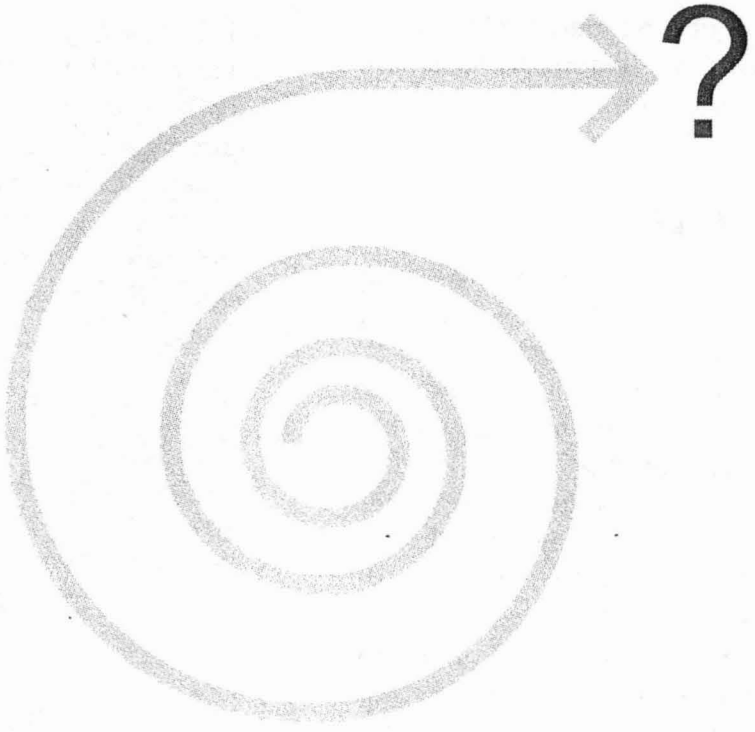
A Special Update

Understanding the Results of the AIDSVAX Trial



This version, dated May 14, 2003, will be updated as more information becomes available.

AVAC
AIDS Vaccine Advocacy Coalition

Understanding the Results of the AIDSVAX Trial

In late February 2003, the world heard preliminary results of the first large scale human trial of a vaccine designed to prevent HIV infection. The results for the overall trial cohort were clear and disappointing. The results for a relatively small subset of trial participants are less clear, and they have sparked controversy and require further analysis. This brochure will help you understand what we do and do not know about the experimental vaccine known as AIDSVAX. *AVAC will update this document as more data becomes available.*

What's the bottom line?

AIDSVAX did not prevent HIV infection in the study population (see "Who Were the Trial Volunteers?"). But VaxGen, the vaccine's maker, presented its analysis of subgroup data that the company said showed "a statistically significant reduction of HIV infection in certain vaccinated groups," including lower infection rates in "ethnic minorities, other than Hispanic individuals". The company reported this trend in "subgroups" was particularly strong in Black trial volunteers, and VaxGen also presented data that showed lower infection rates among Asian/Pacific Islanders and individuals whose race was categorized as "other". (*A couple of notes:* The term "Black" is used instead of "African-American" in order to reflect people in the trial of African descent who are not from the United States. The term "other" was used in the study to refer to anyone who did not classify themselves as Asian/Pacific Islander, Black, Hispanic or White.)

What do we know from the AIDSVAX trial?

- The vaccine did not protect against HIV infection in the overall study group.
- The company that makes AIDSVAX presented interesting data on subgroups and this data should be thoroughly and openly analyzed. If warranted, further study should be done.
- It is too early to draw any conclusions about the effects of AIDSVAX in any subgroup.
- AIDS vaccine efficacy trials are possible. The AIDSVAX North American trial demonstrated that it is possible to recruit and retain thousands of individuals for AIDS vaccine trials. Trial volunteers appeared not to put themselves at increased risk of HIV infection.
- The trial results point out the importance of diversity in recruiting AIDS vaccine trial participants, including people of color, women and youth.

What do we hope to learn soon?

- Whether the data on subgroups justifies further study or turns out to be a chance occurrence.

Understanding the Results of the AIDSVAX Trial

Why the controversy?

The AIDSVAX results have stirred controversy because the reported findings among Blacks, Asian/Pacific Islanders and "others" were based on small numbers of trial participants and the trial was not designed to determine vaccine efficacy in these groups. Several observers, including AVAC, raised concerns that overly optimistic statements about the vaccine had been made in the absence of in-depth analysis of the data.

Many leading scientists, including Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, cautioned against jumping to conclusions without further analysis. "Professional statisticians warn us that one must be very careful in doing subset analyses when the primary endpoint of a given study shows no effect (or in this case lack of efficacy)," Fauci said. "Therefore, one really cannot say at all that the vaccine is effective in Blacks without a very careful scrutiny of the data and the statistical analysis of the data."

It is customary to recalculate levels of statistical confidence when researchers do multiple subgroup analyses. Dr. Fauci commented that, "In this context, most statisticians say that with the penalties that one must apply in this type of subset analysis, the results in the Black subset would not be statistically significant."

It would be detrimental to current prevention efforts if the public is led to believe an efficacious AIDS vaccine has been developed before this has been proven.

The AIDSVAX trial was not designed to determine efficacy in subgroups, meaning the trial was not set up to look at protection from HIV infection within race or gender categories. Also, VaxGen's data on ethnic minorities was based on a very small number of volunteers who represent these communities. *None of this proves the vaccine was not effective in a subgroup, but it does mean that we need to examine the data more carefully before jumping to conclusions about the AIDSVAX results.*

AVAC believes now is the time for thorough and open review of all study data and further research if warranted. Everyone wants the AIDSVAX results to be investigated fully. If, in fact, the vaccine does provide protection from HIV infection to people of African, Asian/Pacific Islander, mixed race or other descent this would be outstanding news and an extremely important advance in the fight against AIDS.

But until such protection is confirmed it makes sense to be cautious in interpreting the partial, preliminary results we have. In addition, affected communities need clear communications regarding the results and ongoing analyses of the AIDSVAX data.

AIDS vaccine advocates, including AVAC, have urged VaxGen to release its data to an outside panel of experts so the findings for sub-groups can be subjected to external review. *In April 2003, National Institute of Allergy and Infectious Diseases and the Centers for Disease Control held a meeting to review the AIDSVAX data, and the two agencies have announced they will collaborate in supporting a series of meetings with VaxGen to "independently examine the data to determine if any further government-supported research and development are warranted."*

Understanding the Results of the AIDSVAX Trial

Until a fuller analysis is conducted the only thing that can be said for certain about AIDSVAX is that it didn't work in a clinical trial conducted among 5,417 people, predominantly men who have sex with men (MSM). Of those, one-third got a placebo (an inactive substance), and two-thirds got AIDSVAX. In each group, slightly more than 5.5 percent became infected over the three year course of the trial, indicating the vaccine did not offer any advantage in protecting trial participants as a whole from HIV.

It took Thomas Edison hundreds of tries to invent the light bulb. Developing an AIDS vaccine is a much greater scientific challenge. AIDS vaccine research is a long term effort and this trial has been one important step in that effort.

What is AIDSVAX?

AIDSVAX B/B used in this trial is a vaccine made with genetically engineered proteins designed to be similar to gp120, a protein on the outer coat of HIV. Since it isn't made with actual virus, AIDSVAX can't cause HIV infection. The vaccine used in the North American trial that just concluded is based on two strains of HIV clade B, which is predominant in North America, Europe, Australia, and Puerto Rico. To make the vaccine, scientists combine the artificial gp120 with alum, a common chemical used in many vaccines as an adjuvant to boost the vaccine's effectiveness. The vaccine, which is injected into arm muscle, prompts people to make antibodies to the gp120 portion of HIV. The hope was that these antibodies would prevent people from becoming infected with HIV.

How was AIDSVAX tested?

AIDSVAX was tested in a Phase III clinical trial and trial participants were recruited from communities at high risk for HIV infection. They were provided risk reduction counseling throughout the study. Trial participants received an injection of the vaccine or placebo at 0, 1, 6, 12, 18, 24, and 30 months for a total of 7 shots over the three years of the trial. The trial results reported findings from people who received at least three shots, either of the vaccine or placebo. Of these participants, 1,679 were in the placebo arm and 3,330 were in the vaccine arm of the trial. Scientists then followed the two groups over three years to see whether the vaccinated group had fewer HIV infections, as a percentage of those immunized, than the placebo group.

Who were the trial volunteers?

The majority of people in the trial were men who have sex with men, though a limited number of women at elevated risk of HIV infection were also enrolled. Of the 5,403 trial participants who got at least one dose of the vaccine, 5,095 were men and 308 were women. The self-identified racial composition of the cohort was: 4,489 Whites, 367 Hispanics; 349 Blacks; 77 Asian/Pacific Islanders; and 121 categorized as "other". While the majority of the trial volunteers came from the U.S., the trial also enrolled people from Canada, Puerto Rico and the Netherlands.

Understanding the Results of the AIDSVAX Trial

What was the main goal of the trial?

The main goal, known as the "primary endpoint," was straightforward: to see if the vaccine, when tested in a large group of people at risk of HIV, actually offered any protection from infection.

Were there other goals of the trial?

Yes. One "secondary" analysis was whether AIDSVAX slows viral replication. If so, it might indicate that the vaccine could modulate infection (i.e. slow disease progression) in vaccine recipients who do become infected. Trial volunteers are still being followed and results of the secondary endpoints are not yet available.

Another important goal of the trial was to determine the safety of the vaccine. The trial also studied risk-taking behaviors of participants to determine if participation in an AIDS vaccine trial prompted people to put themselves more at risk of HIV.

Was the trial designed to measure the effectiveness of AIDSVAX in communities of color?

No. It is common for "subgroup" analyses to be done as overall data on clinical trials is reviewed, but the AIDSVAX trial was not adequately sized or enrolled to determine whether the vaccine was efficacious (worked) in any subgroup of the total trial population. In general, subgroup analyses are not given much credibility if the overall goal of the trial is not met.

Did AIDSVAX work?

Not in the overall study population. Among the 5,009 trial participants getting at least three doses of either the vaccine or the placebo, 5.8% of the 1,679 on placebo became infected versus 5.7% of the 3,330 receiving the vaccine. In essence, the vaccine had no impact in protecting people from acquiring HIV.

Reported Vaccine Efficacy
Weighted cohort

	Placebo Infections/Total	Vaccine Infections/Total	Reported Vaccine Efficacy (95.12% Confidence Interval)
All Volunteers	98/1679 (5.8%)	191/3330 (5.7%)	3.8% (-22.9 to 24.7%)
White & Hispanic	81/1508 (5.4%)	179/3003 (6.0%)	-9.7% (-42.8 to 15.7%)
Black-Asian/Pacific Islanders-Other	17/171 (9.9%)	12/327 (3.7%)	66.8% (30.2 to 84.2%)
Black	9/111 (8.1%)	4/203 (2.0%)	78.3% (29.0 to 93.3%)
Asian/Pacific Islanders	2/20 (10.0%)	2/53 (3.8%)	68.0% (-129.4 to 95.5%)
Other	6/40 (15.0%)	6/71 (8.5%)	46.2% (-67.8 to 82.8%)

Data provided by VaxGen

Understanding the Results of the AIDSVAX Trial

Did the vaccine protect certain groups?

More analysis is needed to know for sure. The problem with drawing conclusions from the data presented so far is that the trial was not designed to measure the impact of the vaccine on different racial groups. To do that, researchers would need to enroll many more people from various groups.

Among Blacks, the calculated efficacy was 78.3% but because the number of Blacks in the study was small, the statistical "range" within which the efficacy number could fall was from 29% to 93.3%, according to VaxGen (others felt the statistical range might be much greater if statistical corrections were applied). The different infection rates among Blacks getting vaccine vs. placebo hinges on a difference of just a few infections out of 314 Blacks in the study. As noted earlier, many statisticians have concluded that when the analysis is done appropriately, results for Blacks are not statistically significant.

Among Asian/Pacific Islanders, the potential efficacy range was so wide that much of the value was in negative territory. For those categorized as "other" the number of trial participants was also too small to draw any conclusions.

There will *always* be subgroups within a larger study group that have different infection rates than the total population. Those differences may or may not mean anything, and may be the result of chance and not the vaccine. It is essential to look at those differences cautiously, and not make assumptions without careful analysis.

Did the company combine subgroups in its analysis?

Yes. VaxGen lumped together the data for three racial groups — Blacks, Asian/Pacific Islanders and those categorized as "others." The company asserted that the data suggested an efficacy rate of 66.8% among this composite group. ***One of the criticisms of VaxGen's publicly disclosed analysis is that the grouping of 'Blacks, Asian/Pacific Islanders and others' has no established biological significance.***

It's especially important to be cautious in combining subgroups to get efficacy results. So while the data reported by VaxGen for Blacks-Asian/Pacific Islanders-Others are interesting and require further analysis, we should not draw any conclusions without further study.

Because the trial was not designed to determine efficacy among Blacks-Asian/Pacific Islanders-Others or any subgroup we cannot be sure these numbers reflect protective effects of the vaccine. Vaccine clinical trials are "randomized" so statisticians can determine when differences in infection rates among populations are due to the vaccine or some other variable. But this "randomization" was not done in subgroups because the AIDSVAX trial was not designed to test efficacy in subgroups. Randomization is a procedure by which a large enough number of trial participants are divided into two (or more) groups (e.g. the placebo and vaccine groups) at random so they will tend to have **similar characteristics.** There are a number of possible explanations for the efficacy numbers in subgroups in the AIDSVAX trial. For example, there might be behavioral, geographic, gender or other differences between the placebo and vaccine groups that

Understanding the Results of the AIDSVAX Trial

explain the different infection rates among groups in the study and which may not hold up in a larger study. We won't know until further analysis of the data is completed.

Is there other evidence about protection of subgroups?

At the Keystone Symposium on HIV Vaccine Development in late March 2003, VaxGen presented additional data. The company reported indications of "sieving" — a vaccine's ability to block infection by viruses similar to the virus used to make the vaccine. In a study involving 53 of the Hispanics, Blacks, Asians and other racial minority group members who became infected during the trial, 55% of those in the placebo group were infected with viruses that had the same amino acid sequence in a small segment at the tip of the V3 loop of the envelope gp120 protein as those expressed in the HIV strains used to make the vaccine. By contrast, just 30% of those in the vaccinated group were infected with viruses that expressed that sequence. (The same pattern, the company said, was not observed between placebo and vaccine groups of whites who became infected.)

The company said the finding suggested that, at least among some racial minorities, the vaccine might be preventing infection by viruses that were similar to those on which the vaccine was based. Other scientists pointed out that in a trial where there was no proven efficacy, such a finding might not suggest protection from infection. Instead, it might raise the troubling prospect that the vaccine was exerting selection pressure on the virus, accelerating the development of viral variants that could successfully establish an infection. Another explanation might involve genetically different virus populations circulating in different subsets or at different sites involved in the trial.

VaxGen also reported at Keystone that it saw no differences overall in antibody responses between the infected and uninfected groups, but antibodies that could neutralize the MN strain of HIV, one of the strains on which the vaccine was based, were higher among black men than white men, and women also showed higher antibody titers against the MN strain than men who had sex with men. The company said it was investigating whether those responses correlated with the likelihood of infection.

None of these data provide a clear explanation of the possible effects of AIDSVAX, and further analysis is necessary. As an article in Science Magazine commented, "most researchers were not impressed", however, the data involving viruses and immune responses in minority subsets need to be more fully explored by independent assessments.

Was the vaccine safe?

Initial results indicate that it was. The most common side effect was pain at the site of the injection and such things as headache. Those who received the vaccine were only slightly more likely than those who received the placebo to have some pain, swelling and tenderness at the site of the injection. Further analysis of the data is needed to make a final determination on safety.

Understanding the Results of the AIDSVAX Trial

Did participating in an AIDS vaccine trial increase risk behaviors?

Preliminary results indicate that it did not, but we must still wait to hear complete results from the AIDSVAX study on participant behaviors. According to self-reported data by participants, risk behaviors such as unprotected anal sex, unprotected receptive anal sex and having sex with an HIV positive partner did not increase over the course of the study. This may be, in part, because participants were counseled on safer sex behaviors throughout the trial. *If it is confirmed that trial participants did not put themselves at increased risk for HIV, this is good news for volunteers and for future AIDS vaccine trials because it indicates that if trial participants are appropriately counseled most will not put themselves at increased risk of HIV infection.*

Even though AIDSVAX did not protect the overall study population, will the FDA license it?

It is unlikely the FDA will license AIDSVAX based on data from this trial because it was not designed to determine efficacy in subgroups.

Does the company plan to develop a similar vaccine for sub-Saharan Africa?

Yes. VaxGen has a grant from the National Institutes of Health to develop a version of the vaccine based on a strain of the virus prevalent in sub-Saharan Africa. However, the work is still in the test tube stage. The proposed vaccine based on this different strain has not yet been tested in people.

Are there other large human trials of AIDSVAX underway?

Yes. VaxGen is now testing a different version of AIDSVAX among about 2,500 injecting drug users in Thailand. The vaccine in the AIDSVAX North America trial is modeled on two North American-based strains. The vaccine in the Thai AIDSVAX trial is based on two strains prevalent in Southeast Asia. *The results of the Thai trial are expected later this year and these results may help researchers better interpret the data from the North American trial just completed.*

The Thai Ministry of Health in collaboration with the Walter Reed Army Institute of Research (WRAIR) is planning to start a trial in Thailand later this year. The trial would recruit 16,000 participants to test protection from HIV infection by using two different vaccines in combination, the version of AIDSVAX designed for Thailand and a product called ALVAC, made by Aventis Pasteur, a French company.

Understanding the Results of the AIDSVAX Trial

Did we learn anything else from the AIDSVAX trial?

Yes. We learned important lessons about the logistics of conducting AIDS vaccine efficacy trials. The AIDSVAX trial, the first of its kind ever conducted, proved that thousands of participants could be recruited, counseled, immunized and closely followed over more than 30 months. This is not a trivial task. In fact, the trial had a 95% rate of retaining trial participants — a major accomplishment. *The trial has also underscored the need for better recruiting of minority group members and of women, who were under-represented in the trial cohort.* If more Blacks and Asian/Pacific Islanders had been in this trial, we would have a clearer answer and not be wondering whether the observed differences in infection rates occurred by chance — we would know "yes" or "no". *In some cases it will take extra effort and resources to recruit a more diverse trial cohort, but it's worth the cost.*

So was this clinical trial a "failure"?

No. The vaccine may have failed to protect people, but the trial itself was not a failure. It did what trials are supposed to do: it gave us an answer to the important question of whether this vaccine would work or not. In this case, the vaccine tested did not work in the study group overall. Other vaccines, however, may work. And developing an AIDS vaccine may very well require a series of multiple large scale human trials in many different countries over a number of years. These trials need to be designed so that whether or not any particular trial finds efficacy it at least produces clear results and teaches scientists more about immunization that can lead to development of better vaccines. At the very least we will know what doesn't work, and perhaps be able to analyze the results to understand why.

There's more work (and hope) ahead...

To find an AIDS vaccine and make it globally available, we need to act now — and be ready for a long haul. More work is needed: to make better AIDS vaccines and to prepare for global access to these vaccines when they are ready. One of the surest ways to pave the way for global AIDS vaccine access is to deliver AIDS treatments to people living with HIV around the world. And, of course, researchers must continue searching for a cure that can help the 40 million people who have HIV/AIDS.

Understanding the Results of the AIDSVAX Trial

More vaccines in the pipeline...

The AIDSVAX vaccine attempts to create an immune response by presenting the human body with a copy of the **protein envelope** of HIV. Other vaccines under development now use a variety of different technologies:

- **DNA vaccines:** synthetic copies of HIV genes are injected into the body resulting in the production of "antigens"[I] that hopefully can produce a strong immune response.
- **Bacterial and viral vector vaccines:** copies of HIV genes are inserted into weakened bacteria or viruses that do not harm humans. These bacteria or viruses carry the synthetic HIV genes into the body to induce an immune response. ALVAC, which will be combined with AIDSVAX in the efficacy trial in Thailand (starting later in 2003), is one example of a viral vector vaccine.
- **Other approaches:** include peptide[II] vaccines, pseudovirions[III] and combinations of vaccines with "adjuvants"[IV] that can boost immune responses. In addition, research on improved antibody-inducing AIDS vaccine approaches is moving forward.

How to get more information and/or get involved

More information on AIDS vaccines is available from The National Institute of Allergy and Infectious Diseases (www.niaid.nih.gov), the International AIDS Vaccine Initiative (www.iavi.org), UNAIDS (www.unaids.org), the Black AIDS Institute (www.blackAIDS.org), and the AIDS Vaccine Advocacy Coalition (www.avac.org).

You can also get involved in promoting AIDS vaccine research by joining a community advisory board, encouraging organizations you are a member of to put AIDS vaccine issues on their agenda, thinking about signing up for a vaccine trial yourself, or by joining AVAC. For more information on AIDS vaccine advocacy, write us at avac@avac.org.

I **Antigen:** any substance that stimulates the immune system to produce an immune response. Antigens are often foreign substances such as invading bacteria or viruses.

II **Peptide:** a short compound formed by linking two or more amino acids. Proteins are made of multiple peptides.

III **Pseudovirion:** a virus-like particle that resembles a virus but does not contain its genetic information and cannot replicate. In some viral diseases pseudovirions can interfere with infection by the real infectious virus.

IV **Adjuvant:** a substance sometimes included in a vaccine formulation to enhance or modify the immune-stimulating properties of a vaccine.

About AVAC

AVAC is dedicated to accelerating the ethical development and global delivery of vaccines against AIDS. AVAC does not accept funding from government or the pharmaceutical industry. This publication and AVAC's continuous policy, advocacy, and educational work are made possible by the dedicated labor of AVAC advocates and funding from The Bill and Melinda Gates Foundation, the Ford Foundation, the International AIDS Vaccine Initiative, Until There's a Cure Foundation, Broadway Cares/Equity Fights AIDS, the Gill Foundation, and many generous AVAC Members.

AVAC

AIDS Vaccine Advocacy Coalition

Advocacy to accelerate ethical research & global delivery of AIDS Vaccines

www.avac.org

Concept: Joseph Gordon | Design: Daniel Scharfman Design, Inc.