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In this issue

SPOTLIGHT

◆ Preventing mother-to-child transmission

More than a decade ago, researchers first found that antiretroviral (ARV) drugs given to women during childbirth could greatly reduce the risk of HIV transmission to their babies. Yet children are still acquiring HIV at an alarming rate. A 2004 report from the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimated that 630,000 children worldwide were newly HIV-infected in 2003.

The transmission of HIV from mother-to-child can occur at three points: during pregnancy while the baby is still in the womb; during childbirth; or after birth from exposure to HIV-infected breast milk. Exactly how infection occurs at each of these points is unclear, but ARVs can help prevent a mother from transmitting HIV to her baby at each stage. In 1994, zidovudine (AZT) was the first drug found to reduce the risk of mother-to-child transmission of HIV. AZT was also the first drug approved by the US Food and Drug Administration as a treatment for HIV infection. Mothers who took AZT from early in pregnancy through childbirth could reduce transmission rates to as low as 8% after 18 months if they did not breast feed (PACTG 076), compared to a 25% transmission rate for those not taking AZT.

Another large study found a simpler way of lowering the risk of HIV transmission to newborns. HIVNET 012 was the name of a trial that took place in Uganda with the ARV nevirapine and concluded that just a single-dose given to the mother during labor and a single-dose to the baby (within three days of birth) was also effective at lowering the baby's risk of acquiring HIV. The rate of transmission after 12 months in breast feeding women was 16% with this course of treatment compared to rates upwards of 25% in those not taking nevirapine. Researchers hailed this approach because it was relatively simple to administer and successful at preventing transmission.

"Single-dose nevirapine gave countries overwhelmed by the problem of mother-to-child transmission the ability to start services. These services have provided the foundation for treatment access," said James McIntyre of the University of Witwatersrand in Johannesburg at a major HIV scientific conference held recently in the US.

Nevirapine remains the cheapest and most available method for preventing mother-to-child transmission (PMTCT) of HIV in many countries. But it is not the perfect solution. There is evidence that taking nevirapine only during pregnancy can negatively affect the mother's response to ARVs later on because it allows the virus to develop resistance to this type of drug. A single-dose of nevirapine is also unable to protect babies from HIV infection through breast feeding, which is responsible for many new infections in children.

Also, several other trials have since shown that combinations of ARVs can reduce risk of transmission even further. For these reasons, clinicians in Africa are calling for newer approaches to become available so that mother-to-child transmission can be eradicated.

Creating access and demand

Many countries have designed and implemented national PMTCT programs but the treatments offered can vary greatly by country due to the availability and cost of ARVs. The options can even vary by city. Thailand was one of the first countries to adopt a nationally-supported PMTCT program and now offers a short course of AZT plus single-dose nevirapine to mothers during the last weeks of pregnancy and childbirth and to the baby at all public hospitals. This program prevents 2,600 new pediatric HIV infections every year.

But in some countries where PMTCT programs are available, it is estimated that only 3% to 10% of women who are in need will access them this year. The lack of uptake occurs for many reasons. In some countries women cannot access programs in rural

areas because services are not yet available. Some women may not find out they are HIV-infected until after childbirth. Others may not use any healthcare services at all during pregnancy and therefore miss the chance for PMTCT entirely. "Many women deliver at home and may not ever have the chance to benefit from a simple yet effective intervention," says Chrispin Kambili, IAVI's Regional Medical Director in Kenya.

In addition to getting more women access to PMTCT programs, physicians are also concerned with improving available treatments. In South Africa the only course of treatment nationally recommended for PMTCT is a single-dose of nevirapine. This is a controversial issue in countries like South Africa that are currently improving access to ARVs, according to Glenda Gray, Director of the Perinatal HIV Research Unit in Soweto, South Africa. Despite the simplicity of using nevirapine, taking this drug during childbirth could compromise a woman's response to ARV treatment with other drugs in the future.

After a single-dose of nevirapine during childbirth HIV can develop resistance to this drug that can last from several months to over a year. If a woman is placed on combination ARV therapy with nevirapine or a similar ARV soon after receiving single-dose nevirapine to prevent transmission to her baby, this resistance can result in a poorer response to treatment. Though all ARVs are associated with resistance, it is easy for HIV to develop resistance to nevirapine and other ARVs in the same class. Once this happens the drugs do not work as well against the virus.

Information about how many HIV-infected women will have virus that develops resistance after a single-dose of nevirapine varies between studies. The most recent reports suggest that as many as two-thirds of women in clinical trials may have resistant virus after receiving one dose of nevirapine. But the precise effect this resistance will have on future treatment is unknown.

A recent study by Gray and colleagues provides some of the first information on how resistance to nevirapine affects transmission rates during second pregnancies. This study suggests that single-dose nevirapine is still beneficial for PMTCT during a second delivery.

Apart from potential resistance problems, nevirapine has proven a safe and effective PMTCT drug. The side effects that are associated with long-term use of nevirapine—including possible liver damage—are not a problem when used as a single dose.

Moving beyond nevirapine

To avoid the development of resistant HIV in mothers, researchers set out to find better PMTCT treatments. Treating women with more than one ARV is one way to minimize the development of resistance. One approach is to give mothers a combination of nevirapine and Combivir (AZT and a similar drug called 3TC) during delivery, and Combivir alone to both mothers and babies for a week after childbirth. This can reduce the rate of HIV resistance and lower the HIV transmission rate to below 5%.

According to Gray this course of treatment is the next best thing to putting mothers on a combination of ARVs known as HAART (highly active antiretroviral therapy). Women receiving HAART will have a lower **viral load**, which is the best way to prevent babies from acquiring HIV. Mothers on this treatment have only a 2% chance of transmitting HIV to their babies. Gray hopes the South African government will adopt the nevirapine and Combivir approach for PMTCT in the absence of HAART.

"For us, nevirapine was a good place to start, but we need to move with the times. It is not eradicating pediatric AIDS cases. We should accept nothing less than complete eradication. Anything else is a compromise," she says.

The positive results from recent studies using combinations of drugs have renewed interest among researchers and activists to convince governments to offer treatments that are more effective. The Elizabeth Glaser Pediatric AIDS Foundation recommends single-dose nevirapine as a part of PMTCT programs only in places where there is no other option. The foundation recently released a statement after meeting with leaders in this field and referred to single-dose nevirapine as the "absolute minimum" all women should receive.

Researchers are also emphasizing the need for research into newer drugs to prevent children from contracting HIV. A newer ARV called tenofovir is a promising candidate for PMTCT because it is unlikely to cause resistance and would be easier to administer during childbirth than a combination of drugs. Trials to test its efficacy for PMTCT are still in the planning stages.

Limiting transmission through breast feeding

Researchers are also looking at interventions that can protect babies from becoming infected with HIV during breast feeding. The drugs administered during labor can only partially prevent transmission during the breast feeding period. It is estimated that half of all new pediatric HIV cases in 2003 occurred at this stage. The quantity of HIV in breast milk depends on a woman's viral load. In general, about 80% of breast milk samples from HIV-infected mothers contain the virus.

The most effective approach to avoid transmission through breast milk is to use infant formula for feeding. In more urban areas, women are likely to accept this as an alternative. The South African government provides formula free to HIV-infected mothers for the first six months, which is a relatively short time to transition to solid food. The government of Thailand provides new mothers with enough formula for the baby's first year.

This solution may be impractical in rural areas where women may lack the clean water necessary to prepare formula. Others choose not to use formula to avoid being stigmatized as HIV-infected within their community where breast feeding is more common. For women who breast feed, extended treatment with ARVs and early weaning can help lower the baby's risk of acquiring HIV. "Opportunities exist to

Viral load: A measure of the amount of virus in a blood sample. HIV viral loads refer to the number of copies of virus found in one milliliter of blood plasma.

stop transmission of HIV through breast feeding and should be used," says Gray.

Ideally all women would receive a combination of ARVs when they discover they are infected and this could prevent them from transmitting HIV to their babies during pregnancy, delivery, and throughout breast feeding. This is the goal in countries where treatment programs are becoming more widely available. "There should be no reason why women in South Africa don't receive combination therapy," says Gray.

RESEARCH & TRIALS

◆ New vaccine trial enrolling in New York

The Aaron Diamond AIDS Research Center (ADARC) in New York City and University of Rochester Medical Center at Rochester, NY recently began enrolling volunteers for a Phase I vaccine trial. The trial will test the safety and immunogenicity of a vaccine candidate in 48 healthy volunteers.

The vaccine candidate is called ADMVA and is based on a Modified Vaccinia Ankara (MVA) viral vector. This vector is developed from a virus that is similar to the virus used for the smallpox vaccine.

This vaccine candidate was developed at ADARC and contains genes from clade C HIV, which is prevalent in China, India, and sub-Saharan Africa. "We're particularly excited about this. The epidemic in China is burgeoning and really the only hope for some people is a vaccine," says Sarah Schlesinger, a Research Associate Professor at ADARC, a partner of IAVI and Rockefeller University.

◆ Larger trial of adenovirus AIDS vaccine begins

A Phase II trial of an AIDS vaccine candidate developed by the US-based company Merck began enrolling 1,500 volunteers in December at sites in the US and Canada. Enrollment will continue in the coming months in Peru, the Dominican Republic, Haiti, Puerto Rico, and Australia.

The vaccine candidate uses an adenovirus called Ad5. In its natural form adenovirus can cause severe colds but a weakened version is used to make the vaccine. The adenovirus vector delivers three different HIV genes to the immune system. None of the vaccine components can cause HIV infection. For more about the use of this viral vector see the *Primer* in this issue.

Scientists are hopeful that the vaccine will cause the immune system to raise a strong response against HIV by producing killer T cells to attack HIV-infected cells. The trial is the first large-scale study to test the ability of this vaccine candidate to protect people from infection with HIV. The study will also follow volunteers who later become infected with HIV during the trial follow-up period (four and a half years) to see if the vaccine can help control disease progression.

GLOBAL NEWS

◆ India's first AIDS vaccine trial begins

India began enrolling volunteers for the country's first preventive AIDS vaccine trial in February. The Phase I study will evaluate the safety and immunogenicity of a single shot vaccine candidate in 30 healthy men and women.

The vaccine candidate, called tgAAC09, uses a modified adeno-associated virus (AAV) vector to deliver a small part of HIV's genetic material into the body. The small fragments of HIV used in this vaccine candidate cannot cause infection. The AAV vaccine was developed by Phil Johnson, formerly at the Columbus Children's Research Institute and currently with the Children's Hospital of Philadelphia, and is now licensed and manufactured by the US-based company Targeted Genetics.

The vaccine candidate is now being tested in a joint Phase I clinical trial in Germany, Belgium and India. The clinical trial is sponsored by IAVI and conducted at the National AIDS Research Institute in Pune, an affiliate of the Indian Council of Medical Research (ICMR). The start of the study is an important scientific advancement in a country with the second largest number of people living with HIV in the world.

"With this first trial, Indian scientists are making an important contribution that will bring the world a step closer to an AIDS vaccine," said N.K. Ganguly, Director General of ICMR.

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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.

WHAT IS PRE-EXISTING IMMUNITY TO A VACCINE VECTOR?

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When a person is infected with any disease-causing agent (or pathogen, such as a virus) the immune system makes antibodies and immune cells that recognize the pathogen and control the infection. Many of these antibodies and immune cells disappear after the infection is over. But a group of immune cells remain that are called memory cells. These cells stay inactive in the body until the person is exposed to that same virus again. The memory cells can then quickly recognize the virus and make more antibodies or immune cells to limit and clear out the infection.

A vaccine tries to get your immune system to produce the same immune response as in a natural infection by using immunogens (pieces of viral protein). These small pieces of virus generate memory cells that can rapidly respond if the person is later exposed to that virus. (For more information see the February and March 2004 *Primers* on Understanding the Immune System).

In order to generate an immune response against HIV, an AIDS vaccine will have to contain some immunogens that are copies of pieces of the genetic material of HIV. Because only a part of the HIV genetic material is used, this type of vaccine cannot cause HIV infection. Researchers are trying to design a vaccine so that the protein of HIV will cause an immune response strong enough to protect people if they are later exposed to HIV.

PRIMER
UNDERSTANDING
pre-existing IMMUNITY

First, the immune system must 'see' the vaccine. Many current AIDS vaccine candidates use a vector as a carrier to get to the immune system. The vector is a weakened virus (or bacterium) that is safe for use in humans. Sometimes the vector is developed from a vaccine against another disease. Scientists are working with a number of different vectors for AIDS vaccines (for more about vectors, see the September 2004 *Primer*). Vectors made from other viruses are called viral vectors.

When a common virus or vaccine is used as a vector, some people will have been previously exposed to this virus either naturally or through immunization. Some people will have an immunity to the vector; this is called pre-existing immunity.

When someone has pre-existing immunity to a virus or to a harmless vector, they have immune memory cells or antibodies specific to that pathogen or vector stored in their body. If the vaccinated person's immune response is directed towards the vector, it might limit the immune response to the HIV immunogens. This could make the vaccine less effective. So for each vector it is important to figure out whether pre-existing immunity to it could prevent the vaccine from working.

Current vectors

Several promising AIDS vaccine candidates are using a modified human adenovirus called Ad5 as a vector. Human adenoviruses naturally cause severe colds. After the infection is cleared the infected person has memory cells and antibodies specific to that adenovirus. There are about 40 different groups (called serotypes) of human adenoviruses. About 35% of people in Europe and the US, and as many as 90% of people in some countries (South Africa, Zambia, Botswana, and Thailand), have previously been infected with Ad5. So pre-existing immunity to this vector is common.

An important AIDS vaccine trial is now ongoing with Merck's Ad5 vector, called MRKAd5. This trial will test the ability of the vaccine to either prevent infection with HIV or control disease progression in people who do later become infected with HIV. Researchers hope that the vaccine will stimulate the immune system to produce killer T cells that can kill HIV-infected cells. This is called a cellular immune response.

This vaccine is being tested in 1,500 volunteers in eight countries. Only people with a low level of pre-existing immunity to Ad5 are enrolling in this trial. Without the problem of pre-existing immunity, researchers can fairly assess how effective the vaccine candidate is against HIV. But the results of this trial are not due for about four years. In the meantime researchers are exploring different approaches to improve the adenovirus vector. Some of these approaches include using higher doses of vaccine or using more than one vaccination (what is called a prime-boost strategy). Another approach would be to use a different serotype of adenovirus for which there is less pre-existing immunity, like Ad11 and Ad35. These serotypes are currently being developed as vectors for AIDS vaccines and could be used to get around the problem of pre-existing immunity to Ad5 if the current trial shows promise.

Other viral vectors now being used or developed for preventive AIDS vaccines may also face the problem of pre-existing immunity (such as measles or polio vaccine viruses) but each new vector must be studied to determine the importance of pre-existing immunity. Researchers are yet to determine whether pre-existing immunity will be a problem for the different vectors being developed as AIDS vaccine candidates.

The Modified Vaccinia Ankara (MVA) vector is one example where pre-existing immunity does not seem to be a problem. This vector is part of several ongoing trials, including one that began in January (see *Research and Trials*). MVA is similar enough to the virus used for smallpox immunizations that pre-existing immunity to the smallpox vaccine could possibly affect the efficacy of an MVA-based AIDS vaccine candidate. But this vector may have less trouble with pre-existing immunity because smallpox vaccinations ended in most countries in the mid-1970s. People enrolling in vaccine trials are typically aged 25-40 and therefore pre-existing immunity will be unlikely. It is also no longer a naturally-circulating virus because of the successful worldwide immunization campaign. So far no effect of pre-existing immunity has been seen for MVA vectors but more information is needed.

Until researchers have more data on pre-existing immunity this is just one of the many considerations that vaccine developers must face.