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Clinical trial generates tantalizing hope for a future HIV vaccine, but much research lies ahead

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Some good news

Recently, a team of researchers in Thailand announced that their investigational vaccine was able to reduce the risk of HIV infection in a clinical trial involving approximately 16,000 volunteers. Since this announcement, there has been a wave of interest in the potential for this vaccine to help in the prevention of HIV transmission. A positive result from a vaccine trial is encouraging given the long history of HIV vaccine failures, yet we urge readers not to jump to quick conclusions when assessing the results of this trial. The reported effectiveness of the vaccine is based on a preliminary analysis and many experts believe that it is not effective enough to provide any practical benefit in prevention efforts. Still, the world urgently needs an HIV vaccine and the Thai trial may be an important step towards this elusive, yet vital goal.

Background

Since 1983, when HIV was first discovered, much progress has been made. HIV diagnostic tests are highly accurate and, in some cases, produce results within a few minutes. HIV treatments have become so effective that in high-income countries—with their universal access to health care and social welfare systems—researchers expect that many HIV-positive people will attain near-normal life spans. However, although diagnosis and treatment of HIV can greatly prolong survival, there is no cure. Expensive anti-HIV drugs must be taken every day, indefinitely, and even well-tolerated regimens may have long-term side effects.

Worldwide, most HIV-positive people live in low- and middle-income countries where access to health care and anti-HIV drugs is limited. What's more, every day about 7,000 people are infected with HIV. A recent international report suggests that even in high-income countries and regions, such as Australia, Canada, Western Europe and the United States, rates of HIV infection are increasing among gay and bisexual men. So, even with good treatment there is a desperate need for a vaccine.

Shortly after the discovery of HIV, teams of researchers assembled to work on the development of a vaccine against this virus. After two decades and despite more than 100 clinical trials of over 30 different vaccine candidates, until the Thai trial none had produced a positive result suggestive of protection against HIV.

A history of two vaccines

To put the recent results of the trial in Thailand into the broader context of HIV vaccine efforts, it is helpful to understand the history of the vaccines used in this trial.

The Thai trial used two vaccines—ALVAC (vCP1521) and AIDSVAX B/E (gp 120). ALVAC is made by Sanofi-Pasteur, the vaccine division of the pharmaceutical company Sanofi-Aventis. AIDSVAX is made by Genentech, under license from Global Solutions for Infectious Diseases.

Several small-to-medium-sized trials of ALVAC were conducted in the late 1990s and earlier part of this decade. Independent analysis of these trials found that ALVAC only weakly stimulated the immune system to respond to HIV and, at best, would be weakly protective against this virus. Several years ago, a very large trial of AIDSVAX was completed and this vaccine did not provide protection against HIV.

Back in 2003, the poor results of both ALVAC and AIDSVAX led many researchers to question the value of further large-scale trials of these two vaccine candidates. However, amid some controversy, the U.S. Military HIV Research Program, Sanofi-Aventis and the Thai Ministry of Health decided to conduct a trial, called RV 144, that combined injections of both ALVAC and AIDSVAX. This trial would last six years and end up costing more than $US 100 million.

About the trial

Starting in 2003, RV 144 enrolled about 16,000 HIV-negative participants at average risk of HIV infection. Most participants identified as heterosexual and a small number disclosed that they engaged in high-risk behaviour such as commercial sex work.

Half of the participants were given placebo (fake vaccine) injections and the other half received injections of the two vaccines. This complex regimen involved four injections of ALVAC and two injections of AIDSVAX. In total, each participant received four sets of injections over six months. All participants were regularly counselled on how to avoid HIV infection. They were monitored for an average of three years to determine if they subsequently became infected with HIV. Those participants who developed HIV infection were offered free treatment.

The results—hope tempered with caution

On September 24, 2009, the trial sponsors announced in a press release that the combination vaccine was “safe and modestly effective” in preventing HIV infections. The results were:

- 51 HIV infections among 8,197 participants receiving ALVAC/AIDSVAX (0.62% rate of infection)
- 74 HIV infections among 8,198 participants receiving placebo (0.90% rate of infection)

The combination vaccine provided a *relative* risk reduction of 31% compared to the placebo. This translates into an absolute reduction of risk of 0.3% This difference was found to be “statistically significant,” meaning that it was likely not a result of chance.

For those who became infected with HIV, it was further expected that the combination vaccine would provide some protection against developing high levels of HIV. Specifically, the researchers theorized that vaccinated people who later became infected with HIV would have lower-than-normal levels of the virus in their blood. Unfortunately, HIV levels (viral load) were the same in infected people whether or not they received the vaccine.

The combination vaccine was designed and tested to work against the types of HIV that are common in Thailand (subtypes B and E). It is not known whether or not the vaccine will work in parts of the world with different subtypes, such as in Southern Africa. Also, the trial recruited predominantly heterosexual people for whom the main route of infection is vaginal sex. Because the main route of infection is different for men who have sex with men and for injection drug users, the clinical trial may not be applicable to these populations. Finally, the study was a “proof of concept” and was not designed to meet the higher standards of evidence required for vaccine licensing.

What do these results mean for people at risk of HIV infection?

For individuals hoping for a vaccine that will protect them from HIV infection, these results are disappointing. A 31% reduction in relative risk has no *practical* significance compared to the reduction in risk that comes from consistently practicing safer sex or using clean needles. All participants in the trial were counselled about the importance of continuing to practice safer sex and avoid sharing needles. The vaccine also has no impact on HIV levels after infection.

What do these results mean in the global fight against HIV?

This vaccine does not provide people with a high degree of protection from HIV to the extent that most conventional vaccines provide protection from other infections. The big hope for this vaccine is that it could be used in combination with other prevention methods, such as safer sex, in order to make a difference in the total rate of HIV transmission *among large populations at risk* . This is a relatively new idea in vaccine research—a vaccine that doesn’t provide much protection for an individual, yet can make a big difference to the global spread of HIV.

There is currently a lot of controversy about how effective a vaccine needs to be in order to make such a global

difference. And the stakes are high because clinical trials and the ultimate roll-out of vaccines are very expensive. If the vaccine isn't effective enough, there may be no impact from a large-scale vaccination program. The results of this trial raise a number of issues that researchers are trying to grapple with.

Is a 31% reduction in relative risk enough to even consider a vaccine like this as potentially effective outside the controlled environment of a clinical trial? Many experts believe that this risk reduction is too low to expect that large-scale vaccination would make any change in transmission rates. One of the biggest concerns about a potential HIV vaccination program is that it would change people's perception of risk. A mere 31% reduction in condom use in the population could wipe out any benefit from the vaccine. Worse still, HIV infection rates might *increase* as a result of changed behavior after vaccination. It is not clear yet how effective a vaccine needs to be in order to work in the "real world."

Number needed to protect

Would it be feasible to implement a vaccine like this on a large scale? The vaccine only provided an *absolute* risk reduction of 0.3%. That means, for roughly every 1,000 people vaccinated, only three HIV infections would be prevented. The vaccine requires a complex regimen of four sets of injections over six months and, so far, there is only evidence of protection for three years. This suggests a very intensive vaccination protocol with a relatively small impact on HIV transmission. Much more research is needed on a potential HIV vaccination program, its feasibility and cost-benefit in comparison to other prevention strategies.

When looking at population-level HIV risk, how "statistically significant" does a clinical trial result need to be if the vaccine's reported effectiveness is very low? HIV risk is affected by a complex set of factors, many of which are poorly understood. The researchers used a statistical significance level of approximately 5% ($p=0.039$) in order to conclude that the vaccine was effective. While this level of significance is widely used when testing new therapies to determine which ones are promising, there is still a 4% chance that the vaccine is not effective after all. Some people are concerned that this level of statistical significance is not adequate to make a strong conclusion about the effectiveness of this vaccine, particularly when the number of infections is very low. No information has yet been provided about the distribution of HIV risk factors between the two arms of the study. "A few more infected vaccine recipients could have tipped the results towards statistical insignificance", writes journalist Jon Cohen in the journal *Science*. The trial's chief statistician, Donald Stablein, has said this: "These vaccines work, and they don't work well enough."

What's next?

More results from RV 144 are going to be released to the scientific community at a conference called *AIDS Vaccine 2009*, to be held October 19-21 in Paris, France. Researchers hope that these results can shed light on how the vaccines might have worked. A very important step is for researchers to analyse the blood samples of participants from this study to determine which immune responses protected them.

The effort to create a successful HIV vaccine gets to the core of scientists' understanding of how the immune system works, how it interacts with HIV, and how this virus disables immunity. For the first time, a positive signal of protection has emerged from an HIV vaccine trial—this is something that should be celebrated. But, despite this result, much work lies ahead as researchers try to find the underlying reasons for RV 144's hint of success. If researchers can both verify that the results are a consequence of the vaccine *and* uncover the reasons that the vaccine worked in this study, then their findings could help guide the development of other candidate HIV vaccines and future clinical trials.

Resources:

- Canadian HIV Vaccine Initiative: www.chvi-icvv.gc.ca/index-eng.html
- Canadian Institutes of Health Research (CIHR): www.cihr.ca/e/13533.html
- AIDS Vaccine Advocacy Coalition (AVAC): www.avac.org
- International AIDS Vaccine Initiative (IAVI): www.iavi.org/Pages/home.aspx
- Global HIV Vaccine Enterprise: www.hivvaccineenterprise.org/
- Agence Nationale de Recherche sur le SIDA (ANRS): www.anrs.fr/index.php/anrs/VIH-SIDA/Vaccin/Actualites
- U.S. National Institutes of Allergy and Infectious Diseases (NIAID):

www3.niaid.nih.gov/topics/HIVAIDS/Research/default.htm

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—Sean R. Hosein

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