Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention

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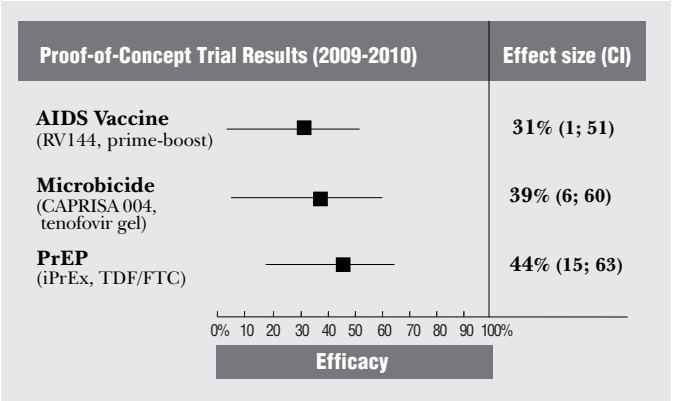
AVAC's Take

In just over a year, three large-scale trials provided evidence of efficacy for long-sought biomedical prevention strategies: a vaccine (a prime-boost evaluated in the RV144 trial), a microbicide (1% tenofovir gel evaluated in the CAPRISA 004 trial) and an oral pre-exposure prophylaxis (PrEP) strategy (daily TDF/FTC evaluated in the iPrEx trial). At first glance, the outcomes appear similar—each had a point estimate of efficacy between 30 and 44 percent. But scratch the surface and it becomes clear that the interpretations and ramifications for each of these trials are quite distinct. In this exciting time, advocates' voices are needed to guide next steps. This is why we've chosen to start 2011 with a review of what's happened and what lies ahead for each strategy.



AIDS Vaccines

It's been 15 months since the team behind the 16,400-person Thai prime-boost trial (also known as RV144) announced that a strategy, comprised of ALVAC-HIV (vCP1521) and AIDSVAX B/E, reduced risk of infection by 31 percent overall. The trial was a huge undertaking and the results were a big surprise, in large part because of the evidence that the vaccine regimen protected against infection but did not have any impact on viral load in HIV-negative people who received it and later became HIV-infected. There is no clear explanation for the immunologic basis of the protection. A range of questions also remains about the durability of protection, whether the result can be repeated, or whether the finding would be the same for a high-risk population. Future efficacy trials using a similar prime-boost regimen are planned to begin in 2014 in Thailand and southern Africa, and it is likely that new lots of vaccine will need to be manufactured for these efficacy trials.

At present, the only ongoing large-scale vaccine trial is HVTN 505, a trial of a DNA prime/Ad5 boost vaccine strategy that is being studied in the US. Its researchers are considering the implications of the positive iPrEx data on the HVTN 505 protocol. Like iPrEx, HVTN 505 is targeting gay men and other men who have sex with men (MSM). Therefore iPrEx has raised questions like: Should the protocol for 505 be amended to evaluate PrEP as well as the vaccine strategy? What data on informal PrEP use could the trial collect—and how?

What lies ahead for AIDS vaccines?

- RV144 data are still being analyzed. A working group of leading researchers is vetting and conducting a range of immune analyses designed to identify a correlate of protection.
- RV144 participants are still being followed and plans are underway to obtain informed consent from participants to receive an additional boost with a yet-to-be-determined vaccine candidate to learn more about immune responses over the long term.
- The RV144 trial partners are developing a follow-up trial in Thailand that would enroll MSM and could serve as a confirmatory trial for the initial RV144 finding in a higher-incidence cohort. Key questions include: What vaccine regimens will be used, and how will the iPrEx findings impact trial design?
- HVTN 505 trial leaders and staff continue to reach out to various community advocates for discussions about what the iPrEx data could or should mean for the HVTN 505 protocol.
- A newly energized search for broadly effective neutralizing antibodies continues in addition to the Thai vaccine follow-up research.

ARV-based prevention (microbicides and PrEP)

In July 2010, the CAPRISA 004 trial team announced the finding that the microbicide 1% tenofovir gel reduced women's risk of HIV infection by an estimated 39 percent overall when applied within 12 hours before and after sex. This was a relatively small, proof-of-concept trial, and there has been general consensus that more trial data are needed before asking regulators to evaluate 1% tenofovir gel for licensure. There are open questions about what additional data are needed for regulators in South Africa, the US and elsewhere, and what trials in addition to CAPRISA 004 and the ongoing VOICE study might be necessary for regulatory approval and/or for optimizing future delivery.

In November 2010, the iPrEx trial team announced that the PrEP strategy daily oral TDF/FTC (brand name Truvada) reduced risk of HIV infection by an estimated 44 percent overall in sexually active MSM and transgender women from four continents. This widely anticipated result involved a pill that is already licensed for use as an HIV treatment. This means that PrEP using TDF/FTC is far more readily available than vaccines or microbicides, which are not available outside of clinical trial settings.

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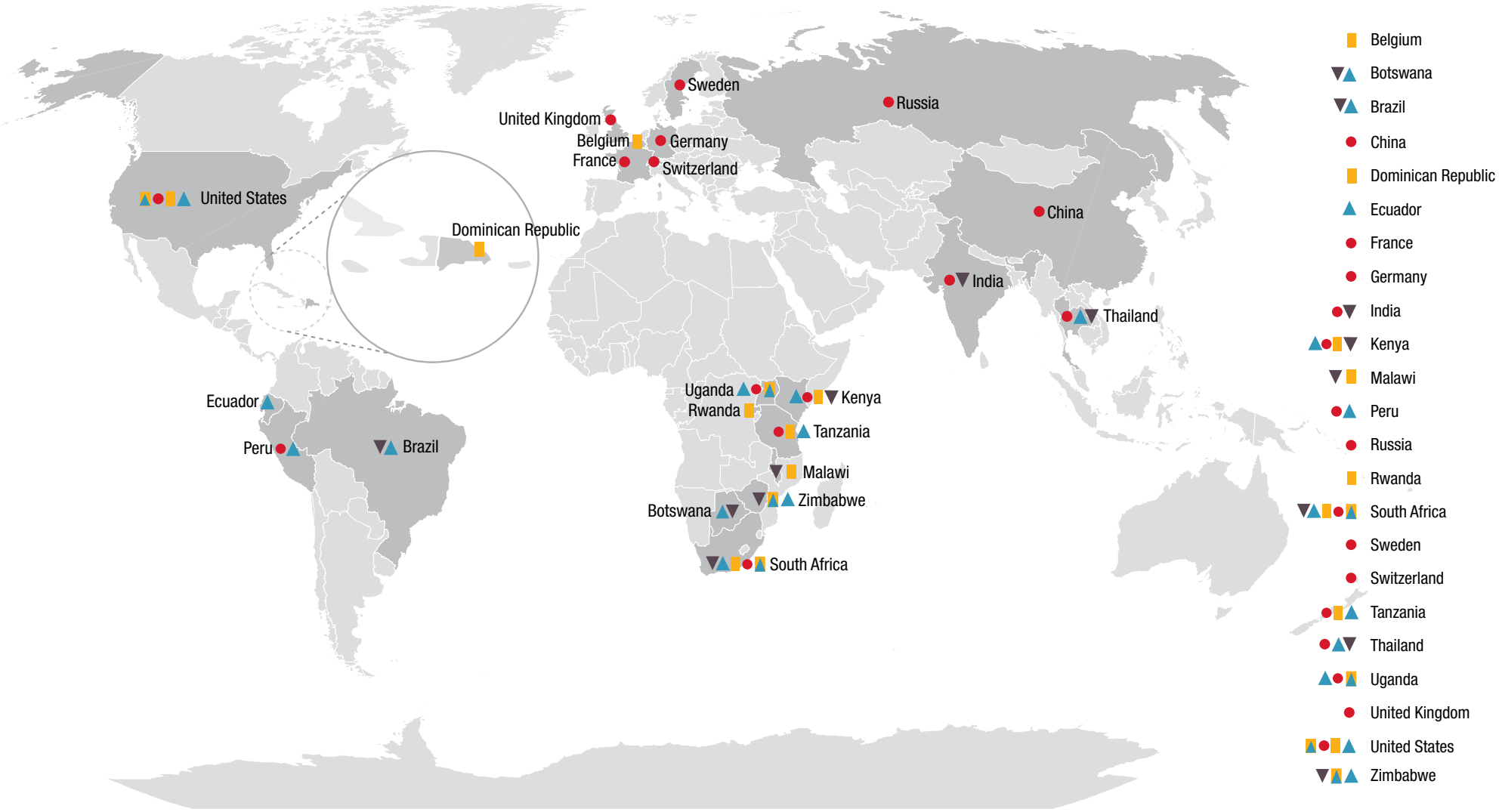
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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)
Initial data showed that vaccine recipients were 31 percent 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

CAPRISA 004
Phase IIb trial to evaluate the safety and effectiveness of 1% tenofovir gel to prevent HIV infection in women (South Africa)
There were 39 percent fewer infections among women who received 1% tenofovir gel compared to women who received the placebo gel.

CDC 4323
Phase II trial to evaluate the clinical and behavioral safety of daily oral TDF among men who have sex with men (US)
The trial reported no serious adverse events and preliminary data showed PrEP use did not have a significant effect on HIV risk behavior. Additional data expected in 2011.

iPrEx
Phase III trial to evaluate the safety and efficacy of daily oral TDF/FTC to prevent HIV infection among men who have sex with men (Brazil, Ecuador, Peru, South Africa, Thailand, US)
Showed that daily TDF/FTC reduced risk of HIV infection by an average of 43.8 percent in gay men, transgender women and other men who have sex with men.

2011

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

2012+

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

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

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

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

* *The trial end-dates are estimates—due to the nature of clinical trials the actual dates may change. Trials listed here are subject to interim analyses.*
To view this timeline online with trial details please visit *www.avac.org/timeline.*

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What lies ahead for microbicides?

- The CAPRISA team is preparing the 004 trial data for regulators and developed two follow-up studies with CAPRISA 004 participants and communities: one on questions relevant to program design that will provide ongoing access to the gel for trial participants; and one to provide care, treatment and monitoring for seroconverters from CAPRISA 004. The latter trial will compare treatment outcomes among women who received 1% tenofovir gel and those who received placebo in 004. These trials are awaiting funding and approvals.
- The Microbicide Trials Network's ongoing VOICE trial of daily 1% tenofovir gel and two oral PrEP regimens (TDF/FTC and TDF alone) is expected to complete enrollment by mid-2011 and could provide results by late 2012. Participants were informed about the results of CAPRISA 004 and iPrEx, and staff is amending consent forms and other trial materials.
- The US Food and Drug Administration (FDA) has indicated that it will consider licensing 1% tenofovir gel based on data from CAPRISA 004 and the ongoing VOICE study—despite the trials' different dosing. South Africa's Medicines Control Council has indicated informally that it would like additional data from a trial evaluating the dosing strategy tested in CAPRISA 004. This could come from the FACTS 001 trial.
- South African researchers have developed a research protocol for FACTS 001 (Follow-on African Consortium of Tenofovir Studies). The trial would be similar to CAPRISA 004, proposed for several sites in South Africa and one in Kenya. It would enroll women 16–30 years old, and pending approvals and funding could start enrolling by mid-2011. The South African government has committed funding, and other support is pending. Other studies are continuing or being developed to provide additional clinical data on safety in adolescents, menopausal women, pregnancy and rectal use by women and men.
- A technical planning meeting is scheduled to take place in South Africa in mid-2011 and will look at a range of issues related to potential introduction of 1% tenofovir gel. The manufacturing partners are working on the complex arrangements for technology transfer, investment and capacity development to produce 1% tenofovir gel in South Africa and to distribute it in the region.
- A phase III safety and efficacy microbicide trial looking at a vaginal ring carrying the antiretroviral dapivirine is scheduled to launch this year.

What lies ahead for PrEP?

- The open-label follow-up protocol developed by the iPrEx team is expected to begin enrolling as early as March.
- The US Centers for Disease Control and Prevention is drafting PrEP guidelines for US-based health practitioners by the end of the year and interim guidance will be available this quarter. Fenway Health, one of the two US iPrEx sites, recently released its interim guidelines for prescribing and supporting patients seeking more information on PrEP. For details, visit *www.fenwayhealth.org/prepguidance*.
- Gilead, the maker of TDF/FTC, is in conversation with the US FDA to market the drug combination specifically for HIV prevention via a label change to include a preventive indication.
- A range of related PrEP studies continues in other risk groups, locations and with different dosing. For details, visit *www.avac.org/prep*. ■

Recently Released

MSMGF HIV Prevention Services and PrEP Knowledge/Attitudes Survey (Global Forum on MSM and HIV) provides a sobering view of the prevention challenges facing MSM. For details go to *http://www.msmgf.org/*.

Making Medical Male Circumcision Work for Women contains the findings of a five-country community research project undertaken by the Women's HIV Prevention Tracking Project, a collaborative initiative of AVAC, ATHENA and partners in Kenya, Namibia, South Africa, Swaziland and Uganda. It documents women's perspectives on male circumcision for HIV prevention. To download copies go to *www.avac.org/whipt*. ■

Not to be Missed

January 20–23: 2011 National African American MSM Leadership Conference on HIV/AIDS and Other Health Disparities, *Brooklyn, New York*

February 27–March 2: 18th Conference on Retroviruses and Opportunistic Infections, *Boston, Massachusetts*

March 28–31: Microbicide Trials Network 2011 Annual Meeting, *Arlington, Virginia* ■

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.

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