REVIEW ARTICLE

HIV Vaccine: Current Status

Vinod Chandran, Anupam Wakhlu, R.N. Mishra, Vikas Aggarwal*, Annil Mahajan**, Amita Aggarwal

Since its recognition as a new disease in 1981, the acquired immunodeficiency syndrome (AIDS) has now become the world's fourth biggest killer, and the most common cause of death in Africa. More than 2.5 million people died of AIDS in 1999. Almost 40 million people are infected with HIV-1 today, 4 million of which are in India. The United Nations AIDS program estimate that new human immunodeficiency virus (HIV) infections are increasing by at least 6 million each year, with India and Thailand being the new 'hotspots' (1). Vaccines are among the most cost effective health interventions. Control or eradication of a few killer diseases has been possible because of an effective vaccine, the most remarkable being the eradication of small pox. Even though a vaccine will not completely replace other therapeutic or preventive measures, a safe, effective and affordable vaccine offers a chance to control the HIV pandemic.

Host Responses to HIV Infection:

Most viral infections are controlled by cell-mediated immunity (CMI). Though initial viremia after HIV infection is controlled within 2 months, the host immune response is not able to eliminate virus completely. HIV gradually depletes and destroys the host CMI, and therefore, the immune system becomes redundant. Longitudinal studies in HIV infected subjects have shown an inverse correlation between CMI and viral load. Long-term non-progressors tend to have more consistent cellular immune responses than rapid progressors (2). Studies with Simian immunodeficiency virus (SIV) infected macaques have shown that a transient reduction in SIV-specific cellular immunity correlates with a sharp but transient rise in plasma SIV RNA titres (3).

Antibodies synergize with other arms of immune system to provide protection. Studies with SIV and HIV models have demonstrated that passive antibody transfer can mediate protection. Low levels of antibody administered 1 day prior to challenge can alter the course of infection with a pathogenic strain of SIV (4).

Immune correlates of HIV vaccine

Most vaccines elicit neutralizing antibodies or CMI, assumed to be correlates of protection. In animal models monkeys have been protected against an HIV or SIV challenge by immunization with attenuated SIV (inducing cellular immunity) or DNA immunization against HIV envelope proteins (including neutralizing antibodies and cytotoxic cells) (5).

Mucosal immunity is an effective way of inducing herd immunity, exemplified by oral polio vaccine. Some people

From the Department of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow and Department of General Medicine *Govt. Medical College & Hospital Chandigarh and **Govt. Medical College, Jammu.

Correspondence to : Dr. Amita Aggarwal, Associate Professor, Deptt. of Clinical Immunology, Sanjay Gandhi Postgraduate Institute of Medical Science, Raebareli Road, Lucknow-226014.

exposed to HIV do not develop infection (absence of anti-HIV antibodies and viral genome). They are classified as 'exposed uninfected' (EU) and have either HIV specific IgG or IgA antibodies in the mucosal secretions or CTL's or both (6). In a mouse model, rectally immunized mice resisted HIV infection by rectal challenge as compared to mice immunized by subcutaneous route. Assay of CTL's in spleen and intestinal tissues (lamina propria and Peyer's patches) of mice immunized by rectal route revealed higher CTL activity as compared to those immunized by subcutaneous route (7).

Feasibility of HIV vaccine

The following observations provide evidence for the feasibility of an HIV vaccine:

1. 'Sydney cohorts' are a small group of patients who were infected by blood transfusion from a single donor prior to 1984. All the infected individuals continued to have high CD_4 counts and did not develop AIDS even after 10 years of infection. This strain of HIV had a naturally occurring defect in the 'nef' gene (8). It was, therefore, thought that a stable attenuated virus could be used for vaccination. However, after 12 years of infection with the above virus, many subjects developed declining CD4 counts and AIDS defining illnesses (9).

2. The 'exposed uninfected' category of individuals, who exhibit HIV specific IgG or IgA antibodies in mucosal secretions and cytotoxic T lymphocytes in blood (6).

Aims

The aim of an ideal HIV vaccine is to prevent infection. However, there is no vaccine fulfilling this criterion as of date; therefore, acceptable alternative goals are:

1. Allowing transient infection but preventing disease.
2. Increasing the dose of viral inoculum required to prevent infection.
3. Allowing subclinical infection, but achieving a lower viral 'set point'.

Would vaccination against HIV allow infection but be able to prevent AIDS? Rhesus macaques immunized with several doses of a recombinant attenuated vaccinia virus, (Modified Vaccinia Ankara that expresses many structural proteins of SIV) were infected with SIV. The immunized animals were infected, but the viremia was 100 fold lower than the unvaccinated macaques. The unvaccinated macaques developed disease in 3-12 months whereas immunized macaques did not develop the disease within period of observation (10).

There is significant relationship between viral set point (6-9 months after infection) and the time in which the patient will develop AIDS. Patients of HIV with highest set point (29-250 RNA copies/mL plasma) had a 50% AIDS-free survival of three years, as compared to 50% AIDS-free survival of 14 years of those with the lowest set point (0.5-4 RNA copies/mL plasma) (11). Therefore, if HIV vaccine could lower the viral set point, it could delay progression to AIDS.

Challenges in vaccine development

1. Genetic diversity of HIV: HIV isolates have been classified into several genotypes or clades. Most strains constitute a major group (group M) that consists of 10 clades, whereas, a few isolates are classified as either group O (Outlier) or group N (New). In a study of subjects infected with isolates of a broad range of clades, all subjects (n=10) showed neutralization responses to the isolate with a poor cross-clade response (12). The findings are similar for cell-mediated immunity (13).

2. HIV induces an antibody response to many of its viral proteins, which have a limited ability to neutralize wild-type isolates. The difficulty in inducing neutralizing antibody is due to the structure of the gP120 molecule, which has a large number of carbohydrate side chains shielding the potential targets for antibody binding (14).

3. Natural infection with a particular strain of HIV-1 does not protect against super infection with another strain of the virus. In Africa, subjects with high-risk behavior are known to harbor multiple strains of HIV-1.

4. Lack of good animal model and infrastructre and training to conduct trials in most developing countries.

5. Requirement of large number of volunteers for clinical trials.

The various strategies undergoing trials in animal as well as humans have been summarized in Table 1 (15).

Table 1-Vaccine strategies (15)

Strategy	Trial status	Advantages	Disadvantages
Eliciting Antibody			
1. Viral surface protein gp 120	Phase 1, 2	Safe, simple to prepare.	Antibodies elicited failed to recognize clinical isolates.
2. Whole killed	Not under study in humans	Presents sur -face protein in natural conformation	Risk of live virus inoculation
3. Pseudovirions	Close to Phase 1	Presents sur- face proteins in natural conformation	Difficult to produce
Eliciting CMI			
1. Live bacterial vectors	Phase 1	Simple, safe, cheap	Limited gene expression
2. Live viral vectors	Phase 2	Exoress desired genes	Difficult to prepare
3. Naked DNA	Phase 1	Simple, cheap	Integration into host genome
4. Replicons	Close to Phase 1	Safe	Difficult to prepare
5. Peptide epitopes	Phase 1	Simple, cheap	Poor immune response
Eliciting Both			
1. Combination 120+ Canary pox vector)	Phase 2	Stimulates arms of immune system	Modest immune response
2. Live atteuated	Not studied humans	Mimics natural infection	Potential to cause AIDS

"Prime Boost" Strategy

In an effort to induce both, CTL and antibody responses, the "Prime Boost" approach have been used (16). A few doses of recombinant viral vector vaccine (the 'prime', inducing CTL's) are followed by or combined with several doses of a recombinant envelope protein vaccine (the 'boost', inducing antibodies). Several recombinant attenuated vaccine vectors have been evaluated in phase1 trials alone and in combination with a recombinant protein envelope boost. All recombinant viral vectors have been shown to be safe and immunogenic. However, the antibody response in humans has been poor.

Alloimmunization for prevention of HIV infection

HIV virions acquire and express the host's cellular proteins, including HLA antigens (class I and class II), on its envelope. Immunization against these HLA alloantigens has been used as a strategy for vaccination (17). In animal models, antibodies to class II molecules have been shown to neutralize SIV and protect against infection. Alloimmune protection would be independent of clade and antigenic changes as a result of mutations. A vaccine recognizing HLA antigens is being tested using SIV-macaque model. The various advantages and disadvantages of this strategy have been mentioned in Table-2.

Table 2-Alloimmunization Vaccine Strategy

Advantages	Disadvantages
1. Potent long term cell mediated immunity	1. Risks similar to blood transfusion
2. Induces high titer anti-HLA antibodies	2. Requirement of immunization against large number of HLA antigens
	3. Effective only for initial HIV exposure
	4. Risk of autoimmunity

Clinical trials

The first phase 1 trail of a candidate HIV-1 vaccine was undertaken in USA in 1987. Till date, more than 60

phase1 trials with approximately 30 candidate vaccines have been conducted in uninfected high-risk volunteers. Most of the trials have been conducted in USA and France. In Thailand, 8 HIV-1 preventive vaccine trials have been undertaken since 1994, including an ongoing phase 3 trial (1) (Table 3).

Table 3-Clinical trials in developing countries

Year	Candidate vaccine	Subtype	Country
Phase 1/2			
1997	Envelope gp 120	B, E, B/E	Thailand
1998	Envelope bivalent gp 120	B/E	Thailand
1999	Canary pox	B	Uganda
2000	Canary pox vector + gp 160 or gp 120	E+E	Thailand
	Canary pox vector + gp 120	E+B/E	Thailand

Initial approaches were focused on vaccination against the HIV envelope protein. At least 13 different envelope protein vaccines have been found to be safe and immunogenic in diverse populations and induced neutralizing antibodies in all recipients. However, these antibodies rarely neutralized the primary isolates of HIV derived from patient blood. Currently, a bivalent preparation of gp120, AIDSVAX is undergoing phase 3 trials in Thailand, and US the results of which will be available by the end of 2002.

'Therapeutic' Vaccination

Patients on highly active anti retroviral therapy (HAART) show a gradual decline in their anti-HIV cellular immune response as the viral load decreases. When HAART is terminated, almost all individuals undergo a re-emergence of viral replication. It may be possible to boost HIV specific cellular immune response by an HIV vaccine after the termination of HAART. This hypothesis was tested in macaques, who were infected with a pathogenic strain of SIV, treated with a combination of antiretroviral drugs, and immunized with an attenuated recombinant vaccinia virus (expressing gag, pol, env genes of SIV). Therapy was terminated, and the animals together with unimmunized controls were followed for viremia. None of the immunized showed a resurgence of viremia after stopping HAART (18). Thus, 'therapeutic' vaccination is a feasible strategy.

Future prospects

Improved understanding of the interaction between gp41/gp120 and host receptors and co-receptors (CCR5 and CXCR4) have led to development of newer strategies for vaccination like fusion inhibitors (19). Researchers at St. Jude's Children's Research Hospital have prepared an immunogen, poly-Env 1, which simultaneously delivers multiple envelope proteins via Vaccinia vector. Initial studies with this immunogen in mice have been encouraging (20). Epitope vaccines, in which epitopes are delivered by DNA, live vector or synthetic peptides, are also under development. Investigators are also exploring the use of 'string of beads' of several epitopes from multiple HIV genes in the same candidate vaccine. The future priorities in HIV vaccine research are to design vaccines that induce strong neutralizing antibody response and strong CTL responses with the use of adjuvant such as interleukin (IL)-2,IL-4, IL-12, IL-15, GM-CSF and dendritic cell targeting. The correlates of immunity need to be further defined with a focus on mucosal immunity. There is also an urgent need to develop better animal models. The relevance of genetic clades and the impact of behavioral intervention in vaccine trails also need to be elucidated.

References

1. Esparza J, Bhamarapravati N. Accelerating the development and future availability of HIV-1 vaccines: why, when, where and how? *Lancet* 2000 ; 355 : 2061-66.

2. Harrer T, Harrer E, Kalams SA, *et. al.* Strong cytotoxic T cell and weak neutralizing antibody responses in a subset of persons with stable non-progressing HIV type 1 infection. *AIDS Res Hum Retroviruses* 1996 ; 12 : 585-92.

3. Schimtz J, Kuroda M, Santra S, *et. al.* Control of viremia in simian immunodeficiency virus infection by CD 8+ lymphocytes. *Science 1999*; 283: 857-60.

4. Shibata R, Igarashi T, Hargwood N, *et. al.* Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infection of macaque monkeys. *Nat Med* 1999; 5 : 204-10.

5. Letvin NL, Montefiori D, Yasutami Y, *et. al.* Potent protective anti- HIV immune response generated by bimodal HIV envelope DNA plus protein vaccination. *Proc Natl Acad Sci USA 1997*; 94: 9378-83.

6. Clerici M, Giorgi JN, Chou CC, *et. al.* Cell mediated immune response to human immunodeficiency virus (HIV) type 1 in seronegative homosexual men with recent sexual exposure to HIV-1. *J Infect Dis* 1992 ; 165 : 1012-19.

7. Belyakov IM, Ahlers JD, Brandwein BY, *et. al.* The importance of local mucosal HIV-specific CD-8+ cytotoxic T lymphocytes for resistance to mucosal viral transmission in mice and enhancement of local resistance by local administration of IL-12. *J Clin Invest* 1998 ; 102 : 2072-81.

8. Deacon N, Tsylun A, Solomon A. Genomic structure of an attenuated quasi species of HIV-1 from a blood transfusion donor and recipients. *Science* 1995 ; 270 : 988-91.

9. Learmont JC, Geczy AF, Mills J, *et. al.* Immunologic and virologic status after 14 to 18 years of infection with an attenuated strain of HIV-1: a report from the Sydney Blood Bank Cohort. *N Engl J Med* 1999 ; 340: 1715-22.

10. Ourmanov I, Brown CR, Moss B, *et. al.* Comparative efficacy of recombinant modified vaccinia virus Ankara expressing simian immunodeficiency virus (SIV) gag-pol and/or env in macaques challenged with a pathogenic SIV *J Virol* 2000 ; 74: 2740-51.

11. Mellors JW, Rinaldo CR, Gupta P, *et. al.* Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996 ; 272 : 1167-70.

12. Nyambi PN, Nkengasong J, Lewi P, *et. al.* Multivariate analysis of human immunodeficiency virus type-1 neutralization data. *J Virol* 1996 ; 70 : 6235-43.

13. Lynch JA, deSouza M, Robb MD, et al. Cross-clade cytotoxic T cell response to human immunodeficiency virus type-1 proteins among HLA disparate North Americans and Thais. *J Infect Dis* 1998 ; 178 : 1040-46.

14. Reitter J, Meam R, Desrosiers RC. A role for carbohydrates in immune evasion in AIDS. *Nat Med* 1998 ; 4 : 679-84.

15. Baltimore D, Heilman C. "HIV vaccines" prospects and challenges. *Sci Am* 1998 ; 279 : 101.

16. Corey L, McEbrath ML, Weinhold K, *et. al.* Cytotoxic T cell and neutralizing antibody responses to HIV-1 envelope with a combination vaccine regimen. *J Infect Dis* 1998 ; 177 : 301-309.

17. Shearer GM, Pinto LA, Clerici M. Alloimmunization for immune-based therapy and vaccine design against HIV/AIDS. *Immunol today* 1999 ; 20 : 66-71.

18. Nathanson N, Mathieson BJ. Biological considerations in the development of a human immunodeficiency virus vaccine. *J Infect Dis* 2000 ; 182 : 579-89.

19. Caver TE, Lockey TD, Srinivas RV, *et. al.* A novel vaccine regimen utilizing DNA, Vaccinia virus and protein immunizations for HIV envelop presentation. *Vaccine* 1999 ; 17 : 1567-72.

20. Caley IJ, Betts MR, Irlbeck DM, *et. al.* Humoral, mucosal, and cellular immunity in response to a human immunodeficiency virus type-1 immunogen expressed by a Venezuelan equine encephalitis virus vaccine vector. *J Virol* 1997 ; 71 : 3031-38.