Px Wire: A Quarterly Update on HIV Prevention Research

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AVAC's Take

In a newly designed *Px Wire* centerspread, AVAC debuts a table of ongoing trials of ARV-based prevention in HIV-positive people. This broad category of research includes trials of the "test and treat" strategy that seeks to initiate ARV treatment in people as soon as they test HIV-positive, and other trials that seek a prevention benefit from starting individuals on ARV therapy at higher CD4 thresholds. One goal of these studies is to assess whether significantly decreasing levels of HIV viral load will reduce the rate of HIV transmission. These trials complement research on PrEP and ARV-based microbicides, which seek to use ARVs as prevention in HIV-negative people.

In the end, the goal remains universal access to AIDS treatment and prevention. AVAC hopes this table will be a tool to help bring the prevention and treatment threads in science and advocacy together into a single conversation and agenda for action. —*AVAC*

Data Dispatch

The recent 18th Conference on Retroviruses and Opportunistic Infections (CROI) provided new findings on medical male circumcision. For AVAC's ARV-based prevention roundup from CROI visit *www.avac.org/prep*. While CROI was kicking off, new AIDS vaccine data was published.

Medical Male Circumcision

One of the key questions with any prevention strategy is how long the protection lasts and whether the level of protection changes over time. New long-term follow-up data from a male circumcision for HIV prevention trial in Rakai, Uganda, suggest that circumcision among HIV-negative men provides a durable risk-reduction benefit, which actually increases over time. The trial halted randomization in 2006 after it found that there were approximately 51 percent fewer HIV infections among men who received circumcision compared to those assigned to the control arm.

At CROI, Xiangrong Kong of Johns Hopkins University presented data on HIV rates among men from the circumcision arm of the trial nearly five years after randomization was halted. HIV rates in this group were 73 percent lower than in men from the control group who chose to remain uncircumcised. She also noted that men from the control group who opted for circumcision when randomization ended had a 67 percent reduction in HIV infections compared to the uncircumcised cohort.

The follow-up Rakai data also show no increase in the number of non-marital partners reported by participants. However, the researchers found that men in both the control group and the circumcised group reported reductions in condom use during follow-up. Study authors suggest that this change in behavior might be related to the fact that participants stopped receiving intensive risk-behavior counseling once the randomized trial was completed.

AIDS Vaccines

Over three years after immunizations were stopped in the Step AIDS vaccine trial, the study is still yielding scientific clues. An article in *Nature Medicine* (17, 366-371, 27 February 2011) described the analyses of viruses obtained from volunteers who received either the vaccine

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Tenofovir Gel: Nine months and counting

In the nine months since the CAPRISA 004 trial results showed that 1% tenofovir gel reduces the risk of HIV infection in women by 39 percent, the field has grappled with how best to follow up on these historic results. Planning, meetings and debates on next steps have dominated this period, yet the field still lacks a clear, streamlined plan for product development and delivery. See AVAC's forthcoming analysis of what is—and is not—happening to move tenofovir gel forward. The report will be available at *www.avac.org/tenofovirgel*.

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July: CAPRISA 004 results announced and published

August: WHO/UNAIDS Meeting: Next Steps with 1% Tenofovir Gel

October: US FDA indicates CAPRISA 004 and VOICE may be pivotal trials sufficient for licensure despite different dosing strategies

November: CAPRISA 008 follow-on study protocol submitted for ethics approval (as of March, no funding confirmed)

November: FACTS 001 protocol submitted to the MCC for peer review (as of March, funding confirmed from SA government and pending from USAID)

November: USAID Stakeholders Meeting; call for comprehensive development plan by January 31, 2011

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February: Boston Consulting Group prepares "Scenario planning for 1% tenofovir gel" at the request of USAID, NIH and the Bill & Melinda Gates Foundation

March: No comprehensive and funded development plan

June: *WHO/UNAIDS meeting on 1% tenofovir gel implementation*

July: *One-year anniversary of proof-of-concept of 1% tenofovir gel*

Today there are several trials evaluating the use of ARV-based prevention in people with HIV. The goal of these "treatment as prevention" strategies is to reduce viral load and thereby reduce individuals' infectiousness. Data gathered from serodiscordant couples enrolled in a trial of HSV-2 treatment for HIV prevention showed that effective ARV treatment reduced HIV transmission by approximately 92 percent. These data were not from a randomized controlled trial and ongoing trials—many listed below—will provide additional information. Not included in this table are the many ecological studies of ART impact on HIV prevalence in different settings.

ARV-Based Prevention in HIV-Positive Individuals: Relevant studies *(April 2011)*

Study	Location	Funder	Population / Mode of exposure	Hypothesis/Study Aim	Status / Results expected
HIV VCT and Linkage to Care in Uganda	Uganda	National Institutes of Health (NIH)	3,314 men and women	Tests the hypothesis that enhanced counseling and testing for HIV among hospitalized adults is more efficacious than traditional counseling and testing in reducing HIV risk behavior. Tests if an enhanced linkage to HIV-specific medical care is more effective than usual referral in receipt of OI prophylaxis, ART and reducing mortality.	Ongoing / Q4 2011
SEARCH: Sustainable East African Research for Community Health	Uganda, Kenya, Tanzania	NIH	Rural populations	Is a streamlined health care delivery approach that combines HIV/AIDS, TB, malaria treatment and community-health screening feasible and does it reduce incidence of HIV, TB and malaria in a community randomized trial?	Ongoing / 2011–12
Methods for Prevention Packages (MP3) Prevention Rx	South Africa, Uganda	NIH	8,000 men and women	The goal is to assess home-based HIV testing as a platform for achieving high coverage of knowledge of HIV serostatus (HBCT+) with point-of-care CD4 testing for HIV-positive persons to facilitate linkages to HIV care and ART. The primary outcome is community viral load at 0, 6 and 12 months in the communities where the HBCT+ intervention is being conducted.	Ongoing / 2012
TLC-Plus (HPTN 065): Evaluating Methods to Increase HIV Testing, Access to HIV Care and HIV Prevention Strategies	US (Bronx, NY, and Washington, DC)	NIH	22,000 men and women	Is it feasible to implement a community-level test, link to care plus treat strategy in the US? What is the effectiveness of a financial incentive intervention versus standard of care in enhancing linkage to care and viral suppression? Does a computer-delivered intervention enhance standard of care for prevention with positives?	Ongoing / 2013
MP3: An HIV Prevention Package for Mochudi	Botswana	NIH	14,000 men and women	What is the feasibility and acceptability of a package of interventions including education for behavior modification, circumcision of adult males and the use of antiretroviral drugs to decrease transmission at the community level? Data to be gathered include incidence, prevalence and behavioral risk factors; uptake of services; and acceptance of ART among HIV-positive individuals with acute infection and/or VL > 100,000 who do not otherwise qualify for treatment based on national guidelines, AIDS-defining illness or CD4 < 250.	Ongoing / 2013
PopART: Population Effects of Antiretroviral Therapy to Reduce HIV Transmission	Uganda (pilot study in Wakiso District), Malawi, Tanzania, Zambia	UK Medical Research Council	15,000 men and women	Is it feasible and acceptable to undertake a study of universal VCT, followed by immediate ART for all testing positive for HIV, to reduce population-level transmission?	Start Q3 2011 / 2014
START: Strategic Timing of Antiretroviral Treatment	Africa, the Americas, Asia, Australia, Europe (30 countries)	NIH	4,000 ARV-naïve men and women with CD4 counts above 500	How does early treatment initiation affect clinical outcomes including progression to AIDS, serious non-AIDS diagnoses and mortality?	Ongoing / 2015
Preventing Sexual Transmission of HIV with Anti-HIV Drugs (HPTN 052)	Botswana, Brazil, India, Kenya, Malawi, South Africa, Thailand, United States, Zimbabwe	NIH	3,500 sero-discordant couples (opposite and same sex)	Does early initiation of treatment for the HIV-positive partner reduce risk of transmission in serodiscordant couples?	Ongoing / 2015
Treatment as Prevention (TasP or Ukuphila kwami, ukuphila kwethu)	South Africa (Kwazulu Natal)	Agence nationale de recherches sur le sida et les hépatites virales (French AIDS Research Agency)	40,000 men and women	After feasibility is established: Does early treatment initiation reduce incidence in a cluster-randomized design?	Start Q3 2011 / 2015
MP3: Acute HIV Infection in Heterosexuals	Malawi	NIH	115 men and women with acute HIV infection	The specific aims of the study are to: 1) Develop a novel program to prevent HIV transmission by identifying and informing persons with acute HIV infection (AHI); 2) Evaluate a short-term, combined behavioral and ART intervention to prevent HIV transmission among persons with AHI, 3) Determine the potential individual and combined impact of each intervention.	Start Q3 2011 / 2015
MP3: Enhanced Prevention in Couples (EPIC)	Lesotho	NIH	1,770 serodiscordant couples	The EPIC study aims to decrease the risk of HIV acquisition in HIV-negative partners within serodiscordant couples in Lesotho through implementation of an Enhanced Prevention Package, elements of which will be evaluated in feasibility studies. These interventions include male circumcision, couples counseling for HIV testing, ART adherence and risk reduction, and could also incorporate new interventions such as PrEP and microbicides identified in ongoing trials.	Start 2011 / To be determined

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

2009

HPTN 035
No statistically significant benefit of PRO 2000 and no evidence of benefit of Buffer Gel

PARTNERS IN PREVENTION
No evidence of benefit of suppressive treatment for HSV-2 on HIV transmission

ALVAC-AIDSVAX (RV 144)
Vaccine reduced HIV risk by 31% (95% CI 1.1 to 52.1; P=0.04)

MDP 301
No evidence of benefit of PRO 2000

2010

CAPRISA 004
Tenofovir gel reduced HIV risk by 39% (95% CI 6 to 60%; P=0.017)

CDC 4323
PrEP with daily TDF showed no evidence of harm or effect on HIV risk behavior

iPrEx
PrEP with daily TDF/FTC reduced HIV risk by 44% (95% CI 15.4 to 62.6%; P=0.005)

2011

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 men and transgender women who have sex with men (US)

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, Zimbabwe)

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)

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

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)

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

** 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.*

ONGOING TRIALS OF NEW PREVENTION OPTIONS WORLDWIDE

Continued from front

strategy or the placebo but later became HIV-positive. The researchers analyzed viral strains from participants in both arms and found differences in the viral genetics of strains from vaccine recipients. They concluded that vaccine-induced T-cell responses had influenced the genetic make-up of the virus with what is known as a "sieve effect". This term is used to describe what happens when immune responses successfully inhibit some virus variants from replicating but not others.

These are the first data to show that a T cell-based vaccine tested in humans can have an impact on the genetic make-up of the virus. Researchers are conducting analyses of viruses isolated from participants who acquired HIV in the Thai trial (RV144) and are looking for similar effects. ■

At a Glance

Planning Ahead for Trial Success

In January in Johannesburg, AVAC partnered with the Microbicide Trials Network (MTN), Southern African AIDS Trust and the Treatment Action Campaign to organize "Next Steps for ARV-based Prevention", a civil society consultation on follow-up research with a focus on what may come after the VOICE trial. (VOICE is evaluating daily TDF, daily TDF/FTC and daily 1% tenofovir gel.) Given the recent results of the CAPRISA 004 microbicide and iPrEx PrEP trials, it is critical to continue to prepare for potential positive results from other ongoing trials of oral and topical ARV-based formulations.

Part of the civil society consultation was allocated to discussions of MTN 018, or CHOICE, a planned follow-on trial that would be initiated if one or more of the strategies being evaluated in the VOICE trial were found to be safe and effective. The forty advocates from East and Southern Africa discussed the proposed MTN 018 trial design as well as the regulatory process for approving the gel should it show effectiveness in VOICE—results are expected in early 2013. (The same gel candidate used in VOICE showed 39 percent protection against HIV in the CAPRISA 004 trial but used a different dosing strategy.) Following this community consultation, the MTN 018 Protocol Development Team met and incorporated the civil society feedback into its deliberations. Engaging civil society while the trial protocol is in development is an example of good participatory practice guidelines in action (see "Coming Soon").

Future Directions for HIV Research

The US National Institute of Allergy and Infectious Diseases (NIAID), a part of the National Institutes of Health (NIH), is in the process of restructuring its $300 million HIV/AIDS clinical trials networks. The awards supporting the six current HIV/AIDS networks are set to expire in 2013 and 2014. A primary aim for the next funding cycle (2013–2020) is to broaden the networks' scope by establishing multi-disease research capacity on the existing infrastructure of the HIV/AIDS trials network. This expansion would accommodate the study of tuberculosis, hepatitis and other HIV comorbidities.

The four priority areas for the newly named "NIAID HIV/AIDS and Infectious Diseases Clinical Trials Network" are HIV Prevention, HIV Vaccines, Therapeutics, and Pediatric and Maternal & Child Health. Funding for the HIV Prevention Network will be divided into two groups: Microbicides and Integrated Prevention Strategies (including PrEP and ARV-based prevention in HIV-positive people). An additional priority area will be funded for non-HIV/AIDS infectious disease research.

Splitting microbicides and PrEP into separate groups could raise questions about leadership of the scientific agenda going forward, since both fields are focusing on ARV-based prevention. AVAC and other advocacy groups have raised this in feedback on the restructuring process and call on NIAID to ensure that there are strong governance structures that support cross-network communication and collaboration.

NIAID is soliciting input into the restructuring process at *http://blog.aids.gov/2010/08/future-directions-for-niaids-hiv-vaccine-clinical-research-consider-and-comment.html* ■

Coming Soon

In April, UNAIDS and AVAC are planning to release the second edition of the *Good Participatory Practice guidelines for biomedical HIV prevention trials*. The GPP guidelines provide funders, sponsors and implementers with systematic guidance on how to engage with stakeholders in the design and conduct of biomedical HIV prevention trials. Since 2007, the GPP guidelines have been applied in different settings and were the subject of formal global consultations. The guidelines will be available for download at *www.avac.org/gpp*—printed copies can also be requested. ■

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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