

Perspectives on HIV Vaccine Development

Jim Tartaglia, PhD

Introduction

Over the past few years, several noteworthy developments have occurred in the global HIV vaccine arena, including disappointing results in several high-profile clinical investigations. Two VaxGen trials with rgp120 vaccine candidates did not show protection against infection, and the recent trials of the DNA/vaccinia virus (MVA strain) prime-boost candidates run by the Oxford University / International AIDS Vaccine Initiative (IAVI) consortium induced low immune responses. Disappointing results have also been reported for the Merck-sanofi pasteur adenovirus prime / ALVAC (canarypox virus vector) boost regimen, despite the promising results from pre-clinical studies in animal models.

As a backdrop to these setbacks, the devastation of the HIV epidemic roars on. Indeed, the prevalence of HIV infection soared to a record level in 2003, with an estimated 5 million people acquiring HIV worldwide, and the prevalence rate in some African countries approaching 40 percent of the population. At a slower pace, HIV infection is also on the rise in the developed world. The Centre for Disease Control and Prevention (CDC) in the United States recently reported that between 2001 and 2003, there was a five per cent increase in HIV infection. Overall, it is estimated that more than 40 million people are currently living with HIV.

It is thought by most that the devastation caused by the HIV/AIDS pandemic will only be controlled by a safe and effective vaccine(s) that can be delivered effectively where HIV/AIDS is most prevalent. In addition to the significant scientific hurdles, formidable practical, political, social and ethical challenges must also be faced in HIV/AIDS vaccine development.

It is clear that HIV/AIDS is larger than any individual government or company, and that strategic partnerships between the public and private sectors will be critical to develop and deliver an HIV/AIDS vaccine(s). To this end, there is now a move to more closely coordinate global efforts for HIV vaccine development through initiatives such as the Global HIV Vaccine Enterprise (GHVE). Further partnerships between government agencies, NGOs and industry will need to evolve, in parallel to the science, that will ensure access and delivery of an effective vaccine in a timely manner to those countries that need it most.

Historical perspective

The development of HIV vaccines has often been described as occurring in four waves over the past 15 years. It is important to note that concepts in HIV vaccine development have evolved faster (approximately every four years) than our ability to fully validate them in human studies (approximately 10 years). Consistent with these timelines, the development of the most advanced vaccine approach, which is presently in Phase III testing in Thailand, was initiated nine years ago and reflected the most advanced concept from that time.

In the early days of HIV vaccine research, from 1988 to 1992, the focus was on the induction of neutralizing antibodies using recombinant envelope subunit preparations, peptides and HIV pseudovirions. It became clear early in the development that the induced antibodies efficiently neutralized laboratory isolates only and not primary field isolates. Thus, most researchers abandoned these approaches. Recently, the data from the two Phase III trials of VaxGen recombinant rgp120 failed to show protection¹. It took 10 years from concept to a definitive answer—albeit a negative one.

From 1992 to 1996, the role of cellular immune responses in controlling HIV infection gained increased attention. Given the state of knowledge at that time, the best hypothesis called for a candidate vaccine capable of inducing both humoral and cellular responses to HIV. This approach—the so-called “prime-boost” schedule—was based on the ability of poxviruses to induce both cellular responses and prime an antibody response that could be boosted with a recombinant envelope protein, thus providing the best option to achieve the broadest constellation of the desired immunological responses. To that end many ALVAC-HIV based regimens with various subunits were studied, culminating with the current Phase III trial in Thailand. The data from this efficacy study will be available at the end of 2009, after another 10-year development cycle for this concept.

By 1996, a large body of pre-clinical and clinical literature showed that protection against high viremia and CD4+ cell loss could be achieved with potent cellular responses (i.e. high frequencies of IFN- γ producing effector T cells). This led to the concept of “heterologous prime-boost,” where two different vectors are associated, instead of a vector and a protein. Experiments in animals showed that such protocols provided synergistically increased cellular responses *in vivo*. The evaluation of the heterologous prime-boost approach includes DNA/poxviruses, DNA/replication defective adenoviruses, ALVAC (canarypoxvirus vector)/ lipopeptides and adenovirus/ALVAC. To date, available data from human studies have been disappointing and seem to indicate a lack of synergy. While not a heterologous prime-boost approach, replication deficient adenoviral vectors (Merck & Co) have entered advanced phase human testing to test if high frequencies of IFN- γ producing effector T cells are associated with viral control.

Around the year 2000, studies in non-human primates following heterologous prime-boost protocols showed that although very high IFN- γ ELISPOT responses could blunt viremia and prevent the loss of CD4+ cells during the acute and chronic phases of infection, they could not prevent infection. Moreover, epitopic escape (CTL escape)

along with superinfection with distant HIV strains has been documented, further adding to the pessimism and swinging the concept pendulum back to a focus on developing reagents that generate broadly neutralizing antibodies. The determination of the 3D-structure of gp120 in 1998, in addition to the better characterization of broadly neutralizing monoclonal antibodies has further renewed interest in this area. Various approaches to unmask hidden neutralizing epitopes have been initiated including deglycosylation, variable loop deletions, stabilization of fusion intermediates, exposure of CD4-induced epitopes using Env-CD4 complexes, mimicking gp41 neutralization epitopes using constrained peptides, as well as the stabilization of gp41 fusion intermediates. Much work lies ahead to bring these concepts to the clinic and to fruition.

Finally, a better understanding of HIV pathogenesis has led to the inclusion of HIV regulatory proteins such as Tat, Rev, and Nef in vaccine candidates². Advances in basic vaccine immunology has also led to a better understanding of the relationships between the innate and the adaptive immune systems (work on the dendritic cells and the Toll receptors) and the role of mucosal immunity. Here, too, science will follow a significant developmental road.

Scientific obstacles to an HIV vaccine

Several highly efficacious viral vaccines have been licensed. Such viral pathogen targets have four common characteristics: (i) they cause acute infections, (ii) natural immunity is protective, (iii) they encode antigens with limited variability, and (iv) they do not integrate into the host cell genome. In this regard, HIV poses some unique challenges, including: (i) the infection is chronic, (ii) natural immunity is suboptimal because it exercises only limited control, (iii) it encodes antigens that are highly variable and tolerates the changes with remarkable elasticity, (iv) it integrates into the host genome, thus establishing virus reservoirs, and making it impervious to immune and treatment interventions and (v) it infects the exact cells that are critical to immunity (CD4+ cells), rendering the immune system defective over time. Protection against infection is often cited as a requirement for an HIV vaccine; however, there is no evidence that any existing vaccine induces “sterile immunity” and solely protects against disease by limiting infection.

Now, 20 years after the discovery of HIV, the failure of several high profile clinical investigations coupled with the difficulty in even protecting monkeys against acquisition of infection—with even the most promising vaccine candidate—has had a demoralizing effect on the scientific community. Some prominent scientists are publicly wondering if a vaccine is even feasible^{3,4}. However, despite the pessimism, there are rare individuals who appear either protected from infection despite being exposed (highly exposed seronegatives) or who do not progress to disease once infected (long term non-progressors), providing hope that a vaccine might be feasible. This will require a new way of looking at protection, as a vaccine that modifies the pathogenesis of persistent infection is not the norm. Indeed, a vaccine that could control viral load over a long period of time would be unprecedented in the history of vaccination. A detailed discussion of the scientific obstacles to the development of an HIV vaccine can be found

in articles from Rolf Zinkernagel^{4,5}, Ron Desrosiers^{3,6}, and Norman Letvin⁷. The optimism for developing an HIV/AIDS vaccine, as well as the scientific hurdles, are summarized in Table 1.

Current approaches to HIV vaccine development

A comprehensive list of the vaccine approaches currently in development is summarized in Table 2, below.

Cellular response induced by vaccination

As discussed above, primary HIV-1 infection results in the induction of strong cellular and humoral responses. As demonstrated in HIV-infected humans and in SIV-infected monkeys^{8,9}, the CD8+-mediated response is responsible for the early control of viremia and the decrease from a peak to a set point that remains stable until the CD4+ count decreases beyond a certain level. However, despite high precursor frequencies, the natural CD8+ response is unable to completely suppress replication and to clear infected cells. Since it is faster to restimulate memory cells, pre-existing cell-mediated immunity induced by vaccination can be expected to clear infection more effectively than the natural response. Numerous immunization experiments were carried out in monkeys by various authors using DNA vaccines, adenovirus and poxvirus vectors and prime-boost combinations of them¹⁰⁻¹³. Both the SHIV and SIV challenge models have been used. Overall, the results show that pre-existing cell-mediated immunity is able to control viral replication and very often to bring the level of viremia below the limit of detection for long periods. Importantly, the follow-up of the monkeys with SIV or SHIV revealed that a significant proportion of the protected animals eventually became symptomatic and that this was due to escape mutations in immunodominant CTL epitopes^{14,15}. Escape is explained by the incomplete control of virus replication that allows the selection of resistant mutants.

In summary, cell-mediated immune responses are unable to completely control virus replication, even if they are present at the time of infection. At best, a vaccine inducing only cell-mediated responses is expected to reduce peak viremia and to decrease the replication set point to an undetectable level with a concomitant delay in the drop of the CD4+ cells, the onset of disease, and prevention of transmission. The appearance of escape mutants is the main limitation of the approach. Lead candidates include poxvirus-based vectors, replication-deficient adenoviruses, DNA-based candidates, alphavirus and peptide-based approaches.

Inducing a broadly neutralizing response

The problem of inducing effective neutralizing antibodies to HIV has been extensively reviewed^{16,17}. Neutralizing antibodies are expected to be very important against HIV/AIDS because they act before infection. The role of antibodies in the control

of HIV replication remains, however, unclear. As shown by the constant evolution of the envelope sequence in the virus population, effective neutralizing antibodies are elicited *in vivo* and exert a selective pressure on the envelope for escape^{18,19}. Experiments done in the SIV model suggest that antibodies are not important in the early phase of natural infection, but that they participate in the reduction of viremia at a later stage²⁰.

The target for neutralizing antibodies is the surface glycoprotein gp160 that produces gp120 and gp41 upon maturation. At the surface of the cell, the envelope protein assembles into oligomers that appear to be trimers. Oligomerization is essentially due to the ectodomain of gp41. The primary sequence of gp120 is comprised of five variable (V) loops and of five conserved regions. The more conserved region folds into a gp120 core that has been crystallized as a ternary complex with CD4 and a neutralizing antibody²¹. Infection requires gp120 to bind to CD4 and to the CCR5 and/or CXCR4 chemokine receptors on the cell surface. Neutralizing antibodies should bind to the envelope protein and interfere with receptor engagement or with the fusion process.

As shown by monoclonal antibodies like b12, 1G12, 2F5, and 4E10 and by the sera of some infected individuals, broad neutralization of HIV is feasible. However, monoclonal antibodies are only effective at high concentrations. A passive transfer experiment in monkeys using a CCR5 SHIV challenge virus showed that the *in vivo* titres of b12 monoclonal antibody needed to confer sterilizing immunity corresponded to a 90 per cent reduction of infectivity *in vitro* at a 1:400 dilution²². Another experiment showed that high neutralizing antibody levels are needed within 6 hours after infection to confer sterilizing immunity²³. Passive transfer after 24 hours was not protective. This excludes an effect of a recall antibody response induced by infection.

So far, it has been difficult to induce broadly reactive neutralizing antibody responses in animals using a vaccine prototype. Numerous research groups are trying to overcome these limitations.

Future perspectives

It is generally accepted that to have the best prospect of success, a candidate HIV vaccine will need to elicit both neutralizing antibody and cellular immunity. To date, there is no immunogen capable of inducing a broadly neutralizing antibody response. Moreover, no breakthrough in this regard is expected soon. Since the role of cellular immune responses in the control of HIV infection has not been tested in humans, it is reasonable to test vaccine candidates that elicit such responses and remains the priority today. However, all vector systems currently in development have industrial and/or biological limitations. Despite disappointing results in humans, heterologous prime-boost regimens are seen as an avenue to circumvent these obstacles by maximizing the CD4 and CD8 response rate and/or reducing the dose to alleviate industrial concerns.

There are two Phase IIB/III studies, which have begun to test the role of cellular immune responses (Table 1). The vaccine candidates used in these trials are the only feasible ones ready to be tested today and should provide us with important additional information about the safety of these approaches and the relevance of CMI responses.

We must remember that HIV vaccine development represents an iterative process with significant cycle times. Through efficacy studies (Phase IIb/III), we must be able to assess whether the ‘best in generation’ candidates are safe and effective in relevant populations, including developing world populations, and increase our knowledge relevant to subsequent improvements related to next generation candidates and their testing. Moving into the future, there is much to learn including enhancing our understanding on the four following questions:

1. Can immunogens be designed that elicit broadly reactive neutralizing activity?
2. Can vaccine-induced cell-mediated immune responses be made to better control infection or ameliorate disease compared to natural infection?
3. Can vaccines be developed that address the global genetic diversity of HIV? and
4. Can post-infection surrogate endpoints, such as viral load and CD4+ count, be used to establish vaccine efficacy rather than prevention of HIV infection?

Table 3 provides a summary of the potential outcomes of vaccine-induced immunity. Each outcome may substantially impact the HIV/AIDS pandemic but may not achieve traditional licensure standards throughout the world. Therefore, an additional difficult question emerges, that is: “What is the definition of success?” The answer will most likely evolve as our knowledge grows and we proceed to new generation vaccine candidates against HIV/AIDS.

Partnerships for vaccine development and delivery

The HIV/AIDS vaccine field is at a crossroads. The most recent results have led researchers back to basics with respect to the biology of HIV-1 infection and pathogenesis and the need to focus on more rational vaccine design. Concurrently, there has been a more significant push for public-private partnerships to promote exchange, to spur innovation, to more effectively consolidate and translate research efforts into the clinic, to harmonize vaccine testing and to develop consensus on criteria for moving vaccines to the next stages of development.

In June 2003, Klausner *et al.* published in *Science* the concept of the Global HIV Vaccine Enterprise (GHVE), which proposed the introduction of virtual vaccine discovery centres (VDCs) through partnerships. These VDCs would be built through partnerships around specific vaccine areas, i.e. B-cell immunity, T-cell immunity and assay development. GHVE is driven by the Bill and Melinda Gates Foundation and, in fact, an initial RFP was issued this past winter around these HIV vaccine areas of interest. Further, GHVE advisory committees and working groups have been convened to discuss moving forward not only HIV vaccine discovery but also perspectives on manufacturing, regulatory, and vaccine access.

Why would access be a concern if an efficacious vaccine is eluding our grasp? This question, coupled with the equally sensitive one of how to define efficacy with the potential for vastly different markers and levels than we are used to seeing, is important to consider now. It would be untenable if we were to produce an HIV vaccine with an

acceptable efficacy—however that will be defined—for key populations, without considering how it will be made, licensed and provided to those who need it most. There will certainly be significant pressure to make a successful vaccine available in developing countries in a timely fashion. However, many hurdles exist today that would preclude or delay the effective delivery of vaccines in these countries. As such, WHO, UNAIDS, IAVI, and others are attempting to understand and address these challenges, with consultations focusing on likely demand, managing vaccine delivery and prioritization, ensuring manufacturing capacity and available financing.

Industry and the public sector have a long history of working together to make vaccines accessible to people in developing countries. For more than 30 years, as part of the global immunization community, vaccine manufacturers have worked with organizations such as the WHO and UNICEF, and more recently, GAVI, to ease access to childhood vaccines. This global approach has been based on a traditional access paradigm, in which vaccines are first licensed in the developed world and then in the developing world, usually after a considerable period of time. However, for HIV, it will not, and cannot, be business as usual. This is due to several factors, including the enormity of the disease burden in developing countries and the potential for initial licensure of an efficacious vaccine in the developing world. This latter factor turns the traditional paradigm upside down.

The reality is that no company, government or NGO alone will be able to solve the question of access nor carry its burden. The time for consideration is now, when we have the luxury of considered thought and its implications. Governments, NGOs, donors and industry must work together to design access programs that will allow a vaccine to get to those who need it as quickly as possible once we have an acceptable vaccine(s).

It is clear that if we are to stem the tide of HIV infections, new models of access are required. The traditional model used for other vaccines will be unacceptable for HIV.

We need parallel tracks with industry, the public sector, NGOs and donors—each working on what they do best, in partnership where appropriate—so that we can ensure that the day after efficacy we have a plan in place that will deliver a vaccine to the people who need it most.

In the traditional access model, industry's responsibility stopped when the vaccine went into the vial. At that point, the public sector and donors stepped in to purchase and deliver vaccines. In this model, tiered pricing and large volume purchasing have been the drivers. Everything has been done sequentially, in that industry licenses and manufactures vaccines in the developed world first, sells them at market value and then makes them available under a tiered pricing structure for the developing world. The traditional model for the developing world has been a passive or a trickle down system and what we need to focus on for HIV is an active system to develop the appropriate infrastructure that puts developing country requirements at the forefront. Clinical trial partnerships are examples that speak to this point. Sanofi pasteur, Merck and other companies are working with the HVTN, Canvac, and EuroVac and governmental organizations like the NIH in clinical trial partnerships in both developed and developing countries.

This however, is just part of the story. In order for this to work, there must be a commitment to purchase vaccines over the long haul. If that commitment is not there, then it will be difficult to dedicate production capacity and rationalize investment. Demand estimates provide another example of activities that are essential, since manufacturers and funders will not be able to plan without it.

Regardless of the access model, we will need to ensure “push and pull” mechanisms are enhanced to facilitate vaccine access. These push/pull mechanisms will have to address key issues around pricing, capacity, and distribution, effectively turning the traditional access model upside down, in that in the past these issues were generally resolved in the developed world first. We need to put the developing countries at the front of the queue instead of at the back of the line in any new model. This will require not only accommodations from industry, but also financing and capacity building from other partners. Meeting our collective goal of providing the quickest possible access to a vaccine will require partnerships among industry, the public sector and donors with guarantees of purchase, regulatory harmonization, tax credits and other incentives for industry to manufacture vaccines for developing countries. This could be complemented by providing greater access to technology or bulk product for eligible countries with capacity and could include new regional plants that are either owned by industry, the public sector, or through joint ventures.

One concrete model for access is the agreement being worked out between the Thai government and sanofi pasteur, should the prime-boost trial show a degree of efficacy acceptable for licensure in Thailand. Sanofi pasteur will provide a donation of doses and access to technology to advance capacity building, giving Thailand important technical knowledge, improving self-sufficiency and providing vaccines for the country that has been at the forefront of AIDS vaccine clinical trials. This, however, is one company, one vaccine, and one country and does not offer a complete solution for access to an AIDS vaccine for all developing countries. Appropriate partnerships, access models and infrastructure are as important as the science. These efforts must proceed in parallel with the science, if we are not to be caught short once an effective vaccine is available.

However, unless plans for success are made now, at the beginning of the long and arduous clinical trials journey, we will risk a disastrous possibility of having a successful vaccine without a reasonable chance of getting it to those who need it most. That is unacceptable to a world—and a population—that has been ravaged by this disease and has waited decades for a potential vaccine.

Dr. Jim Tartaglia is Vice-President, Research & Development, of sanofi pasteur Canada.

Table 1. Summary of Key Points of Optimism and Key Hurdles Related to Development of Vaccine(s) against HIV/AIDS

Key Points of Optimism	Key Hurdles
<ul style="list-style-type: none"> •Experimental vaccines have proven protective in animal models of AIDS ••The immune system can, in some circumstances, control HIV <ul style="list-style-type: none"> ▪acute infection ▪long term nonprogressors ▪children born to HIV+ mothers ▪multiply exposed/uninfected people -•Cross-clade CD8+ CTL responses in vaccinated volunteers have been observed -•Antibodies that can neutralize a broad spectrum of HIV subtypes have been identified, albeit in small quantities ••Mucosal transmission is relatively inefficient ••Efficacy trials among high-risk volunteers appear feasible 	<ul style="list-style-type: none"> •Genetic diversity of virus: 12 HIV-1 subtypes and inter-subtype recombinant viruses ••Persistence of infection ••Various routes of transmission ••Lack of biological/immunological correlates of protection ••Lack of validated animal model ••The best marker of efficacy remains protection in man ••Industrialization – paradigm shift

Table 2. Current Approaches to HIV/AIDS Vaccine Development

Trial No.	Sponsor Manufacturer	Start Date	Sites (No.)	Vaccine(s)	Antigen	Clade	Comment
Phase III (Large-size trials in high-risk populations; test vaccine efficacy)							
RV144	WRAIR, AFRIMS, MoH; sanofi pasteur, VaxGen	October 2003	Thailand (several)	ALVAC vCP1521 AIDSVAX B/E	env (E), gag/pol (B) env (B, E)	B, E B, E	16,000 healthy normal HIV negative adult volunteers
Phase II (Mid-size trials in low- & high-risk populations; test vaccine safety, immunogenicity)							
HVTN 502/ Merck 023	HVTN, Merck; Merck	December 2004	US (12), Canada (1), Peru (2), Dominican Republic (1), Haiti (1), Puerto Rico (1), Australia (1)	MRKAd5 HIV-1 gag/pol/nef	<i>gag, pol, nef</i>	B	To test whether cellular immune response generated by Merck's vaccine is potent enough to impact infection with HIV in 1,500 at-risk volunteers
ANRS VAC 18	ANRS; sanofi pasteur	September 2004	France (6)	LIPO-5	5 lipopeptides containing CTL epitopes (from Gag, Pol, Nef)	B	Compare CD8 response of 3 doses of LIPO-5 versus placebo
IAVI 010	IAVI; KAVI	February 2003	UK; Kenya	DNA.HIVA MVA.HIVA	<i>gag</i> + 25 CTL epitopes <i>gag</i> + 25 CTL epitopes	A A	HIV-DNA +/-MVA boost
Phase I/II (Mid-sized trials in low-risk populations; test vaccine safety, immunogenicity)							
HVTN 042/ ANRS VAC 19	HVTN, ANRS; sanofi pasteur	June 2004	US (13)	LIPO-5 ALVAC-HIV (vCP1452)	See above See above	B B	To evaluate safety and immunogenicity of LIPO-5 alone, vCP1452 alone, and ALVAC prime/LIPO-5 boost
GTU-MultiHIV	FIT Biotech	February 2004	Finland	GTU-MultiHIV B clade	<i>nef, rev, tat, gag, pol, env,</i> CTL epitopes	B	Immunogenicity of GTU-MultiHIV clade B DNA after intradermal and intramuscular injection.
HVTN 052	HVTN; Vical	December 2003	US (10)	VRC-HIVDNA-009-00-VP	<i>gag, pol, nef</i> <i>env</i>	B A,B,C	Phase IB, safety, immunogenicity of multiclade DNA Vaccine
N/A	UNSW; AVC	June 2003	Australia	pHIS-HIV-B rFPV-HIV-B	<i>gag, RT, rev, tat, vpu, env</i> <i>gag, RT, rev, tat, vpu, env</i>	B B	DNA Vaccine + fowlpox boost
Phase I (Small trials in low-risk populations; test vaccine safety, immunogenicity)							
IAVI C002	IAVI; IDT	January 2005	US (2)	ADMVA	<i>env/gag-pol, nef-tat</i>	C	Safety, immunogenicity of an MVA vector vaccine
HVTN 057	NIAID, VRC	November 2004	US (12)	VRC-HIVADV014-00-VP	<i>gag/pol</i> polyprotein <i>env</i>	B A,B,C	Safety, immune response to VRC-HIVADV014-00-VP, when given as a booster to already vaccinated adults (HVTN 052)
HVTN 059	NIAID, AlphaVax	October 2004	US (5), South Africa, Botswana	AVX101 (VEE)	<i>gag</i>	C	Safety, immunogenicity of an alphavirus replicon
VRC 007 (04-I-0254)	NIAID/VRC	August 2004	US (1)	VRC-HIVDNA016-00-VP	<i>gag, pol, nef</i> <i>env</i>	B A, B, C	Safety, immunogenicity of a 6-plasmid multiclade HIV-1 DNA vaccine
HVTN 055	NIAID; Therion	July 2004	US (6)	TBC-M358 (MVA) TBC-M335 (MVA) TBC-F357 (FPV) TBC-F349 (FPV)	<i>env, gag</i> <i>tat, rev, nef, RT</i> <i>env, gag</i> <i>tat, rev, nef, RT</i>	B B B B	Safety, immunogenicity of MVA-HIV and rFPV-HIV alone or in combination.
ANRS VAC 16	ANRS; Biovector SA	July 2004	France (6)	LIPO-4T (LPHIV-1)	4 lipopeptides containing CTL epitopes (from Gag, Pol-RT, Pol, Nef)	B	Safety and immunogenicity of lipopeptides LIPO-4T, by two administration routes.
VRC 006 (04-I-0172)	NIAID; GenVec	May 2004	US	VRC-HIVADV014-00-VP	<i>gag/pol</i> polyprotein <i>env</i>	B A,B,C	Safety, tolerability, immune response of a multiclade HIV adenoviral vector vaccine in uninfected adults.
N/A	AVANT; NIAID; WRAIR	May 2004	US	LFn-p24	Anthrax-derived polypeptide LFn <i>gag</i> p24 protein	B	18 health volunteers. Aim: inducing strong and persistent HIV-1 gag specific CD8 T Cell responses.

HVTN 056	NIAID, Wyeth	April 2004	US (7)	HIV CTL MEP	CTL epitopes from <i>env</i> or <i>gag</i>	B	Safety of and immune response to a new HIV vaccine: HIV CTL MEP
UMMS vaccine	UMMS; ABL	April 2004	US	DNA Proteins	<i>gag</i> + 5 <i>env</i> 5 recombinant gp120	A,B,C,E A,B,C,E	DNA prime: 1 <i>gag</i> gene (C) + 5 <i>env</i> genes (A, 2 B, C, E). Boost: 5 gp120 (same isolates as DNA). Adjuvant: QS21.
HVTN 050/ Merck 018	NIAID; Merck	September 2004	Malawi, South Africa	MRKAd5 HIV-1	<i>gag</i>	B	Replication defective Ad-5 vector
IAVI A001	IAVI; Targeted Genetics	December 2003	Belgium (2); Germany (2); India (1)	tgAAC09 AAV	<i>gag</i> , protease, <i>rt</i>	C	Recombinant AAV vector; single shot
IAVI C001	IAVI; ADARC; Vical	December 2003	US (2)	ADVAX DNA	<i>gag</i> , <i>env</i> , <i>pol</i> , <i>nef</i> , <i>tat</i>	C	Multi-gene approach
HVTN 049	HVTN; Chiron	December 2003	US (8)	Gag and Env DNA/PLG Oligomeric gp140/MF59	<i>gag</i> , <i>env</i> DNA/PLG; Oligomeric gp140	B B	Safety, Immunogenicity of DNA/PLG and <i>env</i> DNA/PLG prime, oligomeric gp140/MF59 boost
HVTN 044	HVTN; Vical	December 2003	US (3)	VRC-HIVDNA-009-00-VP	<i>gag</i> , <i>pol</i> , <i>nef</i> <i>env</i>	B A,B,C	Safety, immunogenicity of of multiclade DNA Vaccine with IL-2/Ig DNA adjuvant
IAVI 011	IAVI, SAAVI IDT	November 2003	South Africa (2), UK (1), Switzerland (1)	MVA-HIVA	<i>gag</i> + 25 CTL epitopes	A	Dose response
EnvPro	St Jude's	September 2003	US	EnvPro protein	gp140	D	Purified <i>env</i> protein
ISS P-001	ISS; Excell	August 2003	Italy (4)	HIV-1 Tat protein	<i>tat</i>	B	Safety, immunogenicity of the recombinant HIV-1 Tat protein in healthy HIV-negative volunteers.
MRKAd5 + ALVAC	Merck; sanofi pasteur Pasteur	2003	US (17)	MRKAd5 HIV-1; ALVAC vCP205	<i>gag</i> <i>env</i> , <i>gag</i> , <i>pol</i>	B	MRKAd5 HIV-1 prime, ALVAC vCP205 boost
HVTN 040	NIAID; SAAVI AlphaVAX	July 2003	US (4); South Africa (2)	AVX101 VEE	<i>gag</i>	C	Safety and immunogenicity of VEE vector
ANRS VAC 14	ANRS; sanofi pasteur	June 2003	France (2)	gp160MN/LAI-2	gp120 (MN strain), gp41 (LAI strain)	B	Safety and immunogenicity, using several routes
HVTN 048	NIAID; Epimmune	April 2003	US (2); Botswana	EP HIV-1090 DNA	21 CTL epitopes from <i>gag</i> , <i>pol</i> , <i>env</i> , <i>nef</i> , <i>rev</i> , <i>vpr</i>	B	Safety and immunogenicity
VRC 004 (03-I-0022)	NIAID/VRC; Vical	November 2002	US	VRC-HIVDNA009-00-VP	<i>gag</i> , <i>pol</i> , <i>nef</i> (clade B); <i>env</i> (clades A, B, C)	A, B, C	Safety and immunogenicity of a multiclade vaccine
B011; RV 138	WRAIR; sanofi pasteur	July 2002	US	ALVAC-HIV vCP205	<i>env</i> , <i>gag</i> , <i>pol</i>	B	Response to vaccine subcutaneously (via dendritic cells), intradermally, or intramuscularly
VRC 004 (03-I-0022)	NIAID/VRC; Vical	November 2002	US	VRC-HIVDNA009-00-VP	<i>gag</i> , <i>pol</i> , <i>nef</i> (clade B); <i>env</i> (clades A, B, C)	A, B, C	Safety and immunogenicity of a multiclade vaccine
B011; RV 138	WRAIR; sanofi pasteur	July 2002	US	ALVAC-HIV vCP205	<i>env</i> , <i>gag</i> , <i>pol</i>	B	Response to vaccine subcutaneously (via dendritic cells), intradermally, or intramuscularly
N/A	Merck	2002	US	<i>gag</i> DNA	<i>gag</i>	B	Dose response
01-I-0079	NIAID/VRC; Vical	January 2001	US	VRC4302 DNA	<i>gag</i> , <i>pol</i>	B	Dose and immune response
N/A	Merck	2001	US	<i>gag</i> DNA Ad5 <i>gag</i>	<i>gag</i> <i>gag</i>	B B	Evaluation of DNA vs. Ad5 prime + Ad5 boost

ABL: Advanced BioScience Laboratories, Inc.; **ADARC:** Aaron Diamond AIDS Research Center; **AFRIMS:** Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand, is a joint U.S.-Royal Thai Army Command; **AlphaVax:** AlphaVax Human Vaccines Inc.; **ANRS:** Agence Nationale de Recherche sur le SIDA; **AVANT:** AVANT Immunotherapeutics, Inc.; **AVC:** Australian Vaccine Consortium; **sanofi pasteur:** sanofi pasteur; CAN: Canada; Chiron: Chiron Corporation; **CTL:** cytotoxic T-lymphocyte; **Epimmune:** Epimmune Inc.; **Excell:** Excell Biotech; **GSK:** GlaxoSmithKline; **HVTN:** HIV Vaccine Trials Network; **IAVI:** International AIDS Vaccine Initiative; **IDT:** Impfstoffwerk Dessau Tornau GmbH; **ISS:** Istituto Superiore di Sanità; **KAVI:** Kenyan AIDS Vaccine Initiative; **MoH:** Ministry of Health (Thailand); **MRC:** UK Medical Research Council; **NIAID:** U.S. National Institute Allergy and Infectious Diseases; **NL:** Netherlands; **PACTG:** Pediatric AIDS Clinical Trials Group; **PR:** Puerto Rico; **SAAVI:** South African AIDS Vaccine Initiative; **St Jude's:** St Jude's Childrens Hospital; **Therion:** Therion Biologics Corporation; **TT:** Tetanus Toxoid; **UMMS:** University of Massachusetts Medical School; **UNSW:** University of New South Wales; **US:** United States; **UVRI:** Uganda Virus Research Institute; **VEE:** Venezuelan equine encephalitis; **Vical:** Vical Inc.; **VRC:** Vaccine Research Center; **WRAIR:** Walter Reed Army Institute of Research Reproduced from: IAVI database of AIDS vaccines in human trials. IAVI report <http://www.iavi.org/trialsdb> (accessed Apr.11/05)

Table 3. Potential Outcomes of HIV Infection in the Setting of Vaccine-Induced Immunity

Sterilizing immunity

- complete protection from HIV infection
- no detectable HIV at any time
- no transmission of HIV to others

Transient infection

- infection occurs, but the immune system is able to detect and kill off infected cells
- seroconversion (becoming HIV+) may or may not occur
- transmission to others might occur within a brief window of time, or might be completely prevented

Long-term controlled infection

- low viral load throughout life
- no harmful drop in CD4 cells
- no disease progression (HIV does not advance to AIDS)
- transmission to others prevented or greatly diminished

Altruistic vaccine

- little benefit to vaccinated individuals; however, the vaccine could help to prevent transmission of infection to others
- HIV transmission to others prevented or greatly diminished

References

1. Cohen, J. Public health. AIDS vaccine trial produces disappointment and confusion. *Science* 299, 1290-1 (2003).
2. Hel, Z. *et al.* Equivalent immunogenicity of the highly attenuated poxvirus-based ALVAC-SIV and NYVAC-SIV vaccine candidates in SIVmac251-infected macaques. *Virology* 304, 125-134 (2002).
3. Desrosiers, R. C. Prospects for an AIDS vaccine. *Nat Med* 10, 221-3 (2004).
4. Zinkernagel, R. M. The challenges of an HIV vaccine enterprise. *Science* 303, 1294-7 (2004).
5. Zinkernagel, R. M. Immunity, immunopathology and vaccines against HIV? *Vaccine* 20, 1913-7 (2002).
6. Desrosiers, R. C. Strategies used by human immunodeficiency virus that allow persistent viral replication. *Nat Med* 5, 723-5 (1999).
7. Letvin, N. L. Strategies for an HIV vaccine. *J Clin Invest* 110, 15-20 (2002).
8. Musey, L. *et al.* Cytotoxic-T-cell responses, viral load, and disease progression in early human immunodeficiency virus type 1 infection. *N Engl J Med* 337, 1267-74 (1997).
9. Schmitz, J. E. *et al.* Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. *Science* 283, 857-60 (1999).
10. Amara, R. R. *et al.* Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science* 292, 69-74 (2001).
11. Shiver, J. W. *et al.* Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature* 415, 331-5 (2002).
12. Hel, Z., *et al.* Potentiation of SIV specific CD4+ and CD8+ T-cell responses by a DNA-SIV and NYVAC-SIV prime-boost regimen. *J. Immunol* 167(12):7180-7191 (2001).
13. Pal, R., *et al.* ALVAC-SIV-gag-pol-env-Based Vaccination and Macaque Major Histocompatibility Complex Class I (A*01) Delay SIV-Induced Immunodeficiency. *J. Virol* 76(1): 292-302 (2002).
14. Barouch, D. H. *et al.* Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature* 415, 335-9 (2002).
15. Barouch, D. H. & Letvin, N. L. Viral evolution and challenges in the development of HIV vaccines. *Vaccine* 20 Suppl 4, 66-8 (2002).
16. Burton, D. R. *et al.* HIV vaccine design and the neutralizing antibody problem. *Nat Immunol* 5, 233-6 (2004).
17. Zolla-Pazner, S. Identifying epitopes of HIV-1 that induce protective antibodies. *Nat Rev Immunol* 4, 199-210 (2004).

18. Richman, D. D., Wrin, T., Little, S. J. & Petropoulos, C. J. Rapid evolution of the neutralizing antibody response to HIV type 1 infection. *Proc Natl Acad Sci U S A* 100, 4144-9 (2003).
19. Wei, X. *et al.* Antibody neutralization and escape by HIV-1. *Nature* 422, 307-12 (2003).
20. Schmitz, J. E. *et al.* Effect of humoral immune responses on controlling viremia during primary infection of rhesus monkeys with simian immunodeficiency virus. *J Virol* 77, 2165-73 (2003).
21. Kwong, P. D. *et al.* Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. *Nature* 393, 648-59 (1998).
22. Parren, P. W. *et al.* Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* 75, 8340-7 (2001).
23. Nishimura, Y. *et al.* Transfer of neutralizing IgG to macaques 6 h but not 24 h after SHIV infection confers sterilizing protection: implications for HIV-1 vaccine development. *Proc Natl Acad Sci U S A* 100, 15131-6 (2003).