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A Safe, Effective and Affordable HIV Vaccine – An Urgent Global Need

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Abstract

The need for a safe, effective and affordable HIV vaccine has never been greater. In 2004 almost five million people became infected with HIV. In addition, providing access to antiretrovirals in Africa remains a huge challenge. A successful vaccine against HIV will probably need to stimulate the innate immune system, generate high levels of neutralizing antibodies, induce strong cellular immune responses and mucosal immunity, and should induce broad-spectrum immunity able to cover all HIV subtypes.

In this review, we describe the limitations and challenges of developing a safe and effective HIV vaccine. We also emphasize possible approaches for overcoming immune escape in HIV infection, the lessons learned from the clinical trials of HIV-1 candidate vaccines, and the most important scientific highlights of the Keystone 2005 Symposium. When an effective vaccine is eventually found, we will face the enormous task of making it accessible to those who need it most. **(AIDS Reviews 2005;7:131-8)**

Key words

HIV. AIDS. HIV/AIDS vaccines. Vaccines. Immune response. Clinical trials.

Introduction

The total number of people living with the human immunodeficiency virus (HIV) has reached its highest level ever: an estimated 39.4 million people are living with HIV and 4.9 million people became newly infected with HIV in 2004. In the past year the global AIDS epidemic killed 3.1 million people, and by 2010 the number of children orphaned by AIDS could be around 25 million[1]. It is estimated that 85% of these new infections occur in developing countries. Highly active antiretroviral therapy (HAART) does not represent a definitive solution in all clinical settings. In addition, ensuring universal access to antiretrovirals in developing countries still presents an enormous challenge[2].

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A successful vaccine against HIV will probably need to stimulate the innate immune system, generate high levels of neutralizing antibodies, induce strong cellular immune responses and mucosal immunity, and should induce persistent and broad-spectrum immunity able to cover all HIV subtypes. Increasing our knowledge of the role of immune responses in controlling HIV viremia would help to define goals for immune-based therapies and new vaccine strategies against AIDS[3]. Human trials of 30 vaccine candidates span 19 countries on six continents[4], but only one candidate has finished human phase III testing. Unfortunately, the results showed the vaccine to be ineffective[5].

Today, many global initiatives are focused on the development of an AIDS vaccine (Table 1). Overcoming the remaining scientific, logistic and financial hurdles to developing an effective HIV vaccine will require real imagination and firm commitment from all stakeholders.

Natural immune response to HIV-1. Failures and challenges

Antibody responses to HIV-1

Even though strong and broadly cross-reactive neutralizing antibodies arise in HIV infections, they appear later than cellular immune responses, do not

Table 1. Global initiatives for HIV vaccine research and development

Organization	Objective
EuroVac (European Vaccine Effort Against HIV/AIDS)	– To develop and test various vaccine strategies and bring European AIDS preventive vaccines into phase I clinical trials. See http://www.eurovac.net
ANRS (French National Agency for AIDS Research)	– Research and development on HIV/AIDS and Hepatitis B and C See http://www.anrs.fr
ORVACS (Objectif Recherche Vaccin SIDA). International Collaborative Network	– To accelerate research on therapeutic vaccines and immune-based therapeutic strategies against HIV. – To conduct complementary research that is required to develop clinical trials for vaccine approaches seen in the pre-clinical area See http://www.orvacs.org
CANVAC (Canadian Network vaccines and Immunotherapeutics)	– To combine efforts from the public and private sectors to develop vaccines and clinical trials in Canada See http://www.canvacc.org
IAVI (International AIDS Vaccine Initiative)	– Funding the development of new prophylactic vaccines, clinical and laboratory facilities as well as the development of therapeutic clinical trials around the world. See http://www.iavi.org
ACTG (AIDS Clinical Trial Group)	– To complement existing efforts to increase research on new concepts on AIDS vaccine and phase I/II clinical trials in USA See http://www.actg.org
AAVP (African AIDS Vaccine Program)	– A network of African scientists working to promote and facilitate HIV vaccine research and evaluation in Africa. See http://www.who.int/vaccine_research/diseases/hiv/aavp
KAVI (Kenya AIDS Vaccine Initiative)	– To combine worldwide efforts in the development of phase I clinical trials in Kenya See http://www.kaviuon.org
HVTN (HIV Vaccine Trial Network), Division of AIDS (DAIDS) of the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)	– To foster the development of HIV vaccines through testing and evaluating candidate vaccines in clinical trials. See http://www.hvtn.org/
SAAVI (South African Vaccine Initiative)	– International movement that aims to develop an HIV vaccine. Several arms of the project will be activated over the next 8–12 years. A clinical trial of one South African vaccine is due to begin early next year. See http://www.saavi.org.za
EGPAF (Elizabeth Glaser Pediatric AIDS Foundation)	– To provide care and treatment to children with HIV/AIDS, and accelerating the discovery of new treatments for other serious and life-threatening pediatric illnesses. See http://www.pedaids.org
The Bill & Melinda Gates Foundation	– The foundation has a program to ensure that all children have access to vaccines and that new drugs, vaccines and diagnostics are developed and deployed on the prevention and control of AIDS disease See http://www.gatesfoundation.org/default.htm
The Global Fund	– Created to finance a dramatic turn-around in the fight against AIDS, tuberculosis and malaria. See http://www.theglobalfund.org/en/

*Many other institutions not mentioned above are also committed to the worldwide effort against the AIDS epidemic.

provide enough titers to control virus replication, and have only weak neutralizing activity for primary HIV-1 isolates[6]. There are several possible explanations for the inability to generate more effective antibody responses:

– The destruction of CD4+ T-lymphocytes by HIV may impair the generation of appropriate antigen recognition and B-cell responses.

– Epitope variation in the hypervariable loops of the gp120[7].

– These antibodies are very effective in inactivating and eliminating free virions from body fluid, but cannot prevent the cell-to-cell spread of HIV infections in the immune synapse[8].

– The trimeric structure and folding of native gp120 in the virion surface mask the more conserved regions of the viral envelope that bind to cellular receptors and appear to be the preferential targets for effective neutralization. Furthermore, conformational changes of gp120 in the act of binding to CD4 receptor and CCR5/CXCR4 coreceptors causes the loop-shaped portions of gp120, exposing part of the viral protein that had remained hidden[9].

– Post-translational modifications of the viral envelope, in particular direct glycosylation of amino acid residues and generation of carbohydrate structures called "glycan shields", hide epitopes and prevent their recognition by neutralizing antibodies[7].

– Finally, broadly neutralizing antibodies should also be generated in mucosal surfaces to avoid viral infection. The generation of this mucosal HIV-1 specific IgA has been proposed as a major mechanism of resistance in highly HIV-1-exposed but uninfected heterosexual women and men during sexual intercourse[10,11].

New immunogenic designs for eliciting neutralizing antibodies have been proposed. Arnold, et al.[12] produced combinatorial libraries of live, recombinant human rhinoviruses (HRV) that displayed HIV-1 immunogens on surface loops connected via linkers of varying lengths and sequences. In a macaque model, Hu, et al.[13] studied the immunogenicity and protective efficacy of recombinant vaccinia virus expressing simian immunodeficiency virus (SIV) Gag/Pol and HIV-1 Env proteins with mutant N-linked glycosylation sites in V2 and V3. In the European Vaccine Effort Against HIV (EuroVac) project (www.eurovac.net), Jeffs, et al.[14] described a set of correctly folded, oligomeric HIV-1 C-clade recombinant envelope glycoproteins that could be used as potential vaccine immunogens.

At the Keystone 2005 Symposium Chen, et al. presented their findings (recently published). Their model predicts that, upon binding to CD4, parts from SIV gp120 will shift around the CD4-binding cavity with very large excursions. These new insights into the dynamic structure and activity will provide for new approaches that will promote the generation of neutralizing antibodies[15].

Cellular immune responses to HIV-1

HIV stimulates a strong CD8+ T-cell response during acute viremia, and this usually persists through the chronic phase of infection. The partial control of viral replication occurs during the early days after infection, and correlates temporally with the emergence of HIV-1-specific CD8+ T-cell response[16].

There is strong evidence of the importance of cellular immune responses in controlling HIV-1 replication in humans and SIV replication in rhesus monkeys. Even though the potential protective mechanism is unclear, it has been suggested that HIV-specific CD8+ T-cell responses detected in cohorts of HIV-exposed/uninfected health care workers and female sex-workers may contribute to preventing HIV-1 infection[17].

The ability of cytotoxic T-lymphocytes (CTL) to control HIV replication may depend on various factors:

– Genetic background: an association has been shown between the presence of increased frequencies of CD45RA+ CCR7- (mature effector phenotype) HIV-specific CD8+ T-cells and viral control.

– CTL escape: a single amino acid change in the immunodominant KK10 peptide in human leukocyte antigen (HLA)-B27 individuals is strongly correlated with loss of immune control of viral replication.

– Defects in CTL maturation or function: the presence of immature CTL (e.g. the lack of perforin expression) or defects in their proliferative capacity has been seen in the non-proliferating, antigen-specific, CD8+ T-cells[18].

Several authors have recently reported the functional defects of the HIV-specific CD8+ T-cell immune responses not measured by the interferon gamma (IFNγ) assays used at present. They observed that the CD8+ T-cell response to HIV is highly complex, and that multiple CD8+ T-cell functions must be measured to accurately assess immune responses in HIV-infected individuals[19].

Challenges and potential approaches to overcome immune escape of HIV

The renewed interest in antibodies derives from the concept that HIV vaccines based on cellular immunity alone will protect against disease but not against infection, and may work only for a limited period of time. Richman, et al. reported that potent, neutralizing, antibody responses generated early after primary HIV infection exert a selective pressure that drives the continuous evolution of neutralizing escape mutants[20]. However, despite the large-scale expansion of the HIV-specific CD8+ T-cell population in acute infection, HIV still es-

capes eradication. Barouch, et al. showed that the simian-human immunodeficiency virus (SHIV) 86.6P strain can escape vaccine-induced immune control by a mutation of a single amino acid in the immunodominant p11 CTL epitope from SIV gag[21].

To overcome the neutralization escape of HIV, several approaches have been described. A recent study showed that gp120 is refractory to the binding of the majority of the antibodies because the molecule is unusually flexible, and the binding regions of the antibodies are specific to a particular part of it. But it is possible that by chemically "rigidifying" the epitope to which CD4 binds, one could obtain antibodies that will neutralize the virus[22]. Burton, et al. have examined the crystallographic structure of the broadly neutralizing monoclonal antibody (MAb) 4E10 bound to a peptide fragment identical to the gp41 domain recognized by the antibody. They hope that the information obtained from the crystal structure will aid scientists in designing immunogens for vaccines with properties similar to 4E10[23]. The generation of antibodies able to find the chemokine coreceptor binding site of gp120 is also often used to induce broadly neutralizing antibodies against HIV-1.

As far as cellular immune responses are concerned, a vaccine should stimulate large numbers of CD8+ T-memory cells that rapidly release cytokines and chemokines on subsequent antigen contact and start killing target cells. In this context, the objectives are the following:

– To elicit CD8+ T-cell responses that are broadly reactive against genetically diverse HIV strains and are qualitatively better than those that occur normally during the natural course of HIV infection.

– To elicit potent virus-specific CD4+ and CD8+ T-cell responses because the lack of adequate CD4+ T-cell help could be one of the main factors in the functional impairment of CTL and the eventual failure of immune control of viremia.

– To further our knowledge of host genetic polymorphisms that have been shown to affect the outcome of HIV infection at the level of virus entry, virus dissemination, and immune control of viral replication[24].

SIV macaque model of simian AIDS

HIV cannot infect small laboratory animals or Old World monkeys. Therefore, investigators have used the SIV or SHIV (SIV-HIV chimera) macaque model of simian AIDS.

Many of the most promising vaccine studies have used the chimeric SHIV 89.6p strain as a challenge virus in immunized macaques. Although these vaccine approaches protect against pathogenic SHIV 89.6p strain challenge in monkeys, they do not protect against SIVMac 239 challenge. The limitation of the SHIV 89.6p challenge is that this virus is extraordinary pathogenic, inducing rapid CD4+ T-cell depletion and rapid AIDS-like illness in rhesus macaques[25]. Several other SIV and SHIV strains have been described, some of which demonstrated a slower progression to AIDS and may be better at mimicking the pathogenesis of human AIDS[26].

Clinical trials of HIV-1 candidate vaccines – Disappointment and confusion

Advances in vaccine design, animal models, and clinical research are converging to create a promising pipeline of candidate vaccines (Table 2). There are now about 30 HIV/AIDS vaccine candidates undergoing clinical trials in 19 countries (Table 3). The first phase I trial of an HIV-1 candidate vaccine was undertaken in the USA in 1987. The first candidate vaccines tested were based on the HIV-1 envelope glycoproteins gp120 or gp160, an approach aimed at inducing neutralizing antibodies.

In June 1998, VaxGen Inc. started the first phase III trial including 5009 volunteers in the USA. The candidate vaccine was AIDSVAX B/B (VaxGen). The reduction of infection in the entire sample of volunteers, including all racial groups, was 3.8%. Protection appeared to correlate with the higher level of vaccine-induced neutralizing antibodies observed in these groups, but failed to elicit a sufficiently high cellular response in the broad population. The results also indicated that AIDSVAX was well tolerated and had a high safety profile, but that overall the gp120 AIDSVAX was totally unable to prevent HIV infection[27]. The same company launched a second phase III trial in March 1999 in Thailand, recruiting 2500 volunteers and using a bivalent gp120 derived from B and E subtypes. The efficacy results have recently shown that gp120 is incapable of preventing or ameliorating HIV-1 infection. Meanwhile, the US government is sponsoring a recently initiated phase III trial in Thailand of a vaccine made from the live replicating canarypox vector ALVAC with a boost of monomeric gp120[28]. This phase III trial of ALVAC-HIV priming with AIDSVAX B/E boosting in 16,000 volunteers was launched in Thailand in 2003, and the findings of this trial will be shared with the international community. Several outstanding researchers opposed this study, claiming that there are no persuasive data to suggest that the combination of ALVAC and gp120 could induce better cellular or humoral responses than either component alone[29]. Nevertheless, the Thailand Ministry of Public Health will pursue this trial in two provinces as planned[30].

In phase I/II clinical trials, recombinant canarypox (rCanarypox) has proved to be safe and immunogenic, inducing low levels of antibody response in 70% of

Table 2. HIV vaccine designs

Vaccine design	Features	Limitations
Plasmid DNA	– Induces HIV- and SIV-specific cellular and humoral immune responses in mice and nonhuman primates. – The DNA prime/live vector boost or IL-2 adjuvant DNA to enhance the immune responses has been tested successfully in preclinical trials.	– Difficulty in achieving sufficient uptake of DNA and low level of HIV-1 gene expression – Limited immunogenicity in humans – Chromosomal integration – DNA alone was not sufficient to induce protective immunity in SIV
Live recombinant vectors Vaccinia	– In nonhuman primates can elicit potent CTL responses to HIV and SIV proteins – High level of heterologous protein expression – Insertion of large DNA fragments	– Disseminate in immunosuppressed individuals – Preexisting immunity
MVA, NYVAC	– Attenuated for pathogenicity in humans – MVA is highly immunogenic in monkeys and confers protection from SIV– and SHIV–induced disease	– Preexisting immunity – Limited experience in humans
ALVAC	– Abortive replication cycle in human cells – People lack immune responses to the vector	– Limited immunogenicity in humans
Adenoviruses	– Tropism for mucosal surfaces inducing mucosal immunity – Impressive immunogenicity in murine and nonhuman primate studies using the serotype 5 adenovirus, made replication defective	– Preexisting immunity
AAV	– Non-pathogenic and stable – Oral administration – Larger insert capacity – Induces CTL immune responses in murine and nonhuman primates studies	– Preexisting immunity – Induces poor humoral responses – Safety concerns regarding to its possibility of integration – Limited experience in humans
VEE	– Same as AAV – No expression of viral structural proteins – Include several viral genes	– Same as AAV – Limit clone capacity – Genetic rearrangements
VSV	– Same as AAV – Ease of cloning and production	– High mutation rate
HSV-I and II	– Target mucosal surfaces – Provide persistence of antigen expression in the host and long-lasting immunity	– Safety concerns regarding to latency and use in immunocompromised individuals – Preexisting immunity
BCG	– Induce long-lasting immunity – Long safety record use in humans – Potential pediatric vaccine – Potent adjuvant effect – Humoral and cellular immune responses have been elicited to HIV and SIV proteins expressed in BCG recombinant.	– Preexisting immunity – Safety concern in immunocompromised individuals – Genetic rearrangements of heterologous DNA fragment – Plasmid stability *in vivo*
Salmonella and shigella	– Ability to induce mucosal immune responses – Delivery system for plasmids bearing HIV gene expression cassettes	– Safety concerns regarding level of attenuation
Recombinant envelope proteins	Approach aimed at inducing neutralizing antibodies	– No neutralizing antibodies for patient isolates of HIV-1 – Absence of CTL responses

Table adapted from references number 3, 50 and 54.
MVA: modified vaccinia ankara; NYVAC: mammalian pox-virus; ALVAC: avian pox-virus; AAV: adeno-associated virus; VEE: Venezuelan equine encephalitis Virus; VSV: vesicular stomatitis virus; HSV: herpes simplex virus; BCG: Bacillus Calmette-Guerin.

Table 3. Ongoing prophylactic HIV vaccines clinical trials

Candidate vaccine	Sponsor	Clade	Phase	Country
ALVAC-HIV Vcp1521,AIDSVAX	VaxGen, HVTN, NIAID,	B and E	III	Thailand
ALVAC vCP 1452 / rgp120	NIAID, Aventis/VaxGen	B	II	Brazil, Haiti, Peru, Trinidad Tobago
LIPO-5	ANRS; Aventis	B	II	France
HIVA.DNA / HIVA.MVA	IAVI, KAVI	A	II	UK, Kenya
MRKAd5 HIV-1 gag/pol/nef	HVTN, Merck	B	II	UK, Kenya
PHIS-HIV-B; rFPV-HIV-B	UNSW,AVC	B	I/II	UK
PGA2/JS2 DNA	HVTN, NIAID	B	I	USA
EnvPro gp140	NIAID, Chiron	D	I	USA
MRKAd5/ ALVAC vCP205	Merck, Aventis Pasteur	B	I	USA
ADVAX DNA	ADARC,IAVI	C	I	USA
tgAAC09 AAV	CCRI, IAVI	C	I	Belgium
NYVAC-HIV C	Eurovac, A.Pasteur	C	I	Switzerland, UK
gp160 MN/LAI-2	ANRS, A. Pasteur	B	I	France
tat DNA	ISS, Parexel	B	I	Italy
EP HIV-1090 DNA	NIAID, HVTN	B	I	Botswana, USA
MRK Ad5-gag	NIAID, HVTN, Merk	B	I	USA
HIVA.MVA	IAVI, Cobra, IDT	A	I	Peru, Thailand
AVX 101 VEE	NIAID, HVTN, Alpha Vax	C	I	USA
HIVA.DNA and/or HIVA. MVA	IAVI, UVRI, Cobra	A	I	Uganda
VRC-HIVADV014-00-VP (env)	NIAID/VRC	A, B, C	I	USA
Nef-Tat fusion/gp120	NIAID	B	I	USA
GTU-Nef DNA	FIT Biotech	B	I	USA
LIPO-4T (lipopeptides with CTL epitopes)	ANRS	B	I	France
ADMVA (env/gag-pol,nef-tat)	IAVI, IDT	C	I	USA
TgAAC09	ICMR	C	I	India
ADMVA	ADARC	C	I	USA (New York)

Table adapted from Vaccine Trials Database of IAVI, website: http://www.iavi.org (Last update, 28 February 14, 2005)
Abbreviations: ADARC: Aaron Diamond AIDS Research Center; ANRS: Agence Nationale de Recherche sur le SIDA; ATVC: Australian-Thai HIV Vaccine Consortium; CCRI: Columbus Children's Research Institute; EuroVac: European Vaccine Effort Against HIV/AIDS; HVTN: HIV Vaccine Trials Network; IAVI: International AIDS Vaccine Initiative; IDT: Impfstoffwerk Dessau Tornau GmbH; ISS: Instituto Superiore di Sanità; KAVI: Kenya AIDS Vaccine Initiative; MRC: UK Medical Research Council; NIH: National Institutes of Health; NIAID: National Institute of Allergy and Infectious Diseases; SJCRH: St Jude Children's Research Hospital; UNSW: University of New South Wales; UVRI: Uganda Virus Research Institute; ICMR: Indian Council of Medical Research.

vaccinees and CTL responses in 30% of individuals at any single time point after vaccination[31]. Because of this limited ability of rCanarypox vectors to prime antiviral CTL responses, phase III studies of rCanarypox± gp120 vaccine regimen were cancelled last year by the HIV Vaccine Trial Network (HVTN) in the USA. Harari, et al.[32] described the immunogenicity data of a poxvector (NYVAC-HIVC)-based HIV vaccine in 12 healthy, low-risk, HIV-negative volunteers. Vaccine-specific positive responses were observed in 50% of the individuals at week six; only one was positive at week four, three at week eight, and one at week 24.

Immunogenicity results of adenovirus serotype 5/Gag (subtype B) HIV vaccine demonstrated significant CTL responses in humans and exhibited cross-clade reactivity. But the data also showed a clear blunting of responses in people with preexisting immunity to Ad5[33]. Merck's adenovirus (Ad5) vaccine may be the first adenovirus-based vaccine to be tested in large-scale clinical trials[34].

At the Keystone 2005 Symposium, Graham reported on the phase I clinical trial data of the HIV vaccine candidate developed jointly by GenVec Inc. and the Vaccine Research Center (VRC) of the NIAID/NIH. The vaccine was generally well tolerated in 36 healthy adult volunteers, and produced both antibody and cellular immune responses to the three different HIV antigens in the vaccine. This vaccine is the first of its kind to use an adenovector (gene carrier) to deliver genes from all three of the major subtypes, or clades, of HIV causing the global AIDS pandemic, and responses were detected to each of those subtypes[35].

India began enrolling volunteers for its first preventive AIDS vaccine trial in February 2005. The recombinant adeno-associated vaccine (known as tgAAC09) contains HIV's gag, protease and RT sequences and is designed to stimulate both a cellular and humoral immune response to HIV clade C[36].

In Africa, the first phase I/II HIV vaccine trial was undertaken in Kampala, Uganda, assessing ALVAC vCP205, a canarypox construct based on HIV-1 B (env, gag and pol genes) from two HIV-1 subtype-B strains. Although the immunogenicity of this vaccine was low, it elicited CD8+ T-cell responses with detectable cross-activity against clade A and D antigens in a significant proportion of vaccine recipients[37]. The first HIV vaccine trial in Africa of a product based on HIV strains from that continent began in Nairobi, Kenya, in 2001; the candidate vaccine tested was DNA and modified vaccinia Ankara (MVA) on the basis of the gag gene and multiple CTL epitopes from HIV-1 A subtype[38,39]. The first phase I trial in the UK in 120 HIV-negative volunteers to evaluate priming with different doses of DNA HIVA followed by booster with MVA HIVA was presented by Guimeraes-Walker, et al.[40]. The vaccine was safe and well tolerated; HIV-specific CD8+ CTL immune responses were observed in 18% of all vaccinees and neither dose of DNA had a significant priming effect. The phase I clinical trial results in Nairobi of DNA and MVA HIVA vaccines using priming or prime-boost regimens was presented by Jaoko, et al.[41], who found that 10–25% of volunteers in vaccinated groups had a positive immune response. The International AIDS Vaccine Initiative (IAVI) has announced that it does not plan to carry out further trials of its main HIV vaccine candidate. McMichael reviewed the reasons for this decision for the participants of the Keystone 2005 Conference[42]. He suggested that perhaps a better detection of immune reactivity to the vaccine antigens could be obtained by culturing the PBMC from vaccinated people *in vitro* with HIV peptides and IL-2 for 7–14 days before testing for IFN-γ production producing cells by ELISPOT assay. He proposed that perhaps this "reactivated response" would be more representative of long-term memory.

For ethical reasons, only 2% of the 110 HIV-vaccine trials completed to date have included children in their clinical trials. While it is certainly inappropriate to include children in every vaccine trial, we cannot simply assume that a vaccine developed for adults will work in infants[43].

Therapeutic vaccination

Antiretroviral therapy against HIV is limited by the cost, toxicity, emergent resistant virus, and the inability to eliminate all reservoirs. Some researchers have proposed that vaccines might be useful for augmenting the specific immune response against HIV[44].

Lu, et al. have recently published the results of a preliminary investigation of the efficacy of a therapeutic dendritic cell (DC)-based vaccine for people with chronic HIV-1 infection. This is the first report in humans that shows that a therapeutic vaccine based on autologous monocyte-derived DC pulsed with autologous aldrithiol-2-inactivated HIV-1 was capable of inducing an effective HIV-1-specific T-cell response and sustained viral suppression[45]. They had previously shown that an effective and durable SIV-specific cellular and humoral immunity is elicited by a vaccination with chemically inactivated SIV-pulsed dendritic cells[46]. Bhardwaj, et al[47] reported that targeting canarypox virus vector to mature DC could potentially elicit both anti-HIV CD8+ CTL and CD4+ T-helper responses *in vivo.* These results are encouraging and support the notion that combining HAART with monocyte-derived dendritic cells (MD-DC) pulsed *in vitro* with autologous heat-inactivated virus for inducing/boosting specific anti HIV-1 CD4+ and CD8+ T-cell response might help to achieve an immune control of HIV-1 replication after stopping HAART[48].

In a phase I trial of MVA vector expressing the HIV-1 nef gene, administration of three doses of the vaccine to 14 subjects on HAART with plasma HIV-1 levels < 50 copies/ml and CD4+ counts > 400 cells/μl induced CD8+ and CD4+ T-cells to recognize new epitopes in 10 out of 16 subjects[49].

Conclusions and remarks

It was originally thought that HIV-1 vaccines need to induce sterilizing immunity, but now it is agreed that they may also be considered effective if they induce immunity capable of reducing viral load[50].

We may include means of programming more effective innate immunity, such as stimulation of HIV-inhibiting chemokines, or more likely downregulating cellular factors, such as the CCR5 chemokine receptor[51].

Large-scale phase III trials of inadequate HIV-1 vaccines are obviously counterproductive. Consensus should be reached on the immunologic end-points accepted by all the scientific community to move forward from phase II to large phase III human trials[52].

As regards therapeutic immunizations, the use of dendritic cells in developing a therapeutic vaccine offers promise for the future.

Accessing and recruiting hard-to-reach HIV high-risk cohorts is an important challenge for HIV vaccine preparedness studies. Researchers must develop strategies to link community-based outreach to drug users, sex-workers, and minorities with referrals and access to health centers for HIV counseling, screening and diagnostic testing and medical care[53].

Although difficult hurdles remain, with the efforts of researchers to find innovative vaccine designs, and the commitment of the international community to provide resources for developing countries, it is likely that a successful vaccine for controlling the global HIV epidemic will eventually be developed.

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