Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention

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AVAC's Take

It's been another busy quarter in the biomedical prevention research field. Below, we review some of the key findings, starting with data from a trial of HSV-2 suppression in more than 3,400 HIV-serodiscordant couples. This trial didn't show an HIV risk reduction benefit, but it still has a lot to teach the field. Even as we plan ahead for results, we have to be sure that current trials are well-resourced and well-designed—and the HSV-2 trial is a terrific source of insights on that front. The same team that worked on the HSV-2 trial is currently conducting Partners in Prevention, a PrEP trial in seriodiscordant couples. We cover more PrEP developments below. As we head into the second half of 2009, please be in touch, and stay tuned for our new, expanded website to be launched in August 2009!
—*AVAC*

Data Dispatch: A Field on the Move

In the previous issue of *Px Wire*, we presented the "2009 Trial Milestones to Watch." The biomedical HIV prevention research field moves quickly—and midway through 2009, there are already many changes worth noting. Here's a closer look:

HSV-2 Treatment: Disappointing data on HIV risk reduction

May brought the announcement of results from the Partners in Prevention study of suppressive HSV-2 treatment to reduce transmission of HIV. The study, which enrolled more than 3,400 HIV-serodiscordant couples (one HIV-positive, one HIV-negative), tested whether ongoing suppressive treatment of HSV-2 in the HIV-positive partner reduced the risk of HIV transmission to the HIV-negative partner. Volunteers who were HIV- and HSV 2- positive and received suppressive acyclovir had lower HIV viral loads and lower rates of genital ulcers than volunteers who received placebo. The finding that HSV-2 suppression is linked to lower HIV viral load underscores the connection between the two viruses. However, suppressive HSV-2 treatment did not reduce rates of HIV transmission.

PRO 2000 Microbicide: Planning ahead

In May, WHO and UNAIDS convened a meeting of HIV prevention stakeholders to explore the implications of results from an ongoing microbicide trial expected to be completed at the end of this year. The trial, called MDP 301, is testing the candidate PRO 2000. This meeting is an indication of the interest in PRO 2000 that sprang up after findings from HPTN 035—a different trial also testing PRO 2000—were announced in February. In HPTN 035, the women who used PRO 2000 along with a standard prevention package had fewer HIV infections than the group of women who used the standard prevention package alone. But the difference in rates of infections was not statistically significant—meaning that no one could say for sure whether it was a promising sign, or a coincidence. (There was no evidence of risk reduction in the women using BufferGel, the other candidate being tested in 035.)

Next steps will depend on whether there is clear evidence of risk reduction, another indeterminate finding, or no evidence of benefit in MDP 301. There was also discussion about the timelines for scaling up the manufacture of PRO 2000 for widespread access, should the data warrant licensure. The consultation raised many issues, not least of which was the need for up to two years or more for manufacturing scale-up and licensing of the product for post-trial access and broader availability, should it be warranted.

HVTN 505: Approved, enrolling and engaging questions

The US National Institutes of Health (NIH)–funded HIV Vaccine Trials Network (HVTN) has begun screening volunteers for HVTN 505, a test-of-concept vaccine study. The NIH's Vaccine Research Center's strategy being tested consists of three DNA "prime" immunizations and a single adenovirus 5–vectored "boost." The projected 18-month enrollment period began in June and will follow trial participants for approximately three years. The trial is recruiting gay men and other men who have sex with men in the US who are circumcised and adenovirus 5–negative. The trial is primarily focused on understanding whether the vaccine can reduce viral load setpoint among volunteers who are immunized and go on to become HIV-infected through unprotected sex or other exposures. Both the enrollment criteria and the primary endpoint of a viral load reduction are complex concepts. Community stakeholders

Continues on back

At a Glance: Safer breastfeeding

In June, the Bill & Melinda Gates Foundation awarded $100,000 to Family Health International for the study of a nipple shield to help prevent HIV transmission during breastfeeding. The money is part of Gates' Grand Challenges Exploration grant for innovative global health research. The study will look to see if a felt-like piece of textile soaked in sodium dodecyl suflate—a compound that inactivates HIV—could be placed on the nipple and act as a safe way to filter HIV out of breast milk.The project, known as "Just Milk," aims to identify a safe, simple, inexpensive strategy for reducing HIV transmission during breastfeeding.

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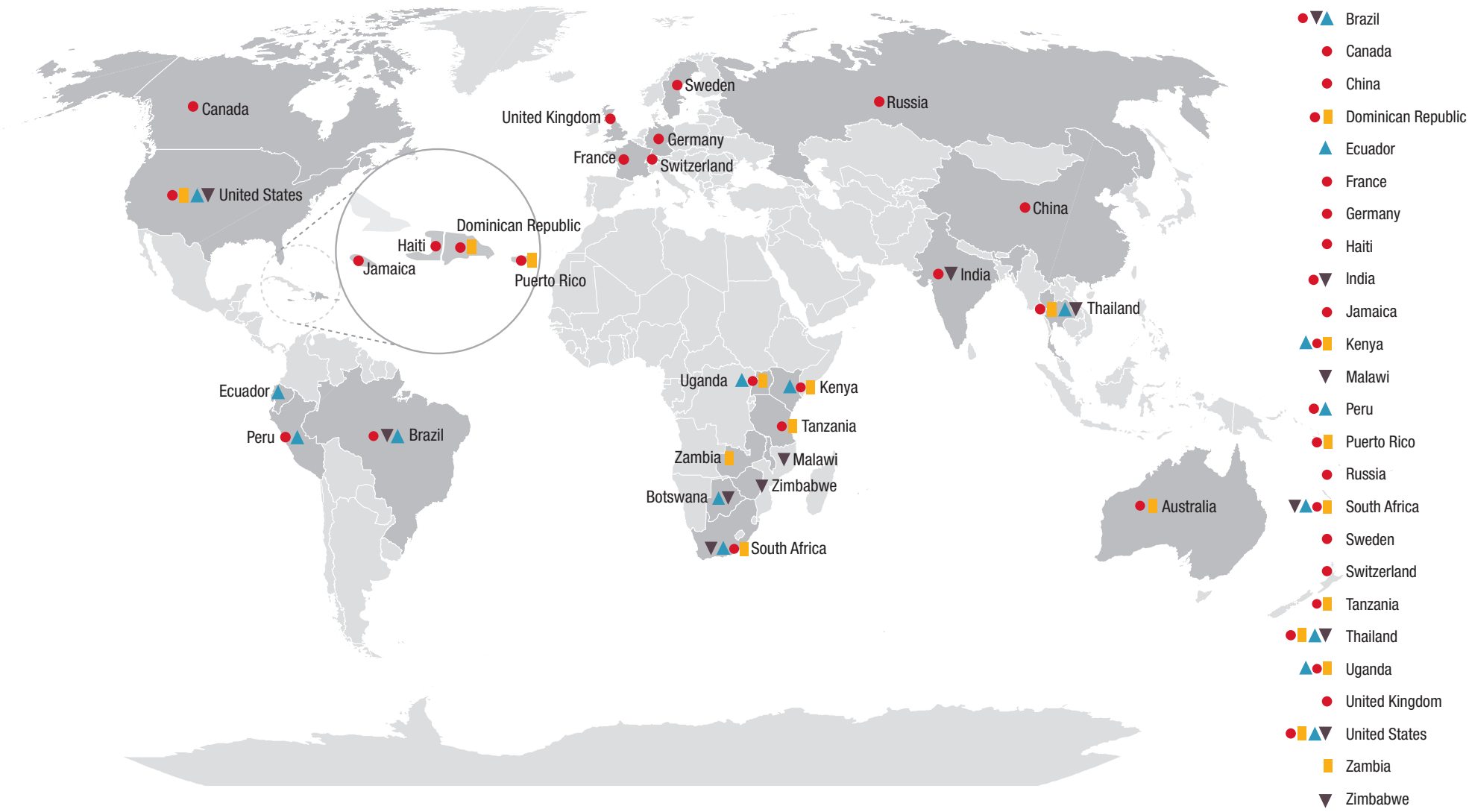
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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)
Release of results expected in October 2009.

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)
Release of results expected in November 2009.

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 in 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)

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)

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

2011

CDC 4940
Phase III trial to evaluate the safety and efficacy of once-daily oral TDF/FTC to prevent HIV infection in heterosexual men and women (Botswana)

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)

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, Malawi, South Africa, Thailand, US, Zimbabwe)

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

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)

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)

- VACCINE
- PRE-EXPOSURE PROPHYLAXIS (PrEP)
- HERPES SIMPLEX VIRUS 2 (HSV-2) TREATMENT/SUPRESSION
- MICROBICIDE
- MALE CIRCUMCISION
- CERVICAL BARRIER METHOD
- PARTNER TREATMENT
- 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.*

Data Dispatch continued from front

have been raising concerns about the ways that these concepts are being presented to those who might be asked to participate in or support this trial. The trial will take place in 12 US cities, each of which will be holding a town hall meeting in the coming six months to clarify some of these issues. (For information on the history of this candidate, visit *www.avac.org/vax_update.htm*.)

PrEP: Intermittent dosing trial to begin

The International AIDS Vaccine Initiative (IAVI) is planning the launch of a small study on the safety of and adherence to intermittent versus once-daily oral PrEP dosing. The trial is scheduled to begin in July, pending regulatory approval. The trial will take place in collaboration with IAVI's partners in Kenya and Uganda. All of the current oral PrEP efficacy trials are looking at whether daily use of ARVs by HIV-negative people may reduce their risk of HIV infection. The term "intermittent dosing" can refer to a range of strategies including taking PrEP some days, but not others, or taking it only when a person feels he or she is at higher risk. [A glossary of intermittent PrEP strategies can be downloaded at *www.prepwatch.org*.] The IAVI trial will begin to address this priority issue for PrEP stakeholders: in the real world, people might not take PrEP drugs every day, and there is a need to know whether other dosing strategies work safely. In December 2008, AVAC held a think tank to help grapple with these issues—the meeting summary is available at *www.prepwatch.org*. ■

Recently released

AVAC's annual report on the biomedical HIV prevention research field was released in May. This year's report—*Piecing Together the HIV Prevention Puzzle*—takes stock of vaccine science, the Global HIV Vaccine Enterprise, the global need to plan ahead for PrEP and other forms of ARV-based prevention, research related to gay men and other men who have sex with men—and more. To download or order printed copies of the report visit *www.avac.org/reports.htm*.

Coming Up

- This August, AVAC will unveil a redesign of its website—*www.avac.org*. The new site will provide comprehensive coverage of the full range of interventions under study today, including AIDS vaccines, PrEP, microbicides, treatment as prevention, and herpes suppression, along with the proven intervention medical male circumcision. It will feature fact sheets at basic and intermediate levels, an event calendar, research updates, easy-to-understand guides to research and rollout, and more.
- *Adapting to Realities: Trends in HIV Prevention Research* Curious about how HIV prevention research dollars were allocated in 2008 and how it compares to years past? In its fifth edition, the HIV Vaccines and Microbicides Resource Tracking Working Group report documents investment trends since 2000. It will be available from mid-July at *www.hivresourcetracking.org*. ■

Not to be Missed

July 19–22: 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, *Cape Town, www.ias2009.org*

- **Sunday, July 19, 10:15–12:15: Satellite, Session Room 4:** Rectal Microbicide Development—An African Perspective, convened by AVAC, IRMA, MTN and Health4Men
- **Sunday, July 19, 14:45–18:00: Satellite, Mini Room 2:** The Promise and Perils of ARV-based Prevention: A dialogue of optimism & informed skepticism, convened by AVAC and IAS

For a biomedical HIV prevention research conference roadmap, go to www.avac.org/IAS.htm

August 23–26: CDC's 2009 National HIV Prevention Conference, *Atlanta, www.2009nhpc.org*

- **August 23, 8:00–15:30:** Preparing for PrEP: A Stakeholder's Dialogue, one-day pre-conference session Register at *http://chipts.ucla.edu/PrEP*

December 13–15: Fifth African AIDS Vaccine Programme (AAVP) Forum: Building a Common Platform for HIV Prevention Research in Africa, *Kampala, Uganda www.who.int/vaccine_research/diseases/hiv/aavp/en*

About AVAC

AVAC
Global Advocacy for HIV Prevention

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.

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