Management of HIV/AIDS - Current Practice And Future Hopes

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Abstract : HIV/AIDS pandemic, that started in the late twentieth century has continued unabated into the 21st century despite all the research and effort to control it. It is estimated that more than 34.3 million people worldwide are infected with HIV and 18.6 million deaths have occurred. By 2020, about 20 million will be orphaned due to the virus. India has the highest number of people with HIV globally, second only to South Africa. There are approximately 16,000 new infections every day. The advent of ART revolutionized the lives of people living with HIV/AIDS but ART is not a cure; ART merely keeps the viral replication suppressed. When ART is stopped, the virus rebounds within a few weeks in almost all infected individuals.

Recently, UNAIDS has recommended the new strategy for control of HIV infection (Test and Treat) and laid down new targets ("90-90-90" by 2020).

This article reviews the current practices in management of HIV/AIDS and highlights the future diagnostic, therapeutic and preventive modalities that may soon become available to the clinicians.

Introduction : It is estimated that more than 34.3 million people worldwide are infected with HIV and 18.6 million deaths have occurred. By 2020, about 20 million will be orphaned due to the virus. India has the highest number of people with HIV globally, second only to South Africa. There are approximately 16,000 new infections every day.

Antiretroviral therapy (ART) has revolutionized the lives of people living with HIV and in many countries, life expectancy for someone living with HIV is now almost the same as someone without HIV infection. Around 17 million people living with HIV are receiving antiretroviral treatment therapy, 20 million are not. We now know that 20 million people are at increased risk of developing tuberculosis and cancers-even if some of them still have high CD4 counts.

But ART is not a cure.[1] When ART is stopped, the virus rebounds within a few weeks in almost all infected individuals, even after many years of suppressive therapy. Understanding where and how HIV persists on ART and using these insights to develop therapies, which will ultimately enable us to cure HIV infection, or allow people living with HIV to safely stop ART with the virus staying under control, remain key goals in HIV research.

What Is HIV Infection?

The Human Immunodeficiency Virus (HIV) is the etiological agent responsible for the pandemic of Acquired Immune Deficiency Syndrome (AIDS). HIV is an RNA virus and belongs to the class of retroviruses. The origin of HIV1 has been found in chimpanzees. HIV2 has been traced to the rural population of Guinea-Bissau.

Virology: The target cell is the T-helper lymphocyte[2]. The virus attaches itself to the T-cell surface by interaction of the viral coat protein gpl20, and T-cell surface receptor CD4. After fusion, the viral core enters the cell and the single- stranded RNA is copied to DNA via an enzyme called reverse transcriptase. The newly-made provirus enters the cell nucleus and integrates into the host genome with the help of virus integrase. This pro-viral DNA then acts as a template for making new virions, which are finally released from the cell surface, thus completing the HIV life cycle. HIV gradually destroys the immune system by attacking and killing the CD4 cells to multiply and spread throughout the body, making the individual susceptible to various acute and chronic infections.

The Main Barriers to Cure: It is now clear that integration of the HIV genome into long- lived resting cells in a dormant form is a major barrier to a cure, and is capable of re-igniting viral replication if ART is stopped. This is called the HIV latency. The virus persists in certain tissues, where it is protected from immune effector cells and also, sub-optimal penetration of ART into some tissues.

Transmission

There are three possible methods of transmission:

- Sexual
- Perinatal (mother to child)
- Parenteral (through blood and intravenous route)

HIVInfection and The Immune Response

The natural history of HIV infection is divided into the seven following stages:

1. Viral transmission.
2. Primary HIV infection.
3. Seroconversion.
4. Clinical latent period with or without Persistent Generalised Lymphadenopathy (PGL).
5. Early symptomatic HIV infection (previously known as AIDS-related complex or ARC and more recently as the 'B symptoms').
6. AIDS: According to the revised CDC criteria, this includes a CD4 cell count of less than 200 cells/mm3.
7. Advanced HIV infection with a CD4 cell count of <50 cells/mm3.

Classification of Hiv-associated Conditions (Centre of Disease Prevention and Control (CDC) Classification) :

GROUP A: Patients with acute HIV infection or who are asymptomatic.

GROUP B : Have symptoms but do not have an AIDS-defining condition. Fatigue, fever, weight loss, diarrhea, wasting, oral Candida and oral hairy leukoplakia are some of the clinical presentations.

GROUP C: Includes patients who have AIDS, meeting the CDC case definition. Severe infections with extra-pulmonary or pulmonary tuberculosis, Pneumocystis carinii pneumonia, cryptococcosis, Kaposi's Sarcoma, toxoplasmosis of the brain, disseminated cytomegalo virus infection and other severe infections. The CD4 count is generally less than 200 cells/mm3 amongst these patients.

Diagnostic Work Up:

The CDC and Association of Public Health (APHL) continue to recommend that laboratories use a lab-based HIV antigen-antibody HIV screening assay, followed, when reactive, by an HIV1/HIV2antibody differentiation immunoassay [3]. When the differentiation immunoassay returns a negative or indeterminate result, a HIV-1 nucleic acid test (NAT) is to be performed. In addition to being accurate, HIV testing should be expedited to reduce the time to antiretroviral treatment because infected persons have better health outcomes when they are treated earlier and treatment of the infected person reduced transmission of HIV to others.

The current diagnostic assays are not sensitive enough to detect very early and very low viral load. If the UNAIDS "90-90-90" target is to be met with by 2020, the following diagnostic and evaluation challenges will have to be overcome.

The Challenges For Diagnostic Work-up : A more efficient and sensitive evaluation will require

- More sensitive assays to measure and identify cells infected with functional virus.
- Better methods to measure and visualise HIV persistence in tissues such as gut, lymph nodes and brain.
- More effective interventions to reverse HIV latency and induce an effective and durable anti-HIV immune response.
- A better understanding of the impact of host genetics, HIV subtypes and co-infections.

With the recent revisions to WHO treatment guidelines of "Test and Treat", which recommend ART for all HIV positive individuals regardless of CD4 count or clinical stage. UNAIDS has stated that critical to HIV elimination will be the achievement of the "90-90-90" targets by 2020; 90% of the HIV –positive population needs to be diagnosed, 90%of diagnosed individuals need to be on ART, and 90% of patients on ART need to be virologically suppressed.

Therapeutic Approaches To HIV Infection : Many programmes in different parts of the world have been implemented in an attempt to prevent the spread of HIV infection.[4]

A. Preventive Measures

1. Sexual

- Public awareness
- Safe sex practices
- Control of sexually transmitted diseases

2. Parenteral

- Routine screening of blood/ blood products for HIV
- Needle exchange programmes for intravenous drug users

3. Perinatal (for mothers with HIV infection)

- Antiretroviral therapy during pregnancy/after delivery
- Avoidance of breast-feeding.

B. Treatment

Diagnosing and managing opportunistic infections :

Most diagnosed infections are treated with specific drugs, antibiotics, antifungal and other agents, as required.

Highly Active Anti-Retroviral Therapy (HAART) :

There are more than 320 drugs available globally, with 16 drugs available in India[5]. More than 1700 combinations are available for treatment.

Antiretroviral agents : Nucleoside reverse transcriptase inhibitors (NRTIs): Azidothymidine / Zidovudine (AZT/ZDV), Didanosine (ddi), Zalcitabine (ddC), Lamuvidine (3Tc), Stavudin (d4T), Tenofovir, Emtricitabine, Abacavir.

- **Protease Inhibitors (PI):** Sequinavir, Retinovir, Indinavir, Elfinavir, Atazanavir,
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs):** Nevirapine, Delavirdine, Loviride
- **Entry Inhibitors:** Maraviroc

This is a newer drug available. Entry inhibitors block HIV from getting into and infecting certain cells of the immune system. Maraviroc works by attaching to a protein on the surface of the immune cells called CCR% co-receptors. When this happens, certain strains of HIV, called R5 tropic virus, cannot attach to enter or infect the cell.

- Fusion Inhibitors: Enfuvirtide. This is an injectable antiretroviral drug and can cause injection site reactions like itching.
- Latency Reversing Drugs: The depsipeptide Romidepsin was recently found to be effective latency reversing agent. Romidepsin is a histone deacetylase inhibitors (HDACi) which promises to enforce the "kick and kill" approach for HIV management or even, cure [6].

Caution: Many of these drugs have severe side-effects like bone marrow suppression, pancreatitis, peripheral neuropathy, kidney stones and jaundice, and cannot be used unless the prescribing physician has adequate knowledge. Everyone must know that Nevirapine prevents mother to-child transmission. A single dose of Nevirapine 200mg is given to the mother when labour pains start. These women are preferably delivered by caesarean section and advised not to breastfeed the baby. Nevirapine 2mg/kg is given to the baby. AZT in the last trimester of pregnancy has also been found to reduce vertical transmission from mother to child. Efavirenz can also be used in pregnancy. It has been found to be safe contrary to the earlier studies.

Indications For Using Antiretroviral Therapy: The mandate has changed to "Test and Treat" irrespective of the CD4T cell count. However, in the following conditions ART has been found very useful.

Acute HIV infection.

CD4 <200/mm2 or >10,000 viral copies/mm2.

Only 15 per cent of people can afford antiviral treatment.

The good news is that the cost of treatment has come down to approximately Rs 2000/- per month, as compared to Rs 30,000/- per month in 1998.

Prophylaxis:

D. Prophylaxis For Healthcare Workers

Prophylactic use of anti-HIV drugs is recommended for healthcare workers who have had percutaneous exposure to HIV infected blood following needle-stick injury with surgical instruments. Such an injury carries a risk of HIV transmission of around 0.3 per cent[7]. Adopting universal precautions and taking care in handling sharp objects can reduce the risk of percutaneous injury. The risk of seroconversion is raised with the increase in size of blood inoculum and the disease stage of the patient from which the infected blood was taken. Following needle-stick injury, a rapid decision must be taken and the drugs must be readily available so as to be effective. They must be started as soon as possible after exposure. Current recommendations are that Zidovudine, Lamuvidine and Indinavir should be taken for a 4-week period or Tenofovir with Emtricitabine and Efavirenze as a single daily tablet for 28 days.

Vaccine for HIV/AIDS : There are primarily four basic approaches to creating a vaccine for HIV AIDS. These are summarised in the table.

Various subtype B canary pox -HIV vector primes and booster containing subunit glycoprotein 120 or 160 (gp120 or gp160) have been under evaluation. In 2009, the ALVACHIV priming and AIDSVAX B/E boosting for the prevention of HIV-1 infection in more than 16000 young Thai adults at risk for the disease.[8] This was the only study to show a modest protective effect (31%) of the vaccine and offers new insight for research. Four years later, the multigene, DNA prime–recombinant adenovirus type 5 vector boost (DNA/rAd5) vaccine trial was stopped due to lack of efficacy. The use of broadly neutralising antibody is a relatively new concept. The VRC01 antibody was initially found in HIV infected individuals (> 10 years) but who never developed AIDS. These patients, termed "Elite controllers" were the source for this antibody which has been shown to neutralise more than 90% of the 190 strains it has been tested against. This study, part of the HIV vaccine trials network and the Antibody mediated prevention study, has currently progressed to phase 2b of clinical trials[9].

Table: Strategies for a vaccine for HIV/AIDS

Incorporation of HIV genes into a plasmid and introduced into the human subject, eliciting an immune response.

HIV genes are inserted into the genomes of live, but noninfectious viruses, and the protein expressed by these genes could be the target for the immune response
Chemically synthesized HIV peptides allowed to elicit a B cell response
Empty shells of the viral structure could produce a high titre of neutralising antibodies, but due to lack of genetic material fail to cause infection.

E. Counselling : Counselling is the back bone of care in the Continuum of Care of patients suffering from HIV/AIDS. This requires total commitment and involvement of all healthcare professionals including doctors, nurses, paramedic workers, lab technicians and counselors.

Certain questions that need to be addressed are:

- Are we still afraid?
- Do we discriminate against our HIV positive patients?

F. Care And Support : Our programme today links care with prevention. "Our motto while dealing with HIV/AIDS patients is "CARE WITH COMPASSION"

We usually admit HIV/AIDS patients for management of opportunistic infections and use this opportunity for counselling and teaching prophylactic measures both for preventing spread of HIV and acquiring opportunistic infections. We counsel them using trained social workers in the outpatient department, in the wards and also in the homes of patients. We teach home-based care to the family of the patient, thereby transferring skills and the ownership of the problem to the caring family. We encourage the patient and his/her family to attend the positive persons' support group, which meets twice a month in the hospital[10]. This support group is a very effective tool in the programme because counselling does improve the quality of life and definitely prolongs life. Those attending the support group regularly are healthier, live longer and with less fear. The reasons are that their infections are picked up early, they are less depressed, are able to vocalise their fears and hopes, and become more knowledgeable about the disease and the affiliated problems.

Community Counselling : Our work takes us out into the community where the answers to HIV/AIDS really can be found. Over the past 14 years from 2003 to 2017, the physicians from DVVPF's Medical College, Ahmednagar have been providing diagnostic and therapeutic support at "SNEHALAYA". Snehalaya, an NGO, is a rehabilitation centre for children of commercial sex workers who may or may not be HIV positive. In addition, we follow the patients by invitation into their homes, neighborhoods and communities. Through systematic home-to-home visits and through local teams in the community, we discuss the problem of HIV/ AIDS. The methodology used is of home visits and community discussions. Change can only happen once people realise "I am at risk unless I change my behavior." We see the impact of HIV/AIDS on the youth, and on families; we see behavioral changes beginning to happen. There is less drunkenness; less high-risk behavior but it is a slow process and yet very heartening.

The Future :

Future Anti-retroviral Drugs And Strategies: Unprecedented amount of research is going on in the field of HIV/AIDS. Several other exciting advances might offer new options for treatment.

- The first of these is the potential for ART to be given by long-acting (LA) injections rather than pills. The two injectable drugs are- a new integrase inhibitor called Cabotegravir LA and NNRT called Rilpivirine LA. Both are combined into the one dual injection, which only needs to be given once every two months. There are few important cautions to be aware of. The first is that the injection needs quite a large volume. Currently each treatment needs several injections into the buttocks. Even though most people reported discomfort from the injection, over-all people in studies were happy with results compared to taking pills.
- Secondly, these drugs stay in the body for a long time. This makes it important to start with oral medication in case someone has serious side effects.
- Thirdly, we need to understand how to safely stop long acting drugs in order to minimise the chance of drug resistance.

Conclusion : The human immunodeficiency virus remains a global health problem since its discovery in 1983. The WHO now recommends that anti-retroviral therapy must be initiated for all patients, irrespective of CD4 counts. Starting ART at progressively higher CD4 counts has shown to lower the risk of some toxic effects associated with anti-retroviral therapy. Early ART initiated also prevents neurocognitive declines, increases chances of CD4 normalisation, and lowers the risk of development of IRIS. In India, the backbone of first line anti-retroviral therapy remains Lamivudine (3TC) or Emtricitabine, Tenofovir (TDF) and Efavirenz or Nivirapine. The current research is focused, in addition to HIV vaccine, on the latency reversing agent, Romidepsin, a depsipeptide.

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