CHAPTER VII
CONCLUSIONS
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RECOMMENDATIONS
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With no known cure and a need for lifelong treatment, coupled with the stigma and discrimination unique to the disease, HIV/AIDS has caused unprecedented distress and death among people all over the world. A safe and effective HIV vaccine is the need of the hour. But the progress has been slower for a variety of reasons.

Variability of the virus, probability of having different strains of virus in the same individual, capability of virus in evading immune surveillance, chronic and latent nature of illness etc are few of the many unique characteristics of HIV which scientists have to tackle. Lack of appropriate animal models and uncertainty as to the correlates of protection makes the scenario even grimmer.

HIV mutates constantly in the body of the individual, eventually becoming resistant to the drugs being administered. Since those infected individuals remain infected all through their life, they can transmit drug resistant virus to others.

Drug therapy is prohibitively expensive and compliance is cumbersome. Ensuring lifelong compliance in those affected with HIV is a herculean task. Thus the therapeutic treatment of AIDS, which is a cocktail of highly potent medicines, is not a practical one. In this dark scenario, a preventive vaccine only offers a ray of hope.

The potential value of a preventive HIV vaccine to protect individuals from AIDS is thus indisputable. It has been speculated that a preventive vaccine that confers 100% protection in 95% of all vaccine recipients could almost eradicate HIV within 25 years. Scientists believe that, even a low efficacy vaccine, that only provides protection for a few years, can save many lives if significant coverage is maintained over years.

Drug discovery process involves complex human experimentation in a phased manner. Conducting a methodically and culturally valid research on HIV vaccine
stretch the current norms of both medical ethics and capabilities of regulations. Historically, individual conscience, training and ethical culture were considered sufficient. These had repeatedly fallen short of expectations in the history of human experimentation. It is highly insensitive to conduct such complex research by simply depending on non binding ethical documents, many of which were formulated even before the disease causing virus was discovered.

Many puzzles are yet to be solved in relation to HIV vaccine pathogenesis. The ethical dilemmas that can arise out of HIV vaccine clinical trials are very complex that a separate set of regulations giving attention to all ethical issues are needed to address them. Regulatory amendments guarantee nothing but the enforceability of the same, compels those involved to be more conscious. Simplifying these complex ethical dilemmas and streamlining of procedures require deliberations at various levels with all stake holders and community members.

It is a known fact that industry funds trials that tend to produce industry friendly results. They collaborate with industry friendly investigators and industry friendly institutions. Institutional mechanisms for ethical reviewing of research involving human subjects in India are still in infancy. Tremendous effort is required to strengthen them, making them capable of fulfilling their stated missions. All professional associations involved in the clinical trials have collective responsibility to scrutinize the ethical competence, capacity and practice of their member’s research.

There is no single legislation in India and many other countries which may address various ethical issues involved in HIV vaccine clinical trials.

The development of the law relating to experimentation on human subjects is also related to the sufferings of the innocent, on whom the experimentation was conducted without compliance of the ethical principles related to human research. The evolution of law related to clinical research can be traced from the Nuremberg code, international conventions and guidelines. The Universal
Declaration of Human Rights, Helsinki Declaration, Belmont report, guidelines issued by WHO and CIOMS viz the International Ethical Guidelines for Bio Medical Research Involving Human Subjects, Good Clinical Practice Guidelines, Universal Declaration of Bio ethics and Human Rights, the Joint United Nations Program on HIV and AIDS or UNAIDS, etc has contributed considerably to the law relating to clinical trials as it stands today.

Among the countries analyzed, no country or region has a law which addresses all the ethical issues involved in the preventive HIV vaccine clinical trials. United States has a more comprehensive regulatory system and anti discriminatory laws, which may protect the trial participants. The partner notification laws in various states pose a challenge to balance the confidentiality issues and public health safety compliances. Some of state laws can compel a person to disclose the HIV status. It is not mandatory to provide free medical treatment in case of trial related injuries in connection with the participation in clinical research or to provide for long term treatment, post completion of the trial, unless it is specifically agreed at the time of enrolling for the trial. Informed consent process is stringent, which will not include any exculpatory language which may waive of the legal rights of the participants against sponsor from liability against negligence.

FDA issues various guidance documents, which brings clarity and assistance in complying with the regulations. The federal regulations does not provide for appeal against the decisions of Institutional Review Boards. However transfer of clinical trial review responsibility from one IRB to another is permitted under US law.

The legislative frame work in European Union with regard to clinical trial is an umbrella legislation, the enforceability of which may also depend upon the national legislations. The clinical trial approval happens at a national level. The new clinical trial directive which is to be effective from 2016 is expected to bring more significant changes in the clinical trial industry. European union is having a
well guarded data protection system, with the data subjects having more control to personal data.

Indian clinical trial scenario has changed drastically in view of the intervention of Supreme Court and certain other legislative changes. The changes have brought more protection to the trial participants; however, there is more scope for change.

The fundamental principles related to human experimentation like the requirement of informed consent, recognition of inherent dignity, equal rights of members of human fraternity, concept of bodily integrity, right to life, liberty and security of persons need to be protected.

Many of the ethical issues in HIV vaccine trials are not addressed in the legal and regulatory frame work for vaccine trials in India, viz,

1. **Whether randomization in HIV vaccine trial is ethical or not? Is placebo control mandatory?** Randomization is a process by which the participants are grouped together on a random basis and deployed to either a placebo arm or test arm during the clinical trial. Even after amendments to Helsinki declaration, more clarity is required with regard to placebo control in clinical trials and more deliberations are required in this regard. The study may be either single blinded or double blinded. The participants deployed in the placebo arm, if engaged in high risk activities, thinking that they got vaccinated, will get infected with HIV. Though they are counseled during informed consent process regarding test arm and placebo arm in the clinical trial, denying the benefit of vaccine to a person who was willing to risk his health for the benefit of the community, could be argued as a violation of right to health and healthy life. Randomization is arbitrary and can be considered as discriminatory since it violates autonomy of the subject, i.e., and the subject choosing which arm he wants to be in. It could be argued that such a clinical trial could be violative of Article 21 and Article 14 of the Constitution of India. Further, placebo control can be considered as deception, given the social and educational background of the participants is
concerned. Confirmatory HIV vaccine clinical trials which are intended to validate the results of previous experiments should not begin with an assumption of 
*equipoise* since prior information about efficacy and safety exists. Hence it would 
be more beneficial if CDSCO issues a guidance document in this regard after initiating a consultation process.

2. *Why should any healthy individual volunteer to participate in HIV Vaccine trial?* A successful vaccine trial is only possible through the participation of healthy individuals. So there has to be sufficient number of willing individuals to be available for recruitment. If safety of the participants is assured, then more people will be available for recruitment. Most of the international guidelines suggest that there shall not be any inducement for participation in HIV vaccine clinical trial. The participants are generally of high risk group and belong to the socially and economically weaker sections of the society. The motive for participation could be altruistic motive or based on therapeutic misconception, though counseling is given to remove all such misconceptions. An individual is not personally benefitted otherwise by the participation. The participant is risking his life for the benefit of the society. Thus he needs to be protected, though it can be argued that offering too much protection can also be inducement. It is equally important to exercise vigil in providing fair and not excessive compensation and health care benefits to avoid inducement of subjects.

At present the Drugs and Cosmetics Rules offer, compensation for any trial related injury, and in case of death, treatment for any trial related injury as long as it is required. However the basis suggested for calculating the compensation is inadequate. There is no mechanism to enforce the statutory provisions, other than the penal provisions which may indirectly compels compliance, however the Drugs and Cosmetics Act (Amendment ) Bill 2015 is still at a draft bill stage.

The principles of justice and fairness require that the participants are to be adequately compensated, apart from the concept of redistribution of benefits and burdens. There are arguments that if a subject is injured during the trial due to high risk behavior, there may not be any obligation on the part of the sponsor to
compensate. Those who advocate this view is not considering the fact that a participation in a clinical trial might have contributed to the increase in risk behavior of the participant. One could also find that in India, the person who falls in the category of upper sections of the society, who are informed and educated, may not participate in the HIV vaccine clinical trials, primarily due to their awareness of the risks involved. It is incorrect to argue that only the socially and economically backward sections of the society are having altruistic motives. The fact is that, subjects generally belong to the poor, uneducated class of society, who can be influenced and easily recruited.

Adding to the perplexity of this complex issue of compensation of subject is the fact that, it is *not possible* as on today to attribute many of the side effects of HIV vaccines which may develop many years post vaccination. This is due to the fact that HIV belongs to the family of retro viruses in lentiviridae which are very latent in action. Thus, development of tumor, HIV or many such diseases years after vaccination, as a sequel of the vaccination may not be attributed to the participation in HIV vaccine trial.

How could we ever compensate non physical injuries? Till now, no country has developed an effective guideline for compensating the non medical social injuries to be borne by a HIV vaccine trial participant and his significant others. More deliberations are needed in this regard.

A vaccine will be a distant dream and delayed further, if the subjects are not available or recruited in sufficient number. So, the state as well as the sponsor has a duty to protect and care for the subjects who were willing to take a risk for the benefit of the humanity.

Hence a *Clinical Trial insurance* has to be made compulsory for HIV vaccine trials, with *unlimited liability* for compensating the trial participants, and reimbursing the treatment expenditure as long as it is required, keeping in view of the lifelong infectivity of the disease. Any injury which is directly or indirectly
attributable to the participation in the HIV vaccine clinical trials needs to be compensated.

3. **Informed consent issues in HIV vaccine trials:** The scientific community involved in HIV vaccine research for more than three decades are yet to unveil many of the characteristics of this highly evading virus. The exact risk in participation of a HIV vaccine trial is not known and thus obtaining “true” informed consent is impossible. Hurdles in obtaining a true consent also stems from the fact that the complex medical jargons maybe perplexing to a non medical personnel. The recent changes in the regulatory scenario making it mandatory to conduct audio and video recording of the informed consent process will help to understand to what extent the participant understood the risks which he is undertaking. But in case of HIV vaccine trial, how to give consent for undertaking risk which cannot be ascertained, at the time of enrolment of the trial and the social stigma and discrimination associated with the participation?. The capability to understand the risks and issues involved in the participation of the vaccine trial for each participant may be different. Hence it could be possible that with regard to consent to be given or contract to be entered by the participants, there can be situations where there is no consentus ad idem, ie meeting of minds, which is a basic requirement of the contract, in the absence of which the contract may be vitiated.

4. **Confidentiality issues in HIV Vaccine trials:** The provision of Information Technology Act 2000 and Good Clinical Practice guidelines ensures the confidentiality of the personal data of the subjects. India does not have any law which requires compulsory disclosure of HIV status like in US, or partner notifications laws. However judicial view is in favour of partner notification, in case of HIV infected persons. India being still a male dominated society at least in rural areas, a decision taken by an individual, may have an impact on the family as well. The issues related to vaccine induced seropositivity can be better managed if the family is aware of his participation. Where community is involved in the HIV vaccine trial, confidentiality could be an issue, within the community.
The breach of confidentiality can increase the chances of discrimination and other social stigma, remedy against which, lies with implementation of the HIV and AIDS (Prevention and Control) Bill 2014 which has not yet become a statute. If mandatory, post trial counseling, as long as it is required, should be provided at the instance of the regulatory authorities, the participant may be able to overcome the stigma and discrimination attributable to the participation in the clinical trials. On top of all this complexities, majority of the information shared by the participants (high risk activities) are not socially acceptable and are even criminal in nature. Thus the participants should be entitled for further compensation and protection in the event of disclosure, which should be incorporated in the statute.

5. Conflict of interest: India needs a regulatory guidance on what amount to conflict of interest and what not, rather than leaving it to the Ethics committee to decide based on various ethical guidelines. The conflict interest can be academic interest, to get fame in successful testing of a vaccine or it can be financial interests by way of grants or employee stock options in case of industry sponsored research. There can be situations where the researcher is counseling with dual intent, ie he is vested with the ethical responsibility to counsel the participants against indulging in any high risk activities, whereas he may be interested in the subject engaging in high risk activities, though he may not expressly disclose it. At present the right to decide on conflict of interest is vested with the ethics committee. It would be more appropriate if the regulatory authorities could initiate a consultation process and issue guidance documents to avoid any possible conflict of interest.

6. Stigma and discrimination: Successful trial of an HIV vaccine can bring fame and honor to a researcher, whereas considering the social realities in India, the participant of a HIV vaccine trial, who risked his health and contributed to the development of the vaccine by way of participation in the trial could face stigma and discrimination in the society. Lack of awareness and the fear associated with the transmission of HIV are one of the reasons for such discrimination. At present
India does not have any anti discrimination law similar to American with Disabilities Act? The HIV and AIDS (Prevention and Control) Bill 2014, prohibits discrimination against persons infected with HIV. However the Bill does not address the issues of people who are living with Vaccine Induced seropositivity which is a different entity altogether. The Bill, once become law will help in addressing the stigma and discrimination faced by the participants of HIV vaccine trials.

7. **Fraud and abuse risk, coercion, undue inducement, and exploitation of vulnerable populations in HIV vaccine trials:** The participants of the clinical trial are generally high risk group people, vulnerable population, who are recruited by reference of NGOs, who may work for these populations. The participant who has participated in one trial cannot join another trial due to antibodies present in the body due to vaccination, and the possible vaccine induced seropositivity status .Given the fact that later vaccines may be any way better in many aspects; this excludes the people who had already participated in HIV vaccine trials. Participants may face abuse risks in many ways, including exercise of coercion; undue influence etc can be exercised against the vulnerable populations. The treatment naïve Indians are popularly ever ready to accept the paternalistic role of the medical professional, thus making therapeutic misconception a reality. A truly independent ethics committee can play a crucial role in preventing those risks. Further the regulatory authorities can also provide help line numbers for providing assistance to needy participants.

Various ethical guidelines suggest that there shall not be undue inducement to the participants to participate in the trial. This was with an objective that people should not risk their life looking at the benefits of participation in the trial. The motive of the participants could be altruistic motive or for a better protection through vaccine. The altruistic motives of trial participants in Indian context are doubtful, that too in a risky trial like that of HIV vaccine. Generally if too much protection is offered that will also amount to undue inducement. In HIV vaccine trials, participant safety is more important as the participants are healthy
individuals. Continued protection, and follow up post trial, should not be considered as undue inducement, in view of the right to life and healthy life guaranteed under the constitution.

Fraud can be on the subjects as well as on the research data, i.e., manipulating results, falsifying the data etc, against which remedies are available under the general law. Any kind of deception can vitiate the contract and informed consent process to participate in the trial. Stringent penal provisions against ethics committee and investigators are required to prevent any kind of research fraud, abuse on the subject as well.

8. Compensation for disability and trial related injury: The Drugs and Cosmetics Rules were amended to provide compensation for death and trial related injuries to the clinical trial participants and treatment to the participants so long as it is required. However, the compensation formula suggested is inadequate. HIV and AIDS are not considered as a disability in the Indian context. Many of the clinical trials related to HIV vaccine, failed and have not given the desired results. The complications which an HIV vaccine trial participant may face are uncertain, in the present scenario. Any health complications which may occur after a long period of time could be contested by the sponsor against any compensation claims as not falling within the ambit of trial related injury and it would be difficult to prove also. Hence a revised compensation formula, especially for HIV vaccine trial participants is required.

There is no employer employee relationship between the trial participants and the sponsor. Thus participants are not entitled for workman compensation or compensation for any accident, or disability during the course of employment. Hence, if any of the trial participants gets infected with HIV, during the course of clinical trial, even though it could be attributable to their risk behavior, may be considered as a disability occurred during the trial and disability compensation is required to be granted to such participants. Special guidance and amendments to the Drugs and Cosmetics Act, 1940 is required in this regard.
9. **HIV insurance as a part of health insurance**: In India, some of the insurance companies are providing life insurance to people living with HIV and AIDS and health insurance for people acquiring HIV after the commencement of the insurance policy, which was a welcome step initiated by IRDA. However, the companies are not considering HIV and AIDS as a pre-existing disease for the purpose of health insurance. A comprehensive clinical trial insurance policy is required to be mandatorily taken by the sponsor to cover the follow-up treatment expenditure and medical expenses to treat any trial-related injury. The Drugs and Cosmetics Act 1940 with rules needs to be amended to incorporate the same.

10. **Sharing the benefits of vaccine trials with the community**: Once a HIV vaccine is successful it is not clear at present, how the benefits of the vaccine will be shared with the country where the vaccine trial is conducted. The principle that the benefits and burden needs to be shared equally applies in this context. The vaccine once successful should be available at a much lower rate in the country where the trial was conducted, and there needs to be separate agreement with the sponsor in this regard, though the Government (the Controller of Patents) has the power to order for compulsory licensing after following the procedure under the Patents Act, 1970.

11. **Standard of care**: More deliberations are required on the standard of care required to be provided to a trial participant. Continuous post-trial monitoring of the participants on long-term basis are required in HIV vaccine trials in the best interests of the participants to see whether any complications are developed due to his participation in the trial. However, any complications developed in the long run may be disputed on the ground that it is not attributable to the participation in the trial. Industry may find it difficult and it may not be economical to monitor a participant for a considerably long period. The current regulations in India suggest that treatment for any trial-related injury is to be provided as long as it is required. In the above backdrop, the state should step in to protect the participant if the sponsor fails to provide the treatment and medical care. Also, provisions
should be made to differentiate the seropositivity of HIV and vaccine induced seropositivity to all trial participants, in case of need. (eg, insurance, travel etc.).

When researchers from developed countries were conducting clinical trials in developing countries, the issue of standard of care was a debatable issue. The treatment given will be as per the standards of the host country. However in a trial like HIV vaccine trials, the participants are required to be provided with the best care available in the world, which should not be less than that of the developed country. Regulatory guidance in this regard is required to make the best treatment available to the participants keeping in mind the altruistic motives of these subjects.

12. Risk of individual vs. Benefits to society: The participants of an HIV vaccine trial are taking a big risk on their health with lot of uncertainties. They are not personally benefitted in the event of discovery of the vaccine but the society will be tremendously benefited by a vaccine. It would be a gift to the mankind indeed.

13. Human rights issues and HIV vaccine trials: Human rights in HIV vaccine trials are closely related to the ethical issues as well. Human rights are mainly concerned with the relationship between individual and the state. The rights of the HIV vaccine trial participants need to be respected, protected and enforced. The public health strategy for HIV vaccine trial participants should be focused on ensuring the safety and enforcement of rights of the participants. The right to highest attainable standard of health needs to be recognized. Given the possible complexities in the health of HIV vaccine trial participant, the right to health and continued enjoyment of the same needs to be enforced.

Right to privacy, and confidentiality of the data related to HIV vaccine trial participants needs to be protected. The existing legal frame work also protects the confidentiality of the data. Legislature should ensure that the antidiscrimination laws are passed to eliminate any stigma associated with HIV vaccine trial participation.
Findings of a study by Nyamathi had revealed that involvement of sexual partners in a clinical trial would facilitate recruitment and retention; since vaccine induced sero positivity could create fidelity problems among marital partners.

It is crucial that we work and analyze and understand the ethical dilemmas. The future of the global HIV/ AIDS epidemic and of millions of lives affected by it, will depend on the ways in which we confront these dilemmas. Since the benefits of HIV vaccine are to be available globally, in terms of universal access principle, there is a great need to develop a global fund in order to compensate the harms of multicentre HIV vaccine studies.

State should mandate a guarantee from the sponsor that he will be providing for post trial compensation of trial participants. State should develop a parallel system of funds to cater for the compensation of trial related injuries of subjects of HIV vaccine clinical trials.

Government could develop alternatives to government directed R & D by buying out patents in exchange of lump-sum payment, committing to purchase certain quantity of vaccine at a certain price, instituting awards to a developer of vaccines. It has been observed that compulsory licensing can reduce the cost of drugs to 75%. Alternatively, government or any private foundation could make an advance commitment to purchase a certain quantity of a vaccine at certain price, if invented. The commitment could take the form of a contractual or binding agreement to buy from the vaccine developer, any new vaccine that meets specified criteria. Since private foundations have continuity of leadership, they can more easily make credible commitments to purchase new vaccines.

Providing access keeps human life and the principle of distributive justice at high regard. It also sends out a message to the host nation that people are not exploited in their country. The international and national guidance documents are not enforceable. They do not create any legal duty to provide for any free / subsidized vaccines. The guidelines provide a moral basis for providing access, but they do not ensure it. These principles are vague as they are drafted to meet
a variety of circumstances. Thus they do not necessarily define what constitute access and how it should be provided. Thus no enforceable international guideline exists that require sponsor to provide access.

Thomas Kerns had proposed a *Participants Bill of Rights*. An American community based group; The AIDS Vaccine Advisory Coalition also advocated the same. A similar document could be globally prepared and disseminated to all the nations participating in clinical trials. *A Proposed Draft Bill for the Protection of the Participants of Preventive HIV Vaccine Clinical Trials* is prepared by the scholar and is annexed.

Despite of all the hurdles discussed at length, the outlook for a preventive HIV vaccine appears to be considerably brighter. Nevertheless, there still remain major obstacles and considerable gaps in our knowledge. Thus, at present, a guarded optimism that an utilizable vaccine could well be available in not too distant future.

Schoub had commented that a HIV vaccine would be an even more valuable achievement than the fulfillment of President Kennedy's pledge three decades previously of putting a man on the moon.

There are no quick fixes to the myriad of problems in HIV vaccine development. It may be many years before a safe and effective HIV vaccine is finally created. But these trials are on the way to bring the world closer to a HIV vaccine. Sustained will, persistence and perseverance only will help us to attain a 'wonder' vaccine.

Building and maintaining trust amongst scientific society, community and larger population is necessary in the HIV vaccine trial process to develop a widely useful and accessible vaccine to fight HIV. What is the need of the day is that laws are to be *honestly* implemented by the regulatory authorities.