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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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RESEARCH & TRIALS

Microbicide Trials Set to Begin

An AIDS vaccine is one experimental approach to preventing HIV infection; a microbicide is another. A microbicide is a topical cream, gel, ointment or suppository that could be used vaginally or rectally to protect against sexual transmission of HIV. No effective preventive microbicides that protect against HIV have been developed yet - like AIDS vaccines, all microbicide candidates are still in various stages of experimental evaluation. By the end of 2005, as many as five large-scale trials of six microbicide candidates could be underway (see below). To learn more about microbicides see this month's *Spotlight.*

GLOBAL NEWS

New Prevention Technologies Highlighted During Transfer of EU Presidency

On 24 June 2004, a one-day conference titled *New Preventive Technologies: Providing New Options to Stop the Spread of HIV/AIDS* was held in Dublin to mark the transfer of the European Union presidency from Ireland to the Netherlands. Ireland is an active supporter of both AIDS vaccine and microbicide research (through IAVI and the International Partnership for Microbicides). The focus of the meeting marked the hope that these issues will continue to receive attention during the following Presidency. Speakers at the conference included Kapil Sibal (Minister of Science and Technology, India), Tom Kitt (Minister for Development Cooperation, Ireland), Zeda Rosenberg (CEO, IPM) and Seth Berkley (CEO and President, IAVI). After the meeting, Kitt said that they had "agreed on priority actions to improve and speed up the development of urgently needed new preventive technologies such as HIV vaccines and microbicides."

Group of 8 Leaders Endorse Proposed AIDS Vaccine Enterprise ▸

Planned or ongoing microbicide efficacy trials: 2004-2005

Product (class)	Primary research group	Proposed start date	Sites and sample size
BufferGel (acid buffer) PRO 2000 0.5% (polyanion)	HIV Prevention Trials Network	September 2004	3,100 women at 8 sites (Malawi, South Africa, Zimbabwe, Zambia, Tanzania, India, USA)
Cellulose sulfate (polyanion)	Global Microbicide Project	Q4 2004	2,574 women at 6 sites (Benin, Burkina Faso, Kenya, India, South Africa)
Cellulose sulfate (polyanion)	Family Health International and Global Microbicide Project	June 2004	2,160 women at 2 sites in Nigeria
Carraguard (polyanion)	Population Council	March 2004	6,300 women in South Africa
PRO 2000 2% (polyanion) Dextrin-2-sulfate (polyanion)	UK Microbicides Development Programme	Q1 2005	~12,300 women in Uganda, Zambia, Tanzania, Uganda
SAVVY (surfactant)	Family Health International	March 2004	2,142 women, 2 studies combined (Nigeria, Ghana)

The leaders of the Group of Eight (G8) nations have endorsed the establishment of a global AIDS Vaccine Enterprise to help enhance international coordination, information sharing and collaboration in the development of an AIDS vaccine. The G8 nations are the United States, Britain, France, Germany, Italy, Canada, Russia and Japan.

The concept for a global vaccine enterprise was first proposed in a paper published in *Science* magazine in June 2003 by an international group of leading AIDS experts organized by the Bill & Melinda Gates Foundation.

The G8 issued its statement of support on 11 June 2004 during their most recent meeting. The statement calls for the Enterprise to "establish a strategic plan that would prioritize the scientific challenges to be addressed, coordinate research and product development efforts, and encourage greater use of information sharing networks and technologies. This plan should serve as a blueprint for helping to align better existing resources and to channel more efficiently to the needs at hand new resources as they become available."

Key AIDS vaccine stakeholders are already working to develop the strategic plan for the proposed Enterprise. The final document will be based on the recommendations of the five working groups formed during an August 2003 meeting held by the Bill & Melinda Gates Foundation to help develop firm objectives and activities.

◆ New Report Urges More AIDS Prevention Along With Treatment

Prevention programs and research must be strengthened and expanded alongside of antiretroviral treatment (ART) initiatives, says *HIV Prevention in the Era of Expanded Treatment Access*, a report from the Global HIV Prevention Working Group that was released in early June. The Working Group is a panel of nearly 50 leading public health experts, clinicians, biomedical and behavioral researchers, and people affected by HIV/AIDS that is organized by the Bill & Melinda Gates Foundation and the Henry J. Kaiser Family Foundation.

This is the third report issued by the group and its focus reflects the increased attention to and funding for ART programs around the world. The report celebrates these programs as a welcome and long-overdue response to the AIDS pandemic and says that "the world has a unique opportunity, as ART programs are launched and expanded, to simultaneously bolster prevention efforts." This is because in many regions ART programs decrease HIV-related stigma and increase people's willingness to learn their HIV status at voluntary counseling and testing (VCT) centers, a crucial entry point for both prevention and treatment programs.

The new ART programs may also create a new climate for AIDS prevention. The report notes that in some settings in the industrialized world, ART programs can alter people's perception of the risk associated with HIV and can lead to increased risk behavior. There is therefore an urgent need for innovative, integrated programs that provide both prevention and treatment and enable better access to both types of services. The report estimates that globally fewer than one in five people at high risk of infection have access to proven prevention interventions, including HIV counseling and testing, male and female condoms, treatment for sexually transmitted infections, harm reduction programs for injecting drug users, and mother to child transmission prevention programs.

The report also calls for funding for AIDS vaccine and microbicide research to double by 2007.

To read a copy of the full report:
www.kff.org/hivaids/hivghpwgpackage.cfm

SPOTLIGHT

◆ Update on Microbicide Research

The AIDS vaccine field faces many unique scientific hurdles but still it is closely tied to treatment and other areas of AIDS research. In particular, the AIDS vaccine field has much in common with the field of microbicide research, which is seeking to develop an effective gel, cream or suppository that could be used vaginally or rectally to prevent sexual transmission of HIV.

AIDS vaccines and microbicides are both being developed because of the urgent need for new prevention strategies in addition to existing interventions like male and female condoms and clean needles. AIDS vaccines and microbicides could both be powerful prevention strategies for women, who are infected with HIV through sexual contact at high rates often because they cannot negotiate condom use with their partners.

At present there are no effective preventive AIDS vaccines or microbicides, but the next few years will bring several large-scale efficacy trials of candidates. Some of the planned (see *Research and Trials*) and future microbicide trials will take place in the same countries, and perhaps the same communities, as vaccine trials. This increases the importance of coordination between the two fields to share resources like laboratories and clinics and to collaborate on outreach and education campaigns.

Measuring microbicide efficacy

Large-scale microbicide efficacy trials share similarities with AIDS vaccine efficacy trials (see *VAX* August 2003 and May 2004). In both cases, the candidate is tested in a population with a known rate of HIV infection or 'incidence rate.' Microbicide trial volunteers are randomly assigned to different groups, with one group receiving the experimental candidate while the other receives an inactive "placebo" gel. In some trials there is also a group that is "randomized" to a condom-only arm. All groups receive intensive ongoing counseling on the importance of using condoms and on the fact that none of the women receiving gel should assume that they are protected against HIV infection.

Trial volunteers are monitored and receive regular HIV tests over the course of the trial. At the end, researchers analyze the data to find out if the incidence rate was lowered among women who used the microbicide candidate. Neither the trial staff nor the volunteers know who has been assigned to receive the microbicide candidate or the placebo until the study is over.

For a microbicide to provide protection it will have to be used correctly (e.g., in the right volume and at the right

time) and consistently over time. One of the key challenges in designing microbicide efficacy trials is how to measure frequency and consistency of use. This is important because even a very effective microbicide will not provide protection if it is used incorrectly. If many trial volunteers did not use the candidate regularly and correctly then it is possible that a candidate with some protective benefit would appear to be ineffective at the end of the study.

Microbicide trial sponsors are using a variety of strategies to measure and ensure consistent use. In some instances sponsors are conducting short pilot studies in which women are given intensive counseling and education about proper use of the candidate. These pilot studies can be used to identify women who are likely to use the gel consistently throughout the trial and to develop education and information strategies that can increase consistency of use. Researchers also use diaries, interviews and questionnaires to gather information about use over the course of the trial.

The need to gather data on consistent use also affects the length of the trial since it is possible that use may become less consistent over time. Most microbicide trials are also relatively short, often following women for only 12 months.

In contrast, AIDS vaccine trials may ask for a two to three year commitment from volunteers and may involve several years of follow up for volunteers who become infected with HIV through high-risk sexual behavior, to learn more about how a vaccine affects the course of HIV disease. Microbicides do not affect the immune system and are not expected to modify the course of HIV disease, so microbicide trial volunteers who become HIV infected are not involved in long-term follow up. Trial sponsors in both fields are working to ensure that all HIV-infected volunteers have access to antiretroviral (ARV) treatment when needed.

The rationale for upcoming trials

Four out of the six candidates in the planned microbicide efficacy trials are from the same "class" of compound, and several of the trials involve similar or identical candidates. At first glance this may seem strange: given the cost and complexity of mounting a large-scale trial, why would product developers conduct two trials of the same candidate? The answer lies in part with the regulatory guidelines for microbicide development that were recently issued by the US Food and Drug Administration (FDA). The guidelines describe the types of information that the FDA would like to see in an application for licensure and approval if a candidate does show efficacy in a large-scale trial. Sometimes this will require more than one trial. Also, some studies are using slightly different formulations of the same microbicide candidate.

It is important to remember that the FDA only issues guidance for products to be used in the US. Additional or alternative regulatory agencies will also be involved in approving microbicides for use in other countries, particularly resource-poor countries which may have limited regulatory capacity. The World Health Organization and the European Agency for the Evaluation of Medical Products recently announced plans for a collaboration that would provide regulatory review for new medical technologies (including microbicides and vaccines) at the request of developing countries.

New approaches to next generation candidates

As the microbicide field prepares for large-scale trials of current candidates it is also looking for new approaches to blocking sexual transmission of HIV (see *Primer*). Recent scientific advances have allowed researchers to pinpoint the types of cells that HIV infects during male-to-female sexual transmission. This knowledge is guiding the design of new candidates that could block some of these virus-cell interactions.

Some of these candidates are called "co-receptor blockers" and they prevent HIV from attaching to molecules, or "receptors," that cover the surface of cells so that the virus cannot enter and infect the cells. Another approach uses ARV drugs in a gel formulation. These drugs are very similar to those used to control HIV in people who are already infected with the virus. There are also plans to test combinations that contain compounds with different modes of blocking viral activity. Many microbicide researchers think that the highest levels of protection will be achieved with a combination approach.

In the future an effective preventive microbicide could also be used in combination with an AIDS vaccine. In both cases the first effective products are not likely to provide complete protection against HIV infection when used alone. But used together they might be able to significantly reduce vulnerability to HIV infection in situations where it is not possible to use a condom.

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HOW DOES SEXUAL TRANSMISSION HAPPEN AND HOW CAN IT BE BLOCKED BY VACCINES OR MICROBICIDES?

Globally, 80% of the 40 million people now infected with HIV acquired the virus through sexual contact with an HIV infected partner. The vast majority of these infections occurred as a result of vaginal or anal sex without a condom (although there are extremely rare reports of HIV transmission through oral sex). It is important to remember that not all forms of intimate contact transmit HIV; the virus cannot be transmitted by kissing, hugging or holding hands.

When used correctly and consistently, male and female condoms are highly effective at preventing the transmission of HIV. More than half of the estimated 14,000 new infections every day worldwide occur in women, who often cannot negotiate condom use with their partners. Addressing social issues including poverty, gender stereotypes, women's lack of education and autonomy can help prevent HIV infections. But there is also an urgent need for additional prevention strategies like vaccines and microbicides that could be used by both women and men to help protect themselves against HIV infection.

Condoms are a simple barrier method that work by preventing contact with bodily fluids containing HIV (semen or vaginal secretions). But blocking infection with a vaccine or a microbicide is a far more complicated task and both areas of research are now carefully studying the biology of sexual transmission.

PRIMER

UNDERSTANDING

the sexual transmission of HIV

Studying sexual transmission

Until relatively recently there was very little information about the early biological events in sexual transmission. This is because it is impossible to identify the exact time of HIV transmission and extremely difficult to study the tissues in the genital tract. Scientists have developed systems for studying these early events of sexual transmission. One system called the "cervical explant model" uses small pieces of human cervical tissue (obtained from healthy women undergoing hysterectomies) that can be maintained in a healthy state in a laboratory "culture" system. Scientists can also study the infection of various types of cells found in the genital tract. They also study early events of sexual transmission with SIV (the monkey version of HIV) in non-human primates.

CURRENT UNDERSTANDING

Physical barriers and immune defenses

For someone to become infected during sexual contact, the virus must cross a physical barrier: either the skin covering the penis or the mucosal membrane lining the vagina and cervix. In addition to these physical barriers there are also mucosal immune defenses (including immune cells and antibodies) that work with the physical barriers to protect the body from foreign invaders, or "pathogens."

Together these defenses do provide some protection against HIV. We know this because HIV does not infect 100% of the people who are exposed to the virus during a single act of unprotected sex. Instead, the risk of transmission varies widely depending on many contributing factors, including the type of sexual contact (e.g., anal or vaginal sex), sexually transmitted infections (STIs) other than HIV, and the amount of virus in the semen or vaginal secretions of the infected partner. However it is very important to remember that no one can accurately estimate the likelihood of infection at any given time and that every sexual contact has the potential to transmit HIV infection.

Target cells

Sexual transmission starts when HIV infects immune cells in the genital tract or rectum. Much of the research on early events of sexual transmission focuses on the mucosal immune defenses, which include $CD4^+$ T cells, dendritic cells (DCs), and macrophages.

The surface of these cells is covered with molecules called "receptors" which allow the cells to interact with each other and with pathogens. HIV uses different receptors to enter these cells, including CD4 and CCR5 for T cells and DC-SIGN and mannose receptor for DCs.

DCs in the genital tract can pick up HIV and carry it to the lymph nodes, which are hubs of immune activity in the body. Once HIV reaches the lymph node it rapidly infects $CD4^+$ T cells and establishes "systemic" infection, meaning that the virus can be found in the blood and throughout the body.

Role of STIs and bacterial infections

Studies have found that people who are infected with STIs other than HIV (herpes, Chlamydia, gonorrhea, syphilis and others) are at greater risk for becoming infected with HIV. Also, people who are already infected with HIV and have other STIs and/or bacterial vaginosis often have high levels of HIV in their semen or vaginal secretions, and this may make them more infectious to their sexual partners.

There are several explanations for why these infections increase the risk of transmitting or acquiring HIV infection. Some STIs (e.g. herpes simplex virus type 2) can cause genital ulcers that make it much easier for the virus to cross the body's physical barrier and reach its target cells. These infections also cause increased immune activity in the genital tract and various aspects of this may actually increase the risk of HIV infection. For example, some STIs can increase the number of activated $CD4^+$ T cells that are key targets for HIV infection.

Diagnosing and treating STIs and bacterial infections in men and women—whether they are HIV-infected or -uninfected—is an important part of AIDS prevention.