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RESEARCH & TRIALS

◆ Kenya tries new viral-load test

Thirteen health organizations in Kenya will be using a new method to measure viral load in HIV-infected people. The company that manufactures the test, Sweden-based Cavidi Tech AB, claims this is an "affordable" test. Viral load tests measure the amount of HIV present in an infected person. This new test is called the ExaVir Load test and it measures the amount of the HIV protein reverse transcriptase in a blood sample, which is related to the number of virus particles.

Viral load counts are important in determining the stage of HIV infection, and in determining whether an infection is being treated successfully with antiretroviral drugs or if the virus has become resistant to the treatment. Unfortunately in many places these tests are prohibitively expensive. The equipment for the ExaVir Load test is being supplied to the health centers free of charge for one year through a partnership with the Swedish International Cooperation Development Agency.

◆ Vaccines against cervical cancer show protection

Two vaccine companies, Merck & Co. and GlaxoSmithKline (GSK), are racing to get approval for their vaccines against human papillomavirus (HPV). HPV is transmitted sexually and causes genital warts in men and women, and can cause cervical cancer in women. About 99% of all cases of cervical cancer are caused by HPV. Fifty percent of cervical cancers are from a virus strain called HPV 16, while another 25% are from HPV 18. A vaccine that protects against HPV 16, 18, and other strains is likely to nearly eliminate cervical cancer if widely distributed to uninfected women.

In October researchers from Merck reported that their vaccine against HPV 16 protected 94% of vaccinated women against infection. Merck is developing another version of the vaccine that will protect against HPV 18 and other strains.

GSK's HPV vaccine covers the two major HPV strains, 16 and 18. In clinical trials the vaccine gave women 100% protection against infection with these two strains.

More than half a million women worldwide are diagnosed with cervical cancer each year, and every year nearly 300,000 women die of this cancer. In most of the world cervical cancer screening is not done on a regular basis. A multistrain HPV vaccine given before a girl becomes sexually active should prevent her from becoming infected with HPV. It is still likely to be a few years before an HPV vaccine is on the market.

GLOBAL NEWS

◆ Global Fund short of finances

There are fears that the Global Fund to Fight AIDS, Tuberculosis and Malaria will come up almost US$2 billion short of its goal to fund new projects in 2005. Such a shortfall could be catastrophic, noted Richard Feachem, Executive Director of the Global Fund. To date, the Fund notes that it "has so far committed $3 billion to over 300 programs in 128 countries." More than 50% of this money is for HIV/AIDS programs.

Funding has come up short this year partly because the US government has withheld $120 million of its planned contribution to the Fund and also has just cut its 2005 pledge by $200 million over its 2004 donation. Its total contribution for 2005 will now be $350 million. Germany has doubled its pledge to the Fund to $108.5 million for 2005.

◆ Europe urges international cooperation on AIDS vaccine research

In mid-October representatives of seven European countries and the European Union called for international coordination and collaboration in developing a vaccine against HIV. Concerned about the scale of the epidemic and the "necessity" of a vaccine, the health ministers or their representatives from the UK, France, Germany, Italy, the Netherlands, Spain, Sweden, and the EU urged that researchers work cooperatively to accelerate AIDS vaccine candidates through research and clinical trials. Although they did not promise additional funding for the endeavor, the group was anxious to adopt a unified position before attending the G8 meeting in Washington, DC later in the week. France advocated that Europe should take a leading position in the development of an AIDS vaccine.

SPOTLIGHT

◆ Women in AIDS vaccine clinical trials: Making sure they're comfortable participants

In the more than 20 years since it was first identified, the HIV/AIDS epidemic has changed. What was first described as an infection of gay men in developed nations has become a disease that increasingly affects women worldwide. Today, younger women are more likely to be infected than younger men. In sub-Saharan Africa women now make up more than 57% of the people infected with HIV, and 76% of people aged 15-24 infected with HIV.

Biological and social factors may increase women's vulnerability to HIV/AIDS infection. Some studies have indicated that because of biological differences between the female and male genital tracts, women may become infected more readily than men do. But social issues are probably even more important in increasing women's vulnerability to HIV infection, particularly young women's. In many societies women have unequal power in sexual relations so they are often unable to negotiate condom use, may be forced into relationships with older men, and may be victims of domestic violence and rape. It is therefore essential that any effective AIDS vaccine protects women and girls, as well as men, from infection.

Test to know

The only way to know if a vaccine will work the same way in women and men is to test the vaccine in both. A sufficient number of women must be included in AIDS vaccine clinical trials so that if there is any difference in protection between men and women it will be obvious from the trial results. There are hints that vaccines against other diseases may work differently in women and men. A vaccine against herpes simplex virus-2 (which causes genital lesions) was 75% effective in preventing symptoms of genital herpes in women in a Phase III clinical trial, but it did not protect men at all. Additional studies are now taking place to see if this is a true effect or just a result of too few women in the trial. A vaccine against human papillomavirus (which can cause cervical cancer) is only being tested in women at this time (see *Spotlight*, August 2003.)

Importantly, for any AIDS vaccine to be licensed by governmental authorities there must be enough information on the immune responses of both sexes. Testing vaccine candidates in women as well as men will also improve the acceptability and accessibility of these products.

Problems facing recruitment

Studies in Africa of the **prevalence** of HIV within the population have more female participants than male. But AIDS vaccine clinical trials are not the same. In a prevalence study a healthcare worker simply takes a blood sample and then tests it for antibodies against HIV. AIDS vaccine trials administer the vaccine candidate and then study the volunteer's immune responses over time. Just to be on the safe side, volunteers are asked not to be pregnant or breast-feeding during the trial. This is standard practice for most drug and vaccine clinical trials. Trial participants are also counseled to use barrier methods, such as condoms, to prevent getting HIV or other sexually transmitted infections.

Asking women not to become pregnant during a trial is a huge request for many. Avoiding pregnancy is not a decision that women in many cultures can make on their own. A woman's ability to conceive a child and her role as a mother may be paramount and may be related to a woman's value to her society and family—the decision may rest with her husband, other male family members, or the family as a whole. This is probably one of the biggest barriers to recruiting more women into AIDS vaccine trials.

In some cases women express concerns about the vaccine itself: is it safe for them personally and will it affect future pregnancies? They may also be concerned that participation in an AIDS vaccine trial might stigmatize them in their community. It may be impossible to keep such participation confidential, especially in rural villages and small communities where everyone knows everyone else.

Another major issue in many societies in convincing women to participate in an AIDS vaccine clinical trial is their lack of empowerment, which may mean they are not able to independently take such decisions. Their unequal relationship with men may extend outside the family and throughout the society, so a community elder may influence the decision to participate in a trial. And because a woman may not be viewed as an equal to a man within

Prevalence: The number of cases of infection in a population at a given time. This figure is generally given as a percentage or as the number of cases per 100,000 people.

her society, she may find it difficult to question or disagree with the medical team conducting the trial, especially if the team is predominantly male. She may therefore not be able to give truly informed consent.

Poverty may be an added problem. In some cases, as occurs in developed countries like the US, poverty may require that a woman relocate to another area away from the vaccine trial site. In this case, she may now be too far away to contact the people conducting the trial or she may leave no forwarding address so that she cannot be contacted. In a developing country, her lower socioeconomic status could mean she is in a migratory job or that she cannot afford to lose her daily wages to attend the clinic. She may have the added responsibilities of childcare, care of elderly family members, or general household responsibilities that may make it difficult to keep clinic appointments. She may not be able to visit the trial site unless there is childcare available at the site.

Information collected during clinical trials is always confidential. But a woman may still fear that someone will find out her HIV status (which will be tested a number of times during the trial), infection with other sexually transmitted infections, and information on her sexual partners.

Creating a comfort zone

Women have been more than willing to participate in AIDS vaccine clinical trials in the US. Women who have a low risk of becoming infected with HIV, who may be in long-term, stable relationships and are not injecting drug users, join trials because they want to help other people. In both developing and developed countries, women at higher risk of becoming HIV infected do so for similar reasons but also because they appreciate the help with health problems and the counseling and advice on protecting themselves from HIV and other sexually transmitted infections.

For women in developing countries or in any environment where healthcare is not optimal, participation in a clinical trial has advantages. Participants have access to better-trained physicians and better-quality counseling.

A unique strategy that has been successful in bringing women into AIDS vaccine clinical trials offers trial participation to women not infected with HIV whose partner is HIV infected. These are known as discordant couples. These couples usually have very close and supportive relationships and are willing to attend HIV testing and counseling together.

Treating participants well

In places where women are not treated as equals or where HIV infection carries a stigma, it is especially important that the women are treated as equals by the clinic staff. Gender sensitization training for clinic staff members can assist them in understanding the realities of women's lives and creating a comfortable environment for women. Having female staff members may also help put them at ease.

The location and facilities of the clinic must be considered. It should be in a place that participants can easily get to and should make the trial participants comfortable. It should have areas for women and children and childcare should be available. Appointments should be offered at hours that are convenient for the trial participants.

Staff members should be alert to problems outside of HIV infection, such as whether a woman has been a victim of domestic violence or has other problems at home.

In some cases, making the woman feel important and cared for may require giving her a small stipend to cover her travel costs, or making food and drink available at the clinic.

Working with the community is very important to ensure cooperation. Community leaders should be kept informed from the very beginning so that there is full cooperation. Working with community groups—athletic teams, clubs, social groupings—may increase community participation.

Although 5-10,000 women have participated in AIDS vaccine trials throughout the world, in some places these trials are relatively new. With more social research on the factors that would encourage women to participate in these trials and as more trials progress, scientists will have a better idea of what to do to guarantee that women are well represented in AIDS vaccine trials. Encouraging women to participate will ensure the development and acceptability of a vaccine that will protect and be accessible to women as well as men.

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

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.

HOW ARE VACCINE IMMUNE RESPONSES STRENGTHENED?

PRIMER
UNDERSTANDING
Vaccine
Adjuvants

Vaccines work by stimulating the immune system to produce antibodies and immune cells that recognize the antigens—foreign proteins—in the vaccine. These antigens are normally found in harmful pathogens (viruses and bacteria) which cause disease. The idea is to prepare the immune system so that if a person is exposed to the pathogen later, the immune system can respond and prevent an illness from developing.

The immune system has two separate arms (see *Primer*, March 2004). One arm is responsible for the cell-mediated response. In this arm, certain kinds of immune cells called killer T cells are produced that can destroy infected cells. These killer T cells are sometimes called $CD8^+$ T cells. Another kind of immune cell is the helper T cell, and these cells help coordinate the other parts of the immune response. Helper T cells are sometimes called $CD4^+$ T cells and are what are measured when people refer to "CD4 cell counts" in HIV infection.

The second arm of the immune response is called the antibody or humoral response. Here, B cells recognize the antigen and produce antibodies that can attach to it. When these antibodies attach to the antigen on the pathogen they "neutralize" it. This means that the pathogen can no longer infect cells and cause infection.

Once T or B cells have been exposed to a foreign antigen, they produce memory cells that remember that antigen (see *Primer*, February 2004). If the pathogen with that antigen enters the body at a later time, these memory cells can respond quickly and strongly to stop any infection and disease. So, for example, if someone who has been vaccinated against measles is exposed to the measles virus, his or her body will immediately recognize the virus and will destroy it.

Helping hand

But most antigens in vaccines do not stimulate the immune system enough on their own, they need a helping hand. This extra help can be provided by compounds called adjuvants. Different adjuvants can increase the strength of the immune response in a number of different ways. After a vaccine is injected, over time it is cleared away by the body. Some adjuvants can increase the amount of time that the vaccine antigen remains at the injection site, allowing the immune system to respond for longer and more strongly. It is a type of sustained-release mechanism, a so-called "depot effect."

Other adjuvants can cause helper T cells and other immune cells to become active by "showing" (or presenting) the vaccine antigen in a better way. Since helper T cells help coordinate many other parts of the immune response, adjuvants that work this way can strengthen killer T cell and antibody responses to the vaccine antigen. Other adjuvants work by causing a granuloma to form. This is a mass of cells loaded with other immune cells called macrophages. Macrophages work by presenting foreign antigens to other immune cells so that they can recognize it and make an immune response. In addition, some adjuvants can stimulate immune cells to produce factors called cytokines. These cytokines can then act on a variety of immune cells to produce more antibody or stronger immune cell responses.

Adjuvants and AIDS vaccines

Although scientists do not know if an AIDS vaccine will need an adjuvant, it is likely that it will. Some licensed vaccines against other diseases contain whole viruses or whole bacteria in them. But the kinds of vaccines that will be used against HIV will contain only portions of HIV's genetic material, to ensure that it is safe (see *Primer*, September 2004). These portions will probably not be as good at causing an immune response as the whole intact virus would be. Because of that, AIDS vaccines will likely need adjuvants to help make the immune response stronger.

The most commonly used adjuvants are aluminum (alum) based compounds—for example aluminum hydroxide. This has been used in billions of doses of vaccines for other diseases and is effective at increasing the length of time an antigen is present, from days to as much as weeks. Recent studies on aluminum hydroxide adjuvant show that it stimulates the production of specific types of immune cells called antigen presenting cells (APCs). These APCs pick up the antigen and present it to T cells.

Various adjuvants are now being tested or considered for use with candidate AIDS vaccines. These range from adjuvants designed to act on specific parts of the immune response to bacterial protein adjuvants which will stimulate immune cells more generally.

Mixtures of adjuvant compounds are becoming increasingly popular. Among these is a mixture of MPL (monophosphoryl lipid A) plus alum, called AS04. It is now being tested in Phase III clinical trials, the large clinical trials that test the safety and effectiveness of a vaccine. AS02 is an adjuvant that contains an oil-in-water mix and MPL plus saponin, a plant extract. A malaria vaccine with AS02 has demonstrated promise in a recent efficacy trial, a study which showed actual protection against disease.

Toll-like receptors (TLRs) are areas on various immune cells that "sense" the initial presence of pathogens by attaching to it. Once TLRs have attached to a pathogen a whole range of inflammatory and immune responses involving many cells are set in motion. New adjuvants are being developed that target different TLRs and will activate only certain parts of the immune response.

Because AIDS vaccines will be unlike most other vaccines that have been licensed, specifically targeted adjuvants may lead them to produce a stronger, longer-lasting immunity.