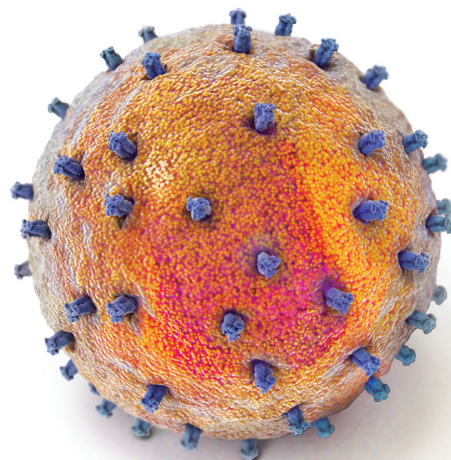


# vax

The Bulletin on AIDS Vaccine Research



[SPOTLIGHT]

## In the Epidemic's Heart

The Centre for the AIDS Programme of Research in South Africa, CAPRISA, is working to unlock the secrets and weaknesses of HIV and TB in one of the most highly affected populations on earth. *By Michael Keller*

In a waiting room inside Durban, South Africa's eThekweni research clinic, Dr. Nigel Garrett, wearing a white lab coat and a couple of days of facial stubble, talks with five waiting volunteers. Between Garrett and the volunteers is a side table stacked with slices of white bread for noshing as they wait for their names to be called.



Nurses and case workers emerge from and enter the door to a small examination and treatment room connected to the waiting area. Inside that room, one woman sits at a table and records numbers on spreadsheets, the anonymized identifications of the people outside and the trial biopharmaceuticals they are about to receive. Next to her are bags of liquids for infusions that are waiting to get hung beside an easy chair facing her table.

The waiting volunteers, all HIV free, are some of the first to receive an experimental prevention approach—repeat infusions of powerful proteins known as broadly neutralizing antibodies (bNAbs) to see if they are effective at preventing transmission of HIV. These volunteers are enrolled in the multinational Phase IIb Antibody-Mediated Prevention (AMP) Study and will receive repeat injections of a bNAb known as VRC01. This antibody is one of several that has recently

shown early promise in preventing infection in animal studies. The Centre for the AIDS Programme of Research in South Africa (CAPRISA), a consortium of five institutions in South Africa and the US, started enrolling participants in May at eThekweni clinic and will eventually recruit more than 100 people in this two-year trial. The facility is one of 15 sub-Saharan African sites chosen to be part of the randomized, placebo-controlled study. Volunteers will receive the VRC01 antibody or placebo by intravenous infusion every eight weeks and be monitored to see if they contract HIV.

“These people are really so generous with their time,” says Garrett, an HIV and sexual health specialist who relocated from the UK because of his desire to be at the center of the epidemic. “For the AMP Study, the first infusion takes an hour and then we monitor them for negative reactions for another 30 minutes, then it takes 30 minutes for every infusion after. We have a party every three months to give people updates about these studies, and they're generally very positive about them. These participants are making a real contribution.”

Volunteers for trials that CAPRISA runs at eThekweni clinic, which involve testing

HIV vaccine candidates and other prevention approaches as well as possible treatments, enroll either after walking into the clinic or through community recruitment efforts, Garrett says. To recruit participants, teams canvass neighborhoods to identify people willing to take part. Each volunteer is paid up to US\$25 per visit, depending on travel time and the onerousness of the procedure. Recruiters don't stress the compensation, though, because “we don't want to give people the wrong incentive to take part,” Garrett notes.

Inside the clinic, all is peaceful. Outside the facility's walls is a different matter. eThekweni clinic is situated in the heart of the city's transportation hub. Trains and buses arrive at their respective stations throughout the day from the outlying townships. Mini-buses and taxis take the people who arrive there to and from work all over Durban. And

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the whole hub rises up amidst the city's main outdoor markets, where sellers in stalls and out on the street hawk fruits, incense, beads, and music. Charcoal smoke and the smell of cooking meat waft through the air as several old men play a game of pool on a table that has been wheeled onto the sidewalk.

eThekwini adjoins the Prince Cyril Zulu Communicable Disease Center, the largest outpatient tuberculosis (TB) and sexually transmitted infection (STI) treatment facility in Durban. Their location is strategic—some 460,000 commuters and at least 6,000 street vendors come through the area on an average day. The two clinics receive the sick who are city residents or coming into Durban to shop or work from villages in the surrounding KwaZulu-Natal province. Patients start lining up for diagnosis or treatment beginning at five in the morning, and more than 300 can come through the door in a day. Many have TB, and 80 percent of the people presenting with that disease also have HIV.

One of CAPRISA's main research focuses is HIV and TB coinfection. In 2012, 88,000 South Africans living with HIV died of TB. That's more coinfection deaths than in the next three African countries with the highest coinfection rates combined.

But CAPRISA is making significant progress in tackling the co-mingled TB and HIV epidemics. The widely cited 2010 CAPRISA 003 TB-HIV treatment study helped optimize the starting time of antiretroviral treatment (ART) during TB therapy. Up to that point, many clinicians had delayed ART because it could negatively interact with TB drugs. But the researchers found that treating both infections at the same time reduced overall patient mortality by 56 percent. This evidence helped accelerate the international adoption of new treatment guidelines. CAPRISA says the combined therapy now saves an estimated 10,000 South African lives a year.

"The problem in South Africa is that we started HIV treatment very late—that's

why we've got such a problem here," says Garrett. "The idea now is to test as many people as possible for HIV, treat as many as possible, and keep the virus suppressed in their system. We treat TB at the same time."

## On the frontline

eThekwini is one of three research clinics CAPRISA runs. It also operates the nearby Springfield clinic at Durban's King Dinuzulu Hospital, which focuses on clinical studies to treat drug-resistant TB, and the Vulindlela clinic outside Durban in rural KwaZulu-Natal province, the epicenter of the decades-long AIDS epidemic. In 2012, the last year official data is available, the southeastern province had an HIV prevalence rate among all people age two years and older around 17 percent. If looking at only people 25 years and older, the prevalence in the province shoots up to 30 percent. By comparison, the global rate was around 1 percent. These provincial numbers represent the highest percentage of people living with HIV in South Africa, which itself has the most infected people—around 7 million—in the world.

It is these stark statistics, along with CAPRISA's cutting-edge work on understanding the virus and developing prevention and treatment approaches, that have made the organization and its 200 scientists and graduate students a renowned research and educational center on the frontline of the epidemic. The effort is coordinated from an office on the campus of the University of KwaZulu-Natal's

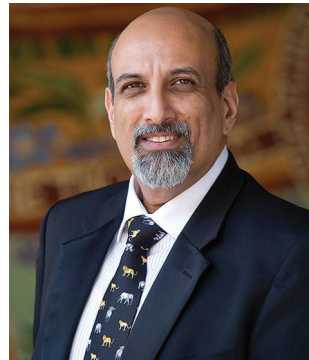
Nelson R. Mandela School of Medicine. The headquarters is a modern work of glass-and-concrete architectural art.

In the waiting area outside CAPRISA's offices on the second floor stands a working child's toy—a maze where anyone can pick up a marble from below, drop it in at the top, and watch as it careens down wire pathways like a roller coaster ride. Plastic arms randomly send the marble down different avenues to the bottom—perhaps a fitting analogy for CAPRISA's scientific pursuits. The organization currently lists 24 trials and studies ongoing or in some stage of approval or data analysis. Promotional materials proudly

announce that institute researchers have been authors of more than 350 articles published in peer-reviewed journals, and the organization's scientists produce an average of 50 new journal articles a year.

With so much research news to share, it is understandable that Salim Abdool Karim, an infectious diseases epidemiologist who is CAPRISA's director and cheerleader-in-chief, could rarely be found around the office when the 21<sup>st</sup> International AIDS Conference, the preeminent meeting on the epidemic, came to town in mid-July. During that week, he and wife Quarraisha Abdool Karim, another infectious disease epidemiologist who is also CAPRISA's associate scientific director, were a blur. The power couple

remained in motion except when planted on one of the stages inside Durban's International Conference Center.



Salim Abdool Karim



Quarraisha Abdool Karim

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On the last day of AIDS 2016, the two finally got a chance to sit down for a quiet working lunch at the center's headquarters. A couple of days before, Salim's lunch hour was spent on a stage with Bill Gates in front of thousands of researchers and advocates packed into a dark auditorium. Now Salim and Quarraisha shared quiche and salad while providing a narrative of CAPRISA's past and future for a couple of visitors. Salim, in a tan suit and light blue, short-sleeved shirt, leaned back into the office chair. His face seems to be permanently open in a warm smile beneath his salt-and-pepper goatee. While Quarraisha comes off as quieter, studious, and more comfortable rattling off deeply complex biomedical research data, Salim appears relaxed and gregarious as he lists the recognitions his team has earned.

He takes special pleasure in informing guests of the overwhelming number of women—82 percent of the staff—working throughout CAPRISA. “We are essentially a women's organization,” he says. “We have a policy of giving women preference, and it just turns out that we get a lot of women who apply. We don't have a male statistician or pharmacist in the organization.”

CAPRISA's focus on women extends beyond its internal staff. The organization is also heavily invested in countering the unequal burden AIDS places on girls and young women. In 2012, more than 14 percent of all South African women had contracted the virus compared to a prevalence rate of under 10 percent of men.

During AIDS 2016, researchers released findings that illuminated a reality in South Africa's epidemic that at least partially answers why this is so. From population studies, investigators could see that women were getting infected years before males of the same age. CAPRISA scientists analyzed the genetic code of HIV found in 1,589 people living in either rural or urban settings. In their still unpublished study, the team was able to connect new infections in girls and young women to men eight years older than them on average. This characteristic perpetuates a cycle of infection that continues when the newly infected females transmit the virus to males of similar age. “It's not about having sex at this

young age. Sex with peers gets you pregnant and other STIs,” says Salim. “Having sex with older men gets you HIV. Older men allow HIV's entry into younger women. If you can keep the 15- to 24-year-old group uninfected, you can break the chain of transmission.”

CAPRISA has been developing tools specifically for young women to prevent HIV



transmission. A study whose results were released in 2010, the CAPRISA 004 tenofovir gel Phase IIb trial, was the first to show that an antiretroviral-based topical microbicide was effective at preventing sexual transmission of HIV. The product, a vaginally applied gel, was meant for women to take prevention into their own hands, and the initial results excited the scientific community. The team of scientists from CAPRISA, Family Health International, and South Africa's National Institute of Communicable Diseases found that vaginal administration of a gel containing 1 percent tenofovir up to 12 hours before sex and as soon as possible within 12 hours afterwards reduced HIV infection in women by 39 percent. It also reduced genital herpes infection by 51 percent. When the results were announced during AIDS 2010 in Vienna, the crowd broke out into applause and a standing ovation.

This unabashed optimism was tempered later by less favorable results with this pre-exposure prophylaxis [PrEP] approach. “The data on tenofovir gel and tablets in women has been all over the place,” says Salim. “It's about adherence. You have to focus on drug levels—if a woman misses one dose out of seven, her tenofovir levels are wiped out.”

Researchers at CAPRISA and elsewhere are working to produce a PrEP product for women that isn't as dependent on user adher-

ence. Current candidates include a vaginal ring and an injectable antiretroviral (ARV). The center contributed to one study called ASPIRE, which used a vaginal ring containing the experimental ARV dapivirine. Results published in February showed the ring modestly reduced the rate of infection by 27 percent. Another analysis of the ASPIRE data

released in July at AIDS 2016 showed that in those women who used it as directed the ring reduced the infection rate by 65 percent across all age groups. Meanwhile, CAPRISA is also taking part in another, ongoing Phase III dapivirine ring study called MTN 020.

“We know the more you use a product, the more protection you have,” says Quarraisha. “But even among high adherers, you don't get complete protection. What else is a factor? We know the amount of ART at the point of infection is important because commensal bacteria in

the vagina are depleting the drug. So we have to look beyond adherence to the biology of women.”

These considerations have led CAPRISA's researchers to investigate how the populations of bacteria in the human body, referred to as the microbiome, may play a role in HIV infection, protection, and drug interaction. In a small, unpublished analysis of the vaginal microbiome of 119 South African women, scientists recently found that an overgrowth of one particular bacteria, *Prevotella bivia*, increased the chance of HIV infection 13 times over those with less or none of the bacteria. Salim and his colleagues published studies last year that showed certain bacteria can recruit immune cells to the vagina that provide targets for HIV.

Another cohort analysis showed how the complexities of the microbiome can impact the efficacy of HIV prevention approaches by interfering with the concentration of ARVs in the vagina. This work has opened up new research pathways that could aid in creating more effective preventions. “Here we are three decades into the epidemic and we are trying to find preventions in women when we haven't figured out some of the basics of women's biology. If the genital tract's health is playing an important role in infection, it behooves us to understand this better,” says Quarraisha.

## A search for the ultimate

But to the Karims and the rest of the CAPRISA staff, any means of prevention that requires daily, monthly, or sexual-activity-based maintenance to impart protection from infection is not the ultimate breakthrough against the epidemic they're hoping to find. The most tantalizing aspect of their work, says Quarraisha and Salim, is the possibility of developing an effective and long-lasting vaccine to impart immunity against HIV.

To this end, CAPRISA has become a study site and research partner for several vaccine candidates. During AIDS 2016, the partnership running HVTN 100, a Phase I/II safety and immune system-response trial of the ALVAC/gp120 prime-boost vaccine candidate, released preliminary safety immunogenicity data from the approximately 250

South African participants, of which 44 were given the experimental vaccine candidates at the eThekweni clinic. Based on the results of this trial, officials green-lighted the large-scale follow-on Phase III efficacy trial HVTN 702, which will begin enrollment soon. CAPRISA intends to enroll 400 of HVTN 702's 5,400 total participants.

"People wonder how South Africa has made such an investment in finding a vaccine. It all started when we set up CAPRISA in 2001," says Quarraisha. "This consortium let us follow cohorts before, during, and after infection. We could look at the immune response and at what was going on with the virus at the same time."

Salim is particularly excited about the burgeoning field of research into bNAbs (see *Primer*, page 5). CAPRISA researchers

isolated a family of bNAbs called CAP256 from a local schoolteacher who was a volunteer in one of their long-term studies of HIV infection. Salim said the promising bNAb should go into trials next year.

"I have never been as optimistic about our prospects of developing a safe and effective vaccine than I am today," says Salim. "Now that I see what we can do with these broadly neutralizing antibodies, I am full of hope." ■

*Michael Keller reports from the frontiers of science, technology, and international affairs. His writing has appeared online and in newspapers, magazines, and books, including the graphic novel Charles Darwin's On the Origin of Species.*

*All photos courtesy of CAPRISA.*

## SOME OF THE VACCINE-RELATED SESSIONS AT HIV R4P



Time	Type	Title	Location
<b>Monday, October 17</b>			
08:30 - 12:30	Satellite	HIV Vaccine Design and Development Partnerships in Africa: Showcasing African-led Basic HIV Prevention Science Research	Chicago Ballroom IX
09:00 - 10:30	Satellite	From Basic to Population Sciences: How to Understand and Prevent HIV Transmission: Vaccines and Sexual Transmission	Chicago Ballroom X
12:00 - 15:00	Satellite	Vaccine Elicited Immunity in the Pediatric Immune System	Sheraton Ballroom III
12:30 - 15:30	Satellite	Germline Targeting Immunogens: Taking the First Steps Toward bNAb Development	Chicago Ballroom VIII
13:00 - 15:00	Satellite	Target Product Profile for HIV Vaccines	Erie
13:30 - 15:30	Satellite	Designing Prevention Clinical Trials in the Era of Highly Effective Combination Prevention	Chicago Ballroom IX
<b>Tuesday, October 18</b>			
15:30 - 17:00	Symposium	Vaccine-Induced Humoral Immunity	Chicago Ballroom VI-VII
17:15 - 18:00	Poster Discussion	Evaluation of Vaccine Concepts	Sheraton Ballroom IV-V
18:00 - 19:30	Poster	Novel Vaccine and Prevention Concepts	River Exhibit AB
<b>Wednesday, October 19</b>			
08:30 - 10:00	Plenary	Which Way is Forward: Emerging Challenges and Opportunities	Chicago Ballroom IV-VII
10:30 - 12:00	Oral	Testing Vaccine Concepts: Where the Rubber Hits the Road	Chicago Ballroom VI-VII
13:00 - 14:30	Oral	Teaching the Immune System New Tricks: Vaccine-Induced Immune Responses	Sheraton Ballroom IV-V
15:30 - 17:00	Symposium	Effective Cellular Immune Responses	Sheraton Ballroom II-III
<b>Thursday, October 20</b>			
08:30 - 10:00	Symposium	Entering the Dark Zone: Germinal Centers in Immune Response	Sheraton Ballroom II-III
10:30 - 12:00	Oral	Cellular Immunity Matters!	Sheraton Ballroom II-III
13:00 - 14:30	Oral	Human Vaccine Clinical Trials: Reality Check	Sheraton Ballroom IV-V
<b>Friday, October 21</b>			
09:00 - 11:00	Satellite	Antibody Mediated Prevention and What It Takes to Make an HIV Vaccine	Chicago Ballroom X
09:00 - 11:30	Satellite	Systems Biology and Vaccines – Implications for HIV Vaccine Design	Sheraton Ballroom I
09:00 - 12:00	Satellite	Strengthening Community Advocacy and Solidarity for HIV Vaccine Research	Sheraton Ballroom II

# Understanding Sequential Immunization Strategies

How are researchers using a step-wise approach to try to train the immune system to fend off HIV? *By Kristen Jill Kresge*

Antibodies are one of the main ways the body fights off infection. These powerful proteins are also the key to the protection afforded by most, if not all, vaccines. So it is not surprising that HIV vaccine researchers have set their sights on antibodies. However, HIV presents some extraordinary challenges.

One of the challenges is that HIV is constantly changing or mutating in an effort to evade the immune responses the body mounts against it. Many people who are infected with HIV develop antibodies against the virus, but because the virus mutates so quickly, these antibodies are typically ineffective at controlling HIV infection. HIV's furious mutation also results in the numerous different strains of the virus that are in circulation around a globe. Ideally, a vaccine would be able to protect against the majority of these strains, which is another challenge for vaccine researchers. It takes a special type of antibody to block most HIV strains. Researchers refer to these antibodies as broadly neutralizing because they are capable of inactivating or "neutralizing" diverse strains of HIV.

In recent years, researchers have identified scores of broadly neutralizing antibodies (bNAbs) from HIV-infected individuals. The immune systems of a small percentage of HIV-infected individuals make these antibodies after years of infection. These antibodies have been shown to neutralize most HIV strains in laboratory tests. Scientists are studying these antibodies extensively to learn how and why they develop, and what makes them able to neutralize HIV so well. They also have tested these bNAbs in animals and shown that they can protect against infection. This suggests that a vaccine that induces such antibodies might protect against HIV. Inducing these antibodies through vaccination, however, is a difficult task.

Now, thanks to new technologies and a clearer picture of how these antibodies bind to and interact with the heavily armored and notoriously unstable outer surface of HIV, researchers are developing multiple vaccine components and testing them in sequence to

see if they can guide the immune system to make these highly specialized antibodies. Researchers have tested this sequential vaccination strategy in mice and have shown that this step-wise approach can induce antibodies that are able to neutralize some strains of HIV. Although these antibodies are not as broadly neutralizing as the antibodies isolated from naturally infected people, researchers think these studies in mice provide proof that a sequential immunization strategy can induce bNAbs and that this approach should be further optimized and eventually studied in human trials.

## Why is sequential immunization necessary?

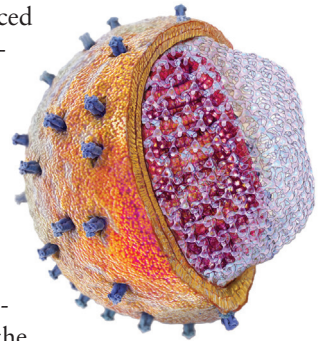
There are many reasons why bNAbs may be difficult to induce through vaccination. These antibodies only rarely develop in natural HIV infection because the immune cells that give rise to them aren't that common. And when bNAbs do develop naturally, it usually only occurs after a couple of years of infection. Also, all of the bNAbs that researchers have isolated to date are unusual. These antibodies have many characteristics that make them more sophisticated than normal antibodies.

One of their unique characteristics of these antibodies has to do with their structure. The bNAbs against HIV that researchers have isolated and studied so far have all accrued many changes in their structure that occurred in response to constant exposure to the ever-mutating virus. The changes in the structure of the antibodies make them better able to bind to and neutralize HIV. The more times that the antibody changes or mutates, the more "mature" the antibody becomes, and the better it is at neutralizing HIV.

The process of maturation, through which an antibody mutates and becomes better at neutralizing HIV, is critical to the design of vaccines. Many scientists have hypothesized that multiple different vaccine components (the active ingredients of vaccines that are known as immunogens) would likely be required to guide the human

immune system to make such "mature" antibodies. To test this, researchers from several different institutions have developed a series of vaccine immunogens and tested them in mice engineered to have more human-like immune systems. The first immunogens are intended to activate the appropriate immune cells, and the subsequent immunogens are meant to guide the antibodies produced by these cells to undergo the changes that will make them better at neutralizing HIV.

A batch of recently published studies shows that this sequential immunization approach did encourage the antibodies induced by the vaccine candidates to undergo the process of maturation. This approach led to the development of antibodies that were similar to, but not as good at neutralizing HIV as the bNAbs that were isolated from HIV-infected volunteers. Although this was only tested in mice so far, researchers are calling these studies a "significant milestone" in HIV vaccine development.



## Of mice and men

Now that researchers have shown that a sequential immunization approach can be used to shepherd the development of bNAbs, they are eager to further refine and optimize this approach. First, researchers want to optimize the vaccine immunogens so that they can induce antibodies capable of neutralizing even more HIV strains. Second, they need to take into consideration that humans have a much more diverse and complex immune system than humanized mice, and so even an approach that is successful in animals may not work as well in humans.

Eventually, researchers hope to advance some of these sequential immunization strategies into early-stage human trials. ■