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The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

## A Year of Progress

On World AIDS Day, scientists marked a promising year on both research and policy fronts *By Regina McEnergy*

AS IT DOES EVERY YEAR, the global AIDS community marked World AIDS Day, December 1, with programs intended to raise awareness about the pandemic. Countries entered the year stuck in a global recession that has cast a shadow on funding for AIDS programs. But despite the economic uncertainty, 2009 turned out to be a promising year on both the research and policy fronts, with many of these developments highlighted, if not announced, on or around World AIDS Day.

The biggest burst of news in HIV prevention this year emerged from the AIDS vaccine field in September. RV144, a 16,000-person trial conducted in Thailand, provided the first evidence of vaccine-induced protection against HIV. This finding, along with other scientific developments, helped energize the field. The discovery of several potent new antibodies—Y-shaped proteins that bind to HIV and stop it from infecting cells—was also a major finding in 2009. The five new so-called broadly neutralizing antibodies, the first to be discovered in more than a decade, are capable of inactivating multiple variants of HIV strains in the laboratory. Two of these antibodies also bind to HIV at a different site, providing a new target for vaccine researchers to exploit (see VAX October 2009 *Spotlight* article, *Vaccine Research Gains Momentum*).

“This has been a banner year in the AIDS vaccine effort,” said Wayne Koff, the senior vice president of research and development at IAVI, during a World AIDS Day seminar in New York City about recent progress and future directions in AIDS vaccine research and development. The event was co-sponsored by IAVI, the AIDS Vaccine Advocacy Coalition (AVAC), and the Global HIV Vaccine Enterprise.

Magda Sobieszczyk, a Columbia University AIDS researcher, who spoke at the seminar about recently completed and ongoing HIV prevention trials, said RV144 “piqued people’s interest” and mobilized the field. The results of RV144 also took center stage at a World AIDS Day event in Washington, D.C., sponsored by more than a dozen organizations, including AVAC, IAVI, and the Vaccine Research Center at the US National Institute of Allergy and Infectious Diseases.

Other AIDS vaccine-related events included a two-day rally, seminar, and workshop at the Global Science Academy in Basti, India, and a presentation in Maryland by the Walter Reed Army Institute of Research and the US Military HIV Research Program, major collaborators on the RV144 trial. Elsewhere around the world, organizations pledged solidarity to the search for an AIDS vaccine by holding rallies, debates, lectures,



sports events, and plays designed to raise awareness and dispel myths and misconceptions. The Desmond Tutu HIV Research Center in South Africa sponsored a soccer tournament for young people, hoping to use the event as a way to spread information about the importance of HIV testing and counseling and to encourage adolescents to inform their peers about how to reduce the spread of HIV. An event in Amsterdam sponsored by IAVI, AIDS Fonds, and Stop AIDS Now, centered on new prevention technologies, while vaccine trial sites in the Dominican Republic held a video forum on vaccine research and sponsored a frank discussion about the commercial sex trade in Santo Domingo.

### Shifting attitudes

World AIDS Day also provided a stage for the announcement of several policy shifts. In South Africa, the epicenter of the

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AIDS pandemic, President Jacob Zuma announced that antiretrovirals (ARVs) would be made available to all HIV-infected pregnant women and infants, that HIV testing would be expanded, and that he was planning to get tested for HIV as well. Treatment will also be expanded to those with tuberculosis, the leading cause of death among South Africans infected with HIV.

Reflecting a change in treatment guidelines unveiled by the World Health Organization (WHO) the day before, Zuma said his country would also offer treatment sooner to all HIV-infected individuals.

The WHO's previous recommendations called for treatment to be initiated when a person develops AIDS (as defined by having fewer than 200 CD4<sup>+</sup> T cells in a microliter of blood) or an AIDS-related illness. But on November 30, the WHO announced that it was raising the minimum threshold for ini-

tiation of treatment to 350 CD4<sup>+</sup> T cells. The WHO's updated guidelines are now in line with those of leading government health agencies in the US and Europe.

The new WHO guidelines also recommend the prolonged use of ARVs to reduce the risk of mother-to-child transmission of HIV. For the first time, the WHO recommends that HIV-infected mothers or their infants take ARVs while breastfeeding to prevent HIV transmission.

Zuma's policies stand in sharp contrast to those of his predecessor, Thabo Mbeki, whose administration was heavily criticized for its HIV/AIDS policies. Glenda Gray, executive director of the Perinatal HIV Research Unit at the University of Witwatersrand in Soweto, South Africa, described the government's commitment to expanding access to treatment as "incredibly ambitious and incredibly right."

Gray says there are 1.4 million people in South Africa who need to be on ARVs. "So we basically need to double the amount of people on treatment by 2011," she says. "How to get there will be another challenge."

This will be a global challenge. There are an estimated four million HIV-infected individuals worldwide who are currently receiving ARVs. However, approximately five million HIV-infected individuals who were eligible for treatment based on the old WHO guidelines still do not have access to therapy. With the updated guidelines in place, the number of people eligible for therapy could potentially double, substantially increasing the demand for ARVs.

### US policy shifts

After announcing that it planned to lift a controversial policy that prevented HIV-infected individuals from entering the US beginning next year, the Obama administration announced on World AIDS Day that Washington, D.C., the nation's capital, would host the XIX International AIDS Conference in 2012. The International AIDS Society (IAS), which sponsors the biannual conference, had opposed the travel ban, which was instituted in 1987, and made it clear it would not hold the conference in the US until the ban was lifted.

"Everybody recognized that the US travel ban had no scientific merit and no public health merit," says IAS President Julio Montaner, noting that 14 other coun-

tries still have similar travel bans in place. "It was based on ignorance and discrimination, and persisted on the books for historical reasons. It was a serious infringement on the rights of people with HIV."

Montaner says the fact that the US capital—which has the highest HIV/AIDS prevalence in the country—will be hosting the 2012 AIDS conference is significant. "We hope the conference will serve as a catalytic event in trying to rally the necessary forces around addressing the epidemic, not just in the inner city of D.C., but elsewhere," says Montaner. The last time the AIDS conference was held in the US was in 1990 in San Francisco.

The US government also unveiled a new five-year strategy for the US President's Emergency Plan for AIDS Relief (PEPFAR) on World AIDS Day. Notably, this new strategy signals a transition for PEPFAR from an emergency response to HIV/AIDS to the promotion of sustainable programs in individual countries. Prevention, care, and treatment services provided through PEPFAR will still be expanded, but efforts will also be made to integrate HIV/AIDS initiatives into broader global health and development programs to maximize the impact on health systems in developing countries. PEPFAR will now focus on strengthening capacity in its target countries to enable them to take the lead on their responses to AIDS and other health demands and improve service delivery. US Global AIDS Coordinator Eric Goosby said the current economic realities are forcing changes in the way the government is approaching the program. The Obama administration is seeking to make PEPFAR part of a US\$63 billion Global Health Initiative that will also focus on other major public health challenges such as nutrition and maternal health (see *VAX* May 2009 *Spotlight* article, *Despite Recession, New Funding Stimulates Research*).

Goosby also emphasized the need for more evidence-based prevention strategies that are targeted to high-risk populations, when he spoke at a World AIDS Day discussion about food security, HIV/AIDS, and maternal and child health sponsored by the World Bank and held in Washington, D.C.

PEPFAR-funded programs are at work in more than 30 countries. In 2009, the program provided antiretroviral drugs to more than 2.4 million HIV-infected people and plans are to provide treatment to four million



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IAVI is a global not-for-profit organization working to speed the search for a vaccine to prevent HIV infection and AIDS. Founded in 1996 and operational in 24 countries, IAVI and its network of partners research and develop vaccine candidates. IAVI also advocates for a vaccine to be a global priority and works to assure that a future vaccine will be accessible to all who need it. For more information, go to [www.iavi.org](http://www.iavi.org).

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people by 2014. But AIDS advocates fear that the global recession and a shift in political priorities in the US could hinder the success

of PEPFAR. Michel Kazatchkine, executive director of the Global Fund to Fight AIDS, Tuberculosis and Malaria, stressed the

importance of remaining committed to the goals of universal access to treatment, when he spoke at the World Bank event. ■

## GLOBAL NEWS *By Regina McEnery*

### New HIV Infections Steadily Declining

IN ITS ANNUAL UPDATE on the status of the global epidemic, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported a 17% drop in the number of new HIV infections over the past eight years and suggested that the spread of HIV appears to have peaked in 1996, when 3.5 million new infections occurred.

According to the report, which was released last month in advance of World AIDS Day, an estimated 2.7 million new HIV infections occurred in 2008. This brings the estimated number of people living with HIV to 33.4 million, slightly higher than in 2007 when 33 million were estimated to be living with the virus. This is largely due to the life-prolonging effect of antiretrovirals (ARVs). UNAIDS estimates that there are now about four million people in low- and middle-income countries receiving ARVs—a 10-fold increase over the past five years. AIDS-related mortality peaked in 2004, when there were 2.2 million deaths. Last year, it is estimated that there were two million AIDS-related deaths.

The 2008 data reflect advances in software that have enabled epidemiologists to more reliably estimate HIV incidence using updated mathematical models. The more accurate accounting is expected to help countries more precisely define the scope of the epidemic in high-risk regions and populations. A dozen countries have used a model to analyze HIV incidence by the mode of

transmission. This enables epidemiologists to predict where new infections are likely to occur, both generally and within pre-identified subgroups. This approach enabled Uganda to identify an estimated number of new infections that may occur among heterosexual couples considered at low risk of HIV infection.

The latest data also found dramatic variations in HIV prevalence within countries, a sign that prevention strategies need to be tailored to local needs and that national responses to the AIDS epidemic should be decentralized, according to UNAIDS. “The common failure to prioritize focused HIV prevention programs for key populations is especially apparent,” according to the report. “Even though injecting drug users, men who have sex with men, sex workers, prisoners, and mobile workers are at higher risk of HIV infection, the level of resources directed toward focused prevention programs for these groups is typically quite low, even in concentrated epidemics.”

For instance, although serodiscordant couples—in which one partner is HIV infected and the other is not—account for a substantial percentage of new infections in some African countries, HIV testing and counseling programs are seldom geared specifically toward this risk group, the report said. Similarly, many programs that have targeted adolescents fail to grasp some of the key determinants of their vulnerability to HIV.

### Microbicide Gel Fails to Protect

THE FIELD OF MICROBICIDE research was dealt a blow this month when a gel known as PRO 2000, which had shown some promise in an earlier study, failed to have any effect in preventing HIV infection in a Phase III efficacy trial involving 9,385 women in the UK, Tanzania, South Africa, Zambia, and Uganda.

At the conclusion of the MDP 301 trial, which lasted four years, 130 HIV infections had occurred among women who received PRO 2000, compared to 123 infections among those who received an inactive placebo gel. This analysis excluded HIV-infected women who became pregnant during the trial, as well as women whose HIV infections were detected within a year after their first study visit. Another analysis that included all HIV infections, regardless of pregnancy or time of infection, was equally disappointing: 145 HIV infections in the microbicide group compared to 143 in the placebo group.

PRO 2000 is a topical gel that women apply before intercourse. It is composed of a synthetic compound that was non-specifically designed to block attachment of HIV to host cells and thereby prevent infection. Women in the MDP 301 trial were also

given condoms and regular HIV prevention counseling. The trial was conducted by the Microbicide Development Programme, a partnership of 16 African and European research institutions, and was primarily funded by the UK's Medical Research Council.

A year ago, researchers reported results from a smaller Phase IIb study of 3,099 women in South Africa, Malawi, Zambia, Zimbabwe, and the US, which showed that women who received PRO 2000 gel along with condoms had 30% fewer HIV infections than those who received the placebo gel and condoms (see VAX February 2009 *Spotlight* article, *Canvassing CROI*). This finding, though promising, was not statistically significant.

HIV prevention advocates expressed disappointment at the results of MDP 301, but said the field should continue to press forward in developing microbicides that are gel formulations of existing antiretrovirals (ARVs). “The need for a microbicide is as great as ever,” says Salim Abdool Karim, a clinical infectious disease specialist who led the Phase IIb trial of PRO 2000. “This should not be a time for despondency, we need to move on.”

# Understanding Vaccine Licensure

What factors do regulatory bodies consider before licensing a vaccine for public use? *By Regina McEneary*

THE DEVELOPMENT OF A VACCINE is a long and complicated process that often takes several decades.

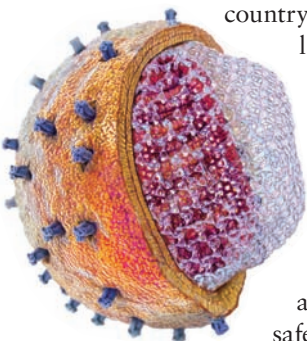
Vaccine candidates undergo a rigorous sequence of laboratory, preclinical, and clinical testing to determine both their safety and efficacy. Phase I and II trials are designed to determine whether the vaccine is safe and if it triggers immune responses. It is not until large Phase IIb test-of-concept or Phase III efficacy trials are conducted that the efficacy of the vaccine candidate is actually evaluated. For HIV, these trials determine whether the candidate provides protection against infection or reduces the quantity of virus in people who receive the vaccine yet still became infected through natural exposure to the virus.

Phase III trials typically involve thousands of volunteers. When a Phase III trial delivers a positive result, vaccine developers may decide to submit an application to regulatory agencies for approval and licensure of the vaccine (see *VAX* April 2004 *Primer* on *Understanding Vaccine Development*). Once a vaccine is licensed, it can be distributed and administered more broadly within a given population.

## Regulatory review

There are no universal standards for vaccine licensure. Rather, regulatory bodies review all of the safety and efficacy data collected for a particular candidate, and determine on an individual basis whether it should be licensed. For approval to occur, a vaccine must consistently meet specific quality standards and be manufactured according to stringent standards set by the particular country that is granting the

license. One of the major issues in manufacturing is consistency. Every time a vaccine is made, the process has to be the same because even slight alterations can impact safety and efficacy.



All countries have some form of regulatory approval system that oversees the licensure and approval of new medicines and vaccines. The US regulatory body is the Food and Drug Administration (FDA), in South Africa it is the Medicines Control Council, and in Thailand it is the Thailand Food and Drug Administration. The European Medicines Agency is a centralized regulatory body that reviews licensure applications for all European Union countries.

In developing countries, regulatory agencies vary in size and experience. Some countries will wait until the US or the European regulatory bodies have licensed a vaccine before deciding whether to also license it in their countries. Many countries also seek guidance from the World Health Organization before licensing a vaccine.

In the US, new medicines are expected to be tested in two pivotal Phase III efficacy trials to be granted approval for public use. However, vaccine developers may, under special circumstances, only need to demonstrate efficacy with one well-conducted, well-designed trial of sufficient size. A vaccine against hepatitis A virus was approved by the US FDA based on one Phase III trial. But the Rotateq vaccine, which combats a virus that is a common cause of diarrhea, required three Phase III trials before licensure was granted because of specific safety concerns.

## Considering RV144

Recently, a large-scale HIV vaccine trial known as RV144, which involved 16,000 participants in Thailand, provided the first clinical evidence of vaccine-induced protection against HIV (see *VAX* September 2009 *Spotlight* article, *First Evidence of Efficacy from Large-Scale HIV Vaccine Trial*). The two vaccine candidates, tested in what is referred to as a prime-boost combination, appeared to lower the risk of HIV infection by about 31%. This spurred some discussion about whether this prime-boost regimen should be licensed.

The vaccine candidates were specifically designed to combat the most common HIV serotypes or clades currently circulating in Thailand. It is therefore unlikely that this prime-boost combination would be considered for licensure anywhere else unless vaccine developers tested the vaccine in other countries to determine how effective it is in preventing infection with other HIV serotypes.

While the licensure decision ultimately rests with the Thai FDA, there are several factors that make licensure of the vaccine candidates tested in RV144 unlikely. Perhaps the most significant is the low level of efficacy observed in RV144. There is no specified level of efficacy required for vaccine licensure, but early on, the RV144 trial investigators stated that a vaccine efficacy of at least 50% was necessary to trigger discussions of possible licensure. Vaccine regimens used in childhood immunization programs usually protect at levels of 80%, while the annually administered influenza vaccine has about a 60% efficacy. However, it is possible that a partially effective HIV vaccine with only 50% efficacy could prevent thousands of new infections in high-incidence areas.

The lengthy six-shot, six-month inoculation schedule tested in RV144 is another factor regulators would likely consider before licensing this vaccine regimen. Additionally, while the organizers of RV144 initially conceived the study as a Phase III trial, it was ultimately launched as a Phase IIb trial after Thailand's HIV incidence declined dramatically because of successful HIV prevention campaigns. The lower HIV incidence in the country when the trial started meant that the number of infections likely to occur among trial participants during the course of the study would also be lower than originally predicted, thus limiting the overall power of the study. For that reason, the trial organizers decided to launch RV144 as a Phase IIb study, which is not generally considered a launching pad for licensure (see *VAX* September 2005 *Primer* on *Understanding Test-of-Concept Trials*). ■