

vax



The Bulletin on AIDS Vaccine Research

[SPOTLIGHT]

Microbicides Finally Gel, Securing Spotlight in Vienna

The efficacy of a microbicide candidate was the definitive bright spot at this year's International AIDS Conference *By Kristen Jill Kresge*

2010 WAS TO BE A LANDMARK YEAR in the global response to HIV/AIDS. Following the endorsement by the member states of the United Nations (UN) at the 2005 UN Millennium Summit, this year was when the international community was to achieve universal access to HIV treatment, prevention, and care. But it came as no surprise to the more than 19,000 delegates from 193 countries who gathered in Vienna from July 18-23 for the XVIII International AIDS Conference (IAC) that this goal is far from being met, despite substantial progress in delivering antiretroviral therapy (ART) to those in need.

"We are nowhere near delivering on the promise of universal access," said Julio Montaner, outgoing president of the International AIDS Society, which hosts the biannual IAC.

The hopes of achieving universal access any time soon were dampened by the lingering economic slowdown that has gripped many of the nations that are the biggest funders of HIV/AIDS treatment and prevention. Concerns about future financing of the HIV/AIDS response dominated this year's IAC.

But amid the clouds of economic uncertainty, a bright spot emerged in HIV prevention efforts with the results of the Centre for the AIDS Programme of Research in South

Africa (CAPRISA) 004 trial, which showed that a microbicide candidate consisting of a gel containing 1% of the antiretroviral tenofovir, which is used in the treatment of HIV infection, was able to reduce the HIV incidence in a group of South African women by 39%. Even with this level of efficacy, one of the trial's principal investigators, Salim Abdool Karim, said that mathematical models indicate "this gel could prevent 1.3 million new HIV infections and over 800,000 deaths in South Africa alone." However, as Karim explained, the CAPRISA 004 results are really just the "first step and additional studies are needed to confirm findings from this trial."

Luckily, one of those trials is already underway. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study is comparing daily application of a tenofovir gel to oral administration of either tenofovir or Truvada (a single pill combination of tenofovir and another antiretroviral emtricitabine) in 5,000 women in southern Africa. Results from this trial are expected in 2013.

After successfully hosting this year's World Cup, South Africa, or at least HIV prevention researchers in that country, had another reason to celebrate. "Today we celebrate the proof-of-concept of microbi-

cides," said Gita Ramjee, director of the HIV prevention research unit at the South African Medical Research Council, who spoke at the session in which the CAPRISA 004 results were presented.

A South African victory

Delegates and researchers were unabashedly gleeful about the results of the CAPRISA 004 study—the first efficacy trial of any microbicide candidate to show a statistically significant reduction in risk of HIV infection. The audience at the standing-room-only session, which occurred the day after the news dominated the headlines, greeted the data

ALSO IN THIS ISSUE

GLOBAL NEWS

- ▶ First US National AIDS Strategy Aims to Cut New Infections
- ▶ Vaccine Candidate Targeting Dendritic Cells Enters Clinical Trial

PRIMER

- ▶ Understanding the Costs and Benefits of AIDS Vaccine Efficacy Trials

and the trial's co-principal investigators, the husband and wife duo Quarraisha and Salim Abdool Karim, with multiple standing ovations. Researchers also expressed their excitement. "These groundbreaking results mean a lot to me personally," said Ramjee.

The proof-of-concept, double-blinded, placebo-controlled trial known as CAPRISA 004 tested the safety and efficacy of the tenofovir-based vaginal microbicide in 889 women at high risk of HIV infection. Women in the trial received regular HIV prevention counseling and were instructed to apply the gel up to 12 hours before sex and as soon as possible following intercourse, but within 12 hours—a regimen referred to as BAT24.

How well women adhered to this dosing regimen had an obvious impact on whether or not they were protected against HIV infection. Researchers classified women who used the gel more than 80% of the time as "high adherers." Among this group, the efficacy of the tenofovir

gel was a statistically significant 54%, as compared to placebo, higher than the overall efficacy of 39%. The efficacy was markedly lower, only 28%, among the group of "low adherers," who used the gel less than 50% of the time. Researchers are now studying the drug levels in both blood and cervicovaginal fluid among CAPRISA 004 volunteers to look for possible explanations for why some women who used the gel still became infected.

Over the course of the study, researchers found that gel use tapered off. This could be a cause for concern, as adherence will obviously impact the real-world efficacy of any behaviorally dependent intervention. "I think we will see very different gel use outside of a trial setting," says Salim Abdool Karim. He thinks gel use may actually be higher in a real-world setting because women would be receiving more positive messages. In a clinical trial, Salim Abdool Karim said women are repeatedly told that they might be getting placebo or that the gel might not have any effect.

CONRAD, Family Health International, and CAPRISA collaborated to conduct the CAPRISA 004 trial, with 90% of the funding provided by the United States Agency for International Development, and the remainder contributed by the South African Department of Science and Technology.

PrEP and circumcision update

In addition to antiretroviral-based microbicides, researchers eagerly await results from other trials designed to determine if antiretrovirals provided orally to HIV-uninfected individuals may be able to protect them against contracting HIV, a strategy referred to as pre-exposure prophylaxis (PrEP). The first efficacy results from trials of daily PrEP dosing are expected later this year or early next year, but in Vienna researchers reported some interim results from smaller safety studies of this approach. Data from a placebo-controlled Phase II trial in the US indicate that there were no significant safety issues associated with administration of once-daily tenofovir to HIV-uninfected men who have sex with men (MSM). The overall number of adverse events that occurred in men receiving tenofovir was similar to that in the placebo group. The study, conducted by the US Centers for Disease Control and Prevention, enrolled 400 MSM in Atlanta, San Francisco, and Boston.

Researchers also presented data on the safety of intermittent dosing of Truvada in five

female sex workers and 67 MSM in Kenya, as well as 36 serodiscordant couples (in which one partner is HIV infected and the other is not) in Uganda. In this study, researchers compared daily dosing of Truvada or placebo with an intermittent dosing schedule consisting of a fixed dose on Mondays and Fridays and a dose following each sex act, without exceeding one pill per day. At the conclusion of the four-month study, researchers found that the safety profiles of the daily and intermittently scheduled dosing of Truvada were similar, however, the adherence differed somewhat.

Adherence was primarily assessed using the medication event monitoring system (MEMS), an electronic pill bottle cap that records each date and time that the bottle is opened. Investigators also collected self-reported behavioral data through questionnaires and with an interactive cell-phone-based short message service (SMS). The overall adherence rate to the daily dose was high—83% among the MSM and female sex workers at two sites in Kenya, and 96% among serodiscordant couples in Uganda. Adherence in the intermittent-dosing group was lower, with an overall adherence rate of 68% in Kenya and 80% in Uganda. In both groups, adherence rates among serodiscordant couples were significantly higher than in MSM or female sex workers.

This study, conducted by IAVI in collaboration with the Kenya AIDS Vaccine Initiative, the Kenya Medical Research Institute, the Medical Research Council in Uganda, and the Uganda Virus Research Institute, was the first to compare the safety of and adherence to an intermittent PrEP regimen with daily use.

While several trials of microbicides and PrEP are underway, Bill Gates, co-chair of the Bill & Melinda Gates Foundation, reminded the delegates in Vienna that several proven HIV prevention strategies, including adult male circumcision, the prevention of mother-to-child transmission, and syringe exchange, still need to be implemented more widely. He said these strategies were "so cheap and effective it's more expensive not to pursue them," and he emphasized the need to scale up strategies as soon as they're proven to work. "Male circumcision is an amazing advance in prevention," said Gates.

Efforts to scale up adult male circumcision, which was found to be about 60% effective in reducing HIV infection risk among heterosexual men in three large trials,

vax

MANAGING EDITOR

Kristen Jill Kresge

SENIOR SCIENCE WRITER

Andreas von Bubnoff, PhD

SCIENCE WRITER

Regina McEnery

PRODUCTION & WEBSITE MANAGER

Nicole Sender

FREE SUBSCRIPTIONS:

To obtain a FREE subscription to VAX by e-mail, change your subscription details, or receive multiple print copies of VAX to distribute and/or use in your programs, please go to www.iavireport.org and click on the Subscribe link.

VAX is a monthly bulletin from IAVI Report, the publication on AIDS vaccine research published by the International AIDS Vaccine Initiative (IAVI). It is currently available in English, French, Spanish, and Portuguese as a downloadable PDF file or an e-mail bulletin.

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 25 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.

Printed with soy-based ink on FSC-certified paper. Copyright 2010.



have been underway in several African countries. But perhaps nowhere has there been more progress than in Kenya, where between November and December 2009, the country conducted a campaign in 11 districts of Nyanza province and performed voluntary circumcisions of 36,077 men in 30 days.

The funding forecast

Economic concerns loomed over nearly all the discussions at the IAC this year. In 2008, the global investment in HIV/AIDS reached a record high of US\$15.6 billion, a 39% increase in funding from the previous year, according to a recent report issued by the Joint United Nations Programme on HIV/AIDS (UNAIDS).

But following the recent economic crisis, many countries are freezing their investments in global health. “The idea that we should cut back now is ridiculous,” said Michel Sidibé, executive director of UNAIDS. An analysis by UNAIDS and the Kaiser Family Foundation that was released in Vienna found that contributions from the Group of Eight Nations, the European Commission, and other governments provided \$7.6 billion for AIDS in developing countries in 2009, nearly level with their \$7.7 billion contribution in 2008. This was the first year of flat funding, following a substantial increase in donor support for AIDS since 2002, when the total contribution was only \$1.2 billion.

Funding for HIV vaccine research was also

flat in 2009. According to the HIV Vaccines and Microbicides Resource Tracking Working Group, the total global investment in HIV vaccine research and development held steady last year at \$868 million, due primarily to the economic stimulus funding the US government provided, some of which went to preventive HIV vaccine research projects funded by the US National Institutes of Health.

“We’re not seeing the increases we’ve seen in the past,” said Gates. “Today, skeptics say we can’t beat AIDS because of these financial limitations,” he added. But while acknowledging that these are tough economic times, Gates said he is still an optimist and emphasized the need to “push for efficiency in both treatment and prevention.” ■

GLOBAL NEWS *By Regina McEnery*

First US National AIDS Strategy Aims to Cut New Infections

US PRESIDENT BARACK OBAMA’s administration released the nation’s first National AIDS Strategy in July that pledges to reduce the number of new HIV infections by 25% within five years. The 60-page report, which was prepared by the White House Office of National AIDS Policy, also aims to increase access to care, optimize health outcomes for people living with HIV/AIDS, and reduce HIV-related health disparities by reducing stigma and discrimination. The strategy also mentions the need to develop, evaluate, and implement a combination of effective HIV prevention strategies, including AIDS vaccines and microbicides, as well as strategic use of syringe exchange and expanded HIV testing to reduce HIV transmission rates.

Approximately 55,000 Americans are newly infected with HIV each year, an estimate that epidemiologists say has remained static for the past 15 years despite ongoing efforts to try to reduce HIV incidence rates. The US Centers for Disease Control and Prevention estimates that there are now more than

one million people living with HIV/AIDS in the US, and that about 20% of them are unaware that they are HIV infected.

Mark Harrington, executive director of the Treatment Action Group, a New York-based AIDS research and policy organization, says he thought the US aim of reducing new infections by 25% within five years wasn’t nearly aggressive enough. “If we really did a good job, we could reduce infections by 50% and really make an impact,” says Harrington. “This is not a strategy to end AIDS; this is a strategy to manage AIDS.”

Judy Auerbach, vice president of Science & Public Policy at the San Francisco AIDS Foundation, was one of the founders of the Coalition for a National AIDS Strategy that secured a commitment from Obama to develop such a plan when he was seeking the presidency. “It was striking, not just to Americans, but to the rest of the world that we did not have a singular plan,” says Auerbach. “So from my point of view, it’s really encouraging that it happened as quickly as it did.”

Vaccine Candidate Targeting Dendritic Cells Enters Clinical Trial

SCIENTISTS AT ROCKEFELLER UNIVERSITY in New York City began testing a novel AIDS vaccine candidate in July that specifically targets dendritic cells, specialized cells of the immune system that can scoop up HIV proteins that are included in the vaccine candidate and present them to other immune cells such as CD4⁺ T cells and B cells, thereby helping to trigger an immune response against HIV.

The vaccine candidate contains an antibody, engineered to recognize a protein found on the surface of dendritic cells, fused to an HIV protein. The three-year, randomized, placebo-controlled, Phase I trial, known as DCVax-001, will enroll 45

healthy HIV-uninfected volunteers in New York City. Investigators will evaluate both the safety of the candidate as well as its ability to induce immune responses against HIV at three different doses. This is the first time a dendritic cell-focused approach is being tested as a preventive HIV vaccine candidate.

The vaccine candidate is also being administered along with a fixed dose of an experimental adjuvant called Poly ICLC (Hiltonol), which was designed to augment the immune responses induced by the candidate. Volunteers will receive three injections of either the vaccine candidate or placebo over 12 weeks, and will then be monitored for 12 months.

Understanding the Costs and Benefits of AIDS Vaccine Efficacy Trials

Why are late-stage trials so expensive and why is it important to invest in them? *By Regina McEneary*

DURING THE EARLIEST STAGES of AIDS vaccine development, researchers use animal models to evaluate the safety and efficacy of various vaccine candidates. The most promising AIDS vaccine candidates are then evaluated in early-stage clinical trials that are specifically designed to determine whether the candidates are safe, and whether they are capable of eliciting immune responses against HIV, what is known as immunogenicity. Such early-stage clinical trials are classified as Phase I or II trials and are generally small, involving approximately 300 volunteers per study.

It is the larger Phase IIb test-of-concept or Phase III trials that are specifically designed to evaluate whether an AIDS vaccine candidate is effective in preventing HIV transmission. Or, in the case of some studies, whether the candidate is capable of slowing progression of HIV disease in individuals who become HIV infected despite vaccination (see VAX March 2005 *Primer on Understanding Clinical Research Studies*). These so-called efficacy trials determine whether a vaccine can be approved and licensed for use by the public. Phase IIb and III trials are much larger, involving several thousands of volunteers, and are often conducted at multiple clinical research centers. Because of their size and complexity, vaccine efficacy trials are both expensive and difficult to execute. However, because these trials can provide surprising results that may inform the design of improved vaccine candidates, they are also widely viewed by researchers as an important way to advance AIDS vaccine research.

Factors that influence trial cost

One major factor influencing the cost of efficacy trials is the HIV incidence rate—the number of new HIV diagnoses in a given population during a set period of time. The lower the HIV incidence rate in a population, the more volunteers that have to be screened and recruited into a clinical

trial for researchers to determine if the vaccine is effective in preventing or controlling HIV. For the RV144 trial in Thailand, which provided the first evidence of efficacy for an AIDS vaccine candidate, investigators had to recruit 16,000 volunteers because the HIV incidence was so low in the trial population.

The criteria that are used to determine if an individual is eligible to join a trial can also increase the number of volunteers that must be screened, and therefore add to the costs. For example, researchers involved in the HVTN 505 trial are seeking to enroll HIV-uninfected men who have sex with men who are circumcised and who have not been previously exposed to a common cold virus known as adenovirus serotype 5 (Ad5), which is used in the vaccine candidate being tested in this trial to deliver non-infectious fragments of HIV to the immune system to try to induce immune responses against HIV. The additional criteria (being circumcised and having no pre-existing immunity to Ad5) were added to the HVTN 505 study after the results of the STEP trial. This trial, which tested a similar Ad5-based vaccine candidate, showed that male volunteers who received the vaccine had a higher risk of acquiring HIV if they were uncircumcised and had been previously exposed to the Ad5 virus (see VAX July 2009 *Primer on Understanding Inclusion/Exclusion Criteria*).

The collection and storage of laboratory specimens can also contribute to the cost of conducting efficacy trials. Blood, cell, and tissue samples must be taken periodically during a clinical trial so researchers can compare both the types and levels of immune responses among volunteers who receive the vaccine candidate with those who receive an inactive placebo, and hopefully glean information that will be useful in determining what is required for vaccine-induced protection against HIV. Both the volume and types of samples col-

lected can add substantially to the cost of a trial because some specimens, including tissue samples, are difficult and time-consuming to procure and analyze. Once these specimens are collected, researchers also must store and preserve them properly in freezers, sometimes for years, for future analysis, which is also quite expensive.

Additionally, the process of manufacturing vaccine candidates can also add to the costs of conducting a clinical trial.

Clinical research

In the nearly 30 years since the AIDS pandemic began, scientists have evaluated just three AIDS vaccine candidates in efficacy trials. Two recently conducted clinical trials, STEP and RV144, yielded surprising results. While many scientists agree that basic research is necessary to advance AIDS vaccine development, more recently, many researchers are extolling the unique power of clinical trials to provide clues that can inform design of future vaccine candidates.

A well-designed, well-executed AIDS vaccine efficacy trial, even one where the vaccine candidates fail to prevent transmission or lower disease progression, can provide clues to what triggers vaccine-induced protection against HIV. Researchers are still mining the data collected in the STEP trial to gain information that will be useful in developing better vaccine candidates. Meanwhile, teams of researchers are carefully analyzing samples from RV144 in an attempt to understand what led to the modest efficacy of the vaccine candidates tested in that trial. Such information would be valuable to advancing the quest for an AIDS vaccine. ■

