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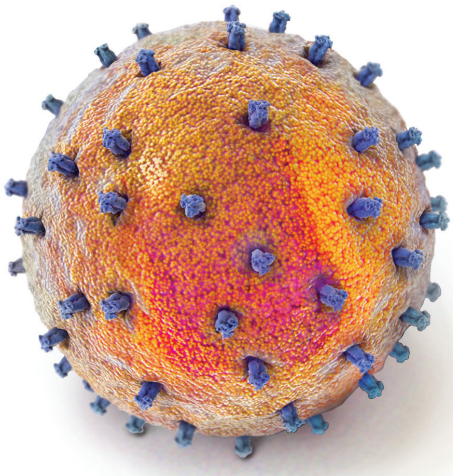
The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

What an HIV Vaccine Would Mean: One Advocate's Perspective

Last month in Cape Town, South Africa, scientists from around the world met for the bi-annual HIV Vaccine Trials Network meeting. Human rights activist Tian Johnson was there and writes about what the discovery of an HIV vaccine would mean to him.

My sister Miranda died of AIDS in 2007 at the age of 35, a year older than I am now. She was a mother to three boys who had yet to reach their teens when she took her last breath. That last breath came in a hospital that, even after a prolonged stay, was unable to provide her with the most basic care.

My family, just like many other families, spoke in hushed tones about the cause of her death: pneumonia, tuberculosis… anything but AIDS. It was almost as if the mention of her name and the disease in the same sentence would erase everything she was and everything good that she had done. She was a sister to me (which alone required the patience of a saint) and a mother who did everything she could to provide her boys with the best childhood she could—far from the turmoil that surrounded our shared upbringing in Zimbabwe.

As I landed in Cape Town for the bi-annual meetings of the HIV Vaccine Trials Network (HVTN)—a global network whose goal is to develop a safe, effective vaccine as rapidly as possible for prevention of HIV infections globally—I wondered what a world with a vaccine for HIV would look like.

I have worked in HIV prevention for nearly two decades now. So as I imagine a world with an HIV vaccine part of me can't help but be skeptical. I wonder if it would have made a difference to Miranda at all. Would she have been able to access the vaccine before she contracted HIV? Would she even have regarded herself as being "at risk" of infection? Would the nurse or doctor giving her the vaccine have judged her? In all likelihood, the same nurse probably would have judged her when she asked for a contraceptive just a few weeks before coming in for the vaccine. I wonder if Miranda would be able to live with the stigma of being "that woman" who got the "AIDS vaccine" at the clinic. Would her husband have gone with her? Would he take the vaccine too?

The other, more idealistic part of me imagines that she could access the vaccine with ease, that she would have received it like a hero at her local clinic by health workers who were proud of her: this beautiful African goddess who had chosen to make the journey that day to get herself vaccinated, to keep herself safe, to keep herself alive. Alive for me, her brother. Alive for her three boys.

From a distance, vaccine research can be unnerving. It's a deeply scientific and privileged world (a world that I think needs many, many more black faces in it). Talk of "non-human primate" [monkey] studies and acronyms like RV144 can be intimidating to an activist who is programmed to get on with asking what this all means for communities and how can this benefit us all today!

ALSO IN THIS ISSUE

PRIMER

Part of my journey as a member of the Vaccine Advocacy Research Group (VARG) is to bring advocates from related areas of HIV prevention advocacy into the vaccine fold in order to build our capacity around the science of vaccine research and to build relationships between us and the trial sites. As scientists inch closer to developing a vaccine that prevents HIV, the existence of groups like the VARG is increasingly important. The VARG is supported by AVAC (a global NGO) that supports advocates and community members to play a leading role in defining the HIV research agenda.

Although the world still does not have an HIV vaccine, research has been underway for many years, much of it built on work that is happening in South Africa. In addition to the many new vaccine candidates that are being pursued, just this month the University of Maryland School of Medicine in Baltimore launched the first phase of clinical trials for an exciting new product. In this trial the vaccine is intended to tackle the virus at the moment of infection, when there is a greater chance of neutralizing it. Some pretty impressive people are leading this work, including Robert Gallo, who was part of the team that identified HIV as the cause of AIDS and developed the HIV blood test.

As ground-breaking science happens around the world, we have a moral obligation to ensure that advocates are brought along for the journey in a meaningful way. Space must be created for learning and sharing and opportunities made for mentoring and engagement. As we have found out in the past, creating these spaces takes time and resources—resources that are usually the first to be cut when budgets are tight. The reality is that no matter how impressive the science is, it will have been in vain if it doesn't fit into people's daily lives and realities. Sadly, this is what we have seen too often over the years with male and female condoms, treatment, and other HIV prevention methods. A product can only work if it gets used. A key barrier to a product getting used is stigma, perhaps the most difficult aspect of uptake and use. As long as sexuality is scandalized and individuals do not see their health, success, and prosperity as being linked to that of their neighbors, we truly have a momentous task ahead of us. The work of changing minds and hearts is never easy, but it is essential. And it's work that advocates and activists must lead, hand-in-hand with scientists.

As the first vaccine is likely many years away, we must keep the discussion alive. We need to force ourselves to imagine what the future of HIV prevention could look like. Imagine having a basket of options that we could pick and choose from depending on where we are in our lives: a daily pill to prevent HIV, an annual vaccine to do the same, a female condom when I want or a male condom when I want, a vaginal or a rectal gel to stop me from getting HIV. They say when you become a parent you do everything you can to ensure that your own children have a better life than you had. This is the same reason we need to keep on working, keep on moving forward with HIV vaccine research. The benefits if we succeed are not just for us now, but for those who are growing up in this challenging world. It is so boys like my nephews can access options that my sister, their mother, never had.

I'm glad I spent a week at the HVTN meetings. They were insightful and filled with equal parts of hope and anxiety about the momentous task ahead of us as we collaborate, learn, engage, and take time to listen to the multitude of lessons this virus has and continues to teach us about our resilience and tenacity to push ahead in spite of it. As we look forward to many more years of research and advocacy in the quest for an HIV vaccine, we will also keep the faces and memories of those that did not make it along the way first and foremost in our minds. We must imagine and act to realize a better future.

**A version of this article appeared in NGO Pulse, a weekly online publication focusing on non-governmental organization-related issues in Southern Africa.*

Tian Johnson is a human rights advocate whose career has spanned the development sector in Africa, with a particular focus on women's rights, sexual and reproductive health and rights, and HIV prevention. He has worked on conducting a national gender analysis in South Africa for the introduction of the tenofovir microbicide gel, set up national networks of female condom distribution and training programmes, and is a founding member of Project ARM (the African Rectal Microbicide Movement), GLAM—the Global Lube Access Movement, The International Female Condom Advocacy Platform, convenor of the 2014/5 HIV Prevention Research Advocacy Expert Group, and member of the Global Vaccine Advocacy Research Group housed at AVAC. He founded the African Alliance for HIV Prevention in 2011 where he consults today.

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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. For more information, see www.iavi.org.

[PRIMER]

Understanding Germinal Centers

What are scientists learning about the structures within which antibody-producing cells develop and mature? ***By Kristen Jill Kresge***

Researchers are investigating multiple ways to develop a vaccine capable of preventing HIV infection. One of the main approaches relies on the induction of infection-fighting proteins known as antibodies. These typically Y-shaped proteins can work against viruses in various ways and are the reason most, if not all, vaccines provide protection. Some antibodies work by binding to viruses and preventing them from infecting cells, thereby marking the virus particles for destruction. This type of antibody is referred to as a neutralizing antibody (see *Understanding Neutralizing Antibodies*).

Researchers are pursuing many different strategies to induce neutralizing antibodies against HIV through vaccination. And because HIV is so variable, with multiple subtypes circulating globally, researchers are interested in antibodies that can neutralize a broad swath of HIV variants, which are referred to as broadly neutralizing antibodies.

In 2009 researchers identified a slew of new, more potent broadly neutralizing antibodies. Since then new antibodies have been identified at nearly break-neck speed. Now researchers have isolated more than 200 broadly neutralizing antibodies from blood samples collected from HIV-infected individuals. Close study of these antibodies is providing researchers with valuable information about how these antibodies form in response to HIV infection and clues about how they might induce such antibodies through vaccination.

Not your mother's antibodies

Although many antibodies have been isolated, development of broadly neutralizing antibodies is still a rare occurrence—only a minority of HIV-infected individuals develop them and only after years of infection. HIV has a furious mutation rate and outpaces the immune system's response. By the time antibodies are generated, HIV has mutated enough to avoid them, thereby escaping neutralization. This process of mutation and escape is necessary for the production of broadly neutralizing antibodies, researchers surmise.

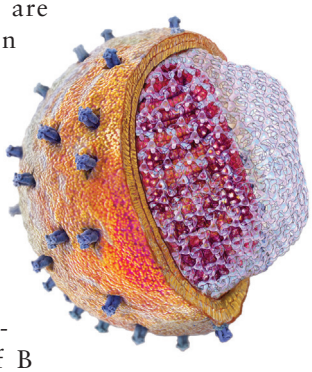
Analysis of the hundreds of antibodies isolated so far shows that they are not just rare, they are also unique. These antibodies are highly mutated and have various other characteristics that make them unusual compared to other antibodies. These highly optimized antibodies are the result of a two-step process known as affinity maturation (see *Understanding How Broadly Neutralizing Antibodies Evolve*). Through affinity maturation the B cells that make and secrete antibodies accumulate multiple mutations in their genes that allow them to more efficiently bind to and neutralize HIV. After this process occurs, the more superior B cells that bind the strongest to HIV undergo additional cycles of mutation and differentiation. With each round, the B cells are said to become more mature. The more mature these B cells become, the antibodies they make become better and better at neutralizing HIV.

Germinal center dynamics

This process of affinity maturation takes place in germinal centers. Germinal centers are unique structures that form within lymph nodes or other peripheral lymphoid organs such as the spleen. Optimized B cells that leave germinal centers can go on to become antibody-secreting plasma cells or long-lived memory B cells, which are the type researchers hope to induce through vaccination (see *Understanding the Immune System, Part I*).

While researchers may not know precisely how antibody maturation in germinal centers unfolds, they know it is terribly important. Given the high level of affinity maturation seen in all of the broadly neutralizing antibodies against HIV identified so far, researchers think that formation of these antibodies must require optimal germinal center dynamics. For this reason, trying to better understand the processes that occur in germinal centers and figuring out ways to manipulate these reactions to improve the protection afforded by vaccines is now a major area of research.

The selection of vaccine adjuvants is one way that researchers are attempting to manipulate the complex process of affinity maturation in germinal centers. There is some evidence from studies in animals that suggest certain adjuvants—components that are added to vaccines to boost immune responses—can directly stimulate B cells and drive their accumulation of genetic mutations (see *Understanding How Adjuvants Boost Immune Responses*).



Researchers are also focused on understanding how a specialized subset of helper T cells that resides in germinal centers may also influence the affinity maturation process of B cells in germinal centers.

Part of the reason germinal centers and the processes that occur within them is such a mystery is that these sites are difficult to study. In some ways researchers are groping in the dark when it comes to analyzing germinal centers. Researchers can only access germinal centers that are hidden within lymph nodes by biopsy, which makes studying them less feasible in human volunteers.

Despite major gaps in understanding how germinal center reactions occur, this is a burgeoning field of research, and one that has seen quite a few advances in recent years, according to researchers. Next year, for the first time, HIV vaccine researchers will be mingling with immunology experts at a meeting solely on this topic, evidence of the growing importance of understanding and influencing germinal center reactions. ■