CHAPTER IV
HIV VACCINE CLINICAL TRIALS
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Most of the scientific and ethical perplexities related to HIV vaccine clinical trials will be better understood, if the reader is acquainted with:

a) The present state of HIV / AIDS pandemic.
b) Unique characteristics of HIV.
c) Basic nature of human immune system.
d) Various kinds of vaccines and how they work.

Accordingly, this chapter is outlined in such a way that the reader proceeds with ease from one concept to another with clarity of thought.

4.1 INTRODUCTION:

One of the salient achievements of the twentieth century science is the triumph of medical fraternity over various infectious diseases that have plagued the mankind through the ages. The modern medicine has assured a reasonably good quality of life to mankind. But this happy scenario was rudely shattered in the early eighties when a new virus, later identified as Human Immunodeficiency Virus (HIV), struck the human race with consequences. Till date, all the ingenuity of man, money, effort & power has not found a way to counter the relentless onslaught of HIV which respects no territorial boundaries, makes no distinction between the race, creed or color and spares neither the rich nor the poor, the old or the young. HIV/AIDS (Acquired Immuno Deficiency Syndrome) continues to pose a grave threat to health and living standards.¹ AIDS is uniquely destructive to economies because it kills people in the prime of their lives.² HIV/AIDS exemplifies the complexities of access to health care for chronic life threatening

¹The Impact of HIV/AIDS on Business and the need for Company involvement, available at HIVAIDS@worldbank.org (Last visited on September 4, 2014).
diseases. With no known cure and need for lifelong treatment, HIV/AIDS has caused unprecedented distress and deaths among the poor countries with a total death toll of over 39 million people since 1981.³

Since the dawn of mankind, no other disease has so menaced the mankind as AIDS. The potential for mass destruction of such large sections of humanity has never been as great as is the case with this disease. *Those infected with HIV form an enormous reservoir of infection, which acts as a source for yet further infection of an even greater proportion of men and women. In no other disease of humans, are all those who are infected potentially able to transmit the infection for the duration of their lifetime.* It is known that untreated HIV disease progresses relentlessly in almost all infected persons, from a clinically silent infection to severely damaged immunologic function resulting in AIDS. The disease if left untreated, progresses to death over a median period of about 10 years.⁴ Over and above, this frightful specter of the disease itself is the stigma and the discrimination on the sufferers of AIDS. No other disease has had so much fear, superstition, prejudice and myth attached to it as in AIDS. Former US Surgeon General C. Everett Koop had called AIDS “the number one health problem of the planet”. It is as much a political, social, economic problem as much it is a medical problem.

As the world is about to enter the fourth decade of the AIDS epidemic, the evidence of its impact is undeniable. The disease has grown into one of the greatest pandemic in human history, spreading to every corner of the globe and causing enormous devastation. HIV/AIDS is not simply a health issue; it affects virtually all aspects of human development. It is a *development problem* with the potential to threaten and even reverse many of the achievements that have been made over the past five development decades. It has been robbing

countries of their resources and capacities on which human security and development depends. AIDS continues to be the leading cause of death in the ten highest HIV prevalence countries, with a 1.5 million death toll in 2013.\textsuperscript{5}

The UN Security Council and the US government are explicit in their recognition of AIDS as a security threat to the survival of nations.\textsuperscript{6} The overwhelming suffering caused by AIDS and the threat it poses to prospects for human and economic development were recognized by world leaders at Millennium Summit in 2000 in New York. Hence they included Goal 6 (Combat HIV/ AIDS, malaria and other diseases) in Millennium Development Goals (MDG). The aim is to halt and reverse the spread of HIV/AIDS by 2015.\textsuperscript{7} Global Commitment of Joint United Nations Programme on HIV/ AIDS (UNAIDS) had formulated 2011- 2015 strategy as – Getting to Zero- where they visualize zero new infections, zero AIDS related deaths and zero discrimination.\textsuperscript{8} Past few years have seen an upsurge in political commitment, strong policies and boosted funding. This momentum in the right direction has to be maintained if the epidemic is to be reversed.

4.2 GLOBAL EPIDEMIC:

HIV/AIDS global epidemic has greatly exceeded earlier predictions and it is now clear that it has the potential to affect all countries and all population groups. About 95\% of all HIV/ AIDS infected people live in developing countries, and have to cope with the huge burden of suffering and death. HIV /AIDS remain the biggest health and development challenge that developing countries are currently facing. Africa continues to bear the brunt of the epidemic. In December 1999, the


\textsuperscript{6}R. Moodie, Should HIV be on the development agenda? DEVELOPMENT BULLETIN No 52, June 2000. UNAIDS Asia Pacific Inter Country Team.

\textsuperscript{7} Combating AIDS in the Developing World, TASK FORCE IN HIV/AIDS MALARIA, TB AND ACCESS TO ESSENTIAL MEDICINES, UN MILLENIUM PROJECT, 2005.

government of Zimbabwe declared AIDS epidemic to be a ‘national disaster’. Zimbabwe has one of the highest reported HIV sero-prevalence rates in Africa. Furthermore, the seriousness of the epidemic is seen in the increased morbidity and mortality. The decreased productivity of the workforce has detrimental effects on family and community. Indeed, the epidemic is having far reaching consequences and no aspect of the economy or society will be left untouched. Although HIV/ AIDS can affect people of all ages, about a half of new infections occur in young adults under 25 years old and who, if untreated, will die within ten years of contracting the infection.  

An estimated 35.3 million people worldwide were living with HIV at the end of 2012; and 2.3 million became newly infected with HIV and 1.5 million lost their lives to AIDS. Africa alone has over 14 million AIDS orphans. The already grim global orphan crisis is growing far worse due to AIDS. Women account for 50% of all adults living with HIV worldwide. The number of people living with HIV has risen from around 8 million in 1990 to 35.3 million today, and is still growing. Around 70% (22.4 Million) of people living with HIV are in the Sub Saharan Africa where one in every 20 are infected with HIV. South and South – East Asia has third ranking with 3.9 million people living with HIV/AIDS, in the end of 2012. Of the world’s population living with HIV/AIDS, more than 93% live in developing countries. The prevalence of HIV infection in Washington DC is at least 3% among people aged over 12 years, as high as that in several African countries. As per latest available statistics, more than 6500 people are newly

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13 HIV- AIDS Fact Sheet, supra note 3.
infected with HIV every day of which 700 are children below 15 years of age. More than 1.1 million are living with HIV in U.S. 1 in five infected with HIV are unaware of their status. Someone in US is infected with HIV every 9.5 minutes. As per latest UN report, 19 million of the 35 million people living with HIV today do not know that they have the virus.

AIDS thus has become a health epidemic that no community, nation or continent can ignore. HIV thrives where social and economic vulnerability is greatest. AIDS is the “first modern infectious disease to strike the developed and the developing world simultaneously and to give both a large stake in finding a cure.” The impact is staggering and unprecedented; the UNAIDS estimates the lifetime risk of death from HIV disease for 15 year old boys to be 30% and more in Cambodia, more than 60% in South Africa and nearly 90% in Botswana.

The United Nations Development Programme’s (UNDP) Human Development Report had considered HIV to have inflicted a major reversal in human development. Since HIV affects people in the prime of their lives, the work force of entire countries are being decimated as they are laden with sickness, or lost to death. Victims and those around them suffer social and psychological costs like stigma and discrimination. These altogether is detrimental to the economy of these nations. When measured in terms of years of potential life lost (YPLL), the economic impact of the disease is devastating.

Increasing number of new HIV infections has other impact as well. There is an increase in viral pool with a subsequent increase in new and more variants of HIV.

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18 D.J. Rothman, The Shame of Medical Research, NEW YORK REV OF BOOKS 60, (November 30, 2000).
UNAIDS and the World Bank predict that HIV, which was responsible for 8.6% of deaths from infectious disease in the developing world in 1990, will be responsible for 37.1% of such deaths among adults between the ages 15 to 59 by 2020.20

Beyond the sheer weight of the numbers, what is perhaps most important about the shape of HIV pandemic is the fact that global distribution of the infection has been anything but equal. AIDS has been called “an unprecedented crisis………….that demands an exceptional response.”21

4.3 HISTORY OF HIV/AIDS IN INDIA:

India is one of the largest and most populated countries in the world, with over one billion inhabitants, around a half of whom are sexually active age group. Among these, it is estimated that around 2.27 million people were living with HIV in 2008 22 and a 2.1 million in the year 2011.23

HIV emerged later in India than it did in many other countries. Infection rates soared throughout the 1990s, and today the epidemic affects all sectors of Indian society, not just the groups – such as sex workers and truck drivers – with whom it was originally associated. In a country where poverty, illiteracy and poor health are rise, the spread of HIV presents a daunting challenge.

At the beginning of 1986, despite over 20000 reported AIDS cases worldwide, India had no reported cases of HIV or AIDS.24 Later in the year, India’s first case of HIV was diagnosed among sex workers in Chennai, Tamil Nadu.25 It was

noted that contact with foreign visitors played a role in the initial infections among sex workers. The National AIDS Control Organization (NACO) states that the virus has spread from urban to rural areas and from high risk to the general population.\textsuperscript{26}

By the end of 1987, out of the 52,907 who had been tested, around 135 people were found to be HIV positive and 14 had AIDS.\textsuperscript{27} Most of these initial cases had occurred through heterosexual sex, but at the end of the 1980s a rapid spread of HIV was observed among Injecting Drug Users (IDUs) in Manipur, Mizoram and Nagaland.\textsuperscript{28}

At the beginning of 1990s, as infection rates continued to rise, responses were strengthened. In 1992, the government set up NACO to oversee the formulation of policies, prevention work and control programmes relating to HIV and AIDS.\textsuperscript{29} In the same year, the government launched a Strategic plan, the National AIDS Control Programme (NACP) for HIV prevention. This plan established the administrative and technical basis for programme management and also set up State AIDS Control Societies (SACS) in 25 states and 7 union territories. It was able to make a number of improvements in HIV prevention such as improving blood safety. By this time, cases of HIV infection had been reported in every state of the country. Throughout 1990s, it had spread to the general population, even to those at low risk.

The second phase of NACP was launched in 1999, with the aim of reducing the spread of HIV through promoting behavior change. It was during this time that Prevention of Mother to Child Transmission (PMTCT) and provision of free retroviral treatments were started for the first time.

\textsuperscript{26} I. Gupta, The HIV/AIDS epidemic in India: Are we doing enough? DEVELOPMENT BULLETIN NO 52, UNAIDS Asia Pacific Inter country Team.

\textsuperscript{27} D. N. Kaker and S.N. Kaker, COMBATING AIDS IN THE 21\textsuperscript{ST} CENTURY, ISSUES AND CHALLENGES, 31, Sterling Publisher Pvt Ltd.


In 2007, the third phase (NACP III) was started with the intention to reach 80% of high risk groups including sex workers, men who have sex with men and injecting drug users.

Over the period 2012-2017, NACP IV aims to accelerate the process of reversal, further strengthening the epidemic response in India through a cautious and well-defined integration process. The main objectives of NACP-IV are to reduce new infections and provide comprehensive care and support to all PLHIV and treatment services to all those who require it.

4.4 HIV/AIDS STATISTICS IN INDIA:

In 2006 UNAIDS estimated that there were 5.6 million people with HIV in India, which indicated that there were more people with HIV in India than in any other country in the world. In 2007, following the first survey of HIV among the general population, UNAIDS and NACO agreed on a new estimate – between 2 million and 3.1 million people living with HIV. As on 2011, 2.08 million people live with HIV / AIDS in India thus ranking it third in the world in terms of greatest number of people living with HIV. Among the Indian states, Andhra Pradesh has highest prevalence followed by Goa, Karnataka, Maharashtra, Tamil Nadu, Manipur, Mizoram, Nagaland and Punjab. The national adult prevalence remained stable around 0.4 percent between 2002 and 2006. 

HIV infection in vulnerable groups has grown rapidly in India, where control of HIV and sexually transmitted infections used to be poor. The conditions for further rapid growth are also in place: paid sex is common, rates of Sexually Transmitted Infection (STI) are high, male mobility is high, rates of condom use in risky sex are low, and rates of circumcision - a presumed protective factor – are low.

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30 HIV SENTINEL SURVEILLANCE AND HIV ESTIMATION 2007: A TECHNICAL BRIEF.
Even an increase to a modest 5% infection level in India, the lower end of the African epidemics, in 2025, would represent 25-30 million infected adults and, over the next 25 years, approximately 50 million cumulative HIV-I infections and 40 million cumulative deaths. This is twice the cumulative number of global deaths due to HIV/AIDS over the past two decades.\textsuperscript{34}

A representative mortality survey of 1.1 million homes on HIV mortality and infection in India found that HIV accounted for 8.1% of all deaths among adults aged 25-34 in 2004. In this age group, about 40% of deaths from HIV were due to AIDS.\textsuperscript{35}

The median incubation periods for progression were found to be 7.9 years for HIV to AIDS, 1.9 years for AIDS related complex to AIDS and 19.2 months for the median survival after developing AIDS.\textsuperscript{36}

Several characteristics of the viral epidemics of India are unique and distinct from the epidemics of other countries.\textsuperscript{37} First, the viral epidemics of India, by and large have been driven primarily by the HIV-1, subtype C strain (85-99%).\textsuperscript{38, 39} The molecular nature of the viral strains circulating in the north eastern states of India is quite distinct from that of the other parts of the country.\textsuperscript{40} Further, since the first report in 1991, a large number of publications reported the presence of HIV-2 in India.\textsuperscript{41}

\textsuperscript{35} P. Jha et al, \textit{HIV Mortality and Infections in India: Estimates from nationally representative survey of 1.1 million homes}, 340, BRITISH MEDICAL JOURNAL, 519, (March 6, 2010).
\textsuperscript{36} V. Ranga et al, \textit{HIV/AIDS research in India: past, Present and Future}, 98(3) CURRENT SCIENCE 335, (February 10, 2010).
\textsuperscript{37} Id.
\textsuperscript{40} S. Chakrabarti et al, \textit{HIV-1 Subtypes in Injecting Drug Users and their non injecting wives in Manipur, India}, 111 INDIAN JOURNAL OF MEDICAL RESEARCH 189 (2000).
It is thought that HIV has spread among the general population in India because the epidemic has followed what is known as a ‘type 4’ pattern. That is, new infections occur first among the most vulnerable populations (such as injecting drug users & female sex workers), then spread to ‘bridge’ populations (i.e., clients of sex workers & sexual partners of drug users) and then finally enter the general population.\footnote{UNGASS, \textit{India – Country Progress Report}, (2008).} Even if the country’s epidemic does not match the severity of those in South Africa, it is clear that HIV/AIDS will have devastating effect on the lives of millions of Indians for many years to come. It is essential that effective action is taken to minimize this impact.

\textbf{4.5 VULNERABLE POPULATION AFFECTED BY HIV/AIDS IN INDIA:}

HIV and AIDS affects all segments of India’s population, from children to adults, businessmen to homeless, female sex workers to housewives, and gay men to heterosexuals. There is no single group unaffected by HIV. However, HIV prevalence among certain groups (sex workers, injecting drug users, truck
drivers, migrant workers, men who have sex with men) remains high and is currently around 6 to 8 times more than that of general population.\textsuperscript{43}

In contrast to the common perception that HIV is transmitted predominantly through injecting drug use and sex between men, the overwhelming majority of infections in India occur through heterosexual sex.\textsuperscript{44, 45} In many cases married men have acted as ‘bridge population’ between vulnerable populations and general populations. Women who believe that they are in monogamous relationships are becoming infected because their husbands have had multiple sexual partners. Often, social norms restrict women from making decisions about their sexual relations, contributing to their vulnerability to HIV.\textsuperscript{46} Studies have shown that intimate partner violence is also a risk factor for women.\textsuperscript{47}

Another significant trend is that most of the people becoming infected are in the sexually active and economically productive 15 to 44 age group. This means that most of the people living with HIV are in the prime of their lives.

**Sex Workers:**

Prevalence of HIV among sex workers varies widely between districts and states: Study conducted by Ramesh et al found that the prevalence ranged between 2% and 38% among the four high prevalence South Indian states (Andhra Pradesh, Maharashtra, Tamil Nadu and Karnataka).\textsuperscript{48} It was detected that a quarter of the sex workers in Mysore were infected with HIV.\textsuperscript{49} This was not surprising as it was revealed in a study that only 20% of the sex workers always used condoms with

\textsuperscript{43} Core Epidemiology Slides – UNAIDS, supra note 15.
\textsuperscript{44} S. Ramalingam et al, *Per Exposure rate of transmission of HIV -1, HIV-2 from Women to Men may be Higher in India*, 25 JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME 97-98 (2000).
\textsuperscript{45} S.M. Mehendele et al., *Incidence and predictors of Human Immuno Deficiency Virus Type I Sero Conversion in Patients attending Sexually Transmitted Disease Clinics in India* 172(6) THE JOURNAL OF INFECTION DIS EASES 1486-1491 (December 1995).
\textsuperscript{46} Core Epidemiology Slides – UNAIDS, supra note 15.
\textsuperscript{49} Id.
commercial clients in the past month.\textsuperscript{50} However, National AIDS Control Organization’s report of 2008-2009 showed that female sex worker sites in the three large cities –Mumbai, Pune and Thane- had an HIV prevalence of more than 30%. Also there had been a decline in the southern states, compared to an increase in the north east.

\textit{Truck Drivers:}

India has one of the largest road networks in the world. Since they spend long periods away from home, a study conducted had revealed that nearly a third of the long distance truckers had paid for sex in the past twelve months.\textsuperscript{51} However, a survey of truck drivers in Tamil Nadu reported that there had been a decrease in the proportion engaged in commercial sex from 14% in 1996 to 2% in 2003. Also among those who engaged in commercial sex, there had been a decrease in the proportion of those who had not used condom from 45% to 9%.\textsuperscript{52}

\textit{Injecting Drug Users (IDUs):}

HIV prevalence among injecting drug users declined slightly to 7% in 2006. The same has risen to 9.2% now.\textsuperscript{53} In the north eastern states such as Manipur and Nagaland, transmission through injecting drug use is a major driving factor in the spread of HIV. Currently added to this list are Punjab, Tamil Nadu, West Bengal, Kerala and Maharashtra.\textsuperscript{54} There are certain remarkable features of HIV infection among injecting drug users. \textit{First}, epidemics of HIV among injecting drug users have spread with astonishing speed in many countries. \textit{Second}, the multiplier effect of HIV infections from injecting drug users to the general population is


\textsuperscript{54} Id.
probably greater than for any other group at high risk of AIDS. Third, the prevention of HIV transmission among IDUs is one of the most effective interventions in the entire HIV/AIDS repertoire. Of all the different modes of spread, directly injecting a substance contaminated with HIV into the blood stream is by far the most efficient way, much more so, in fact, than through sexual means. Drug injecting and HIV form an explosive combination. The reasons for sharing the injecting equipment may be poverty, cultural factors, lack of availability of or access to needles and syringes, the illegality of carrying injecting equipment and lack of information about HIV and injecting drug use.

Men Who Have Sex with Men (MSM):

Sex between men is highly stigmatized in India & is not openly talked about. The estimated HIV prevalence is 7% among MSM in India but difficulties in surveying this stigmatized group means that the prevalence could be much higher.

Men who have sex with men are a neglected group in India. In India, many men who have sex with men have female partners and are not homosexual. A study conducted in Andhra Pradesh found that 42% of MSM in the sample were married, 50% had had sexual relations with a woman within the last three months, and just under half had not used a condom. One study conducted in suburban Mumbai (which included men and transgender) reported an HIV prevalence of 33% among the study group. All the individuals in the study had reported anal sex and 13% had never used a condom, highlighting the need for increased attention and prevention efforts in this group. This is contrary to the case in US, where 72% of the HIV case is seen in men. Among men, the most

55 A. Wodak, The Challenge of HIV spread among and from Injecting Drug Users in Asia. DEVELOPMENT BULLETIN No 52. UNAIDS Asia Pacific Inter Country Team.
56 P. Deany and N. Crofts, HARM REDUCTION, HIV AND DEVELOPMENT. DEVELOPMENT BULLETIN No 52. UNAIDS Asia Pacific Inter Country Team.
57 L. Dandona, et al., Sex Behavior of Men who have Sex with Men and Risk of HIV in Andhra Pradesh, India, 19, ACQUIRED IMMUNODEFICIENCY SYNDROME, 611, (2005).
common mode was sex with another men (37%), followed by heterosexual contact(28%)and injecting drug use(18%).

Later, expansion of surveillance among MSM has identified new pockets of the epidemic. While nationwide HIV prevalence is 7.4 %, the prevalence mounts especially high among MSM in Karnataka (17.6%), Andhra Pradesh (17%), Manipur (16.4%) and Maharashtra (11.8%).

WHO evidence showed that unprotected male to male sexual intercourse was fuelling the spread of HIV in Asia, where homosexuality is considered illegal or is associated with social taboo. WHO has called for “swift action to address this growing health crisis“ and has called Asian governments to expand access to preventive sexual health services and to clamp down on the discrimination against homosexual men.

**Migrant Workers:** It is estimated that 258 million adults in India are migrants, the majority of this being men migrating for employment. Studies from across the world have linked migration to multiple sexual partners and increased HIV infection.

“**Being mobile in and of itself is not a risk factor for HIV infection. It is the situations encountered and the behaviors possibly engaged in during mobility or migration that increase the vulnerability and risk regarding HIV/AIDS**”

   - UNAIDS.

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63 UN AIDS Technical Updates, **Population Mobility and AIDS**, 2001 available at www.unaids.org (Last visited on September 4, 2014)
In addition, a high proportion of female sex workers in India are mobile. The mobility of sex workers is likely a major factor contributing to HIV transmission by connecting high risk sexual networks. 64

4.6 THE EVOLUTION OF AIDS

One of the World Health Organization’s major functions is international tracking and monitoring of human diseases. Disease monitoring and surveillance in developed and developing countries are carried out by institutions and agents of varying sizes and one such is Centers for Disease Control and prevention (CDC) in USA. CDC performs a lion’s share in international disease monitoring. Information and details of human diseases are fed to CDC by a wide reporting network where it is investigated in detail by epidemiologists, statisticians and data processors. This information is communicated to public health workers and scientists throughout the world by means of regular publications such as the weekly Morbidity and Mortality Weekly Report.

Between Oct 1980 and May 1981, an alert physician Dr Michael Gottlieb together with colleagues at three different hospitals in Los Angeles, became intrigued by a cluster of five young male patients, whose ages ranged from 29 to 36 years under their care. Two of them died and the remaining three were seriously ill. All of them were diagnosed as having a highly unusual form of pneumonia due to a parasite called Pneumocystis Carinii (PCP). Pneumocystis Carinii Pneumonia was previously associated with patients with severe immunosuppression only. In addition, all of them were infected with Cyto Megalo Virus (CMV) and had thrush, all of which is characteristic of immuno suppressed patients. In three of the five who were tested had marked disturbances in their functional capacities of their immune system. Another striking feature was that all of them were sexually active homosexuals but none of them knew each other. 65

64 B.M. Ramesh, supranote 49.
These observations were first reported in *Morbidity and Mortality Weekly Report* of the CDC on 5 June 1981. The 3rd July issue had the report of 26 homosexual men, 20 from New York and 6 from California with a very uncommon tumor called Kaposi’s sarcoma (KS). These men were also found to be harboring CMV, thrush and PCP\textsuperscript{66}.

Thus, it was at the beginning of the 1980s that the relatively unremarkable few cases of homosexual male patients with unusual infections and tumors heralded in an epidemic of one of the most devastating of all diseases of humankind. Because of its striking effect of the suppression of the immune system of patients, it was named Acquired Immuno Deficiency Syndrome (AIDS).\textsuperscript{67}

Similar patterns emerged elsewhere in other countries in the developed world and developing countries as well. In developed countries it was found among homosexual men and persons who injected themselves intravenously with illicit drugs. In developing countries it was spread mainly by heterosexual contact and was common in female prostitutes.

4.7 DISCOVERY OF THE CAUSAL AGENT OF AIDS:

A few of the early possibilities under consideration as cause of AIDS were semen, cytomegalovirus and African Swine Fever Virus (ASFV). Two important scientific discoveries published a decade previously paved the way for the development of a technology that ultimately enabled the causative virus of AIDS to be isolated. First of such discovery in 1970 was that of an enzyme called reverse transcriptase, which was responsible for the formation of a Deoxyribonucleic Acid (DNA) copy from a Ribonucleic Acid (RNA) template, the reverse order of the accepted sequence in biology. This key discovery earned for its discoverers, David Baltimore and Howard Temin, the Nobel Prize\textsuperscript{68}.

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The second important discovery on the road to elucidating the cause of AIDS was made in the laboratory of Robert Gallo at the National Cancer Institute, Washington DC. In 1976, Gallo discovered a growth factor for mature T-lymphocytes which would permit these cells to grow in culture in the laboratory. With the ability now available to grow T-lymphocytes in culture came the discovery of a number of viruses which specifically infect lymphocytes (lymphotropic viruses).

Thus, following these two important breakthroughs, first human retrovirus (viruses possessing the enzyme reverse transcriptase and belonging to the family retroviridae) was isolated from a patient with leukemia of mature T-lymphocytes. This virus was called by Gallo as Human T- Lymphotropic Virus I(HTLV-I). A second virus, HLTV-II, was isolated shortly thereafter from a patient with T-lymphocyte leukemia.69

Another offshoot of these two discoveries was the finding of a group of viruses named thereafter as slow viruses (Lenti Virus) in the retroviridae family. These caused slow and prolonged disease and were responsible for degenerative diseases drawn out over years progressively leading to death.70

In 1983, Dr Françoise Barre – Sinoussi together with Professor Luc Montagnier, the head of the Viral Cancer Unit of the Pasteur Institute, published a paper in the journal Science describing the isolation of a retrovirus from a patient with lymphadenopathy syndrome, one of the disease manifestations that precedes AIDS, and called it the Lymphadenopathy Virus (LAV). The following year, Robert Gallo and colleagues from the National Institute of Health, USA reported isolation of a retrovirus from AIDS patients and called it Human T cell Lymphotropic Virus—III(HTLV-III) . The virus was subsequently given the rather cumbersome name of HTLV-III/LAV to provide equal recognition to both scientific groups. To resolve this nomenclatural confusion, the international Committee on

Virus Nomenclature in 1986 decided on the generic name “Human Immunodeficiency Virus (HIV)”\(^{71}\). Whether Gallo or Montagnier deserve more credit for the discovery of HIV that causes AIDS has been a matter of considerable controversy. Together with his colleague Francoise Barre – Sinoussi, Montagnier was awarded one half of the 2008 Nobel prize in Physiology of Medicines for his “discovery of Human Immuno Deficiency Virus”. Harald Zur Husen also shared the prize for his discovery that human papilloma virus leads to cervical cancer. But Gallo was left out. Gallo said that it was a “disappointment that he was not named a co-recipient.’. Montagnier said that he was ‘surprised’ that Gallo was not recognized by the Nobel Committee. He said that Gallo had a very important role in proving that HIV was the cause of AIDS.

4.8 THE ORIGINS OF AIDS:

The origins of this remarkable virus and its equally remarkable disease have fired imagination ever since it was first recognized due to the intense and unique social, political and human implications. As on now, the answers to both the origin of the disease as well as to the ancestry of the virus remain as unsolved as when the questions were first posed.

One of the earliest of these postulates holds that the disease is not a new disease but is rather one of the old endemic diseases of Africa which has been silent or unrecognized. The earliest serum specimen retrieved from archived frozen material which was positive for HIV antibodies was taken from a patient in 1959 in the Democratic Republic of Congo. It is hardly likely that this virus could have circulated in man much before 1950s and still have been unrecognized.

The second postulated scenario holds that the human virus originated from monkey immunodeficiency virus (Simian Immunodeficiency Virus/SIV). Scientists have known for a long time that certain viruses can pass between species. The most commonly accepted theory is the ‘hunter theory’, ie, humans were infected with SIV when they killed and ate chimps that had the viruses. It may also be that

\(^{71}\)Id.
infected blood got into the cuts and wounds on the hunter. Though the hunter’s body fought off SIV, the SIV virus changed into HIV. One would need to postulate some mechanism by which these viruses could have been transmitted from monkeys to humans. The postulated sequence of events with all these “hypotheses” thus relates mutations in monkey virus leading to infection of humans in Africa followed by the subsequent introduction into the Western world where its spread was accelerated by the sexual revolution and use of hollow bore needle.

4.9 THE UNIQUENESS OF AIDS:

The AIDS epidemic has in many ways been a humbling experience to medical science. AIDS has probably now becomes one of the most formidable of all diseases in human history. The cardinal features which make it unique are:

(a) Unlike almost any other disease, it targets the immune system itself- the very system supposed to be protecting us from disease.

(b) It is infectious and transmissible from person to person. HIV gets itself transmitted from person to person by means of some of the most “biologically urgent” of human behaviors. Since these behaviors are largely private, highly personal choices, often pleasurable and occasionally unlawful, it is rather difficult to exert any social control over these behaviors.

(c) Once infection occurs, it follows an inexorable course and later to death. There is no cure.

(d) Infected persons remain infectious for the rest of their lives. This not only means that this poses an enormous burden of personal tragedy to those affected, but also means that they need to adopt behavioral changes for the rest of their lives.

\[^{72}\text{A brief history of AIDS, available at} \text{http://www.niaid.nih.gov/Publications/hivaids/3.htm(Last visited on November 6, 2014).} \]

\[^{73}\text{UNAIDS – Global Report on AIDS Epidemic, supra note 10.} \]
(e) The total sum of people infected is constantly and progressively expanding. This means that “the reservoir of infection”, ie, the total number of people who can act as a source of infection to others is constantly and progressively increasing. This simply means that the viral reservoir is expanding. This phenomenon, may cause an exponential increase in the number of individuals who will become infected until eventually, the majority of sexually active population will be infected.

(f) The disease has extremely long asymptomatic stage (latency period). During this period, the infected person does not know about his infectivity status and is fully capable of passing the virus to any one with whom there is sharing of blood or body fluid is involved. Except for getting tested, there is no obvious sign of infection for many years after getting infected. Thus, neither the infected person himself, nor his partner has any reason to think they are infected.

Since the cause and effect are years apart, it is very difficult for people to assign any real connection between their behavior now and its possible consequences many years later. Thus it makes governments and organizations to motivate people to take preventive precautions very difficult.

(g) Even more dangerous scenario is that, during the first 4-6 week period following an infection, the routine tests to screen the infectivity cannot diagnose the disease(window period) and people are extremely contagious during this period.

The virus gradually but relentlessly destroys the immune system. The lack of a functional immune system leaves the body open to a variety of malignancies and opportunistic infections. These complications, either alone or in combination eventually prove fatal.
The social, psychological and political dimensions of the disease compounded the terror generated by it. In western and third world countries it affected the marginalized and victimized segment of the society. This association of societal rejection together with a morbid dread of acquiring infection had given rise to unique feelings of revulsion and condemnation of victims of the disease. This had resulted in many issues in all spheres of life which were new to scientists, doctors, psychologists, social workers, theologians, ethicists, legal experts and politicians.

Dr June Osborn, past chair of the US National Commission on AIDS remarked that “the more we learn about this disease, the more we learn that- whatever else AIDS is, it is not just another disease”.

4.10 THE AIDS VIRUS: HIV

An understanding of the general characteristics and morphology of viruses in general will enable us to understand the uniqueness of HIV.

The word Virus is derived from the Latin word meaning ‘poison’ and ‘slimy material’. Viruses do not fall strictly in to the category of unicellular micro organisms as they do not possess a cellular organization. Even the simplest of micro organisms are cells enclosed within a cell wall, containing both types of nucleic acid DNA and RNA, synthesizing their own macro molecular constituents and multiplying by binary fission. Viruses on the other hand do not have a cellular organization. They contain only one type of nucleic acid, either DNA or RNA. It is pertinent to mention that the viruses are unique entities in nature that their genetic information is solely carried by RNA or DNA .They are obligate intracellular parasites.

As a structural entity, the virus represents the simplest biological unit able to exist and to perpetuate itself by making copies of itself (replication).They are the smallest living agents. Given the structural simplicity, functionally the viruses have no capacity to generate their own energy requirements for various biochemical processes such as replication. The viruses make use of the host
cell’s machinery and biochemical facilities for their living. In other words, viruses are nothing but a group of inert cells outside a living cell; they are ‘alive’ only inside host cells.

From a molecular geneticist’s point of view, virus is a biological entity that transmits genetic information between cells thus favoring mutations and genetic changes. Clinically the viruses are transmissible micro organisms which are responsible for a wide variety of human diseases. Thus the viruses are of great medical importance. Their resistance to antibiotics differentiates them from higher microbiological forms of life.

The viruses are the smallest and simplest living agents. Hence the unit of measurement used for a virus is a nanometer.

The broadest grouping of virus is the family. Viruses are classified into two main divisions depending upon the type of nucleic acid family they possess. Thus there could be riboviruses containing RNA and deoxyriboviruses possessing DNA. One among the RNA viruses is Retroviridae Family (re = reverse, tr= transcriptase). These are so named due to the presence of the unique enzyme – reverse transcriptase – which facilitates the production of a DNA copy from an RNA genome. All members of the family possess this enzyme and all make DNA copies of their RNA genomes inside the cells that they parasitize. Retroviridae family has three subfamilies of which HIV belongs to the subfamily Lentivirinae (lenti = slow)

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74 Id.
75 One nanometer (nm) is equal to one millionth of a milli meter (mm).
76 Lentivirus causing immunodeficiencies are (a) in primates (i) Human Immunodeficiency Virus type 1 and type 2. (ii) Simian Immunodeficiency Virus. (SIV) causing Simian AIDS (SAIDS), isolated from sooty mangbeys (SIV-SM) and from rhesus macaque (SIV –MAC) monkeys closely related to HIV type 2. Lenti viruses isolated from chimpanzee are closely related to HIV type 1. (b) IN non primates feline T Lymphotropic virus (FTLV) causing feline AIDS (FAIDS).
The genes of most living things, including humans, are made of DNA. The DNA exists as a sequence of a code that can be read like a book. In a cell, the code is read to make a RNA, which is then used as a code for the construction of proteins. In other words, the flow of genetic information in the cell is usually from DNA to RNA to protein.

HIV virus, on the other hand, has its genetic material made from RNA. It has to insert its genetic code into that of the host cell in order to replicate. In order to achieve this, it must first make a DNA copy, so that, it is compatible with the DNA of the host cell. DNA is then made using the code of RNA. Since this is the opposite of the usual case, the viruses that do this are called the retro viruses.\textsuperscript{79}

HIV is an enveloped virus about 90 to 120 nm in diameter. The virus consists of a nucleic acid surrounded by a protein coat, the capsid. It is the capsids main function to introduce the viral genome into host cells. Virus may either be enveloped or non enveloped (naked). The envelope of virus is usually of Lipoprotein in nature and it is derived from the host cell membrane. The lipid is largely of host cell origin and the protein is of the virus. Viral protein determines the antigenic specificity of the virus. Further, certain protein subunits may be seen on surface of the envelope as projecting spikes. These are called peplomers. (Peplas means envelope).

HIV is a relatively featureless virus, more or less spherical in shape, enveloped and medium sized. The cell membrane component of the envelope is largely composed of lipid or fatty material. Two viral proteins that are anchored into the outer surface of the envelope and protruding to the outside of the envelope are seen. These two envelope proteins are a knob like protein called glycoprotein (gp)120 and a smaller spike like protein called gp 41.

Glycoproteins are molecules composed of carbohydrate component and protein component. (‘Glyco’ from ‘glukeros’, Greek for sweet). The protein is critical for

the initial attachment of the virus to its cellular receptor site. They are most important ‘antigens’\textsuperscript{80} of the virus. Thus the ‘antibodies’\textsuperscript{81} elicited by them would confer protection by preventing the virus from attaching to the cellular receptor sites.

The inner core of the virus which surrounds the nucleic acids as already discussed is the capsid. Inside these cone shaped core, two strands of RNA are coiled up, along with the enzyme ‘reverse transcriptase’. The main protein in the core of the virus, ie 'core protein' is referred to as p24; Like any retrovirus, the genome of HIV is composed of three genes which direct the synthesis of or code for the inner core protein, the envelope proteins and virus enzymes. These genes are named respectively as \textit{gag} gene, \textit{env} gene and \textit{pol} gene\textsuperscript{82}. The pol gene specifies other enzymes: ribonuclease, integrase and protease. The product of \textit{gag} gene are split into three proteins ie matrix protin, core protein (p24) and another structural protein likewise, the products of \textit{pol} gene are split into reverse transcriptase ribonuclease, integrase and protease.\textsuperscript{83\textsuperscript{84}}

\textsuperscript{80}Antigen – An antigen is any substance which when introduced parenterally into the body stimulates the production of an antibody with which it reacts specifically and in an observable manner.

\textsuperscript{81}Antibody – Antibody is a glycoprotein molecule formed by the immune system in response to an antigenic stimulus, is found in blood, body secretions or on mucous membranes binds to the specific antigen responsible for its production, thereby inactivating it.

\textsuperscript{82} -\textit{gag gene} – gag stands for group antigen., \textit{env} gene – env is short for envelope, \textit{pol} gene = ie polymerase, referring to reverse transcriptase which functions as a polymerase.

\textsuperscript{83}Integrase – promotes integration of nucleic acid in to host cells chromosome, Protease – splits proteins in to smaller fragments, Ribonuclease – cleaves RNA.

Also, on either end of its genome, the HIV virus possesses a segment of nucleic acid called LTR (long terminal repeat). These act as regulator button for the genome and are so called because the sequence is repeated on either end. Though they do not code themselves for any proteins, they regulate and control whether the three structural genes are to be ‘turned on’ or to be ‘turned off’.

The two envelops, glycoprotein (gp 120 and gp 41) are crucial for initial steps of infection. The gp 120 is a chain of amino acid building blocks folded to form the characteristic knob like structure. V3 or V3 loop on its surface is responsible for the initial attachment to the receptor site and susceptible cells. (CD₄ receptor site). The gp 120 knob is covered by a sugar coating which protect it from the immune response of the host. A portion of gp 120 is left uncovered by the sugar coating. These hollow depressions are formed by the folding of proteins of the protein chain to bind to the CD₄ protein, the so called CD₄ binding pockets. The V3 loop of the gp 120 protrudes beyond this coating in order to make contact with the cells to be infected. The gp 41 spikes are in other words, trans-membrane proteins. They are inserted through the lipid envelope and do not protrude.

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beyond the outside of the envelope. The function of this gp is to fuse the enveloped virus to the membrane of the host cell. This further facilitates the entry of virus into cell for replication.

4.11 REPLICATION OF HIV

In order to understand replication of HIV, one must first understand the normal process in living beings. The genes of human beings, like most living beings is made of RNA. Protein is constructed by RNA and this RNA is made out of DNA inside the cells. Thus, in other words, the sequence of events is from DNA to RNA to proteins.\textsuperscript{86}

In HIV virus, instead the genetic material is made of RNA. It inserts itself into host cell and makes a DNA copy, which is compatible with the DNA of host cell. Thus, the RNA is utilized for making DNA. Since it is opposite sequence, i.e. RNA to DNA to proteins, it is called a retro virus.\textsuperscript{87}

As discussed, HIV replicates by a series of steps. The first step is attachment of the virus to the host cell via the V3 loop or gp 120. The resultant structural changes in gp 120 exposes the cleavage sites. Hence the cleavage sites get attacked by enzymes, causing it to split open. This thus exposes gp 41, which is otherwise covered over and masked by gp 120. The gp 41 thus results in fusion between viral envelope and cell membrane. Thus the core of the virus enters into the cell. Once it is inside the cell, the core capsid protein breaks open releasing two stands of viral RNA. Once the viral RNA is ‘reverse transcribed’ into a strand of DNA with help of enzyme ‘reverse transcriptase’, the DNA can then be ‘integrated’(inserted) into the DNA of the lymphocyte. The enzyme ‘integrase’ facilitates incorporation of viral DNA into host cell DNA. This integrated DNA is called a ‘provirus’.\textsuperscript{88} As long as the lymphocyte is not activated or ‘turned on’, nothing happen to the viral DNA. If the lymphocyte is

\textsuperscript{86}available at , http://www.vircolab.com/hiv-educational-forum/understanding /HIV. (Last visited on November 6, 2014).

\textsuperscript{87}id.

\textsuperscript{88}All about AIDS Physiology supra note 78.
activated, transcription of the viral DNA begins. Thus, this result in production of multiple copies of viral RNA, which helps in production of viral proteins and enzymes required for formation of new virus.  

One of the most important properties of HIV from clinical point of view is its variability. The variability is mainly due to the inaccuracy of its genetic copying mechanism and the proneness of this mechanism to make errors. On an average, 10-20 mistakes are made during each replication cycle. This could be because of two reasons, i.e. in general terms, RNA viruses tend to be more variable than DNA viruses. Unlike DNA replication mechanism, the RNA replication mechanism does not have any facility to affect the repair to the growing nucleic acid chains. The second reason could be that the enzyme reverse transcriptase is error-prone. Hence it occasionally fails to make a DNA copy from the RNA template; mistakes like this are common in all stage of RNA replication with each stage multiplying the mistake even further.

HIV isolates from different places or person are found to be different. Also sequential isolates from the same person and those obtained from different sites of same person at the same time are different. This great variability is believed to be due to the error prone nature or reverse transcription.

Based on the molecular and antigenic differences, two types of HIV have been recognized. The original isolates of HIV and the related strains prevalent all over the world belong to HIV type I, HIV strains first isolated from West Africa in 1986 which reacts with HIV type I antiserum weakly or not at all have been termed HIV type 2. HIV 2 has only 40 percent genetics identity with HIV 1. It is more closely related to SIV than to HIV 1. It is less virulent than HIV 1. It is largely confirmed to West Africa but is also reported from Western and Southern India. All the states in India have reported presence of HIV 1.

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HIV 1 strains have been further classified into at least ten sub types based on sequence analysis of their ‘gag’ and ‘env’ genes. These sub types are designated as A to J and constitute group M (for major), which cause the large majority of HIV 1 infections worldwide. A few strains of HIV 1 isolated from West Africa do not fall within the sub groups of M and is designated as Group O (for outlier). Some isolates of HIV, different from M & O groups have been called Group N. 92

Sub type A is more prevalent and found worldwide. Sub type B is more common in the America and Europe. Subtype A, C, D are more common in Africa. Subtypes E, D, B are common in Asia. Subtype E is the commonest in Thailand and C is more prevalent in India and China. However there have been occasional reports of HIV -1 subtype A and B. It is a matter of concern that presence of A/C and B/C mosaic viruses are reported from different parts of the country. 93

4.12 HIV AND DISEASE MECHANISM:

HIV is unique in its disease mechanism in many ways. This clearly differentiates HIV from any other disease causing agents. HIV is extra ordinary in true sense. On one hand, it has utmost simplicity having only three genes available to specify its structure. On the other hand, it is rather amazing to note that it has an exceedingly complex mechanism to control the expression of these genes. It is capable of causing one of the most devastating diseases of humankind. Yet it remained as a medical puzzle for about 3 decades. It is really intriguing to know , how much a virus can remain in human body for that long period of time, multiply relentlessly and inconspicuously inside the host thus progressing to the most fatal and dreaded end. It also amazed the medical fraternity for a good fortune of time that the immune system which is an effective defender of the body

92 B. D. Schoub, supranote 65.
against invasion of micro organisms that are apparently far more virulent than AIDS virus appeared to have been defeated by this one virus.

The pathogenesis\textsuperscript{94} of HIV can only be appreciated by understanding the basis of the complex system of immunity.

Though human beings are continuously in contact with a wide variety of potentially pathogenic microorganisms, disease is a rare event. Even if disease does occur, the intact and functioning immune system is able to effectively eliminate the disease causing organism, thus causing a cure by itself. Parallelly, there is an evolutionary process on the part of micro organisms by mutating rapidly to enable them to scope the vigilance of the immune system. The structure of immune system (lympho reticular system) is a complex organization of cells of diverse morphology distributed widely in different organs and tissues of the body.\textsuperscript{95}

The lymphoid and reticulo endothelial components of lymphoreticular system have clearly demarcated functions. The lymphoid cells i.e. lymphocytes and plasma cells are primarily concerned with specific immune response. The reticuloendothelial system has phagocyte cells which are primarily tasked with ‘scavenger’ functions of eliminating effete cells and foreign particles. They remove micro organism from blood and tissues. They also play a role in specific immunity by way of afferent and efferent limbs of immune response.

The immune response to an agent can be of two broad types:

- Humoral or antibody mediated immunity (AMI)
- Cellular or cell mediated immunity (CMI)

Humoral immunity is mediated by antibodies produced by plasma cells, blood and other body fluids (Thus it has received the name ‘humoral’ from ‘Humors’ the old terminology for body fluids).

\textsuperscript{94}Pathogenesis means origin and development of disease.
\textsuperscript{95}B.D. Schoub, Supranote 65.
Cellular immunity is directly mediated through sensitized lymphocytes. The development of these two systems is through different channels, which mostly remain independent of each other.

The lymphoid system consists of lymphoid cells and lymphoid organs. Depending on the varied functions performed by them, lymphoid organs may be classified into primary (central) and secondary (peripheral) lymphoid organs. The lymphocytes proliferate, develop and mature in the central lymphoid organs. The thymus and bone marrow are primary lymphoid organs.

All B lymphocytes originate in bone marrow and T lymphocytes develop in thymus. The thymus is located behind the upper part of sternum. The primary function of thymus is the production of Thymic Lymphocytes (T Cells). It is the major site of lymphocyte proliferation in the body.

After they acquire immuno competence, the lymphocytes migrate along blood and lymphatics. They get further accumulated in peripheral lymphoid organs like spleen, lymph nodes etc. They will be mediating appropriate immune response following antigenic stimulus.

Lymph nodes, spleen and Mucosa Associated Lymphoid Tissue (MALT) are peripheral or secondary lymphoid organs. Lymph nodes filter lymph and they phagocytose\textsuperscript{96} foreign materials invading the body.

The spleen is the largest of the lymphoid organs. It is a graveyard for blood cells. It serves as a reserve bank and settling bed for blood and it is a systemic filter for trapping circulating blood borne foreign particles. Mucosal lining of alimentary, respiratory and genitor urinary tract are endowed with a collection of lymphoid tissue called MALT, both B cell and T cells are present.

\textsuperscript{96} Phagocytose (Phag = Greek for “eat”), thus these cells move slowly in a ponderous and purposeful manner, their abundant cytoplasm thrusting out restless pseudopodia that glide harmlessly past normal body cell but engulf effete cells and foreign particles.
Lymphocytes, phagocytic cells and dendritic cells are cells of the lymphoreticular system. Lymphocytes are small round cells found in peripheral blood, lymph and lymphoid organs. In peripheral blood, lymphocytes constitute 20-40 % of leucocyte (WBC) population. In lymph and lymphoid organs, they form the predominant cell type.

Lymphocytes are major cellular elements responsible for immunological response. Lymphocytes have antigen recognition mechanisms on their surface. This peculiar mechanism enables each cell to recognize only one antigen. The nature of immune response exhibited by the cell upon an antigen encounter depends whether it is a B or T cell. Stimulated T cells produce certain activation products called lymphokines and induce CMI. On the other hand, stimulated B cells divide and transform into plasma cells.

The demonstration of different surface markers for eg; CD3 on T cells and Ig on B cells is the most clear cut differentiation between T cell and B cells.

The plasma cell is the antibody secreting cell. It is about double the size of the lymphocyte. It is structurally designed to be an immunoglobulin producing factory.

With the help of monoclonal antibodies, a number of surface antigens or markers have been identified on lymphocytes and other leucocytes. These surface antigens reflect the stage and differentiation and functional properties of the cells. When a cluster of monoclonal antibodies react to a certain antigen, they are defined as a separate marker and given a Cluster of Differentiation (CD number). This order of markers was introduced at the International Workshop for Leucocyte Differentiation Antigens. Over 150 CD markers have been identified so far.

Phagocytic cells are mononuclear macrophages (of blood and tissues) and polymorphonuclear microphages. The blood macrophages (monocytes) are the largest of lymphoid cells. The tissue macrophages (histiocytes) are larger. The primary function of macrophage is phagocytosis.
Macrophages are polymorphonuclear leucocytes of the blood – Neutrophil, Basophils, and Eosinophils.

Thus, essentially the immune system may be divided functionally into three sections.

(i) Afferent arm which receive the intruding organisms/foreign material. It processes relevant message for conveyance to the second section. The afferent arm consists essentially of macrophages. The foreign material once ingested is acted on by various enzymes inside the macrophage. Thus it is presented in an appropriately processed form to the management team of immune system. The cells which are involved in presenting foreign antigens to the immune system are the dendritic cells. These cells are of great importance in HIV inspection, as they are important vehicles for transporting HIV from the peripheral mucous membranes of the genital tract centrally to the lymph nodes.

(ii) Central management section administers appropriate and effective set of responses. This keeps the memory database for storage of details of intruder. Thus, if the intruder is encountered ever again, the response will be much more accelerated. Hence the intruder will be dispatched much rapidly even before clinical sign/symptom of potential disease manifest. This section is comprised of lymphocytes and lymphoid organ system. T lymphocytes and B lymphocytes are the two main functional subgroup of lymphocytes. CD4 and CD8 lymphocytes are commonest subtype of T lymphocytes. The CD4 lymphocytes are the main regulatory cells of the immune system and interact with both afferent and efferent arms of immune system. Because of this function, they are also called T-Helper lymphocytes (T_H lymphocytes.) The CD8 lymphocytes have the opposing effect to the T helper lymphocytes. Their main function is to balance the effect of CD4 lymphocytes and thus, they are also called cyto toxic T cells or T suppresser lymphocytes. (Ts lymphocytes.) Normally, at any given point of time, there are approximately twice as many CD 4 lymphocytes as there are CD8 lymphocytes.
(iii) Efferent arm deals with and get rid of the intruders. It consists of a number of cellular components.

They are Cytotoxic T Lymphocytes (CTL), Natural Killer cells (NK) and killer cells (K). Cytotoxic T lymphocytes are T – suppressor lymphocytes with CD₈ markers on their surface. They kill the cells which are infected by a particular microorganism. CTLs also attack viruses by producing soluble proteins which inhibit the replication of virus inside infected cells. CTLs thus play a crucial role in the body’s immune response to viral infection. Natural killer cells circulate in the blood stream and recognize infected cell. They further eliminate the infected cells. Killer cells are also called antibody – dependent cytotoxic cells (ADCC). This is because of their specific mechanism of attaching to antigens on the surface of infected cells. Further, another component of efferent arm is activities of soluble proteins called antibodies which are produced by the B lymphocytes. This is referred to as Humoral immune response. Humoral response aims to prevent the entry of pathogen to cells, thus by infecting it. B lymphocytes secretes antibodies which patrol the blood stream and inter cellular spaces. The memory B cells stored in lymphnodes ‘remember’ this encounter and so if the immune system ever comes across it again, the antibody response is even faster.

Hence if a pathogen ever escapes the scrutiny of B lymphocytes and finds shelter inside cells, it is beyond the reach of antibodies. Thus cellular response of cell mediated immunity is adopted by the system. Once a virus invades a cell, it copies itself inside the cell. During this process of replication, the bits and pieces of protein (viral debris) are moved to the cellular surface (exocytosis). These will function as warning flags for T cells, which in turn is the process of scrutinizing the exterior of cells, looking for any such traces of infection. Further action may be taken up by cytotoxic T lymphocytes or CD₄ T lymphocytes.

What is worth mentioning at this juncture is an essential feature of immune system specificity. The recognition of the viral protein structure by the effector cytotoxic T cells or antibody producing B cells (cell mediated or humoral
immunity) is crucial to the success of the immune response. This recognition is highly specific to the antigen.

It is into this powerful, complex and highly efficient system that an apparently frail HIV virus intrudes. The virus is initially met by vigorous CTL on slaughters, which eliminates most, but not all, of the virus. The remaining virus eventually establishes itself. It then progressively and relentlessly overcomes the immune system to cause the lethal disease ultimately.

4.13 VIRUS - HOST INTERACTION IN HIV INFECTION

The outcome of any virus host interaction is influenced by the virulence of the infecting strain and the resistance offered by the host. Given the uniqueness of HIV virus and the varied strains available, the virus host interactions in HIV infection are much intriguing. It is extremely important to be conversant with these steps to know the uniqueness of this event. These can be well understood under following headings

a) Receptors for HIV
b) Mechanism of entry into cell
c) Dynamics of viral replication
d) HIV and Central Nervous System (CNS)
e) Variability of HIV

a) Receptors of HIV

As mentioned before, CD₄ protein which is a surface antigen found on a number of cells is the major receptor site of HIV in the body. These are found in large numbers in the body and are identified surface markers of the T-helper lymphocyte. Unfortunately, T helper lymphocyte is the prime target cell for the virus. Since T helper lymphocytes play a cardinal role in regulating and
controlling immune system, it doesn't come as surprise that severe immuno suppression is resulted from depletion of these cells.

Another cell of importance in the course of HIV transmission is the monocyte/macrophage cell which too has CD₄ antigen on its surface. They do not have CD4 antigen in as much abundance as in T helper lymphocytes. But, their importance lies in another fact that they are instrumental in conveying the virus to the central nervous system.

Another group of cells worth mentioning is the Langerhans cells. These are members of dendritic cell system, which are antigen presenting cells of the body. Dendritic cells support and nurture the 1 lymphocytes. Langerhans cells are found in abundance in the mucosa of the male & female genitalia. They are also found in the skin and mucous membranes of the body. They circulate continually between peripheral mucous membranes and the CD4 lymphocytes found in the lymphocytes and other lymphoid tissue. So they are of particular importance in HIV infection, as they probably constitute the major vehicle for transforming HIV from mucous membranes to the lymphocytes in the lymphocytes. This is of paramount importance in understanding how HIV is transmitted across the intact genital mucous membrane.

It was earlier believed that HIV is transmitted through blood exchange. Break in mucous membrane of the genitalia was considered as prerequisite to allow for blood contact between individuals. But, this was later proved wrong by animal experiments and by demonstrating HIV transmission by artificial insemination. This established that sexual transmission could occur across and intact mucous membrane.

The second receptor (co-receptor) for HIV was identified in 1996 by scientists at National Institute of Health at USA. Two kinds of co-receptors were identified. One is required by Macrophage–Tropic (M-Tropic) variants of HIV to infect macrophage, and is called CCR-5 receptor. The second co-receptor is required by T- Lympho Tropic (T-tropic) variant of HIV and is called CXCR-4 receptor.
(b) **Mechanism of entry of virus into the cell**

The initial step is the attachment of gp 120 envelope protein of the virus on to its specific receptor site, the CD4 protein. This then causes structural changes to the surface of the virus, allowing it to attach to the co-receptor. Thus the gp 41 protein of HIV will come in close contact with the cell membrane. The gp 41 can then mediate fusion of the viral envelope with the cell membrane. This process permits the virus to penetrate into the cell and commence replicating\(^{97}\).\(^{98}\)

(c) **Dynamics of viral replication:**

The cells in a way do undergo a number of biochemical changes leading to their death.

(d) **HIV and Central Nervous System (CNS):**

Damage and destruction of neurons (nerve cells) and the resultant effects are due to the infection of microglial cells. Microglial cells are microphage equivalents of the brain.

(e) **Variability of HIV:**

HIV is a highly variable virus. It has an error rate of about 10-20 per replication cycle. These variants are called *quasi species*. The variants that develop over time are those associated with greater virulence and greater resistance to the body's defenses. It is due to this very reason; resistance of the virus to antiviral therapy is common.

One important characteristic of variants is those related to growth of the virus. Those isolated from early phase of disease were slow type and those isolated in a progressed stage is rapid type.

\(^{97}\) B. D. Schoub, supra note 65.

Depending on the co-receptor used for attachment, variants can be identified. In the early stages of infection, HIV isolates are able to infect the monocytes using CCR-5 co-receptor. With advancing disease, the viral strains are found to be infecting lymphocytes using CXCR4 co-receptor. Also viruses isolated from different parts of the body have a difference in virulence. Those isolated from brain are less virulent compared to those isolated from other parts of the body.

Undoubtedly it is proven fact that HIV is a unique human pathogen. No other pathogen of human kind has evolved such variety of strategies that HIV has adopted to evade the immune response of the host.

**4.14 THE TRANSMISSION OF HIV INFECTION**

The complexity of disease mechanism of HIV in disabling immunological amours held by body’s defense mechanism is already proved. But there is nothing unusual or noteworthy about the transmissibility of HIV. It is one of the least efficient of viruses, in terms of its transmissibility.

The virus is unique because, unlike other viruses any person infected with HIV remains as a source of infection, throughout their life. Like majority of human viruses, human beings are the exclusive source of infection. The amount of virus present in the blood stream (degree of viraemia) fluctuates throughout the course of the disease, maximum being found in the early stages of infection and in advanced AIDS disease. The degree of infectiousness is directly proportional to the degree of viraemia. Degree of viraemia also depends on presence of greater amounts of infectious virus and more virulent strains.

Though HIV has been isolated from most body fluids – e.g. tears, saliva etc, it is regularly isolated from blood, semen and vaginal fluid. In the case of semen and vaginal fluid, these secretions are rich in lymphocytes including CD4 lymphocytes. And the genital mucous membranes are extensively supplied with Langerhans cells. Langerhans cells are highly susceptible to HIV infection as their surface is rich in CD4 receptor sites. In addition, they are the major presenters of foreign antigen to immune system.
Transmission of HIV usually, is followed by exposure to sexual secretions or blood from individuals in either early or terminal stage of illness as these contains relatively large mass of virus.

Transmission of infection could occur after a single exposure even with a very small volume of infectious material, provided that it contained a sufficiently high concentration of virus.

Another way of transmission could be a single exposure to a large volume of virus containing material (e.g. contaminated blood transfusion)

Recurrent and repetitive exposure to the virus is another method of building up the infective dose of virus in the body.

**Access points of HIV**

We have already seen that for the successful transmission of HIV to occur, it should come in contact with CD4 bearing cells. We also know that these cells are in abundance in blood and genitalia. In blood, these cells are found in CD4 lymphocytes and monocytes. Langerhans cells are found in abundance in male and female genitalia. Langerhans cells are also present in other superficial mucous membranes of the body like oral mucous membrane and skin. Transmission of HIV is not readily possible across intact oral mucous membrane. This is because of high dilution factor of saliva and the presence of many antiviral agents present in it which readily makes the virus inactive.

Intact skin remains as a barrier to HIV because it is covered by a layer of dead keratin material called stratum corneum. As like any other virus, HIV is also unable to propel itself and is unable to digest or penetrate through keratin. Thus they are unable to cross and reach living cells on which they can survive, and establish infection. However, any break in the continuity of skin is established by a needle or sharp instrument, it would have access to the underlying Langerhans cells and blood cells. This is the case of needle stick injuries. Same is the case in genitalia.
The rectal mucosa is found to have specialized group of cells called M-cells which transport any foreign material across rectal epithelial layer. M cells are closely associated with lymphoid tissues fund in the lining of the rectum. This rapid transepithelial transport of lymphoid tissue and lymphocytes play an important role in entry of HIV during rectal intercourse. This also establishes that viral attachment and infection can occur through intact genitalia and rectal mucosa membrane. Thus break or laceration in genital mucous membrane is not necessary for transmission to take place. However, infection is far more rapid or sure when there is a break in the continuity of genital mucosa.

### Transmission of HIV

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### Horizontal Transmission

Methods of transmission other than that in mother to child are termed horizontal transmission. This is an ‘umbrella’ term which covers all types of sexual transmission and transmission via blood and blood products. Life style practices have had a prominent role in the transmission of AIDS epidemic in developed countries. In the earlier days it was thought to be only affecting gay men.
1. Sexual Transmission

All forms of sexual intercourse – heterosexual & homosexual, active & passive, vaginal, anal & oral – carry the risk of HIV infection. Use of barrier technique, e.g. condoms can reduce, but not eliminate transmission, because they have a significant failure rate (17-54%) in various studies.  

a) Homosexual Transmission

Lesbianism or female homosexuality has had very little or no role in the epidemiology of AIDS. This may be due to many factors. Vaginal epithelium is multi cell layered and relatively robust and can with stand injuries which may take place during an intercourse. Vaginal wall has only less amount of lymphoid tissue.

The receptive partner is identified to be a very high risk among the male homosexuals. This could be attributed to many factors. The rectal mucosa is relatively delicate and friable. The epithelium of rectum is of one cell thickness only. The rectal wall is richly supplied with lymphoid tissues which provide a ready access for the virus to susceptible lymphocytes. The rectal canal is narrow which makes it more vulnerable to trauma. The M cells in the rectal mucosa are energetic transporters of foreign materials to the underlying lymphoid tissue and lymphocytes. These clearly identify the rectum to be an organ far less adapted to sexual intercourse than vagina. This puts it at special risk for HIV infection. Concomitant practices adopted by these men like insertion of hand /foreign objects to rectum (‘fisting’) or oro-genital and oro-anal (‘rimming’) contacts also have added risk of infection. The risk of male to male transmission per episode of unprotected anal intercourse has been estimated to be between 0.3% and 10%. There are case reports which suggests that oral transmission of HIV occur in homosexual men.  

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in San Francisco\textsuperscript{101} and London suggest that 6% to 8% of those with HIV infection believe that they had acquired it through oral sex.\textsuperscript{102}

b) Heterosexual transmission

Heterosexual transmission appears to be steadily increasing in Western countries, though it is the main route of infection in developing countries. Initially, it was believed that a breach in the integrity of genital mucous membrane was necessary for transmission. Now it is established that transmission occurs even across intact epithelium.

An HIV infected woman may transmit HIV to her sexual partner by infected cervical and vaginal secretions or through menstrual blood. An HIV infected man may potentially transmit HIV to his sexual partner by infected semen & pre ejaculatory emissions during insertive vaginal or anal intercourse. Male to female HIV transmission is twice as effective as female to male transmission.\textsuperscript{103} HIV infected semen can remain in contact with the vaginal or rectal mucosa for prolonged periods of time following intercourse, which increases the risk of infection for the receptive partner.\textsuperscript{104} Overall, the risk of male to female HIV transmission during a single genital exposure has been calculated as less than 0.2%.\textsuperscript{105}

Other sexual practices like 'oral sex' undoubtedly have less chance to transmit infection in comparison with hetero/homo sexual contacts. However, in oral sex, fellatio (oro-genital sex) carries greater risk than cunnilingus (oro-vaginal sex) because of the deposition of semen in the oral cavity, more so when there are

\textsuperscript{101} B. Dillon, et al., \textit{Primary HIV infections associated with oral transmission}, 7\textsuperscript{th} Conference on retroviruses and opportunistic infections, San Francisco, CA (January 30 2000): Abstract 473
\textsuperscript{103} European Study Group on Heterosexual transmission of HIV, \textit{Comparison of Female to Male and Male to Female Transmission of HIV in 563 Stable Couples} BRITISH MEDICAL JOURNAL 304 809-813 (1992).
\textsuperscript{104} Id.
abrasions in the oral cavity. Once swallowed, the virus rapidly gets inactivated in the stomach contents.

However, whether or not kissing including ‘deep-kissing or ‘french kissing’ transmits HIV is not yet established. There is greater risk of infection, if there are abrasions in the oral mucosa. Because of this reasons, exposure to an infected person by deep kissing which involves exchange of saliva is strongly discouraged.

2 Blood and Blood products

a) Blood transfusion

Transfusion could be of whole blood or its various components; whole blood contains plasma and the cells. The direct infusion of a large volume of infected blood containing millions of infected cells into the blood stream of another person results virtually into infection. In clinical practice, various components of blood are extracted and used. Most common are plasma (fluid portion of the blood, after the cells have been removed), packed cells (cells alone) or platelets (a group of cells). Thus, packed cell transfusion and whole blood transfusion carries the same risk.

b) Needle and Syringe Sharing

Intravenous drug usage is commonest mode of transmission after male homosexual transmission. Those individual, who indulge in the act of intravenous drug abuse, habitually inject these drugs directly in to their veins and share needles, syringes and re-use them without sterilization. Various practices adopted by injection drug users facilitate the viral transmission in this population. There is repetitiveness in their needle sharing expediencies. It has been proved by simulation that even though the syringe may look empty, a volume of 18-67 micro litres (ie 0.018 – 0.067 ml) of blood remain behind as film between the barrel and plunger of the syringe as well as inside the hollow bore needle. Even
in single user, in the absence of deliberate sharing, it is quite common to reuse syringes and needles.\textsuperscript{106}

Also there are arrays of co-factors which promote HIV transmission. The vast majority of these individuals are infected by hepatitis B virus, CMV, bacteria and fungi. Sexually transmitted diseases are common in injection drug users. The drugs induce immuno suppression enhancing their susceptibility to infection.

There are several remarkable features of HIV infection among injecting drug users. First, epidemic of HIV among injecting drug users have spread with astonishing speed. Second, the multiplier effect of HIV infection from injecting drug users to the general population is probably greater than for any other group at high risk of AIDS. It was estimated by UNDCP that worldwide, more than 10\% of HIV infection are due to injecting drug use. Of all the different means of spread of HIV, injecting a substance contaminated with HIV into the blood stream is the most efficient way.\textsuperscript{107}

Since, possessing and using these drugs is a criminal offence, educational efforts to reach them are not effective. This is the main reason for the little impact in reducing the transmission of HIV amongst injection drug users.

c) Needle stick injuries:

Penetrating injuries often inflicted on health care professionals by needles or sharp instruments are termed needle stick injuries. This had let loose a wide variety of fear and panic among people that it even affected their career options or compromised quality of medical care. This gives rise to the very question, whether there is any risk involved in needle stick injuries. A Health workers risk for HIV infection from a needle stick injury depends on the stage of infection, susceptibility of the workers in terms of co-factors and the severity of the needle stick. The probability that a single needle stick will result in disease is 3 to 5

\textsuperscript{106}B. D. Schoub, supra note 65.
\textsuperscript{107}A. Wodak, The Challenge of HIV Spread Among and From Injecting Drug Users in Asia ALCOHOL AND DRUG SERVICE, SYDNEY - DEVELOPMENT BULLETIN (June 2000).
chances in 1000 for HIV, 300 chances in 1000 for Hepatitis B and 20 to 50 chances per 1000 for Hepatitis C. According to the ICN (International Council for Nurses), at least one in eight health care workers receives a needles stick injury potentially exposing them to serious or fatal infections. With the introduction of “Universal Precautions” by CDC, this mode of transmission is to some extent under control. Despite all this measures, which are super imposed by regulations, fear persists. The infectivity due to a solid needle (while suturing) or a scalpel blade is much less compared to that due to a hollow needle, considering the volume of blood involved.

2. Vertical Transmission

The transmission of infection from mother to child is referred to as vertical transmission. During the nine months of gestation period, the fetus depends on the mother for its nourishment through placenta. The same placenta though acts as a barrier against any infections, may itself get infection and transmit the disease. HIV infection to fetus /newborn may occur during the intrauterine, peripartum & postpartum periods.( i.e., while the fetus is in the uterus ,during delivery & through breast feeding)

The disease may be transmitted while the foetus is still in the uterus (Intra uterine or Trans placental infection), during the delivery process (Perinatal infection) or by breast feeding. Prevention of maternal to Child Transmission (PMTCT) of HIV has deliberately reduced the incidence.

Impossible Transmission Routes

Having seen these modes of transmissions of HIV, it would also be important to note the routes by which HIV doesn’t get transmitted. First is ingestion through gastro intestinal tract, as it gets inactivated by the gastric secretions. Inhaling the

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virus doesn’t transmit infection. So is the case of inanimate objects. Thus eating in the same place, using toilet seat etc doesn’t carry any risk. Virus is not demonstrated in urine, faceas and droplets excreted during coughing. Also there is substantial epidemiological data available which indicates that HIV transmission does not occur through casual contact like hugging, kissing or by sharing items like clothes or eating or drinking utensils. There is also no evidence that insects can act as vectors for transmission.\textsuperscript{109}

4.15 NATURAL COURSE AND PATHOGENESIS OF HIV INFECTION

HIV-1 infection is characterized by three phases:

(i) \textit{The Primary Infection Phase} is associated with a massive increase in viral load followed by a decrease to a viral load set point following the initiation of antiviral immune response.

(ii) \textit{The Asymptomatic or Chronic Phase}, which is associated with a gradual increase in viral load from primary infection set point, concurrent with a gradual, but irreversible decrease in CD4 T cell numbers.

(iii) \textit{The Symptomatic Phase or AIDS} is associated with the terminal failure of the immune system and disease.\textsuperscript{110}

The pathogenesis of HIV infection and the progression to AIDS are a consequence of the properties of the infecting virus strain and the host’s immune response to the virus. The balance between these two determines the outcome of the infection, from developing AIDS to long term survival. HIV cannot survive outside the bloodstream or lymphatic tissue. The virus is easily inactivated by the exposure to common detergents and disinfectants.


\textsuperscript{110} M. Centlivre \textit{et al.}, \textit{In HIV-1 Pathogenesis, the Die is cast During Primary Infection}, 21(1) ACQUIRED IMMUNE DEFICIENCY SYNDROME (2007).
In case of the infection acquired through heterosexual intercourse, which is the main route of infection, the cervical mucosa is the first tissue being infected. The virus spreads to the regional lymph nodes and subsequently into the bloodstream. After 10-12 days from infection, viral RNA is detectable in the bloodstream. This is a critical point in the natural history of HIV infection because; it indicates that the infected individual has acquired the potential of transmission of infection. These high levels of HIV viremia is short lived and becomes undetectable as the host's immune responses control viral replication.

The time period in which the infection is present, but antibodies are not detectable is referred to as the window period. Ranging from few days to few weeks since exposure to HIV, most of the infected individuals present symptoms resembling flu like illness, lymphadenopathy, arthralgia, malaise, myalgia, weight loss. This symptomatic phase may last for 7-10 days and rarely longer than 14 days. This acute infection is highly nonspecific and goes unnoticed.

Few weeks after the onset of acute infection, most infected individuals enter into a clinical asymptomatic period, generally associated with a drop of viremia and absence of symptoms. This secondary/ chronic phase of HIV infection can vary between two weeks to 20 years. During this phase of infection, HIV is active within lymph nodes, which typically becomes persistently swollen. i.e., HIV continuously replicates in the body compartments, counteracting antiviral immunity and inducing a state of chronic systemic inflammation. In some infected individuals, HIV viremia is not detectable for many years, indicating the occurrence of a very good control of infection. These individuals are termed as controllers.

The destruction of lymphoid system proceeds and the CD4+T cell number reduces to levels less than 200 cells / nano l, cell mediated immunity is lost which expose them at risk of opportunistic infections of varying severity. This phase often termed as AIDS is characterized by diffuse lymph node swelling, severe reduction in body weight, fever, respiratory and gastro intestinal symptoms.
Based on the time duration to progress to full blown AIDS, individuals are classified as either-elite controllers, progressors, rapid progressors, non progressors or long term non progressors.\textsuperscript{111}

4.16 DEVELOPMENT OF ANTIMICROBIAL, ANTIBIOTICS AND ANTIVIRAL AGENTS

The apparent slowness in the development of drugs to cure viral infections had given rise to frustration in general. There was indeed a sense of euphoria when HIV virus was discovered because it was then thought that, having the virus identified; it was only a matter of time to discover drugs that wipe out this dreaded disease. Compared to the wide spectrum of highly effective antibiotics and antimicrobial drugs, there are only a few antiviral medications. Antiviral drug developments are still in a rudimentary stage in contrast to that of antibiotics. The enormous difficulties involved in the development of effective agents to treat HIV infection needs to be understood.

For an antimicrobial to be utilizible for the treatment of infections in the body, it needs to be active against the microbe, but not the cells of the host body. This selective activity is the basis of any antimicrobial design. The value of an antimicrobial drug will be proportional to its selectivity in terms of its effectiveness against the microbe on one hand and its lack of toxicity against the host cell on the other. Occasionally, this gap of selectivity may not be wide enough and such a drug may be quite toxic to both pathogen and the host.

In contrast to this, antibacterial agents are plenty, effective and safe because bacteria are structurally and biochemically different to human cell. The structure and function of the bacterial ribosome are different from that of host cells ribosome. Majority of bacteria are able to survive and multiply outside living cells. Unlike mammalian cells, bacteria have sturdy cell wall. These result in selective activity of antibiotics getting targeted to the bacteria. Depending on the mode of action, antibacterial agents may be classified into bacteriocidal or

\textsuperscript{111} E.F. Belasio, \textit{et al.}, \textit{supra} note 98.
bacteriostatic. If the antibacterial agent is able to eliminate the invading organisms completely, it is referred to as bacteriocidal agents. If the drugs merely reduces the load of the organisms by preventing any further multiplication, and the body’s immune response is then responsible for the limitation of the rest of the organism, it is referred to as bacteriostatic agents.

In contrast to antibacterial drugs, the development of antiviral agents faces greater obstacles. There is an overlap between the biochemical processes of viruses and host cells making it virtually impossible to design chemical agents that would be sufficiently selective to be therapeutically useful. Another difficulty in the development of antiviral drugs is that in acute viral infections the clinical presentation of the disease is evident in relatively late stage during the course of infection when viral replication has almost ceased. Antiviral therapy, to be effective, has to be administered as early as possible after the onset of illness.

Most importantly, it is yet another characteristic of virus that makes the development of antiviral drugs difficult. The status of a virus inside cell is different from that of a virus outside the cell. Virus behaves as an inert chemical substance outside the cell. The viral replication occurs only when it is inside the cell, as a result, for an anti viral drug to be effective, it must be able to penetrate into the interiors of the cell. Antiviral drugs can only be effective by interfering with actively multiplying cells. Any virus in its state of latency and is not multiplying will not be affected by antiviral agents. Hence no antiviral drug can eliminate a virus from the body if it has the potential for latent infection.

Hence each antiviral drug is designed to interfere with a specific step in the replication cycle of the virus. Thus in design of antiviral drugs, each step of viral replication cycle is carefully dissected to exploit any biochemical event that is unique to the virus for utilizing it in the development of the potential drug. This
strategy is referred to as *targeted antiviral drug development*. The main principle used for the design of these drugs is ‘mimicry’\(^{112}\)

### 4.17 THERAPY OF HIV INFECTION AND AIDS

There are essentially three modalities in the therapy of AIDS. Firstly, the mass of virus in the body or viral load is reduced by antiviral treatment. Second, is treatment of opportunistic infections.\(^{113}\) Third strategy is therapeutic approaches for the reconstitution of the damaged immune system or stimulation of immune functions.

The existing options for the control of HIV infection was found to have limited chance of reversing the AIDS epidemic. Non pharmacological efforts at educating the population to make behavioral changes to prevent the infection were ineffective. Even in well motivated groups, reversion to high risk behavior was evidenced. Further it was very difficult to reach this marginalized population as they are mostly IUD, MSM and those who sell sex.

Highly Active Anti Retro Viral Therapy (HAART) only stabilized the patient’s symptoms and viremia. It does not cure the patient with HIV. Most importantly, it does not prevent the spread of HIV through people with undiagnosed HIV infection.\(^{114}\)

To control HIV epidemic in India, National AIDS Control Organization (NACO) had launched the National AIDS Control Programme (NACP-III). The overall goal of NACP III was to halt and reverse the epidemic in India by integrating programmes for prevention, care, support and treatment.

\(^{112}\) *Mimicry* -Molecules are designed to closely resemble the natural building blocks used by the virus. This artificial molecule is often referred to as an analogue of the natural substance. This is usually taken up by the virus as if it were the natural material itself.

\(^{113}\) This is a serious infection with a microorganism which normally has little or no pathogenic activity but which becomes pathogenic in the presence of serious disease, here, due to immunosuppression.

High genetic diversity in HIV strains has implications on the success of antiretroviral treatment. High mutation rates and resultant development of resistance to drug can lead to failure of ART. In 2004, free anti retroviral drugs were made available by Govt of India. Despite of the success of ART, HIV/AIDS still poses a major public health problem globally. Other than development of viral resistance to drug, toxicity and the pharmacokinetic differences between drugs are not common.

National and International responses to the epidemic remain inadequate as evidenced by the limited reach of prevention and treatment program to the population e.g. Only 8% of those who need Anti Retro Viral Therapy (ART) in the developing world are receiving it, only 8% of pregnant women are offered services for preventing transmission to their infants, even in the hardest hit regions, most young people do not have reliable information on protecting themselves from infection.\textsuperscript{115}

The epidemic is now firmly on the agendas of United Nations Development Agencies, the World Bank and many world leaders. There was a session on HIV/AIDS in the 2001 UN General Assembly Special Session (UNGASS). Resources for AIDS program in the developing world have increased more than 6 fold since 1996.

\textit{Goal 6 of the Millennium Development Goals,} “to combat HIV/AIDS, Malaria and other diseases” elevate the fight against AIDS priorities recognizing the enormous suffering the epidemic causes as well as the threat it poses to achievement of the other goals and to place it among the world’s highest development. The target is “to \textit{have halted and begun to reverse the spread of HIV/AIDS by 2015}”.\textsuperscript{115}

\textsuperscript{115} COMBATING AIDS IN THE DEVELOPING WORLD, UN MILLENNIUM PROJECT TASK FORCES ON HIV/AIDS MALARIA TB AND ACCESS TO ESSENTIAL MEDICINES Working Group on HIV/AIDS ( 2005)
HIV prevention efforts have reached a decisive stage. No single prevention measure can stop the spread of HIV. The widely accepted approach is

- Education and communication campaign conveying basic facts about HIV/AIDS and its transmission promoting behavior change, and combating harmful myths and stigma.
- Programme focused on vulnerable groups
- Access to the technical means of prevention: Male and female condoms, sterile needles and syringe.
- Voluntary testing and counseling
- Control of sexually transmitted infections
- Prevention of mother to child transmission (PMTCT)
- Precaution to prevent transmission in health care settings.

(UN General Assembly 2001)

This comprehensive prevention strategy also includes

- Legal and other measures to fight discrimination against people living with AIDS.
- Legal and policy changes to protect the rights of vulnerable populations at high risk of HIV and remove barriers to effective prevention services.
- Broad campaign and specific measures aimed at reducing the special vulnerability of girls and women to HIV, changing harmful gender norms and reducing broader gender inequities.
- Community mobilization to combat HIV/AIDS and mitigate its impact.

These complimentary policies and programs are called “Structural interventions”.

New strategies and technologies like vaccine will help in prevention of disease. An effective and affordable HIV vaccine would be an enormous advance, fundamentally transforming the battle against AIDS and perhaps even offering hope of eradication. Vaccines capable of preventing infectious diseases are generally regarded as the most successful instrument of cost–effective, humane health care. Vaccines are credited with the global elimination of dreaded disease
like small pox, and more recently about to eliminate poliomyelitis. The historical success of conventional vaccines in preventing and even eradicating disease has stimulated an extensive quest for a safe and effective HIV vaccine.

Treatments currently available are inadequate since they do not lead to cure, but at best slow the progression of disease. The most effective treatment — antiretroviral medication — is complicated to administer, requires close medical monitoring, can cause significant adverse effects and is extremely costly. These logistical and economic barriers render treatment inaccessible for many populations, creating a sense of urgency to develop a safe, effective and globally accessible HIV preventive vaccine to complement other strategies.\textsuperscript{116}

It is difficult to over state the desirability of vaccines. Vaccines have prevented more premature deaths, permanent disability and suffering than any other medical discovery or intervention. They are the most effective public health intervention ever devised in preventing infectious disease. Vaccines are cheap per life saved. They are cost effective when the cost of treatment, hospitalization and lost working days are taken into account. People who are not immunized also get benefited by reduced transmission of the pathogen. For every dollar spent on measles, mumps and rubella vaccine, $21 is saved in direct medical costs. Similarly, the diphtheria, tetanus and pertussis vaccine save $6.21 for every $1 spent. The elimination of smallpox is thought to have saved $275m per year in direct health costs and the $ 100m invested in eradicating the disease after 1967 "saved the world about $1.35bn a year". \textsuperscript{117}

Vaccines are easier to administer than many drugs, especially when compared to the complicated drug regime. Further many vaccines require only one dose and


\textsuperscript{117} O. Yaqub, KnowledgeAccumulation and Vaccine Innovation Lesson from Polio and HIV/AIDS –, DPhil Univ of Sussex September 2008 \url{http://epnts.sussex.ac.UK} (Last visited August 28, 2014).
this place less pressure on health infrastructure and budgets. Vaccines are also said to reduce poverty and inequality as by immunization, people are protected from the illness and the long term effects of illness on their physical, cognitive and emotional development.

Thus it is not surprising that a vaccine to halt AIDS / HIV pandemic is much sought after. Vaccines are now on the agenda in the fight against HIV. An effective vaccine is considered to be one of the strategies to deal with the rapid spread of HIV infection in the country. A vaccine is a vital piece in the strategy to defeat AIDS. The best hope for halting the expansion of the global HIV epidemic is an effective HIV vaccine. Thus an HIV vaccine development is a critical path in developing a long term strategy to control the world wide HIV epidemic. Hence efforts of an unprecedented intensity have been focused on the development of a vaccine to prevent HIV infection or treat HIV infection. It has been proved time and again, the awesome power of vaccine to eradicate, eliminate, control or modify infectious diseases. The availability of a cheap, safe and effective vaccine is therefore the first step in controlling the infection.

Even a modestly efficacious first generation vaccine could have a profound effect on the AIDS pandemic. A vaccine with 50 percent efficacy provided to 30 percent of the population would reduce new annual infections by 34 percent. (Seventeen million infections avoided) over fifteen years and result in substantial financial savings. A more efficacious vaccine, combined with expanded delivery, would do even more to control the pandemic. It therefore makes sense to continue investing in AIDS vaccine research and development and eventual manufacture and widespread distribution of a vaccine.

The evaluation of candidate preventive vaccines is a priority for the National Institute of Allergy and Infectious Disease (NIAID) of the National Institutes of Health (NIH) which provides funding and support for preventive HIV vaccine

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trials, both domestically and internationally. Testing safety and immunogenicity of candidate preventive HIV vaccines has been in progress since 1987.\footnote{An HIV Vaccine: How Long Must We Wait? (Editorial) LANCET 352 (9137) 1323 (1998).}

A moderately effective AIDS vaccine introduced in 2015 could avert millions of new infections over the following years.\footnote{E.F. Belasio, supra note 98.}

There have been many false starts on the road to an AIDS vaccine. However, the AIDS research community has become increasingly optimistic about the prospects for developing an effective vaccine that will control and eventually eliminate HIV.


On 24 Sep 2009, a vaccine trial conducted jointly by the US Military HIV Research Programme and Thailand Ministry of Public Health was declared successful. This phase III trial was initiated in late 2003 and was prime boost combination of two vaccine candidates (ALVAC and AIDS VAX). Both these candidate vaccines were earlier tested individually and showed no efficacy. An efficacy of 31.2% was calculated and though not impressive, thus is the first time; any candidate HIV vaccine has shown any level of protection in humans. That shows a ray of hope at the end of the tunnel.\footnote{S. Jameal, A Vaccine for AIDS – Hope, caution and Opportunity, available at http://hivaidsonline.in/index.php/Research /a-vaccine -for aids -hope-caution -and –opportunity – html (Last visited on August 29, 2014).}

“AIDS is uniquely destructive to economies, because it kills people in the prime of their lives”.\footnote{Kofi Annan, supranote 2.} AIDS is a global catastrophe, threatening social and economic
stability in the most affected areas, while spreading relentlessly into new regions. The epidemic is creating a terrible and rapidly growing new crisis of orphans and vulnerable children. The epidemic’s impact on children may pose risk to social stability, cultural continuity and economic development. Thus the humanitarian imperative and obligation under international conventions of caring for vulnerable children can also be seen as part of comprehensive prevention strategy. AIDS mortality and thus the number of AIDS orphans lags well behind the number of people living with the virus as an epidemic grows. For this reason, the number of children orphaned by AIDS is projected to rise in the coming years.

In 1984, US Health Secretary, Margaret Heckler announced the discovery of causal agent for AIDS and declared that a vaccine would be ready within two years. Almost as soon as the cause of the disease was perceived to have been established, talk of a vaccine followed. Now after about four decades, we haven’t reached our target.

UNAIDS and the World Bank predict that HIV will be responsible for 37% of deaths from infectious disease among adults between the ages of 15 to 59 by 2020. It is crucial that we work to analyze and understand the social and economical issues exacerbated by HIV. The future of global HIV/AIDS epidemic and of the millions of lives affected by it will depend on the ways in which we confront these dilemmas.

With close to 16000 people being infected with HIV every day, some have argued that, failing to proceed with HIV vaccine development and testing is unethical and violates basic human rights. The global burden of disease and death related to HIV is increasing at a rate unmatched by any other pathogen. For many countries, it is already the leading cause of death. Currently available treatments are inadequate, because they do not lead to cure, but at best slow the

progression of the disease. Thus there is an ethical imperative to seek, as urgently as possible, a globally effective and accessible vaccine.\textsuperscript{127}

The global HIV epidemic continues to expand, exceeding previous predictions and causing tremendous suffering. An effective HIV vaccine represents the best hope to curtail the HIV epidemic. Thus HIV epidemic is an urgent global priority and a vaccine is the only realistic approach in controlling the expanding global HIV epidemic.\textsuperscript{128}

\textbf{A safe and effective HIV vaccine} ideally would be inexpensive to manufacture, provide protection against all sub types of HIV, required minimal if any boost, protect against all methods of spread of HIV for years, and be easily administered, stable to heat and widely accessible.\textsuperscript{129} The ideal preventive HIV vaccine would be antigenically versatile, so as to confess protection against the different sub types circulating in different part of the world. It would induce both systemic and mucosal immunity with an optimal balance in order to maximize the likelihood of protection against sexual transmission. The immune response produced would be of high titer and long duration. It would require minimum number of doses, would be heat stable and not dependent on a cold chain for its distribution. Finally, such a vaccine would have to be affordable if it is to be made available to everyone in need.\textsuperscript{130}

A safe and effective vaccine presents an attractive alternative for the following reasons:

Once inoculated, an individual would not have to completely alter long practiced patterns and behavior to remain protected. Nor would lapses into risk behavior

\textsuperscript{127} \textit{UNAIDS Guidance Document May 2000: Ethical Considerations in HIV Preventive Vaccine research.}

\textsuperscript{128} P. Smearman, \textit{HIV Vaccine Development: Lessons from the Past and Promise for the Future CURRENT HIV RESEARCH 101-120 (2003).}


\textsuperscript{130} WHO Global Programme on AIDS, 1992-93 Progresses Report.
or barrier failures represent the threat they now do. A vaccine would, to some
degree take away the necessity to supply clean needles to injection drug users.
Finally, many of the drawbacks to AIDS treatments, including prohibitive
expense, compliance issues, toxicity and viral resistance would be eliminated for
a large number of individuals who might otherwise become infected. Thus,
production of a safe, effective vaccine against HIV would be the ideal preventive
measure in the fight against AIDS.

It has been observed that recent advances in treatment do not eliminate the need
for a vaccine. In contrast, the irony is that, advances in AIDS treatment may to
some degree increase the incidence of HIV infection. People when become
aware of the advances in the management of HIV, may return back to the risky
behavior because fear of disease is on the decline. They may consider, the
disease as a treatable disorder, thus their fear of infecting others or getting
infected themselves decrease.

Many people cannot adhere to the drug regimen. Some may not respond well to
the medication. Some have even developed drug resistant strain of the virus,
even with perfect compliance. None of the current ART regimens have proven to
be completely effective against the disease. Also, these treatments are largely
unavailable in developing countries. Thus, in short, the long term prospects for
today’s promising regimens remain as yet uncertain. Finally, although there is
decrease in domestic mortality, there is great expense of caring for people living
with HIV/ AIDS, as more people survive for longer periods of time. Chronic AIDS
care will thus impose heavy economic burden on the country’s economy.
Hence, though the therapeutic regimen seems promising, it will not do the job
alone. Aiming to completely cure AIDS by clearing HIV infection is not feasible,
and it may be better to try and prevent infection. This strongly advocates that the
treatment of AIDS must be supplemented with effective strategies to prevent
infection with HIV.

AIDS vaccine field, for the last nearing three decades yielded a plethora of
disappointing, and sometimes perplexing results. The lack of natural sterilizing
immunity against HIV means that the potential correlates of protection are not known, leaving us without a definite model of protective HIV immunity to emulate through vaccination. Paradoxically, these same results have produced meaningful scientific insights, important among them being details about HIV’s cunning ability to evade immune responses. Thus scientists are propelled with ardent hope that the science will reveal fundamental clues as to how a vaccine must perform to provide protection against HIV infection.\footnote{AVAC Report 2010, Global Advocacy for HIV Prevention, available at, http://www.acvc.org/ht/d/spi/949/TPL/Public (Last visited on August 24, 2014).} Citing the global eradication of smallpox and poliomyelitis as precedents, scientists hope that an AIDS vaccine is the only comprehensive way to stem the epidemic worldwide. This time we must not forget that some vaccines have been developed in a decade while others have eluded development for over a century. International AIDS Vaccine Initiative (IAVI) believes that 2018 is a minimum estimate for a successful vaccine. Two third of the leading AIDS scientists believe that an AIDS vaccine will not be developed for another five years.

The time proven approach of trying to mimic the immune response to natural infection cannot be utilized in AIDS vaccine as in this case, as virus invades the immune system rendering natural immune response by the host ineffective

“We believe the time is right for the major scientific and other stake holders – both public and private sector in developed and developing countries – to come together in a more organized fashion. We endorse this concept and call for the establishment a Global HIV vaccine Enterprise”\footnote{G8 Action to endorse and establish a Global HIV Vaccine Enterprise, available at www.canadainternational.gc.ca/g8/summary (Last visited on September 9, 2014).}

At the 2004 Sea Island Summit, the G8 reaffirmed their long standing commitment towards combating the global HIV/AIDS pandemic. The year 2004 saw the appeal of G8 for the creation of a global HIV vaccine enterprise. The enterprise, as laid out in the G8 action to endorse and establish a Global HIV
Vaccine enterprise is the latest effort in the G8 trichotomy of HIV treatment, care and prevention.

In India, the International AIDS Vaccine Initiative (IAVI) has partnered with the Ministry of Health and Family Welfare (MHFW) through National AIDS Control Organization (NACO) and the Indian Council of Medical Research (ICMR) since 2002 to implement the AIDS vaccine research and development programme.

The Government’s AIDS vaccine programme in India follows these guiding principles:

1. Moving the most promising vaccine candidates to trials
2. Testing multiple vaccine candidate simultaneously
3. Establishing centers of excellence to conduct research at par with international standards.
4. Contributing to the country capacity building for AIDS vaccine clinical trials by providing training of international standards in good clinical practices, good clinical laboratory practice, gender specificities, laboratory and standard operating procedures for clinical trials,
5. Disseminating scientific information generated by International and National AIDS vaccine research.

On Aug 22, 1986 as part of its response to the AIDS epidemic, the Public Health Services (PHS) invited US Industrial firms to collaborate with the Govt in the development of an AIDS vaccine. The overall aim of PHS proposal was to establish a formal frame work for coordinating the existing government and

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133 Id.
private efforts and to foster industry participation in the search of an AIDS vaccine.135

Vaccines are easier to administer than any drugs, especially compared to the complicated drug regime in AIDS therapy. Immunization reduces poverty and inequality. HIV affects people in their most productive phase of life. Thus it is not surprising that vaccine to curb HIV pandemic is much sought after. Considerable amount of money has been spent in HIV vaccine R & D globally. From the history of invention of a vaccine for various diseases, it is evident that some vaccines have been developed in a decade while others have eluded development for over a century.

Worldwide annual income from vaccine sale is on the rise. Despite the rapid growth rate, the vaccine market represents only 1.5% of the pharmaceutical market. This reduces the incentives to invest in R & D. Compared to the amount spent on R & D, eventually all vaccines are made abundantly available at low prices. Also, internationally, centralized purchasing and public pressure continue to depress prices. Further there are only few vaccines tailored to the specific needs of developing world. For eg: since the developing countries have weak infrastructure, vaccines that withstand break in cold chain and that can survive a long shelf life are required.

Also there is an issue that can even if an effective AIDS vaccine is available, it is highly unlikely that sufficient number of people will identify themselves at risk and actually use the vaccine. There may be opposition to vaccination of others arguing that this would alter social behavior e.g.: “use of recreational drugs and practice of deviant sexual activity.” A vaccine with low efficacy and low duration

will have impact on public health if its implementation is accompanied by widespread reversion to riskier sexual behavior.\textsuperscript{136}

There is also fear about the unwanted side effects of vaccination. Even though serious adverse reactions are difficult to be established scientifically, serious side effects had occurred more than once in the past:

- \textit{Cutter incident:} - where one batch of killed poliomyelitis vaccine that had not been properly inactivated caused many cases of paralytic poliomyelitis.\textsuperscript{137}

- \textit{Lubeck disasters:} - Pathogenic mycobacterium for the production of BCG vaccine was responsible for cases of tuberculosis.\textsuperscript{138}

Exposure to liability and litigation is a major disadvantage for the vaccine industry. One reason for this high risk of inability is because, unlike most drugs, vaccines are usually administered to healthy and young people.\textsuperscript{139}

\section*{4.18 POSSIBLE VACCINE EFFECTS:}

An HIV vaccine is an urgent global priority. An \textit{ideal HIV vaccine} would prevent HIV infection in an exposed individual through eliciting an effective immune response, a concept known as \textit{Sterilizing Immunity}. More realistically, an \textit{effective HIV vaccine} would limit HIV replication while not providing sterilizing immunity. This would thus slow the spread of HIV and finally eradicate HIV from human populations.\textsuperscript{140}

\textsuperscript{136} T.K. Gosh, \textit{supranote 24}.
\textsuperscript{137} In April 1955, more than 2 lakh children in USA received a polio vaccine with inactivated live polio vaccine, causing 40,000 cases of Polio, leaving 200 children with varying degrees of paralysis and killing 10. The Cutter Incident : How Americas first Polio Vaccine led to the growing Vaccine crisis http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/ ( last visited on August 16, 2014)
\textsuperscript{138} A disaster caused by BCG struck the German city of Lubeck between 10 Dec 1929- 30April 1930. The vaccine was found to be contaminated with a human tuberculosis strain being studied in the same lab. 72 babies died from Tuberculosis out of 252 vaccinated. M. Fitzpatrick, \textit{The Cutter Incident : How Americas first Polio Vaccine led to the growing Vaccine crisis}, JOURNAL OF THE ROYAL SOCIETY OF MEDICINE ( March 2006), available at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1383764/ ( Last visited on August 16, 2014)
\textsuperscript{139} M.M. Jonathan, \textit{supra} note 126.
\textsuperscript{140} P. Smearman, \textit{supra} note at 128.
The three possible effects of HIV vaccines are

i. **Reduced susceptibility to infection** via protective immunity, i.e.; if the vaccine is administered to HIV negative people, it should be able to provide protection by reducing their susceptibility to a persistent infection, effectively clearing their body of HIV.

ii. **Reduced infectiousness** of vaccinated individuals, i.e.; keeping the amount of virus in a person at a low level so that he/she is not able to infect others, and

iii. **Slower progression to AIDS** progression and death.

Hence, the efficacy of an HIV Vaccine could be evaluated using three parameters:

1. **Vaccine efficacy - susceptibility** \((VE_s)\): the reduction in the risk of acquiring HIV

2. **Vaccine efficacy – disease progression** \((VE_p)\): the reduction in the cumulative risk of progressing to AIDS or death from the time of infection diagnosis.

3. **Vaccine efficacy – infectiousness** \((VE - j)\): the reduction in the risk of transmitting HIV to others. \(^{141}\)

**4.19 HISTORY OF VACCINES**

A vaccine is a substance sufficiently like the organism to generate a specific response in the immune system, but sufficiently different that the vaccine itself does not cause the infectious disease. The response of the immune system is termed Acquired immunity, i.e. deliberately causing mild infection with unmodified pathogen.

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\(^{141}\) D. Follmann, et al., *Endpoints and regulatory issues in HIV vaccine clinical trials*. 44(1) JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME, 49-60.
The germ theory of disease was established in late 19th century. Louis Pasteur, while leaving on holiday, accidentally left a chicken cholera culture outside shelf for two weeks. On his return, he noticed that the culture, though weakened by exposure to air, provided immunity to the disease, rather than cause the disease itself. Thus, attenuation was first ever recognized here, a weakened form of the same organism was used to prevent the disease.

In Jennarian way, related form was used to prevent disease; this idea was quickly developed into a chemically attenuated rabies vaccine five years later. Thus the modern concept of immunization, involving the development of vaccines in the laboratory using the same agent that caused the disease, was originally introduced by Louis Pasteur.

Another major step in vaccine development was the killed vaccine concept, where bacterial are killed by heat.

Nearly all practical advances in the control of viral disease in men and animals spring from the single discovery in 1931 by Ernest Good pasture. He introduced the use of embryonated hen’s egg for growing viruses. Until then, human viruses could only be grown in expensive animals like horse or sheep.

Use of adjuvant is yet another landmark in history of vaccines. The purified antigens do not usually trigger a strong immune response on their own. Hence most a cellular vaccines required the addition of adjuvant to boost their immunogenicity.

**Vaccine**

Vaccine is a material which is administered to an individual to stimulate their immune system to give protection from infection with a specific
microorganism.\textsuperscript{142} A vaccine is a biological preparation that improves immunity to a particular disease.\textsuperscript{143}

“Suspension of live (usually attenuated) or inactivated microorganism (e.g. bacteria, viruses) or fractions thereof, administered to induce immunity and prevent infectious disease or its sequel”

\textit{Louis Pasteur}

The vaccine represents the single greatest promise of biomedicine: disease prevention.\textsuperscript{144} The impact of vaccine on the health of world’s people is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on the mortality reduction and population growth. The historical record shows that the development of vaccines has consistently involved sizable doses of ingenuity, political skill and irreproachable scientific methods. In short vaccines are powerful medical interventions that induce powerful biological, social and cultural reactions.\textsuperscript{145}

It was Edward Jenner, a country doctor from Berkeley (Gloucestershire), England in 1796 performed the world’s first vaccination. In 1770’s he heard a Bristol milkmaid boast “I shall never have small pox for I have had cowpox. I shall never have an ugly pock marked face.” Two decades later he translated this farming lore into the guiding principle of his cowpox inoculation hypothesis.

Jenner inoculated an eight year old boy, James Phipps using the pus from cowpox lesion on a milk maid’s hand. After six weeks, Jenner variolated two sites in Phipps arm with small pox. The boy remained unaffected to this incident, which laid the foundation for modern vaccinology.

\textsuperscript{142}B.D. Schoub, \textit{supra note 65}.  
\textsuperscript{143}What are vaccines, \textit{available at http://www.news_medical_net/health/what-are-vaccines} (Last visited on August 24, 2014).  
The term vaccine is derived from the use of cow pox (Latin variolae vaccinae, adopted from the Latin vaccine-us from vacca=cow) by Jenner.\textsuperscript{146}

**Mechanism of Action of Vaccine:**

To understand the mode of action of vaccines, it is imperative to have knowledge about immunity. The primary function of immune system is to distinguish between what is self and non self and eliminate the non self. Traditionally, the term immunity refers to the resistance exhibited by the host towards the injury caused by microorganism and their products. Immunity against infectious disease is of different types. Irrespective of prior contact with microorganism or immunization, every individual exhibits some resistance to infection by virtue of his or her genetic or constitutional make up. This is referred to as **natural or native immunity.**

However, as distinct from his innate or inborn immunity, an individual acquire some resistance during his life. This is called **acquired immunity.** Acquired immunity is of two type : Active and Passive .

**Natural Active immunity** results from either a clinical or inapparent infection by a microbe. eg A person who has recovered from measles develops natural active immunity against measles virus. This is the same incase of chicken pox and in both cases the immunity is lifelong. **Artificial Active Immunity** is the resistance induced by vaccines. **Natural Passive immunity** is the resistance passively passed from mother to baby. It is for this reason most infections in infants are common only after three months of age. The resistance passively transferred to a recipient by the administration of antibodies is referred to as **artificial passive immunity.** It can be used for prophylaxis, and therapy e.g. Tetanus immune globulin, antivenom etc.

As the immune system is specifically activated by the protein components of the organism, the same immune system response can be achieved by administering the relevant proteins of the organisms. Thus, whole, part, weakened or killed

\textsuperscript{146}Id.
forms of the microbe/toxins may be used as vaccines. These in turn, stimulates the immune system of the body which recognize the agent as foreign, destroy it, remember it (Memory), so that the immune system can easily recognize and destroy these microorganisms if they are encountered any time later. Thus in order words, the vaccine “prime” the immune system to respond to a microorganism, so that, upon exposure to that microorganism, spread of microorganism through the body is dampened before it can cause the disease. This is the mechanism by which traditional vaccines protect against establishment of infection. The branch of medical research dealing with development of new viral vaccines is termed vaccinology.  

There are several types of vaccines currently in use. These use various strategies adopted to induce beneficial immune response.

4.20 TYPES OF VACCINES:

Vaccines can either be prophylactic or therapeutic. Prophylactic vaccines aim to prevent people from contracting disease, where as therapeutic vaccines prevent previously contracted diseases from progressing. Vaccines prevent the development of disease by two basic approaches. One approach works by stimulating the body to produce antibodies that directly attack an invading virus. A successful HIV vaccine would enable antibodies to attach to the AIDS virus and prevent the virus from entering healthy cells. WHO Global Programme on AIDS had identified the possibility of a perinatal vaccine that would prevent the transmission of HIV from infected mother to her fetus/ new born child. This would also be beneficial in delaying the progress of disease in mother.  

There is no disagreement that there is a need for speedy development and trialing of safe and effective prophylactic vaccine in all parts of the world.

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Prophylactic vaccines are essential in the continuing battle to stem the spread of HIV.¹⁴⁹

Another approach would not prevent cell infection, but rather, would prime the body to suppress the virus on a long term basis through cell mediated immunity. This will enable specialized blood cells to identify, attack and kill infected cells. Some scientists believe that a successful vaccine would necessarily utilize both approaches.¹⁵⁰

It is proposed to have an HIV Vaccine for various reasons, the commonest being prevention of HIV infection. Also it is advocated as a therapy (post infection immunotherapy). Immediate post exposure vaccination, targeted prophylactic vaccination, and vaccines to reduce infectivity are other strategies which are being extensively studied.¹⁵¹

The first generation candidate HIV vaccines were developed in the 1980’s and early 1990’s. They were designed to prevent HIV acquisition by stimulating anti-HIV antibodies. However, the antibody based vaccines failed to lower the rate of HIV infection. The absence of protection was partly due to HIV’s expansive genetic diversity and its many mechanisms of evading neutralization. Second generation HIV Vaccine candidates have been designed not to elicit humoral immune responses (antibodies), but rather to elicit cell mediated immune (CMI) responses. Because of the safety concerns about retroviruses, there had been only little effort to develop live attenuated HIV vaccine and killed or inactivated

¹⁴⁹ S. Kippax, HIV And Technology: The Issue Of Prophylactic Vaccines, DEVELOPMENT BULLETIN No 52, June 2000, UNAIDS Asia Pacific Inter country Team.
HIV vaccine. Hence the majority of HIV vaccine developments are concentrated on subunit vaccines, recombinant vaccines and DNA vaccines.\textsuperscript{152}

An HIV vaccine is a theoretical vaccine proposed for prevention of HIV infection, treatment of HIV infection or prevention of transmission of HIV from pregnant woman to fetus/new born child. Thus there could be prophylactic preventive HIV vaccines which prevent infection among persons exposed to HIV.

Therapeutic vaccine treats HIV infection or prevents HIV infected persons from progressing to AIDS. Therapeutic vaccine would be a kind of immune modulator that will possibly change the course of the disease, improve the quality of life, increase the CD4 count, decrease viral loads, reduce opportunistic infections and lower death rates.\textsuperscript{153} Therapeutic HIV vaccines are designed to control HIV infectious people who are already HIV positive. This would strengthen HIV specific immune responses in people already infected with HIV. Preventive HIV vaccines are designed to protect HIV negative people from becoming infected or from getting sick.\textsuperscript{154} Therapeutic HIV vaccine thus treats HIV infected individuals with immunogens designed to boost anti – HIV immune responses, decrease virus infected cells and either eradicate HIV or prolong the time until development of Acquired Immuno Deficiency Syndrome.\textsuperscript{155}

The ultimate goal of an HIV vaccine is to achieve sterilizing immunity. A more realistic goal may be to develop a vaccine that lowers viral loads and prevents clinical disease progression.\textsuperscript{156} The development of effective perinatal vaccines would prevent the diseases getting transmitted to fetus or new born. It would


\textsuperscript{153} S. Mehandale, \textit{available at}http://www.ijme.in July- Sep 2007 1(3) (Last visited on 04 September, 2014).


\textsuperscript{156} A.C.L Angellique \textit{et al, Challenges in the search for an HIV vaccine’ EUROPEAN JOURNAL= OF EPIDEMIOLOGY 19: 513-516 (2004).}
benefit the pregnant mother by delaying the disease progress. A successful HIV vaccine would have a substantial impact on acquisition of infection, progression of disease among the infected or infectiousness of the infected. 157

Vaccines may be Monovalent (Univalent) or Multivalent (Polyvalent). A monovalent vaccine is designed to immunize against a single antigen or single microorganism. A polyvalent vaccine is designed to immunize against two or more strains of the same micro-organism or against two or more microorganisms. 158

May 18 has been called as the “World AIDS Vaccine Day” over the last decade. It was this day in 1997, the then President of US, Bill Clinton made a speech, calling for an AIDS Vaccine in 10 years time. 159

4.21 SPECTRUM OF POSSIBLE STRATEGIES FOR USE OF HIV VACCINES:

HIV vaccines have been proposed for prevention of HIV infection (classic prophylaxis) and for therapy of HIV infection (as a form of post – infection immunotherapy). HIV vaccines have also been advocated as a tool to reduce the infectivity of HIV – infected individuals. (ie; to reduce the risk of HIV from infected vaccines to their contacts or their offspring)

1. Classic Prophylaxis: The classic prophylactic vaccination strategy requires a high rate of vaccination in the general population at childhood or adolescence, yielding individual immunity as well as “herd” immunity (inhibited spread of infection through the population) if a sufficient percentage of the population is immunized.

2. Targeted Prophylactic Vaccination: This approach is to prevent infection by targeting the “at-risk” population for vaccination. One example

157 D. Follmann et al, supra at 141.
158 Dorlands Medical Dictionary.
of this strategy is targeting of tropical disease vaccines, such as yellow fever vaccine, to travelers.

3. **Immediate Post Exposure Vaccination**: Falling between prophylaxis and treatment is the concept of vaccination immediately after exposure to an infectious pathogen to prevent the establishment of permanent infection. An immediate post exposure HIV vaccine would be most useful in cases of accidental exposures to HIV, as in case of needle stick injury.

4. **Therapeutic Vaccination**: Though therapeutic vaccination has a long history as a concept, successful application of this strategy for any infectious disease is yet to be proven.

5. **Vaccines to reduce infectivity**: Vaccination of uninfected members of the high risk groups to reduce their infectivity in the event of subsequent infection is another strategy for use of HIV vaccines. This vaccine is expected to decrease the infectivity by reducing the rate of viral replication. Presumably, the reduction in the rate of viral replication would probably be accompanied by a decreased rate of disease progression.

### 4.22 HIV VACCINES & THEIR IMPLICATIONS FOR SAFETY:

The major types of HIV vaccines with their implications for safety are discussed below:

#### 4.22.1 Inactivated Whole Virus Vaccine / Killed Vaccine:

Inactivated whole virus vaccine was used in classical approaches and was found successful. They are composed of whole virus particle which has been inactivated or killed with chemicals or heat. They do not contain the virus material in its core. e.g. Polio vaccine (Salk), Influenza vaccine, Cholera vaccine, Rabies vaccine. Generally there is no danger that these kind of vaccines are able to produce the disease associated with the virus. But using this strategy for HIV vaccine carries significant risk. A safe inactivated whole virus vaccine means that all the live viruses are inactivated by gentle physical or chemical means,
preserving full immunogenicity. Live HIV has been inactivated by chemicals, irradiation, temperature or other means to render it non-infectious. There is a very narrow margin between surviving virus and destruction of viral immunogenicity. There are chances that the process used to kill or inactivate the virus may have been imperfect and not all viruses get killed. This thus exposes those involved in vaccine trials with killed virus vaccine at risk of accidently injected with an active virus and progressing to AIDS.

The Cutter incident highlights that the licensed salk polio vaccine containing residual live virus had caused paralytic poliomyelitis among many vaccinated individuals in 1954. Among 4 lakh inoculated, 79 people contracted polio. Another 125 individuals become infected through contact with vaccinated people. 3 quarter of these cases involved paralysis and 11 were fatal.

Failing to inactivate HIV virus may give rise to catastrophic effects. Any residual reactive DNA in the product may be fatal.

4.22.2 Live Attenuated Vaccine:

Another alternative approach in making viral vaccine is to keep the virus alive and able to replicate in the host. The natural virus or wild type virus (virus found in the 'wild', i.e. in nature) is genetically altered so that it loses its ability to cause disease. It still retains its potential to stimulate the host's immune system.ie; the attenuated virus continues to reproduce, thereby acting as a constant source of antigenic stimulus to the immune system. Thus attenuated vaccines appear to provide lifelong immunity without requiring periodic boosters. This genetically altered vaccine virus strain differs from the wild type strain by a varying number of mutations. e.g. The live polio virus strain (Sabin) differs from their wild type strain by 2- 56 mutations. This process of reducing the pathogenic potential of a wild type virus to produce a vaccine virus is called attenuation.eg. Polio vaccine (Sabin), mumps, measles, rubella.
The virus is in some way weakened and used in live attenuated vaccine. Immune responses that closely mimic the solid, long-term protective immune response afforded by natural viral infection can be elicited by using live attenuated vaccines. They induce vigorous and broader antibody response. Further they induce cytotoxic & mucosal immunity at par with other vaccines composed of inert antigens.

The advantage is that the attenuated virus continues to reproduce and act as a source of antigenic stimulus to the immune system. Thus, they provide lifelong immunity and do not require periodic boosters. i.e., the virus continues to exist in the vaccinees body, continues to replicate and continues to stimulate an immune response as long as the person lives. Live HIV that has had its disease-producing potential is reduced or removed through the deletion of viral genes responsible for viral replication or disease; nef/vpr/vpu-deleted HIV. This strategy uses active virus in a weakened form which continues to protect the person against the disease for the remainder of their lives. Since lifelong protection is offered, it is extremely desirable to have an attenuated virus vaccine for HIV.

However, it involves tremendous amount of risk in using an attenuated virus vaccine for HIV. First, recipient has a risk of actually contracting the disease through a live attenuated vaccine. Second, since HIV is a retro virus, the live attenuated vaccine would result in a lifelong, latent HIV infection. The presence of this latent infection in the body could enhance the likelihood of developing diseases such as cancer. Thirdly, if the individual is later exposed to the virus, a live attenuated vaccine could combine with and reconstitute the virus into a more potent, infectious form.

These vaccines received little attention in HIV vaccine development because there is always an inherent risk of the viral strains in such vaccines reverting to virulent forms casing infection in those vaccinated. The phenomenon of reverting of virus vaccines to virulence is not very uncommon. The live attenuated polio
vaccine (Sabin oral polio vaccine) had mutated back to its virulent form in the body of the vaccinated individual causing active paralytic poliomyelitis.

HIV is known for its ability to replicate and mutate very rapidly. This simply means that it could mutate back into a very highly virulent form. If it mutates in a person’s body for the rest of his life, it could mean that we are simply infecting the volunteers with real HIV. If the vaccine is safe, the attenuated virus particles may be transmitted to others via blood and other body fluids, which in turn is beneficial by providing herd immunity, but is deadly if it is not.

In SIV/monkey model, these live attenuated vaccines were synthesized using selective deletion of nonessential auxiliary genes which are required for SIV replication. Monkeys vaccinated with SIV nef gene deletion shows protection against challenge with large dose of virulent virus, in comparison to control group of monkeys. One monkey included in SIV vaccine studies in UK using SIV vaccine, contracted AIDS in a very short time, because of the virulence resulting from mutations. This risk of contracting AIDS in human volunteers is serious with HIV, as it is highly and rapidly mutable. Whether HIV will mutate towards greater virulence or lesser virulence is unpredictable.

In addition to this, attenuated virus vaccines pose additional risks to people who are immune compromised. Because of their suppressed immune systems, even a weakened form of pathogen may even flare up the disease in immune compromised individuals.

Malnutrition may contribute to immune suppression in under developed / developing countries. Also the person may be harboring HIV virus and is undetected. Mass screening of the community before administering the vaccine in itself provide lots of logistical difficulties, in addition to that which already exists.
Safety Concerns associated with Attenuated Virus:

The safety concerns associated with attenuated virus are primarily four. They are

- Level of attenuation
- Stability of attenuation
- Possibility of secondary spread
- Possibility of induction of tumors

The risks with level of attenuation are two types. Inadequate attenuation (reduction of virulence) of virus may result in a vaccine that induces a disease that it is intended to prevent. In the contrary, the other side of the spectrum is an over attenuated vaccine failing to induce any protective immune responses. In an immune compromised vaccine recipient, an appropriately attenuated vaccine may show a virulent behavior. The safety of an adequately attenuated vaccine in immune compromised individuals (those on immune suppressive drugs, cancer patients, organ recipients...) has raised serious questions after animal trials in monkeys. The SIV administered orally to Monkeys at birth, before the development of their immune system were found to be highly infectious in nature.

During the lengthy course of replication in the vaccine, the vaccine strain could undergo genetic reversion to a more virulent form. Since HIV virus has unique characteristics for rapid and frequent genetic mutations, the risk of this nature is many fold.

Herd immunity resulting from secondary spread (spread of attenuated virus to contacts of vaccinees) is beneficial in inducing protective immunity. Since HIV belongs to the family retro viridae, there is an assumption that prolonged residence of live attenuated HIV vaccine strain in vaccine in vaccinees may induce tumors in them. Thus there is a greater need to proceed cautiously in this direction.
4.22.3 **Toxoid Vaccines.**

Toxoid vaccines are not made of microorganism, but from their inactivated toxic compounds. They are known for their efficacy e.g. Tetanus toxoid, diphtheria.

4.22.4 **Sub Unit Vaccines:**

Also known as “Component “or “Protein Vaccines”. Unlike the vaccines made of whole live virus or killed virus, subunit vaccines are made of certain key fragments of the virus, often surface protein. A vaccine composed of the antigenic proteins alone is referred to a subunit vaccine e.g. Hepatitis B vaccine is composed of only surface proteins of the virus. Antigenic proteins for subunit vaccines can now be chemically synthesized in the laboratory or on an industrial scale using genetic engineering techniques. This contains only individual parts of HIV, rather than the whole virus.\(^{160}\)

In order to produce a very potent immune response, often a chemical or biological adjuvant is injected/ingested along with the vaccine, which in turn helps the immune system to detect the subunit. The subunit most commonly used were glycoprotein 120 (gp120) or its precursor- gp 160. Even a viral core protein such as p17 is also used.

There are 3 strategies in developing subunit vaccines. In the initial one, subunits are simply grown invitro, collected and injected into the vaccinee. In the second form, a subunit of the subunit called as a peptide of the subunit is developed and injected into the vaccinee. In the third form, a gene that encodes for a particular subunit is taken during the DNA stage of the replication. It is then spliced into DNA of another virus (a vector virus such as vaccinia or canary pox virus). This vector is then injected into the vaccinee where the vector virus replicates in the

cells of the vaccinee. This can stimulate immune response against any virus displaying same subunit. These are called recombinant vector subunit vaccines.

The advantage of first two strategies is that they have no capacity to infect the vaccinee or contacts of vaccinee as they are not whole viruses. The advantage of 3rd strategy is that the immune response would last much longer, since the vector would continue to replicate inside the vaccinee and would continue to express the desired HIV surface subunit.

The disadvantage of initial two strategies is that it is short-lived. Further, the immune response produced is specific to only those subtypes and strains of HIV that have the exact same form of the subunit as in the vaccine, i.e.; homologous strains. The third strategy also has significant disadvantages. This requires that an alive, relatively harmless virus is introduced into a person, who may already be immunocompromised. This means that they do not have enough immunity to fight the disease. Furthermore, purulent sores may be produced in the process of immunization, which may put immunocompromised people coming in contact with them at greater risk of infection.

4.22.5 Mucosal Immunity:

Mucosal membranes of rectum, vagina are sites of sexual transmission of HIV. As yet no vaccine has provided an immune barrier at the mucosal membranes. The mucosal administration of vaccine vectors that grow on mucosal surfaces may provide an artificial role in the prevention of HIV through sexual routes. Since the antigen uptake from mucosal surfaces is poor than from other routes, newer strategies need to be designed to improve the uptake of antigens from mucosal surfaces.

4.22.6 Newer Adjuants

Adjuvants are nonviral materials incorporated into vaccine formulations to augment the magnitude or spectrum of immune responses to vaccines. They are
commonly derivatives of bacteria and plants. Exploration of newer adjuvants for enhancing cytotoxic T cell or mucosal responses is in progress.

4.22.7 Cytokines:

Cytokines can play a significant role in providing protective immune responses following vaccination. Cytokines are a family of soluble substances (e.g. IL-2, IL-4 and Interferon) that mediate functions of immune cells.

4.22.8 Recombinant vaccines / Genetically Engineered Vaccines.

A number of live virus and even bacterial vectors have been examined as possible carriers of protective antigens of HIV. The vaccinia virus, which was used as a vaccine against small pox and that which successfully eradicated small pox from earth, is an attractive option. This virus is comparatively large and so it is easy to genetically recombine foreign genes into the genome of the virus. The resultant vaccine replicate well and produces a strong immune response in the host, both antibody as well as cellmedicated immune responses. The protection is not strain specific. It is relatively easy to administer. The drawback is that unpleasant and often serious side effects may occur. Thus, related strain of virus, the canary pox virus, is viewed as an attractive alternative to vaccinia.

In a recombinant vaccine, genetically engineered parts of the virus are synthesized into a solution which is injected into a recipient. Since only parts of a synthetic virus are used, the vaccine is not infectious. Genetic engineering techniques of splicing a foreign gene into the chromosome of a host cell or host virus are referred to as recombination i.e. the foreign gene is recombined with the host genome. Splicing the desired protein genes into viruses which have already proven themselves to be effective vaccines and causing these “carrier” viruses to vaccinate against recombinant proteins from other viruses is the method adopted.

The disadvantage is that, it is expensive. Further the antibodies produced by a recombinant vaccine may increase, rather than decrease the recipient
susceptibility to the disease. This may increase the possibility of infection rather than to protect against infection.

Non HIV viruses that don’t cause disease in human or that are deliberately weakened so that they can’t cause the disease. These weakened viruses are then used as vectors or carriers to develop copies of HIV genes into the cells of the body. Once inside the cells, the body uses the instructions carried in the copies of HIV genes to produce HIV proteins and thus can stimulate anti HIV immune response.

Thus these are vaccines produced by genetic engineering, simulating a part of the outer surface envelope or other part of the virus. First-generation subunit vaccines were gp160 and gp120 vaccines. Second-generation subunit vaccines use multiple subunits.

4.22.9 DNA Vaccines:

Naked DNA containing the gene coding for a particular antigen could be used as vaccine to elicit an immune response against that antigen. A number of DNA vaccines against important human pathogens, including HIV have been successfully evaluated in experimental animals. The efficacy or performance of a vaccine is dependent on a number of factors:

- the disease itself (for some disease vaccination performs better than for other diseases)
- the strain of vaccine
- whether vaccination schedule is followed.
- Some individuals are ‘non-responders’ to certain vaccines, meaning that they do not generate antibodies even after being vaccinated correctly.

Animal models have confirmed that immunization with DNA vaccine, with or without booster immunization, can control infection. These vaccines consist of segments of genome or plasmid and are administered either intramuscularly or
intra dermally. After injection, the DNA plasmids are taken up by the host cell, and the encoded protein antigens are expressed. A strong neutralizing antibody response and cytotoxic T lymphocyte response is induced.

4.22.10 Prime – boost Vaccination

This is one method of using combined HIV vaccination. Live recombinant vaccine (poxvirus or alphavirus vectors) plus a boost with a recombinant gp120/gp140 vaccine in various combinations. In this approach the administration of one type of vaccine (e.g. DNA vaccine) may be followed by administration of another type of vaccine (recombinant vector vaccine). The goal is to stimulate different part of the immune system and enhance the body’s overall immune response to HIV.\textsuperscript{161}

4.22.11 Internal or core proteins

As opposed to surface proteins, the internal protein of HIV is more conservative and show less variability. They are also believed to be particularly important in the development of cell-mediated immune response including CTL. Example of candidate vaccines under investigation so far include preparations consisting HIV and internal proteins p 17, a portion of p 17/p24, p 24 and p55.

4.23 CHALLENGES IN THE DEVELOPMENT OF AN AIDS VACCINE:

Our struggle with germs is endless and can be completely halted by vaccines no matter how great is their immunological power. Sadly, effective vaccines for two of world’s leading killers, HIV & Malaria remain in the research stage. All aforesaid research technologies have also been investigated in relation to the development of an HIV vaccine. Most attempts to develop an HIV vaccine have ended in failure.\textsuperscript{162} The development of an HIV vaccine is a formidable challenge ever assigned to health sciences. However, the definitive answer at the end of the road is to find a vaccine. The problems in designing a vaccine for a virus which is so highly variable and so efficient in escaping the immune response of

\textsuperscript{161}Id.
\textsuperscript{162} J. Wane, supra note 89.
the host present a unique challenge of daunting complexity. To add on, AIDS vaccine development was burdened with uncertainties from the very outset. It took almost a decade to come to consensus about what caused AIDS and the disease mechanisms. In addition, the people affected initially were those subject to heavy social prejudices (homosexuals, injecting drug users and sex workers).

Public health significance of the disease was initially distorted because the disease was initially linked to as gay disease and attributable to life style choices. These moralizing wasted a lot of time and even then the answer to the question whether AIDS was caused by a virus or life style choices was not made. Almost as soon as the cause of the disease was perceived, talk of a vaccine followed.

The reason for the delay in developing an effective HIV vaccine may be broadly classified into three groups:

i) Virological / scientific challenges
ii) Legal & Ethical challenges
iii) Economic challenges

4.23.1 Scientific Obstacles / Challenges in the development of HIV vaccine:

On the day the AIDS virus was announced, on April 23 1984, Secretary to US Health and Human sciences, triumphantly proclaimed that a vaccine would be tested in two years. In the thirty years that have lapsed after this, much hope have been raised and equally thrashed. Many researchers involved in HIV vaccine research were frankly skeptical about developing a successful HIV vaccine because of their understanding of the unique characteristics of the human immunodeficiency virus and the mechanisms in which vaccines work.

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Dr Barry D Schoub, Director of the National Institute of Virology at the University of Witwatersrand in Johannesburg puts the matter as simply as this:

The ability of the virus to cause a slow progressive and permanent infection with permanent infectivity makes it a unique cause of epidemic disease. Thus with no recovery, no loss of infectivity, no development of individual or herd immunity, there is no known biological mechanism which can stop the continuing expansion of the disease, unless an effective vaccine were to come about.

HIV is able to resist eradication. Even though the treatment reduces the viral load to near undetectable levels for long period, the virus continues to deplete the immune system, eventually causing AIDS. Since the individuals lack natural sterilizing immunity, super infection with another HIV isolate is not very uncommon as having multiple variants in one’s body at the same time. Thus it seems to be rightly said by an AIDS vaccine researcher that AIDS vaccine field is flying without a compass.

Scientific Obstacles to HIV Vaccine Trials are primarily due to unique qualities of the HIV virus and the adverse reactions seen with traditional vaccination / newer generation vaccines. Adverse reactions to HIV Vaccines are well understood, if one understands the type of adverse reactions seen with vaccines. Hence the spectrum of adverse events seen with traditional vaccines is reviewed here. Further, adverse reactions to HIV vaccines are discussed under two subheads: to initial approaches & to newer generation vaccines. In addition to the adverse events that may be associated with biological mechanisms of injury, important adverse social consequences termed “social harms” are unique to HIV infection.

A vaccine is usually given to uninfected healthy individuals to prevent potential disease for which the vaccinee may or may not be at risk at a future point of time. In such a setting, any significant injury, even if it occurs one in a thousand million vaccine recipients is unacceptable. Majority of vaccines were initially designed
for use in children and hence have held extremely high safety standards. Among the medical treatment modalities, the standard of safety applied to prophylactic vaccines are thus higher than any other methods. This is because of the fact that, the people undergoing clinical trials of a drug are those suffering from that disease, for which treatment is sought. Thus there is a better tolerance of the adverse reactions which accompany the administration of a therapeutic drug. This tolerance is in turn proportionate to the severity / seriousness of the disease being treated. E.g. severe side effects are quite acceptable in cancer chemotherapy.

This is not the case with vaccines. The spectrum of adverse events with vaccines may be early adverse reactions or even severe anaphylaxis. The early adverse reactions may be local or systemic. Local reactions include a sore arm & systemic reactions may include fever, malaise etc. These reactions are typically minor, transient & without much of residual effects. Severe life threatening reactions to vaccines are rare. These include anaphylactic reactions (severe allergic reaction due to hypersensitivity as in tetanus toxoid) and neurologic disease as in pertussis vaccine. It is practically impossible to establish causal relationships between vaccination & illnesses occurring long after vaccination. This is because of the fact that these diseases are difficult to distinguish from other unrelated diseases.

If at all a vaccine reaches clinical efficacy trials despite all these hardships, it will be difficult to set an endpoint to the trial. Since it takes decades for developing the disease from the time of getting infected, setting disease as a clinical endpoint will take many years. Retaining participants in trial is equally challenging and costly.

Thus, in order to better appreciate the scientific obstacles, we move on to the unique features of AIDS virus.
i. **Unique features of HIV/ AIDS Virus:**

After thirty years of experimentation, scientists have been unable to manufacture an effective AIDS vaccine. HIV/AIDS poses unique challenges to vaccine researchers. HIV has several unique features. It is believed that it is these properties of the virus and the special relationship between itself and the host which makes the design of an HIV vaccine complicated. HIV is endowed with unusual set of capacities that enable it to evade or manipulate normal immune defence. Most vaccines protect against disease and not infection. HIV infection may remain latent for long periods before causing AIDS. Most vaccines protect against infection that are infrequently encountered. HIV may be encountered daily by the individual at high risk.

1. HIV is capable of evading immune surveillance by integrating its genome into the genome of infected cells. During replication, HIV undergoes a stage where its RNA genome is transcribed into the DNA by a process called reverse transcription. As a part of its life cycle inside the cell, HIV - DNA integrates into the DNA of human chromosome in the cell nucleolus. While the HIV genome is integrated into the human genome, it is hidden from immune surveillance and cannot be recognized and eliminated. It is sheltered from the effects of the host’s immune system. While it is integrated, the HIV genome is latent and not replicating HIV may persist in this sanctuary, later to be reactivated, replicated and shed new virus from the cell.

This particular characteristic of HIV makes the vaccine scientists skeptical about a vaccine. HIV is often referred to as the *Trojan Horse* (the huge hollow wooden horse which helped the warrior’s of Agamemnon in to the city of Troy) since the virus is often hidden inside the cells of infected person and transmitted to another mostly as cell associated transmission or floating freely, which is rare. If it is kept hidden inside the cell, the immune system of the newly infected person may not be alerted to the presence of the invader in the same way it is alerted when the virus is floating free. Almost all sexual transmission is cell associated type and the commonest mode of transmission is sexual transmission (86%).
Thus the virus escapes the immune system either by constantly changing itself antigenic ally or by making itself ‘invisible’ to the immune system or by making itself inaccessible to immune response.

2. Variability of the AIDS Virus:

The virus undergoes genetic change through a process of rapid genetic mutation. Viral mutations can occur on epitopes, which are key sites normally recognized and attacked by antibody and immune cells. These mutations may render the epitopes unrecognizable, allowing the virus to avoid immune elimination.

HIV is highly mutable, i.e., $3 \times 10^{-5}$ per nucleotide base per cycle of replication. HIV isolates are highly variable. This high genetic variability and diversity is a result of its fast replication cycle, with the generation of about $10^{10}$ virions every day. The parent virus and these daughter viruses continue to replicate virtual copies of it. This complex scenarios leads to the generation of many variant of HIV in a single person, during the lengthy course of infection. In fact, HIV is the most mutable virus known. This variability is compounded when a single cell is infected simultaneously be 2 or more different strain of HIV. Due to the mutations, the outside coating of the virus constantly changes. So scientists cannot precisely define to what antibodies must match. Variability is seen with different strains called quasi species, being generated and isolated from the same individual. In other words, scientists who attempt to develop an HIV vaccine must battle a moving target.¹⁶⁴

Genetic diversity or the production of HIV variants is a major problem in vaccine development. In 1988, Robert Gallo...reported that every HIV isolate has been different. Even sequential HIV isolates from the same patient differ and demonstrate different susceptibilities to a standard neutralizing antibody. A report from Gallo’s lab suggests that even a single amino acid change in the envelope protein can result in a virus that resists the same neutralization antibodies that had previously neutralized parent HIV.

¹⁶⁴ B.D. Schoub, supranote 65.
When our immune system is ready to fight a virus wearing one coat, and is challenged with a virus wearing another coat, it may not respond in a way it was meant to respond. It may put new response which is unsuccessful and the person contracts the disease. This is particularly true in case of HIV and AIDS vaccine.

In addition, several different ‘clades’ or genetic subtypes of HIV exist worldwide. Five to seven principal subgroups of the virus have been identified. Although, these variations are generally divisible geographically, two or more viral clades can exist in the same region. In fact, more than one clade can infect a single individual. This is in addition to the variant sub strains of HIV that develop within individuals, as the virus mutates in the body. A vaccine developed against one clade is unlikely to be effective against another. The development of several vaccines may be necessary to eliminate AIDS globally.

These variants have magnified the complexities associated with AIDS vaccine development. One of the most formidable challenges of AIDS vaccine research is to identify a vaccine or vaccines that can protect against all the variation of the virus.

A significant consequence of the genetic diversity of HIV is that the immune response directed to one HIV strain may not necessarily protect an individual from other subtypes of HIV or from different strains within the same subtype of HIV. This is because the immune system is then constantly challenged by new forms of the virus. So each time the immune system encounters a new variant of

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169 B.D. Schoub, supra note 65.
the virus, it is presented with the enormous challenge of recognizing it and adapting new defense against it. The prospect of producing vaccines active against all possible variants of the virus was thought to be an impossibility to achieve, as the constantly changing virus would continue ‘slipping away’ by changing into new variants. HIV is thought to be the most adaptive and genetically variable virus discovered to date. This extreme variation of HIV has caused uncertainties in the vaccine innovation process.

3. Virus spreads through the body soon after initial contact with the mucosa of vagina, anus and penile urethra (the sites of sexual transmission). The virus then selectively invades and can injure the very cells that play central role in immune defense, i.e. the CD4 & (T helper) lymphocytes and macrophages. So a protective HIV vaccine should provide mucosal immunity, in addition to immunity in the blood. A cellular immune response would be required to clear any infected cells and prevent further cellular transmission. A single vaccine providing all aforesaid immune mechanisms is much sought after.

4. **Hiding from Immune Surveillance**: Virus that infects and are sheltered by macrophages may spread to other sites such as central nervous system – a body compartment where access of immune cells and antibody poor. Virus can also spread by direct cell to cell contact through a process of direct fusion, again avoiding immune inactivation. Thus a further mechanism that the virus exploits to escape the immune responses is its propensity to infect sites in the body which are relatively hidden from the immune system. Nervous tissue is somewhat inaccessible to the immune system and can thus become reservoir for persistent infections.

5. **Chronic & Latent nature of Illness**: HIV infection is chronic with variable number of years of apparent clinical wellness preceding the onset of HIV related illnesses. Despite of the presence of vigorous sustained antibody and CTL response to HIV, the virus continues to multiply to high concentration (titers) in the immune cells in lymphoid tissues of the body. The virus remains silently transmissible with no signs of clinical illness. When a sufficient number of CD4
lymphocytes are injured and lost, AIDS becomes clinically apparent. The progression of disease can be monitored by measuring the fall in concentration of CD4 and lymphocytes.

6. **Multiple Mechanisms of Transmission**: HIV can be transmitted by 3 different routes. This itself complicated the task of developing a vaccine that can induce an effective immune blockade. HIV is acquired by sexual contact with mucosa of vagina, anus or penis, by direct inoculation into blood stream or from mother to fetus or infant in utero, at birth or through breast milk. Protecting the mucosa against infection is a special challenge because of the difficulty in inducing mucosal immunity through vaccination. Virus may be transmitted as a free virus or a virus carried inside cells, which itself makes it difficult to counter.

7. **Uncertainty as to the correlates of protection**: 

Classic vaccines mimic natural immunity against re-infection. This is generally appreciated in individual recovered from infection. But ironically, there are almost no recovered AIDS patients. Once testing begins in humans, researchers are faced with another important question: How will they know if a candidate vaccine has actually resulted in some level of protection to an individual? Researchers do not currently know what a protected individual looks like, because humans naturally immune to HIV infection have not been identified.\(^{170}\) Unlike other viral infections that are self limited, there are no instances of recovery from HIV infection. Thus there are no clues for understanding the key immune response elements that are necessary for protection from the virus. In addition, humans lack natural sterilizing immunity against HIV. This is the ability of the immune system to teach itself protection against a virus. People who recover from an infection are often immune from subsequent attack by the same pathogen. This not the case with HIV as no one is known to have recovered from, and completely cleared, acute infection, let alone developed natural

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Immunity to re-infection. In addition, super infection with another HIV isolate can readily occur in infected persons.

8. The Lack of Appropriate Animal Models for HIV/AIDS:

Clinical research involving experimental substances is usually preceded by testing in animals. Before any vaccine is approved for testing in animals, it must be demonstrated to be safe, immunogenic and effective in animals. Scientists evaluate the new vaccine by testing its ability to generate antibodies in animals. Then they test the effectiveness of these antibodies in neutralizing the virus through in vitro laboratory tests.

To date, no suitable animal models for HIV and no reliable invitro markers for efficiency have been identified. The closest one is Simian Immuno deficiency Virus (SIV). Though the rhesus macaque monkey of Asia is not infected with an SIV strain in nature, it can be readily infected with SIV strain in the laboratory. These SIV strains can produce AIDS like disease in these animals. This animal model had proved to be extremely valuable, as the disease was virtually identical to AIDS in humans. Only difference was that the time course of the disease was much rapid, making it convenient for experimental observations. However, it is not yet established that the SIV disease in macaque is biologically equivalent to AIDS in humans.\footnote{P.A. Leider, supra note165.}

AIDS virus restricted to West Africa, i.e.,HIV- 2 is more closely related to SIV than HIV-1. It grows poorly in monkeys and does not grow at all in chimpanzees.

Also, we have no truly useful, small animal model for studying HIV infection. A significant obstacle in HIV vaccine research has been the difficulty in developing an appropriate animal model. Human AIDS cannot be reliably imitated in animals. SIV is a surrogate for HIV, and it is not known whether successful SIV strategies can be translated to HIV.\footnote{id} Lack of appropriate animal model raises a
thorny question to researchers of HIV vaccine: - Should they be testing these vaccines in humans, before they are known to be safe immunogenic and protective in animals? The stakes are quite high because, a preventive vaccine, by definition is to be tested in HIV negative human subjects.

Animal models of human HIV infection using monkeys and other primates have not yet yielded definitive guidance to the immune elements necessary for protection. The chimpanzee is the only animal other than human in which HIV will replicate and which can be infected with HIV. Although they exhibit HIV like symptoms, chimps do not develop T cell deficiencies or other disease symptoms similar to AIDS in humans. The virus establishes itself in this animal and elicits immune response, with no evidence of immune suppression. Thus the animal can be immunized with a potential vaccine and the efficacy can be examined by challenging with the HIV. Since no clinical/ lab evidence of disease is produced, this animal model cannot be used to study the pathogenic consequence of any challenge infection. Hence it is an extremely valuable animal model of HIV infection. Chimpanzees are rarely used for vaccine research as they are expensive and of very short supply. It can cost more than $100,000 to care for a single animal. In addition, being a rare species, chimpanzees are protected by a 1975 treaty that allows them to be used for research only if they are bred in captivity and not caught in the wild.

9. Auto Immunity: Theoretically, it is believed that gp 120 may interfere with the normal working of the immune system. Any protective HIV vaccine needs gp 120 in some form or another (as a subunit vaccine, within a multiplying ‘carriers’ virus such as vaccinia, or as part of a ‘killed’ virus vaccine). The administration of gp 120 envelope proteins or its precursor, gp 160 (which is split into gp 120 and gp 41) is by itself immunosuppressive. One of its potentially harmful effects is its ability to fuse cells to each other. Another potential difficulty with the use of gp 120 as an antigen in a vaccines the fact that its attachment to the CD4 receptor

may compete with the physiological function of the antigen presenting cells, attaching to the CD4 receptor of CD4 lymphocyte to present new antigen to the immune system. Gp 120 thus interferes with the normal working of the immune system. Further, the antibodies elicited by the gp 120 could attach to the surface proteins of antigen presenting cells and block their interaction with CD4 antigen. Again the mirror image antibodies, directed against the anti gp 120 antibodies could similarly attach to and block CD4 antigen of the CD4 lymphocyte. Thus by all these mechanism, the immune response of the host elicited by the vaccine could instead target onto the host itself and cause damage by a disease process called auto immunity. Thus HIV vaccines may cause Immune reaction against body's own tissues. Such 'anti-self' antibodies is the basis for auto immune injury.

10. Antibody Dependent Enhancement (ADE): Some experts have doubted that priming with on HIV vaccine can potentiate subsequently acquired natural HIV infection. This could be due to the fact that the antibodies produced are non neutralizing and are able to attach to the virus and act as a vehicle to transport the virus to monocytes and macrophages. Thus, these non-neutralizing antibodies facilitate the entry of the virus into the cells rather than protect against infection. This antibody dependent enhancement of infection can be demonstrated in the laboratory by an increasing growth of virus in cell culture in the presence of antibodies from the serum of exposed individuals. Many scientists consider ADE to be an unrelated laboratory phenomenon only.

11. The virus is difficult to grow in culture and only yield small amount of viral material in culture.

12. Potentiating Malignancy: HIV virus suffers from the stigma of belonging to a family of viruses (the retroviridae) who are associated with malignancy. This association disqualifies the virus from being used as attenuated, killed or inactivated whole virus vaccines. In all these forms, the nucleic acid is present and thus there is a theoretical danger of transforming the cell into malignancy.
13. Most vaccines protect disease and not infection. HIV infection may remain latent for many years before the development of full blown AIDS.

14. Most vaccines offer protection against diseases that are infrequently encountered. HIV may be encountered daily by the individuals at high risk.

15. Most effective vaccines are whole killed or live attenuated organisms. Killed HIV does not retain antigenicity. The use of live retro virus vaccines raises safety issues.

Although, much has been discovered, the most important scientific lesson likely remains to be learned. More needs to be known about HIV immunopathogenesis, human clinical trials and animal models.\textsuperscript{174}

Having seen the unique features of AIDS virus- HIV, we move on to the potential adverse reactions to HIV vaccines. This can be further sub divided into adverse reactions to HIV vaccines and adverse reactions to newer generation vaccines.

\textit{ii. Potential Adverse reactions to HIV Vaccines}

\textit{(a) Adverse Reactions to HIV Vaccines:}

HIV vaccine development strategies in the initial phases have either utilized envelope proteins or vaccinia virus. The envelope proteins gp160 or gp120 are combined with carrier molecules which are then injected into individuals producing an immune response.

The other method is using live vaccinia virus as a delivery vector. The vaccinia virus genome has been genetically altered to incorporate the HIV envelope gp160 gene. Once introduced into the dermal layer of the skin, the vaccinia virus

\textsuperscript{174} M.J. Mulligan, \textit{Advances in Human Clinical Trials of Vaccines to Prevent HIV/AIDS and other HIV Prevention Interventions}, CURRENT INFECTIOUS DISEASE REPORTS 11 399 (2009)
replicates resulting in the expression of gp 160 protein inducing immune response.

The antibody titers (concentration) found after introduction of envelope based vaccines were 5 to 10 fold lower than those found in HIV infected individuals. These titers were falling rapidly after each dose of the vaccine, thus failing to produce a sustained response.

Adverse reactions following vaccination with envelope – based vaccine have been minimally greater than adverse reactions following placebo vaccination. 175

Hematological, biochemical & immunologic markers showed no vaccine related abnormal findings. It is important that no evidence of adverse effects on immune function, including CD4+ & CD8+ lymphocyte counts were noted. However, few adverse reactions noted are as follows:

(i) Early self limited adverse reactions:

Local reactions at the injection site like mild pain, tenderness, redness & swelling which subsides in 2- 3 days are common with envelope based vaccines having alum adjuvant. These complaints were similar to that of placebo recipients. Development of rashes, painful joints and positive Antinuclear Antibody (ANA) was also found in few vaccinees. Reactions may range from mild systemic reactions to reactions as severe as convulsions.

(ii) Levels of attenuation of the Vaccinia Vector:

Side effects of vaccinia /gp160 vector with commercial vaccinia strain used to prevent smallpox had no difference in the rate of pustule formation at the inoculation site, regional lymph node swelling or other systemic symptoms. Under the controlled conditions of the trials, care of the inoculation site with occlusive dressing prevented secondary spread to other individuals. The vaccinia virus did not appear to be attenuated & hence use of a more attenuated virus vector (eg. Canary Pox Virus) is adviceable.

175OTA 18% of participants in trials of envelope based vaccines received placebo vaccination.
(iii) Neoplasm / Malignancy:

HIV belongs to the family of virus Retroviridae, which has been associated with the development of malignancies. There has been speculation that, because HIV is a retrovirus, an HIV vaccine might cause cancer many years after vaccination. Other retroviruses have been shown to produce tumors. Hence, if the vaccine is a whole attenuated virus, there is risk of malignancies. Thus, theoretically, the prolonged residence of an attenuated HIV strain in humans could allow the production of tumors. Also there is evidence that HIV has a direct role in the etiology of some T-cell lymphomas, a type of immune cell cancer.

Though few neoplasms were found in different HIV vaccine protocols, it failed to establish any evidence that these neoplasms were linked to any vaccine. Any causal relationship can only be established with careful long-term follow-up & independent reviews.

(iv) HIV infections among trial participants:

Many cases of breakthrough infections among vaccine trial participants were reported. All HIV infections among vaccinees accompanied high risk behavior. These breakthrough infections occurred despite rigorous counseling of the vaccinees, because

- Some volunteers received placebo.
- Maximum protection is incurred only after full vaccine dosage schedule, i.e.; 3 or more doses.
- The protective efficacy of the vaccine being tested is unknown.
- Antibody Dependent Enhancement (ADE) of infectivity.

(v) Antibody Dependent Enhancement / Antibody Enhanced Infectivity:

It has been proposed by many experts that priming with an HIV vaccine may potentiate subsequent naturally acquired HIV infection. This phenomenon was demonstrated in the laboratory by an increase in the growth of the virus in cell
culture in the presence of antibodies from the serum of exposed individuals. Recipients of envelope vaccines have been shown to develop small amounts of enhancing antibodies. ¹⁷⁶

HIV antibodies help the HIV to enter the host cells, especially the monocyte cells. In the serum of HIV infected patients & in HIV infected & immunized animals, antibodies that enhance HIV infectivity were identified. This would mean that persons who have developed antibodies to HIV (as stimulated by HIV vaccine) and subsequently become exposed to HIV through any one of the usual routes of infection, they are:

- More likely to become infected with the virus
- More likely to progress to disease
- More likely to develop a more serious form of disease than the non vaccinated.

This phenomenon was already noticed in measles vaccine, rabies & dengue fever vaccine, Respiratory Syncytial Virus (RSV) vaccine.

(vi) Induction of Auto Immunity:

HIV vaccines may have the potential for autoimmunity and such concerns arise because HIV shares several envelope protein sequences that are identical to the sequences on human tissue. This phenomenon is called as molecular mimicry. An example of molecular mimicry is similarity of HIV envelope protein region to a normal human blood type protien. The danger is that immunization with such viral structures may induce immune response to the cells of vaccinated individuals. Thus, the immune responses of the host, elicited by the vaccine could target the host itself & destroy the cells.

(vii) Potential immune Tolerance:

Though relatively small, a remote possibility exists that a subject receiving present HIV vaccine may become immune to the effects of any future HIV vaccines. This phenomenon is termed “immune tolerance”. Until after extensive Phase III trials are carried out, we are clueless about how likely or unlikely this occurrence might be.

Two deadly consequences of this phenomenon are

- A person’s immune system might no longer initiate a response against HIV. Since the immune system would not fight the virus at all, an infected persons disease progression and subsequent death would be rapid than normal.

- Further, even if an effective vaccine against HIV were to be developed and proven successful at some point of time, this volunteer would not be able to use it as they would not respond to it at all. This is a very fatal scenario.

The subjects of present vaccine trials may become immune to the effects of any future HIV vaccines. That means, the subjects will become immunologically unresponsive to the original antigens (HIV viral proteins) which are capable of evoking immune responses. Thus ‘immune tolerance’ prevents the vaccinees immune system from evoking any response upon identifying this antigen again. This may give rise to two life threatening consequences:

- The vaccinees immune system would not evoke any response against HIV. Thus in any future point of time, if this person contracts HIV, his immune system would not fight against the virus & thus the disease process would be more rapid and fatal than normal.

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177 Immune tolerance renders a person immunologically unresponsive to the original antigen (HIV), capable of inducing immune responses. Immune Tolerance prevents the immune system from initiating any response upon encountering this antigen again.
Further, if an effective vaccine against HIV were to be developed in future, it would be of no use to this volunteer as it would not respond at all. If it is a vaccine of whole attenuated type, there is a danger that the vaccine may simply infect them & cause AIDS.

(viii) Neurological Diseases of Unknown Origin:

Thomas Kems believes that our knowledge about the risk of development of neuropathies post HIV vaccination is in the rudimentary stage. This is because of the known fact that severe neurological diseases of unknown etiology are reported among the participants in the 1st week after an injection in any vaccine trial. For e.g. Sheep brain derived rabies vaccine, influenza vaccine, live attenuated polio virus vaccine etc causes MyeloEncephelitis, Guillian Barre syndrome, and Vaccine paralysis respectively.

(ix) Immuno Suppression:

Another danger, even with safer gp120 subunit vaccines is that the virus itself could have a compromising effect on the immune system of the vaccinated individual. The two mechanisms by which immune suppression occur are due to formation of syncytia and decrease in CD4 availability. Syncytium is a pathological bunching together of a cluster of individual T4 cells in to one big lump. All the T4 cells in the lump are disabled and are thus ineffective in their role as chief directing cell in the overall immune system response. This results in a compromised functioning of the person’s immune system. The causes of syncytia are not yet clear but seem to be related to the function of gp120 & its ability to bind to CD4 molecule on T cells.

(b) Adverse Reactions that could arise out of Newer Generation Vaccines:

Since transmission of HIV utilizes multiple strategies, a vaccine that prevents HIV infection should possess the following 3 elements:

• A sustained antibody response that neutralizes any free virus.
• Induction of cytotoxic T lymphocytes which can recognize multiple HIV epitopes, thus destroying infected cells.
• An antibody and cellular response at genital and rectal mucosal surfaces, protecting against sexual transmission.

Some of these concepts are quite novel and are never before applied to vaccines in use in human beings. These new approaches carry special risks, some of which are unique in nature. The laboratory studies and animal studies to test the vaccine safety maybe poor predictors, especially of infrequent and late adverse reactions.

HIV vaccines are unlikely to be completely effective or efficacious. None of the HIV vaccines now in clinical trials have proved to be effective for all the vaccinated population. That means, some of them may become infected after taking a vaccine of limited efficacy, even if the vaccine is not defective. Because of HIV’s unique abilities to invade immune controls, all immune response elements may need to be invoked to provide protection, including humoral immunity, cellular immunity and mucosal immunity. Further, persons who believe that they are protected against infection because of the vaccine may be more likely to engage in high – risk behaviors.

iii. Social Harms / Non Medical Adverse Events:

HIV vaccines may pose risks of social harm that are not ordinarily linked with other vaccines or drugs. Some adverse consequences or harms may be expected which will fall into the realm of ‘social injury’ or psychosocial risks’. In addition there are risks to community involved.

**Psychosocial risks for individual participants** include (1) inconvenience and participation fatigue associated with lengthy research (2) anxiety induced by repeated HIV testing (3) stress caused by exposure to culturally unusual medical and research concepts (4) attendant discrimination accorded to individuals perceived to be at high risk of HIV infection (5) vaccine-induced seropositivity on
conventional screening methods and associated negative consequences, such as the potential for discrimination in employment, insurance and health care(6) raised expectations of gaining immunity to a deadly infection or speedy access to an effective vaccine(7) a false sense of security leading to increase in risky behavior (8) stress between partners as a result of the participation of one partner in a vaccine trial.\textsuperscript{178}

\textbf{Risks to the community} from which participants are drawn include: (1) the stigma that may attach to them from the manner in which they are portrayed in the popular press and scholarly journals; (2) vulnerability to exploitation by research groups from the West and within their own countries, due to prevailing conditions including impoverishment, inadequate health care and lack of familiarity with research methods. \textsuperscript{179}

The non medical adverse events are as follows:

\textit{a. Exclusion from future protocols:}

Volunteers in present experiments would not be probably able to participate in any future vaccine research. The reason for exclusion could be that they are “contaminated” by exposure to a future vaccine. Future vaccines would certainly be more promising than & superior to present vaccines, and for the mere reason that they had participated in an HIV vaccine study would exclude them from participating.

\textit{b. Being Monitored:}

Vaccine trial participants, especially in phase III trials would have to experience the discomfort and hazard of being monitored by the researchers for many years to come, perhaps for the rest of their lives. Prior to vaccination, the vaccinees are screened, educated and counseled. Post vaccination, they need to be checked,


\textsuperscript{179} Id.
tested and counseled regularly during the entire course of the trial. How long the follow up is required depends greatly on the criterion of effectiveness of the study.

If the criterion of effectiveness is prevention of disease - a traditional concept in most vaccines – then we still do not know how long the subjects need to be followed up to make sure that they do not get AIDS. It may be 10 years, 20 years or the rest of their life. This would give tremendous inconvenience to the participants and genuine hardships to their significant others. They would feel that their lives are restricted to this mere requirement - to be available.

c. Feeling Safe:

It is but natural that the participants feel free to engage in high risk behaviors (unprotected sex, sharing needles etc) because they feel more secured and protected after vaccination. The client may have to be thoroughly and forcefully counseled that there is a substantial chance that he/ she may be receiving a completely inert substance that provides no protection of any kind, since the study is double blinded and placebo controlled. Some volunteers may even go to the extent of getting themselves tested for antibodies to HIV from facilities outside the trial. Once found to be possessing the antibodies, they may engage in high risk behavior with a false hope. This un- blinding by the individuals will prove to be harmful to the individual and to the validity of the study.

d. Learning one’s antibody status:

Few subjects in HIV vaccine clinical trials, either in the vaccine or placebo arm may become infected during the course of their study, due to their usual risky behaviors. The surveillance of HIV antibody status would detect this resulting in the subjects being informed of their infection, which otherwise they would have avoided. Many subjects would consider it as a burden imposed on them by participating in the trial. Many have considered their knowledge of positive antibody status as “burdensome knowledge that should not be imposed”.
**e. Stigma and Discrimination:**

HIV/AIDS is as much a social phenomenon as it is about biological and medical concern. Social responses of fear, denial, stigma and discrimination have accompanied the epidemic from the beginning. AIDS stigma evokes negative reactions – denial, shame, fear, anger, prejudice and discrimination. HIV related stigma and discrimination were identified as critical barriers to effectively tackling the epidemic always. Stigma and resultant discrimination is globally pervasive and it operates at multiple levels throughout the society, i.e. within the individuals, families, communities, institutions, media and government policies and practices.

“Since the beginning of HIV/AIDS epidemic, stigma, discrimination and gender inequality has been identified as major obstacles to effective responses to HIV. Stigma harms. It silences individuals and communities, saps their strength, increases their vulnerability, isolates people and deprives them of care and support”\(^{180}\)

Peter Piot
Executive Director
Joint United Nations Programme on HIV/AIDS

“If we do not appreciate the nature and impact of stigma, none of our interventions can begin to be successful. AIDS is probably the most stigmatized disease in history.”

Edwin Cameron

**Stigma** is defined as a social process that marginalizes and labels those who are different. **Discrimination** is defined as the negative practices that stem from stigma or enacted stigma. Discrimination results from individuals being treated less favorably than others on account of some feature or quality. Stigma and discrimination are two primary obstacles to scale up HIV prevention strategies.

Dr Peter Piot rightly expressed that HIV / AIDS related stigma comes from the powerful combination of shame and fear – *shame* because the sex or drug

injecting that transmit HIV are surrounded by taboo and moral judgment and fear
because AIDS is relatively new and considered deadly. HIV / AIDS was linked to
“perversion” and those infected were supposed to be punished.

De Bruyn (1999) had identified the following factors contributing to HIV/AIDS
related stigma\textsuperscript{181}:

\begin{itemize}
  \item[i)] The fact that HIV/AIDS is a life threatening disease
  \item[ii)] The fact that people are afraid of contracting HIV
  \item[iii)] The disease’s association with behaviors (such as sex between men and
            injection drug use) that are already stigmatized in many countries
  \item[iv)] The fact that people living with HIV / AIDS are often thought of as being
            responsible for having contracted the disease
  \item[v)] Religious or moral beliefs that lead some people to conclude that having
            HIV/AIDS is the result of a moral fault (such as promiscuity or deviant sex) that
            deserves punishment.
\end{itemize}

HIV/AIDS related stigma is a process of devaluation of the people, either living
with or associated with HIV / AIDS. The stigma associated with HIV and the
resulting discrimination can be as devastating as the illness itself. It could result
in abandonment by either spouse or family, social ostracism, job and property
loss, social expulsion, denial of medical services, lack of care and support and
violence. It can lead to depression, lack of self worth and despair for people living
with HIV. Self-stigmatization or shame that people living with HIV / AIDS
experience when they internalize the negative responses and reactions of others
can lead to depression, withdrawal and feelings of worthlessness, which could
culminate in suicide.

Due to these consequences or a fear of them, would mean that people would not
come out for HIV testing, or disclose their HIV status to others; adopt HIV

\textsuperscript{181}/d.
preventive behavior, access treatment care and support. If they do so, they could lose everything.

In 1987, Jonathan Mann, then director of WHO’s Global programme on AIDS forecasted three components of HIV epidemic: First component is the epidemic of HIV infection. This enters the community silently and unnoticed. Next follows the epidemic of AIDS, which appears when HIV triggers life threatening infection. Finally, the third component emerges – the epidemic of stigma, discrimination, blame and collective denial – that makes it so difficult to effectively tackle the first two.¹⁸²

In a study conducted by United Nations, majority of the respondents overwhelmingly agreed that the key manifestation of stigma is social isolation and ridicule.¹⁸³

Volunteers may be HIV anti body positive (HIV Ab+) for many years post vaccination. Vaccines may cause ‘false – positive’ screening tests for HIV infection. This vaccine induced sero- positivity can result in discrimination against false positive individuals, such as denial of eligibility for military service, loss of employment, denial of health or life insurance, restrictions to travel abroad, loss of employment or housing, segregation in institutions etc. They may even find it difficult to find a marriage partner.

Sero positivity following inoculation with envelope vaccines can be usually distinguished from HIV infection by the HIV Western Blot test, which is used to confirm the results HIV, from enzyme linked immunosorbant assay (ELISA) tests used in HIV screening. The problem may become more acute as new generation vaccines that include many more types of antigenic proteins that are currently used may render the Western Blot test unable to distinguish vaccine induced sero positivity from true HIV infection. Reliance must then be placed on time

¹⁸² UNAIDS FACE SHEET ON STIGMA AND DISCRIMINATION, supra note 180.
consuming and expensive polymerase chain reaction (PCR) tests which detect the presence of virus directly, and on viral cultures. There is a possibility that PCR may not be able to detect the new mutants as HIV mutates readily.

Participation in an HIV trial, in itself, may invite social harms. Others may perceive a volunteer’s participation in the trial as implying that the volunteer is in a group at special risk of acquiring HIV infection, and it may result in social stigmatization of the volunteer. In addition, a volunteer who is immunized with one candidate vaccine may be precluded from participating in clinical trials of subsequent, possibly more effective, vaccine products. Further, the trial participants may assume that they are protected from HIV infection and as a consequence may increase their risk taking behaviors. This increased risk taking behavior may occur despite intensive counseling on the possibility of assignment to placebo vaccine and the unknown efficacy of the trial vaccine. It is expected that the vaccine may fall short of protecting all recipients. In such a scenario, the failure may be perceived as vaccine induced enhancement of infection, manifested as an increased susceptibility or a more aggressive course of infection. Participants should be made aware that the social discrimination could seriously affect their everyday lives and may not be compensable. Only by confronting stigma and discrimination will the fight against HIV/AIDS be won.

**f. Unwanted or unanticipated risks:**

In addition to all the above mentioned risks, the volunteers may need to be informed about unknown/unanticipated risks which may crop up any time during or after the trial. Phase I and Phase II trials are of shorter duration involving fewer hundreds of volunteers. Thus any untoward hazard may emerge only in Phase III trial, with larger number of volunteers and a longer duration of trials.

Further there is a possibility that the regular sex partners of the subjects may also come up with some unanticipated risks. This problem of endangering third parties put the sponsors at additional risks of potential increased liability. The
third parties were not even informed of potential risks and hence not given consent to accept the risk.

It is actually extremely difficult to fully appreciate the challenges faced by these people and develop comprehensive strategies to address their needs without a full understanding of the complexities of these issues.

4.23.2 Economic Challenges

Looking at the tremendous need for an HIV vaccine, one may expect to have significant number of private investments. However as per IAVI 2004 report, private investment was substantially less than $25m in 1993, against a total global funding for HIV/AIDS vaccine R & D of $160m. In the absence of private funding, governments invested 89% of total global investment in HIV vaccine R & D between 2000 & 2007. The UNAIDS report of 2008 was more promising. As per this, the total global investment in HIV vaccine R & D increased steadily from $327m in 2000 to $961m in 2007.\(^{184}\) A study conducted in 2005 June estimated that $682 million was spent on AIDS Vaccine research annually.\(^{185}\) Like in case of other vaccines in the past, US accounted for 85 to 90% public sector funding of HIV vaccine R & D between 2000 and 2004.\(^{186}\) A latest newsletter by IAVI (March 9, 2015) declares an amount of US$1.2 M from the Collaboration for AIDS Vaccine Discovery (CAVD) Grant of Bill Gates and Melinda Gates Foundation (BMGF) for over three years (2015-2017).\(^{187}\)

The vaccine market is considerably smaller than the pharmaceuticals. This can be made explicit by the following figures. In the year 2001, the annual sales from pharmaceuticals was 350bn as compared to a worldwide annual vaccine sale of

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\(^{184}\) A considerable part of this increase was due to a 100m donation in 2002 by the Gates Foundation.


\(^{186}\) UNAIDS 2008.

a megre $1bn. Vaccine sales represents only about 1.5% of the pharmaceutical market.

The factors that hinder private pharmaceutical companies from committing themselves to HIV vaccine R & D are many fold. The expenses incurred are very high, the legal liabilities are considerable, probable financial return is small and a possibility of complete failure is not to be ignored.

Greco has identified a product- market cycle of vaccines which typically follows a 20 year pattern. In the early years of production, the sale is usually by private market in small quantities at high cost. This will be later replaced by public procurement, and the vaccine at this stage will be available at low cost in large quantities. Private prices are set by manufacturers but at public sector the costs are always less in order to reduce health care cost, suffering and death. This centralized purchasing and public pressures depress the cost. In addition, the possible financial return on a fairly successful vaccine is not expected to be great, because the primary market would be developing nations where a higher rate would be considered exploitative.

Clinical trials take longer time and this adds to their expense. For e.g. an NIH & NIAID trial of 2007 which enrolled just 8000 volunteers cost $130m. Choosing to commit to such large funds represents an uncertain decision with large financial risk.

Vaccines being tested can cause unwanted side effects. Exposure to liability is a major disincentive in vaccine industry. One reason for this is that, unlike most drugs, vaccines are usually administered to healthy and young people. Thus, the potential for being sued by persons or groups who feel they have been harmed by a vaccine could be enormous. This requires that the regular partners of the participants be also included in prescreening processes and counseling. Thus the number of people who are human subjects included in the trial is enormous adding to the existing complexity of HIV vaccine trials.
4.23.3 Ethical Issues Involved In Clinical Trials:

New ethical issues surrounding clinical trials are in the horizon in the 21st century. As the drug companies are multinational in orientation, it is feared that clinical trials are getting “exported” to parts of the world having increased number of under privileged populations such as India. In effect, populations in these parts of the world have become guinea pigs on which to test therapies, which will later be used by inhabitants of richer and more developed countries. From this perspective, contemporary issues in the design of clinical trials could be seen as an issue of global justice. 188

Further to it is a petition filed in the Supreme Court of India which said:

“The poor, illiterate and vulnerable sections of society become subjects to these illegal clinical trials. In conducting these trials with the sole aim of making money, ethical medical practices are grossly compromised. These trials are conducted without regard to the consent of the subjects, despite apparent conflict of interest. The petitioners submit that the manner in which these trials are conducted is grossly illegal and violative of Article 21 of the Constitution. The inaction of the government in not banning or restricting these clinical trials is violative of Article 14 of the Constitution. There has been rampant compromise with human life and the entire episode demonstrates a sordid nexus, which is nothing but a scam.” 189

Thus the questions that arise in any readers mind would be:

- What is the role of ethics in research with human subjects?
- Why is there a need for research ethics?
- What are the key principles of research ethics?
- What makes research ethical?

• What are the ethical challenges in clinical trials and more so in HIV vaccine clinical trials?  

Research aims to develop knowledge. Aims of research are a recognized good, but are not superior to the welfare of humans who participate. Participants should not be used as just “means to an end”; they have dignity. Research participants should be protected from exploitation / harm and their welfare should be promoted. Ethics provide a framework to do this. Ethics is based on what is good, right, fair and just. Ethics promote the rights and welfare of participants in research. Ethics also promote good science as participants who feel respected may follow research requests, answer truthfully, return for follow up thereby, increasing the quality of the data. Human trials cannot go forward without appropriate attention to ethical issues. The term ethics refers to the study of philosophical ideals of right and wrong behavior. Ethics is the study of good conduct, and motives. All biomedical research should be conducted in a manner that seeks not to violate the ethical principles. Biomedical ethics is about the principles and rules we use to decide what is acceptable or ethical when doing medical research in humans. Ethical principles govern the activity of research, regardless of where it occurs. Ethical principles are universal. It ensures that:

- We treat people with dignity and respect
- We protect their rights and welfare
- We promote their welfare and safety.  

History of abusive research on Jews by Nazi doctors in World War II and African-Americans by the USA research establishment in the Tuskegee Syphilis study led to first code of ethics such as the 1947 Nuremberg Code, the 1964/2000 World Medical Association’s Declaration of Helsinki and the

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USA's 1979 Belmont Report *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*. This highlighted the need to protect research subjects from risks, harm and exploitation. There have been several codes since then that describe how researchers should respect the dignity and welfare of human subjects.

Indian Council of Medical Research (ICMR) states that medical and related research using human beings as participants must necessarily ensure the following.

(i) The *purpose*, of such research is that, it should be directed towards the increase of knowledge about the human condition in relation to its social and natural environment, mindful that the human species is one of the many species in a planet in which the well being of all species is under threat, no less from the human species as any other, and that such research is for the betterment of all, especially the least advantaged.

(ii) Such research is *conducted* under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subject to any medical research or scientific experimentation are dealt with in a manner conducive to and consistent with their dignity and well being, under conditions of professional fair treatment and transparency, and after ensuring that the participant is placed at no greater risk other than such risk commensurate with the well being of the participant in question in the light of the object to be achieved.

(iii) Such research must be subjected to a regime of *evaluation* at all stages of the proposal ie; research design and experimentation, declaration of results and use of the results thereof ,and that each such evaluation shall bear in mind the objects to be achieved, the
means by which they are sought to be achieved, the anticipated benefits and dangers, the potential uses and abuses of the experiment and its results, and above all, the premium that civilized society places on saving and ensuring the safety of each human life as an end in itself.\textsuperscript{192}

All international and national ethical guidelines are based on the following ethical principles of Beneficence, Non-Maleficence, Justice, Autonomy and Fidelity.

\begin{itemize}
  \item **Beneficence (Do Good):** Beneficence refers to taking positive actions to help others. The practice of beneficence encourages the urge to do good for others i.e. prevent harm, remove harm and promote good by helping others to advance and realize their interests.\textsuperscript{193} Commitment to beneficence helps to guide difficult decisions wherein, the benefits of a treatment may be challenged by risks to the client’s wellbeing or dignity. Beneficence refers to the moral obligation to minimize possible harms and actively to maximize possible benefits. It involves explicit consideration of benefit in relation to risk and includes stringent obligations not to injure intentionally (sometimes expressed as the separate principle of non-maleficence). In the context of clinical trials, the principle of beneficence requires that the welfare of research participants be protected. There are additional obligations arising out of beneficence. When persons are included in research who might be particularly vulnerable to being exploited (eg; prisoners, women, children, less privileged) beneficence requires us to provide special protections to ensure that these participants are not harmed by the research. Researchers should take active and positive steps to maximize the possible benefits for research participants. Researchers should take

\textsuperscript{192} ICMR.
\textsuperscript{193} M. Chulay and S. M. Burns, ESSENTIALS OF CRITICAL CARE NURSING, 199- 211.(1st edn., 2005)
active steps to reduce possible harms to a minimum. Sometimes benefits are for society or future generations.

- **Non - maleficence (Do No Harm):** Non maleficence means avoidance of harm or hurt. In healthcare ethics, it is vital to remember that it is important to do good, but it is equally important to do no harm. The health care professional tries to balance the risks and benefits of a plan of care while striving to do the least harm possible. There should be no injury or harm to participants as a result of participation. Researchers cannot intentionally harm participants. Researchers also have to consider harms that could result unintentionally.

- **Justice (Persons should receive what is owed them):** Justice refers to fairness in the distribution of both benefits and burdens. There is an ethical obligation to ensure that the burdens and benefits of research are fairly and equitably distributed. One principle underlying the principle of justice is that of fair distribution. Research participants are not to be exposed to a disproportionate share of the research risks without an equal share of the benefits. Health care professionals are expected to strive for justice in healthcare. In research, this requires that no individuals or populations bear a disproportionate share of the risks of research without justification, and all that populations have access to the benefits of research participation. There should be a balance of risks and benefits. Those who carry the risks should have access to the benefits (and vice versa). Researchers must make sure that research participants do not carry risks without a proportionate share of the benefits. Also this means that the subjects are to be treated fairly without any discrimination of caste, creed etc.

\[194/i.d.\]
Autonomy (Self rule/ Self governance): Autonomy refers to a person’s independence. As a standard in ethics, autonomy represents an agreement to respect another’s right to determine a course of action. Autonomy refers to an individual’s personal liberty of thought and action, and is justified by respect for persons with the right to determine their own destiny. Autonomy gives research participants the freedom to deliberate and perform chosen acts, and allows for special measures to protect the interests of those whose autonomy is diminished. Respect for another’s autonomy is fundamental to the practice of health care. The agreement to respect autonomy involves the recognition that clients are in charge of their own destiny in matters of health and illness. The consent process implies that a client may refuse treatment. Researcher should respect a person’s freedom of thought and action. Researchers must respect rights of participants who can make decisions to do so. Researchers must also take special measures to protect vulnerable participants whose freedom to make choices is limited, or those with no capacity to choose.

Fidelity: Fidelity refers to the agreement to keep promises. It is an obligation to be faithful to commitments and promises. The vulnerability of the research subjects increase their dependency thus making the researcher’s faithfulness to that relationship essential. A commitment to fidelity explains the reluctance to abandon clients, even when disagreement arises about decisions that a client may make. The standard of fidelity also includes an obligation to follow through with the care offered to clients.

This would be incomplete without mentioning the following 12 principles given explicitly by ICMR. They are:

i. Principles of essentiality
ii. Principles of voluntariness, informed consent and community participation
iii. Principles of non-exploitation
iv. Principles of privacy and confidentiality
v. Principles of precaution and risk minimization
vi. Principles of professional competence
vii. Principles of accountability and transparency
viii. Principles of the maximization of the public interest and of distributive justice.
ix. Principles of institutional arrangements
x. Principles of public domain
xi. Principles of totality of responsibility
xii. Principles of compliance.

The ethical complexities involved in clinical trials of HIV vaccine are becoming more and more challenging day by day since the population group in which the vaccine is getting tested is among the most disadvantaged, poor, oppressed people. International HIV vaccine trials are large and complex undertakings and are directly affecting hundreds of thousands of human lives. These ethical issues involved are so complicated and are difficult and open to varied interpretations. This is because, the science involved is complex, difficult and rich with ambiguities. The nature of HIV, its transmission, pathogenicity, epidemiology, political and social reactions give rise to some ethical quandaries which are unique to HIV vaccine trials. Thus these ethical difficulties need to be thoughtfully and thoroughly assessed as these have emerged in a scale never before faced by biomedical researchers.

It is our duty to ensure that the individual rights and well being of all those subjects who volunteer for the trials will be protected to the fullest extent possible, as required by The Nuremberg Code and WHO/ CIOMS International Ethical Guidelines For Biomedical Research involving Human Subjects. Failing to comply with these guidelines would be a violation of internationally accepted ethical codes.

At the very onset, numerous questions are raised which throws light on the ethical complexities of the HIV vaccine research. The ethical complexities stem
from the volunteers view point as well from that of the researcher/ sponsor. Under mentioned are few from a volunteers view point as ethicist Thomas Kerns express his concerns:

- Why should any sensible, even moderately self – interested man ever consent to participate in experiments which entail the potential for so much risk to their personal health and their social well being, and which have so little potential for any personal benefit?
- Might the reasons be that, perhaps they simply have not been made fully aware of the degree of risk involved?
- Perhaps they were not fully informed by the researchers?
- Or, if they did participate in an “Informing Session” perhaps the information they were given did not register with them;
- Perhaps they did not fully understand what they were told;
- Or, perhaps they were, in some subtle way, deluded into thinking that there would be some potential benefit to them in the form of possible protection against HIV infection?
- Perhaps they were offered some inducement, by the research sponsors, to participate?
- Perhaps they were in some way persuaded, or possibly even coerced into participation by someone at the institution where the research is being conducted.
- Perhaps they were pressured or coerced by government or community leaders, or perhaps even by someone else close to them, such as a spouse or boss.
- When there is so much to potentially lose, and almost no likelihood of any personal benefit, why should anyone choose to volunteer for such trials?
Thomas Kerns could not but wonder the real motive of the volunteer in such trials.\textsuperscript{195}

Further, there are issues related to obtaining ethically appropriate informed consent from prospective candidates. Also there are problems with improper inducement of volunteers to participate in the trials, issues related to problems of compensating volunteers for injuries suffered as a result of their participation in the studies. Thus from the perspective of researcher/sponsor the issues are as follows:

\begin{itemize}
  \item How will researchers be able to execute ethically adequate informed consent procedure, when the amount of information necessary for subjects to understand is so great and the nature of it so complicated?
  \item How will researchers be able to provide information about the nature of vaccines and immune responses to people (particularly in developing nations) who may hold conceptions of disease and disease causality that are quite different from the conceptions of disease held by the researchers?
  \item How can research sponsors properly assess whether prospective subjects have understood enough information so that they are able to give adequately informed consent?
  \item How can research counselors effectively counsel subjects to not engage in risky behaviors when they themselves realize, at some level, that the research protocol itself requires that subjects do engage in those risk behaviors?
  \item What are some of the potential harms that might reasonably be expected to accrue to subjects who participate in these trials, and what are some
\end{itemize}

benefits they might theoretically expect which could counterbalance the risks they are taking?

- What is to be done about protecting volunteer's confidentiality, and how can these volunteers be protected against unfair discrimination based on their new sero status which (often) result from their participation in the studies?

- And underlying all these specific questions are deeper meta questions, such as:
  
  - Should the main operative ethical principles in this international vaccine research be different in different countries, varying according to the particular cultural standards in each country, or should there be a set of common, agreed upon international ethical standards for the protection of research subjects, applicable to all research protocols regardless of the country in which the research is conducted?  

These questions and numerous others related to them are not easy to deal with nor are the answers to them simple. One might wonder whether the ethical principles in international vaccine trials be different in different countries, depending on the moral and cultural standard of these countries. Whether we should be arriving at a consensus on a set of commonly agreed upon international ethical standards for the protection of research subjects, regardless of the country in which they are conducted? HIV vaccine trials pose ethical perplexities on a scale never before faced by biomedical researchers, and these are complex, powerful and controversial and those ethical difficulties need to be addressed thoughtfully and thoroughly.

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196 Id.
4.23.3.1 How Ethical Is Randomization?

To understand the concept of randomization is very much essential to appreciate the ethical issue raised by it. \textit{Randomization is the process of assigning clinical trial participants to treatment groups.} Randomization gives each participant a known (usually equal) chance of being assigned to any of the groups (1:1). Successful randomization requires that group assignment cannot be predicted in advance.\textsuperscript{197}

The terms \textbf{Randomized Clinical Trials ("RCT")} and \textbf{randomized trial} are sometimes used synonymously, but the methodologically sound practice is to reserve the "RCT" name only for trials that contain \textit{control groups}, in which \textit{treatment groups} are compared with groups not receiving treatment (as in a \textit{placebo-controlled study}). The term "randomized trials" omits mention of controls and can describe studies that compare multiple treatment groups with each other (in the absence of a control group)\textsuperscript{198}

The efficiency of clinical therapeutics can be established in a most valid manner by means of RCT. Ethical standards dictate that patients and clinicians should not consent to randomization, unless there is uncertainty about whether any of the treatment options is superior to the others.

\textbf{(Equipoise)}\textsuperscript{199} Equipoise is the point where there is no preference between treatments, i.e., it is thought equally likely that treatment A or B will turn out to be superior. We have no preference what so ever.\textsuperscript{200} Since in real life settings true

equipoise is rarely present, most randomized clinical trials are faced with challenging ethical dilemmas. Thus, it adds on to the responsibility of the investigator to reduce the tension between science and ethics.

Although the RCT debates the pros and cons of randomized clinical trials, interestingly, much of these literatures predate AIDS, rendering it inadequate in addressing the array of ethical perplexities that accompany HIV vaccine clinical trials.

Theoretically, RCTs are initiated only if there is an uncertainty as to whether any of the alternatives under study is superior. Under traditional ethical paradigms, if the clinicians have any preference for one of the treatment options, they are obliged to inform patients of their preferred approach and reject randomization. An ethical dilemma arises in a clinical trial when the investigator(s) begin to believe that the treatment or intervention administered in one arm of the trial is significantly outperforming the other arms. A trial should begin with a null hypothesis, and there should exist no decisive evidence that the intervention or drug being tested will be superior to existing treatments or effective at all. As the trial progresses, the findings may provide sufficient evidence to convince the investigator of the intervention or drug’s efficacy. Once a certain threshold of evidence is passed, there is no longer genuine uncertainty about the most beneficial treatment, so there is an ethical imperative for the investigator to provide the superior intervention to all participants.\textsuperscript{201}

Confirmatory Clinical Trials (those intended to validate the results of previous experiments) should not begin with an assumption of equipoise, since prior information about efficacy and safety exists.

Thus there exists an ethical dilemma as we continue to perform clinical trials in the absence of true equipoise. Benjamin Freedman (1987) had argued that the

\textsuperscript{201}Randomised Controlled Trials, \textit{supra} note 8.
absence of expert clinical consensus provides adequate grounds for resolving a research question through human experimentation. He strongly insisted that “...the trial must be designed in such a way as to make it reasonable to expect that, if it is successfully completed, clinical equipoise will be disturbed. In other words, the results of a successful trial should be convincing enough to resolve the dispute among clinicians.”

Thus there exist two types of equipoise. The absence of true uncertainty regarding the relative benefits of alternative therapy is termed *theoretical equipoise*. Presence of disagreement among knowledgeable clinicians and investigators is called *clinical equipoise*. Clinical equipoise refers to the state where clinicians are unsure whether the new treatment or intervention is as good as the standard treatment.

_Peto et al. (1976): “Physicians who are convinced that one treatment is better than another for a particular patient of theirs cannot ethically choose at random which treatment to give: they must do what they think best for the particular patient. For this reason, physicians who feel they already know the answer cannot enter their patients into a trial. If they think, whether for a wise or silly reason, that they know the answer before the trial starts, they should not enter any patients...”_\(^{203}\)

Grady C. re explores these ethical controversies in order to protect the rights and welfare of the subjects:

- **What is the justification for doing a randomized clinical trial?** It is generally believed that an investigator must have a null hypothesis or “clinical equipoise” in order to justify beginning a RCT. There must not exist conclusive evidence to demonstrate that the experimental drug is better than (and/or less harmful than) the

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\(^{203}\) Id.
active or placebo control, otherwise the control group would be assigned to no or less benefit (or more harm). Some argue that equipoise is difficult to maintain as soon as there are even preliminary data on efficacy.

- Does randomization violate the subject’s autonomy and is the appropriate point at which to randomize before consent or after? Does consent to randomize adequately protect the interests of the individual subject? Or, should the subject, in the name of autonomy or justice, be allowed to choose which arm or treatment s/he wants? 204

It is extremely difficult and uncomfortable to conduct experimentation with people. Various methods are suggested to resolve these ethical dilemmas and the method of unbalanced randomization is one of such kind. Most clinical trials adopt balanced randomization, i.e., the subjects are randomly assigned equally to various treatment options. Balanced randomization implies a state of true equipoise. Also it is generally regarded as a preferred allocation scheme in clinical trials, since it optimizes statistical power.

Pacock believed that unbalanced randomization, (where more subjects are randomized to intervention than to control arm) has ethical advantages over the balanced design, since more subjects are allotted randomly to that arm, which is thought to be a superior therapy. This is stemmed from the belief that it would make a trial more ethically acceptable, if one adjusts the randomization ratio according to the attitude of the trial subjects, i.e., the informed subjects have some preferences or concerns about one treatment option. 205

Pacock has shown that even randomization ratios as unbalanced as 3: 1 may be used with little loss of statistical power. Also, considering the fact that subjects

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205 Randomised Controlled Trials, supra note 8.
enter a trial in order to gain access to new therapeutics, acknowledging this
desire in setting an allocation ratio shows greater respect for their preferences.

Another issue that arises is: from whose perspective should the allocation
decision be made? Since the subjects ultimately have to bear the risks of the
experiments, we must aggressively explore those designs in which participants
are involved in the design of the study.

Inputs from those experts who understand the scientific issues are essential. For
e.g. In a Cancer clinical trial, MacKillop et al surveyed expert physicians about
their willingness to participate in specific clinical trials and gave this information to
prospective subjects. They found that the prospective subjects' willingness to
enter the study was heavily influenced by the opinions of physician experts. 206

Only truly informed individuals can make independent decisions. Serious
misunderstandings of biomedical issues on the part of subjects may lead to poor
choices. Investigators have the moral obligation to communicate to the members
of the study population, the basic concepts of randomization, i.e., law of chance –
and assure them that the process of random allocation is not discriminatory.
207 Similarly, inadequate appreciation of personal issues by investigators may
produce inappropriate decisions. When clinicians, investigators and potential
subjects, all have the opportunities to share in the design of clinical trials,
research ethics may be greatly enhanced.

Confidence is the heart of Clinician – Patient relationship; which must be a real
human relationship based on love, caring and sharing. The issue here is , is it
ethical of the clinician to behave as though he has no preference- when actually
this is not the case. Though, the ethical problems of experimenting on people

206 Id.
207 WHO- Ethical Guidelines for Epidemiological Investigations, available at http:
can never be entirely resolved, these are some techniques to minimize the dilemmas and it holds true in case of a HIV vaccine clinical trial. Given a chance, all the subjects enrolled in the study would prefer to be in the treatment arm and not in the placebo arm. Considering the altruistic motives of these subjects in entering this study, it is debatable whether it is ethical of the investigator to randomly assign these subjects to different groups.

4.23.3.2 Is Placebo Control Mandatory?

The use of the word ‘placebo’ in a medical context, meaning innocuous treatment to make a patient comfortable, dates back to at least the end of the 18th century. The interest in placebo effects only began with the widespread adoption of the randomized controlled trial (RCT) after World War II. Since then several trials using placebo as a control group have been carried out. However, its use in certain clinical trials remains one of the debated elements.

Generally, a placebo is seen as an inert substance or procedure and the placebo effect (or response) is something that follows the administration of a placebo. The paradox in this statement lies with the fact that if something ‘inert’ by definition should be unable to elicit an effect, and therefore placebos cannot elicit effects. From the psychological viewpoint, a multitude of mechanisms contribute to placebo effects. These include expectations, conditioning, learning, memory, motivation, somatic focus, reward and reduction of anxiety.

To prove a new treatment effective above and beyond the psychological results of a simple belief in the ability of the drug to cure, a researcher compares the results of the experimental treatment for an illness with those obtained from the placebo. The placebo-controlled trial “is widely regarded as the gold standard for testing the efficacy of new treatments.”

The use of a placebo in clinical research continues to be a topic of debate in the medical community in recent times. Some are of opinion that placebos offend
against the fundamental ethical principle of fidelity. Some argue that the use of placebos is often unethical because alternative study designs would produce similar results with less risk to individual research participants. Others argue that the use of placebos is essential to protect the society from the harm that could result from the widespread use of ineffective medical treatments. In either case, use of placebo involves deception of patients and this raises complex ethical issues.

Freedman (1990) had expressed when the control can be a placebo. They are when situations in which no standard therapy, if the standard therapy is not better than the placebo, if the standard therapy is placebo, if there is doubt regarding the therapeutic advantage of standard therapy or in conditions where standard therapy is unavailable owing to less supply or more cost.

On the contrary, if effective treatment has to be withheld, if side effects are not intolerable for most subjects or consequences for personal health are serious, a placebo control is controversial.

Evidence from many studies in which patients on depressive disorders were subjected to clinical trials showed that, those subjects in placebo arms had committed suicide. These studies were thus declared unethical, because the death could have been avoided by placing the subjects on the standard treatment available since depressive symptoms leading to suicide are a known complication of the disease. Why anyone in their senses ever volunteer to enter a placebo controlled trial instead of taking active treatment?

Critics of placebo-controlled trial or trials that include an untreated control group cite Article 11.3 of the Declaration of Helsinki: “In any medical study, every


\[209\] Id.

patient including those of control group, if any, should be assured of the best proven diagnostic and therapeutic methods and no patient should suffer from unnecessary pain.”

In RCTs, for conditions having no effective treatment, the control regimen with which the new treatment is compared, is warranted to establish the evidence. However, when an effective treatment already exists, it is unethical to create a placebo group that will receive no treatment. In other words, patients are deprived from an already existing effective therapy. The objective of testing such drugs to establish whether the new drug is better in efficacy or safety when compared to the existing drug/s placebo controlled trial is considered unethical.

Another argument proposed against placebo-controlled trials is that they potentially violate the concept of clinical equipoise when proven effective therapy is available. Those who reject the use of placebo-controlled trials argue that they violate the therapeutic obligation of physicians to offer optimal medical care. In other words, they compromise the right of the patient to receive the best care possible and violate the ethical principle of therapeutic beneficence. Furthermore, these clinicians have argued that when proven therapy exists, the use of a placebo-controlled trial lacks both scientific and clinical merit.

Declaration of Helsinki states that the benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. . A 2001 clarification issued states that a placebo control is justified if scientifically necessary with compelling methodological reasons for its use and if there is no risk of serious or irreversible harm.211

In this scenario, if we examine HIV vaccine trials, how can one justify placebo control when there is serious risk and irreversible harm?

The Office for Human Research Protection (OHRP) published guidelines in 2008 for the use of placebo and methods to minimize the risk associated with it.

The guidelines state, “Placebos may be used in clinical trials where there is no known or available (i.e., FDA-approved) alternative therapy that can be tolerated by subjects.” The use of placebos in controlled clinical trials must be justified by a positive risk-benefit analysis, and the subjects must be fully informed of the risks involved in the assignment to the placebo group. Continued assignment of subjects to placebo is unethical, once there is good evidence to support the efficacy of the trial therapy.

CIOMS Guidelines or International Ethical Guidelines for Biomedical Research involving Human Subjects has the view that placebos can be used when there is no established effective intervention. 212

Collaboration of Industry and Regulatory Scientists in US, Europe and Japan formulated International Conference on Harmonization (ICH) which issued the guidance statement about control groups in Clinical Trials. (ICH E10)

There should not be a situation of deception. Placebo controls seem optimal when community is unsure of the risk and benefit. In case of HIV vaccine trials, an active control is not scientifically acceptable substitute for placebo control. A known effective agent cannot be used as control, since such an agent does not exist.

Possible liability may be due to the fact that doctors owe a duty of care to their patients. An investigators chief concern ought to be the health and wellbeing of

212 Id.
his subject. (Principle of Beneficence). In such a scenario, assigning subjects to placebo arm may be negligent. \(^{213}\)

Even in the absence of serious irreversible morbidity or mortality, the placebo subjects may undergo intolerable suffering. Permitting subjects to undergo intolerable suffering is inconsistent with the duty to protect their welfare. Given the fact that the subjects had given voluntary consent does not justify a significant increment of risk to the welfare of placebo subjects.

Methods that can be used to minimize risks associated with the use of placebo are that the subjects with an increased risk of harm from non-response may be excluded. Increased monitoring for deterioration of subjects and the use of rescue medications may be included in the protocol. ‘Early escape’ mechanisms and explicit withdrawal criteria may be built in so that subjects will not undergo prolonged placebo treatment if they are not doing well. The size of the population placed on placebo may be kept smaller than the number in the active treatment arms.

If a placebo is used in a study, the informed consent form must include all of the following information: The subjects must be informed that they may be given a placebo. A clear lay definition of the term ‘placebo’ must be given to the subjects. The rationale for using a placebo must be explained to the subjects. If applicable, the subjects must be informed of any viable medical alternatives to being placed on placebo. The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained. Any consequences of delayed active treatment must be explained to the subjects.

A statement in the risk section of the consent that the condition of the subject may worsen while on placebo should be included.

\(^{213}\)Placebo Controlled Trials, supra note 210.
A discussion in the benefits section that subjects who receive placebo will not receive the same benefit as those who receive active treatment if that treatment is effective should also be included. Just including all above information in consent form of HIV vaccine clinical trial will shift the ethical responsibility on the shoulder of investigator? The ethical perplexities are many fold as the subject may engage in high risk behavior believing that he is being protected by the vaccine being administered, not aware that he is administered placebo.

4.23.3.3 Why Should Any Healthy Individual Volunteer To Participate In HIV Vaccine Trial?

The enormous potential benefits of HIV vaccine are accompanied by difficult questions and significant risks. Beyond the physiological unknowns are social complexities. The lengthy trial and error progress of HIV vaccine trials have created many unique issues that are all intertwined as they have never been earlier. It is quite likely that the HIV vaccine trials require a series of human trials requiring tens of thousands of volunteers in several countries. Nobel laureate and head of AIDS vaccine initiative, David Baltimore said repeatedly that this battle of human kind with HIV vaccine would take many years, a lot of money and many people.214

Individuals often participate in clinical trials to seek new therapies and free medical treatment for their illnesses. However, little is known about the motivations of healthy individuals who volunteer for clinical trials of HIV vaccine. A unique set of social risks has presented itself in the testing of HIV vaccine. Many of these potential harms have to do with the motivation of volunteers to participate in clinical trials of HIV vaccine.

It needs more than courage and probably altruism to participate in a trial despite knowing physiological risk of being injected with an experimental product, face possible social discrimination and the fact that their participation may make them

less likely to benefit from a vaccine, when it is eventually licensed. A lot of effort has been undertaken to identify the good reasons an ordinary citizen might have for volunteering in these trials. Few of the motivators identified are altruism, money, medical care, chance of protection etc. High risk community were always more than ready to participate in trials of HIV vaccine.  

Altruism is probably the real motivation for some volunteers. A study was conducted at Los Angeles on 58 subjects of mean age 36 years. The objective of the study was to explore the perceived motivators and barriers for participation in HIV vaccine trial from the perspective of low socio-economic Latino & American communities at elevated risk for HIV. The perceived motivators and barriers to HIV vaccine trials in rank order are enumerated in the table below.  

Increasing social network was also identified as a perceived benefit in a study. It was a mix of optimism, altruism and hope for personal benefit that had made it

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possible for the National Institute of Allergy and Infectious Diseases (NIAID) to recruit over 4800 Americans into a cohort being readied for HIV vaccine trials.  

Perceived motivators and barriers to HIV vaccine participation in rank order:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Motivators</th>
<th>Barriers</th>
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<tbody>
<tr>
<td>1.</td>
<td>Protection against HIV infection</td>
<td>Vaccine induced HIV infection</td>
</tr>
<tr>
<td>2.</td>
<td>Free insurance / Medical care</td>
<td>Physical side effects</td>
</tr>
<tr>
<td>3.</td>
<td>Altruism</td>
<td>Uncertainty about vaccine efficacy</td>
</tr>
<tr>
<td>4.</td>
<td>Monetary Incentives</td>
<td>Uncertainty about other vaccine characteristics</td>
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<tr>
<td>5.</td>
<td></td>
<td>Mistrust</td>
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<tr>
<td>6.</td>
<td></td>
<td>Low perceived HIV risk</td>
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<tr>
<td>7.</td>
<td></td>
<td>Study Demands</td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td>Stigma</td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td>Vaccine induced HIV sero positivity</td>
</tr>
</tbody>
</table>

**Protection against HIV infection** was raised as a motivation for participating in HIV vaccine trial in all groups. An IDU reported: “I would go to a trial to prevent me from getting HIV”. A study conducted in Brazil showed that the study participants were primarily motivated by personal benefits when volunteering for HIV vaccine clinical trials.

**Free Insurance and Medical Care ranked** second in the afore said Los Angeles study. When asked, what would be a good incentive for trial participation, one subject answered, "May be life insurance policy, because, if I die, my family can use it." Another explained, “You can get sick or can have side effects. If it happens----it is important for me having a clinic----that will pay for the medication or treatment you need.”

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A study funded by Ontario HIV treatment network (OHTN) had assessed motivations to participate, had explored reasons and concerns for declining to enroll in an HIV vaccine trial. A few protection motivators identified were

- “Because I think I am at risk for HIV/AIDS.”
- “To get extra protection against HIV.”
- “To protect my partner against HIV.” \(^{223}\)

**Altruism**

Volunteers may be altruistic that they are ready to accept the physiological risk of being injected with an experimental product and face possible discrimination.\(^{224}\) Altruistic intentions were raised as a motivation for participating in an HIV vaccine clinical trial in 4 of the 6 groups. \(^{225}\)

In a study conducted in Thailand among participants of phase I and II HIV preventive vaccine trials, altruistic motives for interest was ranked highest. \(^{226}\)

The single reason identified by Dr Sanjay Mehendale was altruism among all his HIV vaccine trial participants. As the principal researcher in all Indian HIV vaccine trials his findings hold supreme importance. According to Dr Mehendale “….to do good for society. They cared to participate for a social cause. There

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\(^{224}\) C. Collins, supra note 221.

\(^{225}\) P.A. Newman, supra at 219.

were a few who had someone in the family who was affected by HIV... who felt that this was an indirect way of helping them."227

Another study conducted in South India on perceptions of society about participation in future HIV vaccine trials, altruism and desire to have a protective vaccine for the future ranked high. 228 Results of a study involving 66 police officers in Tanzania showed that altruism was the primary motive for enrolling in the trial. 229

A few of the altruistic motivations verbalized are as follows:230

“To help end HIV / AIDS epidemic “

“To help my community “

“To benefit humanity.”

“I feel like I have a moral obligation to participate in these trials just because, if no one does, they will never get anywhere. “

Monetary Incentives also are not insignificant in vaccine research. Thirteen studies involving 2000 healthy volunteers were studied for various reasons on self reported motivation to participate in clinical trials. It was observed that financial incentive was the primary motive for healthy volunteers to participate in clinical trials. Further, other reported motivators include:

230 P.A. Newman, supranote 223.
• Contributing to science and health of others.
• Accessing ancillary health care benefits.
• Scientific interest or interest in the goals of the study.
• Interest in meeting people.
• Curiosity.  

A thesis in China concluded that financial rewards are the priority consideration and it remarkably influences to motivate the healthy volunteers. However a study conducted on overall effectiveness ratings of motivators, the most effective motivator being a treatment that represents an improvement. This was followed by the convenience of the trial site, the prospect of receiving a free treatment, the number and frequency of site visits and short trial duration. Further they found that, in urban settings, compensation was a motivating factor as compared to in rural settings, altruism was the driving force among people who are willing to go out of their way to understand a disease or do something to give back.

One response was “If you offer people enough compensation, they will do it. I think people would do it just for money”.

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A few other responses were:

“One of my close friends died and I was with him until the end. If my participation can prevent even one person from being infected, then it’s all worthwhile.”

“Even though I know my chances of significant side effects or reactions are minimal, it’s still a little overwhelming. In some small way I think it puts me in touch with the apprehension, people who are HIV positive feel.”

“I think AIDS is every one’s problem. I am at no risk myself, but I want to be a part of the solution.”

“Few volunteers mentioned their concerns about a perceived lack of government involvement as a motivation for their participation.”

“Because my doctor asked me to … (Provider recommendation).”

Kerns believes and advocates that the money paid to volunteers must be extremely negligible or else it would violate the undue inducement clause of the International Ethical Guidelines. 235 The same applies for medical care also. Researchers must also be on guard against undue influence and undue inducement to participate. An inducement is defined as an offer to a person of something of value in exchange for his or her agreement to do something that he or she might not do without the inducement. Cash payment can be considered as an example for inducement. A cash payment so large that it overwhelms other considerations – e.g.: risk / benefit assessment – in the decision to be or to continue to be a research subject is called an “undue inducement.”236

Guideline 4 of the International Ethical Guidelines addresses the issue of undue inducement.

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236 Id.
Subjects may be paid for the inconvenience and the time spent and should be reimbursed for expenses incurred, in connection with their participation in research; they may also receive free medical services. However, the payments should not be so large or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment.

The commentary on Guideline 4 says that “the payments in money or in kind to research subjects should not be so large as to persuade them to take undue risk or volunteer against their better judgment.”

However there exists very narrow demarcation between suitable recompense and undue inducement. How a person views monetary or access to medical care differs from person to person. Since majority of these trials are conducted in underdeveloped countries, almost any amount of money paid or almost any medical care might constitute undue recompense, because of the poor economic conditions. In some communities, it would be difficult and perhaps impossible for researchers to satisfy the requirement to avoid undue inducement. If they cannot fully satisfy that ethical requirement, what then?237

The use of payments to encourage participation in research has been termed a “paradox”. Unduly large payments to encourage participation may constitute undue influence or coercion. The participants in an HIV vaccine are in many ways different from other vaccine trial participants. Many of them are of lesser educational background than the researchers. They are dealing with a disease that is invariably fatal. Majority do not have access to medical care other than that which is offered through the trial participation. In such a scenario, any payment may represent a significant amount of income.238

4.23.3.4 Informed consent issues in HIV Vaccine Clinical Trials:

In ancient Greece patient participation in decision making for medical treatment was considered undesirable. It was generally accepted that the physician’s primary task was to inspire the confidence of the patient in the treatment. Any disclosure of possible difficulties might erode patient trust. Later, during medieval times, medical writing encouraged doctors to use their conversations with patients as an opportunity to offer comfort and hope while emphasizing the need for the doctor to be manipulative and deceitful. During the Era of Enlightenment, new views emerged stating that patients had the capacity to listen to the doctor, but it was still felt that deception was necessary to facilitate patient care. During the 1800’s the medical profession was split over whether to disclose a dire prognosis to a patient. However, most physicians of the time argued against informing patients of their condition.\textsuperscript{239}

Informed consent is the most critical aspects of clinical trial, which requires the willingness of a participant to undertake the risks involved on participation in the experimentation, a decision which is taken after analysing the risks and benefits of participation in the clinical trial. Though this is a common aspect in clinical trials, the participant of a HIV preventive vaccine trial, will only face the risks associated with the participation, than any direct or individual benefits associated with it.

In clinical practice, the doctrine of informed consent rose to dominance during the course of the 20th century. It replaced a medical ethos founded on trust in physicians’ decisions—often on the assumption that “doctor knows best”—with an ethos that sought to put patients in charge of their own care. In medical research on human subjects, informed consent requirements gained prominence

\textsuperscript{239} S. Arthur, THE LAW OF HOSPITAL AND HEALTH CARE ADMINISTRATION, p. (2\textsuperscript{nd} edn,1988).
in reaction to abuses\textsuperscript{240}. This term was first used in a 1957 medical malpractice case by Paul G. Gebhard\textsuperscript{241}. Historically the issue related to informed consent was also referred in the Nuremberg Trial\textsuperscript{242}.

Over the last 150 years, the concept of physicians establishing a "standard of care" has gradually been replaced by the idea that the well informed patient can be the master of his/her own body\textsuperscript{243}. The physicians’ duty to disclose is the main component of Informed consent.

Informed consent (IC) is a cardinal principle in research with human beings. It is a central tenet of research ethics reflected in documents and guidelines dating back to the Nuremberg Code (NCPHSBBR 1949), through the Declaration of Helsinki (1964) and its versions, the Belmont Report (1979), the Council of Europe (1997) and the Nuffield Council on Bioethics Guidelines (2002)\textsuperscript{244}. IC is a cornerstone of clinical trials and is a fundamental requirement for participation in studies to test HIV/AIDS vaccines.

Obtaining informed consent is a much more complex task than getting few papers signed. Ensuring informed consent and voluntary participation is one of the most complicated aspects of conducting any clinical trial. The complexity

increases many fold as many of these trials are often conducted in resource poor settings, thus posing greater ethical and practical challenges.

Firstly, HIV/AIDS remains highly stigmatized in many of the settings where clinical trials of prevention trials are being conducted. Often the participants are from marginalized or stigmatized community because of factors such as gender, sexual orientation, poverty, and education, use of injecting drugs or sex work. Secondly, these trials involve many sensitive issues, including sexuality, trust and gender based power dynamics. Finally, since these trials are mostly conducted in areas of high incidence of HIV, researchers must recruit healthy volunteers who are economically and socially vulnerable, but are at substantial risk of HIV infection.

It has been identified that introducing HIV vaccine trials to research naïve populations, especially to those in resource poor settings in developing countries, may pose many obstacles. Though the aim of informed consent process is to inform potential participants, its efficacy is vital to protect the vulnerable populations. The responsibility vested on researcher is compounded in these trials as they are not to exploit or increase the vulnerability of these otherwise under privileged population.

IC is premised on the notion that individuals have the right and the ability to make decisions in their own interest and to act upon them. Respect for autonomy and self-determination, based on the belief that a person has a right to bodily integrity, is a main principle underlying informed consent doctrine. This in turn is based on the fundamental principle of respect for persons. But in many settings, important decisions are not made by individuals alone. Decision making process is influenced by many people. It could be another family member, employer, community and especially in case of women, the decision may be made by men. The participants exist within a complex web of relationships that may have a strong influence on their perceptions and decision making. This

\[\text{supra note 195.}\]
complexity is exacerbated by the stigma, judgment and fear inherent in HIV vaccine trials.

Most participants and occasionally the researchers regard IC as merely a bureaucratic requirement for enrollment in order to comply with legal and regulatory codes. In such a setting, IC takes place as a onetime one way communication which once furnished is rarely revisited.

But IC has a major role in recognizing and compensating the inherent conflict of interest between the researcher and the prospective participant. Thus, it provides both substantive and procedural protection for the subjects involved in human research.

Substantively, IC protects an individual's right to exercise sovereignty over one's own body and to be free from assaults. Procedurally, IC protects the interest of the subject where there is a conflict of interest with that of the researcher. This is because, though the researcher may claim to have the best interest of the subject in mind, he may as well have his personal and professional interests that are conflicting with those of the subject. The often paternalistic role adopted by the researcher makes the scenario further worse as the researcher may consider that he is acting on the best interest of the patient.

According to Stanford Professor David Katzenstein, “researchers often treat potential volunteers like patients, who mean deciding best for them…. .” Another Physician from Ghana, Dr Peter Lamptey noted, “if you interviewed the people in the study, most wouldn't understand to what they had really consented.”

The emerging view is that IC is an agreement between the researcher and the participant that should be based on dialogue and to be reinforced through an

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David Katzenstein is associated with AIDS vaccine trials in conjunction with the University of Zimbabwe and Peter Lamptey is Head of AIDSCAP programme, Ghana.
ongoing process throughout the trial. Irrespective of these view points, informed consent is based on the following three components: Disclosure (Providing information), Appreciation (participants understanding) and Voluntariness (the ability to enroll in a trial and leave it at ones will).

The four essential components incorporated in IC as given by Lindegger are i) disclosure of all relevant information about the research ii) comprehension by the prospective participant of this information to make informed decision iii) freedom from all coercion of the prospective participant iv) explicit and formal consent by the participant, usually in written form.\textsuperscript{247}

IC is the first of the 10 principles of Nuremberg Code. Nuremberg code was formulated in 1947 and it states that voluntary consent of the human subject is absolutely essential “… the need to respect the humanity and self determination of all humans is central to the ethos not only of medicine and human experimentation but of all civilized societies.”\textsuperscript{248} The code grew out of Nuremberg Trials held in 1945 by the Nazi physicians during Second World War and is thus intended to prevent all types of medical abuses.

The Nuremberg Code guarantees that subjects should be so situated as to exercise free power of choice. However, the very nature of the subject’s life threatening disease, their low education, the researcher’s offer of payment and lack of alternative medical options denied these subjects the ability to make any informed choice. Thus the consent obtained from them is purely “illusory.”\textsuperscript{249}

IC has been considered as the foundation of ethical research on human beings from the time of Nuremberg Code and it has been articulated with the same weightage in the Declaration of Helsinki, the Belmont Report, and the Guidelines

\textsuperscript{249}S. Loue, supra note 238.
of the Council for International Organizations of Medical Sciences. The International Committee on Harmonization (ICH), the US Food and Drug Administration (FDA) and the US Office of Human Research Protections (OHRP) are few international bodies providing guidance and regulations on the conduct of IC. The point 12 of UNAIDS guidelines for HIV research reads:

Independent and informed consent for participation, based on complete accurate and appropriately conveyed and understood information as well as its consequences, should be obtained from each individual who is legally competent to give consent. Consent should be obtained for screening for eligibility for participation in an HIV preventive vaccine trial, and before a participant is actually enrolled in a trial. Throughout the trial efforts must be made to ensure that participants continue to understand the consequences of participation and that they participate freely as the trial progresses. Informed consent, with pre- and post-test counseling, should also be obtained for testing HIV status before, during, and after the research.

This was further elaborated in the document as follows:

A process of consultation between community representatives, researchers, sponsors and regulatory bodies should be used to design an effective informed consent strategy and process. Issues such as illiteracy, language and cultural barriers and diminished personal autonomy should be addressed in this consultative process. In some communities, special efforts may be required to achieve adequate understanding of cause and effects, contagion, placebo, double blind and other concepts involved in the scientific design of the research.

Further, the guidelines state that informed consent must be obtained at all stages of the trial — screening, testing, vaccination, repeat HIV testing and any other

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250 B.M. Meier, supra note 246.
examinations involved. Principal investigator is responsible for providing information in a manner that is understandable to the research participant. Enough time is given to assimilate the information and to decide whether to participate or not. This would maximize autonomy of the participant.

Prospective participants should also be informed that:

- they have been selected for participation because they are at relatively high risk of HIV infection;
- they will receive advice and access to means to reduce their risk (for example, condoms), but that some of the participants in the trial may nonetheless become infected as a result of their high-risk status;
- only some of the participants will receive a vaccine, while others will receive a placebo;
- the effectiveness of the vaccine to be tested in preventing HIV infection or AIDS disease is not known.

Prospective participants must also be informed of the specific risks of physical, psychological and social harm associated with the vaccine, only some of which are currently known or anticipated — such as a positive HIV test as a result of vaccination. Thomas Kerns is of opinion that the prospective candidates should be informed of their rights as participants in the trial and responsibilities as well. He had formulated a “Bill of Rights and Responsibilities”. 252

As important as the content of what they must be told, subjects must also be able to competently deliberate and freely choose “without the intervention of any element of force, fraud, deceit, duress, overreaching or other ulterior form of constrain or other ulterior form of constraint or coercion.”253

Lastly, participants must be informed of the nature and duration of care and treatment that is available to them, if they become infected with HIV during the

252 T.A. Kerns, supra note 195.
253 Nuremberg Code, supra note 248.
course of the trial. This latter point is part of an ongoing controversy regarding the level of treatment to which participants in trials are entitled. For example, triple therapy with antiretroviral drugs is not routinely available in South Africa, but it is provided internationally. A further question arises as to the potentially undue influence to participate in trials when drugs that are not routinely available are provided to participants.

The process of informing prospective volunteers of the nature of research in which they will participate has undergone several changes. Efforts have been undertaken to achieve consensus in the International arena about these issues. 254 HIV vaccine trials in Haiti had excluded less educated individuals in an effort to ensure participant understanding. Another vaccine trial in Haiti had demonstrated increased understanding of volunteerism correlating with that of participant’s recognition of risk. 255

ICH guidelines suggest that the principle investigator is responsible for ensuring that “information in the consent form and any other written information was accurately explained to and apparently understood by the subjects....” (ICH 1996:16). It is important to note that ICH guidelines offer no specific guidance or standards for assessing this explanation or understanding.

Similarly, the United States Code of Federal Regulations, which applies to studies conducted under the auspices of the US FDA, states that, “the information that is given to the subject or to the representative shall be in a language understandable to the subject.” This too offers nothing about the researcher’s responsibilities for ensuring study participants comprehension, (OFR 2002).

There is a distinction between the application of doctrine of informed consent in research context and in treatment context. The law as it relates to the failure of investigators to disclose risks in the research context developed statutorily, rather than judicially. This fundamental distinction in the doctrine of informed consent between treatment and research is central to the absence of judicial recourse for research participants who are harmed as a result of investigators’ failure to disclose the risks of research. Scientific misconduct or fraud in clinical research, which may involve fabrication of informed consent documents, or non-disclosure of risks can vitiate the informed consent and give rise to a judicial recourse against the researchers and sponsors. HIV vaccine trials are conducted on healthy individuals who may not gain from the participation in the research, as such the chances of fraud or misconduct could be high in HIV vaccine clinical trials. Scientific misconduct is a violation of the standard codes of scholarly conduct and ethical behaviour in clinical research, which may not be intentional and may be the result of poor management of the trial, failure to follow established protocols whereas fraud is intentional deception, or breach of trust made for personal gain or to damage another individual.

A researcher conducting a trial on participants without obtaining a proper informed consent as required under the laws could be charged of committing a tort of battery. A battery is the intentional and direct application of any physical force to the person of another.


Placebos and randomisation are conceptually challenging issues, which must be explained to the participants to understand the research in a manner to ensure that explanations are clear and translations are appropriate. In Thai –HIV Vaccine clinical trial, when the U.S. and Thai consent forms were compared, it was determined that the Thai form was less clear in its definition of a “placebo”.260

Any deception perpetuated by the investigator regarding the purpose, risks or benefits of the experiment would compromise subject autonomy and undermine the subject’s self determination. This not only results in violation of the doctrine of informed consent, but also could result in cognizable psychological and emotional harm to the subject regardless of whether they experienced any physical harm or not.

Further, Jennifer Berman in his article argues that the researchers have the ethical and legal obligation to discuss with trial participants what steps will be undertaken to ensure that they gain access to any vaccine that result from their participation.261 This is rather novel in that it is an expansive interpretation of the doctrine of informed consent. Here, the researchers are required to discuss not only with the participants but also with representatives of the country hosting trials, prior to commencing trials. Any such an agreement could be considered as an enforceable contract which would prevent unfair exploitation of the trial participants. This would promote the value of autonomy that informed consent aims to maximize.262

Informed consent is a complex and, as has been noted, somewhat idealized process. Certain technical features of vaccines are known and understood only

262 Id.
by specialists. Often the trial participants find it difficult to understand dense, visually complex, highly technical text presented to them. Translation may make the terms and concepts even difficult to understand. Adding to the complexity of the scenario is when local languages have no appropriate terms for key research concepts and the setting is of little or no literacy.

In addition, the reasons why certain levels of care are available in one country and not another requires a view of comparative economics that also has a small audience. In many ways, the formalistic requirements of IC are almost impossible to meet, a reality that necessitates a careful analysis of the aims of IC as an ethical rather than formalistic condition.

IC concept broadly falls into the realm of preventive ethics, which in turn identifies the potential areas of ethical concern or conflict in advance and prevent them from arising. Thus IC has two sides: the legal and the moral.\textsuperscript{263} IC in an institutional sense refers to the application of legal side based on a defensive medical approach, whereas the autonomous sense denotes the mutual understanding between the researcher and the participant. Thus the shared decision making can be considered as a higher level of moral commitment. The core belief is based on the assumption that research participants are autonomous individuals with an intrinsic right to make decisions about their bodies and their lives.

HIV vaccine trials recognize the legal and moral aspects of IC. Legally, IC is a formal record of a person’s willingness to participate in a clinical trial. Ethically, it is a decision – making process during which a person who is thinking about volunteering collects and then weighs the available information.\textsuperscript{264} The success of these trials depends not only on the legal protection of both the parties involved, but into autonomy of participants and into informed decision making.

\textsuperscript{263} B.M. Meier, supra note 246.
Thus, HIV vaccine trials must be based on sound ethical considerations. Further, it is a crucial protection for study participants and researchers in HIV vaccine trials.

Why should any otherwise healthy individual ever consent to participate in the HIV vaccine clinical trial full of uncertainties and scary details? These concerns were shared by ethicist Thomas Kerns in his work. 265

Let's see how a prospective participant makes a decision to participate in research and how and why they agree and continue to participate. This decision making has cognitive, emotional, and motivational and value based components. All these play a major role in the decision to participate.

In addition to this, an array of other factors like medical benefits, monetary benefits etc may also influence an IC decision.

It is human tendency to try to please others, especially those perceived as having power or control, either consciously or deliberately. In this aspect, social desirability may influence IC process and its authenticity significantly. Thus, volunteers in HIV vaccine clinical trials may behave and respond in ways they presume to be befitting the social norms for the situation, in order to create an impression and winning the favors of the researchers. In other words, they try to be ‘good subjects’. In the IC scenario, though the participant says that he has understood and he feels free to withdraw from the trial any time, he may not feel or believe any of these. Participant’s perceptions or experience with authority may make them feel unable to leave a trial even if they are assured repeatedly that they have a right to do so. This raises doubt about the true ethical nature of IC, though the legal requirements are fully met. The only way to counter this is by empowering the participants through Community Advisory Boards.

Understanding/ Comprehension of participant is another core issue in IC. Since understanding is a very elusive concept, it is extremely difficult to assess the

265 T.A. Kerns, supra note 195.
nature and level of one’s understanding. It is comparatively easy to assess the adequacy of the information disclosed, but equally difficult to assess whether and how the information and its implications are truly understood. While the legal requirement of disclosure of comprehensive information may have been satisfied, the ethical requirement of understanding in order to make decisions in one’s own best interest may not. 266 Since the declared understanding on the part of research participants is not a guarantee of their true understanding, there exists a danger that the IC may be manipulated and the autonomy of individuals may be compromised. Thus the researchers of HIV vaccine trials are vested with extra responsibilities to guarantee that the participants have sufficient understanding to make fully informed decisions.

In a study designed to assess the understanding of research participants in South Africa, it was found that measured levels of understanding are dependent on the tools used. In this study, four measures of understanding were compared. 267

Understanding of technical, product and methodological information is mandatory. The researchers should ensure the understanding of participants of the following: the rationale for the study (such as the reason for developing a local HIV vaccine); technical issues (of the nature of the products); technical consequences (possible side effects); unknown outcomes (that there is no guarantee that HIV vaccines will offer any protection against HIV infection); methodological issues (placebo and randomization); practical aspects involved in personal participation (e.g., the kinds of procedures and tests that participants will undergo); the costs and benefits of participation in the study (e.g., reduced benefits from future vaccines or access to treatment); and the personal implications of participation in the study (e.g., discovery of one’s HIV status and

266 B.M. Meier, supra note 246.
the psychosocial effect of this knowledge). The amount of explanation required to make the clients understand the basic difference between vaccine induced sero positivity and virus induced sero positivity and the difference between both is insurmountable. This leaves the researcher with the following question: Will it actually be possible to fully inform all prospective subjects?

There is no surety that even if a subject may be able to recall the finest details of information provided to him by virtue of his short term memory, it may not involve understanding. Thus, the legal requirements for indemnity may be satisfied, but not the ethical ones. Adding to the complexity of issues are emotional factors of the participant. Anxiety arising from excess of information or apprehension of risks may hamper understanding.

In *Salgo v. Leland Stanford etc. Bd. Trustees*, the medical malpractice case where the term informed consent was used, the plaintiff contented that he was not informed of anything in the nature of an aortography was to be performed. The respondent doctors admitted that that the details of the procedure and the possible dangers there from were not explained. The court observed that it is the duty of a physician to disclose to the patient "all the facts which mutually affect his rights and interests and of the surgical risk, hazard and danger, if any. A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment. Likewise the physician may not minimize the known dangers of a procedure or operation in order to induce his patient's consent. At the same time, the physician must place the welfare of his patient above all else and this very fact places him in a position in which he sometimes must choose between two alternative courses of action. One is to explain to the patient every risk attendant upon any surgical procedure or

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268B.M. Meier, supra note 246.
operation, no matter how remote; this may well result in alarming a patient who is already unduly apprehensive and who may as a result refuse to undertake surgery in which there is in fact minimal risk; it may also result in actually increasing the risks by reason of the physiological results of the apprehension itself. The other is to recognize that each patient presents a separate problem, that the patient’s mental and emotional condition is important and in certain cases may be crucial, and that in discussing the element of risk a certain amount of discretion must be employed consistent with the full disclosure of facts necessary to an informed consent. However the capability of the patients to make a risk benefit analysis of the treatment varies from the social and educational background of the patients.

In Cobbs v Grant, the California Supreme court has observed that a physician’s duty to disclose is not governed by the standard practice in the community; rather it is a duty imposed by law. A physician violates his duty to his patient and subjects himself to liability if he withholds any facts which are necessary to form the basis of an intelligent consent by the patient to the proposed treatment.

The patients cannot be required to accept treatment no matter how painless, beneficial and risk free the treatment may be and no matter how dire the consequences of a refusal of treatment may be. This proposition is recognised as both an ethical principle and a legal rule, and is founded, ultimately, on the principle of respect for the patient’s autonomy, or, expressed in more compelling terms, on the patient’s "right" to self-determination. This ethical principle affirms respect for persons by giving legal protection to a patient’s bodily integrity, irrespective of their mental capacity.

270 Id
The researchers thus have the added responsibility to ponder the following points: what kinds of information should be given to the clients to optimize understanding? How can the information optimize decision making? How can personal understanding of this information and its implications best be facilitated and assessed? How can the IC process, including voluntary participation and retention in the study, be evaluated? Some suggestions by Lindegger are: ensuring that the participants have a degree of value match with the participants, inviting the participants to speak to family, friends and other volunteers about the personal meaning and impact of the decision to participate in the research before making decisions, requesting participants to explain other prospective participant of the nature of the study.273

Belmont report as old as 1979 had identified this fact:

“If reasonable participants do not have an adequate understanding of that to which they are consenting, given their own concerns and situations in life, then they cannot be said to have given informed consent.....even if they possess all the information relevant to decisions of a hypothetical “reasonable person”.”274

In this complex scenario, Lindegger has proposed that two aspects of understanding have to be carefully considered. Firstly, it involves comprehension of essential technical / objective information and secondly is optimizing personal decisions by understanding of essential personal issues and implications of research /subjective elements. They have further proposed two principles to be adhered in HIV vaccine trials: one is the principle of respect for individuals, protection of their rights and autonomy. Also, in particular contexts where cultural norms define the person as someone in relation to others, it will also be

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necessary to establish which other members of the community should be consulted and how they might be incorporated into IC process. Further, attention should also be given to issues such as the right to withdraw from the trial without any prejudice/disadvantage.

The HIV Network for Prevention Trials (HIVNET) developed a prototype IC process for a hypothetical future HIV vaccine efficacy trial in order to assure that participants in future trials understand the implications and potential risk of participating. Such procedures must be developed in order to ensure that valid IC is obtained from participants in HIV vaccine efficacy trials. Australia had drafted a vaccine trial consent form which contained over four pages of detailed and complex information, later proved to be highly ineffective.

For the AIDS vaccine Trials at the National AIDS Research Institute (NARI) in Pune and Tuberculosis Research Centre (TRC) in Chennai, IAVI and its partner, ICMR put together great efforts to prepare the consent form.

In the absence of consistent regulations and guidance, informed consent documents and processes can be influenced heavily by ethics committees or Institutional Review Boards (IRBs). IRBs in many settings may work with little or no transparency, standardization and accountability. In the context of large international and multisite HIV vaccine trials the IRB members may have little or no familiarity with the trial setting.

Few ethicists consider that the sexual partners of participants are also to be considered as subjects and IC has to be obtained from them. Enrolling both

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275 T.A. Kerns, supra note 195.
partners in trials pose problems of its own. In large scale multicenter studies, enrolling both partners may not be feasible. Further, many participants may have complex partnerships which they may not wish to acknowledge, like multiple partners, extramarital relationships, commercial sex worker partners. Addressing these issues is complex.

4.23.3.5 Confidentiality Issues In HIV Vaccine Trials:

Confidentiality refers to the legal and ethical obligation that arises from a relationship in which a person receives information from or about another. The recipient has an obligation not to use that information for any purpose other than for which it was given. Confidentiality refers to the right of the trial participants to protection from unauthorized disclosure of personal information to third parties during data collection, storage, transfer and use.

Confidentiality in the context of HIV research is of prime importance. This emphasis is based on the ethical principle of autonomy and respect, which again includes the individual’s right to control personal information and to protect his or her privacy.

Confidentiality in the field of HIV vaccine research raises serious concerns: Firstly, the trial participants are vulnerable to social risks as a result of their participation. Secondly, many of the information shared by the trial participants are socially not acceptable and even criminal in nature. Bayer, Levine and Murray (1984) had identified the tension that could arise due to the special need to maintain confidentiality of HIV research. They suggested that a balance should be struck between the principle of respect for persons (which requires that the individuals should be treated as autonomous agents who have the right to control their own desires) and the pursuit of the common good (which requires

279 S. Loue, supra note238. Any information involving a possibly communicable disease poses a tension between an individual’s desire to control personal information and the desire of others to have access to that information. Although this information is not unique to AIDS, it is particularly sharply drawn in this case because those groups that have been identified as a high risk group are also highly vulnerable socially, economically and politically.
maximizing possible benefits and minimizing possible harms, to society as well as to individuals). They further added that those who are entrusted with confidential information should be prohibited by law from unjustifiable voluntary disclosure. This further is based on the fact that we all owe a moral commitment to the principle that all persons are due full measure of compassion and respect.

There have been many incidences in the past where those entrusted in keeping confidentiality of information has made it public. This shows the conflicting rights of confidentiality vs. right to information. The classic example is the case of a positive groom whose status was informed to the would be bride by the physician and the Supreme Court of India upheld the action when the groom pleaded for breach of confidentiality. It also added that an HIV positive person who marries and transmits the infection to the spouse would be criminally liable under Sections 269 and 270 of the IPC (Indian Penal Code) which criminalize those who perform a negligent or malignant act likely to spread a disease dangerous to life. The court however, did not lay down any condition or protocol by which such disclosure was to be made. Ideally partner notification is done by the individual themselves or with their informed consent. The case in question is an exception where the girl’s right to safety and information was considered more important than the privacy issue. However, in situations related to employment, insurance, etc. privacy should be maintained.

Confidentiality arises when there is a confidential relationship: the nature of which may be dependent on factors of trust, knowledge and skill. Usually confidential information is imparted in circumstances guaranteeing confidence. A breach in confidentiality may result in many untoward effects on the patient: discrimination, eviction, loss of relationships, loss of job, denial to travel, denial of

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280 Id The CDC had many times released the names of persons living with AIDS to local health agencies without the consent of individuals.
medical care among the many. This could also result in reducing participant’s confidence in the researcher. He would believe that the participant is self-oriented and insensitive to others.

The state has the responsibility to assure that the data entrusted to their care should be kept confidential. The principle of privacy and confidentiality are incorporated in the Constitution of India (Article 21) which states that the confidence entrusted by a patient to a physician and defects/dispositions in character of a patient observed during medical attendance should never be revealed unless required by the laws of the state. More so, because many of these trial participants have enrolled with altruistic motives, for the welfare of the society. Thus it is more than social obligation to ensure confidentiality of data obtained and anonymity of the subjects.

Various mechanisms available for enhancing the ability to safeguard research participants from breaches of confidentiality are blinding (single blinding, double blinding), assigning unique identifiers, employee training, usage of lockers with theft alarm for the soft/hard copy of the data obtained.

Researchers at times find themselves facing the conflict between ethical relativism and ethical essentialism. This may be so in occasions where they are dealing with communities which do not value privacy and confidentiality. In such a scenario, the researchers would be faced with serious meta-ethical dilemma: should they impose strict confidentiality standards on the community in order to protect the welfare of the volunteers, even though confidentiality and privacy do not have a place in the values of the community. This is a very complex and multifaceted issue.

Various guidelines and regulations help in resolving the issue. The WHO/ CIOMS committee that drafted the *International Ethical Guidelines For Biomedical

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The position of *ethical relativism* holds that no values are universal and hence no values hold true absolutely, always answer everywhere. Ethical essentialism on the other hand holds that not all values and actions are equally valid or worthy. *Ethical essentialism* holds that some acts are wrong, even if there is a whole community that endorses them.
Research Involving Human Subjects had meticulously tried to attempt and face the complex issue of medical-ethical imperialism. CIOMS guidelines very explicitly state the importance of confidentiality of research subjects.

But however this document is not without limitations. The limitation is in fact expressed in guideline 12 of the document. 283

ICMR guidelines have 12 general principles of which principle of privacy and confidentiality is the fourth principle. 284

Privacy and confidentiality are two concepts: Privacy is a concept that each individual has the right to control personal and sensitive information about him/her. Confidentiality is a concept that the parties who obtain private information from patients/subjects will: (i) protect the information itself and any records that contain such information from deliberate or accidental disclosure, (ii) develop and follow measures for release of the information only to authorized parties who have a legitimate need for it, including notification of the subject/patient prior to the disclosure. 285

4.23.3.6 Conflict of Interest:

Conflict of Interest refers to situations in which financial or other personal considerations may compromise, or have the appearance of compromising, an investigators professional judgment in conducting or reporting research. (AAMC Guidelines)286

The investigator must establish secure safeguards of the confidentiality of research data. However, the subjects should be told of the limits to the investigator’s ability to safeguard confidentiality and of the anticipated consequences of breaches of confidentiality.  
284 Ethical Guidelines For Biomedical Research On Human Participants. ICMR; 
NEWDELHI:2006.  
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Perlis et al observed that investigators of biomedical research involving human subjects often receive funding from sponsors, either directly or indirectly with an interest in the outcome and reporting of these trials. Such a relationship may create a conflict of interest for these investigators. This often interferes with their interest in the objective description of the outcome and may compete with their obligation to the sponsor, either perceived or real. Because of this reason, industry favored trials are more likely to be reporting favorable outcomes. Conflict of interest influences the study design, conduct and reporting of clinical trials.

Industry has increasingly replaced government as a primary source of research funding. The potential conflicts of interest that arise out of the relationship between industry and physician investigators possibly jeopardize the rights and wellbeing of research participants as well as the integrity of research results. A physician’s decision to participate as an investigator in HIV vaccine clinical trials should be unrelated to any benefits.

Any physician entering the Clinical trial as an investigator has many primary and secondary obligations.

Primary obligations are:

(i) Promoting and protecting the scientific integrity of the research.
(ii) Protecting the well being of the participants
(iii) Contributing to scientific advances.

Secondary obligations are:

(i) Earning the respect of the colleagues

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288 Id. Out of the 397 studies examined, 187 (47%) had at least one author with potential financial conflict of interest. Also it was observed that author’s conflict of interest was significantly associated with positive trial outcomes in all studies.
(ii) Supplementing income

(iii) Advancing careers \(^{289}\)

This is more so to be expected in HIV vaccine clinical trials. Compensation for research may be in the form of per capita payments, global payments, payments in the form of equity, recruitment and retention bonus and finder’s fee. \(^{290}\)

Although this interest may sometimes conflict with the best interests of participants, it is an accepted element of research, in part, because it is open and acknowledged. However, some conflicting interests, particularly financial ones, create ethical problems because they may influence the myriad decisions researchers make over the course of a study. For example, such interests may lead researchers to overestimate the benefits of a study, underestimate the risks, fail to objectively review existing evidence, and, if necessary, halt an on-going study. \(^{291}\) These could influence investigator decisions about the eligibility of potential participant and many vital decisions placing participants at risk or undermine the scientific integrity of the study.

In legal scenario, the term conflict of interest is used in connection with fiduciaries. A fiduciary holds some form of power that is to be used for the benefit


\(^{290}\) R. Sara, supranote 272. The sponsoring company usually pays the investigator a fixed amount per research participant enrolled. This per capita payment usually covers the physician time, payment for clinical procedures, Laboratory or pharmacy fee. Cost of time spent on recruitment, informed consent etc.

Some trial sponsors remunerate investigators with company stock. This compensation with equity in the sponsor creates a conflict of interest for the investigator since it gives them a stake in the outcome of the research. Bonuses could be for exceeding enrollment goals, securing IRB approval or for meeting some deadlines or study milestones. New Jersey’s Attorney General in 2009 asserted that payment with stock or stock options is ‘outrageous and unacceptable’. Finder’s fee refers to the payment solely for referrals. Though American College of Physicians and American Medical Association had rejected the use of finder’s fee as it is unethical, its widespread use is rampant.

of another, based on specialized knowledge or expertise. A fiduciary relationship involves dependence, reliance and trust and legally is held to the highest standard of conflict. Many aspects of a fiduciary relationship exist between a physician and patient, which explain why physicians also have an ethical duty to avoid conflict between their commitment to heal patients and their economic self interest. 292

One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study." Further interest may be related to academic research environment. 293 FDA notes this in the Code of Federal Regulations (CFR). 294 The guidance specifically looks at the requirements of 21 CFR 54, Financial Disclosure by Clinical Investigator. Thus, FDA requires applicants looking to conduct a clinical trial to submit a list of all investigators who will be working on the trial paired with a certification that either no financial arrangements exist that would cause a problem, or explaining the nature and extent of those holdings and why they do not pose a problem to the conduct of the trial. (See: 21 CFR 54.4(a)295

IOM has recommended that investigators with a significant financial interest in an existing product could be affected by the outcome and hence should not be permitted to conduct research, unless their participation is justified by compelling circumstances and is effectively managed by the institution. 296

295 http://www.law.cornell.edu/cfr/text/21/part-54
296 R. Sara, supra note 286.
Current regulations fail to address institutional / individual financial interest that could give rise to a conflict. IRBs lack the guidance, expertise to act as conflict committees to identify and manage conflicts. In addition, IRBs usually comprise of physicians. Thus there is no single mechanism to monitor financial relationships between sponsors and investigators or to address any conflict of interest that could influence recruitment and enrollment prior to commencement of the trial.

Failure to disclose risk of participation and financial interest of investigators has given rise to many law suits. Thus American Medical Association (AMA) warrants that once potential conflicts are identified, they may be avoided, disclosed or mitigated. Although the complete avoidance of conflict may be ideal situation, it is likely to be unrealistic in most of the situations. As a result, disclosure of conflict may function as the primary mechanism to reduce the effect of the conflict. Some steps can be taken to minimize conflicting interests. These include:

i) openly discussing research plans with colleagues and ensuring peer review of research protocols

ii) blinding investigators and participants to which intervention participants are receiving

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298 Report 3 of the Council on Ethical and Judicial Affairs, supra note 292.
iii) using an independent data safety monitoring board to interpret interim data and assess reports of adverse events\textsuperscript{299}

Some conflicts of interest are so problematic that they should be prohibited, not merely disclosed. In particular, all researchers in clinical trials, and their immediate families, should be prohibited from holding stock, options, or management positions in the company making the product or technology tested, its competitors, or the sponsor of the study\textsuperscript{300}

Further, in addition to all these, there is a moral dilemma experienced by the researcher contributing to counseling with dual intent. We want the subject to engage in high risk behaviors to test the vaccine. On the other hand, the researcher is vested with the moral responsibility of counseling the subject against high risk behaviors. Thus, the message to the volunteer is “\textit{don’t do it, but do it}”\textsuperscript{301}

\textbf{4.23.3.7 Stigma and Discrimination}

Though HIV has evolved from a fatal diagnosis to a manageable chronic illness, the social aspect of the illness, i.e.; stigma of HIV continues to threaten the emotional, mental and physical well being of people living with HIV and AIDS.\textsuperscript{302} Thus HIV is increasingly recognized as not merely a medical problem, but of a social problem as well.

\textsuperscript{299}L.E. Wolf and B. Lo, supra note 291.
\textsuperscript{300}Id.
\textsuperscript{301}T.A. Kerns, supra note 195.
Stigma is a complicated issue that has deep roots in the convoluted domains of
gender, race, ethnicity, class, sexuality and culture.\textsuperscript{303} Stigma is “an attribute that is deeply discrediting” and results in the reduction of a person or group “from a whole and usual person to a tainted, discounted one” (Goffman, 1963). Thus, the ultimate effect of stigma, as noted by Goffman, is the reduction of the life chances of the stigmatized through discriminatory actions. Thus discrimination is the end result of the process of stigma—in effect, “enacted” stigma. Discrimination (or enacted stigma) is the negative acts that result from stigma and that serve to devalue and reduce the life chances of the stigmatized. (Carael \textit{et al.}, 2000).\textsuperscript{304}

Discrimination is defined as “\textit{when in the absence of objective justification, a distinction is made against a person that results in that person being treated unfairly & unjustly on the basis of belonging or being perceived to belong to a particular group.}”\textsuperscript{305}

Discrimination can be self imposed, structural or individual. \textit{Self imposed} discrimination arises out of fear of rejection and priori act as if discrimination has already been imposed. \textit{Structural} discrimination refers to institutional practices against stigmatized individuals even in the absence of individual prejudices. \textit{Individual} discrimination implies more overt and obvious discrimination between two people.\textsuperscript{306}

UNAIDS commissioned, in July 2009, International Center for Research on Women (ICRW) to conduct a review of empirical literature published since 2005

\begin{footnotesize}
\begin{enumerate}
\item\textsuperscript{303} \textit{HIV/AIDS Stigma: An Impediment to Public Health}, AMERICAN JOURNAL OF PUBLIC HEALTH, 92 (3)
\item\textsuperscript{305}M. Allen \textit{et al.}, \textit{Trial-Related Discrimination In HIV Vaccine Clinical Trials}, AIDS Research and Human Retroviruses (May 2001) available at http://online.liebertpub.com/doi/abs/10.1089/088922201750236942 (Last visited on October 22, 2014).
\item\textsuperscript{306} \textit{Id.}
\end{enumerate}
\end{footnotesize}
on HIV-related discrimination. The purpose of the work was to collate recent data and evidence related to the prevalence of HIV-related stigma and discrimination; the relationship between stigma and HIV prevention, treatment, care and support; and results of evaluations of programmes to reduce stigma and discrimination.

Stigma may be enacted, perceived, internalized or layered. Many studies have demonstrated the public’s persistence of discomfort with people with HIV. 307, 308 HIV-related stigma—whether measured by stigmatizing attitudes, fear of or perceived stigma, or enacted stigma — is pervasive and negatively impacts the quality of life of people living with HIV. The AIDS epidemic has often been associated with severe negative public reactions ranging from banning entry of HIV infected individuals to isolating an individual in the family.

“Stigma remains the single most important barrier to public action. It is a main reason why too many people are afraid to see a doctor to determine whether they have the disease, or to seek treatment if so. It helps make AIDS the silent killer, because people fear the social disgrace of speaking about it, or taking easily available precautions. Stigma is a chief reason why the AIDS epidemic continues to devastate societies around the world.”

- UN Secretary-General Ban Ki Moon.

Fear of contagion coupled with negative, value-based assumptions about people who are infected leads to high levels of stigma surrounding HIV and AIDS. Double Stigma of AIDS stemmed from the identification of AIDS and from the identification of AIDS with already stigmatized groups. 309

Fear of stigma may dissuade many individuals to get them tested. Stigma and discrimination act as impediments to uptake of HIV testing, treatment and care

and to adherence to treatment. A consistent, negative association has been found between fear of stigma (or perceived stigma) and use of testing and treatment services. However, it is not yet known if decreased stigma causes increased uptake of services, or if increased access to testing and treatment causes stigma to fall.

Four interrelated components leading to the discrimination as conceptualized by Bruce Link and Jo Phelan are as under:

- Individuals distinguish and label human differences
- Dominant cultural beliefs link labeled persons to undesirable characteristics or negative stereotypes
- Labeled persons are placed in distinct categories to accomplish some degree of separation of “us” from “them”
- Labeled persons experience status loss and discrimination that lead to unequal outcomes

There is scanty evidence as to a consistent relationship among gender, stigma and use of services. The studies that do exist provide only a fragmentary picture. It suggests that men and women experience stigma differently. According to one study, men may experience more internalized stigma than women while another study indicates that women experience more enacted stigma. Further evidence suggests that women are more easily deterred by stigma from being tested for HIV or seeking care. More studies with an explicit focus on gender are needed to fully understand the full relationship between stigma and use of services among men, women and sexual minorities.

In a cross sectional study conducted on 202 People Living with HIV/AIDS (PLHA) in Los Angeles County in 2007, one third of the participants reported high levels of stigma and 77% reported poor access to care. It was also found that

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those reporting high levels of stigma were more likely to report poor access to care.\textsuperscript{311} Another study in Thailand indicated that the people who are most unwilling to participate in the vaccine trials were those who expected higher levels of discrimination.\textsuperscript{312}

In recent years, progress has been made in measuring stigma. However, comparative studies of the prevalence of stigma across settings or populations are rare and made difficult by the diversity of measures used to capture stigma.

Stigma and discrimination reduction programmes are too seldom evaluated, and where they are, their evaluation results are too seldom published. Those that have been published indicate that stigma may be decreased through programmatic action using the media, stigma reduction work in communities, through strengthening networks of people living with HIV to take the lead in addressing stigma, and among health care professionals, and possibly through the expansion of treatment services.

Evaluated programmes represent a narrow range of all intervention approaches and omit several important and promising programmatic approaches. More evaluations are in need of:

- Initiatives that seek to empower people living with HIV or to reduce internal stigma and thereby contribute to reducing broader stigma in the community and increasing uptake and adherence of treatment;
- The costs and cost-effectiveness of stigma-reduction programmes;
- Programmes implemented at national levels; and
- Stigma reduction programmes with uptake of testing, treatment, or care and support services as outcome measures.\textsuperscript{313}

\textsuperscript{311} J.N. Sayles \textit{et al.}, supranote 302.
\textsuperscript{312} R.A. Jenkins \textit{et al.}, \textit{supra} note 226.
Numerous studies are conducted worldwide depicting the stigma and discrimination faced by PLHA. Two UK based studies on discrimination revealed 41.4% faced employment related discrimination & 13.8% had immigration related discrimination. 314 HIV/AIDS related employment discrimination is rampant in many parts of the world thus affecting the fundamental rights of PLHA at work. 315 In this study, which was carried out in six enterprises in Hatay (Vietnam), 2/3rd of the respondents believed that workers with HIV belonged to evil group.

PLHIV Stigma Index findings drawn from nine countries revealed that stigma and discrimination remains as a major barrier for productive employment and decent work amongst people living with HIV. 316 27% of respondents in Nigeria were refused the opportunity to work. 28% in Kenya had their nature of work changed and had been refused promotion due to their HIV status. 54% in Malaysia reported discriminatory reactions from employees, coworkers once they are aware of the HIV status. It was observed that HIV related stigma and discrimination directly impedes access to work by people living with HIV by:

- Obstructing entry to the labour market.
- Changing the type of work individuals are allowed to perform.
- Preventing promotion to a senior position.
- Triggering people being fired from their jobs.

• Impeding access to adult education and training.  

This further adds to personal frustration and fuels individual and familial disaster. The local and national economies are weakened and underperform. Hence the consequences of stigma and discrimination in workplace remain economically and socially profound. Since the PLHA are socially excluded and their social standing and capacity to contribute to their communities is undermined at significant psychological and social cost, the consequences of stigma and discrimination are far beyond economies.

In 2002 United States Agency for International Development (USAID) convened a small group of experts – Stigma and Discrimination Indicators Working Group (SDIWG) to begin the process of developing and testing indicators. The key goal was to develop indicators to measure stigma and enacted stigma, i.e: discrimination. They have tried to measure stigma for three populations (community, health care workers and people living with HIV/AIDS) in four key domains:

• Fear of casual transmission and refusal of contact with people living with HIV/AIDS (PLHA);
• Value- and morality-related attitudes— blame, judgment and shame;
• Enacted stigma (discrimination);
• Disclosure.

International Labour Organization Programme on HIV/AIDS and the World of Work (ILO/AIDS) had supported the production of a briefing on the findings from the people living with HIV stigma which was highly appreciated by The Global

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317 Id.
319 Id.
Network of People Living with HIV (GNP+).\textsuperscript{321} Action by government, international agencies and civil society is urgently required to protect the rights of HIV infected at work, by implementing the recommendations of ILO/AIDS.

Every human being has a right to earn a living and to social participation through work. Article 23 of The Universal Declaration of Human Rights\textsuperscript{322} and The International Covenant on Economic, Social and Cultural Rights had propagated the same.\textsuperscript{323} Full and productive employment and decent work for all are considered as a target of Millennium Development Goal.

UN member states have pledged to develop national, legal & policy frameworks that protect the workplace rights and dignity of people living with and affected by HIV & AIDS. The recent political declaration on \textit{HIV/AIDS: Intensifying Our Efforts to Eliminate HIV/AIDS (2011)} reaffirms governments commitments to mitigate the impact of the HIV epidemic on workers, their families, their dependents, workplaces and economies including considerations of ILO conventions and particularly ILO’s recommendations concerning HIV/AIDS and the world of work (2010) which outlines the interrelationship of HIV/AIDS and work and general principles to inform states responses. These principles states that there should be no discrimination against or stigmatization of workers in particular on the ground of real or perceived HIV status or the fact that they belong to regions of the world or segments of the populations perceived to be at greater risk or more vulnerable to HIV infection.\textsuperscript{324}

The ILO Recommendation concerning HIV and AIDS and the World of Work, 2010 (No. 200) provides that there should be no discrimination or stigmatization

\textsuperscript{321} Global Net work of People Living With HIV, supra note 316.
\textsuperscript{322}\textsc{UN GENERAL ASSEMBLY, Universal Declaration of Human Rights,} (December 10, 1948), 217 A (III), available at: http://www.unhchr.org/refworld/ docid/3ae6b3712c.html (Last visited on December 27, 2014).
of workers, particularly job applicants and jobseekers in either access to employment or occupation, terms and conditions of work or the right to remain in employment. Retention in work and recruitment of persons living with HIV needs to be promoted, and programmes of care and support should include measures of reasonable accommodation in the workplace. Real or perceived HIV status should not be a ground of discrimination for employment purposes, including in access to employment and occupation.

Women are more vulnerable as they have little or no control over their bodies, low level of education and patriarchal system. Fear of stigma and discrimination has deterred individuals from being tested for HIV, disclosing their seropositivity status to partners, family and friends. Since women face heavy social, economic, legal, cultural and social disadvantages, the impact of HIV & AIDS on women is marked.

Stigma has an association with HIV risk behaviors, as it is the process of othering, blaming & shaming. It was found that in South Africa, among PLHA, those who experienced stigma and discrimination were less likely to disclose their HIV status to their sexual partners and this non disclosure was associated with transmission of disease. In a similar study in France, in a sample of over 2000 sexually active PLHA, HIV / AIDS, discrimination was associated with increased unsafe sex.

In this backdrop, the participants in preventive HIV vaccine trials will experience negative social consequences of trial participation, including problems related to a vaccine induced positive HIV antibody test. 1516 volunteers who participated in AIDS Vaccine Evaluation Group (AVEG) were assessed for reports of Trial Related Discrimination (TRD). Ninety TRD events were reported by 76 volunteers. The most commonly reported events were negative reactions of friends, family and co- workers.

325 J. Sayles, et al., supra note 302.
326 Id.
14203 participants in 4 countries completed a survey including a scale measuring HIV/AIDS related stigma and discrimination. The result of this survey recommended strategies like HIV testing, discussion on HIV/AIDS & education regarding Universal access to ARVs to reduce HIV/AIDS related stigma & discrimination.  

18 focus groups with a total of 133 participants were interviewed at Nairobi, Kenya at two AIDS vaccine trial centers. Four prominent stigma related barriers to participation emerged among all respondent groups. They were

1. Volunteers are often assumed by family & community members to be HIV positive.
2. HIV related stigma is perceived as pervasive & damaging in The communities where volunteers live & they fear consequent stigma if people fear them to be HIV positive.
3. Potential volunteers fear being tested for HIV.
4. Volunteers must carefully manage information about participation because of misperceptions & assumptions about HIV vaccine volunteers.

Monitoring HIV related stigma and discrimination, raising awareness about their impact and utilizing this knowledge to inform education and advocacy efforts is essential in combating the epidemic. Challenging stigma and discrimination requires the promotion and protection of human rights more broadly. There is an urgent need that the public policies address issues of treatment & prevention to establish social norms based on acceptance & respect for HIV infected persons. This should keep in mind the foremost issue of human rights

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that includes by its very definition: social acceptance, respect, compassion & support without blame. Stigma, suffering, shame and silence are mutually supporting concepts that challenge health promotion efforts and hence there is an increased need for political and social commitments at local, national and international levels.

A study was conducted by School of Health Systems Studies at Tata Institute of Social Sciences, and recommends developing a national agenda on AIDS stigma research and interventions to help realize the government’s goal to stigma reduction. This depicts how HIV related stigma & discrimination influence people’s decisions to join HIV vaccine related research. Another study conducted in 4 countries presents evidence suggesting that there are many similarities in the key causes of stigma, the forms stigma takes and the consequences of stigma.

The International Center for Research on Women (ICRW), in partnership with organizations in Ethiopia, Tanzania, and Zambia, led a study of HIV and AIDS-related stigma and discrimination in these three countries. This project, conducted from April 2001 to September 2003, unraveled the complexities around stigma by investigating the causes, manifestations and consequences of HIV and AIDS-related stigma and discrimination in sub-Saharan Africa. It then uses this analysis to suggest program interventions. There are also many positive aspects of the way people deal with HIV and stigma. People express good intentions to not stigmatize those with HIV. Many recognize that their limited knowledge has a role in perpetuating stigma and are keen to learn more. Families, religious organizations and communities provide care, empathy and

support for people with HIV and AIDS. Finally, people with HIV themselves overcome the stigma they face to challenge stigmatizing social norms. This study points to five critical elements that programs aiming to tackle stigma need to address: Create greater recognition of stigma and discrimination. Foster in-depth, applied knowledge about all aspects of HIV and AIDS through a participatory and interactive process. Provide safe spaces to discuss the values and beliefs about sex, morality and death that underlie stigma. Find common language to talk about stigma. Ensure a central, contextually-appropriate and ethically-responsible role for people with HIV and AIDS. While all individuals and groups have a role in reducing stigma, policymakers and programmers can start with certain key groups that our study suggests are a priority: Families caring for people living with HIV and AIDS: programs can help families both to cope with the burden of care and also to recognize and modify their own stigmatizing behavior. NGOs and other community-based organizations: NGOs can train their own staff to recognize and deal with stigma, incorporate ways to reduce stigma in all activities, and critically examine their communication methods and materials. Religious and faith-based organizations: these can be supportive of people living with HIV and AIDS in their role as religious leaders and can incorporate ways to reduce stigma in their community service activities.332

A change in the attitude of service providers through greater knowledge and political will is considered as the most significant approach to challenge the existing stigma in health care settings & in the community as well. This changed attitude would only facilitate people to join HIV vaccine clinical trials.

4.23.3.8 Fraud & Abuse Risk in HIV Vaccine Clinical Trials:

Fraud and abuse are not new to health care arena. Since there exists little or no mechanism to detect, investigate or prosecute fraud in most countries, fraud in clinical research is very rampant. Sheehan et al. reported in 2005 that 17% of surveyed authors of clinical drug trials reported that they personally knew of fabrication in research occurring over the previous 10 years. Pharmaceutical giants like Pfizer, Glaxo Smith Kline etc are alleged to have paid $3 billion, $ 2.3 billion in criminal & civil fines for improperly marketing drugs, failing to provide safety data from post marketing studies etc. New York State’s attorney general Eliot Spitzer alleged the company engaged in “repeated and persistent fraud” for concealing the results of clinical studies. Another scientist from Merck admitted the presence of AIDS & cancer viruses from infected monkeys in polio vaccine developed.

Definition of fraud as defined in court is “the knowing breach of the standard of good faith and fair dealing as understood in the community, involving deception or breach of trust, for money.” Reasons for fraud in clinical research could vary from personal to professional. Fraud could be a result of professional over ambition to become famous, a gain in prestige by being a part of international clinical trials or for financial interests. Pressures for promotion and tenure, competition amongst investigators, need for recognition, ego, personality factors.

333 Fraud is an intentional deception or misrepresentation of fact that can result in unauthorized benefit or payment. Abuse means actions that are improper, inappropriate, outside acceptable standards of professional conduct or medically unnecessary.
335 O. Dyer, Glaxo Smith Kline faces lawsuit over concealment of Trial Results, BRITISH MEDICAL JOURNAL (June 12, 2004 ) available at http://www.bmj.com/cgi/content/full/bmj:328/7453/1395 (Last visited on July 19, 2014).
and conflicting personal and professional obligations are some factors, which can influence certain individuals to involve in fraud/misconduct. There could also be associated environmental factors such as amount of oversight of the study, existence of explicit versus implicit rules, penalties and rewards attached to such rules, extent of training imparted, regulations involved and insufficient mentoring. Fraud in clinical trials may affect the rights and safety of subjects involved and trust of common man. There is a greater impact that spurious and substandard chemicals are marketed. When the product in question is HIV vaccine, the impact is many fold.

Fraud and abuse risk in HIV vaccine clinical trials are not uncommon. This at times put the entire industry surrounding HIV/AIDS in skeptical air. It often raises the question- how honest and ethical is the industry surrounding AIDS. AIDS drug experiments are alleged to have been conducted amongst orphan children in New York City of which 200 were reported to have died. A celebrated HIV vaccine researcher admitted fraud in clinical trials of HIV vaccines, revealing an overzealous medical culture that cannot be trusted. This extraordinary fraud of tampering rabbit blood samples with human antibodies to make the experimental HIV vaccine appear to have merit, is said to have gained millions of dollars in NIH funding. Glaxo Smith Kline is ready to enter vaccine trials with a protein based vaccine. With the given credentials of the company being involved in fraudulent research earlier, this has to be viewed seriously. The researchers may be tempted by the fame and money involved in inventing the centuries most wanted vaccine. Caution may thus be exercised in the credentials of the researchers with their claim.

338S. Lakhane, supra note 114.
4.23.3.9 Coercion & Undue Inducement.

All available ethical guidelines propagate that the subjects should be paid for the inconveniences caused to them, loss of their wages and time spent. They should also be reimbursed for the expenses incurred in connection with their participation in research. They may also receive free medical services. The Nuremberg code, the first ever document in this regard, explicitly gives this view. The issue is to what extent we would be able to abide by this in developing nations where the research is rampant?

Army recruits if involved in HIV vaccine trials or intravenous drug users desperate for their next fix are certainly not exercising free power of choice. These are not easy questions. They are subject to some form of force or duress with regard to their decision to participate in HIV vaccine trials.

Undue inducement & coercion are frequently conflated with unethical, illegal, or imprudent. However, they are different. Inducements are offers that get people to do things they would not otherwise do. Any activity to encourage participation of the prospective subject amounts to inducements in research. Monetary inducements may be undue if they alter patients’ decision-making processes such that they do not appropriately consider the risks of participation.

Undue inducement dangles a positive good, a tempting offer that can cause the bad judgment that leads to harm, while coercion entails a threat that the person considers a worse circumstance if they do not do the desired action.

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The person involved should be so situated as to be able to exercise free power of force, without the intervention of any element of force, fraud, duress, overreaching, or other ulterior form of constraint or coercion.

The various international guidelines have addressed the issue as under:

(1) “An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.”

45 CFR46.116

(2) “Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive... The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence.”

FDA Information Sheets, 1998

(3) “…the IRB should review both the amount of payment and the proposed method of disbursement to assure that neither entails problems of coercion or undue influence. Such problems might occur, for example, if the entire payment were to be contingent upon completion of the study or if the payment were unusually large. Payments should reflect the degree of risk, inconvenience, or discomfort associated with participation.“

Office of Human Research Protection. IRB Guidebook

According to medical ethicists, an undue inducement consists of an offer to a person of something of value, in exchange for his or her agreement to do something that he or she might not do without the inducement. Undue inducements are excessively attractive offers that lead people to do something to which they would normally have real objections based on risk or other fundamental values. An example of this may be a cash payment so large that it overwhelms other relevant considerations: risk/benefit assessment - in a decision
to be or not to be a research subject. 345 Coercion & undue inducement to participate in a trial are unethical.

“Coercion occurs when an overt threat of harm is intentionally presented by one person in order to obtain compliance.”346 To be coercive, a subject who refuses must be made worse off than if he or she would have been if never asked.347

“An offer one could not refuse is essentially coercive (or “undue”). Undue inducements may be troublesome because: (1) offers that are too attractive may blind prospective subjects to the risks or impair their ability to exercise proper judgment; and (2) they may prompt subjects to lie or conceal information that, if known, would disqualify them from enrolling --or continuing --as participants in a research project.


This definition suggests four necessary aspects of undue inducement: (1) an offered good—individuals are offered something that is valuable or desirable in order to do something; (2) excessive offer—the offered good must be so large or in excess that it is irresistible in the context; (3) poor judgment—the offer leads individuals to exercise poor judgment in an important decision; (4) risk of serious harm—the individuals’ poor judgment leads to sufficiently high chance that they will experience a harm that seriously contravenes his or her interests.348

“It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to

345 T. A. Kerns, supra note 195.
347 AIDS Vaccines, supra note 122.
348 An AIDS Vaccine, supra note 120.
participate in research simply to receive such care. A prospective subject may be 
induced to participate in order to obtain a better diagnosis or access to a drug not 
otherwise available.349

The HIV vaccine trial participants are poor, poorly educated, with access to few 
health-care services. They are often powerless, especially compared with 
pharmaceutical companies and researchers from developed countries. When 
outside researchers and funders provide research related payments and/or 
advanced health-care services that are otherwise unavailable, these individuals 
are forced to enroll in the research trial; it becomes an offer they can't refuse.350

The issue is that in underdeveloped countries, almost any payment and almost 
any medical care, might constitute “undue recompense", due to the low economic 
status. In some communities, it will be difficult or almost impossible for 
researchers to satisfy the requirement to avoid undue inducement351. Also, in 
some communities, the decision to provide the best available therapy may also 
constitute unreasonable inducement. 352 We have already seen in an earlier 
section of this study that monetary factors motivate a subject to participate in a 
HIV vaccine trial. Thus, this issue needs to be addressed before we engage in 
any further trials.

4.23.3.10 Compensation For Disability & Trial Related Injury

When a subject is injured as a result of participation in a research study it is 
termed “research related injury”. This can range from minor harms (such as 
bruises due to a study procedure or vomiting) ,to major injuries (such as organ 
damage or temporary physical disability) , to catastrophic injuries(such as

349 J. Thomas, supranote118.
350 S. Jameal, supra note 123.
351 T. A. Kerns, supra note 195.
352 S. Sahay and S. Mehendale, Addressing Ethical Concerns in the Indian HIV vaccine Trials. 
available at http://www.infochangeindia.org/hiv-aids/research/addressing-ethical-concerns-in-the-
permanent disability or death). Injuries can be physical, psychological, social, and economic and may require only acute management or long term medical care.  

Volunteers in a clinical trial put themselves at risk. Thus the researchers and sponsors are entrusted with clear, enormous and uncontroversial responsibility to treat and cure the subjects for any physical problems that might develop in the subject as a result of their participation in the study. Compensation for injury has been justified for economic, ethical/philosophical, pragmatic or social policy reasons. All international ethical guidelines recommend that the trial participants should be compensated for trial related injuries.

Compensation is defined as "the act or process of making amends for something" or “something, typically money, awarded to someone in recognition of loss, suffering or injury”. Damages are financial compensation, the purpose of which is to put the claimant, so far as money can do so, back into the position he would have occupied, had the negligence not occurred. Damages can be awarded for expenses relating to the injury, such as any medical costs occurred, pain and suffering, loss of amenity, loss of earnings where applicable and any potential future losses. Quantifying such losses in monetary terms is always problematic.

Participants in research trials often find it hard to litigate. However, in Newman v Secretary of State for Health, 1800 children were treated for short stature with growth hormone, over a period of 25 years by Medical Research Council in a trial which started in 1959. The trial was stopped in 1985, when it was found to have a link with Creutzfeldt – Jacob Disease (CJD), which is a terrible condition.

354 ADVERSE REACTIONS TO HIV VACCINES: MEDICAL, ETHICAL and LEGAL ISSUES, OFFICE OF TECHNOLOGY ASSESSMENT , CONGRESS OF THE UNITED STATES, 1995
causing progressive mental retardation and death in four months short notice. The unlucky victims had to resort to litigation which ended 13 years after proving the duty of care that was breached. Pearson Commission was setup to make recommendations in such case.  

Though the research scientists undertake all possible measures to minimize harms, it is not entirely possible to predict and therefore eradicate all the risks before the trial begins. Mrs Uma Thatte identified that in a country like India, the issue of compensation for trial related injuries is magnified as most trial participants are uninsured, unlike those in developed countries. Further, in India, the multitude of languages make informed consent difficult and therapeutic misconception is a reality. A study undertaken by Mrs Thatte identified that compensation was limited to acute management of adverse events occurring during the trial. The issue of compensation for lost wages during the adverse event or for death, permanent disability or long-term incapacitation was not addressed by any stake holders. It was noted that the payment of adverse event management was done by the subject and this was reimbursed later. She also mentioned that 83% of EC members were unaware of details of insurance contracts.  

Guideline 19 of The International Guidelines for Biomedical Research Involving Humans Subjects is explicit about the moral obligation of researchers towards subjects. “Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their

357 U.M. Thatte, supra note 353.
participation, their dependants are entitled to compensation. Subjects must not be asked to waive.\textsuperscript{358}

Guideline 19: Right of injured subjects to treatment and compensation.

Reasons for paying and views about paying healthy and patient volunteers was studied by Emily A. Largent etal\textsuperscript{359} and the result is as under:

<table>
<thead>
<tr>
<th>Who agree or strongly agree that it is acceptable to...</th>
<th>Healthy Volunteer</th>
<th>Patient-subjects with no prospect of benefit</th>
<th>Patient-subjects with a prospect of benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offer Money</td>
<td>86.8%</td>
<td>78.7%</td>
<td>71.1%</td>
</tr>
<tr>
<td>Reimburse for expenses</td>
<td>97.9%</td>
<td>95.4%</td>
<td>92.8%</td>
</tr>
<tr>
<td>Compensate for time, effort, inconvenience</td>
<td>94.5%</td>
<td>90.7%</td>
<td>86.2%</td>
</tr>
<tr>
<td>Offer money as an incentive</td>
<td>58.3%</td>
<td>56.2%</td>
<td>50.2%</td>
</tr>
<tr>
<td>Offer money to compensate for risk</td>
<td>36.4%</td>
<td>36.9%</td>
<td>34.6%</td>
</tr>
</tbody>
</table>

There are many issues in this regard. Most of the developed nations are carrying out HIV vaccine clinical trials in developing nations. The rules in these developing countries may be underdeveloped or inadequate to address these trials. The lawsuits demanding compensation are extensive and the legal culture of the developing nation may not be conducive to take up litigation against an affluent nation or sponsor.

Another unsettling dilemma in HIV vaccine trial is the compensation which needs to be paid for non – physical injuries/ social adverse events which are unique to

\textsuperscript{358}UNAIDS, \textit{supra} note 127.

HIV vaccine clinical trials. The reason for the CIOMS Guidelines remaining silent about "Non – Physical Social Harms " is that it is a generic set of guidelines for all biomedical research and not just HIV/AIDS research. The problem is grave as these social harms often cannot be materially compensated. Thus there is a greater need to develop a set of guidelines for research involving HIV/AIDS that recognizes the importance of non-physical injury as much as it addresses physical injury.

How could we ever compensate the injury borne by these subjects? It could be lifelong HIV\textsuperscript{+ve} status, development of carcinomas or HIV as a result of participation in the vaccine trial. Leave alone the non physical damage strand attached to the long list of damages to be borne by the subjects, which cannot be materially compensated.

Pursuant to the report submitted by Prof Ranjit Roy Chaudhury to the Ministry of Health & Family Welfare, Drugs Controller General (India) on 03 July 2014 directed all sponsors/manufacturers to provide compensation to trial participants/nominee, if any drug related anomaly is discerned at a later stage & accepted to be drug related injury or death. Revised Indian Compensation Guidelines advocate the principle of No-Fault Compensation, what and how much to compensate for. This too is gravely insufficient in addressing the compensation issues unique to HIV vaccine clinical trials.

Who will pay the compensation for life long? What is the states responsibility in compensating an individual? How long should be adverse effects be monitored? Here we should recollect that the HIV vaccine related side effects may appear after many years, we are yet to understand the virus & its disease mechanisms fully. Post surveillance period of coverage for compensation is not mentioned in any international/ national documents, as these are not tailored to the needs of HIV vaccine clinical trials.

\footnote{Id.}
The latest guidelines on compensation for trial related injury in India has not considered the ethical and non medical social harm which a HIV vaccine trial participant may face after conclusion of the trial. It is totally insensitive, inadequate and unjustified if a compensation formula is adopted without considering the unique issues related to HIV vaccine clinical trials. It is also not very clear as to how to ensure the compliance of post trial medical access related to trial related injuries.

To add to the existing complexities, there may be bankruptcy issues of sponsor or the sponsor may be no longer in business, leaving behind the trial participant to suffer for his humble attempt to contribute for a noble cause. It is imperative that the regulatory authorities ensure compliance of the sponsor for any trial related injuries by demanding a guarantee or the state should step into the shoes of the sponsor to help the trial participants in view of the benefits the community , should there be a vaccine invented.

4.23.2 .11Non Availability of HIV Insurance as part of Health Insurance

Clinical Trial Insurance is compulsory in certain countries like Germany, France, Japan, Poland, Greece, and it is not mandatory in countries like India, as per the statute\textsuperscript{361}. A clinical trial insurance covering various risks can protect various stakeholders against the risk involved in conducting the trial. A drug manufacturer can have product liability and the investigators as well as the members of the ethics committee may have professional liability insurance. A sponsor may take a general liability/ professional liability insurance. An HIV vaccine trial may involve risks which are unforeseen and it will be in the interest of the participants as well to cover the treatment costs against any injury in connection with the trial.

There are three main types of insurance relating to clinical trial insurance, (a) Bodily injury/death coverage to a patient undertaking the trial as describe and defined by the protocol,(b) Error and Omissions cover particularly in respect of the production of the protocol and Participant Information and Consent form (PICF) (b) Medical Malpractice coverage for the Investigators and clinical staff undertaking the trial\textsuperscript{362}.

The EU directive\textsuperscript{363} provides that a clinical trial may be undertaken only if a provision has been made for insurance or indemnity to cover the liability of the investigator and the sponsor. Further the ethics committee is required to consider the indemnity or insurance to cover the liability of the investigator or sponsor before giving any opinion on matters referred to it .The directive does not specify on the insurance for protection of the subjects or on no fault compensation.

The Indian GCP Guidelines\textsuperscript{364} requires the sponsor to agree, to provide compensation for any serious physical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible, before the research begins.

In India, many insurance companies are providing Clinical Trial Insurance policy indemnifying the insured against any claim on account of injury to research subject caused by or arising out of participation in the clinical trial .The terms and conditions may differ for various companies. The Clinical Trial Liability Insurance (no fault compensation) of Bajaj Allianz General Insurance Co Ltd mentions that the claim period as mentioned in the policy is 90 days following the expiration of the period of insurance. The major exclusions noticed are (1) liability in respect of persons employed unless the employee is a research subject (2) Contractual liability assumed by the insured , except compensation attached under a


\textsuperscript{363}Art.3.2. (f), Directive 2001/20/EC of the European Parliament and the Council.

\textsuperscript{364}Clause 2.4.7.1, Good Clinical Practice Guidelines, ICMR.
compensation agreement (3) Penalties, fines and liquidated damages, exemplary damages arising from a multiplication of compensatory damages (4) amount specified in the retention clause (5) any liability arising from a clinical trial not approved by ethics committee or any other licensing authorities (6) failure of intended medicinal purposes (7) failure or departures from protocol (8) intended or expected injury (9) failure to obtain informed consent (10) pre-existing medical conditions (11) diseases – any claim arising out of any mutant or variant of AIDS etc.

A shorter claim period as stated in the policy document may not be of much assistance to the sponsor or participant of an HIV vaccine clinical trial in view of the possibility of many long term complications that may develop. The period of insurance coverage may play a key role in Insurance of HIV vaccine clinical trials, in order to give effective protection to the subjects.

Clinical Trial (Professional Liability) Insurance by S.B.I .General Insurance Co. Ltd allows claim for damages during the contract period and a post trial period up to sixty months. The policy disallows any personal damages that occurred because the trial subject deliberately, or apparently deliberately, contravened the express instructions of the people in charge of carrying out the clinical trial. Such a condition is not in the best interest of the claims if any of the participants belong to the high risk group, participating in the HIV vaccine trials. Intentional inflicting of injury may not always be covered under insurance, however if the cause of injury is based on the misconception of the therapeutic effect of a vaccine, can a participant claim damages. The limitations cast on an insurance policy will not affect the liabilities and obligations of the sponsor, but policy with better protection to the subjects will facilitate the research industry as well.

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The insurance policy document also excludes personal damages to the extent of known degree of adverse reactions expected from the drug, as per the current state of medical knowledge, and more serious damages could have occurred if the patient had gone for a standard therapy to treat his illness. Personal damages to a person in the control group in so far as they are attributable to the application of drug product that has been licensed for this indication. The policy document also imposes a condition that the trial subject must take or submit to all the appropriate measures that help to identify the cause and the extent of the damage that has occurred, and that help to reduce such damage\textsuperscript{367}. This seems to be unreasonable in many cases given the socio educational back ground of the participants.

Deviation from the protocol knowingly by the CRO or researcher can be exclusion from the liability. In India, the intervention of the Supreme Court on the issues related to clinical trial was believed to lead to a more orderly growth in the Insurance Industry. The clinical trial liability insurance segment could see a period of stable and sustained growth, as the market is expected to become more professional for trials\textsuperscript{368}.

No fault compensation is where there is only a need to prove causation, without admission of any legal liability. In fault-based models, such as tort or the administrative system proposed by the American Medical Association in the late 1980s\textsuperscript{369}, the claimant must prove four elements: duty, injury, causation, and negligence. No-fault systems eliminate the requirement of proving negligence. In

\textsuperscript{367}\textit{Id.}


India, no fault liability is recognised under the Motor Vehicles Act, 1988. It was observed by the Supreme Court that\(^\text{370}\)

*Per* Justice Venkitaraman, E.S.,

“whereas pedestrian without negligence on his part is injured or killed by a motorist whether negligently or not, he or his legal representatives as the case may be should be entitled to recover damages if the principle of social justice should have any meaning at all”.

The principle of social justice demands no fault compensation for HIV vaccine clinical trial participants. Unlike many other clinical trials, these trials are conducted on healthy individuals, who are willing to be the subject of a research for the cause of the humanity. Hence there is a social obligation cast on the government as well as the community to protect them, which demands to make the no fault liability compensation be statutory. Professional liability insurance for investigators and ethics committee and a general liability insurance covering the entire risks in the clinical trial can make a complex HIV vaccine clinical trial much easy and hassle free, which can also help the industry to minimize and cover the enterprise liability and grow further.

**Insurance for Trial Participants**

Health and life insurance will be a challenge for participants having vaccine induced sero-positivity. Many insurance companies will reject the application for persons with HIV sero-positivity in view of the low mortality rate. The Insurance Regulatory and development authority of India (IRDA) has issued a draft circular\(^\text{371}\) which was implemented with effect from 01-April 2014, life insurance

\(^{370}\) Gujarat State Road Transport Corporation v Ramanbhai Prabhattbhai and another, AIR 1987 SC 1690 (Supreme Court of India).

for people living with HIV and AIDS and health insurance for people acquiring HIV after the commencement of the insurance policy. The circular states that the mortality study conducted by the Institute of Actuaries of India may be referred for pricing the risk, apart from following the standard underwriting guidelines for life insurance products framed by the life insurance council of India. However the circular does not consider health insurance for people having HIV as a pre-existing illness. In India, Star Health\textsuperscript{372} has issued a policy for HIV care wherein NGOs and societies working for people living with HIV can propose their members or beneficiaries, for coverage. This is without age limit. Though HIV was exclusion, in the policy, it was clarified that the treatment expenditure of other opportunistic infection of HIV is covered, provided that at the first commencement of insurance under this policy, their CD\textsubscript{4} count is not less than 350.

However in India, the Insurance companies are not providing insurance policies which are specific to individuals participating in the clinical trials save and except those clinical trial insurance policies, which may cover the risk of the sponsor, even post completion of the trial. The HIV Testing Protocol of the Life Offices' Association (LOA) has been adapted to accommodate people who will be participating in clinical trials for an HIV vaccine, The decision by the LOA was seen as a significant step forward within South Africa, ensuring that HIV vaccine trial volunteers are not discriminated against, as a result of their participation, when applying for insurance after HIV vaccination\textsuperscript{373}.

HIV vaccine clinical trial participants are likely to face the issues related to vaccine induced sero positivity, which can deny an insurance policy to them. Even if an insurance policy is provided, it could be with loading, which could


make it unaffordable for a participant from a socially and educationally backward background.

Vaccine induced sero-positivity, the unpredictable nature of the phenomenon, its potentially long duration, and the complexity of social interactions associated with HIV testing make the delivery of these technologies expensive and logistically challenging. Trial sponsors recognize an ethical obligation to support trial participants to the best of their abilities, and many sponsors currently spend considerable resources to study and mitigate the potential harms encountered by participants with vaccine induced sero positivity.\(^{374}\)

In India, many insurance companies are not considering AIDS as a critical illness. HIV/AIDS can be included in the list of conditions that is covered under a Critical Illness policy. This is being done in a number of countries such as Australia, New Zealand, Hong Kong, United States and South Africa. It is usually restricted to medically or occupationally acquired HIV. Medically acquired HIV refers to infection as a result of a blood transfusion. Occupationally acquired HIV would often be restricted to medical professions such as doctors, nurses and laboratory workers.\(^{375}\)

HIV/AIDS exclusion clauses were first introduced in South African policies in 1988. These clauses typically exclude death, disability or critical illness where it is a direct result of HIV/ AIDS or where it is accelerated by HIV/AIDS. The efficiency of these clauses has been extensively debated and it is now widely accepted that they are not effective measures for controlling HIV/AIDS-related risks. The main concern with exclusion clauses is that at claims stage it is difficult to determine whether a death has been related to HIV/AIDS. The HIV attacks the immune system allowing opportunistic infections such as Tuberculosis and


Karposi Sarcoma to take hold. These conditions are often registered as the cause of death. In fact, in India, hospitals have been instructed not to mention HIV/AIDS on a patient’s discharge or death certificate. The only place where it should be recorded is the case sheet. Also, as there is still a high degree of stigma attached to HIV and AIDS, the doctor may not record the death as due to AIDS. It may also be that the doctor is unaware of the HIV status of the deceased. The point is that while exclusions may sound workable in theory, enforcing them is very difficult. In addition, from a public relations perspective these clauses are not very attractive.

In view of the high risk behaviour exhibited by the preventive HIV vaccine trial participants and also their involvement in the research, it is unlikely that they may get a life or health insurance at normal rate. Chances of any adverse events or long term complications cannot be ruled out; as such the underwriters may consider the HIV vaccine trial participants as a risky investment, which may result in such individuals unlikely to get a normal premium rate.

In view of the need for a HIV vaccine and for greater protection of the HIV vaccine clinical trial participants, it will be beneficial for all the stake holders if insurance protection at individual level also can be available to subjects, as the clinical trial liability insurance policy coverage available through sponsor could be of limited period linked with the trial, or a specified follow up period thereafter.

4.23.3.12 Sharing Benefits of Vaccine Trials with Subjects

Once the vaccine is proved to be effective, it should be made available to the populations in the countries where the trials were conducted at an affordable cost. However, two questions arise: How can accessibility be ensured and how broadly can the product be made available? Should access be limited to those at risk for acquiring infection or to be extended to the general population?  

376 S. Jameal, supranote 123.  
The persistence of controversies related to reasonable availability of vaccines/interventions proven to be useful during the course of clinical trial reflects that the existing ethical guidelines can be interpreted in multiple ways, are sometimes contradictory, or rely on unstated, yet controversial, ethical principles. 378

Access to a demonstrably safe and effective HIV vaccine finds ethical justification in both justice and beneficence obligations. Access is also a critical human rights issue involving complex questions of equity and global availability of appropriate health care. There had been debates about which groups should have access — trial participants (especially placebo recipients), the community from which they are drawn, high-risk groups residing in the host country, other inhabitants of the host country — and about mechanisms for ensuring such access. Another issue is that who would take the decision. This would be a herculean task as the vaccine would be quite expensive initially, at least in the first years of development and thus mass use in economically backward countries would be problematic. Accessibility of the vaccine at an affordable cost becomes an issue to be addressed.

Access to a low cost vaccine, or a free vaccine post trial was identified as a facilitator of HIV Vaccine clinical trial participation. 379

UNAIDS guidelines recommend that: any HIV vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials, as well as to other populations at high risk of HIV infection. 380

379A.M. Nyamathi, supra note 228.
Exploitation of Vulnerable Population

Exploitation of vulnerable population is nothing new in clinical research field. There have been countless examples of research subjects being exploited during the course of the study. Thomas Kerns in his book narrates few examples:

There had already been allegations of serious ethical misconduct in the performance of early HIV vaccine clinical trials. It is accused that the giant pharma companies intentionally initiate vaccine trials in developing countries since there is little or no provision for ethical review of research. Also it is accused that HIV vaccine clinical trials were conducted on small children who were too young to know what was happening to them. There has also been a charge of withholding data about deaths of vaccinated subjects in order to make the results appear better. 381

Women, adolescents & children are at high risk of development of AIDS due to their vulnerability, social status, lack of access to HIV prevention education and means. As per CIOMS guidelines, children should not be included in a trial if that might equally be carried out in adults. That left us with one option, i.e. to carry out Phase IV trials in children, once Phase III trials in adults have demonstrated efficacy. This time lag of several years would make many more children infected with HIV, before a vaccine is approved for them. 382

Subjects from developing countries also get exploited as mentioned earlier. There were allegations of developing country subjects as guinea pigs for their wealthier counterparts in developed countries. As per Belmont Report, under the principle of Justice, research subjects should be chosen “for reasons directly

381 T.A. Kerns, supra note 195.
related to the problems being studied” and not “because of their easy availability, their compromised position or their manipulability”. Even the case in India was not different till the time the Apex Court intervened in relation to the PIL submitted before it. The issues still remain unanswered.

4.23.3.14 **Standard of Care**

The initial vaccines may not be 100% effective. This will create a set of ethical problems unique to HIV vaccine clinical trials. A few subjects in the test arm of the trial may get infected with HIV. Also those in the control arm who received placebo may get infected despite of the counseling provided. The treatment to be provided to those who seroconvert due to the trial has attracted attention globally. Ethical considerations relevant to treatment for trial participants include global equity for participants in HIV vaccine trials and sponsor obligation to provide care and treatment according to their resources. These ranges from providing “best proven treatment” to “the prevailing standard of care available in the host country”. The therapy, ie: antiretroviral drug are expensive, availability is limited and may have to be taken lifelong. This requires that the therapy is lifelong failing which resistant strains of the HIV virus will be common. In such a scenario, asking the sponsor to give treatment to subjects for lifelong is not economically feasible. There are researchers of the opinion that researchers are ethically not obliged to provide treatment, HIV vaccine not being a therapy and only a vaccine.385 386

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386 id.
It has been argued that providing the highest standard of treatment (including antiretroviral) fulfils ethical obligations most faithfully. In resource-poor communities, however, where individuals do not have routine access to such treatment, the availability of drugs solely through participation in a trial is likely to constitute undue inducement. Participants have the right to receive direct benefits as a result of their participation, but it is not easy to determine what is an acceptable treatment package that constitutes benefit for participants without exposing them to undue coercion. The level of treatment provided must also be sustainable beyond the end of the trial, so that participants are not compromised.

Debate has focused on whether treatment should be offered at the level available in the sponsor country (including antiretroviral therapy), at the level available in the host country, or at a level decided upon by the host. The UNAIDS guidelines present all three as possible levels of treatment, but assert that account must be taken of the higher standards and additional resources brought in by the sponsor. Participants are not, therefore, to be consigned to poorer standards of treatment than could reasonably be provided for them as part of the research protocol.

Sanctioning treatment provision at the level available in the host country may effectively consign participants in resource-poor countries to inadequate treatment or even no treatment at all. There is no definitive answers to dilemmas whether the ART need to be provided for the duration of the trial, for a specified period after the termination of the trial or for life.

Deliberations should involve multiple relevant parties. The UNAIDS guidelines provide detailed criteria, and suggest including some or all of the following options: counseling, treatment for STDs, prevention and treatment of opportunistic infections, palliative care, home-based care and antiretroviral

\footnote{Post Note, Research Ethics in Developing Countries, 4, No 304, (April 2008) available at http://www.parliament.uk/parliamentary_offices/post/pubs.cfm (Last visited on July 19, 2009).}

\footnote{J. Thomas, supra note 118.}
therapy. Benefits must be balanced, but not operate as inducements to volunteers.\textsuperscript{389}

4.23.3.15 Risk of Individual Vs Benefits of Society

The procedure of testing vaccines in pre clinical animal studies is quite simple and clear. It involves that the animal is injected with the vaccine to be tested and wait for the immune response to develop. Later, this is challenged by deliberately injecting the animal with the virus. We watch and see whether the animal develops the disease or not.

Testing vaccines in a similar fashion in human beings is not ethical. Unfortunately, similar direct vaccine challenge experiments were carried out in Jewish prisoners at Buchenwald and Natzweiler concentration camps between 1941 & 1945. Though it is unethical to deliberately inject healthy human beings with such virulent pathogens, many such incidences are available in the pages of history.\textsuperscript{390, 391}

An average of 1000 soldiers was being lost to Typhus everyday and the situation was so urgent and a vaccine was desperately needed. Thus a group of

\textsuperscript{389}UNAIDS, supra note 313.


\textsuperscript{391}"Most of them are trained physicians and some of them are distinguished scientists. Yet these defendants, all of whom were fully able to comprehend the nature of their acts, and most of whom were exceptionally qualified to form a moral and professional judgment in this respect, are responsible for wholesale murder and unspeakably cruel tortures." Grave and unusual charges were imposed on these physicians for murder, torture & other atrocities committed in the name of Medical Science.

concentration camp inmates were injected with antityphus vaccine, the efficacy of which had to be tested. Later all inmates were infected with typhus. The inmates who were not injected with vaccine were considered as control group. Similar experiments were carried out against spotted fever, influenza etc.\textsuperscript{392} The risks borne by the individual subjects were weighed against the benefits that might occur to the society at large. Dr Gerhard Rose, Head of Institute of Tropical Medicine in Berlin was made to believe so.\textsuperscript{393} This approach of moral decision making by attempting to make moral judgments based on a quantification of cost and benefits of human act is called utilitarian approach. The Nuremberg Tribunal observed that the application of utilitarian justification to human suffering is heinous.

The Royal College of Physicians took the view that the subjects should be enrolled in clinical trials only if the knowledge gained from research is likely to be of great practical benefit and there is no other means of obtaining that knowledge. Declaration of Helsinki stressed that this is especially important when human subjects are healthy volunteers.\textsuperscript{394}

In HIV vaccine trials, we need volunteers in a regular course of their lives, putting themselves at risk of infection. This is the only way to test HIV vaccine in human beings. If no subject ever engaged in risky behavior, the vaccine would never be tested against the real virus and there exists no way to find whether it works or not.

The Philosophy behind Doctor’s Trial at Nuremberg was that every human being has worth in themselves, and is not merely to be used as a means for the benefit

\textsuperscript{392} T. A. Kerns, supra note 195.
\textsuperscript{393} OFFICIAL TRANSCRIPT OF THE MILITARY TRIBUNAL IN THE MATTER OF THE UNITED STATES OF AMERICA AGAINST KARL BRANDT ET AL, DEFENDANTS, SITTING AT NURNBERG, GERMANY, ON 21 NOVEMBER 1946, 1000--1110, JUSTICE BEALS PRESIDING. available athttp://nuremberg.law.harvard.edu/NurTranscript/TranscriptPages/10_010.html, (Last visited on January 29, 2015).
\textsuperscript{394} Randomised Controlled Trials, supra note 201.
of others, even if that benefit is very great. It is this very philosophy that was promulgated by noted German Philosopher Immanuel Kant, "so act as to treat humanity, whether in thine own person or in that of any other, in every case as an end withal. never as a means only."

Dr Claude Bernard (1865), one of the classical formulators of medical ethics summarized as under:

"The principle of medical and surgical morality consists of never performing on man an experiment which might be harmful to him to any extent, even though the results might be highly advantageous to the society, i.e.: to the health of others." 395

AIDS Action Foundation Working Group on design of HIV vaccine clinical trial states that "This hope for societal benefit should never be used to justify excessive risk to individual subjects." 396

In HIV vaccine research, there may be temptation to weigh the risk of individual subjects against the benefits of society. The moral charge to expedite development of an effective vaccine appeared at times to conflict with the ethical imperative to safeguard the rights and welfare of subjects. 397 Since there is a serious and urgent need to develop a vaccine, there is a fear that the ERCs make their deliberations pro society. It has often been articulated that ERCs remain as committees to protect the legal and economic interest of the companies or agencies in which they are attached, and not as committees for protecting the interest of research subjects.398, 399 Care should be taken that individuals involved in HIV vaccine clinical trial should be placed at supreme regard and all their rights to be protected. Care should also be taken to minimize

396 Id.
397 A. L. Avins, supra note 199.
398 T.A. Kerns, supra note 195.
399 D. Guenter et al, supranote 116.
risks associated with the trial, as much as possible. Benefits of the society should never be out weighing the risk of the individual subject.

4.23.3.16 Human Rights Issues and HIV Vaccine Clinical Trials

Human rights are an umbrella term encompassing many issues we have already discussed earlier. International law and codes of ethics address both the rights of individual participants in human trials of HIV vaccines and broader issues of equity and access affecting whole populations. While codes of ethics are directed more towards the relationships between individuals (researcher/research subject), the human rights framework addresses state responsibility. These two sources complement each other. As Jonathan Mann observed, rather than seeing human rights and ethics as conflicting domains, it seems more appropriate to consider a continuum, in which human rights is a language most useful for guiding societal level analysis and work, while ethics is a language most useful for guiding individual behavior.\textsuperscript{400}

The Constitution of India upholds the dignity and rights of every single individual and is the supreme document in this regard. Legitimate human rights concerns have been raised most particularly in the context of HIV/AIDS, where affected people suffer extensive stigma and discrimination and where there is a possibility of limited access to HIV vaccine once it is developed. The human rights issues involved in HIV vaccine research are potentially as challenging as other hurdles that are faced by the scientific community. Promoting human rights protects the inherent dignity of persons affected by HIV/AIDS, and is necessary for achieving the public health goals of reducing vulnerability to HIV infection, lessening the adverse impact of HIV/AIDS on those affected, and empowering individuals and communities to respond to the epidemic. Respect for human rights is key to the development and distribution of HIV vaccines. Yet vaccine research on human

\textsuperscript{400} M.M. Jonathan, \textit{supra} note 126.
subjects in developing countries raises considerable ethical and human rights concerns.

Much HIV vaccine development work will take place in under-resourced communities, where people are at high risk of HIV infection, so the human rights implications for participants and other members of the community need careful consideration in issues of resource allocation to HIV vaccine development, the protection of trial volunteers from the risks of participation, and access to a successful vaccine. Access is also a critical human rights issue involving complex questions of equity and global availability of appropriate health care. Vaccines form a very small part of the international pharmaceutical market and vaccine development for years lacked adequate funding or support, so organizations like the IAVI took up the development of an HIV vaccine as a human rights issue of pressing ethical concern.

The ethics of health care and medical research revolve around the issues related to basic human rights and provision of health care, assurance of safety and benefits to the communities, prevention of harm of any kind while protecting privacy and confidentiality and ensuring global justice in these endeavors. The challenges being faced by the policy makers, healthcare providers, biomedical researchers, behavioral scientists, pharmaceutical industry and the International agencies are tremendous, mind boggling, complicated and controversial. There is no easy solution at present. Situational analyses are to be done and decisions taken to suit the local needs and sensitivities while taking into consideration cultural nuisances at different locations. The dream to have a golden, 'universal' ethical standard in the world is totally thwarted by the HIV/AIDS pandemic. However, the silver lining is the emergence of newer partnerships, strategies, policies and political commitments which should help in containment of further

401 P.A. Leider, supranote 129.
403 An AIDS Vaccine, supranote 120.
spread of the disease. 404 If human right is understood to incorporate adequate health care and prevention resources, then an accessible, easy to administer HIV vaccine would be an enormous victory for human rights, particularly in poorer countries hit hard by the epidemic. 405

Thus, we can see that the ethical issues of a HIV vaccine clinical trial is full of complex issues, which if not addressed in an effective manner by policy reforms will make the HIV vaccine trial scenario really worse.

404 V. Muthuswamy, supranote 281.