Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
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AVAC's Take

This July, the 18th International AIDS Conference (IAC) in Vienna marks ten years since the Durban meeting where a cohesive and determined AIDS movement made access to ARV treatment a priority for global health. Taking stock today, the future of this unprecedented commitment to treatment scale-up is uncertain, and prevention still lags while research budgets shrink. The global AIDS response is in trouble just when there is renewed momentum throughout the biomedical prevention research field. The world needs a fully funded, integrated and strategic approach to AIDS prevention and treatment, which includes building on recent AIDS vaccine results and expanding the pipeline of candidates for antiretroviral-based prevention. Seizing upon this momentum, perhaps Vienna will earn a place in conference history as a pivotal moment for a truly comprehensive AIDS response. —*AVAC* ■

Data Dispatch: M2010

Microbicides 2010

In late May, nearly 1,000 delegates gathered in Pittsburgh for the 2010 International Microbicides Conference (M2010). The conference intentionally and successfully focused on a number of HIV prevention research issues that are reviewed here. AVAC is also hosting a series of HIV prevention research webinars based on several M2010 presentations. For more on the series and to download presentations and recordings, visit *www.avac.org/M2010*.

Treatment and prevention on a collision course?

With the increasing discussion of earlier and expanded treatment and the growing ARV-based prevention agenda, M2010 provided a platform for discussions about how to best integrate and optimize prevention and treatment strategies.

This topic was on the agenda at the mini-symposium "ART: Challenges, Pitfalls and Opportunities". John Mellors of the University of Pittsburgh, who has studied the emergence of resistance in cohorts of HIV-positive people on antiretrovirals, shared his thoughts on the risks of resistance should the same drugs be used for prevention in HIV-negative people. As he explained, if someone on PrEP becomes HIV-positive and continues taking the drugs, they would, in effect, be on suboptimal treatment, which may increase the chance they will develop resistant virus.

All of the current PrEP trials are monitoring individuals for the emergence of drug-resistant virus in those who acquire HIV while taking PrEP. The trials are ongoing and there are no concrete findings on resistance emerging in this context. Investigators on these studies have also noted that the relative risk of individual resistance should be weighed against the potential benefits of PrEP, should it prove effective. There are also population level unknowns, as Mellors and others at M2010 noted, including the question of whether or not introduction of PrEP would lead to increased transmission of drug-resistant virus. There are no data on this at the moment, either.

If PrEP is shown to be effective in clinical trials, people taking it would need to be tested regularly so as not to continue with the PrEP regimen in the case of seroconversion; and people should be educated about the dangers inherent in sharing drugs. Moreover, alternatives to TDF and FTC—two broadly used treatment drugs—need to be tested for PrEP and topical ARV-based microbicides.

Not just a gel anymore

Historically, the vast majority of microbicide candidates have been formulated as gels. The field is now reaping the benefits of years of research into different formulations and novel delivery mechanisms, such as vaginal rings, vaginal and rectal tablets and quick-dissolve film.

One of the newer delivery mechanisms for microbicides that was widely discussed at M2010 is the vaginal ring. Long used as a contraceptive delivery device, researchers are looking at the ring's potential to deliver an active microbicide agent. A ring would be inserted prior to and independent of sex on a monthly or similarly infrequent basis and might allow for longer lasting protection. The hope is that this could increase consistent use of the microbicide, a major stumbling block in microbicide development thus far.

The International Partnership for Microbicides (IPM) reported positive results from a placebo ring acceptability study (where there was no active drug in the ring) in South Africa and Tanzania. Shortly after the conclusion of M2010, IPM announced a new trial, IPM 015, which is enrolling 280 women to test the safety and acceptability of a dapivirine-containing ring in a number of sites in southern and eastern Africa.

Expanded pipeline of ARV-based approaches

Data were also presented on new ARVs being developed as microbicide candidates. Current clinical trials of ARV-based microbicides are testing nucleoside reverse transcriptase inhibitors (NRTIs): tenofovir; or non-nucleoside reverse transcriptase inhibitors (NNRTIs): dapivirine and UC781. Several pre-clinical studies of maraviroc, an approved CCR5 inhibitor, were also presented. Additional classes of ARVs that may be less frequently used for treatment are being considered in pre-clinical testing, which might help minimize the risk of resistance or a "collision" of prevention and treatment options.

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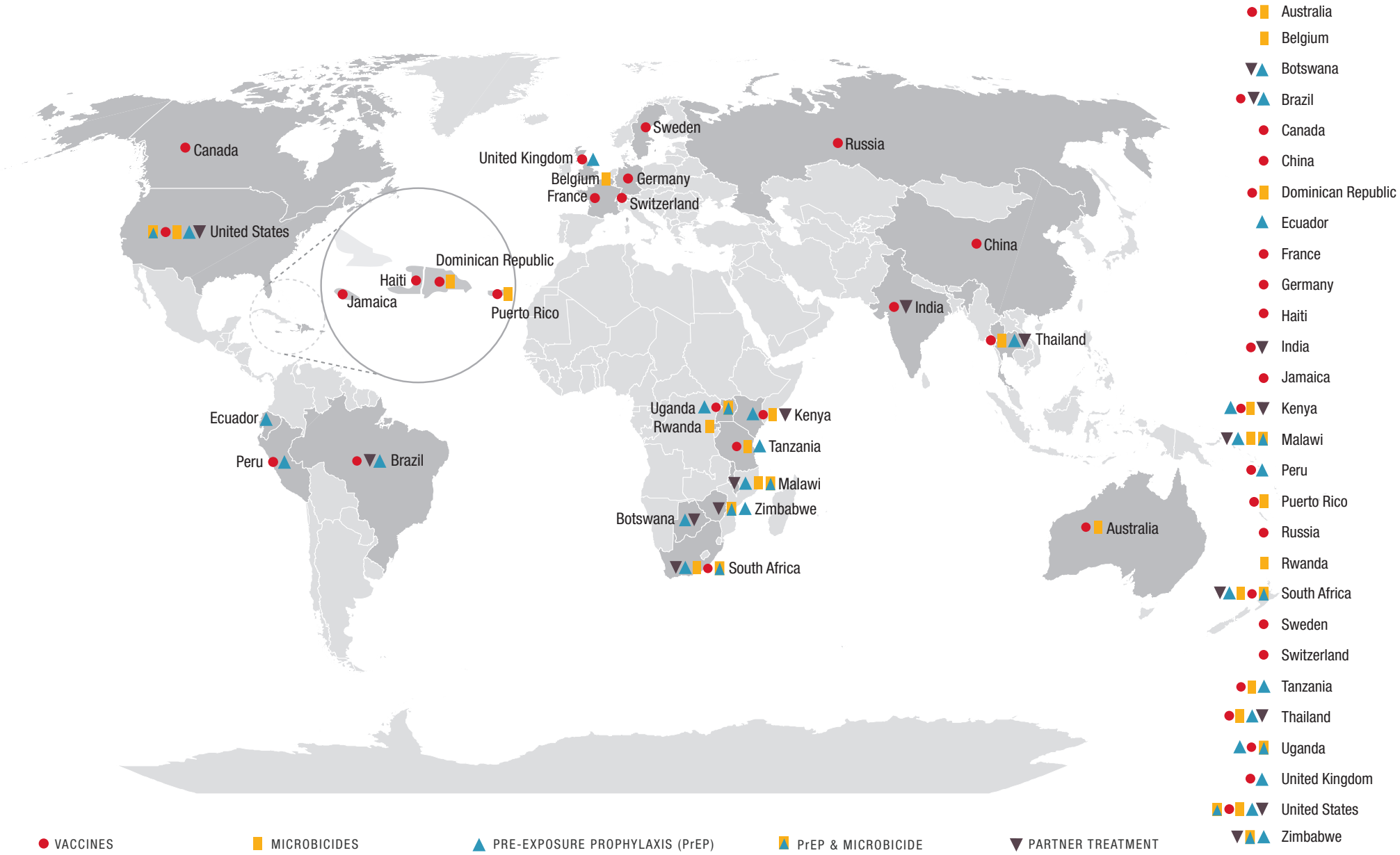
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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 show that vaccine recipients were 31% 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

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 third quarter 2010.

CAPRISA 004
Phase IIb trial to evaluate the safety and effectiveness of 1% tenofovir gel to prevent HIV infection in women (South Africa)
Release of results expected July 2010.

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

2011

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)

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)

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)

FEM-PrEP
Phase III trial to evaluate the safety and effectiveness of once-daily oral TDF/FTC for HIV prevention in women (Kenya, Malawi, 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: once-daily oral TDF, once-daily oral TDF/FTC, and 1% tenofovir gel (Malawi, 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, US, 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

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

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Beyond the vagina

M2010, after five previous biannual microbicide conferences, was the first to address rectal microbicides as a central part of the agenda. Among the many presentations on rectal microbicides, South African researcher Salim Abdool Karim's emphasized Africa's widespread existence of gay men and other men who have sex with men (from 6.2% in Egypt to 30.9% in Cape Town), bisexuality and frequency of heterosexual anal intercourse, underscoring the importance of rectal microbicide research. ■

Recently Released

From Promise to Product: Advancing Rectal Microbicide Research and Advocacy, a report from the International Rectal Microbicide Advocates (IRMA), provides an overview of the maturing rectal microbicide research field, resource mapping and global advocacy goals. *www.rectalmicrobicides.org/materials.php*

Microbicides: Ways Forward is the final in a series of strategy documents from the Alliance for Microbicide Development. In 2009, the Alliance surveyed a number of microbicide experts and key stakeholders in the field in an effort to identify areas of progress, obstacles and priorities for the field, concluding with nine key recommendations for moving microbicides forward. *www.avac.org/orderpublications*. ■

Coming Up

What to expect at the IAC in Vienna (July 18-23)

Results from CAPRISA 004, the first effectiveness trial of an ARV-based microbicide, will be released at the IAC in Vienna. The trial studied the effectiveness of 1% tenofovir gel in reducing the risk of HIV acquisition in women by comparing rates of new HIV infections among women assigned to the tenofovir gel group and those in the placebo gel group. The double-blind, randomized, controlled study enrolled and followed 900 HIV-negative women at two sites in KwaZulu-Natal, South Africa. Look for the July release of a new document in AVAC's *Anticipating Results* series for guidance in interpreting these and other upcoming ARV-based prevention trial results.

In addition, the IAC will likely focus attention on the recent paradigm shift toward ARV-based prevention in its many manifestations—oral PrEP, ARV-based microbicides and treatment as prevention. Look for sessions, symposia and satellites—highlighted in the *Not to be Missed* section—addressing some of the programmatic considerations, including costs, health systems capacity, human rights, ethics, feasibility, community desirability of using treatment as prevention and its potential impact on future treatment options. Vaccines will also be featured at the conference, as the global AIDS community meets for the first time since the release of the promising RV144 trial results. Sessions and speakers will also examine scale-up of male circumcision, an important test case of translating positive clinical trial results into actual prevention. ■

Not to be Missed

Here is a brief list of events in Vienna related to prevention research. For an up-to-date HIV prevention research roadmap, visit: *www.avac.org/AIDS2010*. Planning a related event? Let us know at *avac@avac.org*.

Saturday, July 17:
HIV Testing: Global Challenges, Global Strategies and Global Impact, Pre-Conference symposium, *Radisson Blu Palais Hotel Vienna, Parkring 14–16 (8:30–16:30), www.chipts.ucla.edu/hivtesting*

Be Heard! Global Forum on MSM & HIV, Pre-Conference symposium, *Vienna University of Economics and Business (8:00–21:00), Aids2020@msmgf.org*

Sunday, July 18:
The Search for an HIV Vaccine: Where are we, where are we going, and how can we get there faster? Non-Commercial satellite, *Mini Room 6 (11:15–13:15)*

The Promise and Perils of ARV-based prevention: Making it a reality on the ground, Non-commercial satellite, *Mini Room 6 (15:45–17:45)*

Tuesday, July 20:
Update on Microbicides (including CAPRISA 004 results release), Special session, *Session Room 7 (13:00–14:00)*

Using Antiretrovirals to Prevent HIV: Implications of the CAPRISA 004 tenofovir-gel microbicide trial results, Non-commercial satellite, *Mini Room 10 (18:30–20:30)*

Wednesday, July 21:
Use of Antiretrovirals for Prevention: PrEP, PEP and ART, Symposium, *Session Room 6 (14:30–16:00)*

ART for Prevention: What are the implications? Bridging session, *Session Room 1 (16:30–18:00)*

Thursday, July 22:
Scaling up Male Circumcision: From Research to Practice, Oral abstract session, *Session Room 4 (11:00–12:30)* ■

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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