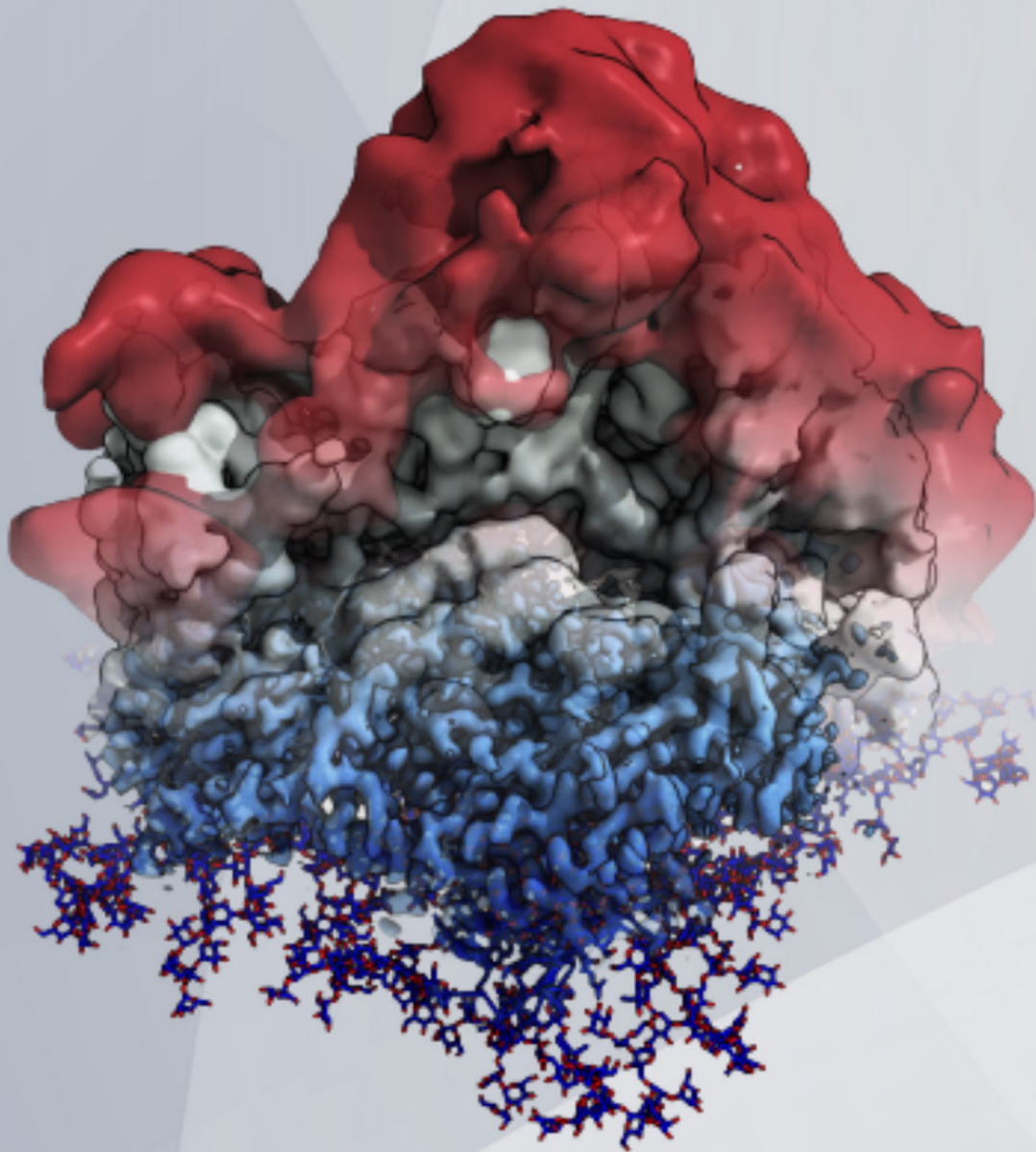


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A tale of two pandemics: HIV and COVID



FROM THE EDITOR

The last time I penned a letter in this publication, nearly a year ago, I closed by saying: “If science is our best hope, we are in good hands.”

That certainly proved to be the case. There are now three authorized COVID-19 vaccines in the U.S., and seven that have received an Emergency Use Listing by the World Health Organization, which is a prerequisite for the vaccines being eligible for global distribution through the [COVAX facility](#). The speed with which these vaccines were developed, and how effective they are at preventing severe disease and, in many cases symptomatic infection altogether, is a truly impressive illustration of the power of science.

In countries with high vaccination rates, SARS-CoV-2 infection rates are largely plummeting. Vaccines have once again proven to be one of the most efficient and effective ways to stop the spread of infectious diseases.

But the virus is striking back — the highly transmissible Delta variant is on the move. The greatest threat is to those who are unvaccinated, and this is still a large proportion of the world’s population. Despite efforts to distribute vaccines equitably, global access remains extremely unbalanced. The race is on to vaccinate more of the world’s population before an even more transmissible and deadly variant emerges.

In this issue, I spoke with Dr. John Nkengasong, director of the Africa Centres for Disease Control and Prevention, on the slow rollout of COVID vaccines in Africa and how he thinks the continent should prepare for future pandemics.

Other voices featured in this issue are those of four leading HIV researchers who are lending the knowledge and experience they’ve honed over the now four decades of HIV/AIDS work to COVID vaccine research. Their efforts are inspiring.

It isn’t news to our readers that developing an HIV vaccine is a far more difficult challenge than developing COVID vaccines. But there is some good news: scientists are making progress on the arduous path to triggering immunity through a stepwise process referred to as germline targeting.

The past year was devastating. But in some ways, we were lucky. The next new virus to infect and kill humans may not be as easy to develop a vaccine against. Should the next pathogen embody the worst of HIV and SARS-CoV-2, the result would be almost unimaginable. But then too, science will be our best hope. And given the elegant science that is underway and the limitless imagination of researchers, I still think we’ll be in good hands.

—Kristen Jill Kresge



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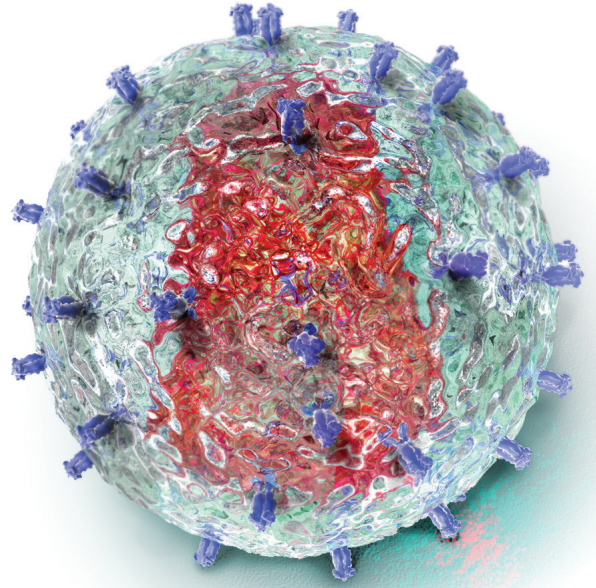
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ON THE COVER

The sugary side of HIV. An artistic rendering — based on cryo-EM maps and computer simulations — shows how glycans create a shield that helps HIV hide from the immune system. Image courtesy of Zachary Berndsen and Faith Hark, Ward lab at Scripps Research.

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A step in the right direction

Researchers describe the experimental HIV vaccine approach called germline targeting as “shepherding” the immune system. They hope it will lead to greener pastures.

By Michael Dumiak

This August a clinical trial testing an experimental HIV vaccine delivered using Moderna’s mRNA system should begin in the U.S. It will be quickly followed in September by a similar trial in South Africa and Rwanda. Harnessing the power of mRNA for HIV vaccine delivery has long drawn interest, but even more so now that mRNA rocketed to prominence with its successful deployment in COVID-19 vaccines.

These trials will be the first in-human studies using an mRNA delivery system for an HIV vaccine strategy called germline targeting — an approach some see as one of the more promising now in development. “It’s a wonderful and fascinating insight into the immune system and how it initiates lineage,” says Peter Kwong, chief of the structural biology section of the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases.

Germline targeting is the term scientists use to describe the process of guiding the immune system, step by step, to induce antibodies that can counteract HIV. As the past 40 years of effort show, this is incredibly difficult to achieve. With COVID vaccines, researchers worry about the vaccine being able to fend off a handful of variants that have become particularly worrisome. But for HIV, there are millions and millions of different viruses that have resulted from the virus’s stealth ability to rapidly mutate its Envelope protein, or Env. It is this astonishing level of diversity that any HIV vaccine must contend with.

To address HIV’s variability, researchers are pursuing vaccines that can induce so-called broadly neutralizing antibodies (bnAbs). These antibodies appear to be able to fend off most if not all HIV isolates in circulation. Developing a vaccine to induce them has meant finding the rare HIV-infected individuals who make bnAbs against the virus, studying these antibodies to see how they interact with specific parts or molecular protein regions of HIV, and then using that information to rationally design — or engineer — vaccine can-

didates that could elicit those specific antibodies. Over the past 12 years, scientists have been able to isolate, study, and manufacture hundreds of bnAbs, some of which, in animal studies, show the capacity to protect against infection.

The problem is that these antibodies aren’t readily generated. It takes some coaxing. Actually, a lot of coaxing. That’s where germline targeting comes in.

Germline targeting begins with a primer vaccine that activates B cells that have the potential to generate bnAbs. The goal is then to use a series of different vaccine immunogens, each more specific than the last, to nudge these B cells along until they are capable of achieving the desired result: broad and potent bnAb responses that can, theoretically, protect against HIV infection.

If this process sounds difficult, that’s because it is. But researchers are encouraged by results from an early-stage clinical trial known as IAVI G001 that shows that the initial step of the germline targeting approach can work. William Schief, an immunologist at Scripps Research and executive director of vaccine design at IAVI’s Neutralizing Antibody Center, developed the priming immunogen that was tested in this Phase I trial: an engineered protein called eOD-GT8 60mer. He presented results from the study earlier this year. Although he declined to comment for this article, others shared their enthusiasm about this early finding. “It’s a delightful result,” says Lawrence Corey, professor of medicine at the University of Washington and principal investigator of the HIV Vaccine Trials Network (HVTN). “Having this kind of start is really wonderful.”

For germline targeting to work at all, researchers need the priming immunogen to target specific naïve B cells. A large part of human immunity is made up of B cells that circulate in blood — perhaps as many as 10 billion of them in total. These B cells are on patrol against invading pathogens.

About two-thirds of the B cells found in blood are naïve B cells. When these B cells come in contact with a foreign pathogen, they travel to germinal centers where they undergo a process called somatic hypermutation. This is the process by which the immune system fine-tunes its responses against a specific pathogen. These hypermutations become a kind of training: it makes the B cells produce better and better antibodies that are more efficient and effective at binding to their targets, which is especially important for HIV. Ultimately, these mature B cells turn into plasma cells that secrete the protective antibody.

In germline targeting, vaccine researchers want to harness the machinery that allows the body to produce better and better antibodies over time to train the immune system to do it against HIV prior to exposure. The immunogen tested in IAVI G001 is focused on inducing a particular class of bnAbs that target the CD4 binding site where HIV docks to and infects human cells. There may be perhaps only one in every 300,000 naïve B cells that even have the potential to induce this type of antibody. The eOD-GT8 60mer is designed to activate and expand those cells and to persuade them to go into germinal centers, where the initial process of somatic hypermutation begins.

The next steps in the germline strategy would be to deploy one or more booster shots with different proteins strategically designed to bind and further activate that pool of memory B cells, and keep it moving in the right direction, a process Schief calls ‘shepherding.’ Then the last step in the vaccine regimen would deliver an immunogen optimized to trigger the most mature version of memory cells and convert them strongly into plasma cells that will secrete bnAbs for a very long time.

At an online conference hosted by Moderna in April, Schief described the approach like this: “You’re going to give multiple shots, with multiple different antigens in each shot, and you’re trying to basically direct the immune system on a path that you’ve predefined.”

In presenting results from IAVI G001, Schief said that ultimately the germline targeting approach would need to induce two or three different classes of bnAbs to be effective against HIV. The results from the [Antibody Mediated Prevention \(AMP\) trials](#), which tested intravenous infusion

of a single CD4 binding site-targeting bnAb (VRC01), also suggest a vaccine may need to induce a more robust and diverse antibody response than previously thought.

IAVI G001 shows that it’s at least possible to design a priming immunogen that can activate the specific kind of naïve B cells researchers seek. This is a key step in what are still early days for the germline targeting concept. “If you can’t get that to work, the whole thing isn’t going to work. Consistent priming of broadly neutralizing antibody precursors is a vaccine requirement. You’ve got to get it to work very, very efficiently. Otherwise, the person who you vaccinated is not going to make a bnAb later on,” Schief said.

The VRC’s Kwong is also exploring whether an engineered immunogen can induce bnAbs against HIV. His group has developed a [fusion peptide immunogen](#), which is a sequence of amino acids that make up the engine that HIV uses to enter a host cell.

Kwong describes his approach as epitope-based, which differs from Schief’s germline-focused strategy. Kwong’s epitope-based formulations consist of just a few components: a prime of the fusion peptide immunogen and a booster with a soluble HIV Env trimer protein, known as BG505.SOSIP, along with assisting adjuvants. The goal is to induce several different lineages of bnAbs, rather than bnAbs from a single class. All of those bnAb lineages would then target one specific epitope on HIV that it uses to fuse with its target cells.

“We start first with a peptide that teaches antibody lineages to get very good affinity for just that epitope. By boosting with a trimer, we can expand the lineages and get broader responses,” Kwong says.

Experiments with the SOSIP trimer alone did not induce bnAbs in human studies, Kwong says. His group has seen positive results with the fusion peptide in preclinical animal studies, but whether it performs in humans — and with powerful enough of a neutralizing response — remains to be seen. “This is important, because we’ve just learned from the AMP study that you have to have pretty potent responses. While the fusion peptide responses we get are very broad, it’s

unclear whether we get high enough potency to protect humans.”

Researchers plan to test the fusion peptide with a new adjuvant made from lipid particles and carboxer homopolymer — an electrolyte which is sometimes used to suspend solids in liquid cosmetics — in clinical trials later this year.

These structure-based strategies are complex, but some see them as the most promising route to a broadly effective HIV vaccine. The all-absorbing global health response to the ongoing COVID-19 pandemic may have obscured it from view but following last year’s failure of its latest large efficacy trial, HVTN 702, the HIV vaccine field is once again absorbing the lessons of a disappointing result. The HVTN 702 trial in South Africa was part of a broader program defining what might be needed for a successful HIV vaccine, according to a recent viewpoint essay from Corey and Glenda Gray, co-founder of the Perinatal HIV Research Unit in Soweto and head of the South African Medical Research Council. The 702 trial was meant to corroborate the very modest vaccine efficacy observed in the RV144 trial conducted in Thailand, but with a vaccine regimen adapted to the HIV subtype most common in South Africa.

The mechanism of protection shown in the RV144 trial was thought to be non-neutralizing immune responses in which antibodies mediated elimination of virus particles and virus-infected cells by a variety of mechanisms. But the failure of the regimen in HVTN 702 to provide any protection is leading researchers to weigh whether bnAb responses — no matter how difficult they are to induce — are the best, or indeed the only way to an effective HIV vaccine.

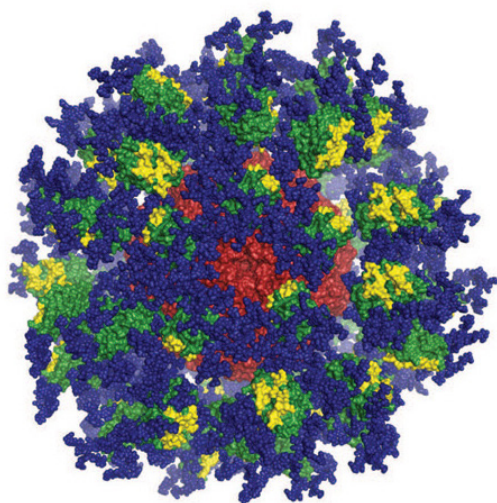
The answer may come from the two ongoing efficacy trials, Imbokodo (HVTN 705) and Mosaico (HVTN 706). These trials, developed and led by Janssen Vaccines & Prevention, part of Johnson & Johnson’s (J&J) pharmaceutical arm, are testing a vaccine candidate consisting of an adenovirus 26 vec-

tor carrying a computationally designed mosaic immunogen. The mosaic immunogen is not thought to induce bnAbs, but rather CD8⁺ T-cell and non-neutralizing antibody responses.

The results of Imbokodo and Mosaico will be critical to determining whether T-cell and non-neutralizing antibody responses are capable of inducing protection against HIV, Corey says. If no positive signal emerges from these trials, Corey believes there’s little point in further efforts that are not focused on inducing bnAbs. “You’d have to have a new conceptual framework for non-neutralizing antibodies in order to move that way toward a vaccine. The path to a vaccine that has multiple neutralizing antibodies is the path where the data tell us to proceed,” he says.

But Dan Barouch sees timing as a factor. “It also depends on how quickly the neutralizing antibody approaches can move forward. As of now, there has not been any vaccine that can reliably generate broad, neutralizing antibodies in humans,” he says. Barouch runs a research program at the Harvard Medical School’s Beth Israel Deaconess Medical Center and at the Ragon Institute of Massachusetts General Hospital, MIT and Harvard. His lab designed the Janssen/J&J COVID-19 vaccine and also developed the vaccines being tested in Imbokodo and Mosaico. “People are looking at many different approaches, but apart from the J&J vaccine in Imbokodo and Mosaico, everything else is still at a very early stage. All scientifically valid strategies should continue to be pursued.”

Mark Feinberg, IAVI’s president and chief executive officer and someone with experience in mass-market vaccine development and production, is also awaiting the results of the Imbokodo/Mosaico trials before casting judgment. The idea that non-neutralizing antibodies can be protective has been somewhat controversial. There are proponents and skeptics, he says. “It’s fair to say that the results of the 702 study are an important reality check for the non-neutralizing antibody approach. Obviously, we will have to see whether the Janssen studies yield any positive efficacy signal or not,” Feinberg says. “I do think if the Janssen results are negative, then it may be the end of this era of doing large efficacy trials to identify whether a concept surrounding non-neutralizing antibodies is valid.” Or at least, he adds, in the absence of neutralizing antibodies.



Computer image of the eOD-GT8 immunostimulating protein. Image courtesy of Joseph Jardine, Sergey Menis, and William Schief of Scripps Research and IAVI.

Others aren't ready to abandon the hypothesis that non-neutralizing antibody responses can ultimately be protective. Immunologist Susan Zolla-Pazner at Mt. Sinai's Icahn School of Medicine points to multiple factors that were different between HVTN 702 and the RV144 trial, including the adjuvants, the trial populations, and the incidence of sexually transmitted diseases. "Everybody says 702 is a repeat of RV144 and it's not even close," she says. And, given the multiple variables between the two trials, she says it is impossible to account decisively for the different results.

Zolla-Pazner knows that (as for most science) there's limited resources, money, and logistical capacity for pursuing clinical studies. "But I don't believe you can, at this point, remove anything from the table in terms of what kinds of immunogens will be useful and what combinations of immune responses will be most efficacious."

Barouch expects it will be increasingly difficult in the future to fund and organize large-scale efficacy trials for HIV vaccines regardless of the concept and strategy under study, given progress with other prevention approaches, such as long-acting drugs for PrEP (pre-exposure prophylaxis). "Other forms of HIV prevention are improving," he says.

Kwong makes a similar point. It would be one thing if the rational, bnAb-based approaches to vaccine design had lots of clinical results to point to. But most of the promising results so far have come in animals. He recalls the move toward T-cell-based approaches in labs a decade ago. "If you go back and look at the field in 2008 or earlier, everyone was focused on T cells. There's these different pendulums that switch in different ways," Kwong says. "As long as no one has achieved broadly neutralizing responses, I don't think we can say. Until you start getting protective responses, we're still nowhere, and in order for a vaccine to be successful and work, you have to pass through many different hurdles."

Bette Korber of the Los Alamos National Laboratory helped design the mosaic immunogen being tested in the Imbokodo and Mosaico trials. She and her colleague Will Fischer think a successful HIV vaccine may well require multiple beneficial vaccine approaches: bnAb, non-neutralizing antibody, and T-cell responses.

In the meantime, engineered vaccine candidates that are designed to induce bnAbs are showcasing some of the elegant science that is underway in an effort to develop an HIV vaccine.

Schief's germline approach — as he himself pointed out — still faces a lot of hurdles, though it jumped a high one in order to move ahead. And a partnership with Moderna to use its mRNA technologies may help quicken the next steps. Developing and manufacturing proteins, such as that used in the IAVI G001 study, is costly and slow. The next studies later this year, including the African trial that will be conducted by African labs, will use an mRNA platform instead.

The speed and cost advantages of using mRNA means an iterative approach to testing germline targeting concepts can help researchers zero in on answers more quickly. Richard Jefferys, director of the Treatment Action Group's basic science vaccine and cure project, says the platform seems well suited. "I think the encouraging thing about mRNA is the plug and play aspects of it," he says. "If the idea is that you now need to test out different protein constructs to see whether they can take those B cells from one step to the next, then you have a really ideal platform for doing that because you can quickly insert a gene sequence, do the experiment, and move on if it doesn't pan out."

Even if germline targeting is eventually successful, it is difficult to conceive of administering a course of several shots delivering different immunogens — given that it's proving hard enough to get individuals to take one or two shots during a global pandemic in which the pathogen spreads through the air.

Feinberg is quick to say the practical considerations matter. "I'm a big believer in the importance of having vaccines readily delivered in real-world circumstances," he says. But he remains an optimist. "If we can solve the scientific challenges, I'm optimistic that we'll be able to find a way to solve the practical challenges. Right now, we can't work on the practical challenges until we know what the profile of the vaccine is." ■

Michael Dumiak, based in Berlin, reports on global science, public health, and technology.

INTERVIEW

Leading Africa's COVID-19 response

John Nkengasong warns against complacency setting in as vaccines trickle into many African countries.

By **Kristen Jill Kresge**

John Nkengasong, director of the Africa Centres for Disease Control and Prevention (Africa CDC), is one of the [World's 50 Greatest Leaders](#), according to *Fortune* magazine.

Coming in fourth among the top leaders recognized on the U.S. magazine's annual list, Nkengasong was lauded for his pivotal role in steering Africa's response to COVID-19, including instituting curfews and mask mandates early on. These simple public health measures have, at least in part, helped many places on the continent avoid the catastrophic mortality rates that have occurred in North and South America, Europe, and Asia.

Last year Nkengasong was also awarded a Global Goalkeeper Award by the Bill & Melinda Gates Foundation. The Foundation described Nkengasong as a "relentless proponent of global collaboration and evidence-based public health practices, and a champion for minimizing the social and economic consequences of COVID-19 across the African continent." He also serves as a Special Envoy on COVID-19 Preparedness and Response to the World Health Organization's Director General, Tedros Ghebreyesus, and is a member of the board of directors of IAVI and the Coalition for Epidemic Preparedness Initiatives (CEPI).

A native of Cameroon, Nkengasong is a virologist by training with more than three decades of experience in public health. Prior to heading the Ethiopia-based Africa CDC, a specialized unit of the African Union, he was the acting deputy principal director of the Center for Global Health at the U.S. CDC and

associate director of laboratory science and chief of the International Laboratory Branch at the Division of Global HIV/AIDS and TB.

In 2019, the [Global Health Security Index](#) ranked 195 countries based on their health security capabilities. The U.S. ranked first. The majority of African countries ranked among the "least prepared." As COVID-19 began its deadly march across the globe, many warned of the potential for dire outcomes in Africa, where some public health systems were seen as wholly unprepared to be battling yet another infectious disease. But mortality rates remained surprisingly low on the continent, while deaths in the [U.S. and other wealthy countries](#) soared.

There may be various explanations for this difference, including limited testing capacity in many African countries, poor case reporting on the continent, and the fact that the African population is overall younger and therefore at lower risk of the deadly complications of COVID-19. But these factors may not tell the whole story, as Agnes Bingawaho, vice chancellor of the University of Global Health Equity in Kigali, Rwanda, and colleagues note. Writing in the [Annals of Global Health](#), she says that many African countries have successfully contained their COVID outbreaks by implementing simple evidence-based interventions: social distancing, hand washing, mask wearing, contact tracing, and lockdowns.

Nkengasong acknowledges the role the continent's early response to SARS-CoV-2 played in limiting its spread, though he warns against a wave of complacency he sees setting in in many countries. And with vaccine distribution lagging far behind even

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There is not one vaccine that will get us there. We will need to use a combination of vaccines to fight this war.

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what the global community had anticipated, he is now more convinced than ever before that Africa needs to ramp up its capacity to manufacture vaccines for use within its borders. In April, the Africa CDC and the African Union held a two-day vaccine summit at which leaders pledged to boost vaccine production capabilities on the continent from its current level of supplying 1% of the African vaccine supply to 60% by 2040.

I spoke with Nkengasong in April about Africa’s response to COVID-19 and his vision for the role of the Africa CDC in facing future infectious disease outbreaks on the continent. An edited version of our conversation appears below.

How would you describe the current situation with COVID-19 in Africa?

The COVID situation in Africa is, in my view, still evolving, and no one should be complacent at all about that. We are not out of the woods yet. This is a tricky virus that can surprise you at any time, and because there is political fatigue setting in, we have to be careful. What is going on in India today is a wakeup call for Africa.

But, so far, the continent has avoided the high mortality rates from the virus seen in other parts of the world. What do you attribute that to?

We should make a distinction between the extent of the spread of the virus and mortality. Clearly, in Africa the virus has spread far beyond what we currently know. As we speak today, the continent has reported about 4.6 million cases of COVID-19, but that is an underestimate because the serologic data show much more virus than that. If you just look at the serologic data coming out of Lagos, Nigeria, it shows a prevalence of about 20% and that’s a city of 20 million or so people. That means there are probably two million people in that city alone that are infected with this virus.

But there are factors that have limited overall mortality, including early political leadership and early responses aimed at controlling virus spread. Doing the right things early enough has kept us where we are. And while 126,000 deaths, which is what have been so far reported for the continent, may not be a full account of mortality, I don’t think the real number of deaths is five times that or even double that. If the deaths are there, you see it. You cannot hide that. In India we saw all these people being rushed into hospitals, but that isn’t happening in Africa now. What we know is that there are many people who are infected here, but not so many people who are falling sick. Still, we have to continue to be careful because with the variants that are emerging, we can very quickly be surprised.

How is the rollout of COVID-19 vaccines progressing in Africa?

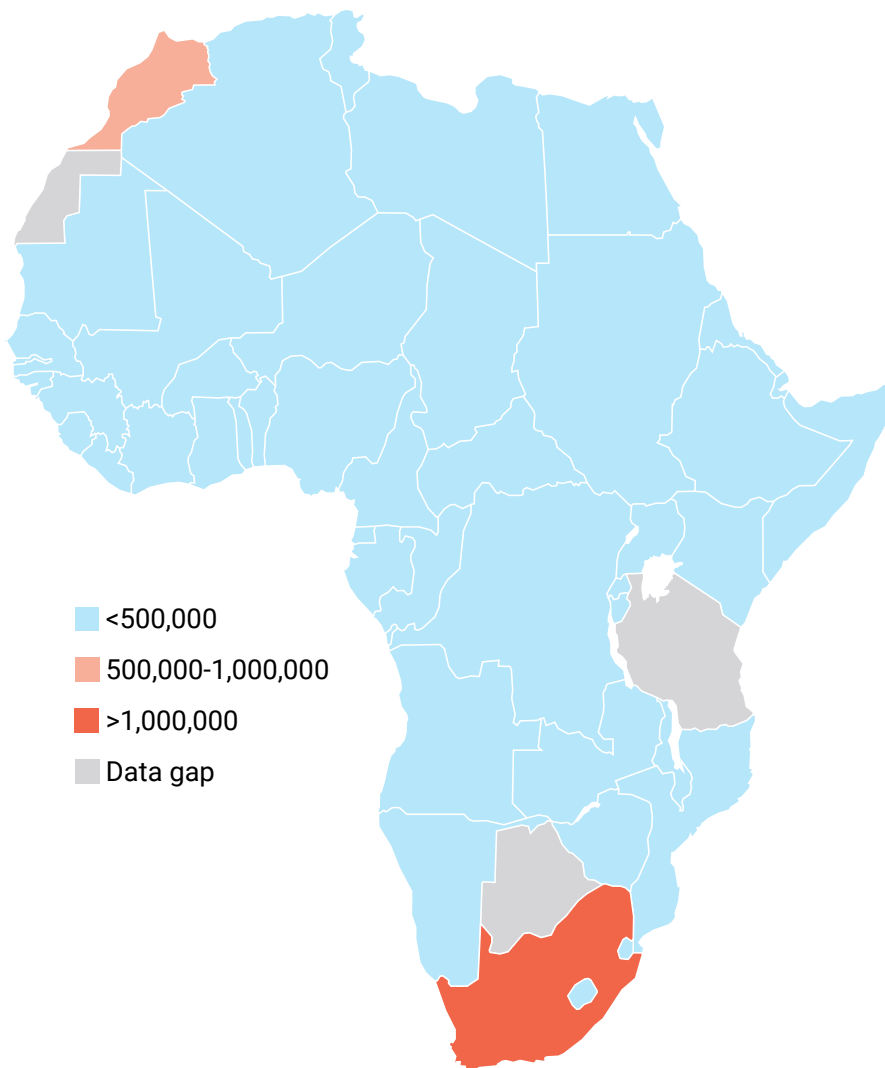
Unfortunately, the rollout has not gone the way we anticipated. Even if you look at COVAX's own projections, we are way, way off from their goals. Our projection is that we need to immunize about 750 million people overall. By the end of this year, we were hoping we would have vaccinated at least 30% of them so that next year when the vaccines become more readily available and the distri-

bution systems are in place, we can actually achieve our target of immunizing at least 60% of our population. But as a continent, we are really falling behind our targets, and it's very concerning. That is not anything we can be proud of, and it speaks to the fact that if we are not very careful, this virus may surprise us by becoming endemic, and that's not what anyone wants.

How has the dire situation in India and the fact that the Serum Institute isn't exporting vaccine doses affected Africa's vaccine supply?

The situation in India has made vaccination efforts in Africa extremely complicated. Limited supply has been one of the biggest factors overall in terms of vaccine rollout on the continent.

Total confirmed cases of Coronavirus in Africa (as of June 28, 2021)



Source: Johns Hopkins University

Will COVID be the impetus for Africa to develop its own low-cost vaccine manufacturing capabilities?

Absolutely. That is why in April we hosted a vaccine conference with the African Union that involved about 40,000 people across the world to discuss vaccine manufacturing in Africa. I don't know of any event, even the United Nations General Assembly, that has attracted more people, so this really stood out as one of the best opportunities in the pandemic. The goal was to make sure that we have a coordinated effort to advance the discussion of manufacturing vaccines on the continent and we are now working to build the right partnerships to promote that idea. As with any new idea, you have to promote it and manage the discussions very well and I continue to hope that there will be full alignment on this issue.

Do you think there are lessons on vaccine access and distribution from COVID-19 that are applicable to other diseases, including HIV?

Well, there are some similarities with COVID, but also a lot of differences. One fundamental difference is that HIV doesn't affect the world in the same way that COVID does. There are 7.8 billion people in the world that are in need of a COVID vaccine now and that is not true for HIV. When HIV vaccines become available, access will be restricted to certain areas that are most in need, and that is many parts of Africa, so we will not see the same issues with access to an HIV

vaccine that we are seeing with COVID vaccines today. The access issue for a potential HIV vaccine will be cost, not availability.

Do you have an understanding of how willingness to be vaccinated against COVID varies across Africa?

Yes. We did a survey last year in which we asked a fundamental question: if COVID vaccines were here, would you take them? The survey included about 15,000 people from 15 African countries. The outcome was that acceptance ranged from about 60% in the Democratic Republic of Congo to about 95% in Ethiopia. But we don't know how that has changed since there have been some concerns raised about some vaccines, including the one from AstraZeneca, which was halted for a time by the Europeans, and the vaccine from Johnson & Johnson, which was stopped temporarily in the U.S. I can't speak to how that has affected people's confidence in the COVID vaccines, but I know that it was originally very good.

What would you like to see from the second-generation COVID vaccines that would make them more feasible for global use?

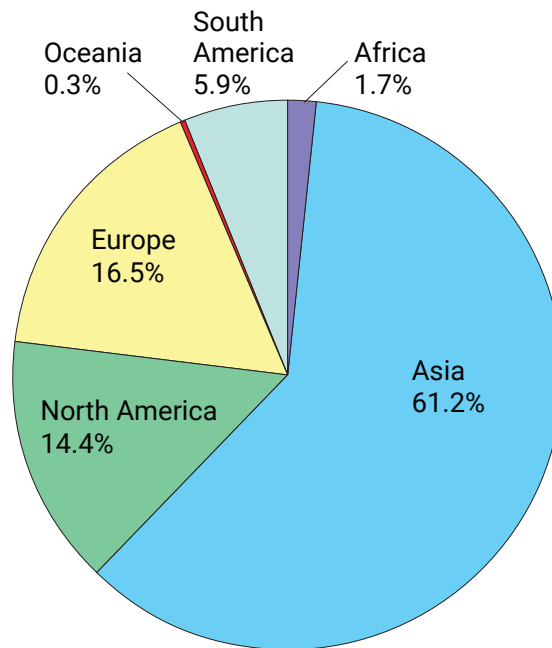
I think for us the best vaccine is the vaccine that is available. I've said several times that you have to go with what you have, not what you need. And if that's the AstraZeneca vaccine, let's use that. But in my view, once the Johnson & Johnson vaccine becomes available it will be the best programmatically because there's nothing as good as jabbing somebody once and not having them have to come back. You can also store it easily, so it has a lot of advantages in terms of vaccine rollout. But there is not one vaccine that will get us there. We will need to use a combination of vaccines to fight this war.

How has COVID changed your thinking about what the Africa CDC can do to prepare for future pandemics?

I think that the Africa CDC, as a young, specialized institution, needs to step back and be courageous. The current global architecture, which is very top down, was set up when the continent of Africa had 250 million people.

Today, we are 1.3 billion people. I use this crude analogy to describe the situation: The house that your great grandparents built may years ago is probably a very different house than what you need today. You need to remodel it somehow so you can accommodate today's family. That's what we need to do. The architecture we settled on in 1947 after the Second World War is no longer working for us in developing countries. We need to have a global mechanism for health security, but we also need regional and national health security. We need to start by more effectively coordinating regional efforts and enhancing collaboration and communication within the regions. Then we'd also like to strengthen and empower the African CDC. You see what the Europeans are doing now with the European CDC — they are saying they need to be more empowered. The continent of Africa should be doing the same thing. It just takes political will and courage to make those things happen. ■

COVID-19 vaccine doses administered by continent* (as of June 27, 2021)



* Total number of vaccine doses administered. This may not equal the total number of people vaccinated, as most vaccines require two doses.

Source: Official data collated by Our World in Data

A tale of two pandemics

In conversation with four experts who are applying lessons from the decades-long battle against HIV/AIDS to the ongoing COVID-19 pandemic.

By Michael Dumiak and Kristen Jill Kresge

Forty years ago this month, the U.S. Center for Disease Control and Prevention’s (CDC) *Morbidity and Mortality Weekly Report* noted an unusual cluster of five cases of *Pneumocystis pneumonia* among gay men in Los Angeles, heralding the HIV/AIDS pandemic. Since then, more than 77 million people have been infected with the virus and nearly 35 million have died from AIDS-related illnesses.

From the time of that first case report in 1981, it took a couple of years for HIV to be identified as the retrovirus that caused AIDS. It wasn’t until four years later, in 1985, that the U.S. Food and Drug Administration licensed the first test to detect the virus in blood. Ten years after the first report of what came to be known as AIDS, scientists discovered combinations of drugs that could help keep the virus in check. Then it took several years until these life-saving medicines made their way to some of the hardest hit countries in sub-Saharan Africa.

Those timelines stand in stark contrast with the scientific and medical progress in combatting COVID-19. Despite several missteps, within a year of when SARS-CoV-2 was identified as the cause of this new human disease, tests, antibody treatments, and vaccines were already available. In a recent [perspective article](#), Kevin DeCock and Harold Jaffe of the CDC and James Curran of Emory University reflected on 40 years of AIDS. They wrote that: “As a result of technologic advances such as whole-genome sequencing, scientific progress on COVID-19 has been breathtakingly rapid compared with early laboratory research on HIV.”

The speed with which scientists were able to develop COVID vaccines can also be attributed, in part, to the remarkable scientific advances by researchers who have spent decades untangling HIV’s thorny traits and applying creative strategies to counteract them. Although none of these vaccine strategies have so far been successful for HIV — one of, if not the, most difficult viral tar-

get researchers have ever faced — this work facilitated the swift progress in tackling SARS-CoV-2.

Now, a major challenge is ensuring COVID vaccines are available globally. Here too, HIV/AIDS can offer valuable lessons. “Although initially slow, the HIV/AIDS response over the years has been a beacon in global health for respect for individuals and their rights and for health equity,” write DeCock, Jaffe, and Curran.

But this is still a work in progress. Despite best efforts, several proven HIV prevention strategies and a highly effective armamentarium of antiretroviral drugs, four decades into the HIV/AIDS pandemic, the virus continues to spread and kill. In 2020, while the world faced the second pandemic in half a century, 1.5 million people were newly infected with HIV and 690,000 people died from HIV/AIDS-related causes, according to the [latest figures from UNAIDS](#). Vulnerable populations still bear the greatest burden when it comes to HIV.

[Data from UNAIDS](#) also suggest progress in treating and preventing HIV is slowing. Disruption of treatment and prevention programs are just one of the many consequences of the COVID-19 pandemic, and UNAIDS warns there may be lingering effects on HIV/AIDS programs if COVID vaccines aren’t made more widely accessible in developing countries.

In the end, the sustained global response to HIV, whether measured through financial investment, community engagement, or scientific progress, may offer important lessons not just for how the world handles COVID, but for pandemic preparedness overall. As Jaffe, DeCock, and Curran conclude: “More reflection is required with regard to what the responses to HIV and Ebola have taught us and how they might be relevant to COVID-19 and other future epidemics.”

We spoke with four experts to explore how the past four decades of HIV/AIDS science have prepared us for ongoing and future pandemics.

Barney Graham

A giant in the vaccine field

There are several heroes in the rapid development of COVID-19 vaccines. Without a doubt, one of them is Barney Graham.

Graham is deputy director of the Vaccine Research Center (VRC) at the U.S. National Institute of Allergy and Infectious Diseases (NIAID) and chief of the Viral Pathogenesis Laboratory and Translational Science Core. In this position, he oversaw the design of the modified SARS-CoV-2 Spike protein and worked with the company Moderna to develop one of the first COVID vaccines authorized in the U.S.

This was the culmination of decades of work, and it started with HIV. “In the late 90s/early 2000s, people started figuring out how to make human monoclonal antibodies. Monoclonal antibody isolation was largely motivated by HIV,” recalls Graham. Technological advances in the early 2000s allowed scientists to more readily isolate and clone human monoclonal antibodies.

This work, in combination with advances in determining the structures of viral proteins, eventually led Graham to pursue a vaccine against respiratory syncytial virus (RSV) alongside Jason McLellan, a structural biologist who started out in Peter Kwong’s lab at the VRC and is now an associate professor at the University of Texas at Austin. “Jason was working with Peter on this HIV structure, and he wanted to work on something else. He asked me whether I had any ideas for him. I said, ‘Well if you’re willing to work on RSV with me, nobody else really cares about it.’ And so, Jason and I built a friendship and we started working on different RSV epitopes.”

The turning point in their work on RSV came when they obtained the crystal structure of the prefusion form of RSV’s F protein using stabilizing mutations they identified in collaboration with Kwong. “This turned out to be a much, much better vaccine antigen,” Graham says. “It gave you a 20-fold boost in neutralizing activity. We’ve done a clinical trial and proved that it really was also good in humans.” This vaccine candidate is now being developed by Pfizer and GSK.

From the work on RSV, scientists were able to develop more stable protein structures for several viruses, including parainfluenza, Nipah, measles, mumps, metapneumovirus, and coronaviruses.

“As we were bringing that first part of the RSV story to a close, that’s when MERS was happening,” Graham recalls. MERS, Middle East Respiratory Syndrome, was first reported in Saudi Arabia in 2012. Its cause was a novel coronavirus. “Our lab made some MERS vaccines, but we were never very satisfied with what we were able to do. Part of the problem was there was no structural information on any coronaviruses.

“Jason [McLellan] was headed to Dartmouth for his first faculty position in late 2013 and he was looking for an area where there wouldn’t be quite so much competition as in HIV. We talked about it and thought coronaviruses would be the perfect place to work because there were no structures. And so that’s what we agreed to work on together.”

Initially, the pair came up empty handed in their efforts to stabilize the Spike protein structures of either MERS or SARS-1. “It wasn’t until we serendipitously started working on the endemic betacoronavirus HKE1, which we did because a post-doc in my lab had gotten sick and he ended up having it, that we got this to work,” says Graham.

He and McLellan engaged Andrew Ward, a professor at Scripps Research and an expert in applying cryogenic electronic microscopy to obtain atomic-level protein structures. Ward was immediately able to obtain the structure of Spike for the HKE1 betacoronavirus. This led Graham and McLellan to try to stabilize the Spike protein.

They identified stabilizing mutations for HKE1, and these same mutations ended up also working for MERS and SARS-1. “It happened to work in almost every coronavirus we tested,” says Gra-



ham. “Now, we thought we had a generalizable approach to stabilizing the Spike protein that could make it a better vaccine antigen. Interestingly and unexpectedly, those stabilizing mutations also improved protein expression from transduced cells, which means if you’re delivering the antigen in a gene-based vector, you’re going to make a lot more protein and it’s going to end up being a better vaccine.”

This was a major turning point in vaccine discovery. “All of that came from RSV, which all came from HIV technology,” he adds.

And all of it led to the fastest vaccine development in history — Graham and McLellan were able to use this same approach to develop a COVID-19 vaccine within a year.

Graham and his NIAID colleagues had been working with Moderna on paramyxoviruses since 2017, so when they suspected that a new human coronavirus was behind the cases of atypical pneumonia being reported in China, they were ready to use mRNA technology to try to rapidly develop a vaccine. As soon as the

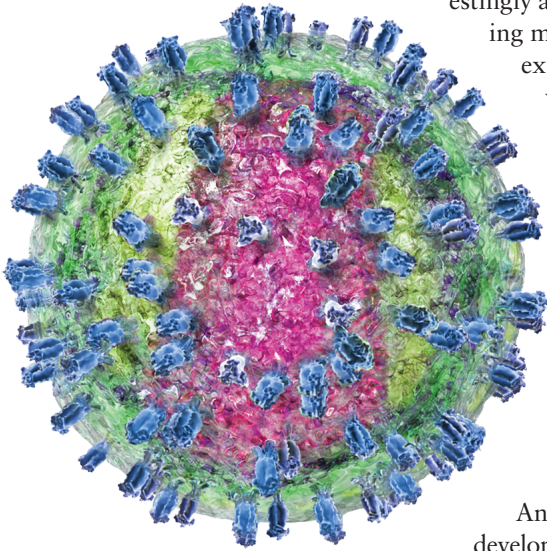
genetic sequence for this new virus was published, Graham and McLellan began designing proteins.

“We were confident enough to apply that same method [of protein stabilization] without any additional experimentation to improve the structure, and it worked,” Graham says, allowing his signature modesty and gentle nature to shine. “We’re very fortunate and happy that it worked out.”

It’s hard to imagine ending your research career on a higher note — at the end of August, Graham is retiring from the federal government. But he still has much to contribute. “I really want to try to help move some of this technology to lower- and middle-income country settings and help people understand that, like we’ve said a million times, a problem anywhere is a problem everywhere.

“Every pandemic threat, including HIV, began as a regional problem that wasn’t recognized and dealt with in time. If we really want to get on top of pandemic threats, we need to use global resources for regional problems,” he says.

And he’s not giving up on the problem that started all of this work in the first place. “I’m still hoping that eventually we can get back around and figure out how to get HIV taken care of.” —*KJK*



Glenda Gray

Drawing on hard-won experience

Talking to Glenda Gray is a good reminder that political and social rancor tied to health emergencies aren't a feature unique to the moment. Here is a person who came of age in medicine in South Africa during the decline and fall of apartheid while, at the same time, HIV was rising to its terrible heights.

And even far along into the struggle to make life-saving antiretroviral therapies affordable and accessible in South Africa, public health workers, including Gray, were having to counter complacency and outright opposition. "Remember, we were still largely denialist at a government level, and patients were being given multivitamins, garlic, beetroot, and ginger," Gray says tartly. "We were in a situation that, in hospitals, these were prescribed."

Glenda Gray is a pediatrician at heart, and some of her early research focused on curbing HIV transmission from mother to child. In just five years, from the late 1980s to early 1990s, HIV prevalence in pregnant women in South Africa shot up from one in 100 to 30 in 100. As a result, more babies were becoming infected. "A lot of women only found out they were infected when their babies got ill," she says. "It just got worse and worse. One in three children who were admitted to the hospital were dying from HIV." In the face of considerable opposition, Gray drove research on the use of antiretroviral therapies that eventually became a mainstay of curbing mother-to-child transmission and found ways to get around what at the time were exorbitant costs for HIV treatment.

Gray is now president of the South African Medical Research Council, a co-principal investigator at the HIV Vaccine Trials Network (HVTN), and an influential academic researcher. She led the research committee advising the South African Health Ministry on the COVID-19 pandemic. The country, like many others, had to make difficult and contentious decisions on lockdowns during the COVID-19 pandemic, with the country at times a global hotspot.

Gray also led Uhambo, HVTN 702, the large, Phase IIb/III HIV vaccine trial that was stopped

in 2020 for lack of efficacy. "It's 10 years of hard work that goes into a trial that has a negative finding. It's devastating," she says, with high stakes and stress at every board meeting.

But Gray and her colleagues keep moving ahead. "We tend to be optimists."

Today, access to antiretrovirals in South Africa is night and day compared to the times of beetroot and garlic. But that didn't happen by itself, Gray says. It took grass roots and legal action to bring more affordable therapies to South Africa, the country hardest hit by HIV/AIDS. It took pressure to convince leery ethics committees to agree to trials in resource-limited settings. "Women drove their agenda. They shook the tree to make sure we were not dispassionate about things like that," Gray says.

Even trials that got negative results created possibilities. "We created these centers that could look after mothers and children, which naturally opened up an avenue for us to do clinical research in children, mothers, and fathers," she says. These became sites that could roll out antiretrovirals. Lab infrastructure followed. "The clinical research and the lab ability allowed us to start working in HIV prevention with microbicides and on monoclonal antibodies — it's a tour de force in Africa." Developing this infrastructure gives opportunity to the African research talent already present.

It also helped with the response to COVID-19. Gray was able to help organize an open-label trial of Janssen's/Johnson's & Johnson's COVID vaccine that inoculated 500,000 South African health care workers in under 16 weeks. "No one's ever done that before here," she says. "When we needed to get the funding to roll this out, people said, 'Have you ever done something like this before?' And we said, well, we've rolled out antiretrovirals, and we rolled out mother-to-child transmission."

In other words, yes, Gray says. "We harnessed the decades of HIV experience to support the COVID response here in the country." —MD





Dennis Burton

Peeling back the layers on pan-coronavirus vaccines

Coronaviruses have likely been infecting humans for centuries. Most of them cause some variety of the pesky, common cold. But as the world has now seen firsthand, they can be far more dangerous. SARS-CoV-2 is the third coronavirus to cause life-threatening disease among humans in the past 20 years. It probably won't be the last.

SARS-CoV, the virus that caused severe acute respiratory syndrome (SARS), emerged in China in 2002, followed by the MERS (Middle East Respiratory Syndrome) coronavirus, which was first detected in Saudi Arabia in 2012. SARS-CoV spread easily and killed almost 10% of those who were infected. While less transmissible, MERS-CoV was much more fatal, killing nearly 35% of those infected. The case fatality rate for SARS-CoV-2 is estimated to be around 2%.

Genomic analysis of SARS-CoV-2 show the virus is approximately 80% similar to SARS-CoV-1 and 50% similar to MERS-CoV. As indicated by the rapid and exponential spread of SARS-CoV-2 around the globe, this is a highly transmissible virus. Fortunately, it is not as deadly as either SARS or MERS.

But the next coronavirus may combine the worst characteristics of both. To be prepared for that eventuality, researchers are calling for development of pan-coronavirus vaccines — vaccines that will be broadly effective against various coronaviruses. “It’s like the layers of an onion,” says Dennis Burton, a professor of immunology and microbiology at Scripps Research in La Jolla, California, and scientific director of IAVI’s Neutralizing Antibody Center. “As you go in, each layer becomes more and more difficult.

“If you begin with the easiest, that would be pan-SARS-related viruses or sarbecoviruses. These would be vaccines that would work against SARS-CoV-1, SARS-CoV-2, and probably viruses in between those two, SARS-3 and SARS-4 if you like, depending on how similar

they were. We know that this is possible in principle because we have antibodies that neutralize SARS-1 and SARS-2 very well. And it is the same principle as with HIV or with a universal flu vaccine — if you have the antibodies that are cross-neutralizing in hand from natural infection, then, in principle, you should be able to design immunogens or vaccine candidates that induce those sorts of antibodies.”

Like HIV, the starting point for this effort is broadly neutralizing antibodies — those that can act against many different strains. For HIV, the virus mutates at such an alarming rate that the diversity of the virus is a huge obstacle to vaccine development. “HIV is the king of antibody avoidance,” says Burton, which is why researchers have been stymied so far in their ability to make a broadly effective vaccine. Researchers estimate that a single HIV-infected person may harbor as many as 100,000 different HIV strains.

“Influenza is also pretty sophisticated,” he notes, which is why annual jabs are required against whichever strains researchers anticipate will dominate from season to season.

But SARS-CoV-2 and other coronaviruses, particularly SARS-CoV-1, are similar enough that antibodies to one can also knock out the other. “Some of the first neutralizing antibodies to SARS-2 that were identified were from SARS-1 infected individuals,” says Burton. “But you can also find SARS-2 infected individuals who make antibodies that are cross-neutralizing to SARS-1. And in animal models, some of these cross-reactive antibodies do protect.”

Fishing out SARS-specific antibodies has proven much easier than it was for HIV. Part of this is because of technological advances, and part of it is just because you aren’t searching for a needle in a haystack. “The technologies are in place to screen sera in donors more rapidly using pseudo-virus assays, and the process of isolating monoclonals from single B cells is also well established

now so it is much easier to get the antibodies than it was 10 or 15 years ago,” Burton says.

“However, SARS-2 is also a much, much easier virus than HIV so there are lots more cross-reactive antibodies around. You don’t have to search through literally thousands of individuals to find what we’ve termed elite neutralizers as we had to do with HIV. There are many more of those sorts of people around with SARS-CoV-2.”

The virus itself, particularly the receptor-binding domain portion of the SARS-CoV-2 Spike protein, is more exposed to antibodies than HIV. “There are large, exposed surfaces on the receptor-binding domain that are very easily recognized by antibodies,” Burton says. This is likely why vaccination with almost any S-protein preparation induces fairly reasonable neutralizing antibody levels, he adds. “You can make antibodies that are very potent against SARS-2 very easily, with a minimal amount of maturation.” And though cross-reactive SARS antibodies require some level of maturation, “it’s still not anywhere near as difficult a problem as it is for HIV.”

This suggests that developing a pan-SARS-related virus vaccine looks feasible, even though SARS-CoV-2 is beginning to show some signs of mutating to avoid antibodies. “The virus is beginning to evolve mechanisms of escape or avoidance of antibody responses,” Burton says. “The variants of concern are the indication that the virus is hitting back.”

The next layer of the onion would be to go from a vaccine that could protect against pan-SARS-related viruses to protecting against all betacoronaviruses, which would include MERS and some of the seasonal cold-causing coronaviruses. Even at this level, Burton says there is already evidence of some degree of cross-reactivity for the antibodies that researchers have identified.

The final layer would be pan-coronavirus vaccines more generally, which would include both

the alpha- and betacoronavirus families. “That, we would guess, would be very difficult because at least so far we’ve not seen antibodies that are cross-reactive between all alpha- and betacoronaviruses.”

However, even achieving the first step would be an accomplishment. “Having antibodies and vaccines that were active against even the SARS-related viruses would be very valuable.

“I think this is a process that will probably be taken in stages and vaccine designs will probably arise with more and more difficult targets in mind,” he says.

Developing pan-coronavirus vaccines will require a long-term investment and research commitment. Burton and his Scripps Research colleague Eric Topol suggest an investment of US\$100 million to \$200 million and several years of work is required to take these concepts from basic research to Phase I trials. But Burton thinks that COVID-19 has convinced almost everyone about the importance of preparing for the next pandemic, no matter what the cost.

“I think the enormity of this pandemic has woken folks up to the dangers of infectious disease so I think that there will be substantial investment in pandemic preparedness, and rightly so because you can see that the economic and health impacts are huge.”

It’s also likely that efforts to develop pan-coronavirus vaccines will return some of the favors HIV research has offered. “There will always be advantages going both ways. We have already been working on the mRNA platform for a number of years with HIV immunogens and they will be coming to clinical trials quite soon, but SARS-CoV-2 has dramatically demonstrated the potential of mRNA vaccines and reduced some of the barriers to using these vaccines, so I think that’s going to be an enormous help to HIV vaccinology for sure.” —*KJK*



Peter Gilbert

The signal finder

Perhaps never has so much of the general public paid attention to clinical trials the way they did in the last 18 months, as scientists raced to develop vaccines to prevent the spread of SARS-CoV-2. The interest in clinical trials — and the unprecedented speed through which vaccine candidates passed through them — was remarkable.

As biostatistician and clinical trial designer for the HIV Vaccine Trials Network (HVTN) based at the Fred Hutchinson Cancer Research Center, Peter Gilbert played an influential role in creating the clinical trial protocols for evaluating some of the vaccines that are proving successful against COVID-19. “It felt like it was reasonably easy and straightforward to pivot from HIV to COVID as a statistician because many of these statistical methods had been worked on for many, many, many years for HIV vaccines,” Gilbert says.

Decades of HIV vaccine research have given statisticians like Gilbert ample opportunity to develop flexible clinical trial protocols. “Many of them really carried over very well, some without any modification at all. They were just ready. We had an opportunity to use these tools that we built for a very pressing situation.” As the pandemic took hold, HVTN could also quickly repurpose some of its clinical trial infrastructure to help test vaccines developed under the U.S. government’s Operation Warp Speed program. Moderna, Johnson & Johnson, and AstraZeneca all made use of the HVTN.

Gilbert calmly recalls those intense days, pausing to think about his answers and showing the kind of sudden insight you see sometimes in those with higher order math skills. Having come to the HIV field in the late 90s as a math major at the University of Washington — following in the footsteps of his parents, prominent statisticians at the Seattle institution — Gilbert has both played a part in and witnessed increasing precision in data analysis over the years, developed to match more sensitive assays and advances in computing power.

“The data get richer and richer over time. Ages ago when I came into the field, we didn’t even have good viral load assays for HIV,” he says. “I remember being a student and sitting in [Jim Mullin’s](#) lab meetings. I remember the big nut they were trying to crack was how to make sure they could quantify viral load. That was the big problem. Now, of course, viral load is a well-accepted surrogate endpoint for HIV treatments.”

Faster lab analytical tools and more robust assays are also helping researchers understand the diversity of HIV — a virus that changes its structure at a dizzying pace after infection — and to do so closer to time of infection, Gilbert says. During HVTN studies Gilbert worked on in the past, single-genome amplification measured perhaps 10 viral sequences per infected individual. Newer deep sequencing can now deliver 200. “The new technology allows us to get deeper biological insights. Technology tends to drive the statistical methods, so the statistics have to catch up and become more complex to capture something about that new biology.” Applying those more complex statistics seems to invigorate Gilbert.

The efficacy of COVID-19 vaccines was in no way ambiguous, but that isn’t always the case. Gilbert points to [results from the AMP trials](#), which tested the ability of an intravenously delivered broadly neutralizing antibody to prevent HIV infection. Even though this single antibody was not effective overall, the trials were large enough, and the analytical tools used by Gilbert and his colleagues were precise enough, that they were able to find a signal of efficacy. “We were able to piece together everything and get an insight that it actually does work if the virus is sensitive — and we can measure that.

“The exciting part is that the planning of the lab work and then the planning of the stats mesh in a cohesive way with the clinical work. It all worked. It was just enough to get an answer.”

And even if that answer isn’t as positive as it was for COVID-19 vaccines, it is still helping to advance the field. —MD