PxWire A Quarterly Update on HIV Prevention Research | Vol. 8 No. 2 | April–June 2015 | AVAC Global Advocacy for HIV Prevention

AVAC's Take

Now's the time to ask "not if, but how?" for oral PrEP

In late March, AVAC and nearly 90 partners and collaborators, largely from sub-Saharan Africa, gathered in Johannesburg to share experiences, talk strategies and set priorities for the coming year. A range of blogs about and presentations from this meeting—the fifth Advocacy Partners' Forum—can be found at *avac.org/partnersforum*.

The wide-ranging conversations touched on microbicides, vaccines, the uses and misuses of the term "key population", PEPFFAR-focused advocacy, the future of AIDS activism and the need for a single agenda that combines human rights and biomedical priorities for marginalized, stigmatized and criminalized groups.

The role of PrEP was also a key topic. Here, a few themes emerged. First, that right now oral PrEP is the only woman-controlled method available that is not linked to use at the time of sex. Second, that access to TDF/FTC (brand name Truvada)—the drug used in oral PrEP—is a fundamental concern for and need of people living with HIV/AIDS. Third, that treatment and prevention agendas can't be dealt with separately. There was a sense that urgent action is needed now to make up for lost time and use ARVs in strong, strategic prevention and treatment programs.

Also in late March, WHO and UNAIDS convened a series of meetings on the place of daily oral PrEP in the context of combination prevention programs. (This series built on a meeting that happened in October 2014, *Success with PrEP: Next Steps to Support Policy Decisions in Southern and East Africa* convened by AVAC, UNAIDS and WHO. This meeting also sought to map key questions and needs such as guidance and decision-making tools for countries. For a meeting report and other materials see *www.avac.org/successwithPrEP*).

Participants at the March meeting series were tasked with helping WHO frame the "PICO" question that will guide review of all of the available data on PrEP—a key step in the development of guidance on PrEP for all populations. (Right now, the 2014 WHO Consolidated Guidance on ARVs for Prevention and Treatment for Key Populations recommends PrEP as an option for gay men and other men who have sex with men and does not address its utility for other populations.)

How you frame a question dictates the answer you'll get, and PICO questions (this stands for Population/Intervention/Comparator/Outcome) are no different. The question that will be asked for PrEP is whether this strategy should be a prevention choice for people at risk of HIV. Choice is key for all health decisions—and the question's wording emphasizes this concept for PrEP. Also key: the decision to frame the question in terms of PrEP's utility for people at risk of HIV. By moving away from specific populations or risk groups, the WHO can help ensure that this intervention isn't positioned for one group and not for another. From hepatitis B vaccines to female condoms, there are examples of interventions initially targeted for one group that only took off when they were introduced at population level.

Over the next few months, WHO will review the evidence for PrEP in order to answer this question. But advocates don't have to wait for new guidance to take action. There is a range of activities that need attention right now. These vary by country and may include: ensuring that Gilead (the patent-holder for the brand-name version of TDF/FTC) has applied to register the drug in country; lobbying government to establish or task a working group to explore the role of PrEP in country; supporting stakeholder engagement in planned or ongoing demonstration projects; and convening civil society groups to explore questions, concerns and common priorities.

If you would like to learn more or be involved, please be in touch! – *AVAC*

Data Dispatch

Taking an active interest in passive immunization

"Passive immunization" is the scientific term for an expanding area of research that's highly relevant to treatment, prevention and cure work. There are trials in humans happening in many regions of the world, and data are beginning to come in that advocates need to understand, analyze and consider.

Continues on back >

AVAC
Global Advocacy for HIV Prevention

Selected Guide to Pipeline of Antibodies, Long-Acting ARVs and Vaccines

	What is it?	What could it do?	Key Facts
Antibodies	• Passive immunization is the transfer of pre-made antibodies to a person. Passive immunization using today's pre-made antibodies can involve infusion delivered in a clinic setting over a period of 30 minutes or more. • An alternative approach using vectors and genes that can be turned into 'antibody factories' within the body is also under investigation. • Both infusion and gene therapy approaches differ from immunization with vaccines that teach the body how to make its own defenses.	• Laboratory-made broadly neutralizing antibodies (bNAbs) against HIV could provide protection against infection in HIV-negative people. • It might be possible to formulate these bNAbs so that a single dose could provide protection for months at a time. • Testing bNAbs for HIV prevention can also provide proof-of-concept for developing HIV vaccine candidates. • This strategy is being considered used for prevention of HIV acquisition in adults and/or breastfeeding infants. • It is also being explored as a treatment modality and perhaps as part of a cure strategy to eliminate viral reservoirs.	• bNAbs are isolated from the blood of people living with HIV. A handful of individuals make these potent immune responses. • The most potent bNAbs come from months of co-evolution with virus during chronic infection. They have unique characteristics. • Some have atypically long regions in the CDR43 loop—a portion of the "arms" of the Y-shaped antibody protein. Others undergo a lengthy process of maturation to become potent against HIV. It will take a long time to create vaccines that elicit such responses.
Long-Acting Injectable (LAI) Antiretrovirals (ARVs)	• Antiretroviral drugs given via injection that persist in the blood for long periods of time. • LAI ARVs need to be dosed every few months. Single-drug LAI PrEP regimens being evaluated utilize injections (one in each buttock) every eight to 12 weeks. • Two-drug LAI treatment regimens being evaluated utilize injections every four or eight weeks.	• In HIV-positive people, LAI ARVs could simplify treatment and change the way ARVs are delivered. • In HIV-negative people, the same ARVs could be long-acting PrEP. This could reduce the burden of adherence and make it easier for some people to take, although issues of regular testing to monitor for HIV infection need to be addressed, as they do for all PrEP strategies (right now PrEP is a daily oral strategy).	• Trials of LAI ARVs start with a lead-in phase where people take oral formulations of the same drugs to establish safety and tolerability in a formulation that can be discontinued. (Injectable ARVs cannot be removed from the body.) • The drugs used as injectables have unique properties that allow them to be formulated into doses suitable for injection. Many other common ARVs can't be used in this way. • The current suite of trials will provide information that could launch expanded trials in 2016/7 designed to test for efficacy and possible licensure for both treatment and prevention purposes.
Preventive Vaccines	• Seeks to teach to the immune system how to protect itself against infection by a pathogen.	• AIDS vaccines have been a key part of the prevention research agenda for nearly three decades. • Existing preventive vaccines for other diseases involve one or a series of immunizations, and can provide long-term or even lifelong protection. • Protection isn't always complete and may wane over time. • The one AIDS vaccine strategy to show efficacy to date (in RV144) involved six immunizations and protection waned after one year. • Current research is focused on improving on these results as well as exploring other vaccine candidates entirely.	• There is a robust pipeline of AIDS vaccine work, some of which overlaps with the investigations of passive immunization. • In Southern Africa, work continues on a suite of trials designed to build on the evidence from the RV144 trial. • A range of early-phase trials of other novel candidates to establish the safety and immunogenicity of other novel candidates are getting underway in 2015.

Product Name(s)	Phase of Research	Research Description	HIV Status of Population	Class of Drug	Location
Antibodies*					
3BNC117	Phase I	• Phase I trial in HIV-negative people and people living with HIV looking at safety, tolerability and virologic impact associated with different doses found safety in all groups and sustained viral load reductions at the highest dose. Further treatment and prevention studies are planned.	⊖ ⊕	Broadly neutralizing antibody	Germany, US
AAV vector encoding PG9 antibody	Phase I	• Ongoing Phase I trial is establishing safety and optimal doses of a gene-therapy approach to passive immunization.	⊖	Broadly neutralizing antibody	UK
CAP256-VRC26	Pre-clinical	• Targeting the V1V2 binding site in development for treatment and prevention, currently in preclinical phase.	N/A	Broadly neutralizing antibody	South Africa
Ibalizumab (TMB-355)	Phase I, II	• Ibalizumab has completed Phase I and II trials in HIV-negative individuals and people living with HIV. It is currently available for treatment (as part of combination therapy) via compassionate access programs.	⊖ ⊕	Monoclonal antibody targeting the CD4 binding site	US
PGT121	Pre-clinical	• Targets the V3 region of gp120 and has shown potency in reducing viral load in SIV-infected non-human primates. It is being developed as a possible treatment and/or a component of a cure strategy for people living with HIV.	N/A	Broadly neutralizing antibody	US
VRC01	Phase I	• Targets the gp120 binding site recently being evaluated in a dose escalation study looking at safety, acceptability, PK and PD in people living with HIV. Preliminary results have been reported showing an impact on viral load. • HVTN 104 is phase 1 trial evaluating safety and drug levels of this antibody in HIV-negative adults. Concept note for follow-on efficacy trial has been developed. • Phase I saftey trial in infants is also being explored. Planned treatment trials will look at VRC01 + ART in acute infection. Additional trials in HIV-positive and -negative individuals are planned.	⊖ ⊕	Broadly neutralizing antibody	US
Long Acting Injectable ARVs					
GSK744 (cabotegravir, GSK1265744)	Phase II	• Ongoing ECLAIR trial evaluating safety and tolerability of injections every 12 weeks in HIV-uninfected men in the US. • HPTN 077 evaluating the safety, tolerability and pharmacokinetics in HIV-uninfected men and women.	⊖	Integrase strand transfer inhibitor	Brazil, Malawi, South Africa (HPTN 077), US (HPTN 077 and ECLAIR)
TMC278 (rilpivirine, Edurant)	Phase II	• Phase I trial evaluating the safety, acceptability, pharmacokinetics and pharmacodynamics of different dosing regimens underway in men and women in the US. • Phase II placebo-controlled HPTN 076 trial is evaluating safety, acceptability, drug presence in the genital tract of injections at eight week intervals among women in sub-Saharan Africa and the US and also gather information on HIV acquisition.	⊖	Nonnucleoside reverse transcriptase inhibitor	South Africa, US, Zimbabwe
TMC278/GSK744	Phase IIb	• A two-drug combination being tested as a "maintenance" regimen in people living with HIV who have achieved virologic suppression on triple-combination oral ARVs.	⊕	Nonnucleoside reverse transcriptase inhibitor plus integrase strand transfer inhibitor	Canada, France, Germany, Spain, US
Preventive Vaccines*					
Ad26/MVA/gp140	Phase I/II	• Trial testing safety and immunogenicity of various regimens containing Ad26 vector (a cold-causing virus, altered to not cause illness) and a "mosaic" immunogen, designed to induce immunity against a range of HIV subtypes.	⊖	Adenovirus 26/ Modified Vaccinia Ankara Mosaic/ glycoprotein 140	South Africa, Thailand, US
ALVAC/AIDSVAX	Phase III follow-up and Phase I	• RV305 is taking place among participants from original RV144 trial to assess impact of additional boosts. • RV306 is testing the boosted regimen among new participants.	⊖	Pox-protein	Thailand
ALVAC/gp120/ MF59 adjuvant Clade C	Phase I/II	• HVTN 100 is testing an RV144-like regimen that has been altered with goal of optimizing for southern Africa. • First trial in the "development track" of post-RV144 trials sponsored by the Pox-Protein Public-Private Partnership (P5).	⊖	Pox-protein	South Africa
ALVAC, DNA, Protein, MF59, AS01B adjuvant (various combinations)	Phase I/II	• Suite of trials in the P5 "research track" will evaluate various vaccine combinations to identify correlates of immunity that could improve future regimens.	⊖	Pox-protein	Malawi, Mozambique, South Africa, Switzerland, Tanzania, US, Zambia, Zimbabwe

* The list of clinical and preclinical trials below is not exhaustive. For details on full range of products in ongoing and completed trials visit *avac.org/pxrd*.

> *Continued from front*

The term passive immunization refers to the fact that the antibodies aren't made by the body itself. Instead, they are either delivered via infusion or made by gene therapy, which seeks to create little antibody "factories" in the body. It's different from vaccine strategies, which teach our bodies how to make antibodies for ourselves.

The science behind passive immunization starts with what's known as HIV-specific broadly neutralizing antibodies (bNAbs). It's a mouthful but breaks down into fairly simple concepts. "HIV-specific" indicates that these antibodies work against the virus. The phrase "broadly neutralizing" refers to the antibody's ability to act against many different genetic variants of HIV. You can have antibodies that only neutralize one or a handful of viruses, and ones that have no neutralizing activity at all.

Passive immunization is being explored in people living with HIV to understand whether bNAbs can help control viral replication and/or serve as part of a cure strategy. It is also being explored for HIV prevention.

Why pay attention? Because this type of research is already showing results. In a recent paper published in *Nature,*[1] a team of researchers from Rockefeller University (US) reported on a trial designed to evaluate the anti-HIV activity and safety of various doses of a bNAb known as 3BNC117. This trial took place in 12 HIV-negative people and 13 people living with HIV, two of whom were taking ART. HIV-positive participants who were not taking ART and who received the highest dose of 3BNC117 saw significant reductions in viral load (from 0.8 log to 2.5 logs). These reductions happened after a single dose and lasted at least 28 days. Amongst the HIV-negative participants, the antibody appeared to be safe and well-tolerated.

More trials are planned and/or ongoing with a number of bNAbs. As the centerspread of this issue shows, there are four bNAbs already in clinical trials that aim to evaluate this effect—prevention in HIV-negative individuals and/or impact on viral load in people living with HIV—and more on the way.

Where do bNAbs come from? They've been found by painstaking examination of samples from people living with HIV. A small number of people living with HIV make bNABs. These individuals don't benefit from the bNAbs they've made. This is because HIV mutates faster than the immune system can keep up. The antibodies a person makes today can often neutralize the virus that he or she had in her blood some months prior—a sign that the immune system is working to fight HIV, and also that the virus is often one step ahead.

Passive immunization trials in HIV-negative people will help answer the question: what would happen if bNAbs were there *before* the virus? If the body already had bNAbs in the blood then perhaps HIV would not be able to establish infection?

The bNAbs moving into clinical trials have been modified to make them even more effective against HIV; reduce the size of the dose needed for impact; and ensure that they are delivered to the sites of exposure—e.g., the vagina and rectum in the case of sexual exposure—where protection is needed most.

A treatment that controls HIV after a single dose for a month or more could have enormous benefits for many people living with HIV. And treatment using bNAbs is just one such strategy being explored. As a range of trials, from long-acting injectable antiretrovirals to AIDS vaccines get underway—often in both HIV-positive and HIV-negative individuals—it will be critical for advocates to understand similarities and differences, and to track levels of investment and commitment from funders and researchers.

Let's Talk Prevention!

AVAC is pleased to announce a year-long series of web-based dialogues delving into issues raised in our recent *AVAC Report 2014/5: Prevention on the Line.* Information on future webinars as well as links to recordings and slides of previous calls in the series are available at *www.avac.org/prevention-line-webinar-series.*

About AVAC

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 HIV biomedical prevention options as part of a comprehensive response to the pandemic.

To receive regular updates via email sign up at *www.avac.org/subscribe.*

423 West 127th St., 4th Floor • New York, NY 10027 USA
Telephone +1 212 796 6423 • *www.avac.org*

[1] *http://www.nature.com/nature/journal/vaop/ncurrent/full/nature14411.html*