

# AIDSVax Fails to Prevent HIV Infection



## AIDSVax

Preliminary results from VaxGen's study of the preventive HIV vaccine, AIDSVax were announced last night, February 23, 2003. The study showed that the AIDSVax vaccine was *not* effective in preventing HIV infection, not even to a small degree as had been previously speculated.

After finding an overall negative conclusion, the company looked at vaccine responses in subgroups composed of racial/ethnic minorities. Based on this subgroup exploration, the company claims the vaccine *might* prove beneficial in some racial subgroups, including Asians and Black people, but only if Hispanics were specifically excluded from the analysis. The study, however, was *not* designed or powered statistically to evaluate such differences between racial groups, rendering any claims of statistically significant results questionable. The company insisted that the subgroup analyses were planned in advance with the FDA, this is not the same thing as saying that the subgroups were sized and powered sufficiently to reach any conclusions. The preliminary report leaves it impossible to assess whether or not the data actually supports the claim, no matter what the company says. Given the level of expertise and experience of the scientists at VaxGen, it can only be assumed that the holes left in understanding these data are deliberate. These results are discussed in greater detail below.

### What Is a preventive vaccine?

The goal of a preventive vaccine is to induce an immune response capable of blocking the establishment of infection or to control disease if a person becomes exposed and infected with a particular organism.

For example, a vaccine to the flu (i.e. a flu shot) induces an immune response to the flu virus. If a person subsequently comes in contact with the flu virus, their immune response is armed and prepared to control the infection before it has the opportunity to cause disease (e.g. cause symptoms of the flu.)

The goal of a preventive HIV vaccine is to induce an immune response against HIV that is able to block the establishment of HIV infection in the event someone is exposed to HIV, or to block the development of symptoms of HIV disease after infection.

### How does AIDSVax work?

AIDSVax is a *gp120*-based vaccine product (see graphic at right). This means that the vaccine is made of a man-made protein particle that resembles part of HIV called *gp120*.

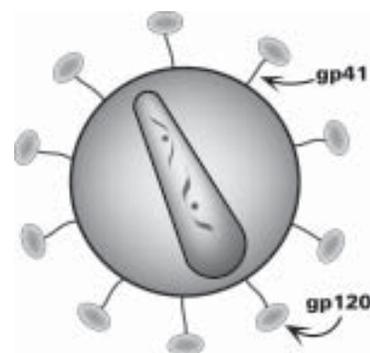
When injected, the immune system mounts a response (largely an *antibody* response) to this protein. It was hoped that a person who had been vaccinated and mounted an immune response would be protected from HIV infection and/or disease if they became exposed to HIV.

Many have been skeptical of *gp120*-based vaccines because this particular protein changes (mutates) a great deal when HIV reproduces. Thus, a response against this particular part of HIV may not be protective because if a person is exposed to HIV the *gp120* on the virus would likely look very different because of these changes/mutations. The immune system would not recognize the virus as the same thing it was boosted to recognize and thus not mount an immediate or effective response to either control HIV infection or disease.

### The study

The study was designed to include 5,400 people enrolled from mid-1998 to late 1999, primarily in the United States, but also included sites in Canada, Puerto Rico and the Netherlands. Volunteers were given either the AIDSVax HIV pre-

### HIV and Its Outer Envelope Protein, gp120



On the surface of its outer envelope, HIV has proteins covered with a sugar-like coating (glyco). These proteins are called glycoproteins (gp). One protein important in HIV infection of cells is called 120, or glycoprotein-120 (gp120).



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ventive vaccine or placebo injections, every six months, for a total of seven injections over the three-year study period. For every two people who received the vaccine, one person received the placebo. The study looked to see differences between rates of HIV infection among those receiving the vaccine compared to those who received placebo.

At the time of preliminary reporting, 5,009 people who had received at least three injections of either vaccine or placebo are included in the analysis. This includes 3,330 vaccine recipients and 1,679 placebo recipients.

## As reported by the company, of the 5,009 participants, demographics were as follows:

White volunteers	4,185
Hispanic volunteers	326
Non-White volunteers (Black, Asian, other, excluding Hispanics)	498
Black volunteers	314

## The results

As noted, overall, the study demonstrated no differences in HIV infection rates among volunteers who received the vaccine or the placebo. This means that the vaccine did not work in preventing HIV infection.

The company then conducted subgroup analyses, looking at HIV infection rates by race/ethnicity. The study, overall, included very few ethnic/racial minorities. The company asserts that there were differences in HIV infection rates in *some* races.

When looking at non-White, non-Hispanic volunteers as a group (i.e. Blacks, Asians and “other”), VaxGen reports 67% fewer HIV infections among non-Hispanic “Blacks, Asians and ‘others’” who received AIDSVax compared to non-White, non-Hispanic placebo recipients. As noted above, there were a total of 498 non-White, non-Hispanic study volunteers. The power or *p-value* of this observation is less than  $p=.01$ , which would normally be considered “statistically significant.”

They also looked at responses solely among Black volunteers and report 78% fewer HIV infections among Blacks who received AIDSVax compared to Blacks who received the placebo. Remembering the total number of Black volunteers was only 314, this again points to the very small numbers. The power or *p-value* of this observation was only about  $p=.02$ .

## There are several problems with these observations:

- The first and perhaps most important is that the study was not designed or powered to evaluate or detect differences in vaccine effectiveness among subgroups. In other words, there were not enough people in the various ethnic subgroups to allow a meaningful analysis.
- The second is that the total number of non-White, non-Hispanic study participants was small. Thus, the conclusions are driven by a small handful of people. To be more specific, among Blacks, there were a total of 9 cases of HIV infection among those receiving placebo and 4 among those receiving vaccine. When Blacks are included with Asians and non-White, non-Hispanic ethnic/racial “others” the numbers aren’t significantly different. In these groups total HIV infection among placebo recipients is 17 for the placebo group and 12 among those receiving vaccine. Ultimately claims of effectiveness for Blacks, Asians and “others” are based on a difference of five people.
- Magic with numbers: the company claims that the *p-value*, or *power* of the observations achieve statistical significance and thus there is a less than 1% ( $p=.01$ ) and 2% ( $p=.02$ ) likelihood that the observation is merely by chance. What is not highlighted, however, is that the confidence intervals for the racial/ethnic subgroup analysis are very wide. Ideally researchers want to see a confidence interval of 95% or greater. The observation regarding the 67% reduction in infection rates in non-Hispanic racial/ethnic minorities, for example, has a confidence interval of 30% to 84%. The confidence interval for observations in Blacks only is 29% to 93%. What these very wide confidence intervals tell us is that despite the seeming statistical significance of the observation, the *confidence* that the observation is *accurate* is extremely low. This is very common when statistical significance is achieved by small numbers. To translate these statistical terms into plain English, what the data are telling us is that *we’re very sure that we don’t know*.

While the company asserts that the vaccine might be effective in non-White, non-Hispanic volunteers and particularly effective in Blacks, thus far a thoughtful examination of factors that may be confounding these observations has not been released to the public. When making strong statements like this, it’s important they be accompanied by more analysis. In a press and investor conference and webcast this morning (24 February), company representatives noted that many of



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the infections happened in Chicago, for example. One question, for example, might be around whether or not the cases of HIV infection happened among people in the same social network(s) and thus merely an artifact. There is absolutely no way to see if people were exposed to HIV but protected from HIV infection due to vaccination. It's not possible to conclude that more Black people receiving the vaccine were exposed and protected from HIV infection, all that can be said is that in the total group, 13 Black people became infected with HIV but nothing can be said about real exposure and protection rates, especially when we're talking about numbers this small. While the company asserts that the FDA approved the subgroup analysis, this does not mean that the study was designed to look at this question.

The company speculates that the reason they believe the vaccine may have worked in these subgroup is that the vaccine caused the development of higher levels of anti-HIV antibodies in these groups. On this point, the company's materials are a bit confusing, as at one time they assert that this is known to be the case, while at another they say they need to conduct further studies to determine if this is true. One thing we do know is true, however, is that there is no known biological basis for the claim. Studies of Blacks and other ethnic minorities have not shown any higher incidence of anti-HIV antibodies than in other populations. If the virus itself does not provoke a higher incidence of antibodies in ethnic subgroups, there is no reason to believe that a vaccine would either.

Another possible confounder of the data is women tend to make up a higher percentage of the infected population in the black community. It is thus possible that the data is hinting at a difference between men and women, rather than between races, in response to the vaccine. There is some known biological evidence that women react differently to HIV than men, so at least this premise has a basis in observed scientific data.

Taken together, the combination of these potential confounders, the small numbers of infections, and the wide confidence intervals in the data call for great caution before accepting the findings claimed by the company.

The company uses these conclusions to promote the need for ongoing study of the failed product. While certainly more detailed analysis is needed, particularly among the different subgroups, it would be rash to jump to conclusions that studies in Blacks and non-white, non-Hispanics should proceed at great pace. To the contrary, greater examination of the data are needed to make sure these conclusions with-

stand scrutiny lest non-White, non-Hispanics and Blacks be unduly coerced and mislead into participating a trial of a failed product. African Americans and other racial/ethnic minorities in the United States deserve nothing less than the best science. However much we all might want find a vaccine that helps prevent infection, it does no one any good to make misleading or unsupported claims.

As more information becomes available, this document will be updated over the coming days, weeks and months. Feel free to call our hotline and visit our website (<http://www.projectinform.org>) for updates.

### Commentary

Releasing scientific information by press release is not the way that most companies conduct business nor does it represent a respected norm or protocol in the scientific community. Many factors influence what a company chooses to report in a press release, not the least of which are stock market forces and investor concerns. These corporate concerns are often at odds with the community's need for accurate, balanced and thorough information. In the case of the recent VaxGen press release, the overall conclusion of the study, the vaccine failed to prevent HIV infection.

Bluntly, when tested in over 5,000 people the vaccine failed to have any impact on HIV infection rates compared to those who received placebo. It would have been responsible for the company to simply announce this information and leave further subgroup analysis and findings until a time when those analyses had undergone thoughtful scrutiny. Companies often need to spin the data to say something positive and this can sometimes get in the way of saying things responsibly. This appears to be the case in this situation, unfortunately.

The worst outcome of the VaxGen news release could be that efforts are mounted too quickly to gear up studies of AIDSVax in Black people before the data are thoroughly reviewed. An examination of preliminary data from earlier versions of AIDSVax product lead to scientific skepticism over this preventive vaccine approach and a decision by the U.S. government not to invest public funds in large studies of the product. These data bore out that the government made the right decision. If there are subgroups, Blacks, Asians and "others" who might still benefit from the product, then research should be designed to answer questions about the possible value of the product. Great care should be taken, however, to evaluate confounding influences that may have affected outcomes in the recent study. There is no great merit in conducting studies targeting racial minorities of products that aren't backed by sound and strong verifiable data.



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## Questions and answers

### ***Q: Does this mean vaccines won't work in white people?***

**A:** It's not clear that there were better responses in any of the subgroups described and more analysis is needed. It would not be surprising, however, if a vaccine or a drug worked better in one racial or ethnic group compared to another, or if a vaccine or drug worked better in one gender or another. However, at the current time, the way these data were reported, by press release, it's extremely difficult to know if the conclusions and assertions made by the company are truly data driven or merely driven by their needs to salvage a market regarding the stock market. Even if these data hold true under more rigorous evaluation, it might simply mean that the product is not potent enough to elicit the kinds of immune responses needed to protect all people. The information learned about what might lead to protection against HIV infection would be key and central to developing new candidate vaccine products which would undoubtedly serve more people. This would be important information that everyone would eventually benefit from.

### ***Q: Does this mean that the vaccine works better in Black people?***

**A:** It's possible that a vaccine or drug will work better in one racial or ethnic group compared to another. At the current time, however, given how much the company has riding (particularly in the stock market), it would be a mistake to latch on to these data before they've been reviewed by other scientists and impartial parties. The study was not designed to look at the effectiveness of AIDSVax in Black people. The way the data were reported left more questions than answers. In short, it's far too early to draw conclusions and there could be large ethical consequences of moving forward with a failed vaccine in Black people. With that said, however, a more detailed examination of the observations that Asians, Black people and "other" people claimed to benefit from the vaccine is critical. Now that the company has released such statements they should be held accountable to back them up, share data sets with impartial individuals and allow for further exploration of the findings in an expedited manner. If these observations hold true under greater scrutiny, the company should be made to act swiftly to design and enroll a study to confirm the findings.

### ***Q: Does this mean that other HIV preventive vaccines won't work?***

**A:** No. While these results are discouraging for other gp120-based vaccine products, there are many HIV preventive vac-

cine products currently in study. Many if not most of these products are not gp120-based and many aim to induce broader and more potent immune responses (*both* cellular and antibody responses), which is increasingly believed to be important to protect against HIV infection. The failure of AIDSVax does not mean other HIV preventive vaccines won't work.

### ***Q: I'm in an HIV preventive vaccine study, is AIDSVax the vaccine I may be receiving?***

**A:** When you join a study, you sign a document called an *informed consent* document. You should have been given a copy of the document you signed and the original is kept in a locked file cabinet at the place where you go to participate in the study. The *informed consent* document describes the vaccine you are receiving. If it is the AIDSVax vaccine, it should say this clearly. If you are unsure what vaccine product is being researched in the study that you're participating in, you can look in the *informed consent* document, call the study nurse, call the doctor who you see as part of the study or contact one of the people listed in the *informed consent* document and ask them.

### ***Q: Does this mean that vaccines to treat HIV won't work?***

**A:** Failure of AIDSVax as a preventive vaccine has little to no implications on therapeutic vaccine research. For people living with HIV, this is a key point and important to emphasize. Failure of AIDSVax doesn't imply failure of current therapeutic vaccines under study.

### ***Q: What other vaccines are being studied?***

**A:** While some of the vaccine products currently being researched contain gp120 or elements of gp120, most contain other/more HIV proteins. Attached is a reprint of materials produced by the International AIDS Vaccine Initiative (IAVI), which lists the *preventive* vaccines currently in development and their stage of testing. Most/many of these products are also being researched to see if they are useful in treating HIV (as a therapeutic HIV vaccine.) Several studies are underway or being planned to combine VaxGen's AIDSVax vaccine with other vaccines. It's possible, in the setting where vaccine approaches are combined, that together they will be effective where one or the other product fails on its own. Even still, it's hard to see how AIDSVax will contribute when on its own it does little to nothing. For more information, go to [www.iavi.org/iavireport/0103/trialswatch.htm](http://www.iavi.org/iavireport/0103/trialswatch.htm).

### ***Q: Is this the same product that was reported on last week, where in animal studies the animals died?***

**A:** No. The study in the news last week was a study of a very different product made by another company altogether.