Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
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AVAC's Take

What to do with the data? This is a question that runs through many of the items in this issue of *Px Wire*—from discussions of AIDS vaccine trials in the post-RV144 era, to mathematical models and corroborative findings about the possible benefits of a "test and treat" approach. As each of these topics reminds us, trial data do not provide final answers about what to do next. Instead, they spark discussions that require careful, creative thinking from all of us involved in HIV prevention. —*AVAC* ■

Data Dispatch

Running with RV144

At a mid-March meeting in Thailand, the Global HIV Vaccine Enterprise, UNAIDS, WHO and the Thai Ministry of Public Health brought ethicists, clinical trialists, scientists and product developers from within and outside the country to deliberate about next steps based on the AIDS vaccine trial known as RV144. In September 2009, trial leaders announced that the vaccine regimen tested reduced risk of infection by about 30 percent (see *www.avac.org/RV144* for background).

Since then, the questions about what to do next have proliferated. Some answers are now starting to come into focus. At the Bangkok meeting, working groups in four areas (ethics and regulatory; clinical trials; science and vaccine development; and public health and access) issued recommendations that will help guide country-level decision-making processes on next steps based on the initial result.

At the same time, there's ongoing discussion about the potential implications of some observed RV144 trends—including the apparent decrease in vaccine protection over time, and a hint that the vaccine may have offered more protection to people who reported lower risk behaviors compared to those who identified as, or reported, moderately higher risk. (Self-reported risk behavior is not always reflective of actual practices.) It is important to note that these post-hoc analyses of the vaccine results are not statistically significant, but they do open up interesting hypotheses to explore further.

The RV144 trialists, along with other researchers, are planning studies of immunologic responses in RV144 vaccine recipients in an attempt to understand the mechanism of protection. There are also ongoing discussions about the types of human clinical trials that could, or should, be launched to follow up and build upon RV144. These conversations, which include groups like the US HIV Vaccine Trials Network, are looking at choices of vaccine regimen, location, risk profile of the study population and trial design. *AVAC Report 2010* will explore these issues in greater detail.

Treatment as prevention at CROI

Several sessions at the 17th Conference on Retroviruses and Opportunistic Infections (CROI) in February were dedicated to the potential of widespread use of antiretrovirals (ARVs) to reduce HIV transmission. The majority of these discussions focused on the use of ARVs in HIV-positive people to reduce infectiousness and thereby reduce the risk of transmission to sexual partners. This type of "test and treat" approach has been a focus of increasing attention globally.

At CROI, Brian Williams from the South African Center for Epidemiologic Modeling and Analysis presented a version of the model that was published in *The Lancet* in January 2009. Williams projected that universal test and treat combined with effective PrEP could greatly reduce new transmissions in South Africa within a decade—while also reducing AIDS-related mortality—and could eliminate HIV infection altogether in 40 years.

The feasibility of a universal test and treat strategy was frequently questioned at CROI. Test and treat would require immediate treatment regardless of CD4 threshold—an approach that would strain many developing country health systems that are already struggling to meet current treatment goals.

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At a Glance

Gates Open

The Global Forum on MSM and HIV (MSMGF) received a two-year, US$1 million grant from the Bill & Melinda Gates Foundation. The funds will go to develop context-specific strategies for integrating new HIV prevention technologies into services for MSM communities at country and regional levels.

Package Deals

The NIH-sponsored program, Methods for Prevention Packages, or MP3, will fund six clinical trials of enhanced prevention strategies based on existing interventions. These trials will compare the enhanced package to standard prevention services and evaluate safety, efficacy and feasibility. Projects include: Prevention Umbrella for MSM in the Americas (PUMA) (*Peru, US*); Packages for Injection Drug Users (*Estonia*); Mochudi: Entire Community Care and Treatment (*Botswana*); Acute HIV Infection in Heterosexuals (*Malawi*); Enhance Prevention in Couples (EPIC) (*Lesotho*); PreventionRx (*Uganda*). ■

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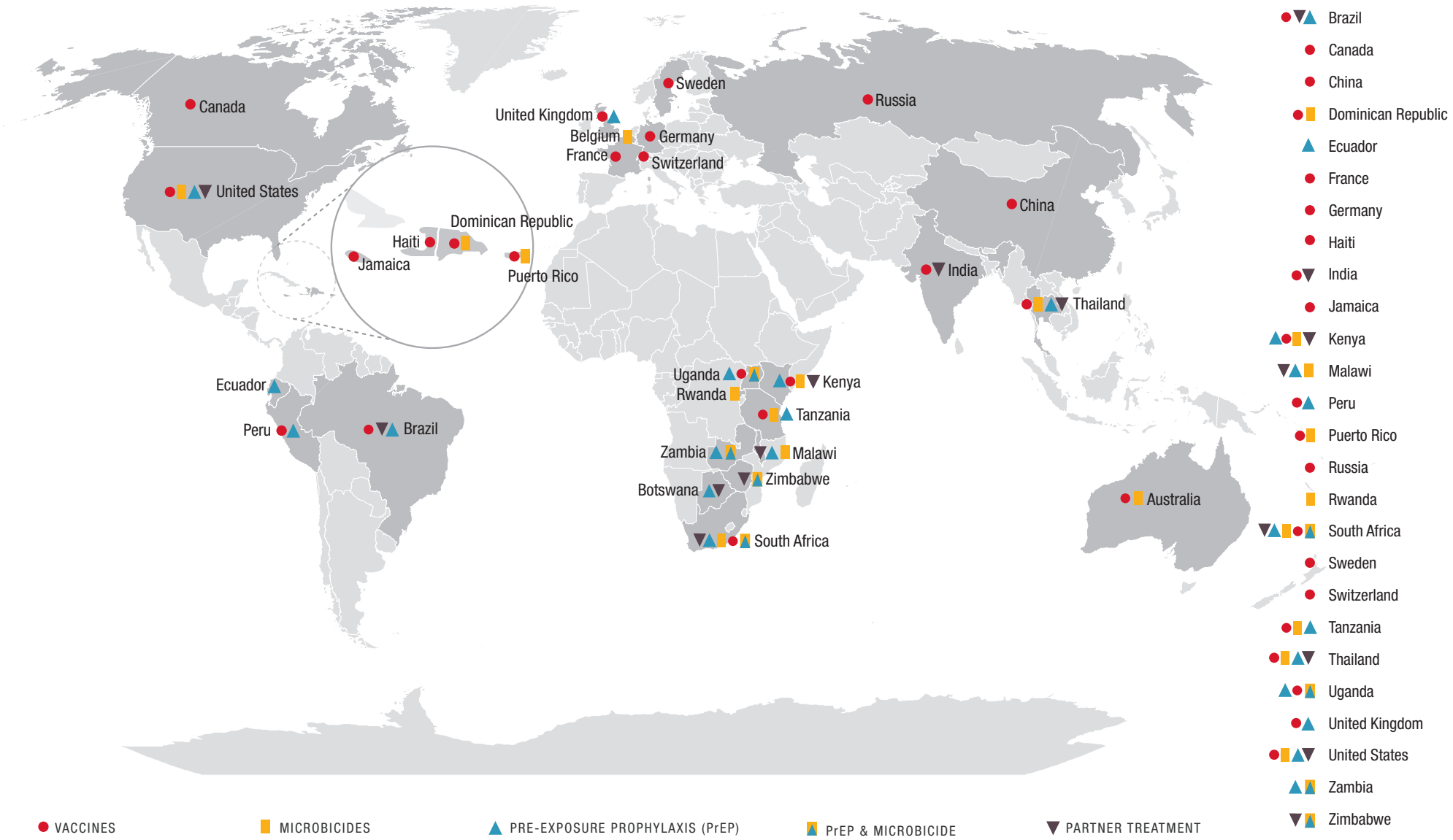
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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.

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)

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

2011

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, Zambia)

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 (South Africa, Uganda, Zambia, 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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A recently published modeling study from researchers at London's Imperial College (*AIDS* 24: 729-735, 2010) affirmed that test and treat could be an effective prevention but stated that the success and cost effectiveness varied based on the characteristics of the local epidemic (e.g., sexual behavior, HIV prevalence).

Models are, by definition, theoretical. But CROI also featured studies from the real world that support effective provision of ARVs as a powerful HIV prevention tool.

Moupali Das-Douglas from the San Francisco Department of Health described a study that used data from San Francisco's HIV/AIDS surveillance system to calculate a "community viral load," which they defined in part as the average of the most recent viral load measurements from all HIV-positive individuals in a specific population. They compared calculated community viral load with rates of new HIV infections over a six-year period (2002–2008) and found a statistically significant relationship between the community viral load and number of new HIV infections—as viral load went down, so did the number of new infections. This kind of analysis is ongoing in various settings. More data on the prevention impact of treatment is expected to come from HPTN 065, a study recently launched in Washington, DC, and Bronx, NY, which will assess the prevention and other benefits of linking people to treatment and care immediately after diagnosis.

In addition, Deborah Donnell from the University of Washington reported on a sub-study of the recently completed Partners in Prevention study of HSV-2 treatment to reduce HIV infectiousness in serodiscordant couples. Donnell reported that ART use dramatically reduced the risk of transmission between the HIV-positive and HIV-negative members of the couple. Of the 103 infections that occurred within the couples enrolled in the study, only one involved a couple where the HIV-positive individual was taking ARVs. A complete summary of the presentation can be found at *hivandhepatitis.com*.

For more on CROI, including recordings of AVAC's HIV prevention research webinar series that took place throughout March, please visit *www.avac.org/CROI2010*. ■

Coming Up

M2010 Pre-Conference Advocacy Workshop

The Global Campaign for Microbicides (GCM), in partnership with the African Microbicides Advocacy Group (AMAG), the International Rectal Microbicides Advocates (IRMA), and AVAC, will hold a daylong pre-conference workshop on May 22 before the official start of the Microbicides 2010 Conference. The workshop will provide the latest updates on HIV prevention research and preview the topics that will be presented at the conference.

AVAC Report 2010

AVAC Report 2010, *Turning the Page*, will be released in the second quarter of 2010 and will explore why recent developments like the Thai RV144 trial, the PRO 2000 microbicide trials and other studies mark the start of a new chapter in HIV prevention research. To pre-order free printed copies of the report visit *www.avac.org/orderpublications*. ■

Recently Relaunched

Earlier this year, AVAC relaunched the *Weekly NewsDigest*—an unedited compilation of media coverage, published research, policy news and other materials on HIV prevention options. Previously published by the Alliance for Microbicide Development (AMD), AVAC took on its production after the closing of the Alliance at the end of 2009. To subscribe to the *NewsDigest*, please visit *www.avac.org/digest* and for additional microbicide resources, including key publications from the AMD archive, visit *www.avac.org/microbicides*. ■

Not to be Missed

April 20–23: The HIV Research Catalyst Forum: Treatment, Prevention, Advocacy (closed enrollment), *Baltimore, Maryland, (www.hivresearchcatalystforum.org)*

May 4–6: HIV Vaccine Trials Network Annual Meeting, *Washington DC, (www.hvtn.org/meeting)*

May 22–25: 2010 International Microbicides Conference (M2010), *Pittsburgh, Pennsylvania, (www.microbicides2010.org)*

June 6–9: HIV Prevention Trials Network Annual Meeting, *Washington DC, (www.hptn.org/index.htm)*

For a full calendar of events, visit www.avac.org/events ■

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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