Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
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AVAC's Take

Over the past 18 months, advocates and activists working in the biomedical prevention research field have plunged into the arena of implementation and post-trial access. What happens after a trial has an initial positive finding? How does the field expand on and confirm positive results, while acknowledging that trials can—and do—yield mixed data as recently seen in Partners PrEP and VOICE studies? (For details, see our write-up of VOICE updates in *At a Glance*.) How do stakeholders keep a broad pipeline of next-generation products moving through development while also advocating for prevention and treatment delivery—especially in the context of constrained resources for the global AIDS response?

Px Wire can't answer all these questions, but in our centerfold timeline and trials table, we've added new categories and types of trials with the goal of helping us all keep track of the constantly evolving landscape. —*AVAC* ■

At a Glance

PrEP: New directions amidst mixed data

In September, as *Px Wire* went to press, the Microbicide Trials Network announced that VOICE, its five-arm HIV prevention trial in women, would be modified: The arm of the trial in which women were taking oral tenofovir (TDF) would be stopped and the women would exit the trial. The announcement came after an interim independent data review showed that there was no possibility that daily oral TDF would reduce risk of HIV in the context of the VOICE trial. There were no safety concerns in the trial, and the daily oral TDF/FTC and daily 1% tenofovir gel arms of the trial, along with two placebo arms, will continue. The trial is scheduled to conclude in 2012 with data available early in 2013.

Thus far, the data related to oral PrEP in women are mixed. The Partners PrEP trial found that both oral TDF and oral TDF/FTC reduced risk of HIV infection among HIV-negative men and women in heterosexual HIV-serodiscordant couples. The TDF2 trial, an expanded safety trial, also found evidence of efficacy for daily oral TDF/FTC in both men and women, though the numbers were too small to draw definitive conclusions by gender. In contrast, there was no evidence of benefit from daily oral TDF/FTC in the FEM-PrEP trial—and, as noted above, the oral TDF arm is stopping in VOICE. The 1% tenofovir gel was found effective in the CAPRISA 004 study. Data analysis is ongoing and will hopefully shed light on why PrEP worked for women in some contexts and not others.

Previously, the iPrEx trial studied daily TDF/FTC as PrEP in gay men, men who have sex with men (MSM) and transgender women. It found that TDF/FTC reduced HIV risk by 42 percent, and additional data will come from a follow-on open-label trial. In January 2011, two months after the iPrEx result, the US CDC released interim guidance for TDF/FTC as PrEP for gay men and transgender women. It is now developing US Public Health Service guidelines scheduled to be ready for public comment early in 2012. These guidelines may only address TDF/FTC as PrEP for MSM. When trial results for heterosexual women and men and IDUs are published and full review of the data is possible, CDC will consider including these populations in the guidelines.

At the same time, Gilead Sciences Inc., the manufacturer of oral TDF and TDF/FTC, plans to submit an application to the US FDA for approval of TDF/FTC for HIV prevention. Currently, TDF/FTC is only approved for HIV/AIDS treatment. Gilead plans to submit all available data from PrEP studies in early 2012. Once the application is submitted, the FDA review process, including a public hearing, will take approximately six to ten months.

If the FDA determines that a prevention indication is warranted, this could increase the likelihood of financing the costs of PrEP. Right now, clinicians who want to prescribe TDF/FTC for patients have to do so as "off-label" use. A prevention label might also give providers more confidence in discussing PrEP with potential users. Internationally, a prevention indication might also facilitate public financing for TDF/FTC for PrEP demonstration projects.

Next steps for PrEP demonstration projects

The University of California, San Francisco, in conjunction with the San Francisco Department of Public Health, was awarded an NIH grant to implement pilot PrEP studies using daily TDF/FTC in gay men and other MSM in San Francisco, set to launch early next year. The two-site demonstration project is a pilot study that would enroll a total of 300 HIV-negative MSM, initiated to help determine optimal programming and monitoring for PrEP in the "real world". San Francisco is expected to partner with counterparts in Miami, enrolling an additional 200 men. The project plans to look at community demand, social equity to ensure low-income and men of color have access, behavior (adherence and risk compensation) and additional effectiveness data. In addition, the CDC is discussing the evaluation of program cost and financing with select Medicaid programs and private insurers.

PrEP: Roadmap to the Real World (www.avac.org/prep/roadmap), a document issued by a coalition of advocates, including AVAC and Project Inform, urges the US Department of HHS to develop a plan addressing the number and geographic location of PrEP pilot projects that will be needed to assess the relevance, feasibility and potential efficacy of PrEP for different communities of MSM and transgender women; the questions to be addressed

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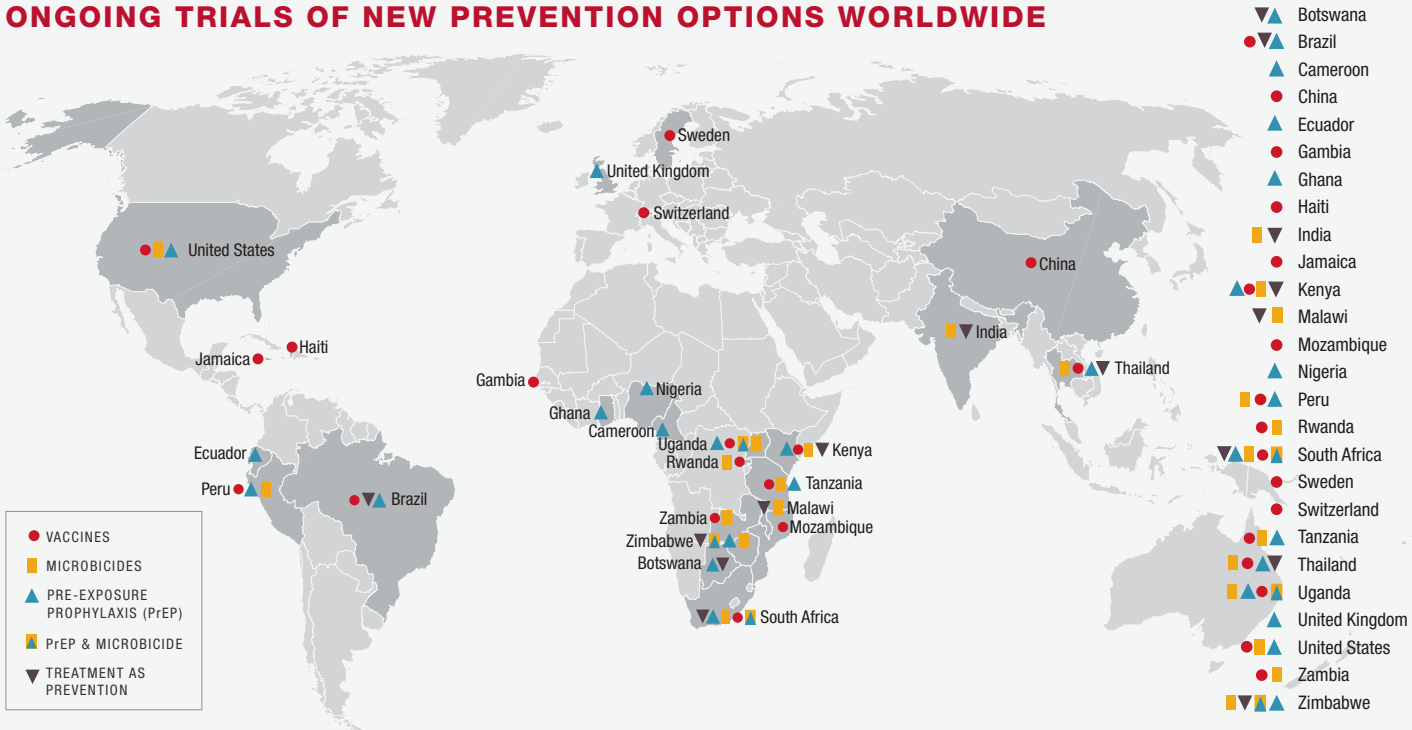
Below is a list of select ongoing and pending Phase I & II studies of ARV-based prevention interventions including trials of intermittent PrEP, alternatives to tenofovir-based strategies, vaginal rings, rectal microbicides and injectables. Not included are several small studies looking at tenofovir-based PrEP and microbicides in special populations such as pregnant and breastfeeding women, and adolescents.

Select Ongoing and Proposed Phase I & II ARV-based Studies *(September 2011)*

Study; Study phase	Location	Start Date	Population	Trial Design / Intervention	Status / Results expected
IPM 015 Phase I/II	Kenya, Malawi, South Africa, Tanzania	Q2 2010	280 women	Evaluation of safety, adherence and acceptability of dapivirine vaginal ring, as compared to placebo vaginal ring, inserted once every four weeks for a total of 12 weeks	Completed / Q4 2011
HPTN 066 Phase I	US	Q1 2011	16 men and 16 women	Evaluation of TDF/FTC levels in blood plasma and genital tract associated with specific oral regimens (daily, weekly, twice weekly and double-dose twice weekly); pill taking is directly observed	Completed / Q4 2011
TMC278LA Phase I	United Kingdom	Q1 2011	66 men and women	Evaluation of safety and tolerability of a single dose of TMC278LA (rilpivirine) injected intramuscularly; trial measures drug levels in the blood, female genital secretions and male rectal compartment	Enrolling / 2012
ADAPT (HPTN 067) Phase II	South Africa, Thailand	Q3 2011	180 MSM and 180 women	Evaluation of adherence to and acceptability of various oral TDF/FTC PrEP regimens: daily; twice-weekly + post-coital; or pre- and post-coital	Enrolling / 2013
MTN 013 / IPM 026 Phase I	US	Q3 2011	48 women	Evaluation of acceptability, adherence and drug levels in blood plasma and vaginal tract, in a study of dapivirine vaginal ring, maraviroc vaginal ring and dapivirine-maraviroc vaginal ring, inserted once every four weeks for 12 weeks	Enrolling / Q2 2012
NEXT-PrEP (HPTN 069 / ACTG 5305) Phase II	US	Q1 2012	400 MSM	Evaluation of safety and tolerability of daily oral maraviroc alone or in combination with TDF or TDF/FTC	Planned / 2014
MTN 017 Phase II	Peru, South Africa, Thailand, US	Q2 2012	120 MSM	Evaluation of safety, adherence, and drug levels in blood plasma, semen and rectal compartment in study of oral TDF/FTC and 1% tenofovir gel reformulated for rectal use; regimens to be determined	Planned / 2013
THE RING STUDY (IPM 027) Long-term Phase II	Multiple sites in Africa	Q1 2012	1,650 women	Evaluation of the long-term safety, adherence and acceptability of dapivirine vaginal ring as compared to placebo ring, inserted once every four weeks for approximately two years; to be conducted in parallel with the ASPIRE Phase III trial	Planned / 2015

ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



TRIAL RESULTS: A COMPREHENSIVE TIMELINE OF HIV PREVENTION EFFICACY AND FOLLOW-ON TRIALS* (September 2011)

2009

HPTN 035
Fewer infections in women using PRO 2000 than women using the placebo gel but difference not statistically significant. No evidence of benefit in women using BufferGel.

PARTNERS IN PREVENTION
No evidence of reduced rates of HIV transmission but reduced rates of genital ulcers and HIV viral load.

ALVAC-AIDSVAX (RV144)
ALVAC-HIV prime/AIDSVAX B/E boost vaccine reduced risk by an average of 31% (95% CI 1.1 to 52.1; P=0.04). No effect on viral load.

MDP 301
No evidence of benefit in women using PRO 2000.

2010

CAPRISA 004
1% tenofovir gel before and after sex reduced risk of HIV by an average of 39% in women (95% CI 6 to 60; P=0.017).

iPrEx
Daily oral TDF/FTC reduced risk of HIV by an average of 44% in gay men and other men who have sex with men, and transgender women (95% CI 15.4 to 62.6; P=0.005).

2011

FEM-PrEP
No evidence of benefit for daily oral TDF/FTC in women. Trial stopped early for futility.

HPTN 052
Early results released based on data from DSMB review in HIV-serodiscordant couples showed that ART initiation at CD4 cell count 350–550 reduced risk of transmitting HIV to the uninfected sexual partner by 96% (CI 73% to 99%; P<0.001).

PARTNERS PrEP
Early results released based on data from DSMB review showed that in HIV-serodiscordant couples daily oral TDF reduced risk of HIV by an average of 62% (95% CI 34 to 78; P=0.0003); daily oral TDF/FTC reduced risk of HIV by an average of 73% (95% CI 49 to 85; P=0.0001).

TDF2 (CDC 4940)
Daily oral TDF/FTC reduced risk of HIV by an average of 62.6% in heterosexual men and women (95% CI 21 to 83; P=0.013).

VOICE (MTN 003)
Oral TDF arm dropped for futility based on data from DSMB review. Study now looking at effectiveness of daily oral TDF/FTC and daily 1% tenofovir gel compared to placebo in women.

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)

2013

VOICE (MTN-003)
Phase IIb trial to evaluate the safety and effectiveness of daily oral TDF/FTC and daily 1% tenofovir gel to prevent HIV infection in women; *Daily oral TDF arm was dropped for futility after DSMB review in Sept 2011.* (South Africa, Uganda, Zimbabwe)

HPTN 052 (follow-up)
Phase III trial to evaluate the effectiveness of two treatment strategies to prevent HIV transmission in HIV-serodiscordant couples: immediate ART and ART as indicated by guidelines. *Since initial results released in May 2011, those receiving ART continue and those in the delayed arm offered early ART.* (Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, US, Zimbabwe)

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. *Since initial results released in July 2011, TDF and TDF/FTC arms will continue and those receiving placebo will be randomized to TDF or TDF/FTC.* (Kenya, Uganda)

iPrEx OLE (Open-Label Extension)
Safety and adherence follow-on trial to evaluate daily oral TDF/FTC in HIV-negative iPrEx trial participants (Brazil, Ecuador, Peru, South Africa, Thailand and the US)

HVTN 505
Phase IIb test-of-concept trial to evaluate the safety and efficacy of a DNA prime/Ad5-boost vaccine strategy to reduce risk of HIV infection and decrease viral load in participants who later become infected with HIV, in gay men, MSM, and transgender women (US)

FACTS 001
Phase III trial to evaluate the safety and effectiveness of 1% tenofovir gel before and after sex to prevent HIV and HSV-2 infection in women. Proposed start date Q4 2011 (South Africa)

CAPRISA 008
Open-label implementation study to evaluate the effectiveness of distributing 1% tenofovir gel in communities where CAPRISA 004 took place. Proposed start date Q4 2011 (South Africa)

ALVAC-AIDSVAX (RV144) Late-Boost Strategies
Phase II trial to evaluate safety, immunogenicity and tolerability of late-boost regimens of AIDSVAX B/E alone, ALVAC-HIV alone, or ALVAC-HIV/AIDSVAX B/E combination in HIV-negative participants from the RV144 trial. Proposed start date Q4 2011 (Thailand)

2014+

ANRS IPERGAY
Phase III trial to evaluate the safety and efficacy of intermittent oral TDF/FTC, before and after sex, in MSM. Proposed start date Q1 2012 (Canada, France, other European countries TBD)

ASPIRE (MTN 020)
Phase III trial to evaluate the safety and efficacy of a long-acting dapivirine vaginal ring, replaced every four weeks. Proposed start date mid-2012 (southern and eastern Africa)

CHOICE (MTN 018)
Phase IIIb open-label follow-on study to VOICE to collect additional data if one or both active VOICE arms: daily oral TDF/FTC and 1% tenofovir gel, proves effective. Proposed start date 2013 (South Africa, Uganda, Zimbabwe)

VACCINE
MICROBICIDE
PRE-EXPOSURE PROPHYLAXIS (PrEP)
TREATMENT AS PREVENTION
HERPES SIMPLEX VIRUS 2 (HSV-2) TREATMENT/SUPRESSION
VAGINAL RING

TRIAL COMPLETED OR STOPPED
PROPOSED TRIAL
INITIAL RESULTS

* *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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through these projects; and the human and financial resources necessary to implement the projects. ■

Data Dispatch

AIDS Vaccine 2011: New signals

In September, for a few nights in Bangkok, the AIDS vaccine field enjoyed the fruits of hard work and exhaustive research.

First and foremost was the announcement that the search for immune correlates from the Thai prime-boost vaccine trial known as RV144 had yielded unexpected success. Analysis of blood samples from volunteers generated two hypotheses about immune responses and their role in vaccine-induced protection. This research was an unprecedented international collaboration led by Barton Haynes of Duke University. With this big news, the field has its first clues about specific immune responses in people who received a moderately effective vaccine.

What's next for the Thai prime-boost regimen?

The short answer is that scientists take these findings and use them in a process that will take several years, the end result of which aims to develop what is hoped to be a more effective vaccine.

"When you come to a crossroads, take it," said US NIH Division of AIDS Director Carl Dieffenbach at the Bangkok meeting. For RV144, there are actually three paths to be pursued simultaneously as next steps. First, the correlates analysis work will continue. Additional secondary analyses include studies of the types of viruses that infected vaccine recipients to see whether there was a "sieve effect". This occurs when vaccine-induced immune responses block some of the HIV strains, but not all.

Looking at the blood samples from trial participants who received the vaccine strategy, the RV144 correlates analysis found one immune response that was linked to lower risk of HIV infection and one immune response that seemed to interfere with vaccine-induced protection.

The second step is to understand why binding antibodies were linked to protection, as it is a surprise. The apparently protective response was antibodies against epitopes (protein fragments) found in the V1/V2 region of the HIV envelope protein (the outer coat of HIV). The antibodies induced by the RV144 regimen are binding antibodies, not neutralizing antibodies. Neutralizing antibodies are thought to be an essential immune response for highly effective vaccines. They bind to foreign invaders and directly block their activity in the body. Binding antibodies also bind to antigens, but they don't neutralize, or stop their activity. Instead they may tag the antigen, sending up a red flag to other arms of the immune system, or have other effects on the course of infection.

Researchers have already developed monoclonal antibodies like the ones seen in Thai volunteers, and they will use them in laboratory and animal experiments to learn about how they interact with HIV.

Finally, work is ongoing to try to improve upon and establish the generalizabilty of the immune protection seen in the vaccine trial. In RV144 the regimen appeared to reduce HIV risk by about 60 percent at 12 months (after the immunization series was complete), and then wane over time.

Other key questions center on whether a similar vaccine would work in other parts of the world or in populations with other risk profiles. Answers to these questions could come from planned follow-on research with an RV144-like regimen in South Africa and in Thailand, among higher-risk volunteers. ■

Recently Released

An Exploratory Analysis of HIV Treatment Research and Development Investments in 2009. This report issued by TAG and AVAC tracks global investment in research and development of new, or enhancing existing, HIV therapeutic regimens. It establishes an investment baseline, starting with 2009 investments. The report will be published annually. *(www.avac.org/resourcetracking)*

Multipurpose Prevention Technologies (MPT) for Reproductive Health: Advancing the Scientific and Product Development Agenda. This report from a May 5 think tank convened by AVAC, CAMI and USAID lays out a scientific rationale and research agenda for development of new strategies that could provide combined HIV, STI and pregnancy prevention. *(www.avac.org/multipurposetech)* ■

Not to be Missed

October 8–13: MTN 2011 Regional Meeting, *Cape Town*
October 12–13: AIDS 2012 Community Program Committee Symposia and Workshop Selection, *Washington DC*
November 7–9: HVTN Conference, *Seattle*
November 10–13: 2011 US Conference on AIDS, *Chicago*
November 21–22: GFATM 25th Board Meeting, *Accra*
December 4–8: ICASA 2011, *Addis Ababa*

About AVAC

Founded in 1995, AVAC is a non-profit organization that uses education, policy analysis, advocacy and a network of global collaborations to accelerate the ethical development and global delivery of male circumcision, PrEP, microbicides, AIDS vaccines and other emerging HIV prevention options as part of a comprehensive response to the pandemic.

Sign up for AVAC's Advocates' Network at *www.avac.org/advocatesnetwork* to receive regular updates via email.

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