusual infections or cancers. When a person with HIV infection gets one of these infections or cancers, it is referred to as “AIDS defining condition.”[9] (Table 1)

<table>
<thead>
<tr>
<th>Table 1: Major Symptoms of AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISEASE</strong></td>
</tr>
<tr>
<td>1. Pulmonary infections</td>
</tr>
<tr>
<td>Pneumocystis pneumonia, Tuberculosis</td>
</tr>
<tr>
<td>2. Gastrointestinal infections</td>
</tr>
<tr>
<td>Esophagitis, Chronic diarrhea</td>
</tr>
<tr>
<td>3. Neurological &amp; Psychiatric involvement</td>
</tr>
<tr>
<td>4. Tumors &amp; Malignancies</td>
</tr>
<tr>
<td>5. Other infections</td>
</tr>
</tbody>
</table>

Treatment of HIV:
There is currently no publicly available vaccine for HIV or cure of HIV or AIDS. The only known methods of prevention are based on avoiding exposure to the virus or, failing that, an antiretroviral treatment directly after a highly significant exposure, called post-exposure prophylaxis (PEP). PEP has a very demanding four-week schedule of dosage. It has also very unpleasant side effects including diarrhea, malaise, nausea and fatigue. Current treatment of HIV infection consists of highly active antiretroviral therapy or HAART introduced in 1996 when the protease inhibitor based HAART initially became available. Current optional HAART options consist of combinations consisting of at least three drugs belonging to at least two types, or “classes” of antiretroviral agents.[10]

Antiretroviral Therapy (ART)
ART is a name for the treatment of retrovirus HIV, which causes AIDS, with drugs that help decrease the HIV levels (viral load) in the blood. ART has evolved from monotherapy with zidovudine (AZT) to the use of combination nucleoside reverse transcriptase inhibitors (NRTIs), to triple therapy with highly active antiretroviral therapy (HAART), to today’s numerous combinations drawn from 6 classes and 32 drugs, including fixed dose formulations, approved by the United States (US) Food and Drug Administration (FDA) Treatment goals have also progressed from achieving viral suppression to regimen simplification, to long term durability, and to the present paradigm of treatment as prevention. In the past two decades, HIV mortality has dramatically decreased reflecting the success of ART. New drugs with fewer side effects and lower pill burden have made long-term viral suppression a reality. As death rates related to AIDS continue to decline in patients receiving treatment, attention has shifted to what have hereto forth been considered non-AIDS-related deaths. [11]

New Strategies:
A) New Drugs
- The integrase inhibitor raltegravir (Isentress) has been recently approved by the USFDA for ART-naive patients, in combination with the NRTIs tenofovir (TDF) and emtricitabine (FTC). [12]
- TDF/FTC in combination with efavirenz (EFV), and with the boosted protease inhibitors (PIs) darunavir/ritonavir (DRV/r) and atazanavir/ritonavir (ATV/r).
• NRTI stavudine (d4T) has been replaced by WHO with AZT or TDF.
• d4T is inexpensive and widely available but causes mitochondrial toxicity that can lead to sometimes permanent peripheral neuropathy and lipodystrophy.[13]
• CCR5 antagonist Maraviroc (Selzentry) prevents HIV entry by blocking CCR5 co receptors. Better lipid profiles were also reported with Maraviroc. [14]
• PI lopinavir/ritonavir (LPV/r) is now an alternate choice except for pregnant women. Ritonavir is a PI that does not affect HIV VL at the booster dose (100 or 200 mg per day) but alters the metabolism of other PIs through inhibition of the cytochrome P450 3A (CYP3A) enzyme. Ritonavir is associated with side effects including dyslipidemia, diabetes, and GI dysfunction. [15]
• SPI-452 and GS9350 have been both shown to enhance safely and effectively the level of PIs.

B) Zinc Finger Inhibitors
The inner core of HIV is called the nucleocapsid. It is held together by structures called “zinc fingers”. Zinc finger inhibitors (or zinc ejectors) are drugs that can break apart these structures & prevent the virus from functioning. Scientists believe that the nucleocapsid core cannot mutate very easily, so a drug that works against zinc fingers might be effective for a long time. Unfortunately, the HIV virus does not use zinc fingers. Drugs that attack them could have serious side effects. One zinc finger inhibitor-Azodicarbonamide (ADA)- has been tested in a Phase I/II trial, but there are no recent reports on its development. SB-728-T by Sangamo Biosciences is a zinc finger gene therapy. [16]

C) Gene Therapies
Several products being developed to interfere with genes used by HIV are:
• HGTV43 by Enzo Biochem is an “antisense” therapy designed to produce CD4 cells that resist infection by HIV. It is in Phase I trials.
• M870 by EUTFETS AG is a gene therapy that makes CD4 cells resist infection by HIV. It is under Phase I trial.
• Mifepristone (VGX410, also known as RU486) by Viral Genomics interferes with the viral protein vpr. It is in Phase I/II trial.
• Modified CD4 and CD8 cells, by Genesys, are genetically modified to block attachment by HIV.
• RRs2 by Johnson and Johnson is a ribozyme that attacks HIV’s gene. It is in Phase II trials.
• VRX496 by VIRxSYS is in Phase II trials. It appears to bind to the RNA of HIV and disrupts it. [17]

Triple Punch Gene Therapy for AIDS
A triple punch gene therapy has cleared its first safety test in humans as it gives human stem cells three ways to defy HIV. Four AIDS patients were injected with these cells and they tolerated the treatment and for up to two years, the cells produced anti-HIV weapons. Researchers are optimistic that after further clinical trials, combination therapy can replace or complement anti-retroviral drugs for treatment of HIV patients. The trial piggybacked on a standard treatment where AIDS patients were given transplants of their previously saved blood stem cells for prevention of development of blood cancer. Besides normal blood stem cells, patients were also injected with cells in which three types of RNA based gene therapies were carried by a lent virus. In the present trial, researchers combined genetic resistance into stem cells for replacing an immune system susceptible to HIV with one, which can resist attack of the virus. [18]

Prevention of HIV
a) The Hope for an HIV Vaccine: Results from the phase-3 Thai vaccine trial using a combination of ALVAC, a recombinant canary pox vector vaccine, and AIDSVAX, a recombinant glycoprotein-120 subunit vaccine, were released in late 2009. Although the two protocol specified analyses (intention-to-treat as per-protocol) only showed a trend toward significance, the modified intention-to-treat analysis excluding 7 subjects who were determined to be HIV-infected at entry showed a 31% (95% confidence interval 1.1-51.2) reduction in the risk of HIV infection making this the first HIV vaccine to have a statistically significant effect. Although the mechanisms by which protection was provided are unknown. [19]

b) Prevention with Microbicide Gel: Disappointing news came from the vaginal microbicide gel PRO 2000 trial conducted by the Microbicides Development Programme (MDP) from 2005 to 2009 in 9385 women in four African countries with high HIV prevalence rates. Women were randomly assigned to receive the PRO 2000 gel (0.5% dose) or placebo, along with free condoms. Despite good adherence and tolerability, no significant difference in infection rates was observed (4.5/100 person-year with the PRO 2000 gel versus 4.3/100 person-year with placebo). [20]

c) Oral ART as Pre-exposure Prophylaxis: Newer drugs with less toxicity have made earlier ART administration feasible, they are also being considered for Pre-exposure Prophylaxis to prevent HIV infection. TDF was effective in preventing Simian Immunodeficiency Virus (SIV) infection in the macaque model and to date use as pre-exposure prophylaxis in human trials has revealed no serious safety concerns. [21]

d) Prevention with Early ART: HIV transmission is strongly correlated to the concentration of virus in blood (VL), and this is usually reflected in genital secretions. ART significantly reduces HIV transmissibility by reducing VL, which is the basis for treating HIV-infected pregnant women.[22]

Multitalented Protein and HIV
New insights into the HIV infection process, which leads to AIDS, may now be possible through a research method recently developed in part at the National Institute of Standards and Technology, where scientists have glimpsed an important protein molecule’s behavior with unprecedented clarity. HIV protein, known as Gag, plays critical roles in the assembly of the HIV in a host cell. The Gag molecule is a microscopic gymnast. At different stages during HIV assembly, the protein twists itself into several different shapes inside a host cell. One shape, or
conformation, helps it to drag a piece of HIV genetic material toward the cell membrane, where the viral particles grow. Gag’s opposite end becomes anchored there, stretching the protein into a rod-like conformation that eventually helps form a barrier surrounding the infectious genome in the finished virus. But while scientists have been aware for years that Gag appears to play several roles in HIV assembly, the specifics have remained mysterious. [23]

**Conclusion:**

Although the complete cure of AIDS is not possible, still antiretroviral therapies have largely benefited the patients. Vaccines, microbicide gels have largely prolonged life of people suffering from AIDS without long-term toxicity or developing drug resistance. With the move towards simpler regimens involving fewer pills and fewer doses, antiretroviral therapy is becoming easier to adhere to. Furthermore, there is hope that toxicity, rather than being an inevitable consequence of all antiretroviral therapy, may occur less frequently with some drugs than with others.

**References:**


**Conflict of Interest: - None.**

**Source of funding: - Nil**

**Corresponding address:-**

Dr. Nahida Tabassum,
Associate Professor, Deptt. Of Pharmaceutical Sciences, University of Kashmir, Hazratbal, Srinagar,
J&K-190006, India.
Telephone No.: 09419906868
Fax. no: 0194-2425195