Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention
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AVAC's Take

In the first issue of *Px Wire* in 2012, AVAC's take is simple: We must continue without delay to build on the momentum that gathered throughout last year, reaching a new height on World AIDS Day 2011, when US President Barack Obama committed the US leadership to make "the beginning of the end of AIDS" a reality.

Realizing the goal articulated by President Obama, US Secretary of State Hillary Clinton, and many other leaders worldwide, depends on full implementation of antiretroviral therapy for HIV-positive individuals to maximize the potential of "treatment as prevention," taking voluntary medical male circumcision (VMMC) to scale in key countries, and ensuring that no infant is born with or infected with HIV during breastfeeding. It also requires a long-term view that supports these efforts, while continuing research on additional tools.

Achieving the beginning of the end of the epidemic requires logistical innovation, political commitment and secure funding. None of these are guaranteed. As 2011 came to a close, the Global Fund to Fight AIDS Tuberculosis and Malaria (GFATM) announced the cancellation of its Round 11 funding—underscoring what perilous financial times these are for the fight against AIDS.

This year could turn out to be a pivotal year for the long-term effort to end AIDS. Here are some of the key outcomes AVAC and our partners will be working towards in the coming months.

- PEPFAR Country Operating Plans, which guide activities at the country level, align with the emerging science of combination prevention.
- Donor commitment and restoration of GFATM Round 11 funding.
- Political leaders in developing and developed countries join the US and match funds to scientific innovation.
- Fast-track US Food and Drug Administration (FDA) review of daily oral PrEP using daily TDF/FTC for HIV-negative individuals and a clear community voice articulating the demand for this strategy as part of combination prevention (for more on this story, see *Data Dispatch* on back).
- Launch of PrEP demonstration projects in MSM in Miami and San Francisco, and, ideally elsewhere.
- Thorough analyses of data from FEM-PrEP and VOICE trials that shed light on why various tenofovir-based strategies (daily oral TDF/FTC in FEM-PrEP and daily 1% tenofovir gel and daily oral TDF in VOICE) did not show benefit for the women in those trials.
- Consultations with women worldwide that explore what is known and unknown about the interaction between injectable contraceptives and HIV risk.
- Intensive preparation and community engagement in anticipation of RV144 follow-on vaccine trials slated to begin in Thailand and South Africa in coming years.
- Launch of trials to evaluate the safety and efficacy of a vaginal ring carrying the ARV dapivirine for HIV prevention in HIV-negative women.
- Key countries implement strategic plans to achieve 80 percent VMMC among adult men by 2015—and new devices such as PrePex and the Shang Ring introduced as additional circumcision tools.

If there is progress in ticking off the items on this list, then, in one year's time, we'll be able to say that we are closer to the end of AIDS than ever before. —*AVAC* ■

At a Glance

IPERGAY, the pilot phase of a planned efficacy trial of coitally-related oral PrEP in MSM and transgender women began enrolling participants in January. The trial is sponsored by the French research agency ANRS. In this initial phase, investigators say they will evaluate the feasibility of the trial design, and may expand to a full efficacy trial. The randomized, placebo-controlled trial will assign participants to either oral TDF/FTC or a placebo pill. They will be counseled to use an "on demand" dosing strategy, taking the drug daily during periods of sexual activity. Results from the pilot phase are expected in 2014. AVAC will be working with partners to explore the implications of and views of such a placebo-controlled trial, in light of Gilead Science's submission to the FDA for a TDF/FTC prevention indication.

MTN 013/IPM 026 began enrolling participants in this Phase I safety study last November. Women in the trial are randomly assigned to use either a vaginal ring containing two ARV drugs (dapivirine and maraviroc), a ring containing maraviroc alone, a ring that contains dapivirine alone, or a ring with no active drug, inserted once every four weeks. This is the first ARV-combination vaginal ring to enter clinical trials. Results are expected in early 2013. MTN and IPM are also each planning to launch an efficacy trial of the ring containing dapivirine alone later this year.

Project ARM (Africa for Rectal Microbicides) held its first meeting in Addis Ababa, Ethiopia, last December. Initiated by IRMA (International Rectal Microbicide Advocates), in partnership with AVAC and others, the meeting developed a rectal microbicide research advocacy agenda specific to Africa. IRMA will release the Project ARM strategy report at the 2012 International Microbicides Conference in April.

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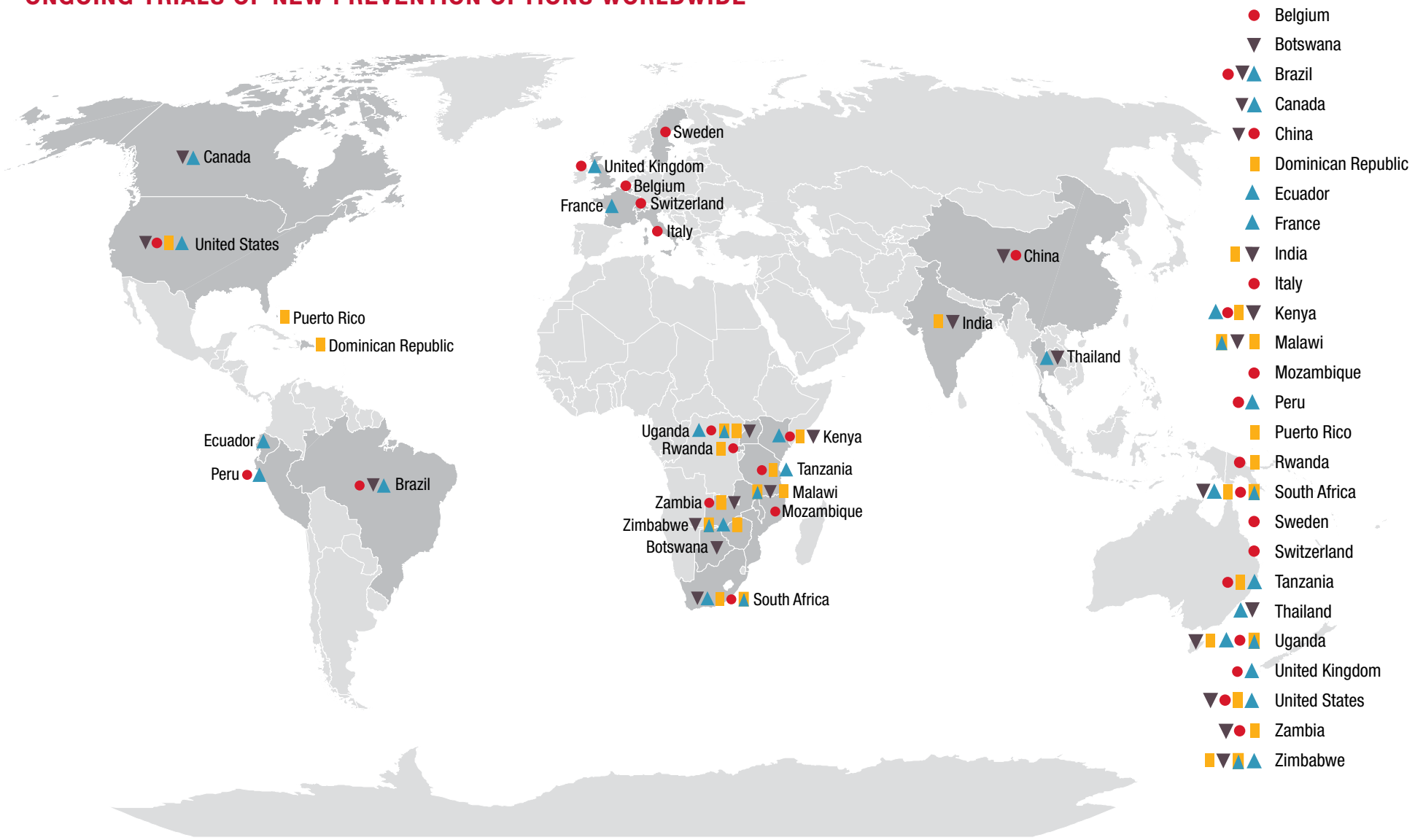
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



TRIAL RESULTS: A COMPREHENSIVE TIMELINE OF HIV PREVENTION EFFICACY AND FOLLOW-ON TRIALS* (January 2012)

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, 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 daily oral TDF/FTC. 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 in seronegative partners 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 63% in heterosexual men and women (95% CI 21 to 83; P=0.013).

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

2012

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

2013

VOICE (MTN-003)
Phase IIb trial to evaluate the safety and effectiveness of daily oral TDF/FTC to prevent HIV infection in women; *daily oral TDF and 1% tenofovir gel arms were dropped for futility after DSMB reviews in 2011.*

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 provided to HIV-negative partners. *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.*

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 (US)

CAPRISA 008
Open-label implementation study to evaluate the effectiveness of distributing 1% tenofovir gel in communities where CAPRISA 004 took place (South Africa) *Proposed start date Q2 2012*

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 (Thailand) *Proposed start date 2012*

TDF2 Open-Label Extension (CDC 494)
Follow-on trial of daily oral TDF/FTC in heterosexual men and women (Botswana) *Proposed start date Q1 2012*

2014+

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 (South Africa)

HPTN 052
Phase III trial to evaluate the effectiveness of two treatment strategies to prevent HIV transmission in HIV-serodiscordant couples: immediate ART (CD4 350-550) and ART as indicated by guidelines. *Since initial results released in May 2011, those receiving ART continue and those in the delayed arm offered ART.*

ANRS IPERGAY
Pilot for a Phase III trial to evaluate the safety and efficacy of intermittent oral TDF/FTC, before and after sex, in MSM and transgender women (Canada, France)

TasP (ANRS 12249)
Phase III trial to assess the acceptability, feasibility, and efficacy of regular and widespread HIV testing with immediate ART initiation (South Africa) *Proposed start date Q1 2012*

The Ring Study (IPM 027)
Phase III trial to evaluate the safety and efficacy of a long-acting dapivirine vaginal ring, replaced every four weeks (Kenya, Malawi, Rwanda, South Africa, TBD) *Proposed start date Q1 2012*

ASPIRE (MTN-020)
Phase III trial to evaluate the safety and efficacy of a long-acting dapivirine vaginal ring, replaced every four weeks (Malawi, South Africa, Uganda, Zambia, Zimbabwe) *Proposed start date mid-2012*

CHOICE (MTN-018)
Phase IIIb open-label follow-on study to VOICE to collect additional data if daily oral TDF/FTC proves effective (South Africa, Uganda, Zimbabwe) *Proposed start date 2013*

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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Data Dispatch

Gilead Sciences submits TDF/FTC for HIV prevention to FDA

This past December, Gilead Sciences submitted a dossier to the FDA requesting a prevention indication for TDF/FTC (marketed as Truvada). If this supplemental new drug application (sNDA) is approved, TDF/FTC will be the first antiretroviral approved for use as a prevention tool in HIV-negative people.

Howard Jaffe, Chairman of the Gilead Foundation, told AVAC, "Per our discussions with FDA, the submission is based on data from the two large clinical trials that support Truvada for PrEP [iPrEx and Partners PrEP], as well as supporting data from several other clinical trials, including CDC 4323 [a TDF as PrEP safety study in MSM in the US] and TDF2 [a CDC-funded trial in heterosexual men and women in Botswana]."

It is also expected that the FDA will review data from trials that did not find effectiveness of tenofovir-based PrEP, such as VOICE and FEM-PrEP. For details on all of these trials and more PrEP research, see *www.avac.org/prep*.

This development is an exciting one, as it could simplify access to and potential insurance coverage of TDF/FTC as PrEP in the US. It could also be used as a regulatory precedent in other countries. If the FDA grants a "priority review" of the application, as is expected, it will take place in the first half of 2012. In the coming months, AVAC will work with partners to bring an informed community voice to the public advisory committee hearings anticipated in May or June. To get involved in this effort, please contact *avac@avac.org*.

More surprises and disappointments for VOICE

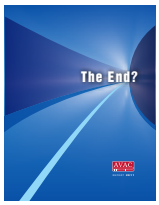
Last November, the Data and Safety Monitoring Board for the VOICE trial met for a scheduled review and recommended that the daily 1% tenofovir gel arm of the trial be discontinued. At the time of the review, the incidence rates (rate of new HIV infections) were equivalent in the group of women who received 1% tenofovir gel plus a standard prevention package compared to the group who received an identical prevention package and placebo gel with no active ingredient. (Neither the women nor the trial investigators or site staff knew who was receiving placebo or active gel.) The development was a further disappointment to VOICE, which had discontinued the daily oral TDF arm of the trial in September following a similar recommendation. The third active arm of VOICE, which is testing daily oral TDF/FTC, continues—and data are expected by 2013.

In 2010, the CAPRISA 004 trial of 1% tenofovir gel found that the gel reduced HIV risk in HIV-negative South African women by 39 percent overall. This trial tested a coitally-related dosing strategy, known as "BAT-24".

The FACTS 001 trial of 1% tenofovir gel continues to evaluate the safety and effectiveness of the 1% tenofovir gel using the same dosing strategy evaluated in CAPRISA 004. The results of this trial are expected in 2014.

One key message from all stakeholders is: Research on oral ARV-based prevention (PrEP) and ARV-containing gels and rings continues. Conflicting results are not a sign to stop research but to intensify it. ■

Recently Released



AVAC Report 2011: The End? AVAC's annual review of the field offers a comprehensive agenda for ending AIDS and was launched online with a variety of multi-media components at *www.avac.org/report2011*.

P-Values, AVAC's new bulletin on our partners' activities worldwide is an opt-in newsletter. You can subscribe and check out past issues at *www.avac.org/pvalues*. ■

Not to be Missed

Jan 9–10: 2nd International Workshop on HIV & Women, *Bethesda, MD*
Jan 17–18: 2012 Black Gay Research Summit, *New Orleans, LA*
Jan 19–20: National AAMSM Leadership Conference on HIV/AIDS and other Health Disparities, *New Orleans, LA*
Feb 15: AIDS 2012 abstract submissions close *(aids2012.org)*
Feb 20–24: MTN Annual Meeting, *Washington, DC*
March 5–8: Conference on Retroviruses and Opportunistic Infections (CROI), *Seattle, WA*
April 15–18: 2012 International Microbicides Conference (M2012), *Sydney, Australia*

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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