# Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
AIDS Vaccine Advocacy Coalition

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*January–March 2009*


## AVAC's Take

Greetings! This is 2009's first issue of *Px Wire*—and what an interesting year so far. Already we've gotten intriguing, if inconclusive news, from the HPTN 035 trial that evaluated two microbicide candidates. The data suggest that one candidate, called PRO 2000, might have reduced women's risk of acquiring HIV. These data need to be confirmed—and we'll learn more from another trial of PRO 2000 called MDP 301 that concludes later this year. The interest around PRO 2000 reinforces the importance of planning in anticipation of prevention research results. In fact, as *Px Wire* went to press, advocates and investigators were gathering in Kampala for a meeting to discuss how positive results from one biomedical prevention trial might affect the design of future studies. See the table below for key trial milestones in 2009. Also in this issue is news from this year's Keystone meeting including data of note for all vaccine stakeholders. Interested? Read on!
—*AVAC*

## Data Dispatch: Keystone Conference

Shortly before *Px Wire* went to press, scientists and clinicians gathered at the annual Keystone Symposium, a highly scientific meeting focused on basic and preclinical science that included important presentations related to AIDS vaccine research.

Susan Buchbinder of the San Francisco Department of Public Health presented data from an additional 15 months of follow-up from the Step vaccine trial of which she is a co-principal investigator. The initial Step data showed that uncircumcised men with pre-existing immunity to adenovirus type 5 (Ad5) who received the Merck Ad5 vaccine candidate were at higher risk of acquiring HIV compared to men in the same group who received the placebo. There was no difference in infection risk among vaccine and placebo recipients who were circumcised and Ad5-seronegative.

At Keystone, Buchbinder reported on data collected during months 35-49 of the trial. There were 48 new infections in male volunteers in the later time period: 26 among vaccinees and 22 among placebo recipients. In a combined analysis of all the available data (months 0-49), Ad5-seropositive, uncircumcised men who got the vaccine were still at increased risk of infection compared to men in the same group who got the placebo. However, this difference in risk was smaller than in the original analysis (months 0-34). Why might the apparent vaccine effect wane when data are pooled? Buchbinder looked at individual

*Continues on back*

## At a Glance: Prime boosts for vaccines

- The Ragon Institute at Massachusetts General Hospital was established with a gift of $100 million from philanthropists Phillip and Susan Ragon to develop an AIDS vaccine. Investigator and Harvard Medical School professor Bruce Walker was appointed as the Institute's founding director. The initial scientific focus will be to expand work with HIV-positive long-term non-progressors to try to identify how their immune responses are able to control HIV infection without the help of antiretroviral therapy.
- The South African AIDS Vaccine Initiative (SAAVI) and HVTN launched trials with the first vaccine candidates to be developed in Africa by African scientists. The prime-boost regimen—SAAVI-DNA-2 and SAAVI MVA-C —is being tested in a phase I trial (HVTN 073/SAAVI 102) with sites in the US and South Africa. US sites began enrolling in late 2008 and the South African sites will begin enrollment once the US sites are fully enrolled.
- IAVI and collaborators recently launched three new phase I vaccine safety trials. Separate dose-ranging studies of a DNA plus modified vaccinia Ankara (MVA) vector-based vaccine strategy are enrolling participants in the UK and in India. The other is a small study in the US evaluating a vaccine that uses an adenovirus serotype 35 (Ad35) vector.
- The US National Institutes of Health HIV Vaccine Trials Network launched a Phase IIa study (HVTN 205) testing a DNA-MVA prime-boost at sites in the US and Peru. ■

## 2009 Trial Milestones to Watch

**1st Quarter**

Results from HPTN 035, phase II/IIb trial of the vaginal microbicide BufferGel and 0.5% PRO 2000 gel for the prevention of HIV infection in women (Malawi, South Africa, Tanzania, US, Zambia, Zimbabwe)

**2nd Quarter**

Launch of FEM-PrEP, phase III trial to test a once-daily dose of oral TDF/FTC in women (Kenya, Malawi, South Africa and Tanzania)

Launch of VOICE, phase IIb trial to test effectiveness and acceptability of vaginal tenofovir gel and oral TDF and oral TDF/FTC (Southern Africa)

Launch of HVTN 505, phase IIb discovery trial of the DNA prime-rAd5 boost regimen in men who have sex with men (US)

**3rd Quarter**

Results from Partners in Prevention, phase III trial of HSV-2 suppression in serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)

Results from Project Unity, behavioral study of different risk-reduction interventions for HIV vaccine trials (US)

Results from ALVAC-AIDSVAX, phase III trial of a prime-boost combination preventive HIV vaccine (Thailand)

**4th Quarter**

Results from MDP 301, phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women (South Africa, Tanzania, Uganda)

Results from CDC 4323, phase II trial to test the clinical and behavioral safety of a once-daily dose of oral TDF among HIV-negative men who have sex with men (US)

*Note: Trial start- and end-dates are estimates. Due to the nature of clinical trials the actual dates may change. Trials listed on the timeline on the next page are also subject to interim analyses during the year.*

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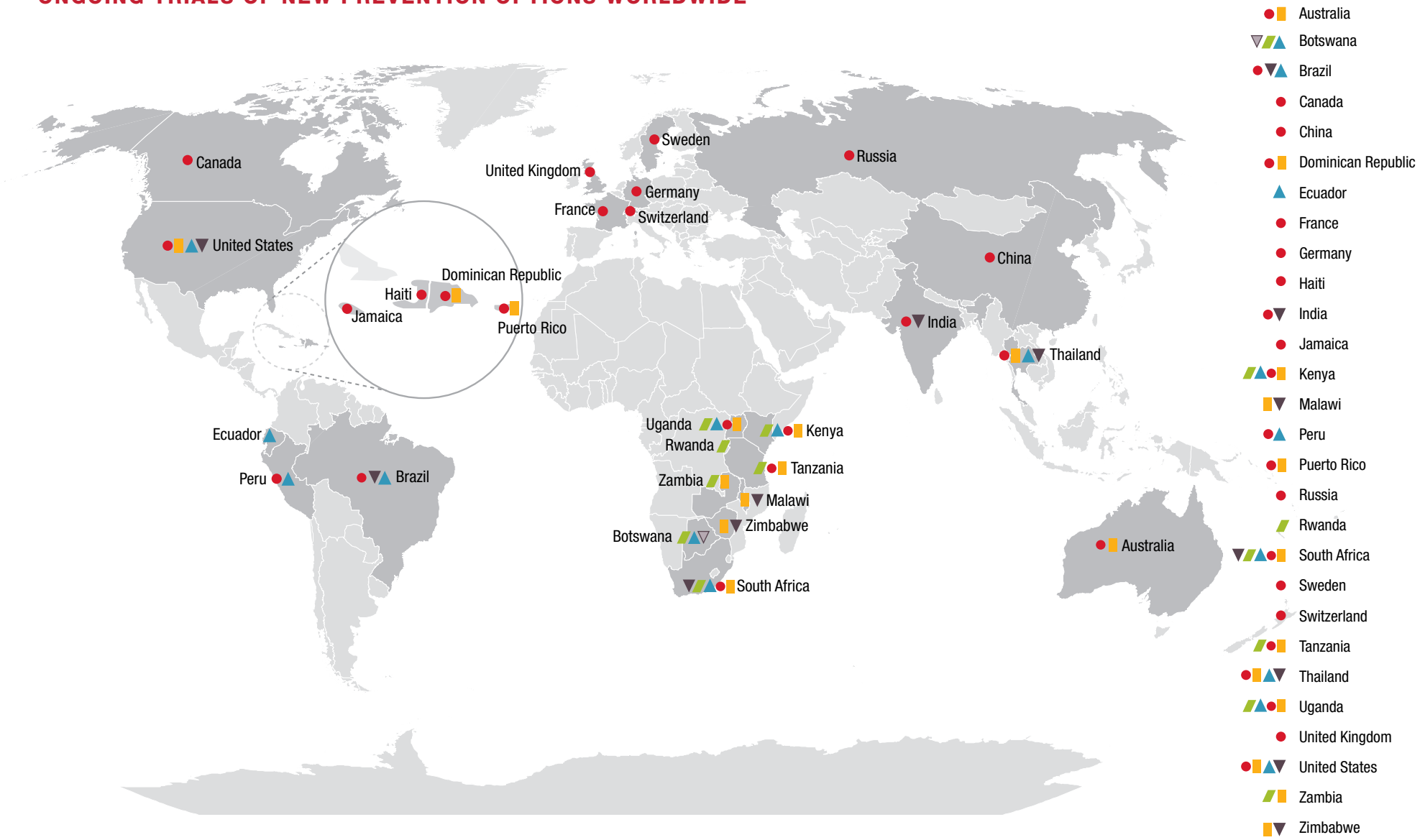
## ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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

## 2007

**FHI CELLULOSE SULFATE**
Phase III trial of the vaginal microbicide cellulose sulfate gel for the prevention of HIV infection in women (Nigeria)
**Trial stopped early January 2007**
**Results announced July 2007**

**CONRAD CELLULOSE SULFATE**
Phase III trial of the vaginal microbicide cellulose sulfate gel for the prevention of HIV infection in women (Benin, India, South Africa, Uganda, Zimbabwe)
**Trial stopped early January 2007**
**Results announced July 2007**

**MIRA**
Phase III trial of the female diaphragm to prevent HIV infection in women (South Africa, Zimbabwe)
**Results announced July 2007**

**STEP**
Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (Australia, Brazil, Canada, Dom. Rep., Haiti, Jamaica, Peru, Puerto Rico, US)
**Trial halted immunizations, September 2007. Follow-up and data collection continue**.

**PHAMBILI**
Test-of-concept trial of Merck's adenovirus preventive HIV vaccine candidate (South Africa)
**Trial halted enrollment and immunizations, September 2007. Follow-up and data collection continue.**

## 2008

**HSV-2 SUPPRESSION (HPTN 039)**
Phase III trial of acyclovir for the reduction of HIV infection in high-risk, HIV-negative, HSV-2 seropositive individuals (Peru, South Africa, US, Zambia, Zimbabwe)
**Results announced February 2008**

**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 and surgeries in December 2006.**
**Results announced February 2008**

**CARRAGUARD**
Phase III trial of the vaginal microbicide Carraguard for the prevention of HIV infection in women (South Africa)
**Results announced February 2008**

## 2009

**HPTN 035**
Phase II/IIb trial of the vaginal microbicides BufferGel and 0.5% PRO 2000/5 gel for the prevention of HIV infection in women (Malawi, South Africa, Tanzania, US, Zambia, Zimbabwe)
**Results announced February 2009**

**PROJECT UNITY**
Study of different risk-reduction interventions for HIV vaccine trials (US)
**Trial completed; results expected this year**

**PARTNERS IN PREVENTION**
Phase III trial of HSV-2 suppression in serodiscordant couples (Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia)
**Trial completed; results to be announced July 2009**

**MDP 301**
Phase III trial of the vaginal microbicide PRO 2000 for the prevention of HIV infection in women (South Africa, Tanzania, Uganda)

**ALVAC-AIDSVAX**
Phase III trial of a prime-boost combination preventive HIV vaccine (Thailand)

**CDC 4323**
Phase II trial to test the clinical and behavioral safety of a once-daily dose of oral TDF among HIV-negative men who have sex with men (US)

## 2010

**CDC 4370**
Phase II/III trial of a once-daily dose of oral TDF to prevent HIV infection in injecting drug users (Thailand)

**iPrEx**
Phase III trial of a once-daily dose of oral TDF/FTC to prevent HIV infection in high-risk men who have sex with men (Brazil, Ecuador, Peru, South Africa, Thailand, US)

**CAPRISA 004**
Phase IIb trial of the vaginal microbicide tenofovir gel for the prevention of HIV infection in women (South Africa)

## 2011

**CDC 4940**
Phase III trial of a once-daily dose of TDF/FTC to prevent HIV infection in heterosexual men and women (Botswana)

**PROJECT ACCEPT**
Phase III trial of community mobilization, mobile testing, same-day results, and post-test support for HIV (South Africa, Tanzania, Thailand, Zimbabwe)

## 2012+

**PARTNERS PrEP**
Phase III trial to determine the effectiveness of two different HIV prevention strategies; once-daily oral TDF and once-daily oral TDF/FTC in serodiscordant heterosexual couples (Kenya, Uganda)

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

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

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

** The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor the trials' progress and will update the timeline accordingly.*

*If you have any questions or comments regarding the information presented here please email avac@avac.org.*

*Data Dispatch continued from front*

risk over time, starting with enrollment in the study and reported that the risk of infection in vaccinees compared to placebo recipients appears to be highest in the first 18 months after enrollment in the study and then lessen. The mechanism behind this is still unknown. Bottom line: there's still an apparent vaccine effect in uncircumcised, Ad5-seropositive men but it declines over time. Importantly, Ad5-seronegative, circumcised men continue to have no increased risk associated with the vaccine.

Keystone also included data from separate animal studies that may be relevant to HVTN 505, a proposed study of a DNA prime-Ad5 boost combination designed by the NIH Vaccine Research Center. Dan Barouch from Harvard Medical School described one study in which two groups of six animals each were immunized with two different DNA prime-adenovirus boost strategies which differed in terms of the adjuvant used in combination with the DNA prime. The adenovirus-vectored component was a chimera of 99 percent Ad5 plus hexon protein fragments of Ad48 with inserts of SIV gag, pol, nef plus/minus env. Six more animals received Ad only; 6 received the Ad without the env insert, and 6 received a placebo. Six months after the last immunization, all of the animals were challenged intravenously with high-dose SIVmac251, a simian immunodeficiency virus engineered to cause infection after a single high-dose exposure in unprotected primates.

While the DNA prime-chimeric Ad vector combinations induced the strongest immune responses, the animals in the prime-boost groups had no benefit in terms of viral setpoint or survival. Animals in both prime-boost groups had viral loads and survival rates (4/12 alive at 500 days) comparable to the placebo group. Ten out of 12 chimeric Ad-alone animals were alive at 500 days. In an exploratory analysis combining both prime-boost groups, the animals that received the DNA-chimeric Ad combinations had significantly higher viral loads than the animals that received Ad alone.

Barouch emphasized that these findings reflect an exploratory combined analysis and thus should be viewed as hypothesis-generating rather than as conclusive.

Another study, presented by Diane Bolton from the Vaccine Research Center, looked at DNA plus Ad5 versus Ad5 alone in rhesus macaques. In this study there was no statistically significant difference in outcomes in the animals that received DNA plus Ad5 versus the Ad5 alone, though there was a trend towards better results in the DNA plus Ad5 vaccinees.

What's the bottom line for advocates who may be unfamiliar with the caveats and complexities of non-human primate data? That there are studies relevant to HVTN 505 which suggest that the regimen may have a benefit and at least one—Barouch's—that suggests that it might not be the optimal regimen to test.

Both positive and negative data belong in discussions of the preclinical rationale for any study, including HVTN 505. While the DNA prime-chimeric Ad regimen is not identical to the VRC strategy to be used in HVTN 505, there are similarities. Public discussions and materials that include the scientific rationale for HVTN 505 are expected to reference both supporting data and negative or flat data. If there is any reference to preclinical data made in the HVTN 505 informed consent, this should also reflect the full array of current findings.

AVAC will be developing additional materials to inform ongoing consultations about HVTN 505. Please send questions or comments to *avac@avac.org*. ■

## Coming Up

AVAC's Annual Report on the status of biomedical HIV prevention research will be released in mid-May. This year's Report takes stock of vaccine science, the Global HIV Vaccine Enterprise, the potential benefits of ARV-based prevention, and more. The Report launch coincides with HIV Vaccine Awareness Day (HVAD), May 18. New York City readers of *Px Wire* are invited to attend a community forum that AVAC is cosponsoring with TAG and the Enterprise. For more information, email *avac@avac.org* To pre-order copies of AVAC Report 2009, email *publications@avac.org* ■

## Not to be Missed

**April 20-22:** Microbicide Trials Network (MTN) Annual Meeting, *Arlington, Virginia*

**May 4-8:** HIV Prevention Trials Network (HPTN) Annual Meeting, *National Harbor, Maryland*

**May 12-14:** HIV Vaccine Trials Network (HVTN) full group meeting, *Washington, DC*

**May 18:** HIV Vaccine Awareness Day, events listed at www.bethegeneration.nih.gov

**May 26-30:** Global Health Council, 36th Annual International Conference on Global Health, *Washington, DC*

**June 22-26:** FORO 2009, Regional meeting on AIDS for Latin America and the Caribbean, *Lima, Peru*

## About AVAC

AVAC seeks to create a favorable policy and social environment for accelerated ethical research and eventual global delivery of new HIV prevention options as part of a comprehensive response to the pandemic.

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