Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
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AVAC's Take

In this edition of *Px Wire,* we look more in depth at some of the issues that emerged as highlights during and after the International AIDS Conference in July. We've synthesized the complex discussions about the trials needed to confirm the CAPRISA 004 finding that 1% tenofovir gel reduced women's risk of acquiring HIV by 39 percent overall. We also take a look at some of the many issues regarding the possible use of ARVs in HIV-positive people to reduce risk of HIV transmission. We're hoping that these brief updates will spark conversations in your communities and with us! —*AVAC* ■

Data Dispatch

Since the announcement in July that the CAPRISA 004 microbicide trial found an HIV prevention benefit for 1% tenofovir gel, stakeholders have turned to the business of mapping next steps—what exactly is happening and what should happen? While these discussions continue, below are some initial answers to the questions AVAC has been hearing.

CAPRISA 004 showed 1% tenofovir gel reduced women's risk by 39 percent overall—is it going to be made available soon?

By the current estimates, 1% tenofovir gel is still several years away from potential licensure and availability outside of a research setting. There has been a range of follow-up discussions about what the results mean both in South Africa, where the trial was conducted, and around the world. The consensus from these conversations is that more data are needed to confirm and better understand to what extent 1% tenofovir gel might reduce HIV-negative women's risk of acquiring HIV through sexual intercourse.

Why are additional trials of 1% tenofovir gel being conducted and considered?

Reproducibility: Observed findings in clinical trials may be due to the effect of the candidate being studied or due to chance. When more than one study is conducted, results can be compared across studies to determine if it is likely that the candidate is really effective or if results in a trial might have been a random finding. Conducting confirmatory trials of candidates that show benefit is generally required by regulatory agencies and a critical step in product development and approval. There is no guarantee that the estimated 39 percent effectiveness seen in CAPRISA 004 would be seen in similar trials of 1% tenofovir gel.

Gaining a better understanding of the level of benefit of 1% tenofovir gel: In the CAPRISA 004 trial, the 95 percent confidence interval associated with the point estimate of 39 percent effectiveness was 6 to 60, and the p-value was 0.017. The 95 percent confidence interval reflects a plausible range for the true effectiveness of 1% tenofovir gel in the study population. Based on these data, it cannot be confidently ruled out that the true effectiveness could be as high as 60 percent or as low as 6 percent. Results from additional studies would help us understand what the true level of benefit of 1% tenofovir gel might be. (For more about understanding statistical terms, visit *www.avac.org/statsguide*.)

Generalizability: CAPRISA 004 showed that 1% tenofovir gel prevents HIV infection among women aged 18 to 40 from two communities in KwaZulu-Natal, South Africa. More information is needed on how the product works in women of different ages, with different patterns of sexual behavior, in the context of anal sex and in different communities and countries.

What additional trials of 1% tenofovir gel are being conducted and considered?

The VOICE trial, conducted by the NIH-funded Microbicide Trials Network (MTN), is currently evaluating the same 1% tenofovir vaginal gel used in CAPRISA 004 but inserted once daily, rather than before and after sex as in the 004 regimen. VOICE is also testing the effectiveness of two forms of oral pre-exposure prophylaxis (PrEP) to reduce the risk of HIV infection.

The MTN is also implementing a series of additional safety, pharmacokinetic and observational studies designed to better understand safety in pregnant and breastfeeding women and safety and acceptability in rectal use. (For a document on previous and ongoing tenofovir gel studies, visit *www.avac.org/tenofovirgel.*)

CAPRISA is designing two studies to follow 004 participants to answer key operational research questions. In addition, there is ongoing discussion about what additional effectiveness trials might be required to confirm the CAPRISA 004 results beyond what will be provided by the ongoing VOICE trial. There are currently two trials being discussed and designed (but not yet approved), including:

- Follow-on African Consortium of Tenofovir Studies (FACTS consortium) in South Africa would test the same dosing strategy as CAPRISA 004 in women from a variety of settings, include sexually active 16- and 17-year-olds, and it would gather more information on 1% tenofovir gel as a tool for HSV-2 prevention.
- The UK MRC's Microbicide Development Programme (MDP) 302 study would be conducted in other African countries and would compare two different dosing strategies—the CAPRISA 004 dosing regimen and use of a single coitally dependent dose.

Who decides what happens next?

This is an essential question. At the moment, the answer isn't as clear as it should be. Many groups, including AVAC, have called for a coordinated, comprehensive product

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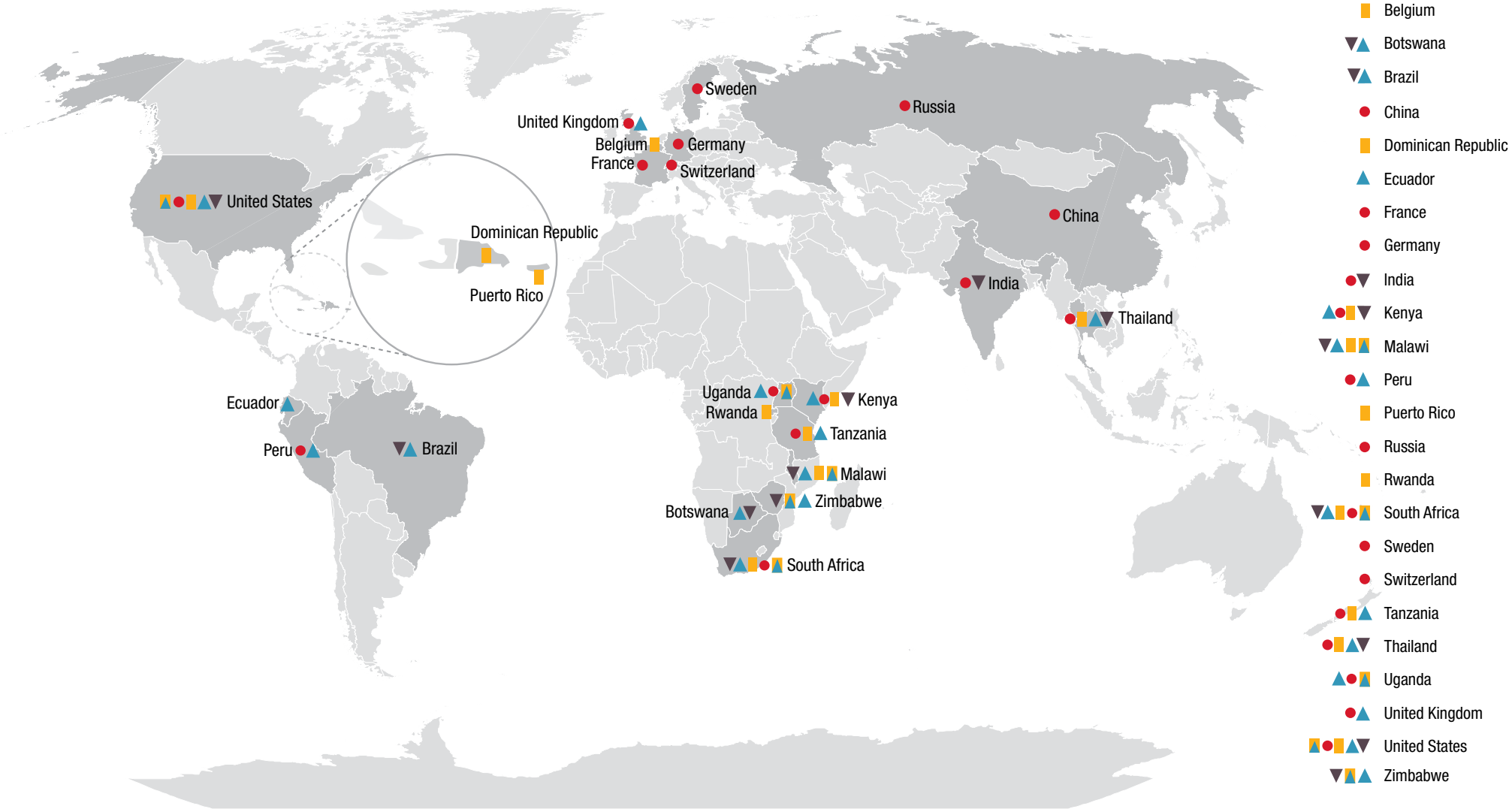
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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

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. Results announced July 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)
The trial reported no serious adverse events and preliminary data show PrEP use did not have a significant effect on HIV risk behavior. Results announced July 2010. Additional data expected Q4 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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development plan that encompasses follow-up research on 1% tenofovir gel as well as on other products; consideration of regulatory issues in South Africa and other high-need settings; accelerated research into vaginal rings and other alternative delivery mechanisms to overcome adherence challenges; and further expansion of the ARV-based prevention product pipeline. Supporting processes that ensure this clear, prioritized and sequenced plan emerges is one of AVAC's top priorities for the coming months. (Additional information is at *www.avac.org/tenofovirgel*.) ■

At a Glance

The term "treatment as prevention" is often used to refer to the use of antiretrovirals in HIV-positive people to reduce their risk of passing HIV to their sexual or needle-sharing partners. At the International AIDS Conference, treatment as prevention was a topic of frequent and often heated discussion. Some highlights include new evidence showing that treating HIV can lower transmission rates. Susan Cowan, of the National Infections Institute in Denmark, presented indirect evidence that testing for and treating HIV appeared to lower transmission rates in Denmark in spite of more people living with the virus and increased rates of reported unprotected anal sex in MSM. Similarly, in British Columbia, decreased numbers of new HIV diagnoses were associated with expanded ART coverage on a population level over five years, as presented by Julio Montaner of the British Columbia Centre for Excellence in HIV/AIDS.

Along with data, there was plenty of debate. There are questions about how feasible it would be to implement treatment as prevention on a wide scale. How would those who are newly infected be identified for treatment? How would the rights of HIV-positive people be safeguarded so that they are not coerced into early but unnecessary treatment? How would the scale-up of treatment be paid for?

Some answers will come from tracking rates of new infections in settings where programs start providing earlier treatment according to the new WHO guidelines. Other answers will come from ongoing and planned trials. (For additional information visit *www.avac/treatmentasprevention.)* ■

Recently Released

- AVAC and UNAIDS released the second edition of the *Good participatory practice (GPP) guidelines for biomedical HIV prevention trials*. This version is open for public comment until October 31 and will be finalized and released later this year. To download a copy go to *www.avac.org/gppdocuments* and email your comments to *avac@avac.org*.
- *Nature Medicine* published the updated 2010 Scientific Strategic Plan of the Global HIV Vaccine Enterprise. AVAC will closely track whether the updated Plan stimulates substantive action in the funding priorities and research goals of Enterprise stakeholders. Download the Plan at *www.vaccineenterprise.org*.
- The White House released the National HIV/AIDS Strategy, the first national plan to address the US epidemic. Experimental biomedical prevention approaches such as PrEP, microbicides, vaccines and treatment as prevention are not mentioned in the Plan. For advocacy activity, go to the Coalition for a National AIDS Strategy at *www.nationalaidsstrategy.org*. ■

Coming Up

Results from the iPrEx PrEP trial are expected in the coming months. This Phase III study is evaluating the safety and effectiveness of once-daily oral TDF/FTC in gay men and other MSM in six countries. It will be the first trial to provide oral PrEP effectiveness data. In anticipation of these results, AVAC will release Volume Three of its *Cascade of Hope and Questions* series, which will focus on the iPrEx trial. (The series is available at *www.avac.org/publications/results*.) ■

Not to be Missed

October 4–7: MTN 2010 Regional Meeting, *Cape Town, South Africa*

October 26: NIAID Town Hall Meeting to Examine Restructuring of HIV/AIDS Clinical Trial Networks, *Arlington, VA*

November 15–17: HIV Vaccine Trials Network Conference, *Seattle, WA*

November 15–18: Europrise Rational Design of HIV Vaccines and Microbicides Network Annual Conference, *Lisbon, Portugal*

November 17–19: 2010 National Summit on HIV Diagnosis, Prevention and Access to Care, *National Harbor, MD*

December 12–15: NMAC 2010 HIV Prevention Leadership Summit, *Washington, DC* ■

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.

101 West 23rd St. #2227 • New York, NY 10011 USA
Telephone +1 212.367.1279 • *www.avac.org*