

Steps to Success

The Step vaccine study's scientific contributions to the field

For the past 18 months, we at AVAC have joined many other stakeholders in stressing that Step wasn't a "failed trial" but a successful trial of a candidate that failed to provide any level of protection. In the first few months after the result was released, we heard from critics who said that this distinction was a forced attempt to be positive about a massive disappointment. To these observers, the trial had failed, and the candidate had not only failed but might also have increased susceptibility to infection in specific subgroups of volunteers. It was easy to counter that the trial had succeeded in getting an answer quickly, recruiting and retaining volunteers, and, with a few snags, communicating the complex results as they emerged. Additionally, the Step and Phambili studies have made strong scientific contributions to the field. We now have far more valuable information to guide the search for an AIDS vaccine in 2009 than we did in 2007—all as a result of a candidate that failed. Below, we've summarized some of the suggested hypotheses or findings. These results are more hypothesis-generating than conclusive. Step has pointed towards questions that we otherwise would not have known to ask. The findings listed below point out clear paths for future work—no small feat for a trial that was used as evidence that the field had lost its way.

SHIV challenge experiment data may not predict the outcome of human trials of disease-modulating vaccines

Different strains of disease-causing simian-immunodeficiency virus (SIV) have been used in challenge experiments to evaluate vaccines and other biomedical prevention strategies in the non-human primate (NHP) model. In general, SHIV strains that are SIV-HIV hybrids are less virulent than disease-causing, lab-adapted SIV strains. Prior to the initiation of the Step trial, there had been debate about the relative merits of SHIV versus SIV. (The SHIV 89.6p virus came into favor because it caused a more consistent CD4 decline than SIVs.)

The best pre-clinical data supporting MRK-Ad5 (the vaccine tested in Step) came from an NHP challenge experiment

in which immunized animals infected with SHIV 89.6p had significantly reduced viral loads out to 900 days after infection. The data from SIV experiments were less promising—mixed at best. Given that there was no overall protection or benefit from MRK-Ad5 in humans, it seems that the more stringent SIV challenge may have more predictive value for non-human primate evaluations of AIDS vaccines. (There may be settings in which SHIV or other challenges are also appropriate.)

Understanding how to use the non-human primate model and how to manipulate its many variables is critical. Although there is no single ideal model for non-human primate evaluations of AIDS vaccine concepts, data like those from Step can be used to refine and focus thinking about future experiments.



Step Data Have Led the Field To:

- Refine expectations of the animal model
- Delve into vector-specific immunity in unprecedented ways
- Reevaluate the qualities of an effective T-cell response
- Refocus on mucosal immunity

The field has a clearer sense of the inadequacy of a specific type of vaccine-induced immunity

There are at least three levels of uncertainty regarding vaccine-induced immune responses:

1. Scientists don't yet know what types of vaccine-induced immune responses are needed to either give durable protection against infection or reduce viral load after infection. Because of this, we also don't know exactly what measurable characteristics of T cells to track in order to predict whether a vaccine-induced immune response will provide a benefit. Potential traits include: how well T cells divide and reproduce (proliferative capacity), maturation state (memory versus effector phenotype), and functional activity (determined by looking at cell surface markers signaling molecules, and cytolytic activity).
2. What we want to measure is limited by what we *can* measure. By definition, the level of any given response is determined by the way it is measured.

The assays for evaluating cell function evolve and often change from the time a candidate is moved into human trials, to when the trial is completed. Hence the definitions of what's measurable change over time.

3. The specific parts of the virus that are targeted by the immune responses are probably just as important as the types and levels of immune responses stimulated by a vaccine. The HIV genes or parts of genes delivered by a vaccine induce immune responses to specific parts of the virus. It is unknown which parts should be delivered or in what quantity. Animal models are of limited use in answering these questions because of differences between the challenge viruses used in animal models and the tremendous diversity of possible viruses that the human immune system might encounter.

Although it's not the result anyone would hope for, the flat result in Step does show us what immune responses, as measured, were insufficient for protection. This could be because of their qualities or perhaps because of the parts of the virus they were directed against. As the authors of the *Lancet* publication of Step immune analyses noted, the "MRKAd5 HIV-1 gag/pol/nef vaccine elicited a higher CD8+ T-cell response rate and magnitude than did that reported for any of the candidate immunisation regimens tested over the past 15 years, although immunological assays have changed greatly during this time."⁴

⁴ McElrath MJ, et al. HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis. *Lancet*. 2008 Nov 29;372(9653):1894-905. Epub 2008 Nov 13.

What are the improvements specifically suggested by these negative findings? There are several possible directions, including screening future vaccine candidates with a wider array of assays. Did Step measure the wrong immune response (i.e., T cells) or the wrong *aspect* of the immune response? Location is also important. Step samples came from the blood as opposed to mucosal surfaces.

Other directions include:

- Developing vaccines that induce both CD4 and CD8 responses (and different subsets of these responses), since only one-third of Step vaccinees developed both CD4 and CD8 T-cell responses.
- Getting a better sense of what's happening at the mucosal sites of exposure—the T-cell responses were measured mainly in the blood, which may or may not be indicative of the quality and magnitude of responses at the mucosal sites of sexual exposure.
- Using expanded and updated assays to evaluate vaccine-induced immune responses.
- Refining goals for breadth and specificity of HIV epitopes recognized by vaccine-induced T cells. The T cells induced by MRK-Ad5 recognized an average of three HIV epitopes.
- Investigating antigen selection. The MRK-Ad5 inserts didn't contain *env*. What are the right inserts and the right insert-vector combinations?

A possible hint of virologic control

The major histocompatibility complex, or MHC region of our genome, contains the instructions for, among other things, the set of proteins called human leukocyte

antigens, or HLA. Previous researchers have shown that HIV-positive people with specific HLA types (and the corresponding MHC alleles) have better control of HIV viral load than people without these traits. This finding has reinforced the importance of host genetics in responses to the virus.

Although no overall benefit from the vaccine was seen in the Step study, there were intriguing differences among subgroups of volunteers. Researchers zeroed in on individuals with (1) MHC alleles associated with better HIV outcomes; (2) MHC alleles with no effect on HIV outcomes; and (3) MHC alleles with negative effects—faster disease progression or higher viral load. They found that among the very small number of individuals in group (1) who acquired HIV in the Step trial, those who had protective alleles and got the vaccine had significantly lower viral loads than those with protective alleles who received the placebo. Simply put: good genes + vaccine appeared to be better than good genes + placebo. The study wasn't set up for such analyses, so this is nothing more than a hint, perhaps a glimmer, of a suggestion of a positive benefit from the vaccine. But it warrants additional study, both of host genetics (see page 17) and of the mechanism of the possible vaccine-induced benefit.

Vector-specific immunity can neither be ignored as a complex factor in vaccine design; nor be blamed for the Step findings

The surprising and disappointing Step finding raised questions about what was known about the immune responses to the

Ad5 vector by itself—without the synthetic HIV genes that were used as the insert in the vaccine construct. The answer was: not much. There wasn't much information on immune responses either to the empty vector or to naturally occurring Ad5. (Ad5 is a cold-causing virus; the vector was altered so that it wouldn't cause any illness.)

In the aftermath of the Step results, scientists looked closely at vector-specific immunity and Ad5-specific immunity. They also examined the differences between vaccine-induced immune responses in people who had pre-existing immunity and in those who did not, and, within these groups, between those who became HIV-positive and those who did not.

Overall, Ad5 seropositivity alone did not affect risk of infection. Instead, the vaccine-related effect is only seen in men who were Ad5-seropositive and uncircumcised.

Beyond this “headline” finding, there are additional findings worth noting:

- The presence of pre-existing Ad5 antibodies (also known as Ad5 seropositivity) wasn't linked to increased CD4 cell activation after vaccination or susceptibility to HIV infection.
- The antibody- and cell-based immune responses to Ad5 don't work in lock step: whether someone is Ad5-seropositive doesn't predict Ad5-specific cellular immune responses, or how these expand when the body “sees” Ad5 in the vaccine.
- Cell-based immune responses to Ad5 are cross-reactive with other Ad viruses, including Ad1 and Ad6. This means someone could be Ad5-seronegative

and still have cellular responses to Ad1 and Ad6, which might be stimulated by and/or respond to Ad5 vector.

Scientists looked for evidence that pre-existing immunity to Ad5 increased susceptibility to infection in vaccine recipients, but they couldn't find a direct link. There's no evidence that Ad5 seropositivity correlates with T-cell activation following vaccination, and strong suggestions that seropositivity—which is a measure of antibody levels—doesn't predict what will happen to Ad5 cellular responses following Ad5-vectored immunization.

The critical, though sometimes mysterious, role of mucosal immunity

Although there is “cross-talk” between immune responses in the blood and mucosal tissues of the body, including the genital tract, gut, and lungs, there are also distinctions. Measuring immune responses in the blood does not give a complete picture of what may be present in or absent from mucosal tissues, such as the rectum, the vagina, and the foreskin,

“Since the Step results were announced, we've been diversifying our research portfolio. We're now actively involved in vibrant clinical research activities in HIV therapeutics, viral hemorrhagic fever vaccines, and surveillance programs for avian influenza. Although we had some of this work already planned, or in progress before the Step announcement, the Step results made it more timely, and more relevant.”

Dr. Hannah Kibuuka, Principal Investigator, Makerere University Walter Reed Program, Uganda

“It’s amazing that we retained so many participants in the trials despite the permanent halting of enrollment and vaccination of the Phambili study, and the negative outcome of the Step study. Getting regulatory approval to conduct the HVTN 073 study, which investigates the SAAVI DNA-C and MVA-C vaccines, was another huge boon for us, post Step/Phambili. Its execution is very exciting to us, as it is a subtype C vaccine and is the first time that an African vaccine is tested both in the Northern and Southern Hemisphere.”

Glenda Gray, Principal Investigator, Perinatal HIV Research Unit, South Africa

in the case of sexual transmission. Obtaining mucosal samples can be invasive, and these tissues vary greatly, which complicates analysis. Despite these obstacles, AIDS vaccine researchers have been paying increased attention to the potential role of vaccine-induced mucosal immune responses as front-line defenses.

The Step study results underscore the need to pay attention to what’s happening in mucosal tissues. In the analysis of all the data to date, increased risk of HIV infection is seen among uncircumcised men and is highest in Ad5-seropositive, uncircumcised men. Looking at individual risk from the time of enrollment in the study, the difference in infection risk between vaccine and placebo recipients is most pronounced during the first 18 months and then wanes. The mechanism behind this is still unknown; one hypothesis might be that vaccine-induced responses in the mucosal tissue of the foreskin provide additional target cells

for infection during the first months post infection. Might the waning risk be linked to waning of vaccine-activated target cells in the mucosal tissue? It’s not possible to answer this question with the available Step data—and it may never be. However, it’s clear that future trials need to address how vaccine-induced immune responses affect protection from and susceptibility to HIV in the mucosal tissue.


These are just some of the findings that have emerged from Step to date. It’s critical to continue learning from the Step trial and to recognize the wealth of information that can be gleaned from well-designed human trials. ■



Figure 3 PAVE 100 to HVTN 505: Key events and communications about testing the VRC strategy*

2007	2008	2009
<p>September 19 Step and Phambili vaccine trials stopped immunizations</p> <p>September 21 NIAID trials of vaccines that used adenovirus vectors, including PAVE 100, were put on hold until Step data could be further reviewed</p> <p>November 7 Step data presented at HVTN Full Group Meeting</p> <p>November 15 NHVREI first annual briefing of leaders of National AIDS Non-Governmental Organizations</p> <p>December 12 AVRS meeting on Step and PAVE 100</p>	<p>May 30 AVRS meeting to discuss PAVE 100A—committee recommended that the study move forward</p> <p>July 17 NIAID announces it will not move forward with PAVE 100A but will consider a smaller trial of the vaccine regimen that had been proposed to be tested in PAVE 100A</p> <p>September 11 NIAID began NGO consultations on HVTN 505</p> <p>November 6 HVTN fact sheet describing HVTN 505 trial distributed</p> <p>November 10 NHVREI annual briefing of leaders of National AIDS Non-Governmental Organizations, where HVTN 505 overview was presented and discussed</p> <p>November 13 NIAID-sponsored HVTN 505 trial telebriefing for community</p> <p>November 24 Black Gay Men's Consultation on HIV Prevention Research where HVTN 505 was discussed</p> <p>December 5 NIAID-sponsored HVTN 505 trial telebriefing for community</p>	<p>March 2 HVTN 505 protocol submitted for FDA review</p> <p>March 9-10 NHVREI Partners Training and Update, where HVTN 505 protocol was discussed</p> <p>March 12 Community town hall meeting in Philadelphia where HVTN 505 was discussed</p> <p>April 2 Notification from FDA that the HVTN 505 protocol may proceed</p> <p>May 6 Community forum for HIV Vaccine Awareness Day, Rochester, NY</p> <p>May / June Anticipated start of enrollment for HVTN 505</p>

Many presentations on Step, PAVE 100 and next steps were done by HVTN and NIAID at national conferences.



* Throughout this period, sites have been engaged with their CBO partners to discuss the upcoming trial, and their CABs have been similarly engaged. NIAID and HVTN, through the NHVREI program (<http://betheneration.nih.gov>), have been in ongoing dialog with both the local and the national partners to keep them informed and to answer questions and concerns that they have had.



A Trial by Any Other Name: HVTN 505 and the VRC candidate

As *AVAC Report* went to press, the US Food and Drug Administration (FDA) had recently approved the protocol for HVTN 505, the test-of-concept study of the National Institutes of Health's Vaccine Research Center's (VRC) strategy that consists of three DNA "prime" immunizations and a single adenovirus 5–vectored "boost." (See timeline on page 37, and for more detailed information on the history of this candidate, please visit www.avac.org/vax_update.htm.)

At roughly the same time, some members of the scientific community were discussing newer animal data that had some relevance to HVTN 505. Much of the talk centered on the results of a study by Harvard's Dan Barouch and colleagues, in which animals received one of two variations on a DNA plus chimeric Ad (Ad5 plus an Ad48 hexon protein), or one of two variations on the chimeric Ad alone.⁵ In that experiment, presented at this year's Keystone conference on HIV prevention, the animals that got the DNA plus chimeric Ad had survival rates and clinical outcomes comparable to the placebo group, while the chimeric Ad-alone animals had improved survival outcomes and, in an exploratory combined analysis, significantly lower viral loads. Barouch noted that his findings should be viewed as hypothesis-generating rather than conclusive.

Monkey studies are, by definition, small and inconclusive. Monkeys aren't humans; the numbers are too small to draw firm conclusions; and in the absence of a correlate of protection, it's difficult to know whether we're measuring the right things. What's more, the data concern a different vector; thus the strategy cannot be directly compared with the VRC strategy.

So why were Barouch's data of interest in the context of HVTN 505?

Primarily because monkey data considered relevant to the VRC vaccine strategy to be tested in HVTN 505 have been part of the scientific rationale for moving the trial forward.^{6,7,8} Monkey data were cited extensively at the December 2007 meeting of the AIDS Vaccine Research Subcommittee (AVRS) of the NIH and mentioned in the fact sheet that the HVTN produced on 505 one year later. Over the past year, AVAC has voiced concern about the lack of clear materials to help lay audiences understand HVTN 505. These include the lack of clarity in explanations of both the scientific rationale and the ways that the trial

⁵ DH Barouch. Novel Adenovirus Vector-based Vaccines for HIV-1 *Keystone Symposia Conference: Prevention of HIV/AIDS (X3)*. Keystone, Colorado, 2009 March 22-27. Abstract #017.

⁶ Shiver JW, et al. Replication-incompetent adenoviral vaccine vector elicits effective anti-immunodeficiency-virus immunity. *Nature*. 2002 Jan 17;415(6869):331-5.

⁷ Bolton DL, et al. Aerosol Adenovirus Immunization Controls Early Viremia. *Keystone Symposia Conference: HIV Immunobiology: From Infection to Immune Control (X4)*, Keystone, Colorado, 2009 March 22-27. Abstract #125.

⁸ Casimiro DR, et al. Attenuation of simian immunodeficiency virus SIVmac239 infection by prophylactic immunization with DNA and recombinant adenoviral vaccine vectors expressing Gag. *J Virol*. 2005 Dec;79(24):15547-55.

was addressing the safety of participants—this in light of its use of an Ad5-vectored candidate that was similar to, though not identical to the candidate used in the Step trial.

Even though they're not directly related, the data presented by Barouch are still relevant to potential trial participants and communities as part of the broader body of knowledge around the proposed HVTN 505 trial, and they point to the unmet need for clear, simple statements of the rationale for the trial and how the varied body of non-human primate and human data have been analyzed to date.

These concerns aren't about whether HVTN 505 adequately addresses participants' safety in light of Step—we believe that this was addressed by the exclusion of Ad5-seropositive, uncircumcised men. The concerns are about the communication around these criteria and how the scientific rationale for the study is being explained to participants and engaged communities.

AVAC has followed and sometimes participated in many discussions about this candidate and whether it should be tested further. We feel that human trials are an invaluable part of the AIDS vaccine discovery process. The Step trial has provided a wealth of information that would never have been obtained otherwise. A trial of the VRC strategy could theoretically do the same. But, is such a trial possible? And have the NIH and the HIV Vaccine Trials Network (HVTN) taken the steps that would lead to such a trial? Here, the answers are more mixed.

The Step results brought an unprecedented dialogue involving NIAID, its Vaccine Research Program, and the broader community of HIV prevention advocates like AVAC who are not part of trial site communities. In the aftermath of the Step finding, there was a high level of information and materials sharing and constructive dialogue about how to craft messages that were accurate and moved the field ahead. This held true around PAVE 100 as well. But with the advent of 505, the gap has increased between the broader community (advocacy groups working on and impacted by HIV prevention research) and the trial sponsors, which has impeded community stakeholders from getting involved. The publicly available materials and consultations have fallen short in explaining such a complex undertaking. Specific concerns include:

- A series of calls held by the NIH allowed community members to hear a description of the trial and to pose questions to investigators in real time. Such forums are important and should be continued. But it's unrealistic to expect anyone to absorb the information for such a complex trial in a single conference call and to formulate the right questions. NIAID and HVTN representatives have made themselves available on an ongoing basis to answer questions. However, there's still a shortfall in terms of community-oriented materials that provide critical information in an easy-to-digest written format, such as a protocol summary, or a more detailed fact sheet addressing questions raised on the calls or

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other topics. Such written materials are key to helping communities navigate the complexities of this proposed trial.

- Confusion and concerns about whether the proposed strategy is safe to test—and how HIV prevention advocates could responsibly represent the trial to their friends, colleagues, and allies—have not been adequately addressed in the forums where AVAC has heard them raised. These are difficult questions to be sure. And the investigators and staff involved have the best intentions. The current fact sheet outlines the safety issues but does not provide a detailed, coherent explanation that can be used as the basis for community-led discussions.
- The public information sheet distributed by HVTN instructed individuals who were interested in learning more about the trial protocol to join community advisory boards (CABs). However, because no details were listed regarding sites or cities where the trials would take place, individuals couldn't easily decide whether the effort was worthwhile. Moreover, the link to the HVTN site led to a map of HVTN sites' own home pages. Some of the links on the individual sites' websites were to staff people who no longer worked there; on others it was difficult to figure out how to join. A far better approach would be to create a link to a page that includes (1) the list of trial sites (or likely trial sites, with a proviso that the protocol is in formation); (2) a list of contacts for these sites; and (3) some explanatory text about what CABs do and what membership entails. As it is, individuals who may have wished to be involved in protocol review had slim chances of accomplishing that.
- Discussions of the scientific rationale for the trial have focused on the data from monkey studies that show a different quality of immune responses in animals that receive the DNA plus Ad5 combination versus Ad5 alone. Several of those studies show no difference in clinical outcomes of viral load or survival in animals that received DNA plus an adenovirus-vectored candidate versus the adenovirus-vectored candidate alone. There are numerous variables in each of these studies as well as others that preclude drawing one over-arching conclusion. This complexity doesn't mean communities can't hear a more detailed explanation of the scientific rationale than they have to date, including the following statement:

There are data suggesting a possible benefit from a DNA + adenovirus-vectored prime-boost strategy, and there are also data suggesting that this is not an optimal strategy to evaluate.

On the positive side, in March 2009 in Philadelphia, HVTN started a series of town hall meetings for community discussion about HVTN 505 and vaccine research in general. These are not recruitment events but discussion sessions that will happen in each city that's home to a site. This is an excellent initiative, and we look forward to learning from these discussions and hope that the questions generated will be documented and shared in broader forums. Principal investigators Scott Hammer and Magda Sobieszczyk have been unfailingly open to conversations, requests for information, and presentations, as have other staff members at the NIAID and the HVTN.

A social science, psychosocial, and behavioral research working group has been convened to look at additional questions that could be posed and possibly answered through HVTN 505. Some of these questions concern data gathering to support trial data analysis. Others are aimed at some of the gaps that have been articulated in the Black Gay Men's Research Agenda, the research agenda articulated at the Gay Men's Health Summit, and similar documents. This approach adds value to the communities involved in the study. Whether there's a direct clinical benefit from the VRC vaccine strategy, there could be useful information gleaned to help communities advocate and implement different types of programs and research.

With FDA approval in place, we're one step closer to posing the question about what the VRC strategy does in humans. Whether that question gets answered depends on how the trial happens. We at AVAC have long argued that this will likely be one of the most complex trials to explain and in which to enroll participants, making the collaborative work that should be in place for any trial all the more important.



Table 1 Ongoing Trials of Preventive HIV/AIDS Vaccines Worldwide (May 2009)

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE III						
RV 144	Oct-03	MHRP, MoPH Thailand, Aventis, Vaxgen	Thailand	16,402	Prime: canarypox viral vector with <i>env</i> and <i>gag-pol</i> Boost: <i>Env</i> protein (gp120 subunits)	B A/E
TEST-OF-CONCEPT						
The two trials that follow, HVTN 503 and 502, stopped enrollment and immunizations, September 2007. Follow-up and data collection continue. For more information visit: http://avac.org/vax_update.htm .						
HVTN 503 (Phambili)	Feb-07	SAAVI, HVTN	South Africa	801	Adenovirus vector with <i>gag, pol, nef</i>	B
HVTN 502/ Merck 023 (Step study)	Dec-04	NIAID, HVTN, Merck	US, Canada, Peru, Dominican Republic, Haiti, Puerto Rico, Australia, Brazil, Jamaica	3,000	Adenovirus vector with <i>gag, pol, nef</i>	B
PHASE II						
HVTN 205	Jan-09	GeoVax, HVTN	US, Peru	225	Prime: DNA vaccine containing <i>gag, pol, env, rat, rev, vpu</i> Boost: MVA vaccine containing <i>gag, pol, env</i>	B
PHASE I / II						
EV 03/ANRS Vac20	June-07	European Commission, ANRS	UK, Germany, Switzerland, France	140	Prime: DNA vaccine with <i>env</i> plus <i>gag, pol, nef</i> Boost: NYVAC-C	C
HIVIS 03	Dec-06	MUCHS, Karolinska Institute, SMI, Vecura, MHRP	Tanzania	60	Prime: HIVIS DNA with <i>env, gag, rev, RT</i> Boost: MVA-CMDR with <i>env, gag, pol</i>	A, B, C A, E
RV 172	May-06	NIH, MHRP, VRC	Kenya, Uganda, Tanzania	324	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus vector with <i>gag, pol + env</i>	B A, B, C
PHASE I						
B001	Mar-09	IAVI, University of Rochester Medical Center	US	42	Adenovirus serotype 35 vector. Ad35-GRIN/ ENV consists of two vectors: Ad35-GRIN vector with <i>gag</i> , reverse transcriptase, integrase, and <i>nef</i> Ad35-ENV vector with gp140 <i>env</i>	A
P001	Mar-09	IAVI, Indian Council of Medical Research	India	32	Prime: ADVAX (DNA vaccine containing <i>env, gag, pol, nef and tat</i>) Boost: TBC-M4 (MVA vector with <i>env, gag, RT, rev, tat and nef</i>)	C
P002	Dec-08	IAVI, St. Stephen's AIDS trust, Chelsea and Westminster Hospital	UK	32	Prime: ADVAX (DNA vaccine containing <i>env, gag, pol, nef and tat</i>) Boost: TBC-M4 (MVA vector with <i>env, gag, RT, rev, tat and nef</i>)	C
HVTN 073	Dec-08	HVTN, SAAVI	US, South Africa	48	Prime: SAAVI DNA-C2 Boost: SAAVI MVA-C; DNA plasmid vaccine with <i>gag, RT, tat, nef, env</i>	C
Ad26.ENVA.01	Apr-08	IPCAVD, Brigham and Women's Hospital, Beth Israel Deaconess Medical Center, Crucell	US	48	Recombinant adenovirus serotype 26 (rAd26) vaccine	A
IAVI C004/ DHO-614	Oct-07	ADARC, Rockefeller University, Gates Foundation, IAVI, Ichor Medical Systems Incorporated	US	40	Serial administration of ADVAX, ADVAX e/g + ADVAX p/n-t, by Ichor TriGrid™ in vivo electroporation. The ADVAX vaccine contains <i>two</i> vectors: ADVAX e/g, with <i>env</i> and <i>gag</i> , and ADVAXp/n-t with <i>pol</i> and <i>nef-tat</i> .	C
HVTN 070	Oct-07	NIAID, HVTN, UPenn/Wyeth	US	120	PENNVAX-B alone, in combination with IL-12, or with 2 different doses of IL-15	B
HVTN 072	Aug-07	NIAID, HVTN, VRC	US	17	DNA and Adenovirus 5 or 35 vectors, all with <i>env</i> in varying prime-boost combinations	A

Protocol #	Start Date	Sponsor, Funder, Developer	Trial Site(s)	# of Participants	Vaccine(s)	Clade
PHASE I						
HVTN 071 [As of Sept 07 enrollment and vaccinations have been discontinued]	Jul-07	NIAID, HVTN, Merck	US	35	Adenovirus 5 vector with <i>gag, pol, nef</i>	B
<i>DVP-1</i>	May-07	St. Jude's Children's Research Hospital	US	20	Prime-boost regimen with <i>PolyEnv, EnvPro, EnvDNA</i>	A, B, C, D, E
VRC 012	May-07	NIAID, VRC	US	35	HIV-1 adenovirus vector vaccine VRC-HIVADV027-00VP: dose escalation and prime-boost with an HIV-1 adenovirus vector vaccine, VRC-HIVADV038-00-VP	A
HVTN 067	Apr-07	NIAID, HVTN, Pharmexa-Epimmune, Bavarian Nordic	US	108	DNA Vaccine EP-1233 and recombinant MVA-HIV polytope vaccine MVA-mBN32, separately and in a combined prime-boost regimen	B A, B, C, D, E, G
HVTN 069	Nov-06	NIAID, HVTN, VRC, NY Blood Center, IMPACTA	US, Peru	90	Prime: DNA vaccine with <i>gag, pol, nef + env</i> Boost: Adenovirus 5 vector with <i>gag, pol + env</i> (intramuscularly, intradermally, subcutaneously)	A,B,C
DHO-0586	Oct-06	ADARC, IAVI	US	8	ADMVA with <i>env/gag-pol, nef-tat</i>	C
HPTN 027	Oct-06	Makerere University, Johns Hopkins University	Uganda	60	Canarypox viral vector with <i>env</i> and <i>gag-pol</i>	B
C86P1	Sep-06	SGUL, Richmond Pharmacology, Novartis Vaccines	UK	31	Prime: HIV gp140 with LTK63 Boost: HIV gp140 with MF59	B
VRC 011	Apr-06	NIAID, VRC	US	60	DNA vaccine with <i>gag, pol, nef + env</i> or Adenovirus vector with <i>gag, pol + env</i>	A, B, C
HVTN 065	Apr-06	NIAID, HVTN, GeoVax	US	120	Prime: DNA plasmid with <i>gag, pro, RT, env, tat, rev, vpu</i> Boost: MVA vector with <i>gag, pol, env</i>	B
HVRF-380-131004	Mar-06	Moscow Institute of Immunology, Russian Federation Ministry of Education and Science	Russian Federation	15	VICHREPOL with polyoxidonium adjuvant	B
HVTN 068	Feb-06	NIAID, HVTN, VRC	US	66	DNAprime/AD boost vs. Ad prime/Ad boost	A, B, C
HIVIS 02	Jan-06	Karolinska Institute, Swedish Institute for Infectious Disease Control, MHRP	Sweden	38	Modified vaccinia Ankara (MVA) viral vector with <i>env, gag, and pol</i> to volunteers from HIVIS 01	A, E
RV 158	Nov-05	MHRP, NIH	US, Thailand	48	Modified vaccinia Ankara (MVA) viral vector with gp160, <i>gag</i> and <i>pol</i>	A, E
<i>EnvDNA</i>	May-05	St. Jude's Children's Research Hospital	US	6	Recombinant HIV-1 multi-envelope DNA plasmid vaccine with <i>env</i>	A, B, C, D, E
RV 156 A	Nov-04	NIAID, HVTN, VRC, MHRP, Makerere U.	Uganda	30	VRC-HIVADV014-00-VP alone or as a boost to VRC-HIVDNA009-00-VP	A, B, C
<i>EnvPro</i>	Jun-03	St. Jude's Children's Research Hospital	US	9	Recombinant Purified HIV-1 Envelope Protein Vaccine	D

ADARC: Aaron Diamond AIDS Research Center

ANRS: Agence Nationale de Recherches sur le Sida (France)

HVTN: HIV Vaccine Trials Network

IAVI: International AIDS Vaccine Initiative

IPCAVD: Integrated Preclinical/Clinical AIDS Vaccine Development

MHRP: United States Military HIV Research Program

MoPH: Ministry of Public Health

MUCHS: Muhimbili University College of Health Sciences

NIAID: National Institute of Allergy and Infectious Diseases

NIH: National Institutes of Health

SAAVI: South African AIDS Vaccine Initiative

SGUL: St. George's, University of London

SMI: Swedish Institute for Infectious Disease Control

VRC: Vaccine Research Center