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HIV Vaccine

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1. Introduction

More than three decades after the discovery of Human Immunodeficiency Virus (HIV) as the causative agent of Acquired Immunodeficiency Syndrome (AIDS), a vaccine is still considered as the best hope for controlling the epidemic. In fact the history of medicine shows that no viral disease have ever been controlled without a vaccine.

Remarkable success in the AIDS treatment has been achieved with the development of antiretroviral drugs that, by interfering with various aspects of the HIV life cycle, allowed an impressive control of infection (Fischl et al., 1987; Egger et al., 1997). The use of these drugs, however, was accompanied by new challenges related to side effects, high cost and resistance development (Carr, 2000; Hawkins, 2010; Menéndez-Arias, 2010; www.hivresourcetracking.org/treatments/vaccines).

Antiretroviral treatment cannot prevent early infection events, such as transmission to sexual partners during the post-infection peak of viremia (Wawer et al., 1999) and the massive destruction of intestinal CD4+T cells during the first weeks of infection (Brenchley et al., 2004). Furthermore drugs delivery to poor and endemic areas is often hard due to practical limitations. In resource-limited countries only 1 out 4 HIV-positive individuals has access to antiretroviral medications, and for each person who begins the therapy, there are about 6 new infections (www.who.int/entity/hiv/mediacentre/universal_access_progress_report_en.pdf). These factors made difficult to control the pandemic through antiretroviral therapy.

Others approaches could be taken in account to reduce HIV-1 infection in subjects at risk of exposure, including public health involvement (i.e.: screening of donor blood products), educational effort (i.e.: risk reduction counselling), or social imprinting (i.e.: male circumcision and behaviour modifications such as condom usage). In high seropositive communities, pre-exposure or post-exposure antiretroviral prophylaxis may reduce susceptibility to HIV infection, as well as the vertical HIV transmission from mother to child.

The creation of an HIV-1 vaccine represents an unprecedented scientific challenge and it's an absolute priority in field of HIV prevention. We must remember that vaccines are one of the most effective public health interventions ever known, but unfortunately, in HIV infection, the current perspective is that we will not have a product, even moderately effective, in the coming years.

The truth is that often in the history of vaccinology it takes a long time since the discovery of infectious agents to the licensing of an effective vaccine (Heyward et al., 1998). This is due in

part to the fact that even today no one knows for sure how the immune system protects us against infections and, consequently, how to handle it for this to occur. In HIV/AIDS, the stimulation of a specific immune response is unlikely to immunize against HIV: there are no established immune correlates of protection (i.e.: humoral or cellular response), no documented cases of spontaneous recovery from AIDS or HIV infection, and no animal model that faithfully predicts HIV disease or vaccine responses in humans beyond the variability of the virus. Moreover HIV enters predominantly through mucosal surfaces, targets preferentially CD4+T cells, and rapidly establishes a persistent reservoir of latently infected cells, making difficult the study of the host/virus interaction as well as the development of an interventional strategy.

Novel approaches for an HIV vaccination need a rational vaccine design, including a better integration of emerging scientific concepts and knowledge derived from vaccinology research fields.

Models of natural resistance to HIV infection, including individuals able to control the infection (elite controllers) and some species of non-human primates, show that some level of control can be achieved (Dunham et al., 2006; Sumpter et al., 2007; Walker, 2007; Lederman et al., 2010; Poropatich & Sullivan, 2011).

The creation of an effective HIV vaccine will require continued scientific research and cooperation between academic community and biotechnology industry with the contributions of brightest scientists, long-term commitments of stable and flexible funding, trials and vaccines accessibility for developing countries. In coming years, the prospect is that several area of scientific community will be involved seeking to combine the knowledge necessary to develop new strategies, new candidates and evaluating these products.

This chapter will describe some aspects of the development of HIV vaccines, with emphasis on scientific efforts and challenges made to producing a safe and effective vaccine, strategies and methods used in the development of anti-HIV vaccines, current outlook and perspectives in this area.

2. Major challenges to get an HIV vaccine

Primary in prevention and control of infectious diseases, vaccines are a highly effective way to stimulate the immune system to fight pathogens. In the case of HIV infection, it has not yet been possible to obtain a vaccine to control infection, despite the efforts of the scientific community, the large financial investment and scientific and technological progress achieved.

Considering the natural history of infection, an HIV vaccine has the principal aim to prevent the integration of HIV genetic material into the genome of the host cell in order to prevent systemic infection and the establishment of viral reservoirs. This occurs within a few days after exposure, when HIV rapidly replicates in the lymphoid tissues, so the window of opportunity to prevent the establishment of a persistent infection is very brief. Therefore an effective HIV vaccine should be able to activate the immune system against the virus very early after the infection.

The complexity and diversity of HIV, its high capacity to evade the immune system and the missing gap in effective host immune response against the virus represent some major challenges to design an optimal vaccine. Moreover the absence of an experimental model able to mimic human infection represents another limit for pre-clinical studies.

2.1 HIV heterogeneity and cell targets

HIV presents a genome of about 10,000 base pairs, composed of three structural genes (*gag*, *pol* and *env*) beyond the six accessory genes (*vif*, *vpr*, *rev*, *tat*, *vpu* and *nef*). The *gag* gene encodes the viral core protein as the capsid, matrix and nucleocapsid, *pol* encodes the viral enzymes (reverse transcriptase, protease, ribonuclease and integrase) and *env* gene encodes the envelope glycoproteins. Some products of these genes are targets of choice for the study of vaccines.

The great genetic diversity of HIV represents a major obstacle to developing an effective vaccine. Such diversity is the result of a highly HIV replicative rate (new 10^{10} viral particles/day) and of its prone to errors retrotranscriptase (1 new nucleotide substitution/replication for a genome of approximately 10 000 bp).

The highest degree of HIV diversity is found in the envelope glycoproteins. The amino acid sequences of Env may differ by about 15% between isolates of the same clade and in more than 35% between envelopes of different clades (Gaschen et al 2002).

As a consequence of this high degree of mutational rate, HIV can counteract the selective pressure imposed by the host immune response, and it soon become able to evade an effective response. This aspect makes it difficult to identify potential HIV targets against which the immune system could be directed.

Another important point is that an effective vaccine may protect against various HIV subtypes and clades prevalent in every region of the world. HIV is classified into two types: HIV-1 and HIV-2 that have a genetic homology around 40-50%. While HIV-2 is less pathogenic and its incidence is confined to Africa, HIV-1 is the causative agent of a worldwide pandemic. HIV-1 is divided into three groups M, O and N. The groups O and N are restricted to Central Africa, while group M is responsible for the AIDS pandemic.

Within group M, HIV-1 isolates are divided into six subtypes and clades (A, B, C, D, E and G) and have distinct geographic distributions. While subtype B is prevalent in the Americas and Europe, subtype C, which accounts for more than 50% of AIDS cases worldwide, is prevalent in Southeast Asia and Africa. The difference between the amino acid sequences among viral clades differs by 20% and the variation within clades can reach over 10% in amino acid sequence. Furthermore, different subtypes may be associated with generating circulating recombinant forms (CRFs), further increasing the viral diversity.

Another major challenge that hinders the design of an effective vaccine is the HIV tropism for immune cells. HIV uses the CD4 molecule as a receptor for cell entry. This molecule, in turn, is expressed mainly by T helper lymphocytes and to a lesser degree by dendritic cells, macrophages and monocytes. Since these are strategic cells within the immune system, the immune response in HIV-infected individuals is compromised (Figure1).

Belonging to retroviruses, HIV integrates its genetic material into host cell genome. Days after infection the virus begins its haematogenous spreading from mucosal to lymphoid sites, particularly gut-associated lymphoid tissue (GALT) where a lot of CD4+ CCR5+ T memory lymphocytes are destructed (Matapallil et al., 2005).

The massive loss of CD4+ T cells compromises the host immune response during the infection. Moreover, since the HIV genome is integrated latently until cells become activated, establishing viral reservoirs that hinder the complete elimination of infection.

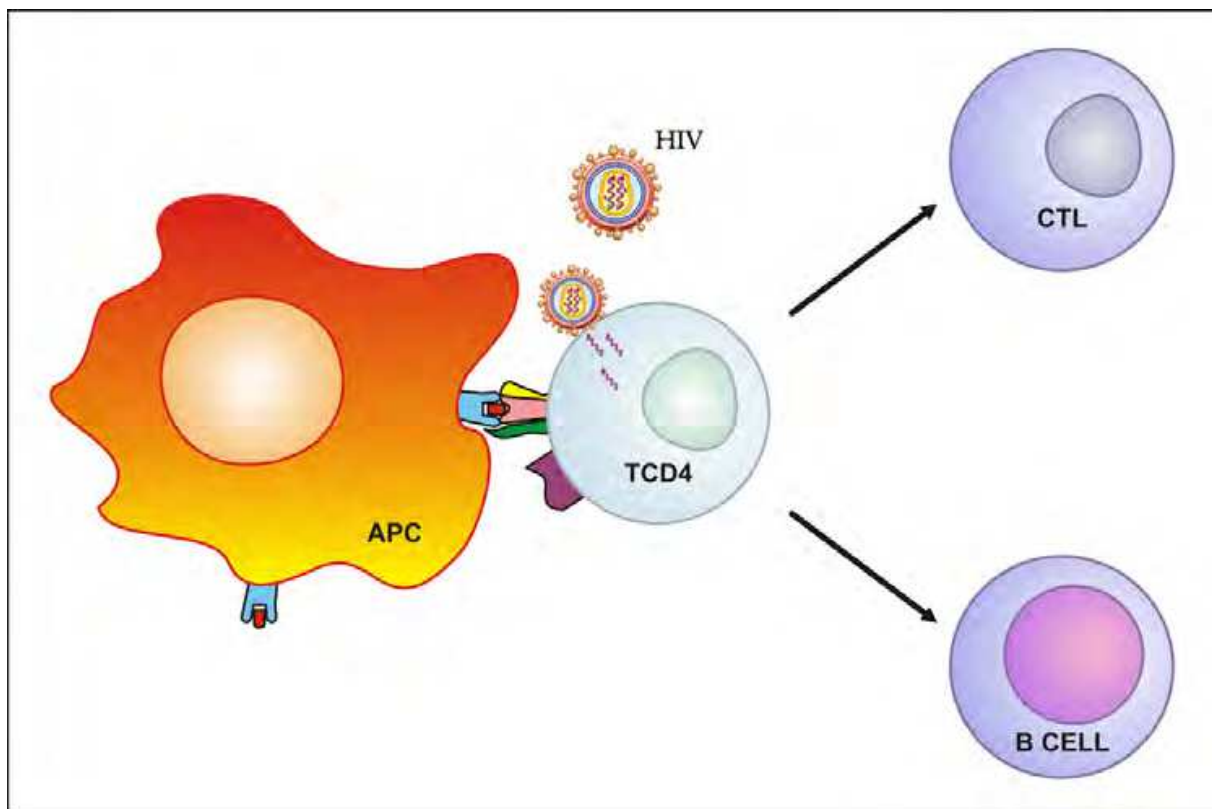


Fig. 1. HIV cell target. HIV predominantly infects CD4+ lymphocytes, which play a fundamental role in the induction of specific immune response.

APC: Antigen-presenting cell

CTL: Cytotoxic T lymphocyte

2.2 Host/virus interaction

A key feature of the immune system is to "remember" and respond to antigens with which they've previously met. This property, called immunological memory, is the basis of the vaccination process. To play its role, a vaccine must therefore deliver the antigen to the immune system in order to stimulate it and to enable the development of memory.

In this sense, a basic problem in developing an HIV vaccine is the lack of definition of the correlates of immune protection in HIV infection, so that is not completely clear what types of immune response should ideally be stimulated by vaccination and consequently what measure and criteria should be used to evaluate the effectiveness of the vaccine.

Initially the first strategies implied to obtain an HIV vaccine were focused on inducing neutralizing antibodies against the viral envelope proteins (Dolin, 1995) and from mid-1990, studies began to focus on the activation of a cellular immune response.

Stimulation of neutralizing antibodies with broad specificity for all HIV variants would be definitely interesting for a vaccine strategy. Evidence in nonhuman primates suggest that a protection could be afforded if neutralizing antibodies could be present in high concentration both in blood and mucosa at the time of first infection (Parren et al., 2001). However, the induction of neutralizing antibodies against HIV is hampered by some specific characteristics of the virus, such as

- a. The high epitopes mutation rate, which causes loss of recognition capacity by antibodies;

- b. The large number of subtypes of HIV that exhibit little cross-reactivity;
- c. The high rate of glycosylation on the viral envelope
- d. The existence of hidden CD4/receptor binding sites which difficult the access of the antibodies. (Figure 2)

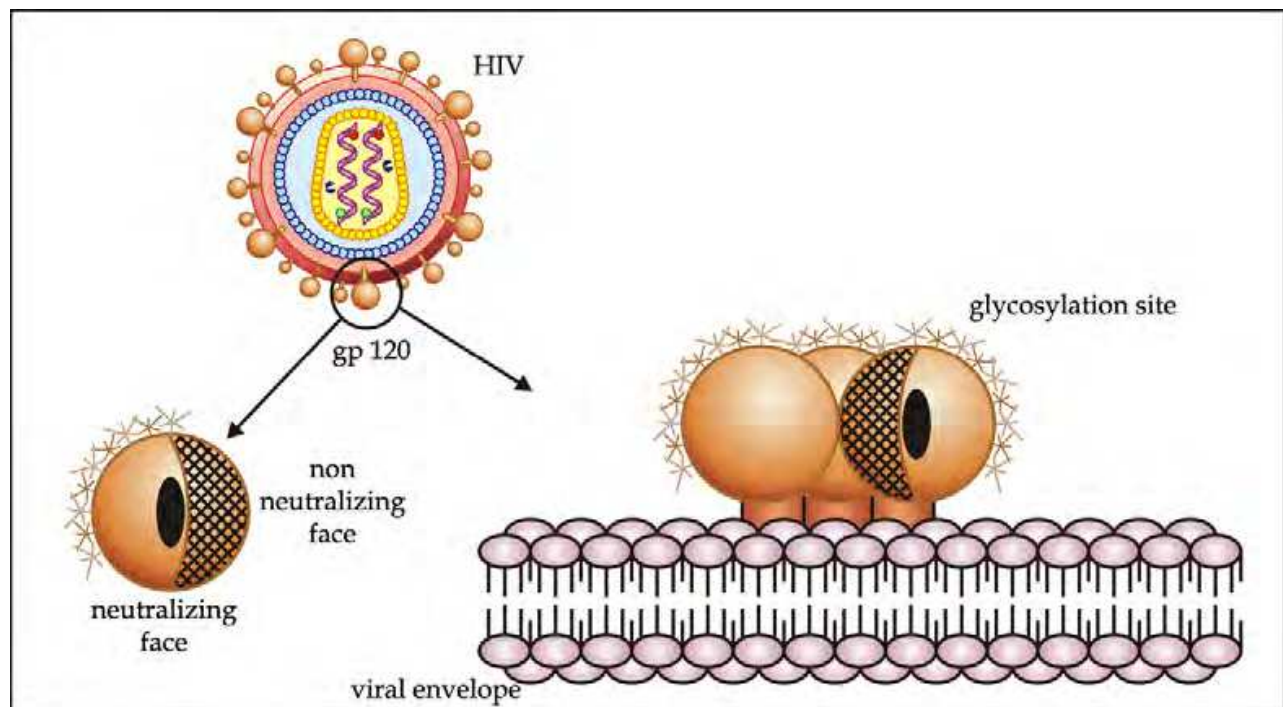


Fig. 2. Sites of antibody binding to gp120. Neutralizing and non-neutralizing sites of gp120. The sites of glycosylation of the molecule are also shown.

Considering that HIV infects CD4⁺ T cells, the stimulation of a cellular response is important for the destruction of infected cells by cytotoxic T lymphocytes (CTLs) before the release of new viral particles. Thus, in a context of an anti-HIV vaccine CD4⁺ T cells should be rapidly expanded to stimulate the right cytotoxic response against infected cells and drive memory cells to sites potentially susceptible to infection such as mucosal and lymph nodes.

Although many studies provide strong evidence that a cellular response can effectively suppress HIV (Rowland-Jones et al., 1998; Hladik et al., 2003), it remains unclear how this viral suppression occurs and how a vaccine could stimulate it. Peculiar characteristics of the virus and the nature of infection hinder the development of an appropriate cellular response, for example,

- a. The reduction of the expression of MHC class I molecules mediated by the HIV Nef protein;
- b. The establishment and maintenance of latent viral reservoirs in cells
- c. The massive destruction of T cells specific or not for HIV, caused mainly by activation-induced apoptosis. (Cadogan & Dalgleish, 2008).

In this context, even though there are not clear evidences regarding the type of immune response to be induced by an HIV vaccine, it is reasonable to assume that elements of the immune response important to ensure a real effectiveness of an HIV vaccine may depend on both neutralizing antibody and specific cellular immunity, and besides, also on innate immunity. In a simplified view, neutralizing antibodies prevent the entry of virus into the

cell by blocking the transmission and infection, while the cellular response would act destroying HIV-infected cells before the release of new viral particles in order to control an yet established infection.

Another interesting tips is that being mucosal the primary site of natural HIV infection (Kozlowski & Neutra, 2003) an effective vaccine must induce anti-HIV-1 neutralizing antibodies at mucosal surfaces to prevent the infection and cytotoxic T lymphocytes (CTLs) in sub-mucosal areas to kill virus-infected cells, or a combination of both. Unfortunately, the immune response within the mucosa may be associated with a high viral replication and dissemination: HIV activates and recruits a lot of target cells and the virus uptake by dendritic cells allow its dissemination to draining lymph nodes avoiding antibody recognition. The challenge to an effective vaccine is to activate mucosal immunity at the right time. Moreover, all mucosal vaccines have to overcome tolerance, which is related with regulatory cells and depend on the nature of the antigen, the dosage, the method of delivery and on whether or not adjuvant is used.

2.3 Lack of animal models

Actually there is no animal model capable of to mimic the human HIV infection and AIDS development. The use of animal models could help the investigation of disease pathogenesis and provide information about toxicity and efficacy of drugs and vaccines to reduce risk, duration and cost of a clinical trial.

Despite its relatively low cost and ease of maintenance in animal houses, the use of small rodents as experimental models for HIV infection is not appropriate since HIV is unable to sustain infection in murine cells. More recently it has been demonstrated the use of humanized mice models (Van Duyne et al., 2009).

Studies in non-human primates (NHP; i.e.: *Macaca rhesus*), when allowed, even if expensive, gave some good results and have the advantage of sharing a high genetic background with humans. NHP are the natural host of a retrovirus of the same HIV family, SIV (Simian Immunodeficiency Virus) which has a very low mutational rate compared to HIV. In some studies the SHIV, a hybrid virus composed of parts of the genome of HIV and SIV, has been implied to create the infection model (Stapransan et al, 2010).

Although providing crucial information about viral immunobiology and vaccine design, it must be taken in account that important differences in the viral infection exist between humans and NHP. Data from NHP models should be critically evaluated for their predictive value in human trials (Shedlock et al., 2009).

3. Strategies and methods used in the development of anti-HIV vaccines

Like most vaccines, candidates for HIV vaccine contained weakened or killed forms of the virus or viral components which resembling original HIV and could be able to stimulate the immune system to develop an appropriate response. Taking in account all these considerations, in the past decades several aspects related to the vaccine composition, route of immunization and vaccine strategy have been tested in the effort to develop an effective HIV vaccine.

3.1 Vaccine composition

3.1.1 Immunogen production

Many techniques have been employed in order to produce relevant immunogenic HIV antigens, such as:

- chemical (eg. alcohols) or heat inactivated virus particles;
- viral proteins or peptides artificially synthesized (mimetopos) or produced by the insertion of relevant genes in biological vectors (recombinants);
- proteins expressed in the form of virus like particles (VLP), consisting of structurally preserved viral epitopes (i.e.: parts of the virus surface proteins), without the viral genetic material, thus preventing their replication.
- HIV genetic material to insert directly into cells that will express their products. Usually this material is inserted in the form of plasmids, which are molecules of extra-chromosomal circular DNA, with independent replication. The insertion of genetic material in the body can be made directly (eg. electroporation or gene guns using compressed gas) or through biological vectors.

Live attenuated virus vaccines have not been investigated in anti-HIV vaccines due to the risk of development of virulence, as evidenced in a model of NHP (Whatmore et al., 1995).

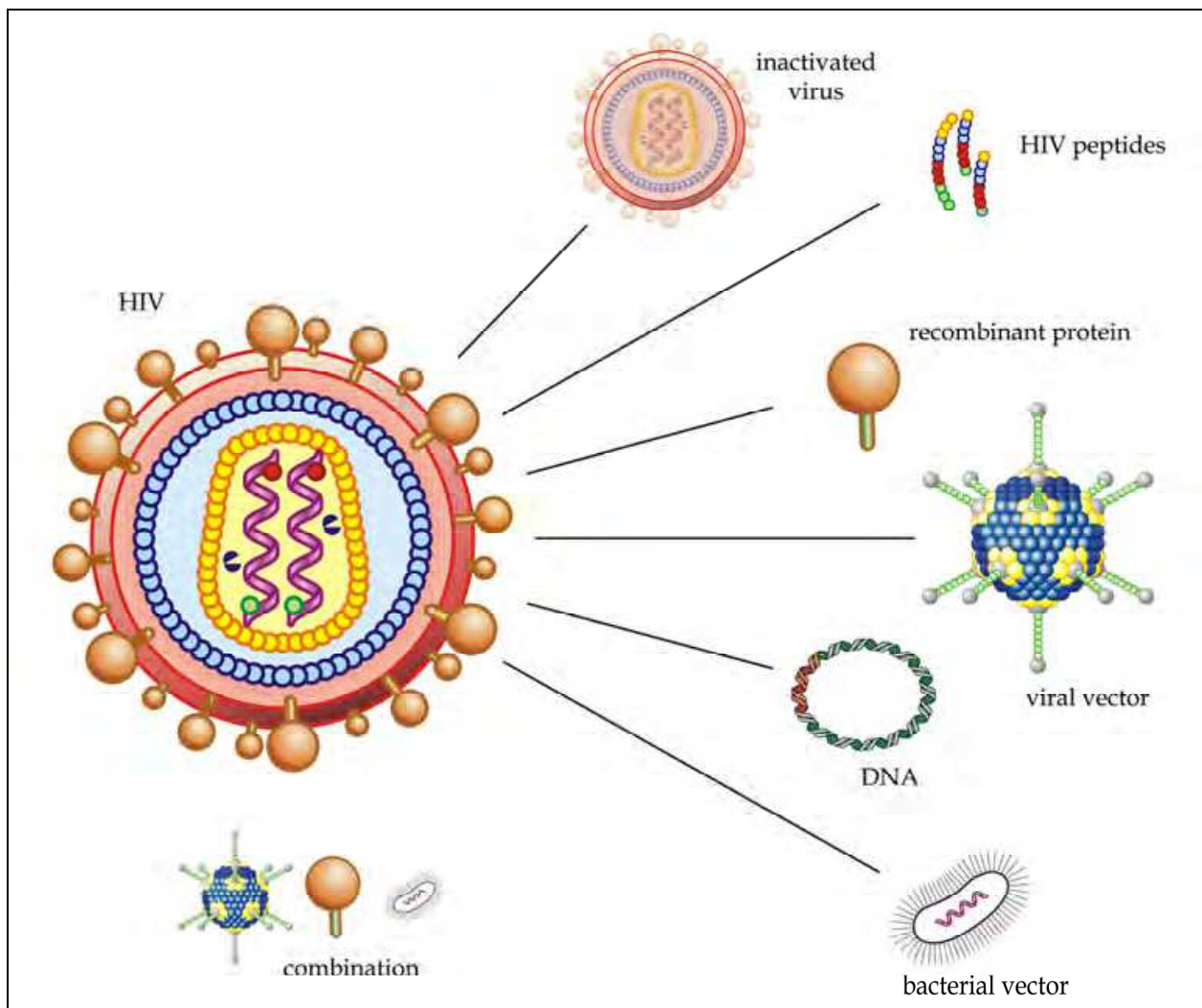


Fig. 3. Immunogens used in the composition of HIV vaccines. There are three types of immunogens: whole vital particle, peptides or recombinant proteins and genetic material of the virus, which may or may not be inserted within vectors. Sometimes the combination of different immunogens can be used (prime-boost strategy).

The advantages and disadvantages of some types of immunogens used in the development of HIV vaccines are summarized in Table 1.

PRODUCT	ADVANTAGE	DISADVANTAGE
Inactivated virus	- whole virus is included in the vaccine	-risk that the preparation contains active virus - difficult to produce in large scale -the response induced by chance is directed only to the type of virus
Peptide	-production relatively simple and inexpensive -safe	-un representative in terms of immunogenic epitopes
Recombinant proteins	-production relatively simple -safe	-low immunogenic
DNA	-production relatively simple and inexpensive	-there are gaps of knowledge about the integration of DNA in the human genome -low immunogenic - limited ability to incorporate HIV genes (in the case of viral vectors)
Vaccines based on biological vectors	-safe -it is possible to control the type and amount of HIV protein	- limited immunogenicity by the existence of prior immunity to the vector - production platforms more complex (viral vectors)

Table 1. Advantages and disadvantages of some types of immunogens used in the development of HIV vaccines

3.1.2 Adjuvants

A vaccine adjuvant is a component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses (i.e.: with respect to immunoglobulin classes and induction of cytotoxic or helper T lymphocyte responses). In addition, certain adjuvants can be used to promote antibody responses at mucosal surfaces. Activation of innate immune system and in particular of dendritic cells (DCs) is a crucial mechanism by which adjuvants stimulate protective adaptive immunity against the vaccine antigen.

As immune response is typically initiated by activation of antigen presenting cells (APCs), notably dendritic cells (DCs). There has been significant interest in improving APC-stimulating adjuvants as a key step in constructing better vaccines

Adjuvants have several forms, ranging from mineral salts such as alum to oil-based emulsions. Moreover molecular adjuvants such as proteins, lipids, nucleic acids, carbohydrates, or chemical compounds have a known receptor in DCs (i.e.: Toll Like

receptors - TLRs) and result in an improvement in the quantity or quality of the ensuing immune response (Kornbluth & Stone, 2006).

CLASS	EXAMPLE
CD40 agonists	CD40L or its derivatives, Agonistic anti-CD40 antibodies, Heat shock protein (Hsp70)
NKT cell ligand	CD1d-binding NKT
TLRs agonists	poly(I:C), LPS, and imidazoquinolines act on TLR3, TLR4, and TLR7 (mDCs) imidazoquinolines and CpG ODP act on TLR7 and TLR9 (pDCs) flagellin act on TLR5 (Vassilieva et al., 2011)
NLRs agonists	MDP act on NOD2 and NALP3, extracellular ATP and pathogen RNA act on NALP3
Chemokines	MIP-1a, CCL19/EBI1-ligand and CCL21/SLC

Table 2. Molecular adjuvants for HIV vaccine strategy.

Many adjuvants have been developed in the past, but were never accepted for routine vaccination because of safety concerns (e.g. acute toxicity and the possibility of delayed side effects).

3.2 Route of administration

Vaccine delivery systems are the sum of pharmacologic technologies (including drug preparation, route of administration, site targeting, metabolism and toxicity) and have the principal aim to make the vaccine preparation faster and easier available to immune system. In its broadest sense, the concept of vaccine delivery systems can be expanded to include a diverse range of devices and physical delivery systems that are designed to improve the potency of vaccines or to allow immunization using novel, non-invasive routes (eg. gene-gun approach, devices designed to fire powdered vaccines into the skin through the use of helium gas and vaccine patches). Delivery systems may function to improve antigen access to lymph nodes in a number of ways:

- increase antigens presenting cells (APCs), generally dendritic cells (DC), infiltration into the injection site;
- promote the uptake of antigen in APCs through activating phagocytosis;
- deliver antigen from the injection site to the local lymph node through into the lymphatic system

Various routes of HIV vaccine administration have been used starting from the most common (eg. subcutaneous, intramuscular) to more specific such as mucosal with different outcomes. HIV transmission occurs through mucosal (specially of the genital tract) and many efforts have been done to better characterize the mucosal associated lymphoid tissue (MALT) and its involvement in early HIV infection, with the final purpose to use the mucosal route of immunization. For vaccine design, the choice of mucosal inductive site is critical in determining the distal effector site to which induced memory cells will home. In

HIV vaccine research, many mucosal sites were chosen to administer the immunogen: nasal mucosal (Vajdy & Singh, 2006), intratracheal/aerosol vaccination (Corbett et al., 2008), oral vaccination (Stahl-Hennig et al., 2007, N. Cuburu et al., 2007), rectal/colonic vaccination (Belyakov et al., 2006), intravaginal vaccination- (Pialoux et al., 2008).

3.3 Vaccination strategies

The vaccination strategy comprehends the combination of diverse types of vaccine (immunogen, adjuvant, route of immunization) with different schedules to increasing the vaccine potential immunogenic effect. In HIV vaccine several combinations of immunogens (inactivated virus, viral proteins, recombinant viral DNA), routes and schedules have been tested to augment the delivery of HIV antigens to the immune system.

For example, viral vectors are efficient to place HIV relevant epitopes within the target cells and, due to their composition, to stimulate the innate response, promoting an adjuvant effect, although it has been observed that the immunogenicity of these vectors could be affected by the competition between HIV and vector epitopes in the context of antigen presentation. For these reason it was developed the strategy to combined this type of vaccine with a vaccine based on HIV proteins or peptides in a such called prime-boost regimen.

Prime-boost strategy was first time used in 1992 in NHP studies (Hu et al., 1992). Briefly, it consists in the administration of one type of vaccine, such as a live-vector vaccine, followed by or together with a second type of vaccine, such as a recombinant subunit vaccine. The intent of this combination regimen is to induce different types of immune responses and enhance the overall immune response, a result that may not occur if only one type of vaccine were to be given for all doses (Ranasinghe et al., 2009).

3.4 Steps of vaccine development

The development of a vaccine is a process that requires several steps aiming to answer specific questions and to test concepts through experimental practice. Scientific knowledge generated from the execution of each stage or phase will give useful data for planning the next step.

The development of an effective vaccine against HIV infection, due to its unique aspects, will be an unprecedented challenge, and scientific rigor and discipline, statistical principles and bioethics should be required to achieve success.

The preliminary step is to generate more ideas. Established scientists in universities, research institutes and industry use the existing scientific knowledge and technology to develop ideas of how a vaccine might work.

From there, preclinical studies should be performed before human trials to assess whether a novel product has scientific merit to be a candidate vaccine. Such pre-clinical studies involve *in vitro* experiments and *in vivo* tests in available animal models to obtain information regarding the efficacy, toxicity and pharmacokinetics, using varying doses of the product being tested.

The transformation process of a candidate product in a vaccine logarithmic increases the cost and complexity of the research, as it moves from laboratory to clinical application. It is also important to emphasize that only a small percentage of the candidate products being studied in preclinical development is considered safe and promising enough to be evaluated in humans (clinical phase).

Once proven its potential as a vaccine candidate, the clinical phase of the study will start to evaluate safety, immunogenicity and efficacy of the product. Phases I-III are required for licensing the product. In the process of vaccine development, clinical trials may last for many years and the number of volunteers is increasing at every step. The goals set for each stage involves pharmacological and clinical issues, evaluated in a progressive manner throughout the process (www.ich.org - General Considerations for Clinical Trials).

The clinical trial itself begins in Phase I: the candidate vaccine is first evaluated in a small group of human volunteers in order to evaluate its safety, tolerability, pharmacokinetics and pharmacodynamics and identify possible side effects.

In Phase I trial it is also possible to evaluate efficacy markers (e.g.: the generation of antibodies and/or cytotoxic T response), allowing a preliminary assessment of the ability of the vaccine to generate an immune response. Once the safety of the candidate product has been checked, the research could proceed to the next step (Phase II).

The objective of Phase II is to test the candidate vaccine in a larger number of volunteers with two principal purposes: identify side effects related to the product use (within the perspective of future safety analysis, i.e.: toxicity) and collect preliminary indications of product potential effectiveness (efficacy).

Sometimes these aims are studied in different moments and the Phase II trials are divided into:

- a. Phase IIa: designed to determine the optimal dose of vaccine (dose-response studies).
- b. Phase IIb: designed to study the vaccine efficacy.

The Phase III trials are the last stage before possible licensing of the vaccine for marketing. They are randomized controlled trials, often multi-centric, involving large numbers of patients. The primary objective of this step is to evaluate the effectiveness of the product. Achieving a high level of effectiveness at this stage, however, does not necessarily guarantee that the product is effective in the general population, which will be evaluated in phase IV.

Phase IV trials, also called post-evaluation of efficacy, are pharmacovigilance studies performed after licensing the product and that aim to measure the effect of the product in a population. The importance of this phase is to assess the real impact of a vaccine in the epidemic.

The conduct of clinical trials involving prophylactic and therapeutic vaccines for HIV remains a challenge. In terms of design and implementing Phase I and early Phase II are relatively easy to do, although studies involving analysis of effectiveness show a higher degree of complexity. For prophylactic vaccines, the statistical requirements to demonstrate a real prevention of infection require a very large number of patients and they are sometimes prohibitive. Clinical trials for HIV vaccines require the appropriate preclinical studies and the development of better laboratory markers of efficacy.

The role of society is essential for the success of all the program to develop HIV vaccines and the establishment of a genuine dialogue with the community facilitates clinical research with HIV vaccines.

4. Current outlook

Obtaining an HIV vaccine has been one of the biggest challenges of this century. To date numerous clinical trials have been conducted to test candidate products as prophylactic vaccine.

Most initial approaches have focused on the gp120 HIV envelope protein. At least thirteen different gp120 candidates have been evaluated in Phase I trials in the USA predominantly through the AIDS Vaccine Evaluation Group, showing to be safe and immunogenic in diverse populations. They have induced neutralizing antibody, but rarely induced CD8+ cytotoxic T lymphocytes (CTL). Moreover it was very difficult to induce and maintain the high anti-gp120 antibody titers necessary to have any hope of neutralizing an HIV exposure. The availability of several recombinant vectors (adenovirus, canarypox) carrying HIV genes (*gag*, *pol*, *nef* or *env*) has provided interesting results characterized principally by a poly-functional CTL responses.

Currently, about 20 clinical trials are underway, most protocols for Phase I.

PROTOCOL	SPONSOR	PRODUCT	N	TRIAL SITE	phase
HVTN 082	NIAID, HVTN	VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP		USA	I
PedVacc001 & PedVacc002	Medical Research Council	MVA.HIVA	48	Kenya	I
HVTN 078	NIAID, EuroVacc, HVTN	NYVAC-B; VRC-HIVADV038-00-VP	80	Switzerland	I/II
HVTN 505	NIAID, HVTN	VRC-HIVDNA016-00-VP; VRC-HIVADV014-00-VP Prime: VRC-HIVDNA016-00-VP Adenovirus serotype 35 vector. Ad35-GRIN/ENV consists of two	1,350	US	II
B001	IAVI, University of Rochester Medical Center	vectors: Ad35-GRIN vector with <i>gag</i> , reverse transcriptase, integrase, and <i>nef</i> Ad35-ENV vector with gp140 <i>env</i>	42	USA	I
HIVIS 05	Swedish Institute for Infectious disease Control	MVA-CMDR	24	Sweden	I
P001	IAVI, Indian Council of Medical Research, Tuberculosis Research Centre, Chennai; National AIDS Research Institute, Pune	Prime: ADVAX (DNA vaccine containing <i>env</i> , <i>gag</i> , <i>pol</i> , <i>nef</i> and <i>tat</i>) Boost: TBC-M4 (MVA vector with <i>env</i> , <i>gag</i> , <i>RT</i> , <i>rev</i> , <i>tat</i> and <i>nef</i>)	32	India	I
Tiantianvaccinia HIV Vaccine	Chinese Center for Disease Control and Prevention, National Vaccine and Serum Institute, Peking Union Medical College	HIV-1 CN54 <i>gag</i> , <i>pol</i> and <i>env</i> genes with DNA and rTV vectors	80	China	I
Ad5HVR48.ENVA.01	NIAID, Brigham and Women's Hospital	Recombinant Adenovirus HIV-1 Vaccine, Ad5HVR48.ENVA.01 Prime: DNA vaccine containing <i>gag</i> , <i>pol</i> , <i>env</i> , <i>rat</i> , <i>rev</i> , <i>vpu</i>	48	USA	I
HVTN205	GeoVax, HVTN	Boost: MVA vaccine containing <i>gag</i> , <i>pol</i> , <i>env</i>	225	USA, Peru	II
HVTN 073	HVTN, SAAVI, Brigham and Women's Hospital CRS, Fenway Community Health, Clinical Research Boston,	Prime: SAAVI DNA-C2 Boost: SAAVI MVA-C; DNA plasmid vaccine with <i>gag</i> , <i>RT</i> , <i>tat</i> , <i>nef</i> , <i>env</i>	48	USA, South Africa	I

PROTOCOL	SPONSOR	PRODUCT	N	TRIAL SITE	fase
VRC 015 (08-1-0171)	Crossroads, Chris Hani Baragwanath Hospita NIAID, VRC, NIH Clinical Center	Multiclade Recombinant HIV-1 Adenoviral Vector Vaccine, VRCHIVADV014-00-VP	40	USA	I
Ad26.ENVA.01	NIAID, IPCAVD, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Crucell	Recombinant adenovirus serotype 26 (rAd26) vaccine	48	USA	I
NCHECR-AE1	NCHECR, University of New South Wales, Thai Red Cross AIDS Research Centre	A candidate prophylactic DNA prime-rFPV boost HIV vaccination strategy (rFPV-HIV-AE;pHIS-HIV-AE)	8	Thailand	I/II
VRC 012	NIAID, VRC	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	35	USA	I
HVTN 077	NIAID, HVTN, Alabama Vaccine, San Francisco Vaccine and Prevention, Hope Clinic of the Emory Vaccine Center, NY Blood Ctr./Union Square, NY Blood Ctr./Bronx, University of Rochester HVTN	Recombinant Adenoviral Subtype 35 (rAd35) and Subtype 5 (rAd5) HIV-1 Vaccines When Given as a Heterologous Prime-Boost Regimen or as Boosts to a Recombinant DNA Vaccine in Healthy, Ad5-Naïve and Ad5-Exposed (VRC-HIVDNA044-00-VP;VRC-HIVADV027-00-VP;VRC-HIVADV038-00-VP)	192	USA	I
HPTN 027	HVTN, International Maternal Pediatric Adolescent AIDS Clinical Trials Group, Makerere University, Johns Hopkins University, Mulago Hospital, Sanofi-Pasteur	Canarypox viral vector with <i>env</i> and <i>gag-pol</i>	50	Uganda	I
HVRF-380-131004	Moscow Institute of Immunology, Federal Medical and Biological Agency, Russian Federation Ministry of Education and Science	VICHREPOL with polyoxidonium adjuvant	15	Russia	I
RV 138; B011	Walter Reed Army Institute of Research, US Military HIV	Sanofi Pasteur Live Recombinant ALVAC-HIV (vCP205, HIV-1 Env/Gag/Pol) subcutaneously, intradermally, or intramuscularly	36	USA	I
EnvDNA	St. Jude's Children's Research Hospital	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	6	USA	I
RV 156A	NIAID, HVTN, VRC, MHRP, Makerere U.	VRC-HIVADV014-00-VP alone or as a boost to VRCHIVDNA009-00-VP	30	Uganda	I

Table 3. Ongoing clinical trials (www.avac.org/ht/a/GetDocumentAction/i/3436).

The results of Phase II and Phase III major prophylactic trials are summarized above.

4.1 VAX 004 trial (Phase III, USA 1998-2002)

The phase III VAX 004 trial enrolled 5,403 USA participants between 1998 and 1999. Volunteers received 7 injections of either vaccine or placebo (ratio, 2:1) over 30 months.

The study vaccine contained 2 rgp120 HIV-1 envelope antigens (300 mg each of two recombinant proteins rgp120/HIV-1 MN and GNE8) (AIDSVAX B/B; VaxGen) that had been derived from 2 different subtype B strains and that were adsorbed onto 600 mg of alum. GNE8 gp120 was cloned directly from peripheral-blood mononuclear cells and had the CCR5 phenotype; the GNE8 gp120 DNA sequence was deposited in GenBank.

The vaccine did not prevent HIV-1 acquisition and there was no overall protective effect (Flynn et al., 2005).

4.2 STEP trial (Phase II, USA, 2004-2007)

On December 13, 2004, the HIV Vaccine Trials Network (HVTN) began recruiting for the STEP study, a 3,000-participant phase II clinical trial of a novel HIV vaccine, at sites in North America, South America, the Caribbean and Australia.

The trial was co-funded by the National Institute of Allergy and Infectious Diseases (NIAID/NIH, USA), and the pharmaceutical company Merck & Co. Merck developed the experimental vaccine called V520 which contains an adenoviral vector rAd5 carrying three subtype B HIV genes (*gag/pol/nef*). The vaccine was administered in a prime-boost regimen at 0, 1 and 6 months. The follow up of vaccinated subjects showed the lack of efficacy of this vaccine, as well as an increment in HIV-1 infection in individuals with prior immunity to adenovirus. Adenovirus vectors and many other viral vectors currently used in HIV vaccines, will induce a rapid memory immune response against the vector. This results in an impediment to the development of a T cell response against the inserted antigen.

For this reason the phase II trial was closed in September 2007 and other vaccine protocols in progress including the same vector vaccine such as the HVTN503 (Phambili) were cancelled or modified (Barouch & Korber, 2010).

While the final results of STEP have been disappointing, this study has raised its contribution to redefine the priorities in HIV vaccines research field, demonstrating the need to focus on basic research, preclinical and clinical studies.

4.3 RV144 trial (Phase III, Thailand, 2003-2009)

The phase III HIV vaccine RV144 involved more than 16,000 young Thai adults at variable risk for infection between October 2003 and September 2009. Every six months, volunteers received a prime-boost vaccination including six injections of a vaccine called ALVAC-HIV (vCP1521, Sanofi Pasteur) with the last two of the six injections being a combination of that vaccine and another one called AIDSVAX B/E (gp120, Genentech).

ALVAC-HIV consists of a viral vector containing genetically engineered versions of three HIV genes (*env, gag* and *pro*). The ALVAC vector is an inert form of canarypox, a bird virus which cannot cause disease or replicate in humans. AIDSVAX B/E is composed of genetically engineered gp120. The RV 144 protocol was sponsored by the Surgeon General of the United States Army and conducted by the Thailand Ministry of Public Health with support from the United States Army Medical Research and Materiel Command and the NIAID/NIH.

The rate of HIV infection among volunteers who received the experimental vaccine being tested in the trial was 31% lower than the rate of HIV infection among volunteers who received placebo (Rerks-Ngarm et al., 2009).

Although showing only a modest benefit, this work has renewed optimism in this field of research. However, criticisms related primarily to the study design and statistical method employed to analyse data generated debate about the results (Cohen, 2009; Letvin, 2009).

4.4 Dendritic cell based immunotreatment

In addition to trials aimed at obtaining prophylactic HIV vaccine, has been also developed protocols for therapeutic vaccination using dendritic cells (DC) for the treatment of individuals already infected with HIV.

DCs are potent antigen presenting cells that act as controllers and regulators of the immune system and are the only cells capable of fully activate naive CD4 lymphocytes and thus initiate a specific response (Banchereau & Steinman, 1998). In the context of an HIV vaccine

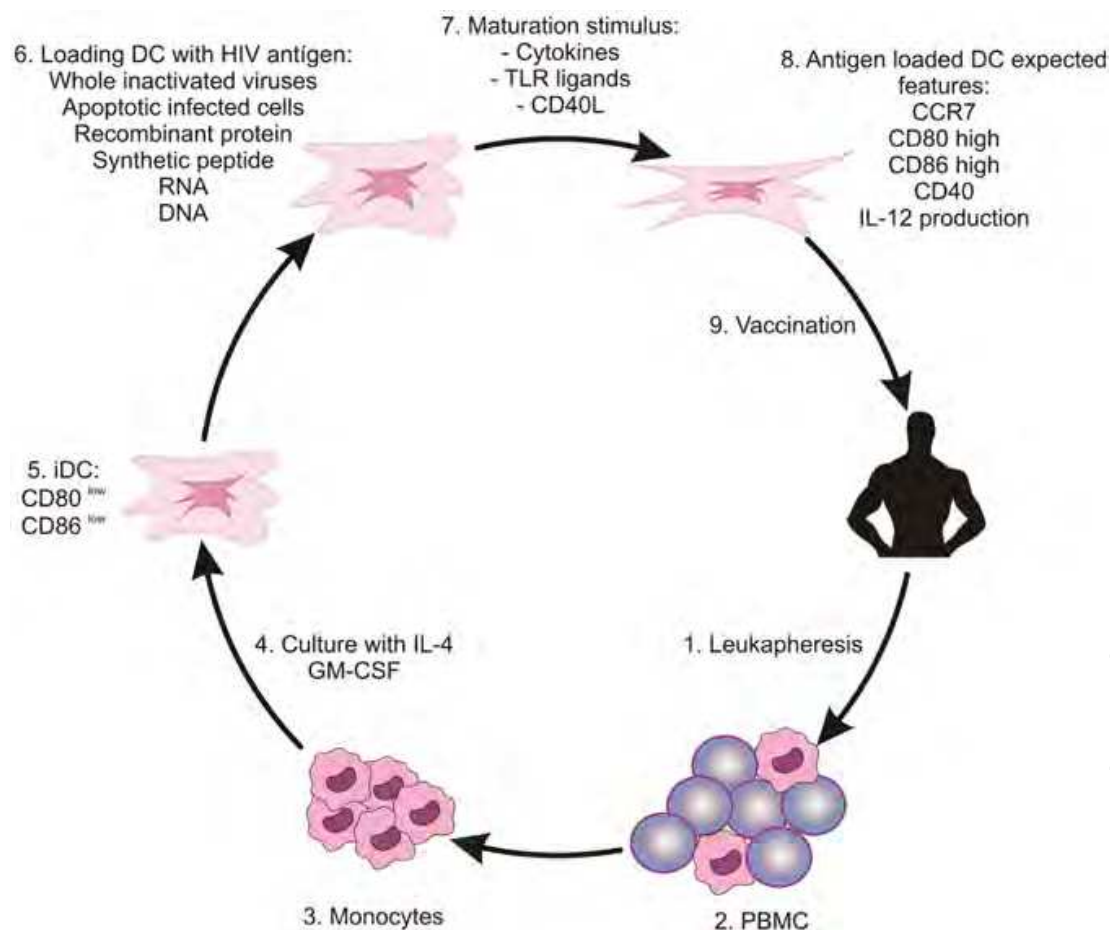


Fig. 4. Treatment of HIV infected patients with monocyte-derived DCs. Peripheral blood mononuclear cells (PBMC) are obtained by leukapheresis and monocytes are separated and cultured in the presence of IL-4 and GM-CSF to obtain immature DCs (iDCs). iDCs are loaded with the antigen of interest and are activated by different stimuli for maturation. Mature DCs (MDCs), potentially able to migrate and to present antigens, are reinoculate into the patient.

AUTHORS	n	TYPE OF ANTIGEN	IMMUNOGENICITY ASSESSMENT
Kundu et al., 1998	6	Recombinant HIV-1 MN gp160 or HLA-A2-restricted synthetic peptides of envelope, Gag, and Pol	Envelope-specific CTL- and lymphocyte-proliferative responses, IFN-gamma and IL-2 production, peptide-specific lymphocyte-proliferative responses Serum neutralizing antibody titers, HIV-1-specific interferon- γ (IFN- γ) expressing CD4 ⁺ T and CD8 ⁺ cells, HIV-1-specific IL-2- expressing CD4 ⁺ T cells, HIV-1 gag-specific CD8 ⁺ T cells, HIV-1 gag-specific CD8 ⁺ T cells expressing perforin
Lu W et al., 2004	18	Chemically inactivated autologous HIV-1	Lymphoproliferation, Th1 cell levels, cytotoxic T lymphocyte [CTL] levels, serum neutralizing antibody titers and changes in lymphoid tissue
Garcia F et al., 2005	12	Heat-inactivated autologous human immunodeficiency virus type 1 (HIV-1)	IFN-g production in CD8 lymphocytes
Ide F et al., 2006	4	HIV-1-derived cytotoxic T lymphocytes (CTL) peptides	Gamma interferon (IFN- γ)-producing cells (PBMC)
Connolly NC et al., 2008	18	Gag, Env, and Pol peptides	Gamma interferon (IFN- γ)-producing cells (PBMC), lymphocyte-proliferative responses
Ghandhi RT et al., 2009	29	Viral vector (canarypox) expressing HIV-1 env and gag and a synthetic polypeptide encompassing epitopes from nef and pol	Lymphoproliferation, serum neutralizing antibody titers, ELISPOT
Garcia F et al., 2011	24	Heat-inactivated autologous human immunodeficiency virus type 1 (HIV-1)	

Table 4. Parameters used in the post-vaccine immune response assessment
 HLA= **H**uman **L**eukocyte **A**ntigen. IL-2= **I**nterleukin-**2** . PBMCs=Peripheral Blood Mononuclear Cells.

becomes desirable to induce a specific and effective activation of the immune system against the viral chronic infection.

Protocols of immunotherapy with DCs began in the late 1990 and since then a growing number of studies evaluating this strategy. Because it is an individualized protocol, the number of individuals in the tests is always limited, never exceeding a few tens of individuals.

It is a strategy that involves the collection of mononuclear cells from HIV-infected individual, separation of monocytes and stimulation of these cells with cytokines to differentiate into immature dendritic cells. Dendritic cells are then sensitized (pulsed or loaded) with the antigen of interest, activated and reinoculated into the individuals (Figure 4). The objective of this strategy is to stimulate the immune response by enhancing antigen presentation mediated by dendritic cells.

An overview of the works conducted so far (Table 4) shows although that the products are always safe and the results are quite heterogeneous (Kundu et al., 1998; García et al., 2005, 2011; Ide et al., 2006; Connolly et al., 2008, Lu et al., 2004, Gandhi, 2009)

Considering the difficulty to obtain an HIV prophylactic vaccine, the immunotherapy offers a unique opportunity to study the mechanisms of immune response against the virus and contribute to the definition of correlates of protection in HIV infection. Knowledge generated from studies of DC-based immunotherapy may contribute also to the development of prophylactic vaccines.

5. Conclusions

Despite numerous difficulties and great scientific challenges that must be overcome to obtain an HIV vaccine, the extraordinary advance in biomedical research and the remarkable progress achieved show clear reasons for optimism.

Knowledge has been accumulated on the biology and diversity of HIV; new methods have been used for the production of immunologically relevant antigens; the study of immune response in exposed not-infected individuals and in elite controllers has generated important information regarding the type of effective immune response against HIV. Furthermore, immunotherapy protocols in infected individuals provide a unique opportunity to studying immune mechanisms against the virus.

Lessons from the failure of the previous protocols can effectively guide the design and refinement of the next generation of candidate vaccines. In this scenario, the perspective is that knowledge of the various interdisciplinary areas of science can provide an environment leading to overcome these scientific challenges.

6. References

- Banchereau, J., Steinman, R.M. (1998). Dendritic cells and the control of immunity. *Nature*, Vol 392, No. 6673, (Mar 1998), pp. 245-252, ISSN 0028-0836.
- Barouch, D.H., Korber B. (2010). HIV-1 vaccine development after STEP. *Annu Rev Med*, Vol. 61, (Feb 2010), pp.153-167, ISSN 0066-4219.
- Belyakov, I.M., Kuznetsov, V.A., Kelsall, B., Klinman, D., Moniuszko, M., Lemon, M., Markham, P.D., Pal, R., Clements, J.D., Lewis, M.G., Strober, W., Franchini, G. and Berzofsky J.A. (2006). Impact of vaccine-induced mucosal high-avidity CD8+ CTLs

- in delay of AIDS viral dissemination from mucosa. *Blood*, Vol. 107, pp. 3258–3264, ISSN 1528-0020.
- Brenchley, J.M., Schacker, T.W., Ruff, L.E., Price, D.A., Taylor, J.H., Beilman G.J., Nguyen P.L., Khoruts, A., Larson M., Haase, A.T., Douek, D.C. (2004). CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med*, Vol. 200, No. 6, (Sep 2004), pp. 749-759, ISSN 0022-1007.
- Cadogan, M., Dalgleish, A.G. (2008). HIV immunopathogenesis and strategies for intervention. *Lancet Infect Dis*, Vol. 8, No. 11, pp:675-684. ISSN 1473-3099.
- Carr, A. (2000). HIV protease inhibitor-related lipodystrophy syndrome. *Clin Infect Dis*, Vol 30, Suppl 2, pp.S135-42, ISSN 1537-6591
- Cohen, J. (2009). HIV/AIDS research. Beyond Thailand: making sense of a qualified AIDS vaccine "success". *Science*, Vol. 326, No. 5953, pp. 652-653, ISSN 1095-9203.
- Connolly, N.C., Whiteside, T.L., Wilson, C., Kondragunta, V., Rinaldo, C.R., Riddler, S.A. (2008). Therapeutic immunization with human immunodeficiency virus type 1 (HIV-1) peptide-loaded dendritic cells is safe and induces immunogenicity in HIV-1-infected individuals. *Clin. Vac. Immunol.* Vol. 15, No 2, pp. 284-92, ISSN 1556-679X.
- Corbett M., Bogers, W.M., Heeney, J.L., Gerber, S., Genin, C., Didierlaurent, A., Oostermeijer, H., Dubbes, R., Braskamp, G., Lerondel, S., Gomez, C.E., Esteban, M., Wagner, R., Kondova, I., Mooij, P., Balla-Jhagjhoorsingh, S., Beenhakker, N., Koopman, G., van der Burg, S., Kraehenbuhl, J.P. and Le Pape, A. (2008). Aerosol immunization with NYVAC and MVA vectored vaccines is safe, simple, and immunogenic. *Proc Natl Acad Sci USA*, Vol. 105, pp. 2046–2051, ISSN 1091-6490.
- Cuburu, N., Kweon. M.N., Song, J.H., Hervouet, C., Luci, C., Sun, J.B., Hofman, P., Holmgren, J., Anjuere, F. and Czerkinsky, C. (2007). Sublingual immunization induces broad-based systemic and mucosal immune responses in mice. *Vaccine* Vol. 25, pp. 8598–8610, ISSN 0264-410X.
- Dolin, R. (1995). Human studies in the development of human immunodeficiency virus vaccines. *J Infect Dis*. Vol. 172, No. 5, pp.1175-1183,ISSN 1537-6613.
- Dunham, R., Pagliardini, P., Gordon, S., Sumpter, B., Engram, J., Moanna, A., Paiardini, M., Mandl, J.N., Lawson, B., Garg, S., McClure, H.M., Xu, Y.X., Ibegbu, C., Easley, K., Katz, N., Pandrea, I., Apetrei, C., Sodora, D.L., Staprans, S.I., Feinberg, M.B., Silvestri, G. (2006). The AIDS resistance of naturally SIVinfected sooty mangabeys is independent of cellular immunity to the virus. *Blood*, Vol. 108, No 1, pp. 209-217, ISSN 1528-0020.
- Egger, M., Hirschel, B., Francioli, P., Sudre, P., Wirz, M., Flepp, M., Rickenbach, M., Malinverni, R., Vernazza, P., Battegay, M.(1997). Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. Swiss HIV Cohort Study. *BMJ*, Vol. 315, pp. 1194-1199, ISSN 09598138.
- Fischl, M.A., Richman, D.D., Grieco, M.H., Gottlieb, M.S., Volberding, P.A., Laskin, O.L., Leedom, J.M., Groopman, J.E., Mildvan, D. Schooley, R.T et al. (1987). The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related

- complex. A double-blind, placebo-controlled trial. *N Engl J Med*, Vol.317, pp. 185-191, ISSN 1533-4406.
- Flynn, N.M., Forthal, D.N., Harro, C.D., Judson, F.N., Mayer, K.H., Para ,M.F.; rgp120 HIV Vaccine Study Group. (2005). Placebo-Controlled Phase 3 Trial of a Recombinant Glycoprotein 120 Vaccine to Prevent HIV-1 Infection. *J Infect Dis*, Vol. 91, pp. 654-65, ISSN 1537-6613.
- García, F., Lejeune, M., Climent, N., Gil, C., Alcamí, J., Morente, V., Alós, L., Ruiz, A., Setoain, J., Fumero, E., Castro, P., López, A., Cruceta, A., Piera, C., Florence, E., Pereira, A., Libois, A., González, N., Guilá, M., Caballero, M., Lomeña, F., Joseph, J., Miró, J.M., Pumarola, T., Plana, M., Gatell, J.M., Gallart, T. (2005). Therapeutic Immunization with dendritic cells loaded with heat-inactivated autologous HIV-1 in patients with chronic HIV-1 Infection. *J. Infect. Dis.* Vol. 191, pp. 1680-1685, ISSN 1537-6613.
- García, F., Climent, N., Assoumou, L., Gil, C., González, N., Alcamí, J., León, A., Romeu, J., Dalmau J., Martínez-Picado, J., Lifson, J., Autran, B., Costagliola, D., Clotet, B., Gatell, J.M., Plana, M., Gallart, T. DCV2/MANON07- AIDS Vaccine Research Objective Study Group. (2011). A therapeutic dendritic cell-based vaccine for HIV-1 infection. *J Infect Dis*, Vol 203, No. 4, pp. 473-478, ISSN 1537-6613.
- Gaschen, B., Taylor, J., Yusim, K., Foley, B., Gao, F., Lang, D., Novitsky, V., Haynes, B., Hahn, B.H., Bhattacharya, T., Korber, B. (2002) Diversity considerations in HIV-1 vaccine selection. *Science*, Vol. 296, No 5577, pp. 2354-2360, ISSN 1095-9203.
- Gandhi RT, O'Neill D, Bosch RJ, Chan ES, Bucy RP, Shopis J, Baglyos L, Adams E, Fox L, Purdue L, Marshak A, Flynn T, Masih R, Schock B, Mildvan D, Schlesinger SJ, Marovich MA, Bhardwaj N, Jacobson JM; AIDS Clinical Trials Group A5130 team. (2009). A randomized therapeutic vaccine trial of canarypox-HIV-pulsed dendritic cells vs. canarypox-HIV alone in HIV-1-infected patients on antiretroviral therapy. *Vaccine*, Vol 27, No. 43, pp. 6088-6094, ISSN 0264-410X.
- Hawkins, T. (2010). Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Res*, Vol 85, No 1, pp. 201-209, ISSN 0166-3542.
- Heyward, W.L., MacQueen, K.M., Goldenthal, K.L. (1998). HIV vaccine development and evaluation: realistic expectations. *AIDS Res&Hum Retroviruses*, Vol. 14, Suppl 3:S205-10, ISSN 1931-8405.
- Hladik, F., Desbien, A., Lang, J., Wang, L., Ding, Y., Holte, S., Wilson, A., Xu, Y., Moerbe, M., Schmechel, S., McElrath, M.J. (2003). Most highly exposed seronegative men lack HIV-1-specific, IFN-gamma-secreting T cells. *J Immunol*, Vol. 171, No 5, pp. 2671-83, ISSN 1550-6606.
- Hu, S.L., Abrams, K., Barber, G.N., Moran, P., Zarling, J.M., Langlois, A.J., Kuller, L., Morton, W.R., Benveniste, R.E. (1992). Protection of macaques against SIV infection by subunit vaccines of SIV envelope glycoprotein gp160. *Science*, Vol. 255, No. 5043, pp. 456-459, ISSN 1095-9203.
- Ide, F., Nakamura, T., Tomizawa, M., Kawana-Tachikawa, A., Odawara, T., Hosoya, N. and Iwamoto, A. (2006). Peptide-loaded dendritic-cell vaccination followed by treatment interruption for chronic HIV-1 infection: a phase 1 trial. *J. Med. Virol*, Vol. 78, No. 6, pp. 711-718, ISSN 1096-9071.

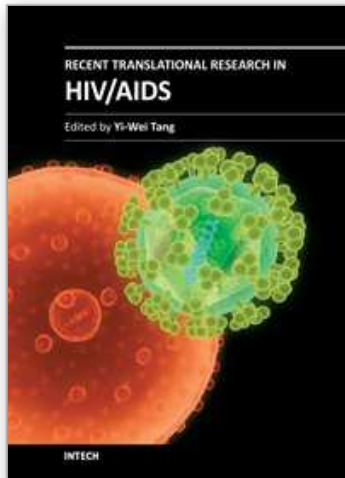
- Kornbluth, R.S., Stone, G.W. (2006). Immunostimulatory combinations: designing the next generation of vaccine adjuvants. *J Leukoc Biol*, Vol. 80, No. 5, pp.1084-1102, ISSN 0741-5400.
- Kozlowski, P.A., Neutra, M.R. (2003). The role of mucosal immunity in prevention of HIV transmission. *Curr Mol Med*, Vol. 3, No 3, pp. 217-228, ISSN 1566-5240.
- Kundu, S.K., Engleman, E., Benike, C., Shapero, M.H., Dupuis, M., van Schooten, W.C., Eibl, M., Merigan, T.C. (1998). A pilot clinical trial of HIV antigen-pulsed allogeneic and autologous dendritic cell therapy in HIVinfected patients. *AIDS Res. Hum. Retrovir.* Vol. 14, pp. 551-560, ISSN 1931-8405.
- Lederman, M.M., Alter, G., Daskalakis, D.C., Rodriguez, B., Sieg, S.F., Hardy, G., Cho, M., Anthony, D., Harding, C., Weinberg, A., Silverman, R.H., Douek, D.C., Margolis, L., Goldstein, D.B., Carrington, M., Goedert, J.J. (2010). Determinants of protection among HIV-exposed seronegative persons: an overview. *J Infect Dis*, Vol. 202, Suppl 3:S333-8, ISSN 1537-6613.
- Letvin, N.L. (2009). Virology. Moving forward in HIV vaccine development. *Science*, Vol. 26, No 5957, pp. 1196-8, ISSN 1095-9203.
- Lu, W., Arraes, L.C., Ferreira, W.T., Andrieu, J.M. (2004). Therapeutic dendritic-cell vaccine for chronic HIV-1 infection. *Nat. Med*, Vol, 10, pp. 1359-65, ISSN 1078-8956.
- Mattapallil, J.J., Douek, D.C., Hill, B., Nishimura, Y., Martin, M., Roederer, M. (2005). Massive infection and loss of memory CD4+ Tcells in multiple tissues during acute SIV infection. *Nature*, Vol. 434, pp. 1093-1097, ISSN 0028-0836.
- Menéndez-Arias L. (2010). Molecular basis of human immunodeficiency virus drug resistance: an update. *Antiviral Res.* Vol. 85, No. 1, pp. 210-231, ISSN 0166-3542.
- Parren, P.W., Marx, P.A., Hessel, A.J., Luckay, A., Harouse, J., Cheng-Mayer, C., Moore, J.P. and Burton, D.R. (2001). Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol*, Vol. 75, No. 17, pp. 8340-8347, ISSN 1098-5514.
- Pialoux, G., Hocini, H., Perusat, S., Silberman, B., Salmon-Ceron, D., Slama, L., Journot, V., Mathieu, E., Gaillard, C., Petitprez, K., Launay, O. and Chene, G. (2008). Phase I study of a candidate vaccine based on recombinant HIV-1 gp160 (MN/LAI) administered by the mucosal route to HIV-seronegative volunteers: The ANRS VAC14 study. *Vaccine*, Vol. 26, pp. 2657-2666, ISSN 0264-410X.
- Poropatich, K., Sullivan, D.J.Jr. (2011). Human immunodeficiency virus type 1 long-term non-progressors: the viral, genetic and immunological basis for disease non-progression. *J Gen Virol*, Vol. 92 Pt 2, pp. 247-68, ISSN 1465-2099.
- Ranasinghe, C., Ramshaw, I.A. (2009). Genetic heterologous prime-boost vaccination strategies for improved systemic and mucosal immunity. *Expert Rev Vaccines*, Vol. 8, pp. 1171-1181, ISSN 1476-0584.
- Rerks-Ngarm, S., Pitisuttithum, P., Nitayaphan, S., Kaewkungwal, J., Chiu, J., Paris, R., Prensri, N., Namwat, C., de Souza, M., Adams, E., Benenson, M., Gurunathan, S., Tartaglia, J., McNeil, J.G., Francis, D.P., Stablein, D., Birx, D.L., Chunsuttiwat, S., Khamboonruang, C., Thongcharoen, P., Robb, M.L., Michael, N.L., Kunasol, P., Kim, J.H. and MOPH-TAVEG Investigators. (2009). Vaccination with ALVAC and

- AIDSVAX to prevent HIV-1 infection in Thailand. , Vol. 361, No. 23, pp. 2209-2220, ISSN 1533-4406.
- Rowland-Jones, S.L., Dong, T., Fowke, K.R., Kimani, J., Krausa, P., Newell, H., Blanchard, T., Ariyoshi, K., Oyugi, J., Ngugi, E., Bwayo, J., MacDonald, K.S., McMichael, A.J. and Plummer, F.A. (1998). Cytotoxic T cell responses to multiple conserved HIV epitopes in HIV-resistant prostitutes in Nairobi. *J Clin Invest*, Vol. 102, No. 9, pp. 1758-1765, ISSN 1558-8238.
- Shedlock, D.J., Silvestri, G., Weiner, D.B. (2009). Monkeying around with HIV vaccines: using rhesus macaques to define 'gatekeepers' for clinical trials. *Nat Rev Immunol*, Vol. 9, No. 10, pp. 717-728, ISSN 1474-1733.
- Stahl-Hennig, C., Kuate, S., Franz M., Suh, Y.S., Stoiber, H., Sauermann, U., Tenner-Racz, K., Norley, S., Park, K.S., Sung, Y.C., Steinman, R., Racz, P., and Uberla, K. (2007) Atraumatic oral spray immunization with replication-deficient viral vector vaccines. *J Virol*, Vol. 81, pp.13180-13190, ISSN 1098-5514.
- Stapransa, S.I., Feinberga, M.B., Shiverb, J.W. and Casimiro, D.R. (2010). Role of nonhuman primates in the evaluation of candidate AIDS vaccines: an industry perspective. *Current Opinion in HIV and AIDS*, Vol. 5, No. 5, pp. 377-385, ISSN 1746-6318.
- Sumpter, B., Dunham, R., Gordon, S., Engram, J., Hennessy, M., Kinter, A., Paiardini, M., Cervasi, B., Klatt, N., McClure, H., Milush, J.M., Staprans, S., Sodora, D.L. and Silvestri, G. (2007). Correlates of preserved CD4(+) T cell homeostasis during natural, non-pathogenic simian immunodeficiency virus infection of sooty mangabeys: implications for AIDS pathogenesis. *J. Immunol*, Vol. 178, No. 3, pp. 1680-1691, ISSN 1550-6606.
- Vajdy, M. and Singh M. (2006). Intranasal delivery of vaccines against HIV. *Expert OpinDrug Deliv*, Vol. 3, pp. 247-259, ISSN 1742-5247.
- Van Duyne, R., Pedati, C., Guendel, I., Carpio, L., Kehn-Hall, K., Saifuddin, M., Kashanchi, F. (2009). The utilization of humanized mouse models for the study of human retroviral infections. *Retrovirology*, Vol. 6, pp. 76, ISSN 1742-4690.
- Vassilieva, E.V., Wang, B.Z., Vzorov, A.N., Wang, L., Wang, Y.C., Bozja, J., Xu, R., Compans, R.W. (2011). Enhanced Mucosal Immune Responses to HIV Virus-Like Particles Containing a Membrane-Anchored Adjuvant. *MBio*, Vol. 2, No. 1, ISSN 2150-7511.
- Walker, B.D. (2007). Elite control of HIV Infection: implications for vaccines and treatment. *Top HIV Med*, Vol. 15, No. 4, pp. 134-136, ISSN 1542-8826.
- Wawer, M.J., Sewankambo, N.K., Serwadda, D., Quinn, T.C., Paxton, L.A., Kiwanuka, N., Wabwire-Mangen, F., Li, C., Lutalo, T., Nalugoda, F., Gaydos, C.A., Moulton, L.H., Meehan, M.O., Ahmed, S., Gray, R.H. (1999). Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomized community trial. Rakai Project Study Group. *Lancet*, Vol 353, pp. 525-535, ISSN 0140-6736.
- Whatmore, A.M., Cook, N., Hall, G.A., Sharpe, S., Rud, E.W., Cranage, M.P. (1995). Repair and evolution of nef in vivo modulates simian immunodeficiency virus virulence. *J. Virol*, Vol. 69, pp.5117-5123, ISSN 1098-5514.

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WHO, UNAIDS, UNICEF, 2007. [www.who.int/entity/hiv/mediacentre/
universal_access_progress_report_en.pdf](http://www.who.int/entity/hiv/mediacentre/universal_access_progress_report_en.pdf)
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The collective efforts of HIV/AIDS research scientists from over 16 countries in the world are included in the book. This 27-chapter Open Access book well covers HIV/AIDS translational researches on pathogenesis, diagnosis, treatment, prevention, and also those beyond conventional fields. These are by no means inclusive, but they do offer a good foundation for the development of clinical patient care. The translational model forms the basis for progressing HIV/AIDS clinical research. When linked to the care of the patients, translational researches should result in a direct benefit for HIV/AIDS patients.

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