Px Wire: A Quarterly Update on HIV Prevention Research

AVAC
Global Advocacy for HIV Prevention

Volume 2 | No. 3
July–September 2009

AVAC's Take: The Thai prime-boost trial – Celebrating possibility

The news of the initial findings from the Thai prime-boost AIDS vaccine efficacy trial broke as this quarter's issue of *Px Wire* was set to go to press. Given the array of questions, statements and assertions—some well-founded, others inaccurate—that emerged within days, if not hours, of the release of initial data, we decided to refocus this edition specifically on the Thai trial.

This is the first of several updates and publications we anticipate around the trial results in the coming months. An expanded guide, *Understanding the Results of the Thai Prime-Boost AIDS Vaccine Trial*, will be released later in October after more data are available.

In the meantime, and in the face of a finding that's complex to interpret and to explain, here are some simple statements of key issues, questions and answers that AVAC hopes will remain at the fore as the discussion moves forward.

Why the excitement?

The result from the Thai trial is the first indication in humans that an AIDS vaccine can be protective. However, the excitement about the result is due to the sense of possibility that it brings to AIDS vaccine research—not the sense that a specific product is around the corner.

Vaccines are designed to manipulate the immune system so that it is prepared to fend off foreign invaders. HIV targets the immune system. The field of AIDS vaccine research has, since its inception, sought to identify candidates that could get one, or more, steps ahead of the virus. This has proved incredibly challenging—so much so that in recent years there have been serious and compelling arguments about why an AIDS vaccine that prevents infection might be an impossible goal. The Thai trial data suggest that such a preventive AIDS vaccine might be achievable.

Why the caution?

There are many reasons to treat the result with cautious optimism.

- The confidence interval around the point estimate of 31.2% efficacy is wide. This means that the estimate of the vaccine regimen's impact on risk of HIV is far from precise.
- These are data from a single trial in a specific location. The vaccine included synthetic fragments of genetic material from HIV subtypes B and what is often referred to as subtype E, but is more accurately classified as CRF01 AE. These are two of roughly nine circulating subtypes, or clades, of HIV worldwide. Subtype E is common in Thailand and south-east Asia, so this study tells us about a situation in which the vaccine matches one of the predominantly circulating subtypes. It doesn't provide information on whether this specific strategy would have benefit in areas where other subtypes are predominant.
- These are data from a specific population. The trial didn't specifically look at how the vaccine worked in gay men or other men who have sex with men—although there were some enrolled in the trial. It also didn't target people who reported high rates of HIV risk behavior. There were men and women aged 18-30 enrolled in the study but questions about how the vaccine regimen might work in adolescents need to be even further explored.
- These are summary data. In this initial announcement, the trial team shared the results of an analysis of all HIV-negative volunteers who received any immunizations. This intent-to-treat analysis is considered the more rigorous way to look at data. But it will also be important to look at data from the per-protocol analysis, which includes only those volunteers who received all six immunizations (either vaccine or placebo).

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At a Glance: Thai trial results to date

- Trial duration: 2003-2009
- Total participants: 16,402
- Infections: 74 out of 8,198 volunteers who received placebo immunizations became infected with HIV compared to 51 out of 8,197 volunteers who received the vaccine regimen of ALVAC vCP1521 and AIDSVAX B/E.
- Reported efficacy: 31.2%, with a wide confidence interval (95% CI: 1.1%-52.1%) (A confidence interval is a statistical measure of the degree of precision or uncertainty associated with a result.)
- The vaccine regimen had no effect on post-infection viral load levels among the recipients who became infected.

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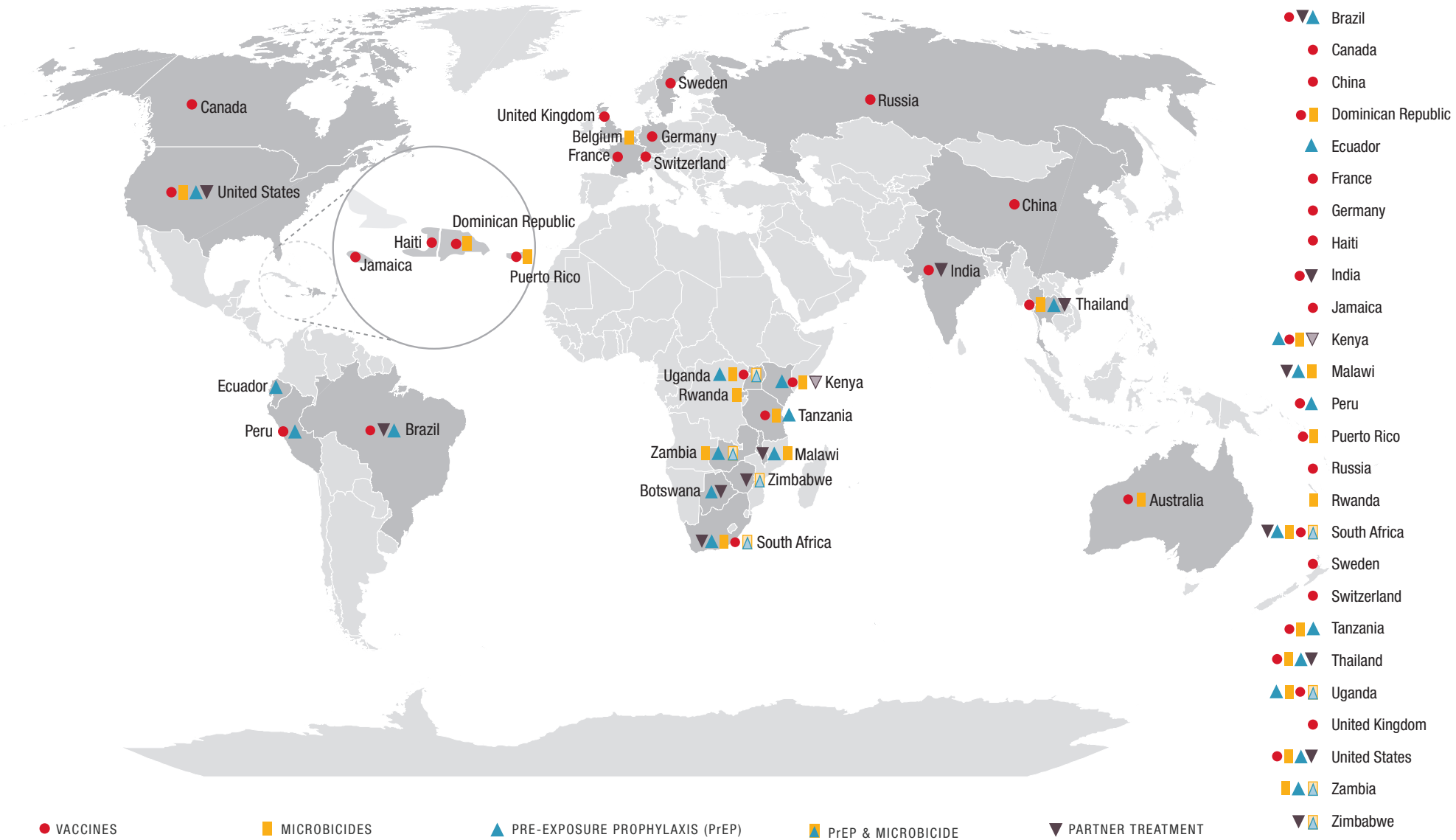
ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE



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)
Release of results expected in November 2009.

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 February in 2010.

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)

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

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 4940
Phase III trial to evaluate the safety and efficacy of once-daily oral TDF/FTC to prevent HIV infection in heterosexual men and women (Botswana)

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)

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, Malawi, South Africa, Thailand, US, Zimbabwe)

FEM-PrEP
Phase III trial to evaluate the safety and effectiveness of once-daily oral TDF/FTC for HIV prevention in women (Kenya, South Africa, Tanzania, Zambia)

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)

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)

- VACCINE
- PRE-EXPOSURE PROPHYLAXIS (PrEP)
- HERPES SIMPLEX VIRUS 2 (HSV-2) TREATMENT/SUPRESSION
- MICROBICIDE
- MALE CIRCUMCISION
- CERVICAL BARRIER METHOD
- PARTNER TREATMENT
- TRIAL COMPLETED OR STOPPED

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

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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Why were the results released without more details and before they were peer reviewed?

There are many instances in the past few years of HIV prevention research in which initial results were made public before peer-reviewed publication in a scientific journal. The efficacy trials of male circumcision for HIV prevention in Kenya and Uganda, the Step AIDS vaccine trial and multiple microbicide trials are all examples of studies where initial findings came out months before peer-reviewed publication. Withholding public release of data until peer-reviewed publication or even presentation at a scientific conference almost always privileges the scientific community over the populations involved in the trials as volunteers and supportive communities. The strategy taken by the Thai trial team and by the teams working on the studies cited above ensured that communities heard at the same time, if not before, the general public did. Other approaches can achieve the same goal but there is nothing inherently wrong—and much to be said for—an approach that ensures trial community members hear essential findings as soon as possible. In this instance, the information available included the absolute numbers of infections in both arms of the trial, the point estimate of vaccine efficacy and the confidence intervals around that estimate. Additional information on rates of infection by gender, age, risk group et cetera weren't part of this first announcement, but will be critically important to understand the results and guide decisions about further studies.

With so few infections, how can any conclusion be drawn?

Coverage of the Thai trial has generated some confusing statements about how the results should be interpreted. As the box on the first page describes, there were 125 infections total in the trial. This is a small number compared to the 16,000 volunteers enrolled in the study. However, for statistical purposes, what is important is the total number of infections and the difference between the numbers of infections in the vaccine and placebo groups. There were 23 fewer infections in vaccine compared to placebo recipients. This number of infections comes from the trial team's intent-to-treat analysis, which looks at infections in volunteers who received any immunizations, from one shot to the full course of six injections. Intent-to-treat, or ITT, is one of the analyses that will be done to understand the data. It is the only one that has been reported to date. In the ITT analysis this difference in numbers of infections was statistically significant, meaning that it was highly likely to be a real effect of the vaccine and not a coincidence.

Did both of the vaccines fail in previous efficacy trials?

No. Only one component of the regimen, AIDSVAX, was evaluated for efficacy on its own. There was no evidence of benefit in either of the two trials it was tested in. ALVAC vCP1521 was never evaluated in an efficacy trial. This was the first efficacy trial testing the ALVAC plus AIDSVAX combination. There will be important questions about what each vaccine component contributed to the observed effect, which will be explored as data analyses unfold. The Treatment Action Group has produced an excellent history of the development—together and separately—of these two candidates that can be viewed at *www.treatmentactiongroup.org/basicsciblog.aspx*, and we will provide additional information in our expanded report.

What's next?

The next weeks and months will continue to challenge all HIV prevention research stakeholders to strike a balance between caution and optimism. The more complete data set must be presented for discussion more widely within Thailand and at the international level for researchers, policy makers and advocates. In addition to reviewing further data from the trial, the wider scientific community will need to clarify how these results impact the broader vaccine research agenda.

What's the bottom line?

The Thai trial moves the AIDS vaccine field into a new and exciting stage of scientific inquiry. It doesn't tell us what the next AIDS vaccine will be. It doesn't mean that we'll have an AIDS vaccine tomorrow. But the Thai trial result did change the outlook of the AIDS vaccine field overnight. As US National Institute of Allergy and Infectious Disease head Tony Fauci said, "This is by no means our final destination. Rather, it is an opening of a gateway to a path that now has brighter lights." ■

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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