AVAC
25 Years and Counting

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Understanding Results of the AMP Trials

In February 2021, two large-scale proof-of-concept trials of antibody-mediated prevention (AMP) announced results. Antibody-mediated prevention is a strategy that seeks to protect people from getting HIV by giving them antibodies that block the virus. Antibodies are made by the immune system to protect or eliminate foreign pathogens. When a person receives a vaccine against a virus, that vaccine teaches the body to make immune responses (antibodies) that protect against infection if they are ever exposed. Antibody-mediated prevention, unlike a vaccine, does not teach the body how to make a defense. Instead, it delivers the antibody directly into the body.

The AMP trials—HVTN 704/HPTN 085 and HVTN 703/HPTN 081—tested whether an antibody called "VRC01" could reduce the risk of HIV infection. The trials showed that VRC01 did not reduce the overall risk of acquiring HIV. However, VRC01 protected some individuals from infection by HIV viruses that were particularly vulnerable or "sensitive" to the antibody.

This protection was seen in a small number of people, against a small subset of viruses. Now, the task for prevention advocates and researchers is to figure out what the results mean for the future. This document is designed for advocates who want to participate and influence decisions in these discussions.

TOP-LINE FINDINGS TO DATE

- Overall, VRC01 did not reduce risk of acquiring HIV in participants who received it, compared to those who received a placebo.
- VRC01 did reduce the risk of acquiring a small subset of HIV strains classified as "highly sensitive" to VRC01.
- In two trials, intravenous infusions of VRC01 delivered every two months were safe and well tolerated by participants.
- A neutralization assay used to test VRC01 against a range of HIV strains can be used to predict which antibodies work in humans. This virus neutralization assay (assay is another word for a test) measured the activity of different bNAbs against different strains of HIV. There are different kinds of neutralization assays. The one used as part of the AMP studies is called the TZM-bl assay. Before the trial, the assay tested VRC01 against a "library" of viruses in the lab. Then the test was used on samples from participants. The results were consistent. This is the first time that a neutralization assay has been validated, with lab results predicting findings in humans.
- There is an open question, and some controversy, about how VRC01 impacts HIV in people's bodies. Even though this is speculative—and public discussion has generated debate—we note it here because it is relevant to other emerging prevention strategies and because some of the AMP researchers discussed this finding at this year's CROI conference, where Peter Gilbert from Fred Hutchinson Cancer Research Center stated, "We have data in the higher-dose VRC01 group—more cases occurred in the tail of the study than in the placebo arm." Gilbert thinks this might be because VRC01 suppressed the virus at the site of infection (i.e., in the genital tract) for a time, so that it did not spread into the bloodstream, where it would have been detected by an HIV test. Others are not so sure that this is the way to interpret the finding.

TOP-LINE TAKEAWAYS FOR ADVOCATES

- **Antibody-mediated prevention of HIV is possible.** The AMP trials show that a broadly neutralizing antibody can reduce the risk of acquiring viruses that are very sensitive to that antibody. This is welcome news. It is the first evidence in humans that intravenous infusions of a broadly neutralizing antibody can reduce a person's risk of acquiring HIV via sex.
- **Developing AMP for HIV prevention will not be easy—or fast.** The AMP results demonstrate the scope of the challenge that lies ahead for broadly neutralizing antibodies (bNAbs) to prevent HIV. There are many strains of HIV circulating in populations. While the trial team used lab tests to predict how many HIV strains in trial communities would be sensitive to VRC01, the trial data didn't match the predictions. When looking at the viruses in the communities where the AMP trials took place, far fewer were highly sensitive to VRC01 than the AMP team had hoped.
- **Combinations are key.** The trials suggest that a single bNAb like VRC01 is unlikely to be effective for HIV prevention, as it does not offer sufficient protection on its own. A combination of bNAbs or a more complex engineered bNAb, also known as bi- or tri-specific antibody, is likely necessary to achieve broad protection.
- **Not everyone interprets the results the same way.** Some see a "proof of concept" that an antibody could protect against some viruses. Others see evidence that it will be very difficult to develop an effective antibody product. Some researchers, including those who conducted the study, assert that the trial results demonstrated that a lab test called TZM-bl can predict which antibodies or combinations are most likely to be effective as HIV prevention products. Other researchers are skeptical.

What is antibody-mediated prevention?

Antibody-mediated prevention is a strategy that seeks to protect people from getting HIV by giving them antibodies that block the virus. When a person receives a vaccine against a specific virus, that vaccine teaches the body to make immune responses (antibodies) that protect against infection if they are ever exposed. Antibody-mediated prevention skips the step of teaching the body how to make a defense. Instead, it delivers the antibody directly into the body. But the current antibodies being studied only stay in the body for a matter of months. And these delivered antibodies don't multiply when confronted with virus, as immune memory cells would with a vaccine.

What is VRC01?

VRC01 was developed by the US National Institutes of Health's Vaccine Research Center (VRC) as a broadly neutralizing monoclonal antibody (bNAb). "Broadly neutralizing" means that in lab tests it blocked the activity of many different strains of HIV. "Monoclonal" refers to the fact that all of the VRC01 antibodies given to participants are essentially identical and are not a mixture of different antibodies. Studies in animals and in lab tests had previously shown that this antibody, VRC01, blocked or neutralized many HIV viruses. This research supported moving VRC01 into human trials. Laboratory results and animal studies do not provide the information needed about whether a product is safe and effective in humans. With VRC01, as with other experimental products, the early lab data have suggested promise but did not guarantee success. Many other bNAbs that are more potent and broad have been developed and are in the research pipeline. For more information, visit *www.avac.org/prevention-option/antibody-related-research*.

What are the basic facts about the trials?

The trials enrolled cisgender women in sub-Saharan Africa and gay men and transgender people who have sex with men or transgender people in Brazil, Peru, Switzerland and the United States. Participants received one of two doses of VRC01 or a placebo, with each administered intravenously every eight weeks. Neither participants nor the trial teams knew who was receiving VRC01 and who was receiving the placebo. Participants were monitored for side effects and adverse events and were tested for HIV at every study visit. The AMP Studies were conducted jointly by the HIV Prevention Trials Network (HPTN) and HIV Vaccine Trials Network (HVTN) and were funded by the US National Institutes of Health. Some participants in both the placebo and VRC01 arms acquired HIV despite receiving counseling, condom provision and PrEP referrals at every visit. This is not a result of the product being tested, but because of high rates of HIV in many parts of the world.

	HVTN 703 / HPTN 081	HVTN 704 / HPTN 085
POPULATION	1,924 women	2,699 men who have sex with men (MSM) and transgender men and women (TG)
LOCATION	Botswana, Kenya, Malawi, Mozambique, South Africa, Tanzania, Zimbabwe	Brazil, Peru Switzerland, USA
INTERVENTION	Participants are randomized to one of three groups to receive an IV infusion every 8 weeks, for a total of 10 infusions over about 22 months: • VRC01 mAb at a dose of 10 mg/kg based on weight • VRC01 mAb at a dose of 30 mg/kg based on weight • Placebo infusion	
OBJECTIVES	**Primary 1:** Evaluate the safety and tolerability of VRC01 administered through IV infusion. **Primary 2:** Determine if VRC01 prevents HIV-1 infection and estimate the level of efficacy in each population by week 80. **Secondary:** Develop markers of VRC01 that correlate with the antigenic specificity of protection to provide insight into mechanistic correlates of protection. **Exploratory 1:** Assess PrEP use. **Exploratory 2:** Assess if prevention efficacy is modified by PrEP use. **Exploratory 3:** Understand changes in risk behavior overall. **Exploratory 4:** Measure antibodies that bind to VRC01 (anti-idiotype antibodies).	

What were key measurements and findings from the AMP trials?

- **The AMP trials evaluated side effects and adverse events.** They did not find any significant issues associated with either dose of VRC01 or placebo.
- **The AMP trials measured rates of HIV infection in VRC01 and placebo recipients.** Overall, the rate of HIV among people receiving VRC01 was comparable to that among those who received a placebo. Among the 1,924 participants in HVTN 703/HPTN 081, infection occurred in 28 in the low-dose group, 19 in the high-dose

group, and 29 in the placebo group. The incidence of HIV-1 infection per 100 person-years in HVTN 704/HPTN 085 was 2.35 in the pooled VRC01 groups and 2.98 in the placebo group (estimated prevention efficacy, 26.6%; 95% confidence interval [CI], −11.7 to 51.8; P=0.15), and the incidence per 100 person-years in HVTN 703/HPTN 081 was 2.49 in the pooled VRC01 groups and 3.10 in the placebo group (estimated prevention efficacy, 8.8%; 95% CI, −45.1 to 42.6; P=0.70). (N Engl J Med 2021; 384:1003-1014. DOI: 10.1056/NEJMoa2031738.)

- **The AMP trials analyzed the genetic sequence of HIV isolated from participants who acquired the virus during the trial.** This lab-based sequencing and analysis included testing the viruses acquired by participants against VRC01, using the neutralization assay described below. Using this analysis, the AMP researchers looked at the number of people who acquired HIV whose virus was highly sensitive to VRC01. VRC01 and placebo participants were randomly assigned and were comparable in terms of age, gender and other characteristics. More placebo recipients had this type of virus than people who received either dose of VRC01. Researchers believe that this is likely because VRC01 blocked HIV strains that were highly sensitive to it. Viral sensitivity refers to the amount of antibody needed to block or inhibit viral activity. If a small amount of antibody effectively blocks a virus, then the virus is considered "highly sensitive". Viruses neutralized with less than one microgram/mL of VRC01 were classified as highly sensitive.
- **The AMP studies gathered information on how VRC01 worked in certain populations living in regions where different types of HIV predominate.** The trials did not show any statistically significant difference in safety, tolerability, antibody levels in the blood or protection by gender—populations enrolled in the study were cisgender women, gay men, other men who have sex with men, and transpeople who have sex with men and other transpeople, or geography—whether Clade B (more common in the Americas) or Clade C (more common in South Africa) virus predominated.

What else did the trials find?

The trials provided useful information about the neutralization test used in the study, known as the TZM-bl assay. Before the trial started in humans, scientists used the TZM-bl neutralization assay to evaluate VRC01 against a "library" of different strains of HIV selected because they were believed to be similar to those likely to be circulating in the communities where the trial would take place. Later, researchers isolated, sequenced and analyzed viruses acquired by trial participants. As it turned out, the library of viruses tested in advance didn't overlap with the actual viruses people acquired as much as researchers anticipated. Some of the strains in the library were highly sensitive to VRC01—meaning that a relatively small amount of the antibody blocked all viral activity. In the AMP studies, people who received VRC01 were less likely to acquire those highly sensitive strains compared to people who received the placebo. Researchers think this is because VRC01 blocked infection by that small subset of highly sensitive viruses—just as the pre-trial analyses predicted it would. This is the first time that the field has validated a test that yields consistent results with viruses selected by scientists and with those from an actual study population under real-world circumstances. To the VRC01 trial team and others in the field, this is evidence that evaluation of bNAbs against various strains of HIV by TZM-bl might be used to predict whether future bNAbs or bNAb combinations will protect people against HIV, and therefore which candidates to move into human trials.

In order to conduct the TZM-bl test scientists sequence the viral genome and then isolate the gene for HIV's envelope protein, known as "env". Next, they fit this snippet of HIV—the genetic code for env—into a generic virus backbone, called a "pseudotyped virus". This backbone of pseudotyped viral genes can be compared to a watch band, where many different watch faces (that is, genetic codes such as the env sequences) can be attached to the same band. This allows researchers to test different strains with consistency.

Not all researchers agree that TZM-bl will be predictive. A pseudotyped virus is not the same as a fully cloned virus. Some researchers cite bNAbs that have different antiviral effects depending on whether they were tested against pseudotypes or full viruses. Given this, they think that TZM-bl isn't a perfect solution for predicting whether a bNAb will protect humans, but it is an advance that moves the field a step in the right direction.

What questions did the trial raise?

• What trials should happen next and how should they be designed?

A combination of broadly neutralizing or bi- or tri-specific antibodies could be a potent prevention option. Future trials will take place in a rapidly evolving prevention landscape that presently includes daily oral PrEP, voluntary medical male circumcision, condoms, counseling, harm reduction and behavioral and structural interventions, and which soon may include long-acting injectable cabotegravir (CAB-LA) and the Dapivirine Vaginal Ring (DVR).

These strategies require programs that center human rights and choice, and acknowledge that an individual's ability to use any given product correctly and consistently is determined by a range of social, economic and stigma-related factors. With all of this complexity, work is needed—as it always has been—to effect social change while also exploring new products.

When it comes to evaluating other bNABs—and other next-generation prevention products—researchers and product developers will need to design trials that evaluate new options in the context of an expanding landscape of prevention options, which may include long-acting products like the Dapivirine Vaginal Ring and CAB-LA, as they are licensed by country regulators and recommended by WHO.

Futhermore, traditional efficacy trial designs evaluate experimental products by measuring and comparing rates of new HIV diagnoses in groups of participants some of whom will receive the active product and some who will receive a matched placebo. Next-generation trial designs that estimate impact in different ways may be needed, and tests that help predict whether a bNAb or other product will work are also going to be important. The precise design and research pathway will need to be set by civil society—including people most at risk of HIV—through frank and open conversation with researchers, regulators, ethicists and policy makers.

• What do the AMP trials results say about the possibility for a protective vaccine?

Antibodies are just one arm of the body's immune response. Cellular and innate immune responses also provide protection against HIV, as shown in laboratory and animal studies. Since its inception, the vaccine field has pursued candidates that elicit both cellular and humoral (antibody) responses. The field is also focused on the dynamics of these immune responses in the blood and at mucosal surfaces, such as the lining of the vagina or rectum. Prior to the AMP trials, the field operated from the assumption that a vaccine might need to induce a range of immune responses to protect against HIV. The AMP trials reinforced this assumption; they also suggest that effective antibody-mediated prevention will likely require combinations of bNAbs or more potent candidates.

• Is there a place for an antibody-based product in the prevention toolbox?

Condoms, oral pills, injections of different types, vaginal rings, infusions or perhaps in the future an implant, insert and douche are all very different prevention options. The field has moved forward assuming that more choices will lead to more success. Desirability and convenience (for users, providers and health systems), cost, potential side effects and risk of resistance are all important factors to consider. Future bNAbs and combinations are being formulated as injections so would not require lengthy intravenous infusions. It is important that people at risk of HIV weigh in about the types of products they want for different points in their lives.

What should advocates watch—and influence?

- **Which bNAbs, if any, move into efficacy trials—and why.** Advocates can hold researchers and funders accountable in establishing transparent processes for product selection and advancing only the most promising candidates into the next efficacy trials.
- **Next-generation trial design.** The prevention landscape is changing, and this requires a firm commitment to the guidance points in the recently revised UNAIDS/WHO Ethical considerations in HIV prevention trials guidance. This will require new, innovative trial designs—an arena in which many advocates and research groups are already working. See these resources:
  - *Trial Design in Focus*, *avac.org*
  - *Advocates' Perspectives on Next-Generation HIV Prevention Trial Design*, presentation at AIDS 2020.
  - *Designing a New Generation of Prevention Efficacy Trials*, blog post by Bill Snow.
- **Community, government and funder support for bNAb and vaccine research.** It is critical to continue the search for HIV vaccines and potent bNAbs as part of the HIV research pipeline. Advocates can let their governments and the funders of research know that sustaining the search is essential, and that with sufficient financial resources, political will and community involvement, new potent strategies will be identified. The AMP trials suggest what is possible. It's imperative to move forward without delay.

ADDITIONAL RESOURCES

- Dive into the AMP Trials, *Px Pulse* podcast
- Broadly Neutralizing Antibody Combinations, graphic
- HIV-Specific Neutralizing Antibodies by Target, graphic
- Antibody-Mediated Prevention Studies resource page, *avac.org*
- The future of antibody-based HIV prevention, *IAVI Report*
- AMP-ticipation: Context and concepts for understanding the AMP Trials, *avac.org*

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 new HIV prevention options as part of a comprehensive response to the pandemic. For more information, visit *www.avac.org.*

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