

In Search of AIDS vaccine.

Outline

Introduction.

1. Possible ways AIDS vaccine might work.
2. Problems with the development of an AIDS vaccine.
3. Phases of testing a potential AIDS vaccine.
4. AIDS vaccine trials.
5. Support for AIDS vaccine research and development.
6. How soon could we have an effective AIDS vaccine?
7. Reaching people in need.

Conclusions

Introduction.

An AIDS vaccine does not yet exist, but efforts to develop a vaccine against HIV and AIDS have been underway for many years. Since 1987, more than 30 vaccine candidates were tested.¹

Even a partially effective AIDS vaccine could save millions of lives. Experts have calculated that an AIDS vaccine that is 50% effective, given to just 30% of the population could reduce the number of HIV infections in the developing world by more than half over 15 years. An AIDS vaccine that was more than 50% effective could cut the infection rate by more than 80%.²

An AIDS vaccine would have a number of key advantages over today's HIV prevention options. In particular, the protection offered by a vaccine during sex would not depend on the consent of both partners (unlike condom use), and would not require behaviour change (unlike abstinence). An AIDS and HIV vaccine would also be invaluable for couples wishing to conceive a child while minimising the risk of HIV transmission.

Children could be given an HIV and AIDS vaccine before ever being exposed to the HIV virus, and ideally this would subsequently protect them from all routes of HIV transmission. Vaccinating large numbers of people would probably require relatively little equipment and expertise, and would be much simpler and cheaper than providing antiretroviral treatment for those already infected.

1. Possible ways AIDS vaccine might work.

An AIDS vaccine could be effective in either of two ways. A “preventive” vaccine would stop HIV infection occurring altogether, whereas a “therapeutic” vaccine would not stop infection, but would prevent or delay illness in people who do become infected, and might also reduce the risk of them transmitting the virus to other people. Although a preventive vaccine would be ideal, a therapeutic vaccine would also be highly beneficial.

1 Ross, A.L, Br ave, A, Scarlatti, G, Manrique, A & Buonaguro, L (2010) '[Progress towards development of an HIV vaccine: report of the AIDS Vaccine 2009 Conference](#)', Lancet Infectious Diseases, Vol 10, May 2010

2 International AIDS Vaccine Initiative (2006) '[Estimating the impact of an AIDS vaccine in developing countries](#)'.

The basic idea behind all AIDS vaccines is to encourage the human immune system to fight HIV. The immune system works using a combination of cells and chemicals called antibodies. Early vaccine research focused on teaching the immune system to produce antibodies that would block HIV entering human cells. However, products designed to work this way failed in clinical trials because the antibodies worked only against lab-cultured HIV, not against the wild strains of the virus.

Research has found a very small number of HIV-infected people produce 'broadly neutralizing antibodies' to HIV.³ These antibodies, which neutralize a high percentage of the different types of HIV, are now the basis for new research into vaccine development.⁴

Other research has focused on encouraging the immune system to produce cells to fight HIV. Nevertheless, many scientists believe such “cell-mediated” approaches will not be very effective on their own, even as therapeutic vaccines. It seems likely that a really effective vaccine will have to take a two-pronged approach involving both cells and antibodies.

2. Problems with the development of an AIDS vaccine.

Developing an AIDS vaccine is a very difficult challenge for scientists. There are many reasons for this, including:

- Nobody has ever recovered from HIV infection, so there is no natural mechanism to imitate
- HIV destroys the immune system cells that are meant to fight against it
- Soon after infection, HIV inserts its genetic material into human cells, where it remains hidden from the immune system
- HIV occurs in several subtypes, each of which is very different from the others
- Even within each subtype, HIV is highly variable and constantly changing

3 International AIDS Vaccine Initiative (2009, 3rd September) ['Two new antibodies found to cripple HIV'](#)

4 International AIDS Vaccine Initiative (2010) ['The Antibody Project'](#)

- There are no good animal models to use in experiments although the use of non human primate (NHP) models could become a more significant model for HIV vaccine design and testing in the future.⁵

However, there are reasons to be optimistic about the search for an AIDS vaccine, despite the difficulties and the slow progress so far. Vaccines against other diseases took many decades to develop, and HIV was only discovered in the mid 1980s. It is therefore much too early to give up hope, especially given the current speed of scientific progress. In the past, some experts doubted the possibility of an effective polio vaccine, yet today polio is close to being eradicated thanks to successful vaccination programmes.

One particular reason for remaining hopeful is that most people remain healthy for several years after becoming infected with HIV, and a small number of people have survived as long as 20 years without developing AIDS, even though they never entirely rid themselves of the virus. In addition, neutralizing antibodies that have been found among a minority of people suggest that the immune system can be quite effective at controlling HIV.

3. Phases of testing a potential AIDS vaccine.

Any potential AIDS vaccine must pass through three phases of clinical trials before being judged safe and effective. The first phase usually lasts from twelve to eighteen months, whereas the last phase can take three or four years to complete.

- **Phase I** involves a small number of volunteers to test the safety of various doses
- **Phase II** involves hundreds of volunteers to further assess safety and, in some cases, positive responses
- **Phase III** involves thousands of volunteers to test safety and effectiveness

A recent innovation is the Phase IIb trial, a larger form of the Phase II trial that provides some

⁵ The Council of the Global HIV Vaccine Enterprise (2010, September) '[The 2010 scientific strategic plan of Global HIV Vaccine Enterprise](#)' in Nature Medicine 16:9; 981-988

indication of effectiveness.

In most cases volunteers taking part in the trial must be HIV-negative at the start of the trial, though it is important also to test safety in those who are already infected. Some therapeutic vaccine candidates may be tested on HIV-positive people to see if they can delay disease progression.

Trials of AIDS vaccines are made more difficult by the ethical obligation to provide condoms and prevention counselling to all those who take part. Providing such services lowers the overall rate of HIV transmission, which increases the number of volunteers required to produce a significant result.

4. AIDS vaccine trials.

The AIDSVAX vaccine trials

The first AIDS vaccine candidate to undergo Phase III trials was called AIDSVAX. Two separate studies were conducted. One had around 5,400 participants - mostly gay American men - while the other involved around 2,500 injecting drug users in Thailand. The vaccine was made from a single HIV protein and was meant to stimulate a protective antibody response. The trials began in 1998 and 1999 respectively, and ended in 2003. No beneficial effect was found in either population group.⁶

The STEP and Phambili vaccine trials

Two Phase IIb trials of a vaccine candidate created by the pharmaceutical company Merck were halted in September 2007. The studies - known as STEP and Phambili - had been expected to produce their first results by 2010. The trials were stopped when researchers found people receiving

⁶ BBC (2003, 12th November) [‘HIV vaccine trial ends in failure’](#).

the vaccine were no less likely to become infected with HIV than those given the placebo - the version that had no medicinal properties. The STEP trial had started in 2004 in the USA, Canada, Australia, Peru and the Caribbean; the Phambili trial had begun in January 2007 in South Africa.⁷

There is some concern that slightly more HIV infections occurred among people who received the Merck vaccine than among those who took a placebo. The vaccine was delivered using adenovirus type 5, which causes the common cold. It has been suggested that the vaccine may have provoked a different immune response among people who already had some immunity to the adenovirus strain, and that this may have made them more susceptible to HIV infection. This hypothesis - which is supported by laboratory evidence⁸ - raises questions about the use of adenovirus in future vaccines.⁹ It has also been noticed that uncircumcised men were four times more likely to become infected with HIV if they received the vaccine than if they received the placebo.¹⁰

Following the failure of the trial several other trials were delayed to ensure the design of the trail took into account what had been learnt from the Merck vaccine study.

Leading vaccine researcher Dr. Gary Nabel described the results of the Merck vaccine trial as “a big blow to the field”.¹¹ Nevertheless, Dr. Seth Berkley, President and CEO of the International AIDS Vaccine Initiative, has stressed that the outcomes are not all negative:

“Though the Merck candidate failed, the trial did not. The contribution of the volunteers was not in vain. As a result of their dedication, the field will have new data that will inform future vaccine design, help with the prioritization of candidates in the pipeline and guide decisions on how to best proceed with ongoing and upcoming trials.”¹²

7 HIV Vaccine Trials Network (2007, 8th February) [‘Africa’s first large-scale HIV vaccine study launches’](#); BBC (2007, 21st September) [‘Merck abandons HIV vaccine trials’](#).

8 Perreau, M, Pantaleo, G & Kremer, E.J (2008) [‘Activation of a dendritic cell-T axis by Ad5 immune complexes creates an improved environment for replication of HIV in T cells’](#), The Journal of Experimental Medicine, 2008 Nov 24;205(12):2717-25.

9 The New York Times (2007, 8th November) [‘In tests, AIDS vaccine seemed to increase risk’](#).

10 HIV Vaccine Trials Network [‘Step study results’](#).

11 Baltimore Sun (2007, 14th November) [‘AIDS vaccine’s failure deals big blow’](#)

12 EurekAlert! (2007) [‘IAVI statement on new analysis of STEP large-scale AIDS vaccine trial’](#).

The ALVAC / AIDSVAX vaccine trial

In 2006 AIDSVAX was used in another Phase III trial in combination with ALVAC.¹³ It was hoped that a trial combining AIDSVAX, which promotes the production of antibodies to HIV, and ALVAC, which is designed to stimulate a cellular response to the virus, would prove more effective than the previous AIDSVAX trial.¹⁴ The trial recruited 16,402 young adults in Thailand.

The results, published in late 2009, showed that 74 trial candidates who received a placebo became infected with HIV, compared to 51 who had received the vaccine candidate.¹⁵ Although further examination produced mixed results, the analysis which the authors claimed was most relevant showed the vaccine prevented HIV infection by 31.2%. Drawing on this statistically significant result, the authors concluded that the trial showed a "modest protective effect of vaccine".¹⁶

Opinion differed over the significance of the study. Seth Berkley, of the International AIDS Vaccine Initiative was optimistic:

“The outcome is very exciting news and a significant scientific achievement. It’s the first demonstration that a candidate AIDS vaccine provides benefit in humans. Until now, we’ve had evidence of feasibility for an AIDS vaccine in animal models. Now, we’ve got a vaccine candidate that appears to show a protective effect in humans, albeit partially.”¹⁷

However, Dr. Otto Yang, an immunologist at University of California, LA, said:

"the results are weak enough that we need to be very careful about assigning too much optimism to them... It seems not so likely that the vaccine really did what it was intended to do".¹⁸

The International AIDS Vaccine Initiative's database shows that by July 2010, there were two Phase II, three Phase I/II, and seventeen Phase I ongoing clinical trials of preventive AIDS vaccine

13 ClinicalTrials.gov (Updated 22nd June 2009) '[HIV vaccine trial in Thai adults](#)'.

14 AVAC (2009) '[Piecing together the HIV prevention puzzle](#)'.

15 Rerks-Ngarm, S et al (2009) '[Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand](#)', The New England Journal of Medicine, October 2009;361, Massachusetts Medical Society

16 Ibid.

17 IAVI (2009, 24th September) '[IAVI statement on results of Phase III ALVAC-AIDSVAX trial in Thailand](#)'

18 Los Angeles Times (2009, 20th October) '[Results of AIDS vaccine trial 'weak' in second analysis](#)'.

candidates taking place.¹⁹

5. Support for AIDS vaccine research and development.

In 2008, the public, philanthropic and private sectors invested around \$868 million in preventive AIDS vaccine research and development.²⁰ The public sector provided around 84 percent, the philanthropic sector accounted for 12 percent, and the commercial sector accounted for the remaining 4 percent. Although funding for vaccine research has increased substantially since 2000, the 2008 contributions were a 10 percent decrease from 2007.²¹

AIDS vaccine research is aided by the not-for-profit International AIDS Vaccine Initiative (IAVI), which helps to support and coordinate vaccine research, development, policy and advocacy around the world. In addition an alliance of organisations called the Global HIV/AIDS Vaccine Enterprise exists to coordinate research and promote scientific cooperation and collaboration.

6. How soon could we have an effective AIDS vaccine?

“The path forward is not clear. I think there is agreement on that. Anybody who talks about a timeline for a vaccine is being silly and uninformed.”

John Mellors, 2008 CROI co-chair

In 1984, at the press conference arranged to announce the discovery of HIV, the US Health and Human Services Secretary Margaret Heckler said she hoped a vaccine against AIDS would be ready for testing in about two years.²²

Unfortunately, the problem has turned out to be much more challenging than Secretary Heckler expected. Today’s researchers agree that the development of an AIDS vaccine still has a long way to go. It is possible that the search could last decades.

¹⁹ International AIDS Vaccine Initiative (2010) '[Database of AIDS vaccine candidates in clinical trials](#)'

²⁰ HIV Vaccines and Microbicides Resource Tracking Working Group (2009, July) '[Adapting to Realities: Trends in HIV prevention research funding, 2000 to 2008](#)'.

²¹ HIV Vaccines and Microbicides Resource Tracking Working Group (2009, July) '[Adapting to Realities: Trends in HIV prevention research funding, 2000 to 2008](#)'.

²² The New York Times (1984, 24th April) '[New U.S. report names virus that may cause AIDS](#)'.

“HIV infection has never provided scientists with a proof of concept of predictable protection, which historically has been the guiding principle for successful vaccine development.” *Dr Anthony S. Fauci, Director of NIAID*²³

The failure of the STEP trial in 2007 in particular has led some scientists to question whether the current approach to AIDS vaccine development has much chance of success, given that it favours products that work in a similar way to the failed Merck candidate.

“The path forward is not clear. I think there is agreement on that. Anybody who talks about a timeline for a vaccine is being silly and uninformed. It will require an incremental process of knowledge, and experimentation, and testing of ideas.” *John Mellors, Co-chair of the 15th Conference on Retroviruses and Opportunistic Infections*²⁴

The news media regularly announce a new “breakthrough” in AIDS vaccine research. However, most of these stories refer to products in Phase I or Phase II trials, where there has been no evidence of the product actually working in humans. Such stories are realistically talking only about potential breakthroughs.

Few if any vaccines are 100% effective. Most probably the first AIDS vaccines to succeed in trials will offer only partial protection, and these may need to be improved or combined with other products before being suitable for widespread use. Vaccine development is likely to proceed by small, incremental steps; we are unlikely to see an immediate “miracle breakthrough”.

7. Reaching people in need.

If trials conclusively find a particular AIDS vaccine to be safe and effective then the next challenge is to distribute it and help people access it. In addition both governments and individuals will need to be convinced that the product is worth investing in. The process of getting a vaccine to all the hundreds of millions of people in need could take many years.

An important consideration is whether a vaccine could undermine the popularity of existing

²³ News24 (2009) ‘[AIDS vaccine ‘no magic cure’](#)’.

²⁴ Bay Area Reporter (2008, 7th February) ‘[NIH HIV vaccine program criticized](#)’.

HIV prevention methods, such as condoms. If a product is only partially effective (as is almost inevitable) then experts will have to weigh up the potential risks and benefits very carefully before considering distribution. Upon release of any product, awareness-raising and prevention efforts will need to be redoubled to counter the risk of complacency.

Conclusions.

It is very unlikely that HIV and AIDS will ever be eradicated without new scientific developments. Eventually, unless great progress is made in prevention, the number of people living with HIV will outstrip the resources available for treatment. Many people therefore believe that the search for an effective AIDS vaccine must be one of the highest priorities for scientific research.

However, it is not realistic to expect such research to produce a major breakthrough for some time yet, and it is important to be wary of news stories suggesting otherwise. Any new discovery needs to undergo trials lasting years, and must then be distributed around the world before its full benefits will be seen. There is also a danger that too much emphasis on the development of an AIDS vaccine will divert both attention and resources away from existing HIV prevention initiatives and antiretroviral treatment programmes.

“The world is jumping into a flurry of excitement about a possible solution many years down the line – nobody seems to be in a similar flurry about the fact that, right now, two out of three people who need ART to stay alive aren’t receiving it.” *Paula Akugizibwe, AIDS and Rights Alliance for Southern Africa.*²⁵

²⁵ The New York Times (1984, 24th April) [‘New U.S. report names virus that may cause AIDS’](#).