Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
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AVAC's Take

June was a jam-packed month for the AIDS epidemic, with a flurry of news media about the 30th anniversary of the first report of AIDS. In addition, the UN High Level Meeting on AIDS convened on the 10th anniversary of the 2001 UN General Assembly Special Session on AIDS that was the first such session devoted to a disease.

In much of the media coverage, "treatment as prevention" grabbed the spotlight and sports metaphors abounded. The phrase "game-changer" was a favorite term for describing the results from HPTN 052, the landmark trial which found that early initiation of antiretroviral therapy (ART) substantially reduced the risk of transmission within serodiscordant couples.

Many stakeholders are arguing that the HPTN 052 results signal a paradigm shift in the global AIDS response, since they clearly show that treatment *is* prevention. An international coalition of scientists, activists and advocacy groups, including AVAC, launched a sign-on statement containing a common platform that identified ART as a cornerstone of evidence-based prevention to end the AIDS epidemic. To read the statement, *We CAN End the AIDS Epidemic* and add your voice, go to *www.endtheepidemic.org*.

At a UN briefing on the US response to the epidemic, NIAID head Tony Fauci borrowed from basketball when he described the 052 result as "a slam dunk". But at that session, Dr. Fauci reserved "game-changer" for a vaccine—a powerful reminder that the search for this intervention must continue even in the context of emerging data on PrEP, microbicides and treatment as prevention. "If we could get a vaccine that is moderately effective and put that as one of a combination of multifaceted prevention modalities, that will be a game-changer."

With this in mind, AVAC highlights some of the developments in AIDS vaccine research that have received less attention but may, in the long-term, be no less important for ending the epidemic.

Changing the HVTN 505 protocol

Launched in 2009, HVTN 505 is a Phase IIb, test-of-concept AIDS vaccine trial in the US in men and transgender women who have sex with men. It tests a prime-boost strategy comprised of a DNA prime and an adenovirus-vector boost carrying HIV genes from three major subtypes of HIV-1. This strategy induces cellular immune responses that may be able to block HIV activity once it has established infection. This vaccine strategy does not induce neutralizing antibodies, which are traditionally considered to be the prerequisite for preventing infection. But the strategy does induce production of binding antibodies to the envelope insert in the vaccine.

The trial was originally designed to determine whether the vaccine strategy reduced viral load in participants who were HIV-negative when they received the vaccine, and later acquired HIV during sex or other risk-related behavior. In June, the Prevention Sciences Review Committee of the Division of AIDS, at the US NIH, approved a protocol change to the trial design that elevated HIV acquisition from a secondary to a co-primary endpoint. This means that the trial will now also be able to determine whether the strategy reduces the risk of HIV infection, in addition to asking its original question: does the regimen reduce viral load in people who receive the vaccine and later become infected?

HVTN 505 co-principal investigator Scott Hammer explains that this change was made in light of emerging scientific evidence. This includes the surprising evidence of modest protection observed in the Thai prime-boost trial known as RV144, which did not induce neutralizing antibodies, and evidence of protection seen in non-human primate trials of similar regimens. "RV144 raised the ante for looking for vaccine effect on acquisition," Dr. Hammer said, adding, "The science supporting the HVTN 505 regimen justifies modifying the trial to be sure that we can answer the acquisition question."

Also in June, a new collaboration called Pox-Protein Public-Private Partnership or "P5" continued planning trials designed to confirm and improve upon the results seen in RV144. Specifically, the P5 is developing a clinical trial strategy that may include two proposed Phase IIb trials—one in Thailand for MSM and the other in southern Africa. These two trials would evaluate ALVAC (used in RV144) plus a protein boost. According to current plans, selection of protein candidates for southern Africa will be made this quarter and trials will start in 2014.

How do recent results affect ongoing trials?

The question looming large for vaccine trials—and indeed for all other planned or ongoing biomedical prevention trials—is "What do recent results mean for trial design?" For example, what does the iPrEx trial result, which showed that daily oral TDF/FTC reduced

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At a Glance

Recently launched PrEP trials: Results expected 2013

ADAPT (HPTN 067)
Phase II behavioral trial to evaluate adherence and tolerance of intermittent oral TDF/FTC comparing daily, time-driven and event-driven dosing in women and MSM (South Africa, Thailand)

iPrEx OLE (Open-Label Extension)
Follow-on trial to evaluate safety and adherence of daily oral TDF/FTC in HIV-negative participants (MSM and transgender women) at all iPrEx trial sites (Brazil, Ecuador, Peru, South Africa, Thailand, United States)

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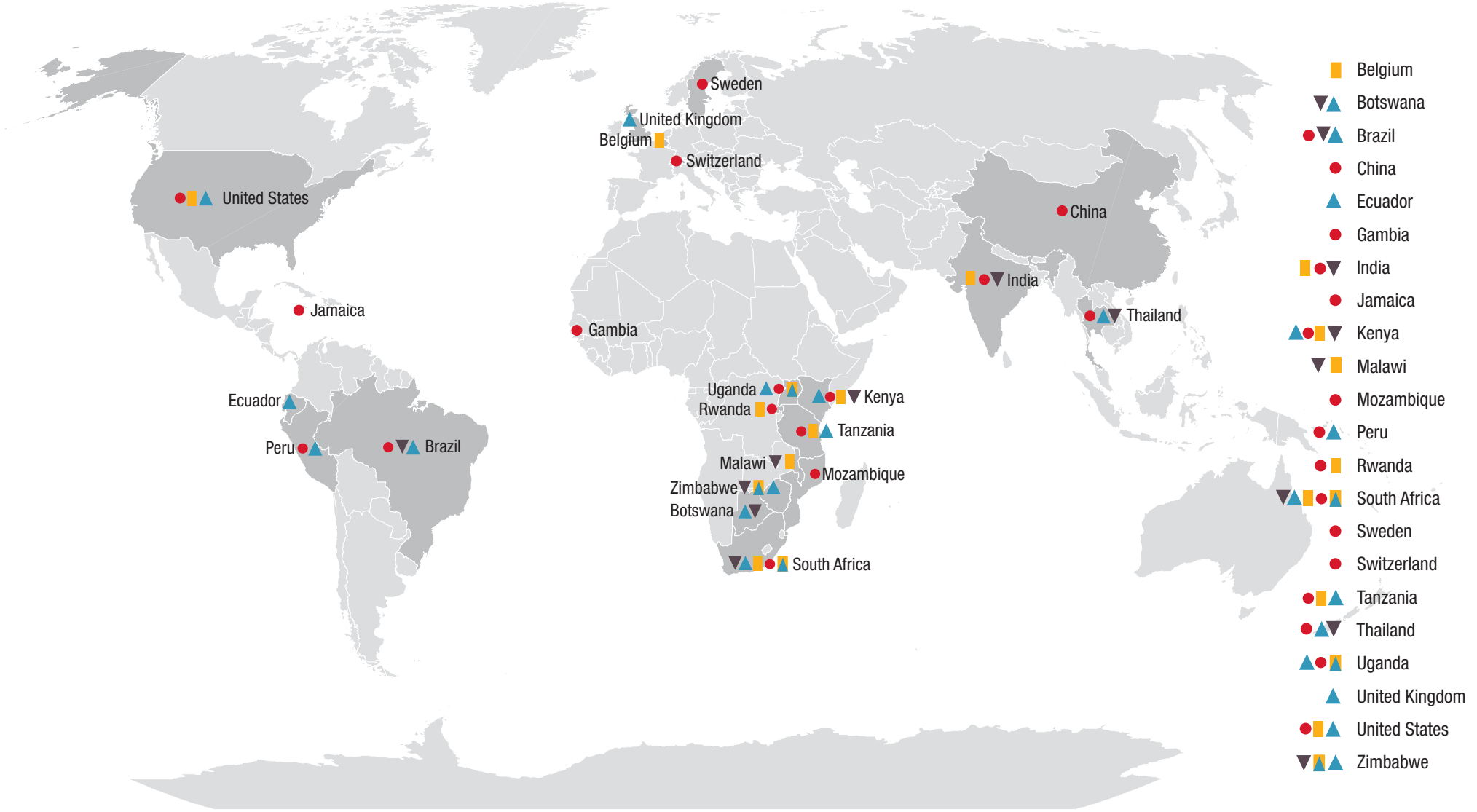
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



BIOMEDICAL HIV PREVENTION RESEARCH: A COMPREHENSIVE TIMELINE OF EFFICACY TRIAL RESULTS*

2009

HPTN 035
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
No evidence of reduced rates of HIV transmission, but there were reduced rates of genital ulcers and HIV viral load.

ALVAC-AIDSVAX (RV144)
Initial data showed that vaccine recipients were 31 percent less likely than placebo recipients to become HIV-infected (95% CI 1.1 to 52.1; P=0.04). There was no observed effect on viral load. Additional data analysis is ongoing.

MDP 301
No evidence of benefit.

2010

CAPRISA 004
There were 39 percent fewer infections among women who received 1% tenofovir gel compared to women who received the placebo gel (95% CI 6 to 60; P=0.017).

CDC 4323
The trial reported no serious adverse events and preliminary data showed PrEP use did not have a significant effect on HIV risk behavior. Additional data expected in 2011.

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

2011

FEM-PrEP
In April, DSMB recommended early trial closure based on futility analysis that the trial would not be able to show whether daily oral PrEP with TDF/FTC was effective in the prevention of HIV in women.

HPTN 052
In May, DSMB recommended early results be released based on data in serodiscordant couples showing that ART initiation at CD4 cell counts between 350 and 550 reduced risk of transmitting HIV to the uninfected sexual partner by 96 percent (P≤0.0001).

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

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)

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 MSM and transgender women; Prevention of HIV infection proposed as additional primary endpoint in June 2011, pending FDA approval (US)

2013

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 (Kenya, Uganda)

VOICE (MTN-003)
Phase IIb trial to evaluate the safety and effectiveness of three different strategies to prevent HIV in women: daily oral TDF, daily oral TDF/FTC, and 1% tenofovir gel (South Africa, Uganda, Zimbabwe)

FACTS 001
Phase III trial to evaluate the safety and effectiveness of 1% tenofovir gel to prevent HIV and HSV-2 infection in women (South Africa)

- 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

* *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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participants' risk of HIV, mean for trials like HVTN 505 or RV144 follow-up studies? And what does the HPTN 052 result mean for future trials in these and other cohorts?

While there are no simple answers to these complex questions, various context-specific answers are emerging. In its updated protocol, HVTN 505 is now providing clear information on the benefits and risks of PrEP as a prevention option to all participants. The trial is collecting self-reported information from participants who choose to use PrEP while in the study, as well as blood samples that will be tested for the level of PrEP drugs. The presence or absence of drugs used as PrEP will be analyzed in terms of impact on infection risk.

These shifts were made after much discussion about the possibility of adding PrEP to the official trial protocol. Hammer and his co-principal investigator Magda Sobieszczyk said that this decision would be revisited if/as findings or recommendations change and develop. Such changes could include US Public Health Service guidelines for PrEP use that are currently being developed, additional data from the iPrEx extended analysis and/or other ongoing trials, or a possible FDA-approved label change indicating TDF/FTC efficacy in prevention amongst gay men and transgender women. (Gilead Sciences, manufacturer of TDF/FTC, has indicated its intention to file a request for a prevention indication with the FDA based on the iPrEx results.)

The question of how the HPTN 052 data will or should impact future trial design is one that AVAC and other stakeholders are already discussing and following closely. Look for alerts on our Advocates' Network in the months to come about opportunities to discuss this issue. In the meantime, we're betting on ARV-based prevention and the possibility of a vaccine so that in another 30 years, HIV will be the losing team in this all too real epidemic. ■

Recently Released

Capitalizing on Scientific Progress: Investment in HIV Prevention R&D in 2010. The sixth annual report on investment in biomedical HIV prevention looks at spending in 2010 on preventive and therapeutic HIV vaccines, microbicides, PrEP, male circumcision, prevention of vertical transmission, and HSV-2 suppression and prevention. *(www.hivresourcetracking.org)*

Good Participatory Practice guidelines for biomedical HIV prevention (second edition). The GPP document provides systematic guidance on how to engage with stakeholders in the design and conduct of biomedical HIV prevention conduct. *(www.avac.org/gpp)*

Mapping Pathways. An online survey was launched by the AIDS Foundation of Chicago with the goal of developing a community-led global understanding of the emerging evidence base around the adoption of antiretroviral-based prevention strategies to end the HIV/AIDS epidemic. *(www.surveymonkey.com/s/MappingPathwaysIndiaSouthAfricaUSA)* ■

Not to be Missed

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, ***July 17–20, 2011***—*The biennial HIV/AIDS conference examines developments in HIV research and how these scientific advances can be put into practice. A full roadmap of HIV prevention research-related sessions is online at* www.avac.org/IAS2011. *Here are some highlights:*

Sunday, July 17

- **10:15–13:15, Satellite, MR 1:** Controlling the HIV Epidemic, the Promise of ARV-based Prevention
- **12:30–14:30, Satellite, MR 2:** GPP in Action: Introducing the 2nd Edition of Good Participatory Practice Guidelines for Biomedical HIV Prevention Trials
- **12:30–14:30, Satellite, MR 3:** From Proof to Delivery: Scaling up HIV Prevention for Women
- **14:45–16:45, Satellite, MR 2:** HIV Vaccines and the Prevention Revolution: Shortening the Path to the End of the Epidemic
- **17:00–19:00, Satellite, SR 3:** HIV Serodiscordant Couples: Opportunities and Challenges for Testing and Counseling, Prevention and Treatment
- **17:00–19:00, Satellite, MR 1:** The Cutting Edge: What's New in Male Circumcision

Monday, July 18

- **16:30–18:00, Oral Abstract Session, SR 2:** Treatment as Prevention: Results from HPTN 052
- **18:30–20:30, Satellite, MR 1:** Respect-Protect-Sustain: Developing Guidelines for MSM/HIV-related Researchers and Community-Based Organizations
- **18:30–20:30, Satellite, MR 3:** What Does the Future of ARV-Based Prevention Look Like?

Tuesday, July 19

- **7:00–8:30, Satellite, MR 4:** Zeroing Out New Infections Through Prevention Tools and Technologies
- **16:30–18:00, Bridging Session, SR 1:** Use of Antivirals in Prevention
- **18:30–20:30, Satellite, MR 3:** Can We End the Epidemic?

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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