Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention

Volume 3 | No. 1
January–March 2010

AVAC's Take

The last three months of 2009 took us to an unprecedented place in the field of HIV prevention research. For the first time in history, a clinical trial showed that the prevention of HIV through vaccination is possible. Researchers also discovered the first new neutralizing antibodies in over a decade that may be helpful in the creation of new vaccine candidates. At the same time, news from microbicide and PrEP trials provided reminders of the challenges and complexities of biomedical HIV prevention trials.

In the broader world of HIV/AIDS, the US government repealed the decades-long bans on federal funding for syringe exchange and on entry to the US for people with HIV. Both of these moves represent important steps forward for evidence-based HIV prevention.

Looking ahead in 2010, we anticipate a cascade of safety and adherence data from oral PrEP trials; results from a phase IIb trial of tenofovir gel; the launch of new trials looking at intermittent PrEP and the "test-and-treat" strategy; and other events we can't predict. We hope you'll continue to join with AVAC as we navigate what promises to be an exciting year together.

Data Dispatch

PRO 2000: The final word

Last December, the Microbicides Development Programme (MDP) released results from the microbicide trial MDP 301. The trial showed that PRO 2000 (0.5%) gel is safe but not effective in reducing women's risk of HIV infection during vaginal sex. Analysis of the trial data found no difference in rates of HIV infection between the PRO 2000 and placebo arms—a 4.1 percent rate in the PRO 2000 arm compared to a 4.0 percent rate in the placebo arm. The unambiguous results from the trial give a definitive answer that PRO 2000 is not a viable microbicide.

Despite disappointing results, there is still much to be learned from this trial. Spanning four years and four countries—South Africa, Tanzania, Uganda and Zambia—MDP 301 can serve as a model for future HIV prevention trials. In addition to critical scientific information, it will provide important data from its extensive social science component and lessons from the comprehensive community engagement and preparation undertaken by the trial staff.

MDP 301 also underscores the need to continue the search for new laboratory assays and animal models for assessing safety and finding correlates of protective efficacy in humans. In both animal studies and the laboratory,

Continues on back

At a Glance

- In October, the US National Institute of Allergy and Infectious Diseases (NIAID) held a workshop, *Beyond 2010: Gaps, Challenges, and Priorities for the Future of Preclinical PrEP,* to discuss opportunities, challenges and priorities related to the development and discovery of new PrEP agents.

  The two-day meeting featured presentations from drug development and animal research scientists geared toward defining the target product profile for new PrEP agents, identifying priority areas for investigation in animal models, and establishing a research agenda around correlates of protection.

- In December, AVAC collaborated with amfAR in convening a special scientific think tank on intermittent PrEP research. This meeting considered both biomedical and social science elements of a developing intermittent PrEP research agenda. ■

2010 Trial Milestones to Watch*

1st Quarter

- Launch of HPTN 066, phase I trial to evaluate the pharmacokinetics of intermittent oral TDF/FTC (US)
- Results from CDC 4323, phase II trial (US)

2nd Quarter

- Launch of HPTN 065 TNT-Plus, a study to evaluate the feasibility of an enhanced "test-and-treat" approach for the prevention of HIV transmission (US)
- Launch of HPTN 067, phase I/II feasibility trial to evaluate the behavioral aspects of fixed interval vs. coitally dependent intermittent oral TDF/FTC in women and MSM (Thailand and select African countries)

3rd Quarter

- Results from CAPRISA 004, phase IIb trial to evaluate the safety and effectiveness of 1% tenofovir gel to prevent HIV infection in women (South Africa)

4th Quarter

- Results from IAVI's phase I/II trials to evaluate the safety, acceptability, adherence and drug levels of oral TDF/FTC taken once daily vs. intermittently by men and women (Kenya, Uganda)
- Completion of CDC 4940 (TDF2) (Botswana)
- Completion of CDC 4370, phase II/III (Thailand)
  Results expected first quarter 2011.

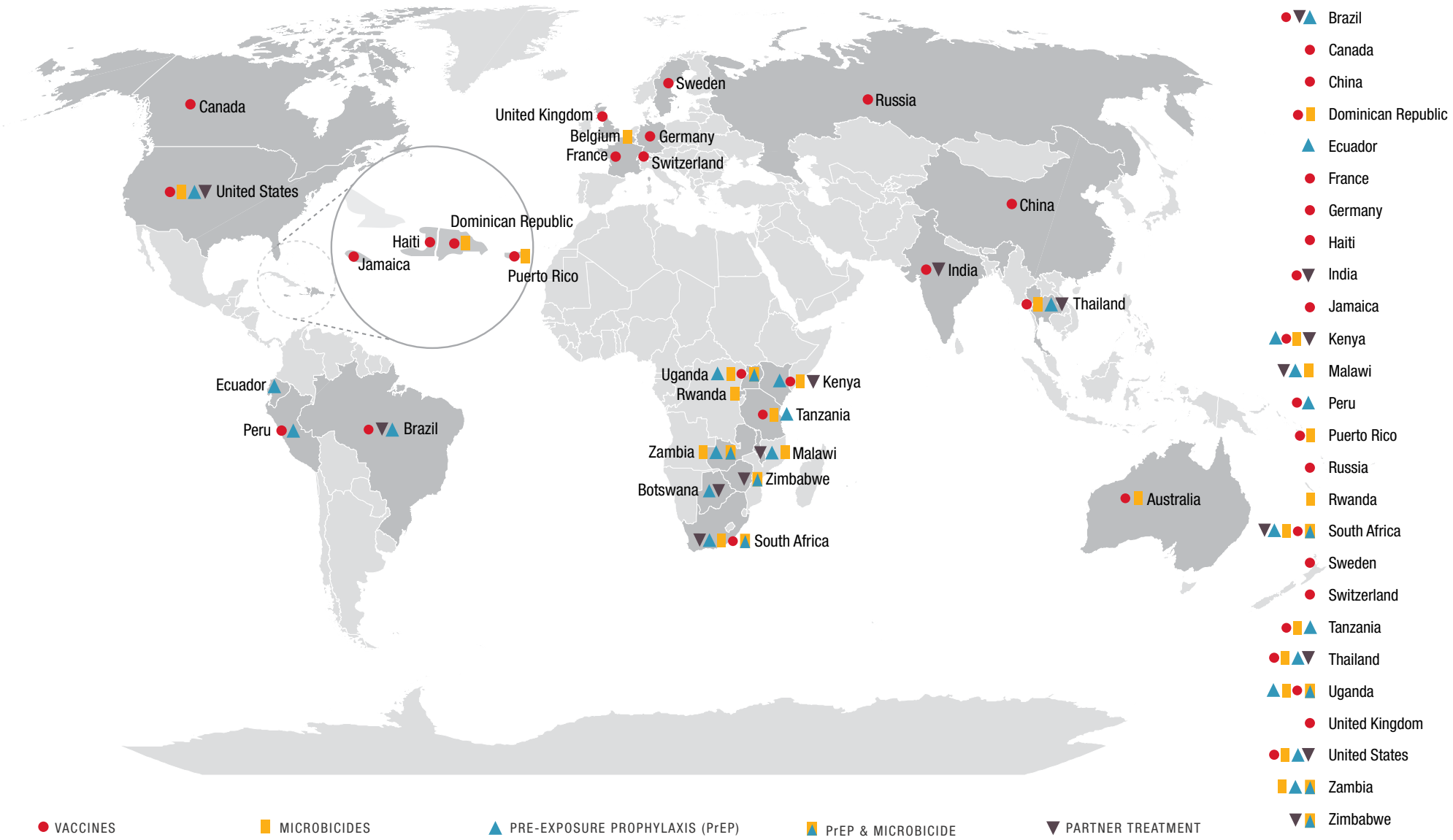
PRE-EXPOSURE PROPHYLAXIS (PrEP)
PARTNER TREATMENT
MICROBICIDE

** Trial start- and end-dates are estimates—dates may change. Additional efficacy trials and details are available on the timeline inside. Trials listed on the timeline are subject to interim analyses during the year.*

Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention
Volume 3 | No. 1
January–March 2010

ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



- Australia
- Belgium
- Botswana
- Brazil
- Canada
- China
- Dominican Republic
- Ecuador
- France
- Germany
- Haiti
- India
- Jamaica
- Kenya
- Malawi
- Peru
- Puerto Rico
- Russia
- Rwanda
- South Africa
- Sweden
- Switzerland
- Tanzania
- Thailand
- Uganda
- United Kingdom
- United States
- Zambia
- Zimbabwe

BIOMEDICAL HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE OF EFFICACY TRIAL RESULTS*

2007

CONRAD CELLULOSE SULFATE
Phase III trial to evaluate the effect of cellulose sulfate gel on vaginal HIV transmission in women (Benin, India, South Africa, Uganda, Zimbabwe)
Trial stopped early. No evidence of benefit. There were more infections among women using the gel than those using placebo, but this was not statistically significant.

FHI CELLULOSE SULFATE
Phase III trial to evaluate the safety and effectiveness of cellulose sulfate gel to prevent HIV infection in women (Nigeria)
Trial stopped following announcement of data from CONRAD trial. No evidence of safety concerns or of effectiveness.

MIRA
Phase III trial to evaluate effectiveness of the female diaphragm to prevent HIV infection (South Africa, Zimbabwe)
No evidence of benefit.

STEP (HVTN 502/Merck 023)
Phase IIb test-of-concept trial to evaluate safety and efficacy of Merck's Ad5 candidate (Australia, Brazil, Canada, Dom. Rep., Haiti, Jamaica, Peru, Puerto Rico, US)
Trial halted immunizations, September 2007. Data analysis found no evidence of benefit and potential for increased risk of HIV infection among Ad5-seropositive, uncircumcised men; follow-up continues.

PHAMBILI (HVTN 503)
Phase IIb test-of-concept trial to evaluate the safety and efficacy of Merck's Ad5 candidate (South Africa)
Trial halted enrollment and immunizations, following Step; follow-up continues.

2008

HSV-2 SUPPRESSION (HPTN 039)
Phase III trial to evaluate suppressive acyclovir treatment for the reduction of HIV infection in HSV-2 seropositive women and men who have sex with men (Peru, South Africa, US, Zambia, Zimbabwe)
No evidence of benefit.

MALE CIRCUMCISION IN HIV-POSITIVE MEN
Large-scale trial to evaluate the safety of male circumcision and its potential protective effect for HIV-negative female partners of HIV-positive circumcised males (Uganda)
Trial stopped enrollment, December 2006. No statistically significant conclusions could be drawn from sample size. However, men who resumed sex prior to wound healing were more likely to transmit HIV to their female partners.

CARRAGUARD
Phase III trial to evaluate the safety and efficacy of the vaginal microbicide Carraguard to prevent HIV infection in women (South Africa)
No evidence of benefit.

2009

HPTN 035
Phase II/IIb trial to evaluate the safety and effectiveness of the vaginal microbicides, BufferGel and 0.5% PRO 2000/5 gel, to prevent HIV infection in women (Malawi, South Africa, US, Zambia, Zimbabwe)
There were fewer infections in women using PRO 2000 than women using the placebo gel, but this difference was not statistically significant. No evidence of benefit in women using BufferGel.

PARTNERS IN PREVENTION
Phase III study to evaluate the effect of suppressive acyclovir treatment for HSV-2 on HIV transmission in HIV-serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)
No evidence of reduced rates of HIV transmission, but there were reduced rates of genital ulcers and HIV viral load.

ALVAC-AIDSVAX (RV 144)
Phase III trial to evaluate the safety and efficacy of a prime-boost vaccine strategy (ALVAC plus AIDSVAX) to prevent HIV infection (Thailand)
Initial data show that vaccine recipients were 31% less likely than placebo recipients to become HIV-infected. There was no observed effect on viral load. Additional data analysis is ongoing.

MDP 301
Phase III trial to evaluate the safety and efficacy of the 0.5% PRO 2000/5 to prevent HIV infection in women (South Africa, Tanzania, Uganda, Zambia)
No evidence of benefit.

2010

CDC 4323
Phase II trial to evaluate the clinical and behavioral safety of once-daily oral TDF among men who have sex with men (US)
Release of results expected February 2010.

CAPRISA 004
Phase IIb trial to evaluate the safety and effectiveness of 1% tenofovir gel to prevent HIV infection in women (South Africa)
Release of results expected July 2010.

CDC 4370
Phase II/III trial to evaluate the safety and efficacy of once-daily oral TDF to prevent HIV infection in injecting drug users (Thailand)

CDC 4940 (TDF2)
Phase II trial to evaluate the safety of once-daily oral TDF/FTC in heterosexual men and women (Botswana)

2011

iPrEx
Phase III trial to evaluate the safety and efficacy of once-daily oral TDF/FTC to prevent HIV infection among men who have sex with men (Brazil, Ecuador, Peru, South Africa, Thailand, US)

2012+

PARTNERS PrEP
Phase III trial to evaluate the safety and efficacy of two different strategies to prevent HIV transmission in HIV-serodiscordant couples: once-daily oral TDF and once-daily oral TDF/FTC (Kenya, Uganda)

FEM-PrEP
Phase III trial to evaluate the safety and effectiveness of once-daily oral TDF/FTC for HIV prevention in women (Kenya, Malawi, South Africa, Tanzania, Zambia)

HVTN 505
Phase II test-of-concept trial to evaluate the safety and effect on post-HIV infection viral load of the VRC's DNA prime / Ad5-boost vaccine strategy in HIV-negative, Ad5-seronegative and circumcised men who have sex with men (US)

VOICE (MTN-003)
Phase IIb trial to evaluate the safety and effectiveness of three different strategies to prevent HIV in women: once-daily oral TDF, once-daily oral TDF/FTC, and 1% tenofovir gel (South Africa, Uganda, Zambia, Zimbabwe)

HPTN 052
Phase III trial to evaluate the effectiveness of two antiretroviral treatment strategies to prevent HIV transmission in HIV-serodiscordant couples (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, US, Zimbabwe)

- VACCINE
- MICROBICIDE
- PRE-EXPOSURE PROPHYLAXIS (PrEP)
- PARTNER TREATMENT
- HERPES SIMPLEX VIRUS 2 (HSV-2) TREATMENT/SUPRESSION
- MALE CIRCUMCISION
- CERVICAL BARRIER METHOD
- TRIAL COMPLETED OR STOPPED

To view this timeline online with trial details please visit www.avac.org/timeline-website/.

Trials listed here are subject to interim analyses throughout the length of the trial.

** The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change.*

Continued from front

PRO 2000 was effective at blocking HIV from infecting human cells, though this was not so when it was actually tested in people.

PRO 2000 belongs to a class of compounds known as "non-specific entry inhibitors." The term "non-specific" refers to the fact that it does not attach to specific targets on HIV. Several non-specific entry inhibitors have been found ineffective in preventing HIV infection when tested in women. But around the world today, researchers and thousands of trial participants are pressing forward with the important work of developing and testing new potential microbicides, including candidates containing antiretrovirals (ARV), which specifically target HIV and inhibit it at the site of exposure. Many researchers believe that given the targeted mechanisms of ARV-containing microbicides, they may prove more effective than candidates like PRO 2000.

PrEP trial modified

Also in December, the US Centers for Disease Control and Prevention (CDC) announced that it would adapt its CDC 4940 (TDF2) PrEP trial in Botswana to focus exclusively on behavioral and clinical safety and adherence. The study was intended to evaluate the PrEP regimen of daily tenofovir and emtricitabine for its ability to reduce the risk of HIV in heterosexual men and women in Botswana. Now, the researchers do not believe that the trial, a joint effort of the CDC and the Botswana Ministry of Health, will be able to meet the original efficacy endpoint due to lower-than-anticipated HIV incidence rates and difficulties with retention of trial participants.

The adaptation of the CDC 4940 trial to a safety, behavioral and adherence study does not affect the suite of other ongoing PrEP trials in different populations, but highlights yet again how complex and difficult HIV prevention trials can be to design and implement. More information is available at *www.prepwatch.org*.

Interpreting the Thai vaccine trial (RV144) results

In October, additional results from a large vaccine clinical trial in Thailand were presented at the AIDS Vaccine Conference in Paris. These data provided the first direct evidence from human clinical trials that it is possible to reduce the risk of HIV infection with a vaccine. Results from the trial, known as RV144, showed a modest 30 percent protective effect against HIV transmission in those receiving the experimental prime-boost vaccine regimen—ALVAC plus AIDSVAX.

The search for answers about how the vaccine actually worked is just beginning. The trial team is working with independent scientists to build a research agenda designed to understand the reason(s) the vaccine regimen protected some people from HIV and to identify possible correlates of protection in those protected individuals. The "RV144 Scientific Steering Committee" and its four working groups on humoral immunity/innate immunity, host genetics, animal models, and cellular immunity will generate ideas that will help guide future research.

New Initiatives

Rectal microbicide momentum

Last November, the US National Institutes of Health (NIH) granted US$17.5 million for two new studies that will advance the rectal microbicide research agenda. A five-year, US$11 million grant was awarded to the multisite CHARM (Combination HIV Antiretroviral Rectal Microbicides) program, headed by Ian McGowan, to support advancement of rectal microbicide candidates. A separate four-year, US$7.5 million award went to Columbia University's Alex Carballo-Dieguez to evaluate the safety and acceptability of rectal microbicides in MSM of color. This infusion of funding almost doubles the total current global spending on rectal microbicide R&D.

African AIDS Vaccine Programme relocates

The headquarters of the African AIDS Vaccine Programme (AAVP), a network of African scientists and other stakeholders founded in 2000, is slated to move to the Uganda Virus Research Institute in Entebbe, Uganda. It is currently hosted at WHO in Geneva. ■

Not to be Missed

January 21-24: 2010 National African American MSM Leadership Conference on HIV/AIDS and other Health Disparities, *Atlanta, Georgia*

February 16-19: The 17th Conference on Retroviruses and Opportunistic Infections, *San Francisco, California*

March 15-17: Microbicide Trials Network Annual Meeting, *Arlington, Virginia*

March 21- 26: Keystone Symposia-HIV Vaccines, *Banff, Alberta, Canada* ■

About AVAC

Founded in 1995, AVAC is an international, non-profit organization that uses education, policy analysis, advocacy and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other new HIV prevention options as part of a comprehensive response to the pandemic.

101 West 23rd St. #2227 • New York, NY 10011 USA
Telephone +1 212.367.1279 • *www.avac.org*