CHAPTER VI

MEDICAL & BIOLOGICAL ASPECTS

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CHAPTER VI
MEDICAL & BIOLOGICAL ASPECTS

6.1 Introduction

As Human Immunodeficiency is basically a viral infection, its effects on the human body are the cause of the epidemic from a biological front. It is important to identify the well established facts about HIV disease in a study like this. As its understanding focuses on the virus, infection, disease, diagnosis and treatment from a physician, these issues are discussed in this chapter.

In a short span less than that of a generation, the intricacies of the complicated mechanisms how this virus affects the most crucial aspect of human protection against the myriads of opponents in the microscopic world have been unleashed.

In an unparalleled historical development, all nations of the world are united and speak the same language when it came to improving the knowledge about this dreaded virus. No event in the history of medicine has parallels in the way in which tests were developed, therapies introduced, drug deliveries speeded up and vaccines invented and tried.¹

²³⁴
Newer drugs came with many international caveats including controversies on patents, property rights and some of these were considered above human rights.

6.2 The Human Immunodeficiency Virus

Ever since human beings were dying from illnesses people had been on the lookout for causes. That’s how the microorganisms (germs) causing diseases were discovered. They were grouped as fungus, bacteria, protozoa (ameba, malarial parasite etc.) and viruses. Viruses are the smallest living organism although smaller infective particles (like prions) have been discovered. Most of the viruses can exist many animals and produce disease in them. There are certain viruses that can infect only human beings. The Virus thought to be responsible for AIDS is one among them. The viruses are grossly classified into two depending on the nucleic acid (genetic) chain in the core. They are RNA (RiboNucleicAcid) and DNA (Deoxyribo Nucleic Acid) viruses. Some of them have a single strand of chain and others have two. The Human Immunodeficiency Virus is a double stranded RNA virus. This virus belongs to a family of viruses called “retroviruses”. (Most of the retroviruses are cancer producing viruses.)
The Human Immunodeficiency Virus (HIV) was discovered in an AIDS patient in France by the famous Pasteur Institute scientist Dr. Luc Montagnier in 1983. This virus is supposed to be a new virus which has its origins probably linked to another retrovirus which affects the macaque monkeys of Central Africa. This virus called as "Simian Immunodeficiency Virus" underwent lot of genetic changes and the genetic materials got transformed into the HIV. This process called mutation has probably taken place in a very slow manner over many many years or decades. The virus gradually becoming more and more aggressive started attacking the tribal people and from them got transferred to the populations across the globe. There had been some unverifiable allegations of some artificial genetic changes that could have played a role.³ ³

The HIV is grouped into two major viruses HIV-1 and HIV-2. HIV-1 is divided into categories M and O. The M virus is again divided into many substrains. The O stands for Outlier virus which is a small group. Recently a new virus has been reported from W. Africa.⁴ This division is useful for tracing occasional transmission investigations and for academic purposes only. (Fig. 3 page 237)
Fig. 3 The Human Immuno deficiency Virus - Structural Diagram
6.3 HIV Transmission

HIV is not a strong virus. It is not passed on by coughing, sneezing, by touching or hugging someone who has the virus, by insect bites, in air, water or in food. This means the virus is not passed on by everyday activities such as using cups or bowls, nor in clothes or from toilets, nor by looking after people infected with the virus, or who have AIDS. HIV is passed on (1) By sex with an infected person (2) By infected blood (3) From an infected mother to her unborn child.456

If a person, a man or a woman, has the HIV virus, it is strongly present in their blood and in their sexual fluids, semen or vaginal fluids. This means that the HIV virus can be passed on by any behaviour where infected blood, semen or vaginal fluids get into the body of the other person through the very thin skin of their sex organs, mouth or anus, or through sores or cuts on their mouth, hands or body. This happens most commonly during sex. The virus gets attached to certain specific cells in the human blood. These cells belong to the group of cells called T lymphocytes, particularly to a subtype called T4 or CD4 cells which are the master cells in immunity (protection) against infections. These cells contain a receptor called
CD4 through which the virus gets attached and gets bound to the genetic material (human DNA) in the nucleus. Once this happens the presence of the virus in the human body is a permanent irreversible affair. The person remains infected thereafter till his death. It is the reduction in the number of CD4 cells that pave the way for immunodeficiency and other problems in AIDS. Subsequently many or all other cells in the body gets infected and the virus is present in all body fluids (blood, semen, vaginal secretions, breast milk, peritoneal fluid, CSF etc.). Even though tears, urine, saliva and sweat may contain the virus, they are never present in any significant concentrations as to be infective.

How is HIV passed on during sex? This could happen in the following ways. 1. Sexual intercourse between a man and with a woman - penis in the vagina or anus. 2. Sexual intercourse between two men - penis in anus. If instead of having sexual intercourse a couple enjoy oral sex, this is much less risky, but HIV could still pass into any sores or cuts on the lips or mouth.

**How can HIV be passed on by infected blood?** If blood from a person infected by HIV gets into the blood of another person, it will infect them also with the HIV. This can happen: (1) From a blood
transfusion with infected blood. (2) When the skin is pierced by Acupuncture Tattooing, Ear piercing, Having injections. It can be prevented if the equipment used is new, or is carefully sterilised each time it is used.

How can people be infected with HIV by injections? If people inject themselves (or someone injects them) with medicines or drugs using a needle or syringe which has been used by someone else, who might have HIV, they will be at high risk of getting HIV themselves. It is never safe to share someone else's needles or syringes. All trained health workers should sterilise needles and syringes before they are used again, because they understand how important this is.7

How might people get infected with HIV through blood transfusions? Blood transfusions may be necessary after a bad accident, if someone has lost a lot of blood, during a hospital operation, after childbirth, if the mother has lost much blood. If the blood or equipment used is infected with HIV, this will be transmitted to the person receiving the blood, and so they will also become infected. There is no risk in donating blood if the equipment is new or properly sterilised.
How can HIV be passed from mother to child? If a woman has been infected with HIV, either from her infected husband or partner, or from an injection with an unclean needle or syringe, and she then becomes pregnant, the HIV virus can pass from her blood (through the placenta) into the growing baby. The HIV may also be transmitted to the baby during birth. About one quarter to one half of babies born to HIV positive mothers are in fact infected with HIV and in a few years they will develop AIDS and die.

6.4 Early HIV infection

When HIV gets inside a person's body, and into their blood and other body fluids, it usually does not make them feel ill, and they have no symptom at all. They look and feel well. They may not know they now have the virus, but could pass it on to someone else through having sex, or by sharing needles or syringes. The white blood cells try to fight off the HIV and after about 3 months or more, and do make some antibodies, but these antibodies do not kill the HIV. A blood test can now detect the HIV antibodies. The person is said to be HIV Positive. They then still look and feel well for many years. They have not yet got AIDS. Being HIV Positive is not the same as having AIDS. The fight between the virus and the
body goes on for years. David Ho proposed that the dynamics of virus replication happens from the first day of infection and it is a very lively fight. After many years only, the body’s defenses are weakened and the virus wins the battle.8,9,10.

After about 5 to 10 years the HIV virus multiplies and begins to kill the white blood cells, so the immune system becomes 'deficient' and cannot fight off infections as it used to. Eventually the infected person may lose weight and become ill with diseases like persistent diarrhoea, fever, pneumonia, or skin cancer. He/ she has now developed AIDS.10

People with AIDS can be helped with medicines for the different infections and support from other people which enable them to continue working and live an active life as long as possible11. At the moment though, in spite of much research, there is no cure for HIV or for AIDS and so, sadly, it is almost certain that people diagnosed with AIDS will die.
Fig. 4 The Course of HIV disease
6.5 Diagnosis

6.5.1 HIV antibody testing

It is possible for people to have their blood tested. The testing that is most commonly done is an Enzyme Linked ImmunoSorbent Assay (ELISA) where the presence of specific antibodies are detected. People who think they may have HIV have to consider carefully whether or not they wish to be tested for the HIV antibodies. The test cannot be done before 3 months after they may have been infected. It should be done in confidence and with counselling support before and after the test. It might prove positive, showing they have HIV. They then have to consider how they feel about it, and who they should tell, including their partner.  

The advantages of knowing this are, given good community care: They can get help as soon as they feel ill for any reason; They can make sure they don’t pass HIV on to anybody else; They can try to keep their immune system strong by eating healthy food and reducing smoking and alcohol; They can make plans about how their children and families will be looked after if they do become ill; They can gain help and support from other people.
The disadvantages of having a test are that if other people find out, they may show prejudice, and reject infected people and their families, making their lives even more difficult.

6.5.2 Problems of PLWHA in early identification

The person gets infected through an act that occurs at an instance most people do not desire to recall. In fact many will seek medical care for any ailment that develops following such an instance. But the chance for the person to be made conscious of the chance for such an infection is remote. Even when alerted, performing any of the available tests will not identify him / her as being infected with HIV. The fact that the common antibody tests are likely to become positive only by the eighth to twelfth week is likely to be overlooked or improperly interpreted.

There is a probability of false positives occurring in the Indian scenario too. It has been estimated that about 50 – 60 % of all seropositivity identified in Indians can be false positives. This is due to two main reasons. The first is the increased incidence of illnesses causing false positivity in the population eg. acute viral infections, malaria, chronic renal, hepatic disease, alcoholic liver diseases. The second and perhaps more important reason is the low prevalence of
HIV infection in the community. It has been well worked out that the positive predictive value of the antibody test depends on the point prevalence of the disease in the community. Thus in many African countries where the prevalence is quite high (10% or more) in the general population, the positive predictive value of the test is quite high and the false positivity is very low. This might result in even a casual test detecting somebody who is truly infected.\textsuperscript{13}

The peculiar nature of this chronic infection presenting years later also poses problems. When a person presents with a disease many years after an exposure, it is so difficult to link the two. The problem is confounded when the intervening period has been very normal even when he/she had many health visits for different purposes. To say that the person had been harboring the organism all these years and that this is linked to such a commonplace event as having had sex with an apparently healthy person eight or ten years back defies common man’s logic.\textsuperscript{10}

\textbf{6.6 The Disease AIDS}

\textbf{Three phases of the illness}

HIV infection does not lead to immediate changes in the person’s body. After about two to six weeks the person develops a
feverish illness. At this time he will have slight fever with aches and
pains all over the body, running nose, small swellings in different
parts of the body due to enlarged lymph glands and occasionally
rashes all over the body. This picture which looks like a viral fever
usually lasts for two three weeks. Called as acute retroviral illness this
occurs in about 50 % of all individuals who are infected with HIV.
During the gap between the entry of the organism and this illness the
viruses are multiplying and establishing themselves in the human
cells. The body is targeting all defenses against the virus and even
produces antibodies. It is this antibody that helps us in identifying the
infected individual as one HIV positive person. Thus till this time
even though the person had the virus, the usual antibody tests were
all negative. The above illness is also referred to as Acute
seroconversion illness.

After the acute seroconversion illness the person remains
totally free of all symptoms for many many years which may be upto
ten or twenty years. This asymptomatic period is due to a dynamic
state where new viruses produced in the body are continually
destroyed by an efficient immune system. The person looks very
healthy and leads a normal life.
The typical symptomatic illness that occurs after many years is itself divided into three.
The early symptomatic phase – during which the person develops those illnesses very common in the society as well as those rare diseases but with increased severity and relative resistance to treatment. e.g. Pneumonias, typhoid fever, sinusitis, usual fungal infections etc..
The late symptomatic phase – in the next two or three years This is what was previously referred to as AIDS related Complex (ARC). This is a cluster of symptoms usually characterised by Persistent Generalised Lymphadenopathy – swelling of two or more extrainguinal lymph nodes persisting for more than a month-
Tuberculosis occurring in sites other than the lungs etc.

Finally the person reaches the stage of "AIDS". This stage has got varying definitions depending on what is being looked at.

The clinical case definition given by WHO\textsuperscript{17} is as follows. "AIDS in an adult is defined by the existence of at least two of the major signs associated with at least two major signs associated with at least one minor sign in the absence of known causes of immunosuppression."
Major signs

1. Fever of one month duration (unexplainable)
2. Diarrhoea of one month duration
3. Weight loss of more than 10% (recent, unexplained)

Minor signs

Persistent Cough of more than one month’s duration
Unexplained itching due to Generalised pruritic dermatitis
Recurrent Herpes Zoster
Oropharyngeal candidiasis
Chronic progressive and disseminated herpes simplex infection
Generalised lymphadenopathy

The modified Indian case definition (NACO)\textsuperscript{18} is as follows.

“AIDS in an adult is defined as one who has positive test for HIV antibody detected by two separate tests using two different antigens AND any one of the following”

1.(a) weight loss of more than 10% body weight or cachexia
(b) chronic diarrhea of more than one month’s duration

OR chronic cough of more than one month’s duration

2. Disseminated miliary or extra pulmonary tuberculosis
3. Neurologic impairment restricting daily activities (not to be due to a condition unrelated to infection)

4. Candidiasis of the Esophagus diagnosed as Painful dysphagia along with oral candidiasis

5. Kaposi's sarcoma

Centre for Disease Control, Atlanta (U.S) has been putting forth regular updates of diagnostic criteria based on certain tests to count the CD4 cells (the cells getting infected with HIV and responsible for the immune system abnormalities). Their criteria also takes into account the presence of indicator diseases to diagnose AIDS too. The CDC criteria has identified certain situations where AIDS can be diagnosed even with a negative HIV antibody test.¹⁸

However a simple and easily understandable definition of AIDS is that AIDS is a situation when an HIV infected person develops opportunistic infections or certain malignancies (cancers). The occurrence of AIDS is associated with a short lifespan and unless intensively treated the person dies in less than two years’ time.

**Opportunistic infections**

Normally all the organisms (germs) are not able to produce a disease in us because our body has sufficient defenses. But in a
situation where the immune systems become weak, almost any organism can make us sick. Such organisms are referred to as opportunistic and the diseases are called opportunistic infections. In this age, AIDS is the commonest cause for such a disease. Examples of such illnesses are diarrhea induced by an ameba like organism- Cryptosporidium, pneumonia produced by a fungus - Pneumocystis carinii pneumoniae, and meningitis produced by Cryptococcus. The presence of an opportunistic infection is sufficient evidence of immunosuppression. The fortunate thing is that most of these are treatable even though they have a tendency to recur very often. There is practically no risk of a healthy person contacting an opportunistic infection from an AIDS patient. Opportunistic infections are less common in HIV infected children compared to adults.\textsuperscript{19,20,21}

6.7 Medical Treatment of AIDS

Medical Treatment of AIDS which was a very confusing issue is showing signs of settling. What was considered a total failure, is now offering rays of hope. Management of HIV infected persons is mainly considered along three lines.

6.7.1 Interventions in the asymptomatic stage
Interventions in the early stage of infection, particularly in the first few years are not well defined. Improvements in lifestyle, hygiene and sanitation infection control etc. are suggested as useful. Changes in working environments leading to changes in stress and strain (physical as well as emotional) have shown improvements in survival and delay in onset of evident disease. As the major illnesses are infections, improvements in hygiene and sanitation will limit the exposure to dangerous organisms. These organisms are not only the usual pathogens, but also the microbes that will not produce any effect in normal persons. It has been demonstrated that just by drinking boiled water, the incidence of diarrheas can be reduced by as much as 60%. This and other similar steps will go a long way not only in prolonging life, but also in realizing that the persons do have a way in their control by which they can modify their own future life.  

The earliest clinical intervention is in the form of prophylactic vaccines and drugs. There are many situations where clinicians use vaccines and drugs to modify the capability of persons to fight illnesses. Many vaccines including the BCG vaccine, Hepatitis B vaccine, Pneumococcal vaccine have been demonstrated to be useful in many instances. Knowing fully well that these infections are
commonplace in these persons, they are advised at a very early stage where the persons have sufficient immunity left to develop their own immune mechanisms. Thus the chance of fresh infections and reactivations (which are very high) are significantly reduced. There are certain infections, which develop only at certain stages of the disease. Pneumocystis carinii pneumonia, Candidiasis, Herpes Zoster, Tuberculosis, Mycobacterium avium intracellulare infection are certain infections which are predictably associated with different stages of the disease. If the progression of illness can be assessed, the persons are advised to take certain drugs that will kill the organisms. This form of prevention is known as primary chemoprophylaxis. Many persons who develop very serious infections like tuberculosis and candidiasis are treated for their illness and most of them initially respond to treatment as well. But as days pass by, these illnesses recur and become more and more resistant to treatment.  

6.7.2. Role of Counselling in healthy life

The first and foremost is enabling the person to live a healthy and positive life. This is achieved by resorting to principles of counselling. The person is encouraged to lead a healthy infection free, hygienic living. The person need not take rest and can engage in ways
of earning livelihood. Once he indulges in self hygiene and protection, he also is unlikely to transmit the infection to others too. In order to protect himself from getting further infections, he has to use condoms. This type of an approach enables him to present and discuss his situations with a counsellor who with empathy considers and guides him to choose a healthy lifestyle, in which his psychological, physical and spiritual needs are addressed to.

HIV counselling has been defined as "a confidential dialogue between a person and a care provider aimed at enabling the person to cope with stress and make personal decisions related to HIV/AIDS. The counseling process includes an evaluation of personal risk of HIV transmission and facilitation of preventive behaviour."\textsuperscript{21,22} The objectives of HIV counselling are the prevention of HIV transmission and the emotional support of those who wish to consider HIV testing, both to help them make a decision about whether or not to be tested, and to provide support and facilitated decision-making following testing. With the consent of the client, counseling can be extended to spouses and/or other sexual partners and other supportive family members or trusted friends where appropriate.
Counsellors may come from a variety of backgrounds including health care workers, social workers, lay volunteers, people living with HIV, members of the community such as a teachers, village elders, or religious workers/leaders.

HIV counselling can be carried out anywhere that provides an environment that ensures confidentiality and allows for private discussion of sexual matters and personal worries. Counselling must be flexible and focused on the individual client’s specific needs and situation. In some settings HIV counselling is available without testing. This may help promote changes in sexual risk behaviour.

Many people are afraid to seek HIV services because they fear stigma and discrimination from their families and community. VCT services should therefore always preserve individuals’ needs for confidentiality. Trust between the counsellor and client enhances adherence to care, and discussion of HIV prevention. In circumstances where people who test seropositive may face discrimination, violence and abuse it is important that confidentiality be guaranteed. In some circumstances the person asks for shared confidentiality. This is appropriate and often very beneficial.
The counselling process consists of pretest, post-test and follow-up counselling. HIV counselling can be adapted to the needs of the client/s and can be for individuals, couples, families and children and should be adapted to the needs and capacities of the settings in which it is to be delivered. The content and approach may vary considerably for men and women and with various groups, such as counselling for young people, men who have sex with men (MSM), injecting drug users (IDUs) or sex workers. Content and approaches may also reflect the context of the intervention, e.g. counseling associated with specific interventions such as tuberculosis preventive therapy (TBPT) and interventions to prevent mother to-child transmission of HIV (MTCT). Establishing good rapport and showing respect and understanding will make problem solving easier in difficult circumstances. The manner in which news of HIV serostatus is given is very important in facilitating adjustment to news of HIV infection.

The second important line of management is to treat all infections including opportunistic infections. Most of these are treatable and some of them are curable. Most of these can be treated using the common drugs available in any major health setting and
rarely requires specialised care. Some of these infections like the fungal infection - Pneumocystis carinii pneumoniae- are likely to recur. These can be prevented by taking certain medicines regularly. Some situations warrant the use of these medicines even before the disease when they feel a great likelihood of the disease in the persons. This is referred to as primary prophylaxis and is a very important step in illnesses such as Pneumocystis carinii pneumonia, which can be prevented with drugs like Cotrimoxazole, which are very cheap and available\textsuperscript{18,19}.

6.7.3 AntiRetroviral Therapy

The third aspect of management is a rather recent method of using drugs to kill the HIV. These drugs are called as Antiretroviral drugs. The antiretroviral drugs are of four major types in addition to many smaller groups. These act on the various stages in the life of the virus and try to kill them. But they donot succeed in killing all the viruses or making the person free of the virus. They are all very expensive at present and treatment costs are in the range of Rs.50 to
Rs.250 per day and mostly lifelong. Hence there are very few patients who might benefit from this mode of treatment which is not curative also.

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast- and short-lived trends. Those who have experienced the rapid developments of the last few years have been through many ups and downs: The early years, from 1987-1990, brought great hope and the first modest advances using monotherapy\textsuperscript{23}. But, by the time the results of the Concorde Study\textsuperscript{24} had arrived both patients and clinicians had plunged into a depression that was to last for several years. Zidovudine was first tested on humans in 1985, and introduced as a treatment in March 1987 with great expectations. Initially, at least, it did not seem to be very effective. The same was true for the nucleoside analogs zalcitabine, didanosine and stavudine, introduced between 1991 and 1994. The lack of substantial treatment options led to a debate that lasted for several years about which nucleoside analogs should be used, when, and at what dose.
Many patients, who were infected during the early and mid-80s, began to die. Hospices were established, as well as more and more support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. Between 1989 and 1994, morbidity and mortality rates were hardly affected. Then, in September 1995, the preliminary results of the European-Australian DELTA Study\textsuperscript{25} and the American ACTG 175 Study\textsuperscript{26} attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than mono therapy. Indeed, the differences made on the clinical endpoints (AIDS, death) were highly significant. Both studies demonstrated that it was potentially of great importance to immediately start treatment with two nucleoside analogs, as opposed to using the drugs “sequentially”. This was by no means the final breakthrough.

By this time, the first studies with protease inhibitors (PIs), a completely new drug class, had been ongoing for several months. PIs had been designed in the lab using the knowledge of the molecular structure of HIV and protease – their clinical value was initially uncertain. Preliminary data, and many rumors, were already in circulation. In the fall of 1995, licensing studies for the three PIs,
ritonavir, saquinavir and indinavir, were pursued with a great amount of effort, clearly with the goal of bringing the first PI onto the market. The monitors of these studies in the different companies “lived” for weeks at the participating clinical sites. Deep into the night, case report files had to be perfected and thousands of queries answered. All these efforts led to a fast track approval, between December 1995 and March 1996, for all three PIs – first saquinavir, followed by ritonavir and indinavir – for the treatment of HIV.

Many clinicians were not really aware at the time of what was happening during these months. AIDS remained ever present. Patients were still dying, as only a relatively small number were participating in the PI trials – and very few were actually adequately treated by current standards. Doubts remained. Hopes had already been raised too many times in the previous years by alleged miracle cures. Early in January 1996, other topics were more important: palliative medicine, treatment of CMV, MAC and AIDS wasting syndrome, pain management, ambulatory infusion therapies, even euthanasia. In February 1996, during the 3rd Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from
the ABT-247 Study during the latebreaker session. The auditorium was absolutely silent. Riveted, listeners heard that the mere addition of ritonavir oral solution decreases the frequency of death and AIDS from 38 % to 22 %\textsuperscript{27}. These were sensational results in comparison to everything else that had been previously published.

But for many, the combination therapies that became widely used from 1996 onwards, still came too late. Some severely ill patients with AIDS managed to recover during these months, but, even in 1996, many still died. Although the AIDS rate in large centers had been cut in half between 1992 and 1996, in smaller centers roughly every fifth patient died in this year. However, the potential of the new drugs was slowly becoming apparent, and the World AIDS Conference in Vancouver a few months later, in June 1996, was like a big PI party. Even regular news channels reported in great depth on the new “AIDS cocktails”. The strangely unscientific expression “highly active antiretroviral therapy” (HAART) began to spread irreversibly.

By this time, David Ho, Time magazine’s “Man of the Year” in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his breakthrough research\textsuperscript{28,29}. A year earlier, Ho
had already initiated the slogan “hit hard and early”\textsuperscript{30}, and almost all clinicians were now taking him by his word. With the new knowledge of the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T cells, there was no longer any consideration of a “latent phase” – and no life without antiretroviral therapy. In many centers almost every patient was treated with HAART. Within only three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37% to barely 9%, whilst the proportion of HAART patients rose from 2% to 64%\textsuperscript{31}. Things were looking good. By June 1996, the first nonnucleoside reverse transcriptase inhibitor, nevirapine, was licensed, and a third drug class introduced. Nelfinavir, another PI, had also arrived. Most patients seemed to tolerate the drugs well. 30 pills a day.

The number of AIDS cases was drastically reduced. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe was reduced from 30.7 to 2.5 per 100 patient years –i.e. to less than a tenth. The reduction in the incidence of several feared OIs, particularly CMV and MAC, was even more dramatic.

The large OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, which had been receiving
substantial donations, had to shut down or reorientate themselves. The first patients began to leave the hospices, and went back to work; ambulatory nursing services shut down. AIDS wards were occupied by other patients.

In 1996 and 1997 some patients began to complain of an increasingly fat stomach, but was this not a good sign after the years of wasting and supplementary nutrition? Not only did the PIs contained lactose and gelatin, but the lower viremia was thought to use up far less energy. It was assumed that, because patients were less depressed and generally healthier, they would eat more. At most, it was slightly disturbing that the patients retained thin faces. However, more and more patients also began to complain about the high pill burden. In June 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs\textsuperscript{32}. In February 1998, the CROI in Chicago finally brought home the realization among clinicians that protease inhibitors were perhaps not as selective as had long been believed.

One poster after the next, indeed whole walls of pictures showed fat abdomens, buffalo humps, thin legs and faces. A new term was introduced at the beginning of 1998, which would influence
the antiretroviral therapy of the years to come: lipodystrophy. And so
the old medical wisdom was shown to hold true even for HAART: all
effective drugs have side effects. The actual cause of lipodystrophy
remained completely unclear. Then, in early 1999, a new hypothesis
emerged from the Netherlands: “mitochondrial toxicity”. It has
become a ubiquitous term in HIV medicine today.

The dream of eradication (and a cure), still widely hoped for in
the beginning, eventually had to be abandoned, too. Mathematical
models are evidently not suitable for predicting what will really
happen. In 1997, it was still estimated that viral suppression, with a
maximum duration of three years, was necessary; after this period, it
was predicted that all infected cells would presumably have died.
Eradication was the magic word. At every conference since then, the
duration of three years has been adjusted upwards. Nature is not so
easy to predict, and newer studies came to the sobering conclusion
that HIV remains detectable in latent infected cells, even after long-
term suppression. To date, nobody knows how long these latent
infected cells survive, and whether even a small number of them
would be sufficient for the infection to flare up again as soon as
treatment is interrupted. Finally, during the Barcelona World AIDS
Conference, experts in the field admitted to bleak prospects for eradication. The most recent estimates for eradication of these cells were approximately 50-70 years. One thing is certain: HIV will not be curable for at least the next 10 years.

Instead of eradication, it has become more realistic to consider the lifelong management of HIV infection as a chronic disease in the future, similar to diabetes mellitus. This means, however, that drugs have to be administered over many years, which demands an enormous degree of discipline from patients. Those who are familiar with the management of diabetes understand the challenges that patients and clinicians have to face and how important it will be to develop better combinations in the coming years. Hardly anyone will have the discipline and ability, both mentally and physically, to take the currently available pills several times daily at fixed times for the next ten, twenty or even thirty years. But, presumably, this will not be necessary. There will be new and improved treatment regimens. Once daily regimens are coming; maybe even twice-weekly.

At the same time, the knowledge of the risks of antiretroviral therapy has changed the approach of many clinicians towards treatment over the last three years. By the year 2000, many strict
recommendations from previous years were already being revised. “Hit HIV hard, but only when necessary” is now heard more than “hit hard and early”\textsuperscript{33,34}. The simple question of “when to start?” is now being addressed at long symposia. It is often a question that requires great sensitivity.

The drugs are:

a) Nucleoside analogue reverse transcriptase inhibitors - drugs that inhibit the Reverse Transcriptase Enzyme (responsible for the creation of DNA from the Viral RNA).viz. AZT (Zidovudine), ddl (Zidanosine), ddC(Zalcitabine), d4T (Stavudine), 3TC(Lamivudine) & Abacavir

b) Non-nucleoside analogue reverse transcriptase inhibitors Delavirdine Nevirapine Loviride & Efavirenz

c) Nucleotide Reverse Transcriptase inhibitor. Adefovir.

d) Protease Inhibitors - drugs that inhibit protease enzyme (responsible for cleavage of the large protein moieties into smaller viral polypeptides – an important step in the release of new generation virions) viz. Saquinavir Ritonavir Indinavir Nelfinavir.
The drugs are to be taken regularly and adherence is almost always a weak point with many patients. The adherence that is insisted is to the tune of more than 95%.

The treatment recommendations are updated on a regular basis and current recommendation is to use combination therapy rather than monotherapy.

6.8 Women and AIDS

Even though AIDS was for a short time thought to be confined to male homosexuals, very soon it became evident that females are getting affected fast. Thus the male : female ratio which was somewhere at 9:1 in the first days of the epidemic, is fast approaching 1:1. In many of the underdeveloped and developing countries of the world where the plight of the average woman in terms of health is much below the men, the disease manifests earlier in women. In India, the Commercial Sex Workers have been mercilessly pointed as the source of the epidemic, forgetting the fact that males who visit them are the real persons who spread the infection. But now as more and more married women from all social strata are becoming infected, this myth is getting shattered. It is estimated that the majority of HIV infected women in India got their
infection from their "faithful" husbands who were their only sexual partners.

Biologically, women have a higher chance of getting infected with HIV and of harbouring unnoticed sexually transmitted diseases. This is because of two main reasons. The female genital tract, unlike the female is mostly hidden and is not accessible for frequent inspection. Hence many obvious changes like ulcerations, swellings may remain unnoticed for a very long time and hence progress to serious levels. Secondly by the fact that the semen (which may be infected) remains in contact with the soft mucous membrane of Vagina for longer time compared to the exposure of the penis to the female secretions which are less in quantity too. The vulnerability of the female genital tract at the younger age also adds to the gravity of the problem. Thus teenagers engaging in sex have a higher chance to be infected. Coupled with the fact that many men prefer sex with teenagers, the problem is accentuated.35,36

Women are also vulnerable as a result of sociological conditions, some of which may have economic underpinnings. Women frequently lack control over their own sexual lives or those of their husbands outside the house. Women's inability to insist on
protected sex is affected by sociocultural barriers to women as decision makers; limited literacy, mobility, and access to information; and cultural and moral attitudes towards sexuality. Women may not be able to discuss sexuality even with their husbands. Social and sexual passivity makes insistence on the use of condoms difficult. The issues of absolute poverty caused by a customary division of labour, biological factors and labour market stratification all add to the burden of women. The role of commercial sex workers in AIDS epidemic is complex but in many underdeveloped countries, poverty leads women to an avenue for HIV infection.

The role of women in the family as a caretaker for the affected husband is put to severe stress at times when the husband is sick, thrown off from job, requiring extra care. At the same time she is forced to bear the trauma of a possible lack of faithfulness revealed to her only because of the illness now. When every family members tries to shun the responsibility, she most likely looks after this man. She also serves as the unfortunate source of infection for the next generation. Her children develop the illness fast and she is the only one to care for them. When she gets all the problems that go with widowhood, she also is orphaned by the dying husband and children.
She is confronted with the possibility of nobody to look after her when she becomes ill. Presently another burden is added to her agony. It is now known that the remedial measures the woman has to adopt to try for an uninfected child puts her life at jeopardy too.\[37\]

Another unfavourable factor for women is the increased incidence of cancers of the tip of uterus (Cancer Cervix) which an HIV infected person has a chance to get when she is still young. This is behind the recommendation that HIV infected persons must get examined at least once in six months.

6.9 Children and AIDS

Just as women were, children were also considered to be in the periphery of the epidemic in the beginning. Children with Hemophilia and other serious illnesses which required multiple transfusions came with the disease first. As more and more women in the reproductive age group developed HIV infection, the series of children getting infected from these mothers increased. The situation is rapidly changing. It is estimated that there would be millions of children on their own (having lost parents) by the end of this decade in the countries affected by HIV/AIDS.
It is estimated that of the 11.7 million deaths from the start of the epidemic 2.7 million (23%) were children. In 1997 of the 2.3 million people who died of AIDS globally 4.60,000 (20%) were children (below 15 years of age) and about 5,90,000 children (of 5.8 million new infections) became infected with HIV. Of the 30.6 million people world-wide living with HIV 1.1 million (3.6%) are children. Over 90% of these children live in developing countries. Cumulatively by the year 2000 as many as 5 million under fives will be HIV infected through their mothers, the majority of them in Sub-Saharan Africa. According to WHO estimates close to 10 million children (under 10 yr of age) will be orphaned by then.

Overall infant and child mortality rates have exceeded previous projections by as much as 30 percent as a direct consequence of perinatal HIV infection. Consequently, paediatric AIDS is now threatening much of the progress that has been made in child survival in developing countries during the past twenty years.39

There has also been much progress made in understanding the natural course of HIV disease in children. HIV-infected children differ from HIV-infected adults in numerous ways. For starters, there is a much more rapid rate of disease progression in children; the
average time to an AIDS diagnosis is 8 to 17 months in children, compared to 8 to 11 years in adults. Secondly, normal T-cell counts are significantly higher in children younger than 6 years of age and can fluctuate greatly. Thus, it is much harder to determine when opportunistic infections (OIs) might occur in HIV-infected children and to determine whether or not antiviral treatment or combinations of treatments are yielding the desired effect. Finally, HIV-infected children have an increased incidence of recurrent invasive bacterial infections. Moreover, OIs often represent primary disease with a more aggressive course, given lack of prior immunity. For example, an HIV positive child who has never been infected with the chicken pox virus may develop a severe case of chicken pox with initial (primary) infection. In contrast, many OIs in adults are reactivations of latent infections to which some level of immunity may exist. The chicken pox virus, which remains dormant inside the body after the primary infection, may reactivate in an HIV positive adult or a child who has already had chicken pox, as shingles.

The predominant route of infection in children is from an infected pregnant mother to her child. About 10% of children become infected through other routes. Transfusion of HIV positive
blood and blood products is the other major route followed by infection through sexual contact among older children including sexual abuse and sexual exploitation.\textsuperscript{40,41}

Mother-to-child transmission can occur while the fetus is in the uterus, at the time of delivery. It has been shown that breast-feeding may increase the risk of infection by an additional 14\% (95\% confidence interval 7-21\%). A high risk of transmission in the first few weeks of breast-feeding has also been documented. The risk of transmission is higher in women with clinical, immunological or virological markers of advanced HIV-infection and varies from 13\% in Europe to about 45\% in Sub-Saharan Africa.\textsuperscript{37,38}

Transfusion of blood and blood products being the most efficient method of transmission of HIV infection occurs usually in children suffering from thalassaemia, sickle cell anaemia, haemophilia, etc.

In sexually active teenage girls, susceptibility to HIV and other sexually transmitted diseases may be increased because of the immature epithelium of the cervical canal. High-risk behaviours, including unprotected sex, and use of illicit drug potentiates this problem.
Approximately one-third of these children become symptomatic within the first few months of life and are considered 'rapid progressors'. Nearly 70% as 'less rapid progressors' become symptomatic within the first seven years of life. A small percent do not develop evidence of disease progression until after 8-10 years of age, behaving more like 'adult equivalents'. The survival scenario is likely to change in future, as effective antiretroviral drugs become available for use in children and with better management and prevention of opportunistic infections.

Although approximately 75 percent of infants who are exposed to HIV perinatally are not infected, exposed infants will suffer the adverse consequences of being born into a family in which one or more adults is infected with HIV.

Primary care providers can provide routine prospective management of perinatally exposed infants and infected children. This includes follow-up of clinical and immune status and general pediatric care, including immunizations and antiretroviral therapy.\textsuperscript{42}
References


18. CDC. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human
immunodeficiency virus: a summary. MMWR 1995;44(No. RR-8).


23. Volberding PA, Lagakos SW, Koch MA. Zidovudine in asymptomatic HIV infection. A controlled trial in persons with


