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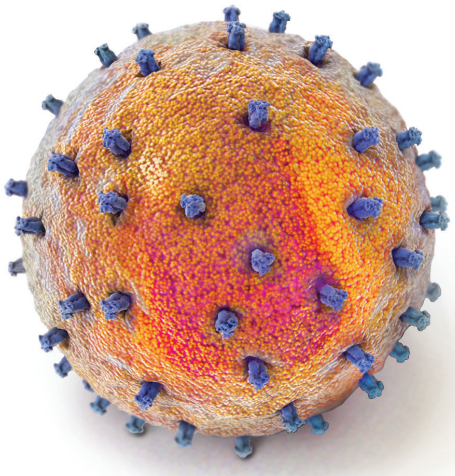

[SPECIAL ISSUE]

Fighting the Good Fight

Meet five prominent women scientists who are making a difference in the AIDS fight. ***By Mary Rushton***

It is no surprise that the AIDS pandemic, which began 34 years ago, altered the career paths of female scientists. The pathogen was mysterious, inscrutable, and killing millions of people around the world. Before long dozens of scientists, male and female alike, were joining the fight, transforming the fields of virology and immunology in particular. Part of their efforts are aimed at developing a vaccine against HIV, a point underscored today, May 18, in observance of HIV Vaccine Awareness Day.

"The minute I started working in infectious diseases, to me there was no other infection I wanted to work on more on than HIV," says Sharon Lewin, director of the Doherty Institute for Infection and Immunity in Melbourne, Australia, and a prominent HIV cure researcher.

French virologist Françoise Barré-Sinoussi is arguably the most famous female face in HIV research. She and her colleague Luc Montagnier at the Institut Pasteur in Paris received the Nobel Prize in Physiology or Medicine for co-discovering HIV, along with US researcher Robert Gallo. Barré-Sinoussi is now one of the most vocal and influential advocates for HIV cure research.

There are many other prominent women making a difference. Ambassador-at-Large Deborah Birx is overseeing the US President's Emergency Plan for AIDS Relief (PEPFAR)—considered the biggest humanitarian effort since the Marshall Plan. As director of the Department of Defense's US Military HIV Research Program, Birx oversaw the launch of the RV144 vaccine trial in Thailand, the first and thus far only trial to show vaccine-induced protection against HIV.

Precisely how many women are studying HIV/AIDS and how this compares to other diseases is difficult to say, although men certainly outnumber women no matter what the discipline. A more sobering statistic that resonates with AIDS researchers is the toll the epidemic has had on vulnerable populations, particularly women. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 64% of new adolescent infections globally were among young women and more than half of people living with HIV/AIDS are now women. In sub-Saharan Africa, young women aged 15 to 24 are almost twice as likely to become infected with HIV as their male counterparts, according to UNAIDS data. HIV/AIDS is also the leading cause of death among women in their reproductive years (ages 15-49).

There are now more HIV prevention options available for women—namely the use of antiretrovirals to prevent HIV infection (the strategy known as pre-exposure prophylaxis, or PrEP)—as well as encouraging research developments on both the AIDS vaccine and HIV cure research fronts, which together will hopefully reverse these trends and make ending AIDS an attainable goal.

In this special issue of *VAX*, we interviewed five leading women scientists from the US, Australia, and Africa to learn more about their careers and what inspires them to continue battling HIV/AIDS worldwide.

Linda-Gail Bekker

With more than six million people living with HIV/AIDS—around 3.5 million of them women—South Africa is Ground Zero of the HIV pandemic. Though new infections have been declining since 2000 and AIDS deaths since 2010, South Africa continues to shoulder the biggest burden. It is here that Linda-Gail Bekker works as a principal investigator and chief operating officer of the Desmond Tutu HIV Centre in Cape Town. Bekker planned to become a geriatrician, but a clinical rotation in KwaZulu-Natal in the 1980s pushed her toward HIV and tuberculosis (TB) clinical research. In Cape Town she works alongside her husband, Robin Wood, who is director of the Desmond Tutu Centre. She is also the President-Elect of the International AIDS Society, the first female African to hold the position, and will take office at the 21st International AIDS Conference when it opens in Durban in 2016.

Are the prevention and treatment programs for HIV and TB succeeding in South Africa?
Linda-Gail Bekker: South Africa has carried an enormous burden of HIV since the 1990s and now the biggest worldwide. Unfortunately a period of AIDS denialism slowed down access to antiretroviral treatment [ART], but attitudes have shifted and the new health administration is now grappling with the day-to-day challenges of getting more people into treatment. There is a real sense of urgency, although health systems are groaning under the load. What is more uplifting and more encouraging, I think, is that we have an administration that supports treatment. With TB, I'm afraid we haven't had epidemic control for more than 100 years. Unfortunately, we don't fully understand what is needed to interrupt transmission so more research is the way to go.

How did you deal with the issue of AIDS denialism in South Africa professionally and personally?
LB: On a certain level it was embarrassing hearing these dreadfully wrong statements. And when asked why these notions existed in government, to this day I don't really have a good answer. Researchers and clinicians did a fantastic job of working around the barriers and obstructions. Academic researchers haven't always agreed with activists in the history of the AIDS epidemic, but in this case civil society across the board formed an alliance and took on the government, providing incontrovertible evidence that, amongst other things, maternal-to-child transmission of HIV can be prevented with antiretrovirals. On other occasions we joined the government and took pharmaceutical companies to court to drive the cost of ARVs and other critical medications down. Thankfully, with the start of PEPFAR, there were others ways to fund ARVs and now South Africa has the biggest treatment program in the world. This is something to celebrate!

What are some of the innovative ways your centre is tackling HIV?
LB: Our mandate is to find innovative ways to tackle the public health challenges of the day. One of the challenges we face in the region is tracking people who move between clinics and are lost to follow-up, so we are testing a biometric system that captures patient fingerprints electronically, along with their medical history, and stores the information in a confidential website. Names are often interchangeable and hard to track—biometric identifiers such as fingerprints are not. Long ago, we also realized the merits of task shifting. We trained community care workers living with HIV to be adherence counselors in order to ensure that people with HIV remain in care. Many of these participants now are the cornerstones of our treatment programs.

The last time the International AIDS Conference was held in Africa in 2000, the major theme was expanding access to treatment in developing countries. What are the key issues on the agenda for Durban in 2016?
LB: I think we are at a critical crossroads. The prevention revolution is truly underway. We have tools to help end the epidemic but we're going to have to take bold steps around prevention and treatment to move towards epidemic control in all areas and all populations. Now is the time to realize full investment and a worldwide concerted and courageous effort. I also think with the converging of global health issues, there are critical lessons we have learned from the HIV/AIDS response that can and must be brought to bare to change the way we do business in public health throughout the world, particularly in those areas where there are still significant healthcare disparities.

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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.

Deborah Birx

Ambassador-at-Large and U.S. Representative for Global Health Diplomacy Deborah L Birx, M.D. is the US's fourth Global AIDS Coordinator in charge of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR)—a US$6. 6 billion program contributing to the HIV/AIDS epidemic response in 65 countries through bilateral and regional programs. This includes supporting live-saving antiretroviral treatment for 7. 7 million people. She also oversaw the launch of RV144 and served as the Director of the US Centers for Disease Control and Prevention's Division of Global HIV/AIDS. Not bad for someone who seemed headed for a career making a better green dye.

How did you become involved in HIV/AIDS?
Deborah Birx: In 1983-84, I was a clinical immunologist doing a joint fellowship at the [US National Institutes of Health] NIH and Walter Reed Army Medical Center. I was working on primary immunodeficiency—stuff like the "boy in the bubble"—when we started getting consulted about patients with this mysterious immunodeficiency. We didn't know what it was at first so we started analyzing their B cells. I was more compelled by the patients, their generosity and human spirit, than I had been with any other disease that I had worked on that I just never left.

And when did you decide on a career in immunology?
DB: My two elder brothers were mathematicians and nuclear physicists, my father was an electrical engineer and mathematician, and my mother taught nursing. In our household, math and science were extraordinarily valued. So not to be the loser of the family, I went to college and majored in chemistry but soon realized that the best jobs in the mid-1970s were making a better green dye at Kodak so the photographic paper wouldn't turn yellow. I realized that I didn't want to spend the next three decades doing that, which is a good thing because when digital cameras came out that skill would have been completely worthless.

After the launch of the RV144 trial a cadre of leading scientists very publicly criticized the rationale saying the money should have been spent on better candidates. Were you skeptical about doing the Thai trial?
DB: I like to believe I am always a skeptic about data and pushing the envelope to understand things in a deeper way. But that Thai trial was only possible, I think, because at the Department of Defense (DOD) you had the ability to fail spectacularly and yet still have a safety net underneath you. I mean to have all these premier scientists write about how the DOD, under the direction of Debbie Birx, was probably doing one of the stupidest things on the planet! If we hadn't been supported by DOD and the NIH that trial could have been shut down before we got started. There was a casualty, however. We had written a companion protocol to the trial which would have put tissue, serum, and plasma samples from a subgroup of vaccines and placebo recipients away so if the [RV144] trial showed promise we would have the ability to do an in-depth immunological analysis of correlates of protection and correlates of immunity. That companion study was stopped. Roll forward 10 years when we found some evidence of vaccine efficacy and everyone is saying, where are the samples?

What is one of the biggest challenges in your current role?
DB: I come from bench-driven research where data is honored. I come from bench-driven research, where data are honored. It's been challenging to figure out how to present data so it is understandable and actionable. We created the PEPFAR Dashboards to make our data accessible to all. It allows for transparency and accountability, which are priorities for us. We are taking slow steps forward but I have been witness to the last 30 years of the epidemic, the sheer magnitude of it—30 million people have died—and I guess I never think we do enough or move fast enough.

Sharon Lewin

Sharon Lewin, the Director of the Doherty Institute for Infection and Immunity in Melbourne, Australia, credits her post-doc training with David Ho at the Aaron Diamond AIDS Research Center in New York City with solidifying her growing interest in an HIV cure. Ho's seminal findings that triple-combination therapy could so effectively and dramatically reduce the levels of HIV to the point where they are undetectable marked a turning point in the pandemic. However, initial theories that it might also eliminate the virus over time proved premature, prompting researchers like Lewin to try and figure out why.

What drew you initially to HIV research?
Sharon Lewin: The minute I started working in infectious diseases, to me there was no other infection I wanted to work on more on than HIV. There were so many areas that were fascinating to me.

The science was changing so quickly and there were all these challenging issues around consent, stigma, and patient inclusion. This was the late 1980s. There was no real treatment—largely gay men were getting infected in Australia—and lots of people were dying. So there was this real urgency to do something.

When did you start focusing on cure research in particular?
SL: My PhD was actually quite relevant to HIV latency and persistence. In those early days, we were still trying to work out which cells HIV really infected. We always knew it infected T cells but there was this question about what other longer-lived cells there were. Then in 1997, I got an opportunity to do my post-doc with David Ho. At the time he and a colleague, Marty Markowitz, had some of the best-studied patients who were being treated with antiretroviral therapy. Some of the early modeling predicted that if you stayed on treatment for three years, the virus would decay to nothing, but that theory only lasted about three or four months when scientists discovered HIV latency—that pools of latently infected cells known as the reservoir were present from the beginning and persisted indefinitely on antiretroviral therapy. The first paper appeared in November 1997, two weeks before I arrived in New York, and so I became involved in that whole pursuit of can ARVs cure HIV and if they can't why and where is the virus sitting in people on ARVs.

What was it like working with David Ho in the 1990s?
SL: The whole environment at Aaron Diamond at the time was just really amazing. David was incredibly innovative—he had a million different ideas—and there were people there from all over the world getting training. I also realized that when you work in big teams the research moves much, much faster than working in isolation. This is an essential part of success in science.

Why did it take the HIV cure field another decade to really take off?
SL: I think there were many other priorities in the 1990s regarding HIV care, such as toxicity and drug resistance, to sort out. And there was a lot of interest in developing a vaccine, which remains of critical importance. And I think those two issues really dominated research. I think the cure field as a whole really took off about five years ago with the Berlin patient [the only person to be cured of HIV] and leadership from people like Francoise Barré-Sinoussi and the International AIDS Society. Until then there was a lot of skepticism about whether we could cure HIV. By 2010, it had also become apparent that we had really good drugs, costs were lower, and we could get them into Africa. The question was how sustainable was this?

Do you think it is possible to cure HIV?
SL: There are a lot of challenges, but I do think the field has moved a lot in the last five years. There are reports of people who have been able to safely stop treatment and achieve antiretroviral-free remission for a period of time. Plus, if you treat people early you can significantly reduce the amount of latency. There are also drugs that clearly activate the virus and push it out of its hiding place. I think we will find more defined ways to achieve antiretroviral-free remission, though how many people will be able to achieve that and for how long I'm not sure. Being able to take a single pill that eliminates HIV—I think we are a very long way from that.

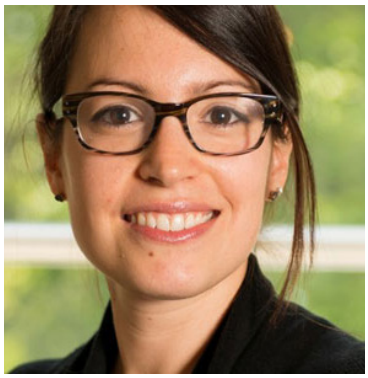
Nelly Mugo

As the AIDS epidemic decimated sub-Saharan Africa, Kenyan Nelly Mugo was beginning her clinical career in obstetrics and gynecology. Nearly two decades later, the principal research scientist at the Kenya Medical Research Institute is part of an AIDS success story—the administration of antiretrovirals to HIV-uninfected individuals prior to exposure, otherwise known as PrEP. Mugo is part of The Partners PrEP Study, which showed PrEP prevented HIV transmission among serodiscordant couples.

What convinced you to become a researcher?
Nelly Mugo: I was working at a hospital in Kenya, and we were seeing a lot of complications from pelvic inflammatory disease, including infertility, infections, and ectopic pregnancies, especially in HIV-positive women. There was also a lot of undiagnosed chlamydia. I thought better research might help improve the clinical care and so I began working with Craig Cohen [a US researcher now at the University of California in San Francisco], who had helped establish the Research Care and Treatment Program in Nairobi. I later got my Masters of Public Health at the University of Washington specializing in epidemiology.

What was it like being on the front lines of the epidemic before there was effective treatment?
NM: It was a tragedy and a very fearful time. There was so much ignorance even among health care providers. There were some who were afraid to treat people and people died from the stigma associated with AIDS. It was such a terrible time for our health care system.

What is the status of PrEP in Kenya?
NM: The Partners Demonstration Project found that daily PrEP use among serodiscordant couples was even more effective than we thought. I'm very excited about that, to be honest. There is still a lot of advocacy that we need to do around PrEP—who should receive it, how will they access it, and what is the role of providers in implementing PrEP? That's what we need to understand. I'm collaborating with LVCT Health, an HIV prevention organization in Kenya that is studying how PrEP can be given alongside other prevention methods to men who have sex with men, female sex workers, and young women at high HIV risk in real-life settings.



Galit Alter

You could say that Galit Alter, an immunologist and principal investigator at the Boston-based Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard, plays the field. It's the goal that remains the same: finding an AIDS vaccine. Alter's earliest research focused on the role of T cells, the immune cells that are considered the soldiers of the immune system. At the time, hopes were riding on a T-cell based vaccine candidate being tested in an efficacy trial known as the STEP study, but when the candidate was found to be ineffective, Alter switched her career focus. She is now studying sugar molecules that enhance the production of potent antibodies that vaccine and cure researchers think may help block or control infection.

Tell us about your early work in HIV and how you came to study antibodies?
Galit Alter: I was working toward my PhD [at McGill University in Montreal, Canada] when people started recruiting HIV-positive people for acute infection studies. There was a massive coordinated effort in Montreal to find patients so we could study the earliest immune responses to infection. That was when there was a lot of momentum and excitement around T-cell biology. But then STEP failed and I didn't want to be in T cells anymore.

How have your research interests evolved?
GA: My inclination has always been to do something a little bit different. If everyone is playing in the sandbox, I want to find a different sandbox. I was working in T cells before it got really popular. Then when everyone jumped on the bandwagon I switched to another type of immune cell, natural killer (NK) cells. Then when the NK cell field got too crowded, I jumped to antibodies. And now that antibodies have gotten popular, I have jumped to sugars.

Is it unusual to move around this much in research?
GA: Virologists tend to be monogamous and focus on one pathogen. But I think that in immunology it is common for people to jump around because you have to keep pushing barriers. If you don't push yourself to explore new frontiers you end up not being funded because you keep doing the same old, same old.

Did you always know you wanted to be a scientist?
GA: I had no idea and I think it was serendipity that I ended up in HIV research. I stumbled on microbiology and immunology and found viruses really interesting, and then my father got me in touch with a physician in Montreal who was treating HIV patients. He told me to come in and work in the lab a little bit to see if I liked it. ■

Mary Rushton is a freelance writer based in Cambridge, Massachusetts.