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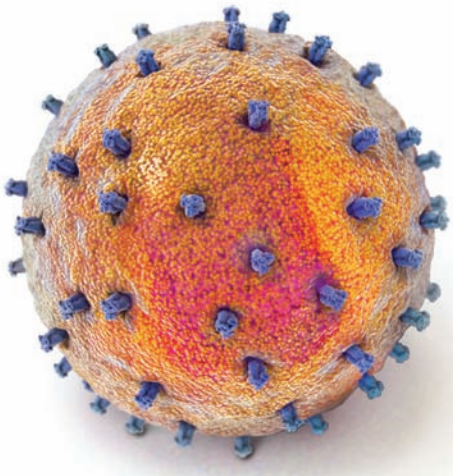
The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

Prepping for the Future

The iPrEx study provides another dose of good news for the HIV prevention field, but implementation is likely to be challenging

By Regina McEnery and Kristen Jill Kresge

SHOULD THE HIV PREVENTION toolbox be viewed as half-full or half-empty?

Last November, on the cusp of World AIDS Day, researchers announced the results of a long-awaited efficacy trial known as iPrEx, which showed that daily administration of the antiretrovirals (ARVs) emtricitabine (FTC) and tenofovir (TDF) was 44% effective in preventing HIV infection among nearly 2,500 men and transgendered women who have sex with men at 11 clinical sites in the US, South Africa, Brazil, Thailand, Peru, and Ecuador. These were the first efficacy results for pre-exposure prophylaxis (PrEP)—the administration of ARVs prior to HIV exposure—and followed a string of good news in HIV prevention research.

Last July, microbicide researchers reported that vaginal application of a 1% gel formulation of TDF was 39% effective in blocking HIV infection, and in September 2009 researchers reported results from the RV144 trial in Thailand that showed a prime-boost vaccine regimen provided about 31% protection against HIV infection.

The iPrEx results, which were published in the *New England Journal of Medicine* (*NEJM*) in December, have accelerated discussions about the possible implementation of PrEP, pending results from other efficacy trials that are expected to be released in the coming months. A host of factors from clinical to financial that could stand in the way of making PrEP a viable weapon in the battle against HIV are now being considered.

One of the biggest obstacles to implementing PrEP as an HIV prevention strategy will be adherence—for the drug to work, individuals at risk of HIV infection must take it consistently. In the iPrEx trial, the odds of HIV infection were 12.9 times lower among individuals in the FTC-TDF group who had detectable drug levels in their blood, corresponding to a 92% reduction in risk of HIV infection, as compared to volunteers in the FTC-TDF group who did not have detectable levels of the drugs in their blood.

And as the iPrEx results suggest, self-reported adherence isn't always accurate. In the iPrEx study, volunteers were counseled on a monthly basis to adhere to the daily dosing regimen and at the monthly visits, investigators collected self-reported information on adherence as well as pill counts. Drug levels were also measured using a blood test designed to detect TDF 14 days or more after the last dose was taken. The drug levels indicated that self-reported adherence was not an accurate measure of how often volunteers had actually taken the pill.

Investigators in the iPrEx trial speculate that side effects, including nausea and unintended weight loss, associated with initiation of the study drugs may have contributed to the low adherence.

Monitoring side effects associated with PrEP will be another important consideration before this strategy is implemented. In the iPrEx study, investigators observed a trend toward more elevated serum levels of creatinine—a chemical waste product that can impair kidney function—in the FTC-TDF group compared to placebo recipients. Although this side effect only occurred in a small subset of volunteers and appeared to reverse upon discontinuation of the study drugs, Nelson Michael, director of the US

ALSO IN THIS ISSUE

Military HIV Research Program, who wrote an editorial in the *NEJM* on the iPrEx study, concluded that "this finding raises both safety and monitoring concerns regarding possible cumulative toxic effects associated with large-scale exposure to daily FTC-TDF therapy for an extended period."

Another concern with PrEP is the potential for development of drug resistance if a person unknowingly becomes HIV infected and continues taking the drugs. In the iPrEx study, none of the volunteers in the FTC-TDF group or the placebo group who became HIV infected during the course of the trial developed drug resistance except for two volunteers who received FTC-TDF because their HIV infections were not detected at enrollment. Researchers speculate that the lack of any drug resistance may have been due in part to the overall low adherence to the study drugs.

Other substantial challenges will be how to pay for PrEP and who receives it. According to the most recent report from the Joint United Nations Programme on HIV/AIDS, an additional 1.2 million HIV-infected people in low- and middle-income countries received ARVs in 2009, bringing the total to 5.2 million, a 30% increase over 2008. Despite this progress only a third of HIV-infected individuals in need of ARVs are currently receiving them. One of the biggest conundrums should PrEP become part of the standard prevention package is whether ARVs should be given to uninfected individuals when so many HIV-infected individuals aren't receiving treatment.

Before any implementation issues are addressed, Robert Grant, an associate professor of medicine at the Gladstone Institute of Virology and Immunology and the principal investigator of the iPrEx study, says researchers must still answer several clinical questions, including whether FTC-TDF is as effective in preventing HIV infection in other high-risk populations, such as injection drug users or women in areas of high HIV prevalence.

Grant says it will also be important to determine if daily dosing is needed, or whether intermittent dosing before and after sex, which is being studied in clinical trials, will be sufficient to protect against HIV infection. "I think the durability of how long people can use this is also an open question," adds Grant. "The median duration of follow-up in the iPrEx trial was 1.2 years, the maximum was 2.8 years. It is conceivable though that people might want to use [FTC-TDF] for a longer period of time."

The iPrEx trial results have prompted discussions among AIDS vaccine investigators and advocates about how or if PrEP might impact clinical trials of AIDS vaccine candidates (see sidebar, this page). There are also discussions about how the iPrEx results may affect ongoing vaccine trials, such as the HVTN 505 trial involving 1,350 men who have sex with men in the US. On January 28, the US Centers for Disease Control and Prevention (CDC) provided interim guidance for healthcare providers on the use of PrEP (to view the guidelines, see http://www.cdc.gov/mmwr). At this time, the CDC recommends PrEP only be considered for adult MSM who are high risk of HIV infection through sex, noting, however, that these drugs are not licensed to be used for HIV prevention and long-term safety of PrEP is not yet known. Formal US guidelines for PrEP use in MSM are in development. ■

IMPLICATIONS FOR VACCINE RESEARCH

The results of the iPrEx trial prompted discussions about how implementation of pre-exposure prophylaxis (PrEP) might affect the research and development of HIV vaccine candidates. To address this question, VAX *turned to Mitchell Warren, the executive director of AVAC, a leading HIV prevention research advocacy organization based in New York City.*

What impact could PrEP have on vaccine trials?

If PrEP is found to be effective and introduced, it makes things more complex. There are already conversations about what to do among the men who have sex with men who are participating in the HVTN 505 vaccine trial (see *Spotlight*, this issue). With that, there is the really immediate issue about whether to integrate PrEP into an ongoing trial. This has implications in terms of a trial's scope and size.

With future trials, even if PrEP works, we don't know where it will be introduced. If PrEP becomes part of the standard prevention regimen among serodiscordant couples [in which one partner is HIV infected and the other isn't], it may no longer be possible to conduct vaccine trials within this cohort. But that is a *big* if, and a reason why the ongoing PrEP study in serodiscordant couples is so important. Even if PrEP works well in this cohort, many people could opt out of it.

There are also opportunities to study the efficacy of these methods [PrEP and vaccines] in combination. If you look at the results of RV144, the vaccine was modestly effective in a low-risk population. It raises the question, could PrEP lower the risk of transmission in high-risk populations enough so a vaccine like RV144 would not have to work as hard? I get very excited about that possibility.

Are there studies planned to look at this?

There are a lot of conversations occurring but I would like to see a specific scientific agenda developed.

Does PrEP lessen the need for an AIDS vaccine?

Not at all. How PrEP is delivered and to whom, and who pays for that delivery, is anything but certain. It will take a great deal of time, effort, and resources to help us understand that. User-controlled methods are a critical backbone of HIV prevention, but they are never enough. We have seen that with condoms. They are more efficacious than PrEP or the vaccine combination in RV144, but adherence matters. In the PrEP trial, adherence was poor, so when I look back at the past year of results from prevention trials like CAPRISA and iPrEx, it tells me how important a vaccine is.

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Research That Sparked Anti-vaccination Campaign Called an "Elaborate Fraud"

An article published this month by the *British Medical Journal* (*BMJ*) concluded that a controversial 1998 study that suggested a possible link between gastrointestinal disease and the onset of behavioral disorders, including autism, in children following receipt of the measles, mumps, rubella (MMR) vaccine was an "elaborate fraud." British investigative journalist Brian Deer, who wrote the *BMJ* article, said the authors of the study, originally published in *The Lancet*, misrepresented the medical histories of most of the 12 children who participated in the study. He also said that Andrew Wakefield, the British doctor who led the study, profited from its findings.

The *BMJ* article is just the latest evidence discrediting the study that is widely acknowledged as one of the main drivers of an anti-vaccination movement in the UK and abroad. "Study after study after study show that there was no connection [between the MMR vaccine and autism]," says Paul Offit, director of the Vaccine Education Center at the Children's Hospital of Philadelphia.

Last year *The Lancet* retracted the 1998 study after a medical regulatory panel in the UK determined the authors had acted unethically (see *VAX* March 2010 *Global News*). Wakefield was later stripped of his medical license in the UK. In response to the *BMJ* article, Wakefield released a statement saying that the health problems identified in the children "were not a hoax and that there was no fraud whatsoever." He also said he did not seek to profit from the findings.

Although public health organizations and pediatricians tried to reassure the public that the MMR vaccine is safe for children, immunization rates in the UK plummeted after *The Lancet* study. In 1997, the year before *The Lancet* study was published, 91% of children in the UK were vaccinated. In 2003, the rate had dropped significantly in some parts of the country. "There were certain sections of London where fewer than 50% of the population were immunized," says Offit.

The decline in vaccination rates extends well beyond the UK. Last year, the US Centers for Disease Control and Prevention reported at a pediatrics conference in Vancouver that the percentage of American parents who refused or delayed vaccination doses had increased from 22% in 2003 to 39% in 2008. Fears about adverse events from vaccines also led to a 10% drop in vaccination rates in the Ukraine between May 2008 and March 2009, according to the United Nations Children's Fund.

And when vaccination rates lapse, it can have dire, even deadly consequences. "We are now seeing outbreaks of infectious diseases that we hadn't seen before, not at this level," says Offit, whose new book, "Deadly Choices: How the Anti-Vaccine Movement Threatens Us All," details the history of the modern anti-vaccine movement and its consequences.

Offit notes, for instance, that in 2010, California experienced the worst outbreak of pertussis (whooping cough) since 1947. California health authorities have reported nearly 9,000 confirmed, probable, or suspected cases since Jan. 1, 2010, and 10 deaths.

"When you choose for your child not to get a vaccine, it's not a choice that you're making for yourself alone," adds Offit. "You're making that choice for other people who are near you who may be too young to be vaccinated, or who are getting chemotherapy for their cancer, or are getting immune-suppressive therapy for their transplants. They depend upon those around them to be vaccinated, and if they are not, then these are the people who are going to be the most likely to suffer and be hospitalized and die from diseases." —*Regina McEnery*

Massive Vaccination Campaign Against Meningitis Launched in Africa

A new vaccine called MenAfriVac that could potentially eliminate meningococcal meningitis in 25 African countries was rolled out late last year by the Meningitis Vaccine Project (MVP), a partnership between the World Health Organization and PATH, a non-profit global health organization based in Seattle.

A vaccination campaign was launched in the western African countries of Burkina Faso, Mali, and Niger, with neighboring countries soon to follow, according to the Bill & Melinda Gates Foundation, a major backer of MVP.

The vaccine was developed to combat the group A strain of meningitis—the most common strain of meningitis in Africa—and when fully implemented will reach an estimated 12.5 million Africans, according to Marc LaForce, the director of the Geneva-based MVP. "Africa is the only place on Earth that continues to have these impressively large outbreaks of group A meningitis," he says, adding that an estimated 450 million Africans are at risk of contracting group A meningitis. Epidemics occur every seven to 14 years on the continent. In 2009, a seasonal outbreak of meningitis cutting across portions of sub-Saharan Africa infected 88,000 people and resulted in more than 5,000 deaths.

LaForce compares the logistics required to carry out the massive vaccination campaign to the invasion of Normandy. "Over a couple of weeks more than 11,000 vaccinators in three different countries will be administering vaccines to 12.5 million people," he says.

continued on next page

[PRIMER]

Understanding How Broadly Neutralizing Antibodies Evolve

As they mature, some antibodies accumulate mutations that make them better at binding to and neutralizing HIV *By Regina McEnery*

Antibodies are one of the main ways the body defends itself against invading pathogens. These infection-fighting proteins can bind to viruses and inactivate them. Antibodies are also thought to be essential to the protection afforded by most, if not all, existing vaccines.

In recent months, researchers have isolated several antibodies from the blood of HIV-infected individuals that are able to inactivate or neutralize a high percentage of HIV strains in laboratory tests (see *VAX* March 2010 *Primer* on *Understanding Advances in the Search for Antibodies Against HIV*). These antibodies are referred to as broadly neutralizing antibodies. Some of these antibodies can even neutralize HIV at very low concentrations, suggesting they are quite potent.

The goal now for AIDS vaccine researchers is to try to design vaccine candidates that can coax the body's immune system to make similar potent, broadly neutralizing antibodies against HIV. Although this is a daunting task, researchers are making considerable progress in understanding how these broadly neutralizing antibodies evolve in HIV-infected individuals.

Antibody formation

There are many components of the immune system that play a role in fending off viruses. Antibodies are made by a type of immune cell produced in the bone marrow that are referred to as B cells. Millions of different versions of B cells exist. These B cells become activated when they come in contact with foreign pathogens, such as HIV. This triggers the B cell to become a plasma cell that is able to produce antibodies that are specific to HIV. Although many HIV-specific antibodies are produced, not all of them are capable of binding to HIV and neutralizing it (see *VAX* February 2007 *Primer* on *Understanding Neutralizing Antibodies*).

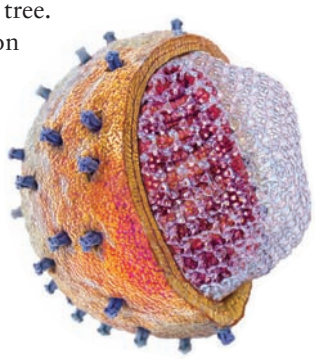
Once B cells bind to HIV, they start to multiply. As they multiply, the B cells begin to mutate or change their genes. Some of these genetic mutations in the B cells result in the production of antibodies that are better able to bind to HIV. These superior B cells then multiply again and again, triggering additional mutations. With each cycle of mutation and differentiation, the resulting antibodies are said to become more mature. The more mature the antibodies become, the better they are. This process is referred to as affinity maturation.

After researchers isolated the most recent broadly neutralizing antibodies against HIV, they began studying the characteristics of these antibodies and they found that they had gone through the process of affinity maturation many times, which is to say that they had accumulated many mutations. Studies have shown that all of the HIV-specific antibodies identified so far are highly affinity matured. In fact, these antibodies have accumulated many more mutations than other antibodies that have been studied.

Researchers do not yet know if all of these mutations are necessary for these antibodies to neutralize many different strains of HIV so well. But in some cases, studies have shown that reversing most of the mutations resulted in an antibody that could not neutralize HIV, suggesting at least some of the mutations are required.

Implications for vaccines?

To further study how broadly neutralizing antibodies evolve in HIV-infected individuals, researchers are going back to one of the original donors from whom some of the recent broadly neutralizing antibodies were isolated to isolate many other antibodies from their blood samples. This way they can identify and study the precursors to the broadly neutralizing antibodies and determine the path of evolution those antibodies had taken, much like constructing a family tree.



This information will likely be useful to researchers as they try to develop vaccine candidates that can induce similar broadly neutralizing antibodies.

GLOBAL NEWS, cont'd

MenAfriVac, which health authorities have held up as a standard for the future of global vaccine development, is based on an older meningitis vaccine that offered short-lived protection coupled with a protein from the tetanus vaccine that produces a more potent immune response. The vaccine was manufactured by the Serum Institute in India at a cost of around US$50 million and is being distributed at a cost of less than 50 cents a dose.

The GAVI Alliance, a Geneva-based nonprofit organization that partners with drug companies, health agencies, and charities to provide support for vaccination programs in developing countries, has contributed more than $85 million to vaccinate Africans against meningitis in three countries, but says an additional $475 million will be needed to complete the campaign. Donors supporting the effort thus far include the Michael & Susan Dell Foundation, Médecins sans Frontières, and the United Nations Children's Fund. —*Regina McEnery*