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AN IAVI REPORT BULLETIN

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VAX is a monthly bulletin featuring shorter, non-technical versions of articles from the *IAVI Report*, the newsletter on AIDS vaccine research published by the International AIDS Vaccine Initiative. *VAX* is currently available in English, French, German, Spanish and Portuguese as a pdf (www.iavi.org/iavireport) or an e-mail bulletin. If you would like to receive *VAX* by e-mail, please send a request including language preference to: VAX@iavi.org

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In this issue

RESEARCH & TRIALS

◆ Brazilian Trial Site Launches Novel Online Recruitment Strategy

The Federal University in Sao Paulo, Brazil has launched a novel, web-based recruitment strategy for its Phase I preventive AIDS vaccine trial, which is scheduled to start in April 2004. The trial site's web page includes an online questionnaire for people who are interested in participating. The questionnaire asks about some HIV risk factors, including numbers of sexual partners and frequency of unprotected sex, and about willingness to participate in an AIDS vaccine trial. This information is kept highly confidential and is only used by trial staff to identify potential trial volunteers. Each person who responds receives an individualized reply and people who might qualify for the trial are invited to the trial site to learn more about the official screening process.

The website received a lot of media coverage prior to its launch on 14 March. On the first day more than 1,500 people visited the site and 125 had filled out the entire questionnaire. "We have had a massive response," says site trial leader Dr. Esper Kallas. He thinks that one reason why so many people filled out the questionnaires is that "Brazil has such a positive attitude towards AIDS today." Kallas says that this attitude comes from a strong sense of national pride in Brazil's highly visible fight against HIV, which includes campaigns to end AIDS-related stigma and discrimination, and a national HIV treatment program.

The Sao Paulo site is one of the first AIDS vaccine trial sites to recruit potential volunteers online. The website also provides information about AIDS vaccine research and the risks and benefits of trial participation.

The Sao Paulo site is part of an international Phase I trial of an experimental vaccine candidate called MRK-Ad5 that has been developed by Merck. The trial is being conducted by the US HIV Vaccine Trials Network (HVTN) and Merck and will include sites in Brazil, Haiti, Malawi, Peru, Puerto Rico, South Africa, Thailand and the US.

■ *To visit the trial website:*
www.vacinashiv.unifesp.br

■ VAX *would like to hear of other sites' recruitment strategies. Send an email describing your strategy to* VAX *at:* vax@iavi.org *Replies may be published in future issues of* VAX *or on our website:* www.iavi.org/iavireport

GLOBAL NEWS

◆ New Report on Global Access to Childhood Vaccines

In January 2004 the Global Alliance for Vaccines and Immunizations (GAVI) published a report on progress and challenges in its campaign to increase access to childhood vaccines in developing countries. Since 2000, GAVI and its partner organization the Vaccine Fund have provided grants and technical assistance to help countries strengthen their existing childhood immunization programs and to purchase additional vaccines for these programs. Although early childhood immunization programs are found in most developing countries, each year an estimated 37 million children do not receive routine immunization against diphtheria, tetanus, and polio (a combination vaccine called DTP3). Even more children do not receive newer vaccines, and so are vulnerable to infection by hepatitis B virus, yellow fever virus, and *Haemophilis influenzae* type b (which causes meningitis).

GAVI-funded programs provide vaccines against these and other serious diseases, including the DTP3 vaccine.

GAVI has helped increase access to vaccines which have not been

widely available in developing countries. One example is hepatitis B vaccine, which was licensed in 1981. Nearly twenty years later, it was estimated that less than half of the world's children received the hepatitis B vaccine at birth. The new GAVI report estimates that more than 35 million children have been vaccinated against hepatitis B virus since 2001.

GAVI found that many developing countries needed financial support to build their health care **infrastructure** before they could begin to deliver childhood vaccines. One critical need is the "cold chain" of refrigerators, refrigerated trucks and storage facilities that are used to keep vaccines at the correct temperature at all times.

The report also notes that interest in manufacturing childhood vaccines has increased since GAVI was created. Currently there is only one manufacturer who produces a vaccine that combines vaccines against diphtheria, tetanus, pertussis and hepatitis B in one shot. But 11 manufacturers have now applied to produce and supply this vaccine combination by 2006. One reason for this is that GAVI and the Vaccine Fund have increased the funding available for purchasing these vaccines. This provides an incentive to vaccine manufacturers to invest in these vaccines.

GAVI's work may hold useful lessons for the AIDS vaccine field. Even though it will likely be many years before an effective preventive AIDS vaccine is developed, there is still a need to plan ahead so that there is adequate manufacturing capacity and so that developing countries have the infrastructure and funds required to supply the vaccine to all who need it once it is available. AIDS vaccines will first be delivered to adults, rather than infants. This means that an effective vaccine will probably not be distributed through existing early childhood immunization programs; additional resources will be needed to design and build systems for delivering an AIDS vaccine to adults.

■ *For more information on GAVI and to download a copy of the progress report:* www.vaccinealliance.org

Infrastructure:

Physical structures and supplies that form the foundation for delivering services. Vaccine-related infrastructure includes refrigeration systems and storage facilities to keep the vaccines at correct temperatures, transport systems to deliver the vaccines, inventory systems to keep track of vaccine supplies, as well as clean water, electrical power, and communications facilities.

SPOTLIGHT

◆ Could a "Therapeutic" AIDS Vaccine Help People Who Are Already Infected with HIV?

The primary goal of most AIDS vaccine trials is to identify a preventive vaccine that could protect HIV-uninfected people from HIV infection or disease. However, many people would also like to know whether the experimental vaccines that are currently being tested as preventive candidates could also be tested as "therapeutic vaccines."

The goal of a therapeutic vaccine would be to strengthen HIV-specific immune responses in people who are already infected with HIV. These strengthened defenses would be very unlikely to control HIV by themselves, if a therapeutic vaccine was to be found. This is why a therapeutic vaccine would almost certainly not be used on its own. However, when used in combination with antiretroviral (ARV) drugs, a therapeutic vaccine might be an additional way to control HIV and help HIV-infected people remain healthier for longer.

At present, there are no therapeutic vaccines for HIV infection—or for any diseases at all. All of the licensed vaccines that are used to prevent other diseases such as measles, mumps or polio are preventive vaccines; none of them can treat or cure people who already have a particular disease. Vaccines against rabies and tetanus may prevent disease if they are given immediately after exposure—such as a dog bite. But these are not true therapeutic vaccines since they are only effective within a very short time period after exposure. This is similar to **post exposure prophylaxis (PEP)**, which uses ARVs to reduce the risk of HIV infection when given to people within hours of high risk contact.

None of the AIDS vaccine candidates tested in HIV-infected people has been effective. The challenge is that HIV attacks the immune system and specifically targets $CD4^+$ T cells (see *Primer*), crucial immune defenses that also play a key role in responding to vaccines. Developing a vaccine to boost $CD4^+$ T cells and other immune responses against HIV in people who are already infected will most likely be very difficult—especially in people who have been infected with HIV for many years and have severely weakened immune systems. Most scientists think that it will be much more difficult to make a therapeutic AIDS vaccine than a preventive AIDS vaccine. It may even be impossible.

However, with around 42 million people worldwide currently infected with HIV, a therapeutic AIDS vaccine that strengthened the body's immune defenses against HIV would be a valuable weapon in fighting the virus. This is one reason why some scientists feel that it is important to evaluate the current preventive AIDS vaccine candidates to see if they have any therapeutic benefit for people already infected with HIV.

What would an effective therapeutic AIDS vaccine do?

The goal of a therapeutic AIDS vaccine would be to strengthen the body's ability to fight HIV. A vaccine might be able to do this by producing or strengthening defenses, including immune cells and **neutralizing antibodies,** that reduce the harm that HIV does to the immune system.

When a person becomes infected with HIV, the immune system responds with defenses that can control HIV for some time. This is why most people with HIV feel healthy for several years after they

become infected. However, eventually the virus begins to win the battle. If a therapeutic AIDS vaccine was able to cause the production of additional HIV-specific immune responses they could potentially work alongside these naturally-occurring immune defenses.

Even if it was effective, a therapeutic vaccine would ***not*** be able to cure HIV. Also, a therapeutic vaccine would not be a replacement for ARVs. But it is possible that a therapeutic vaccine could strengthen the body's ability to fight HIV when used in combination with ARVs and other treatments for HIV-related illnesses.

HIV can change or "mutate" itself so that it becomes "drug-resistant" to one or more of the ARVs that a person is taking. When this happens, ARVs can no longer control the virus. If an effective therapeutic vaccine was available, the immune defenses it produced might improve control of the virus and delay the development of drug-resistant virus. This would allow HIV-infected people to take the same combination of ARVs for longer periods of time without developing resistance.

HIV might also be able to mutate to avoid the immune defenses produced by an effective therapeutic vaccine. This is an additional reason that these vaccines would only be used in combination with ARVs, which would help control the virus and serve as an additional barrier to the emergence of drug-resistant virus.

An effective therapeutic vaccine might also be used as part of a "structured treatment interruption" (STI) strategy in which people infected with HIV stopped taking ARVs for weeks or months, while under close medical supervision to monitor the amount of HIV (viral load) in the blood. STIs are being studied as a way to give people with HIV short breaks from lifelong ARV treatment, which can be complex and can cause severe side effects.

STI strategies are still highly experimental and carry risks, including the possibility that drug resistant forms of HIV will emerge during the period when treatment has been stopped. In some of these STI studies, half of the volunteers receive experimental therapeutic vaccines prior to stopping ARVs, while the other half do not. Scientists are looking to see if people given the therapeutic vaccine can wait longer before their viral load begins to increase and they have to resume treatment. If this group can wait longer before re-starting ARVs it may be because the immune defenses created by the therapeutic vaccine are helping to control the virus.

However, none of the AIDS vaccine candidates that have been tested so far for therapeutic effects have shown these types of benefits.

Research to date

Therapeutic AIDS vaccine research started in the early 1990s when several trials in the US and Europe tested therapeutic vaccines in people taking ARVs. Researchers studied blood samples from these volunteers and found that some vaccines caused very small improvements in some immune responses against HIV. However, none of these vaccines was found to improve the health of patients or slow the rate of HIV disease progression.

Today new vaccine candidates are being tested for therapeutic effects in small Phase I safety studies. These include vaccines which are also being tested in preventive AIDS vaccine trials.

It is important to note that all of these therapeutic vaccine trials are enrolling volunteers who are taking ARVs that effectively control their HIV infection. Without ARVs, the immune system is very vulnerable to the effects of HIV and it is highly unlikely that a therapeutic vaccine could provide any benefits in this situation. Used without ARVs, a therapeutic vaccine might even cause some harm by creating more targets ($CD4^+$ T cells) for HIV infection.

Post-exposure prophylaxis (PEP): *Prophylaxis means disease prevention. The goal of PEP for HIV is to prevent HIV infection by taking antiretroviral medications (for roughly 28 days) starting as soon as possible (usually within hours) after high risk contact. PEP is not 100% effective.*

Neutralizing antibodies: *Immune defenses that coat the surface of foreign invaders (such as HIV) in the blood. Neutralizing antibodies prevent the invader from multiplying itself or infecting cells.*

Immune-based therapies: *Experimental treatments or vaccines given to people infected with HIV to improve their ability to fight the virus; at present, no effective immune based therapies have been identified.*

Scientists are continuing with therapeutic vaccine research in spite of the challenges because there is still a need for strategies other than ARVs to control the virus. Therapeutic vaccines are just one example of **immune-based therapies** that could be used to build immune defenses in HIV-infected people. Even if it proves impossible to develop a therapeutic AIDS vaccine, trials of therapeutic vaccine candidates could provide clues about the types of immune defenses that are—and are not—effective in fighting HIV. These clues could be used to guide the design of future AIDS vaccines.

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International AIDS Vaccine Initiative

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IAVI is a global organization working to speed the development and distribution of preventive AIDS vaccines—the world's best hope for ending the AIDS epidemic. IAVI focuses on four areas: mobilizing support through advocacy and education, accelerating scientific progress, encouraging industrial participation in AIDS vaccine development and assuring global access.

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HOW DO AIDS VACCINES PREPARE DIFFERENT PARTS OF THE IMMUNE SYSTEM TO FIGHT HIV?

The goal of an AIDS vaccine is to produce immune defenses that try to stop HIV infection and disease. There are different ways to try to achieve this goal. This is because the immune system uses several different types of defenses to fight HIV or any other foreign invader or "pathogen" that infects the body. The unique features of these different defenses are helping to guide the design of AIDS vaccines.

Innate and Acquired Immunity

Our immune system is divided into two broad categories: "innate immunity" and "acquired immunity." Innate immune defenses are the first to respond to any foreign invader that enters the body. These defenses are also called "non-specific" or "non-adaptive" defenses; they are like a security force that patrols the body looking for unusual activity, but not a particular intruder.

Innate defenses can protect the body against some infections, but in many cases additional help is needed from acquired immunity. Acquired immune defenses are activated only after our immune system has "recognized" a particular pathogen. These specific defenses are like police tracking down a known criminal; all of their activities are directed towards a single, specific intruder.

UNDERSTANDING
the immune SYSTEM
Part 2

There are two branches or "arms" of the acquired immune system: humoral (or antibody-mediated) immunity and cellular (or cell-mediated) immunity (see Immune System *Primer,* Part 1). These two sets of defenses reinforce each other, and they use different strategies to try to prevent infection or rid the body of foreign invaders.

AIDS vaccines are designed to prepare our immune systems to fight HIV. Since a single vaccine may not be able to stimulate both cellular and antibody defenses, scientists are trying to develop the best possible candidates to stimulate each arm of the acquired immune system.

AIDS Vaccines and Humoral Immunity

Many of today's licensed vaccines, including measles, polio and hepatitis B vaccines, cause the humoral immune system to produce large amounts of antibodies. These defenses are molecules that stick to pathogens and prevent them from infecting cells or doing other damage to the body. It is thought that the antibodies produced by these vaccines play a crucial role in protection from disease.

Humoral defenses are coordinated by B cells which have "receptors" on their surface that allow them to connect with and capture pathogens as they circulate freely in the blood. These receptors also connect B cells to other immune cells, and tell the B cells that there is a new pathogen in the body. The B cell starts to multiply itself and also produce antibodies against the pathogen.

An antibody is shaped so that it attaches perfectly onto a pathogen—the way that a key fits into a lock. There are antibodies that bind to many parts of HIV. Some are called "neutralizing" antibodies because they effectively block the activity of HIV before it infects other cells.

Scientists are now trying to design vaccines that resemble antibody "binding sites" (locks) on HIV. These vaccines aim to teach B cells how to produce HIV-specific neutralizing antibodies that will then be ready to fight HIV if it ever enters the body.

Creating a vaccine that leads to the production of neutralizing antibodies against HIV is a very difficult task. The binding sites on HIV that induce neutralizing antibodies are very well hidden. Some of these sites are exposed briefly, at the moment the virus is infecting a cell; others are masked by an outer protective layer on the surface of the virus. This difficulty is the reason why only a few of the vaccines currently in clinical trials have been designed to stimulate production of neutralizing antibodies.

AIDS Vaccines and Cellular Immunity

Every cell in the body has an outer coating or "membrane." This membrane is studded with small bits of chemical information about the cell, such as what it does or what part of the body it comes from. This information is like a business name on the outside of a building; you can tell what is happening inside the building without entering it.

When a cell has been infected by a pathogen, it puts warning signals on its outer coating—similar to the way a person might lean out of a window and call for help if a building was on fire. Cellular immune defenses respond to these warning signals.

This response starts with $CD4^+$ T cells, which are sometimes called the "generals" of the immune system because they direct many other defenses. $CD4^+$ T cells use chemical messengers called "cytokines" to activate $CD8^+$ "killer" T cells that identify and kill pathogen-infected cells.

Many of the AIDS vaccines in clinical trials today have been designed to prepare cellular immune defenses. Each of these experimental vaccines is designed differently, but all use the same basic strategy: scientists start by manufacturing small molecules that mimic fragments of HIV but cannot cause HIV infection or disease. These fragments are packaged into a vaccine which is delivered into the body (usually via injection). Antigen presenting cells, including dendritic cells (see Immune System *Primer*, Part 1), patrol the body and pick up the synthetic fragments and display them on their surfaces, causing $CD4^+$ T cells to respond. The goal is to create cellular defenses that will react quickly and powerfully if HIV ever enters the body.