A quarter century of reporting on the quest to develop an HIV vaccine
FROM THE EDITOR

This year IAVI is celebrating its 25th anniversary. And so are we.

The first issue of IAVI Report was published in the summer of 1996. It described IAVI’s formation and mission, offered the scientific reasons for why an AIDS vaccine was feasible, chronicled advances in AIDS vaccine research, included the voice of one of Uganda’s leading HIV/AIDS scientists on HIV vaccine research, and provided a perspective from an industry scientist on their role in HIV vaccine development.

This inaugural issue set the tone for the publication. Ever since then we have been returning to these same issues — the science, the progress, the voices of researchers across the globe, and the importance of continuing the quest to develop an HIV vaccine and bring an end to AIDS once and for all.

There have been several ups and downs in the field, for sure, and our goal has always been to provide context and a range of opinions on the scientific issues of the day. We’ve covered major scientific conferences across the globe, tackled complex scientific issues and tried to make them easier to understand, and interviewed experts, including Françoise Barré-Sinoussi, Anthony Fauci, and many others.

We also had fun. There was the article Chemistry Lab, which profiled four pairs of HIV researchers, who also happen to be married; the articles on the intersection of art and science, including this one that provided an artist’s perspective on the HIV Envelope trimer; and the covers that featured striking scientific images shared by researchers, some of which are shown here, including my personal favorite Andy Warhol-inspired cover of native-like trimer structures.

To commemorate IAVI Report’s anniversary, we’ve put together this special issue. In it, we document the major milestones in 40 years of HIV vaccine research; interview IAVI’s founder and CEO Seth Berkley and its current CEO Mark Feinberg; and provide an update on the science and access issues that the field is focusing on now.

We also interview expert vaccine developer Stanley Plotkin, who was interviewed in that first issue of IAVI Report, to reflect on the remarkable progress in vaccinology and the challenges that HIV vaccine researchers still face today.

As with every issue over the past 25 years, we hope this one provides a unique perspective on the inspiring and elegant science that is underway and the dedicated and passionate people who are leading it.

Working on IAVI Report has been a fascinating and rewarding journey — one that I have enjoyed tremendously. I am grateful to IAVI for its support of this publication, the team that makes it all possible, and for you, our readers, who make it worthwhile.

—Kristen Jill Kresge
IN THIS ISSUE

4 The past, present, and future of IAVI
In conversation with IAVI founder Seth Berkley and CEO Mark Feinberg.

9 40 years of AIDS vaccine research
A timeline of major milestones in the decades-long effort to develop an HIV vaccine.

19 What next? HIV science (again) at a turning point
The field seeks to make progress against one of the most difficult pathogens vaccine researchers have ever faced.

25 Vaccinology reaches a new peak
Stanley Plotkin discusses the greatest progress in vaccine development in more than half a century and the lingering barriers to an effective HIV vaccine.

28 The global stakes for vaccine access
COVID-19 has made stark inequities in global access to vaccines, drugs, and diagnostics more visible and alarming than ever.

IAVIReport

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With IAVI marking its 25th anniversary, it is a fitting moment to reflect on the organization’s history and its evolution. It also provides an opportunity to discuss how the organization is preparing to contribute to the effort to address the mounting public health challenges the world will face in the coming decades.

Today, vaccines are a topic of everyday conversation. Ever since the COVID-19 pandemic began its deadly sweep across the globe, the rapid development of and access to vaccines has been at the forefront of everyone’s minds.

When IAVI was founded 25 years ago, HIV/AIDS had been around for more than a decade and more than 20 million people, globally, were living with the virus. A million others had already died. Developing and expediting access to life-saving antiretroviral therapies was a global priority. Yet there was not a coordinated effort to develop an HIV vaccine.

IAVI sought to change that. And in doing so, this newly formed organization wanted to make resource-limited countries that were bearing the brunt of HIV/AIDS a central part of the development and testing of vaccines so that they would be among the first to benefit.

IAVI AT 25

The past, present, and future of IAVI

In conversation with IAVI founder Seth Berkley and CEO Mark Feinberg

By Kristen Jill Kresge

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After 40 years of research, an HIV vaccine is still not within reach. This isn’t because of a lack of investment or effort. Rather, HIV remains one of those most formidable challenges scientists have ever faced. COVID-19 vaccine development may make it look easy — it isn’t. Still, efforts to understand and confront HIV are ongoing and progress is being made. At the same time, this work is helping accelerate other scientific pursuits. COVID vaccines shattered records with their speedy development, but it was the innovation and persistence of HIV researchers that laid some, if not much, of the groundwork for these products.

Today, innovation and a steadfast commitment to access remain at the heart of what IAVI is and what it does, not just for HIV, but for many other existing and emerging infectious diseases.

To discuss IAVI then and now, I recently sat down with two passionate and visionary IAVI leaders: Seth Berkley, IAVI’s founder and first president and CEO who is now leading Gavi, The Vaccine Alliance, where he is overseeing, among many other things, the global delivery of COVID-19 vaccines through the COVAX facility; and Mark Feinberg, IAVI’s current president and CEO, who helped advance the development and availability of several vaccines throughout his career in industry, academia, government, and the non-profit sectors.

These two leaders are ardent believers in the power of science to deliver transformative public health solutions. They also share an unwavering commitment to ensuring equitable global access to the advances scientific innovation delivers. They are unwilling to accept the status quo and are continuously driving toward a better, healthier world.

An edited version of our conversation appears below.

Let’s start at the very beginning. Take us back to 1995. What made IAVI unique in the early days?

Berkley: I think what made it special was that there was a focus placed on the developing world. The consensus was that we needed to focus on the places where the disease was spreading the fastest.

But we didn’t just want to do research in developing countries, we wanted to empower scientists from those countries to do that research. That has a number of advantages. It helps in the actual research itself, because then you have the trust of the communities, as well as local engagement and leadership. It also creates sustainability. We’ve seen that many of these sites today not only work on HIV but also work on many other diseases. That is a really important part of what was done.

One of the things that made us most proud was the quality of the trials and the work that was
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done. When there were problems, they were solved locally. That is really some of the best work we can do to help empower communities for future outbreaks. Global health security is about building capacity across the world.

**Feinberg:** I completely agree. I think that IAVI’s engagement with developing countries and USAID’s [U.S. Agency for International Development] involvement though their support of IAVI have been critically important. And while I think more and more organizations are now embracing the philosophy that Seth articulated, it’s surprising how long it’s taken and that it isn’t more of a routine endeavor because it is so important build sustainable scientific and clinical research capacity in country.

The scientists and public health workers there are the best connected to the communities and they best understand the needs of the communities at risk of these diseases. That is critically important because otherwise you can come up with innovations that are not going to be accepted because you have failed to win the trust and engender the confidence that people need to really embrace new innovations.

**Berkley:** Another factor that made IAVI unique was making sure that we had people who knew how to develop products in addition to doing the basic science. That focus on the product development side was a special niche. It was really about trying to do things at a different level of magnitude. Even in the animal work we did, it was about doing things on a larger scale so we could have statistically significant answers.

We were also trying to pursue a different funding model. Rather than relying only on research funding, we wanted to have large amounts of finances that could be placed on some big bets.

One of the challenges of starting a new initiative in a completely new field is to get people to support you. And, of course, we started with philanthropy. I will never forget when we got the first check in the mail signed by Bill Gates Sr. — it wasn’t even the Bill & Melinda Gates Foundation in those days — and the note with it said, ‘from time to time, let us know how things are going.’ That was the reporting requirements for our first grant! And as the Gates Foundation became a bigger and bigger supporter, I remember Bill Sr. saying, with tears in his eyes: ‘If this isn’t what philanthropy should be used for, then I don’t know what is.’

That funding went to use right away. **Within 10 years, IAVI had sponsored the testing of five vaccine candidates in 11 countries. Did either of you think we’d be here 25 years later still talking about IAVI’s efforts to develop an HIV vaccine?**

**Berkley:** No, at the time I had hoped we would have solved it quicker. It seemed like we were always 10 years away. And I think the challenge is that we...
didn’t fully understand the difficulty of the science. That became much clearer, a lot of that due to work done at IAVI, and I think this is allowing scientists to approach some of these difficulties in new ways.

Feinberg: The COVID vaccine example has made everyone think that it’s possible to make vaccines against every pathogen in a very short period of time. But no one really knows how long it’s going to take to make an efficacious HIV vaccine.

Seth and I, and many others, have been doing this for a long time and I think that at the beginning of our careers we had no idea that we would be doing this for so long. And it’s clearly going to take a lot longer. But the progress that’s been made is amazing, and, in many ways, it does what Seth alluded to — it clarifies why this is so difficult. You never know when you’re going to have that breakthrough, but we can’t count on being lucky. We have to do our best to be as smart as we can. I think a lot of effort is going into that and progress is being made.

Berkley: Sometimes science can move quickly and sometimes it takes longer. But at the end, it’s critical that we trust the power of science — that’s the only way we’re going to solve these problems.

Science and innovation have been critical to IAVI’s mission. Once it became clear that an HIV vaccine wasn’t going to be an easy win, IAVI established various efforts to address some of the major barriers to progress. This led to the establishment of the Neutralizing Antibody Consortium and, subsequently, the Neutralizing Antibody Center at Scripps Research. How have these efforts shaped the HIV vaccine effort today?

Feinberg: When the Neutralizing Antibody Consortium/Center was first set up, the goal was to understand the nature of broadly neutralizing antibodies and to use them specifically as a tool to inform vaccine immunogen design. And it’s done that in an amazingly successful way. Those vaccine concepts are now in the clinic and being tested. Hopefully, they will be refined and validated, and will be key elements on the path to an efficacious vaccine.

The idea that was at the heart of the NAC was to bring together scientists with insights into many different disciplines that are relevant to vaccine development and connect them to the populations who are either infected with or at risk of being infected with HIV, as well with scientists in the communities and countries where the disease burden is greatest. That really had not ever happened before. At that time, this kind of multi-sector, multi-disciplinary collaboration had not really been used in biomedical science, especially in the global health arena.

The list of accomplishments that have come out of this collaborative effort is remarkable and it would not have ever happened without making connections across different geographies and disciplines. It wasn’t just the science. It was the model of doing this type of innovative science. This has become a more common model today. Even if you look at the COVID-19 response, a lot of the progress that has been made so quickly would not have happened without multi-disciplinary approaches.

Berkley: Even going back to the beginning, one of the things that IAVI did was to go out looking for innovations in biotech. One of the most important ones early on was a company called Theraclone Sciences that had the ability to do high throughput isolation of neutralizing antibodies. That led to some of the early breakthroughs that allowed new broadly neutralizing antibodies to be identified. This then led to a flurry of activity in other labs as well to create a whole family of broadly neutralizing antibodies that were absolutely critical to understanding the targets on the virus, which then led to some really spectacular structural biology work. So all of this is the result of a long trail of investments that led to further advancements.

How has IAVI evolved and expanded its mission since then?

Feinberg: It has evolved in significant ways. One element in IAVI’s evolution has been that these tremendous capabilities that were put in place to advance HIV vaccine development also have relevance to other targets in global health, many of which are much easier targets than HIV itself. So IAVI has since taken on many of those challenges. HIV is the discipline that drove monoclonal antibody discovery and optimization technologies to a state of sophistication, which is quite amazing right now, and we’re applying that to other diseases of global health relevance.

The idea also emerged over time that the HIV antibodies themselves could be a useful tool as long acting, pre-exposure prophylaxis to protect people at risk of HIV from becoming infected, as well as possibly treating or curing people with HIV
infection. That remains to be demonstrated, but it did set a vision that had evolved from this being a tool for immunogen design to this being a public health intervention that could be available to meet the needs of people living in low-income countries.

Another approach that was employed at IAVI’s Vaccine Design and Development Laboratory was to focus on live viral vectors and to try to understand which ones would be most effective for an HIV vaccine. The lab settled on vesicular stomatitis virus [VSV] as a broadly applicable and promising vaccine vector candidate, and now we have very promising programs. We have a VSV Lassa fever vaccine that is in the clinic and we have a VSV Marburg vaccine that’s going to be in the clinic next year, we hope, and we also have an Ebola Sudan VSV candidate in development. We also developed a VSV SARS-CoV-2 vaccine candidate in partnership with Merck, which didn’t yield promising results in the initial study, but we are optimistic that we can develop a vaccine candidate that might fill some of the gaps that exist with the first-generation candidates.

How has the focus on access been critical to IAVI’s mission?

Berkley: Early on, IAVI tried to bridge not just the science but also advocacy. The goal was to involve activists and to have a good communications strategy so we could get information out to the people who needed it. Part of this was getting access on the agenda and having it be a critical piece of our strategy because we knew if we didn’t plan for it ahead of time, it would never happen.

Feinberg: Access is one theme that has been constant throughout IAVI’s history because innovation in its own right is meaningless unless it can be available to everyone who needs it.

IAVI is taking on, as best we can, the work that needs to ensure equitable, timely access to innovations that are relevant to people all around the world, including in low-income countries. We’ve built partnerships that not only to bring in the best technologies to support the work in the monoclonal antibody and vaccine space, but also that can help facilitate affordable and scalable manufacturing.

But even the best-laid plans for access seem to be difficult to carry out, as we are seeing with COVID-19 vaccines.

Berkley: Of course, with COVID-19, we knew, given what happened with swine flu, that it was likely that wealthy countries were going to buy up all the vaccines. We tried to design a program based on all that we’ve learned over the years to prevent that from happening, but it was very hard given the fear that was associated with this disease. High-income countries wanted to protect their own populations and invested heavily early on, making it difficult for others to have access. So, this work on access continues, and it’s going to have to include scientists and clinicians around the world to make the case that improvements in technology and science need to be brought to the world. It’s really the same movement that we started at IAVI so many years ago.

Feinberg: I think the history of HIV has set many positive precedents in the access space. Global access to antiretroviral therapy transformed the way people think about access to innovations and equity, and that’s incredibly important. But access needs to be a core element in how one thinks about the product development continuum because you really need to have access front and center in your mind when you start developing a product, otherwise you may end up in a place that doesn’t really enable access.

Access is not the responsibility of any one organization or any one sector. It’s really everyone’s responsibility. We need to figure out how to get people aligned from the beginning to make sure that access happens as widely as possible, as quickly as possible.

Has the public-private partnership model employed by IAVI been an effective way to stimulate innovation and access?

Berkley: I think there is no question that it has been successful. For HIV, it has been able to drive important basic research, clinical research, and design work in a way that has complimented what’s going on in other places and brought in interesting partners to move things forward.

I think there are many examples of very successful public-private partnerships. Gavi has managed to bring together public and private sectors to dramatically increase immunizations, reduce vaccine preventable deaths by 70%, and make immunization the most widely distributed health intervention in the world. That cannot happen without industry, but it also can’t happen without the public sector.
My own belief is that great advances are not going to be made by government, or the UN [United Nations], or the private sector. They are going to be made by interesting combinations of those and others working together. That is the only way we are going to solve big problems.

**Feinberg:** I think collectively we are getting better as public and private sector entities at working together, but the best days are ahead of us in that regard. And, unfortunately, sometimes it takes a crisis to force the issue. We’ve learned a lot from the responses to HIV, Ebola, and COVID. Now we need to take these learnings and really figure out how to put them together into a strategic framework so that each sector contributes in a way that works best and most realistically for them.

I believe that this is a very promising time now with IAVI’s 25th anniversary to think about how to take that model to the next level. Multi-sector collaboration is not only the most promising, but really the only solution likely to be successful for these challenges.

**Berkley:** I agree with Mark. As we have more and more frequent outbreaks, and as more and more new pathogens appear, we’re going to have to be able to jump on those and this is one of the best models for doing that.

**And what is IAVI’s role in that over the next decade?**

**Feinberg:** If I ask myself, what do I want IAVI to be known for? I’d really like it to be known for being not only a great organization scientifically, filled with compassion and a commitment to equitable access, but an organization that’s really good at imagining and implementing new models of collaborative research and development efforts to address the needs of people who would otherwise be left behind.

The organization that I took over in 2015 had so many great elements that could be brought together and what we’re trying to do now is pilot new approaches that others might want to further build upon and refine in the future.

**What inspires you both to keep doing what you’re doing?**

**Berkley:** It is the right thing to do. And when you look at the world, you realize the power of science can make such a difference to people. But market forces help make a difference to people in wealthy countries much more easily than it can for people in developing countries, so making sure that the science that comes out can get to everybody who needs it, and even be specifically designed to work in the places where it can make the most difference, that is really what drives me to keep going and make the world a fairer and more equitable place.

**Feinberg:** I’m fundamentally an optimist. And I know that Seth is too because otherwise we wouldn’t do this kind of work. I’m optimistic that we will have even better models that will become more proactive and more impactful so we will deliver solutions to currently unmet needs, and we will make them available to people faster than what has previously been the case.

This is a great position to be in, where you get to think about interesting science, but you also can think about how that science can make lives better for many people around the world and save the lives of many people around the world.

**And since we are commemorating an anniversary, can you both share your favorite memory of your time at IAVI?**

**Berkley:** I have a million best memories of my times at IAVI. But one I particularly loved was when we were looking at doing very sophisticated T-cell assays across the world and we were at a seminar looking at the results from these analyses, and there were a lot of bumps in some of the results suggesting not very clean data. And then there was one result that had absolutely clean, perfect data. And I remember that everybody thought that clearly it was the Oxford lab that had the best data. But it wasn’t. It was the Rwanda lab. And I remember just thinking, wow, even with all the difficulties, they had the best results. That just made me so proud and showed me that we must have inclusive science.

**Feinberg:** For me it’s just the constant opportunity to work with an amazing group of people who genuinely care about making the world a better place.

Listen to the conversation between Berkley and Feinberg in the latest podcast episode of Inside IAVI.
There are many success stories over four decades of HIV/AIDS research.

Life-saving antiretroviral therapy, introduced in 1995, is one of the most significant. Writing recently in *Nature*, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, recalls that in 1985, a 25-year-old diagnosed with AIDS in the U.S. had a life expectancy of fewer than two years. Whereas, today, a person living with HIV can expect instead to die in old age from causes unrelated to HIV/AIDS.

The heroic efforts of advocates and activists who pressured scientists, governments, and regulators to make these medicines more widely available were another important success story. Advances in HIV prevention science — including using antiretrovirals as pre-exposure prophylaxis — are yet another important success. Since its peak in 2004, AIDS-related deaths have plummeted by 64%.

Together, advances in HIV testing, treatment, and prevention have helped dramatically slow the spread of HIV. But they haven’t stopped it. Last year, 1.5 million people were newly infected with HIV and 700,000 people died from AIDS-related illnesses.

A vaccine is one prevention tool that remains elusive. Research over the past 40 years, as evidenced by this timeline, illustrates just how difficult it is to induce effective immunity against this virus. But with each decade, scientists are making important progress. And, certainly, their persistence is commensurate with that of HIV.

The next decade will likely answer many questions about the feasibility of developing an HIV vaccine and will hopefully bring us closer to the ultimate end of this timeline — the end of AIDS.
## 1980s

As scientists identify and begin grappling with the newly identified retrovirus that causes AIDS, vaccine researchers begin testing protein-based vaccine candidates in the first clinical trials.

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<th>Year</th>
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| 1983 | Pasteur Institute researchers isolate **new retrovirus** from the lymphoid tissue of a gay Caucasian patient that may be the cause of AIDS. The virus is later called lymphadenopathy-associated virus (LAV).  
  
  > First U.S. report of **eight infants** who had a “disease complex comparable to AIDS.” The children, who were born into families with "recognized risks of AIDS," primarily intravenous drug use, had unexplained immune deficiencies and some of them had opportunistic infections that fit the description of AIDS. |
| 1984 | U.S. scientists confirm discovery of new retrovirus, calling it **human T lymphotropic virus** (HTLV) type III because they thought it was related to human T-cell leukemia virus (HTLV type I). This discovery prompts U.S. Health and Human Services Secretary Margaret Heckler to proclaim that an AIDS vaccine candidate would be ready for testing within two years. |
| 1985 | A new syndrome dubbed **Slim disease** is reported in Uganda that is strongly associated with HTLV-III.  
  
  > Anthony Fauci, director of the U.S. National Institute of Allergy and Infectious Diseases (NIAID), **quadruples funding** for AIDS research. The Division of AIDS is established within NIAID a year later. |
| 1986 | International Committee on Taxonomy of Viruses rules that this new virus be called **human immunodeficiency virus** (HIV).  
  
  > After attempting therapeutic vaccination in two HIV-infected women from Zaire (now the Democratic Republic of the Congo), French researcher Daniel Zagury **inoculates himself** and nine HIV-uninfected children in Zaire with a vaccinia viral vector-based candidate, making this the first unofficial preventive AIDS vaccine trial. Zagury is criticized because trial is conducted without regulatory approval or preclinical testing. |
| 1987 | A recombinant vaccinia virus **vector-based vaccine fails** to protect chimpanzees from HIV.  
  
  > First preventive AIDS vaccine trial begins in U.S. NIAID and the biotech MicroGeneSys test the company’s recombinant gp160 vaccine candidate in 81 HIV-uninfected volunteers, mostly men who have sex with men (MSM). |
| 1988 | U.K. Medical Research Council and Uganda Virus Research Institute in Entebbe form **Africa’s first research unit** focused on determinants of HIV infection. |
### 1990s

Advances in treating HIV/AIDS dramatically alter the landscape of the disease in wealthy countries. Vaccine research begins in earnest with the start of the first Phase III efficacy trial and the creation of multiple initiatives focused on AIDS vaccine development.

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<tr>
<td>1992</td>
<td>Rhesus macaques vaccinated with a live, attenuated simian immunodeficiency virus (SIV), are <strong>protected</strong>.</td>
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<tr>
<td>1994</td>
<td>Researchers make a recombinant form of a human antibody called b12 from the bone marrow of an asymptomatic HIV-infected man. It neutralizes more than 75% of HIV strains, making it the first <strong>broadly neutralizing antibody</strong> (bnAb).</td>
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<td></td>
<td>NIAID <strong>refuses to fund</strong> the first efficacy trial of an AIDS vaccine candidate developed by California-based biotech Genentech. The bivalent vaccine candidate, AIDSVAX B/B, is comprised of recombinant gp120 protein.</td>
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<tr>
<td>1995</td>
<td><strong>Highly active antiretroviral therapy</strong> (HAART) is introduced. “From 1985 to 1994 it was all gloom and doom when it came to therapy,” recalls AIDS researcher David Ho, who pioneered the use of protease inhibitors. “Two years later, everything turned around.”</td>
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<tr>
<td></td>
<td>The <strong>AIDS Vaccine Advocacy Coalition</strong> is formed on December 1, World AIDS Day.</td>
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<tr>
<td>1996</td>
<td>The attenuated strain of SIV previously shown to protect monkeys against SIV infection leads to disease when used to vaccinate infant macaques, <strong>dashing hopes</strong> for testing this approach in humans.</td>
</tr>
<tr>
<td></td>
<td>The <strong>International AIDS Vaccine Initiative</strong> (IAVI) is created as a non-profit, public-private product development partnership to ensure the development of a safe and effective preventive AIDS vaccine.</td>
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<tr>
<td>1997</td>
<td>At a May 18 speech, U.S. President Bill Clinton announces national goal to develop an AIDS vaccine within a decade. The day is then known as <strong>World AIDS Vaccine Day</strong>.</td>
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Disappointing results from the largest vaccine trial to date testing a candidate that induces T-cell immunity are followed by a surprising result from the RV144 trial — the first to show any evidence that a vaccine can protect against HIV. Meanwhile, key discoveries related to broadly neutralizing antibodies jump-start a new pathway to HIV vaccine development.

> Genentech spinoff VaxGen launches Phase III efficacy trial of AIDSVAX B/B, enrolling 5,400 volunteers, mostly MSM, in the U.S., Canada, the Netherlands, and Puerto Rico. A year later, another Phase III trial of AIDSVAX B/E candidate starts in Thailand in a trial of 2,500 injection drug users.

> The Vaccine Research Center (VRC) is established on the NIH campus to perform basic research to establish mechanisms of inducing long-lasting, protective immunity against HIV and other pathogens.

> Uganda hosts Africa's first HIV vaccine trial.

> The Kenya AIDS Vaccine Initiative (KAVI) and South African AIDS Vaccine Initiative are established.

> The HIV Vaccine Trials Network (HVTN) is formed by NIAID.

**2000s**

Basic science and clinical development

Funding, collaborations, and advocacy

> NIAID assumes control of the U.S. Department of Defense's HIV Research and Development Program, which had been preparing to launch a Phase III efficacy trial, RV144, in Thailand testing Sanofi-Pasteur's canarypox vector-based vaccine candidate ALVAC-HIV (vCP1521) in a prime-boost combination with VaxGen's AIDSVAX B/E candidate.

> Phase III trials show that AIDSVAX is ineffective in either MSMs or IDUs.

> RV144 prime-boost trial begins in Thailand in 16,000 mostly low-risk volunteers.

> Twenty-four leading AIDS vaccine researchers publish a paper arguing that the insufficient scale of research is impeding development of an AIDS vaccine. Several years later, the Global HIV Vaccine Enterprise is created.

> NIAID announces US$300 million over seven years for virtual consortium, the Center for HIV/AIDS Vaccine Immunology (CHAVI).

> Start of the Phase IIb STEP trial testing whether Merck's adenovirus serotype 5 (Ad5) candidate can either prevent infection or reduce viral load.
2006

> Researchers in Kenya isolate a subtype A transmitted/founder virus from a six-week-old infant in Nairobi who was HIV infected at birth and enrolled in a mother-to-infant HIV transmission study. This virus sequence is referred to as **BG505**.

> With support from USAID, IAVI initiates large multi-center epidemiology studies. One of them, **Protocol G**, aims to identify new HIV-specific bnAbs to inform vaccine design efforts.

2007

> Vaccinations in STEP are discontinued because there is **no evidence of protection**. Subsequent data suggest that vaccine candidate MRKAd5 may have increased risk of HIV among some volunteers. Vaccinations in Phase Ib Phambili trial of same candidate, which launched in South Africa in February, are also halted.

2008

> A hi-res, 3-D image approximates the **trimeric structure** of HIV gp120.

2009

> RV144 results show vaccine candidate reduces risk of HIV infection by about 31%, providing **first evidence** of vaccine efficacy in humans.

> New bnAbs isolated that are more broad and potent, and that target new epitopes on HIV.

> The **Neutralizing Antibody Center**, a partnership of IAVI and The Scripps Research Institute in California, is established.

> The **Ragon Institute** launches with a $100 million gift, joining researchers from three Boston institutions.

> The AIDS Vaccine Conference draws a record number of attendees as the field seems **more optimistic** about the prospects for HIV vaccine development.

> **The Bill & Melinda Gates Foundation awards $287 million to establish the Collaboration for AIDS Vaccine Discovery (CAVD).**

> STEP results prompt NIAID to **reconfigure** Phase Ib PAVE 100 trial of a DNA/Ad5 prime-boost regimen.

> Following STEP results, NIAID sponsors summit about **shifting funding** from clinical development to basic discovery.

> **“We are at the beginning of a new phase of HIV vaccine research.”**

—Yves Levy

> Read the **2009 story** with support from USAID, IAVI initiates large multi-center epidemiology studies. One of them, **Protocol G**, aims to identify new HIV-specific bnAbs to inform vaccine design efforts.
Researchers are exploring multiple paths to HIV vaccine development. One path is to design and test mosaic vaccine antigens that are meant to address HIV’s overwhelming global diversity. Another is to explore the role of non-neutralizing antibodies in the role of HIV protection. At the same time, researchers hone in on HIV’s elusive structure and use this information to design vaccine candidates to induce broadly neutralizing antibodies.

2010

Mosaic antigens, computationally derived to provide maximum coverage against HIV, show promise in monkeys.

Researchers analyze the structure of recently identified bnAbs to determine how they bind to and neutralize HIV. This work shows the extensive affinity maturation that gives rise to these antibodies, which has consequences for vaccine design.

Researchers show that cell-to-cell spread of HIV in vitro is about 10 times more efficient than infection spread by free-virus particles.

In the wake of the RV144 results, researchers home in on the role non-neutralizing antibodies may play in protection against HIV.

Researchers identify crystal structure of PG16, one of the recently identified bnAbs, revealing its unique features.

2011

Researchers continue isolating dozens of new broadly neutralizing antibodies and gather clues about how they develop in infected individuals.

Vaccination with a replication competent CMV vector-based vaccine leads to viral control in SIV-challenged monkeys.

HVTN 505 vaccine trial is expanded to explore whether the DNA/Ad5 prime-boost regimen can block HIV infection.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>2011</td>
<td>Researchers from Emory and Beth Israel Deaconess Medical Center are selected to lead a 5-year, $60 million effort to use NHP models to understand mucosal HIV transmission.</td>
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<td></td>
<td>Researchers debate how adaptive clinical trial designs could speed the evaluation of vaccine candidates.</td>
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<td></td>
<td>IAVI Report interviews four leading researchers on what it will take to go from broadly neutralizing antibodies to vaccine immunogens.</td>
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<td></td>
<td>I think this is a tipping point in a way. The next two, three, four years will tell us a lot about the feasibility of an HIV vaccine. —Dennis Burton</td>
</tr>
<tr>
<td>2012</td>
<td>Additional analyses of RV144 results provide some insight into what types of immune responses may have contributed to protection.</td>
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<tr>
<td></td>
<td>The U.S. NIAID announces two consortia known as the Center for HIV/AIDS Vaccine Immunology &amp; Immunogen Discovery (CHAVI-ID) to tackle scientific obstacles to HIV vaccine development. The two centers were established at Duke University and The Scripps Research Institute (TSRI) in La Jolla, CA.</td>
</tr>
<tr>
<td></td>
<td>IAVI-Translational Health Science and Technology Institute (THSTI) HIV Vaccine Translational Research Laboratory opens in India to study genetic and virological properties of circulating HIV strains in India.</td>
</tr>
<tr>
<td>2013</td>
<td>Scientists at TSRI and IAVI apply computational and genetic engineering techniques to generate a virus-like particle (eOD-GT6) that activates bnAb precursors in the lab — an initial step in developing a vaccine immunogen capable of setting off the development of bnAbs.</td>
</tr>
<tr>
<td></td>
<td>Using BG505 SOSIP.664, researchers capture cryoelectron microscopy and x-ray crystallography images of a native-like HIV Env trimer.</td>
</tr>
<tr>
<td></td>
<td>The Bill &amp; Melinda Gates Foundation awards a grant to IAVI to create the Vaccine Product Development Center (VxPDC) to assist investigators affiliated with the Foundation’s Collaboration for AIDS Vaccine Discovery with the complex process of transitioning vaccine candidates from the laboratory to the clinic.</td>
</tr>
<tr>
<td></td>
<td>IAVI expands the Product Development Center (PDC) to support other products in addition to vaccines and extends its translational expertise to other partners.</td>
</tr>
<tr>
<td></td>
<td>The Human Vaccines Project launches to accelerate the development of new vaccines by decoding the human immune system.</td>
</tr>
<tr>
<td></td>
<td>Researchers publish data on a stabilized HIV trimer protein known as BG505 SOSIP.664 based on an isolate from an HIV Clade A-infected infected infant in Kenya.</td>
</tr>
</tbody>
</table>
Studies in transgenic mice show that the engineered eOD-GT8 60mer immunogen followed by a native like timer immunogen can induce VRC-01-like antibodies.

The AMP studies are launched to test whether intravenous infusions of the bnAb VRC01 is effective at preventing HIV infection.

Researchers at the VRC announce plans to begin a passive immunization clinical trial with the VRC01 bnAb.

It’s really the start of a new generation of immunogens and vaccines that weren’t previously accessible.

—Andrew Ward

Researchers report on the identification of bnAbs from a South African donor, CAP256, which have increased breadth and potency.

The bnAb PIGDM1400 is identified and is among the most broad and potent antibodies isolated to date.

Researchers make progress in developing native-like HIV Env trimers as vaccine immunogens.

Studies in transgenic mice show that the engineered eOD-GT8 60mer immunogen followed by a native like timer immunogen can induce VRC-01-like antibodies.

Researchers generate a trispecific HIV bnAb that can protect against a modified simian/human immunodeficiency virus in macaques.

Researchers at the VRC isolate the N6 bnAb that can neutralize 98% of HIV isolates.

With support from USAID through PEPFAR, IAVI launches Vaccine Immunology Science and Technology for Africa (VISTA) and the International Training Program to strengthen research capacity for HIV vaccine research in sub-Saharan Africa.

The Phase IIb/III HVTN 702 trial, known as Uhambo, is launched to test whether a modified version of the vaccine candidate tested in RV144 is effective at preventing HIV infection in South Africa.

Read the study

Read the study

Read the study

Read the study
2017

- The Imbokodo or HVTN 705/HPX2008 Phase IIb trial begins in South Africa. It is designed to test the efficacy of an **Ad26-vector-based HIV vaccine candidate** that delivers mosaic antigens designed to induce immune responses against a wide variety of global HIV strains.

> At a certain point you have to jump and hope that it works.
—Paul Stoffels, chief scientific officer at Johnson & Johnson

2018

- The European AIDS Initiative 2020 program works to advance several **native-like HIV Env trimer immunogens** into clinical trials.

- IAVI begins the first clinical trial of the eOD-GT8 60mer vaccine immunogen, which is designed to stimulate the immune system to initiate a key first step in the generation of bnAbs.

> Several trials testing **passive administration** of HIV broadly neutralizing antibodies are underway by the VRC and researchers at Rockefeller University.

> “It’s a new era clinically of testing this antibody-based vaccine design concept.”
—John Mascola

2019

- The European Union approves an **Ebola vaccine** that utilizes a vesicular stomatitis virus vector, which is also being explored for HIV vaccines.

> The **Mosaico** or HVTN 706/HPX3002 Phase III trial begins in North and South America and Europe testing the efficacy of an Ad26-based mosaic HIV vaccine candidate in men who have sex with men and transgender people.

- IAVI begins the **Duke Consortia for HIV/AIDS Vaccine Development (CHAVD)** receives a third seven-year grant from NIAID to develop and test vaccine candidates.

> IAVI and the Serum Institute of India partner to develop and manufacture **globally affordable and accessible** antibody products for HIV.

> IAVI Report publishes a special issue on **African-led HIV vaccine science**.
2020s

More disappointing results from clinical trials are reported, causing many in the field to coalesce around the idea that an effective HIV vaccine will need to induce broadly neutralizing antibodies against the virus. In pursuit of that goal, researchers push ahead with structure-based immunogen design efforts.

- IAVI, Scripps Research, and the NIH agree to pool their HIV bnAb assets and expertise to develop a combination bnAb product specifically designed to be available and affordable globally.
- Decades of research on HIV facilitates the rapid development of vaccines against SARS-CoV-2, a novel coronavirus that spreads globally and kills millions.
- IAVI and Scripps Research announce that an experimental HIV vaccine candidate (eOD-GT8 60mer) primed the immune system as the first stage in the production of bnAbs in a Phase I clinical trial (IAVI G001).
- Data from the Phase Ib Imbokodo trial show that the mosaic-based HIV vaccine regimen did not provide sufficient protection against HIV infection.

2020

- Vaccinations in the Phase IIb/III HVTN 702 or Uhambo trial are stopped early because the vaccine candidate did not provide protection.
- The PrEPVacc trial begins enrollment. This African-led Phase IIb/III clinical trial is evaluating two experimental HIV vaccine regimens compared to placebo, as well as a new PrEP combination pill known as Descovy. This is the first time that oral PrEP and experimental vaccines are being tested at the same time.
- Following the results of the Uhambo trial, more and more researchers in the field converge on the idea that an effective vaccine will need to induce so-called bnAbs.
- Results of the Antibody Mediated Prevention trials show that the antibody VRC01 did not protect against HIV infection any better than placebo.
- Vaccinations begin in Zambia for a Phase I trial testing a mosaic HIV vaccine candidate known as HIVconsvX.

2021

- IAVI Report surveys leading researchers, funders, and policymakers on what the AMP results mean for the field.
- IAVI commemorates 25 years of translating scientific discoveries into affordable, globally accessible public health solutions.
- IAVI and Scripps Research announce that an experimental HIV vaccine candidate (eOD-GT8 60mer) primed the immune system as the first stage in the production of bnAbs in a Phase I clinical trial (IAVI G001).
- Data from the Phase IIb Imbokodo trial show that the mosaic-based HIV vaccine regimen did not provide sufficient protection against HIV infection.

Learn more

Photo/image credits: Andreas von Bubnoff; Vaccine Research Center at NIAID; Sriram Subramaniam, NIH; Vanessa Vick; Jean-Marc Giboux/Getty Images; Robert Pejchal, The Scripps Research Institute; PLoS Pathog. 9(9): e1003618, 2013; Peter D. Kwong, Marie Pancera, and Jonathan Stuckey, NIH/NIAID/VRC; Joseph Jardine, Sergey Menis, and William Schief, Scripps Research and IAVI. Alba Torrents de la Peña, Amsterdam University Medical Center; Viruses, April 1: 10(4), 2018; NIAID; Hailee R. Perrett, Scripps Research
Once more the HIV vaccine field is finding its way in the wake of disappointing results from a large, late-stage efficacy trial. At the end of August, Johnson & Johnson announced that a mosaic vaccine candidate offered no protection against HIV acquisition in a trial, called Imbokodo, involving 2,637 women from five sub-Saharan African countries.

“This is hard learning. It was 15 years’ effort, and didn’t work,” says Paul Stoffels, chief scientific officer at Johnson & Johnson, whose pharmaceutical division Janssen managed the trial. “It will be back to research.”

This is familiar territory for the HIV vaccine field (see 40 years of AIDS vaccine research, p. 9). IAVI Report turned 25 this year, and its pages describe both the optimism and setbacks that have abounded during the long quest to develop an HIV vaccine. Now Imbokodo is inviting a discussion of “back to basics” once more.

Dan Barouch, who directs a virology and vaccine research program at the Harvard Medical School’s Beth Israel Deaconness Medical Center and at the Ragon Institute of Massachusetts General Hospital, MIT and Harvard, knows Imbokodo well. His lab developed the mosaic immunogen tested in the trial and conducted extensive evaluation of the candidate in both animal and early-stage human clinical studies. He takes a pragmatic approach to the results. “I would say that some of these late-phase trials have shown disappointing results, but we need to learn from them,” he says. “Basic research never ended. It’s not that there’s anything to go back to — the basic research has continued. Our group is a part of it and many other groups, too.”

Imbokodo, and all large-scale HIV prevention trials for that matter, offer an opportunity to learn about protective immunity against HIV, even if, overall, the candidate didn’t work. Researchers can analyze subgroups of trial volunteers to see if there are any clues about the types of immune responses that may have been protective in some individuals. These so-called correlates of protection can aid vaccine researchers in developing other candidates. “An efficacy trial gives us an ability to actually ask those questions with humans. That’s one thing that is being done now,” Barouch says.

While that work is ongoing, one takeaway from Imbokodo that the field seems to largely agree upon is the need for an HIV vaccine that induces broadly neutralizing antibodies (bnAbs) — those rare antibodies that can fend off the incredible diversity of HIV variants in circulation.

“I think that there needs to be a renewed emphasis on the development of immunogens to raise broadly neutralizing antibody responses as well as combination regimens because there is no broadly neutralizing antibody vaccine on the horizon, at least not that I can see,” says Barouch. “There needs to be combination strategies that try to induce both antibody and T-cell approaches.”

In 2001 Gary Nabel, then director of the Vaccine Research Center (VRC) at the National Institutes of Allergy and Infectious Diseases (NIAID) laid out the state of the field, which at that point was into its 15th year. In the absence of immune correlates of protection, Nabel wrote, it would be most prudent to develop a vaccine that stimulates multiple components of the immune system. Two decades later, that still seems the best hope for protecting against HIV.

But much has also changed since then: researchers have developed and vastly expanded their ability to isolate bnAbs and use them to design vaccine immunogens. This is just one of the scientific themes that emerged over the past two decades of HIV vaccine research. Others include advances in viral vectors and other platform technologies, new types of clinical trial designs, and improved animal models of HIV infection. The recent disappointing results in major late-stage clinical trials make this a good time to take stock of the progress being made in these areas, as well as a look at where the next decade of clinical and basic research might lead.
Broadly neutralizing antibodies (bnAbs)

A significant advance in the last 15 years is the progress made in isolating, characterizing, and developing HIV-specific bnAbs.

In 2009 researchers isolated two potent bnAbs that targeted a previously uncharacterized, stable part of the HIV Env protein. The discovery of these bnAbs and others the following year marked a turning point in AIDS vaccine research — they were the first additions to the antibody armamentarium in a decade.

From there, efforts related to bnAbs accelerated rapidly. Scientists set out to isolate more bnAbs, to characterize the specific regions or epitopes on the virus that these antibodies target, and to use this information to reverse-engineer and design vaccine antigens that would potentially elicit these responses in uninfected individuals. They also began to investigate whether the bnAbs themselves could work on their own for HIV prevention.

At last count the number of bnAbs isolated from HIV-infected people was in the hundreds. They’ve now been used to pinpoint multiple sites of vulnerability on the HIV Env protein (see image below). Researchers are pressing ahead in the hunt for immunogens that can elicit these antibodies.

And one bnAb — VRC01 — was tested in a pair of Phase Ib proof-of-concept studies to see whether directly administering it in monthly infusions to 4,600 volunteers would prevent HIV infection. The results published in March 2021 showed that while the strategy can indeed prevent HIV infection — in some individuals, under very specific conditions — for most trial participants, it did not.

But there is still much to be learned from the Antibody Mediated Prevention (AMP) studies. When researchers did careful subgroup analyses, they found that VRC01 was able to protect against viruses that were highly sensitive to neutralization by this single antibody. “The AMP study failed to meet its primary endpoint, no different than Imbokodo. It was only when people looked at subgroups, the subgroups of exquisitely sensitive virus, then there was protection,” Barouch says.

As Harvard’s Stephen Walsh and Michael Seaman write in Frontiers in Immunology, the AMP studies show that it’s possible bnAbs can prevent HIV infection, but they also show how far passive immunization strategies are from being a successful tool. VRC director John Mascola told IAVI Report last May that it would probably take a combination of three bnAbs to be both highly potent and cover as many viruses as possible. IAVI is sponsoring a safety trial of a combination of three bnAbs — PGT121, VRC07-523LS, and PGDM1400 — for HIV prevention and therapy. The Centre for the AIDS Programme of Research in South Africa (CAPRISA) is working with German biotech EvoOct BioSystems to test a combination of the bnAbs CAP256 and VRC07 as a preventive in clinical trials in Zambia. Results from these studies and others will determine the path forward for the use of bnAbs for HIV prevention.

Vectors

In the mid 1990s researchers began to use recombinant viral vectors as vehicles for vaccine immunogens. Their current success in both SARS-CoV-2 and Ebola vaccines is a testament to decades of work.

Live, recombinant viral vectors, including those based on canarypox and adenovirus, were chosen early on for HIV. The 2004-2007 STEP trial tested the ability of an adenovirus serotype 5 (Ad5) vector carrying HIV genes to induce HIV-specific T cells capable of either preventing HIV infection or controlling viral replication in volunteers who became
infected despite vaccination. Researchers halted the study because of a lack of efficacy. Subsequent analyses indicated that the Ad5 vector-based candidate increased risk of infection in some volunteers, potentially because of previous exposure to Ad5. This was a chastening result that echoes even today: HIV researchers wrote last October to The Lancet warning against using recombinant Ad5 as a vector for COVID-19 vaccines, citing the STEP trial as a “cautionary tale.”

Researchers continued pursuing other Ad vectors, including Ad26 and Ad35, as well as many others. Many of these have proven successful in vaccines for other diseases, just not HIV. “The problem has and continues to be HIV immune evasion, the fact that its immune vulnerabilities are much, much less than that of other viruses, like SARS-CoV-2, and that we struggle to elicit immune responses able to exploit the vulnerabilities that have been defined,” says Louis Picker, a vaccine researcher at Oregon Health & Science University in Portland and co-founder of the biotech company Vir. Picker has long been exploring the use of cytomegalovirus (CMV) as a vector for HIV vaccine immunogens.

Viral vectors, including Ad26 and a chimpanzee adenovirus, are part of four of the currently authorized vaccines against SARS-CoV-2. Two vaccines licensed for Ebola are also based on viral vectors: the vesicular stomatitis virus (VSV)-vector based candidate from Merck and the chimpanzee adenovirus vector-based vaccine from GSK. Prior to that, viral vectors were only used in Japanese encephalitis and dengue vaccines.

Investigators are still pursuing several different types of viral vector-based HIV vaccine candidates, including VSV, an RNA virus in the rhabdovirus family that mildly affects livestock.

With proven track records, many of these viral vectors may well be applicable for HIV vaccine designs — once the ideal immunogen is found. Many researchers now think the problem is more about developing vaccine antigens that elicit bnAbs than finding the way to deliver them. “HIV vaccine research now is an antigen discovery problem,” says Wayne Koff, head of the Human Vaccines Project and former chief science officer at IAVI.

**Immunogens**

COVID-19 has made us all experts of sorts on viral evolution and mutation. But instead of trying to fend off a handful of variants, as is the case for SARS-CoV-2, HIV researchers are facing down one of the most genetically diverse pathogens ever identified.

Given this, many vaccine researchers have long thought it would be necessary to develop a vaccine that would induce bnAbs. Now Imbokodo and Uhambo, a Phase IIb/III HIV vaccine study in South Africa stopped for lack of efficacy in 2020, are pushing the field even further in that direction. “We should redouble our efforts to design vaccines that can induce neutralizing antibodies,” says Rogier Sanders, a virologist at the University of Amsterdam’s Academic Medical Center.

While researchers can now isolate bnAbs, discovering an immunogen that elicits them effectively remains elusive. But there are several avenues currently being pursued to achieve that goal. One is employing an engineered protein called eOD-GT8 60mer, developed in immunologist William Schief’s lab at Scripps Research and IAVI’s Neutralizing Antibody Center, in a strategy called germline targeting. Early tests show the eOD-GT8 60mer immunogen can effectively prime the immune systems in healthy humans, setting off an initial step in the elaborate process of inducing bnAbs against HIV. Now this immunogen is being delivered in a Phase I clinical trial using the same mRNA platform Moderna uses for their COVID-19 vaccine.

Another approach being pursued by Duke immunologist Bart Haynes and his colleagues involves engineering sequences of the HIV Envelope (Env) protein as immunogens that are mapped to match the evolution of the virus in infected individuals. Meanwhile Peter Kwong, chief of the structural biology section at the VRC, is exploring an engineered fusion peptide immunogen with the goal to induce several different lineages of bnAbs, rather than antibodies from a single class. NIAID was originally slated to take the fusion peptide immunogen into clinical trials in 2021, but that trial is now slated for early to mid-2022.

Researchers are also exploring native-like HIV Env trimers as vaccine immunogens. This effort is possible now after a series of incremental but pivotal advances in stabilizing and modifying HIV Envelope’s trimeric structure (see Table 1). Sanders and his colleagues are currently conducting an early-phase clinical trial with one of these immunogen constructs in a germline targeting strategy. “The
next step is to identify optimal sequential vaccination regimens that drive antibody responses primed with these germline-targeting immunogens to become neutralizing antibodies,” he says.

Barouch does not expect quick results in the hunt for more effective immunogens that could induce bnAbs. “If Mosaico also doesn’t work, then it’s probably going to be a long time before we have the next HIV vaccine reach large-scale efficacy trials.”

The antigens used in Imbokodo and its sister trial, Mosaico — to which Barouch is referring — were designed to elicit T-cell responses. Despite the renewed focus on bnAb-inducing immunogen development, T-cell vaccine approaches are not being abandoned. Tomáš Hanke, a professor of vaccine immunology at the Jenner Institute at Oxford University, is developing a T-cell immunogen known as HIVconsv that is designed to induce T cells that target functionally relevant parts of all HIV variants circulating globally. A trial of this candidate started earlier this year as part of the European AIDS Vaccine Initiative (EAVI2020).

Others are still reticent to abandon the role of non-neutralizing antibodies in protecting against HIV infection because of the many differences between the Uhambo trial and the RV144 trial, the only HIV vaccine trial to ever show any efficacy. A recent review article on HIV vaccine research details the substantial differences between the two studies (see Table 2), particularly in the HIV incidence between the two trial populations. The incidence in Thailand, where the RV144 trial took place, was almost 15-fold lower than it was in South Africa during the Uhambo trial.

**Clinical trial design**

The catastrophe of COVID-19 has reshaped public health in many ways. One small but potentially important aspect is in clinical trial design and function. In response to the latest infectious disease outbreaks and pandemics, clinical trials have become more compressed and more flexible. This shift began during the 2014-15 Ebola virus epidemic in West Africa, when “ring studies” helped speed a highly effective vaccine into emergency use.

**Table 1: Key developments in structure-guided HIV-1 vaccine designs in the past decade**

<table>
<thead>
<tr>
<th>Year</th>
<th>Development</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>2013</td>
<td>First structure of a native-like trimer in complex with PG9</td>
<td>Julien et al., 2013</td>
</tr>
<tr>
<td>2013</td>
<td>Development of the BG505 SOSIP.664 trimer</td>
<td>Sanders et al., 2013</td>
</tr>
<tr>
<td>2013</td>
<td>First cryo-EM structure of a native-like Env trimer</td>
<td>Lyumkis et al., 2013</td>
</tr>
<tr>
<td>2013</td>
<td>First crystal structure of a native-like Env trimer</td>
<td>Julien et al., 2013</td>
</tr>
<tr>
<td>2014</td>
<td>First structure of the complete pre-fusion conformation gp41</td>
<td>Pancera et al., 2014</td>
</tr>
<tr>
<td>2014</td>
<td>First dynamics of SOSIP trimers using hydrogen-deuterium exchange analysis</td>
<td>Guttman et al., 2014</td>
</tr>
<tr>
<td>2016</td>
<td>First cryo-EM structure of a native HIV-1 viral envelope</td>
<td>Lee et al., 2016</td>
</tr>
<tr>
<td>2016</td>
<td>Development of the eOD-GT8 germline-targeting immunogen</td>
<td>Jardine et al., 2016</td>
</tr>
<tr>
<td>2017</td>
<td>Development of the germline-targeting BG505 SOSIP GT1 trimer</td>
<td>Medina-Ramirez et al., 2017</td>
</tr>
<tr>
<td>2018</td>
<td>Evaluation of site-specific glycosylation on virion-derived Env s</td>
<td>Struve et al., 2018; Cao et al., 2018</td>
</tr>
<tr>
<td>2018</td>
<td>Analysis of conformational dynamics native-like Env trimers using DEER spectroscopy</td>
<td>Stadtmauer et al., 2018</td>
</tr>
<tr>
<td>2020</td>
<td>First in-human phase I clinical trial started with the eOD-GT8 60mer vaccine candidate</td>
<td>Clinicaltrials.gov</td>
</tr>
<tr>
<td>2018</td>
<td>Development of electron microscopy-based polyclonal epitope wrapping (EMPEM)</td>
<td>Bianchi et al., 2018</td>
</tr>
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</table>

Stoffels credits the networks and engagement established to support HIV vaccine clinical trials with the speed with which the company was able to test its vaccine against COVID-19. “We learned a lot from HIV. We were able to do a clinical trial in three continents in three months,” he says of the Janssen/J&J Ad26 vaccine against COVID-19, addressing a panel of experts recently at a Berlin public health meeting. “The reason was because there was still a significant HIV clinical trial network in place studying HIV vaccines. We could access that, and at its peak we were recruiting 3,000 people a day. That will have to be maintained, even when this is over.”

The COVID-19 pandemic also exemplifies how platform technologies can be used to speed clinical trials and quicken vaccine development. The mRNA platform, which proved itself against SARS-CoV-2, can now be used to test iterative HIV vaccine designs — as is being done in this Phase I trial. Data obtained from this trial can be used to optimize the immunogen, which can then be tested in another Phase I trial.

Adaptive trials, where multiple study arms can remain open or closed based on results, are also going to be increasingly important. One such example is the ongoing PrEPVacc study, which is evaluating pre-exposure prophylaxis alongside two recombinant DNA vaccine candidates.

Platforms

Vaccine technologies that have multiple uses, so-called platforms, have been a focus of vaccine development for some time now. Their prominent role in addressing COVID-19 has brought them to the forefront. “Billions of dollars have been funneled in to accelerate platforms: vaccine platforms, drug discovery platforms, diagnostic platforms, and also clinical trial, regulatory, and digital platforms,” Stoffels says. It will be necessary to maintain these platforms to radically speed responsiveness to novel infectious disease outbreaks.

Robin Shattock, head of mucosal infection and immunity at Imperial College London, sees great promise in mRNA and self-amplifying RNA vaccine constructs well beyond SARS-CoV-2. “Essentially it is plug and play technology,” he says. “Any protein you can encode in genetic material could be plugged into the same platform and used for a vaccine approach.”

Prior to 2020, mRNA technology was seen as unproven. Now the technology’s come of age. “It’s exciting for the future because of the synthetic production of RNA. It has the potential to

### Table 2: Differences between the RV144 and HVTN 702 efficacy trials

<table>
<thead>
<tr>
<th></th>
<th>RV144</th>
<th>HVTN 702</th>
</tr>
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<tbody>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral subtype</td>
<td>AE</td>
<td>C</td>
</tr>
<tr>
<td>Viral diversity</td>
<td>Relatively homogenous</td>
<td>Highly diverse</td>
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<tr>
<td><strong>Population</strong></td>
<td></td>
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</tr>
<tr>
<td>HIV risk/incidence</td>
<td>0.28%</td>
<td>Approximately 4%</td>
</tr>
<tr>
<td>Host genetics</td>
<td>Thai</td>
<td>African</td>
</tr>
<tr>
<td><strong>Vaccine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>Aluminium hydroxide</td>
<td>MF59</td>
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<td>ALVAC inserts</td>
<td>Subtype AE</td>
<td>Subtype C</td>
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<tr>
<td></td>
<td>vCP1521</td>
<td>vCP2438</td>
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<tr>
<td>Protein boost</td>
<td>Bivalent AE/B</td>
<td>Bivalent C</td>
</tr>
<tr>
<td></td>
<td>(A244/MN)</td>
<td>(TV1 C/1086 C)</td>
</tr>
<tr>
<td>Protein dose</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td></td>
<td>(300 μg of each protein)</td>
<td>(100 μg of each protein)</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>M 0/1/3/6</td>
<td>M 0/1/3/6/12 (18)</td>
</tr>
</tbody>
</table>

be done in small modular manufacturing facilities, with an enclosed end-to-end process. If you like: manufacturing in a box,” Shattock says.

More widespread, modular manufacturing could have a profound impact on the way vaccines are made and produced. “The timelines for getting products into clinical use may become quicker. We may see more advances on the timelines for approving new vaccines. It could revolutionize the way vaccines are made through distributed manufacturing,” Shattock says.

And while mRNA gets the lion’s share of attention, viral vectors are also platforms that will become more widely applicable. IAVI currently has vaccine candidates for four pathogens that employ VSV vectors.

**Animal models**

Going into Imbokodo, Barouch’s group showed promising results in animals — using an analog for HIV in monkeys, the vaccine candidate showed 50% efficacy. Given that the trial in humans didn’t work, does that mean non-human primate studies in HIV research should be re-evaluated?

Barouch says no, but rather that the models need to be refined. “I think the protection seen in animal models is very much a function of experimental parameters, such as what dose of virus and how many challenges you do,” he says. “If you give enough challenges then you’ll lead to reduction of protection in any animal model.” He suspects there were more exposures in the Imbokodo clinical trial than what his group modeled in primates. “Animal models should be updated to include either higher-dose challenges or maybe more challenges, or to model biodiversity.”

Protection may be strongly dependent on the amount of virus clinical trial participants are exposed to. David Kaslow, Chief Scientific Officer of PATH, recently published an article in *npj vaccines* in which he discussed how the force of infection can affect vaccine efficacy. “If the force of infection in the clinical trial [Imbokodo] was low, more like Thailand, we would likely have seen a similar effect leaving us with partial efficacy,” Picker says. But, in South Africa, the country with the highest HIV incidence, the level of virus exposure is likely much, much higher, he adds.

The diversity of viruses is also much greater. Larry Corey and Maurine Miner at the Fred Hutchinson Cancer Research Center, and David Montefiori at the Duke University Medical Center — writing in the *Journal of the International AIDS Society* — distinguish between the kind of virus challenges delivered to monkeys during a study and those encountered by humans. The animals are challenged by a homogenous simian immunodeficiency virus/HIV hybrid. Humans encounter viral “swarms.” The authors argue that future non-human primate studies will need to use strain mixtures to more accurately reflect what occurs during human transmission to answer specific questions and provide better comparative strategies.

**The HIV epidemic**

While COVID-19 gripped the world in 2020, 1.5 million people became newly infected with HIV and 680,000 people died from AIDS-related illness. According to the latest statistics, 37.7 million people globally are now living with the virus. Nearly two years into the COVID-19 pandemic, more data is emerging about its effect on HIV prevention and treatment services. Because of COVID, hard-won gains made in HIV prevention are hanging precariously in the balance. A report from UNAIDS from July 2021 warns that the significant disruptions in HIV services could reverse the 23% reduction in new infections observed since 2010.

Michel Kazatchkine, former head of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and Geneva-based fellow at the Global Health Center of the Graduate Institute of International and Developmental Studies, holds hope that new ways of preventing HIV, including long-lasting injectable pre-exposure prophylaxis and the development of a functional cure, will help bring this 40-year epidemic to an end. NIAID’s Director Anthony Fauci, writing in *Nature*, thinks even a moderately effective vaccine combined with more convenient and more widely available HIV treatment and prevention could bring an end to AIDS as a major health concern. But getting there may become more and more difficult as interventions will need to prove their worth against those already in use. “We cannot go on with large Phase III trials versus placebo,” Kazatchkine says. “I see no way out of it — the days of big, randomized trials are over.”

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Michael Dumisk, based in Berlin, reports on global science, public health, and technology.
Vaccinology reaches a new peak

Stanley Plotkin discusses the greatest progress in vaccine development in more than half a century and the lingering barriers to an effective HIV vaccine.

By Kristen Jill Kresge

The first issue of *IAVI Report*, published in the summer of 1996, introduced IAVI and its mission to a broad audience of scientists, policymakers, and activists who were interested in HIV vaccine research. One of the articles in this inaugural issue was an interview with Stanley Plotkin, veteran vaccine developer, Professor Emeritus at the University of Pennsylvania, and expert advisor through his company Vaxconsult.

It is no surprise that the first editors of *IAVI Report* chose Plotkin—he’s written the textbook on vaccines. Now in its 7th edition and titled “Plotkin’s Vaccines,” it is described by Bill Gates as “an indispensable guide to the enhancement of the well-being of our world,” according to the publisher.

As IAVI and *IAVI Report* commemorate their 25th anniversary, I thought it wise to return to Plotkin and ask him to provide perspective on the vaccine field at large, and on the particular challenges of HIV vaccine development. When we recently spoke, he once again offered his sharp insights on this pesky pathogen and described why improving our understanding of mucosal immunology remains critical to developing a broadly effective HIV vaccine.

An edited version of our conversation appears below.

Back in 1996, we asked you, then as a representative of industry, what you thought were the major roadblocks to HIV vaccine development. How would you answer that question today? How has it changed in 25 years?

Well, obviously we still don’t have an HIV vaccine. And I don’t remember, of course, what I said in 1996, but I think the problems are both biologic and immunologic. In the 25 years that have passed, our knowledge on those issues has increased somewhat, but we have been unable, at this point, to demonstrate significant efficacy of any HIV vaccine candidate. There are two main reasons for that. One is that the virus mutates considerably, and the other is that we still have not identified the biological mechanism that protects against infection.

I don’t want to be too pessimistic because there are major projects that are making progress in identifying important immune responses and there has been some success in experimental animal models, but there is still no clinical efficacy. I guess it boils down to the fact that we know how to induce neutralizing antibodies, or complement-fixing antibodies, and several other types of antibodies, but we still haven’t identified the—if there is any—biological mechanism to eliminate HIV at the entry point, which for sexual transmission is the genital mucosa. And once the virus gets into the genital mucosa, it appears to be very difficult to prevent it from spreading. So, I’m not pessimistic, but for HIV there is still a way to go.

Just a few months ago the results from the Imbokodo trial showed that the Johnson & Johnson/Janssen adenovirus vector-based HIV vaccine candidate with a mosaic antigen was not effective. There was promising preclinical and early clinical data to support the development of this candidate. What do you think explains the failure of this candidate to provide protection in humans?

Well, I would be guessing, but I think that the important points are that the virus changes. As a result, what you’ve achieved in experimental animal studies may not translate into a situation in which people are exposed to all kinds of variants and you’re trying to protect them against all of them.

But there are other possibilities. If the challenge dose is quite high, once the virus obtains entry into the first cell, it can move from cell to cell without being exposed to immune factors that, in principle, should kill the virus.

Then is it really a question of inducing immunity at mucosal surfaces? Is it feasible to do that quickly enough to prevent HIV from spreading?
I wouldn’t say it’s not possible. But we still face the biologic problem of interfering with the virus at the earliest phase, when the virus is getting into an exposed cell on the genital mucosa. If you think about it, most of the vaccines we have operate by tamping down replication of the virus once it infects the mucosa and preventing that initial infection from spreading. It appears that in the case of HIV, once the virus gets into that mucosal cell, the mechanisms that we think should prevent it from spreading, apparently don’t, or at least don’t yet. I see that as a biological problem with mucosal infection.

And to some extent this also applies to COVID. I think one could say that the vaccines we have are excellent in preventing serious disease once the virus spreads to the lungs, but we are less able to prevent infection in the nasopharynx. And that is not an all or none phenomenon. The mRNA vaccines, which give very high antibody titers, can prevent infection, but they don’t always prevent infection. And many of the other vaccines don’t have much of an effect on blocking infection.

And when the amount of inoculum is higher, as is the case with the Delta variant, it is then harder to block infection.

Yes, that’s right. Which illustrates the mucosal issue I’m talking about. If somebody is exposed to 1,000 infectious units, they may be able to deal with that. But when Delta comes along with 100,000 or a million infectious units, that’s asking a lot.

Do you think it will be possible to ever induce enough of an antibody response in the mucosa to stop an HIV infection from occurring?

I don’t know that I can answer that question.

If you could, it would be helpful!

[Laughs]. I remain optimistic that an immunization regimen will be developed that will be able to prevent infection in situations in which the viral challenge dose is relatively low, and in epidemiologic situations where exposure is not constant. And, unfortunately, what that suggests to me is that we may well eventually have a measure to reduce infection in, say, gay men in developed countries. But whether we can prevent infection in a pandemic situation, such as in Africa, that’s quite a challenge. One should never be too pessimistic because there can be scientific discoveries that change the situation completely.

In the 1996 IAVI Report interview you spoke about the promise of DNA vaccines. Now we’ve seen the first nucleic acid vaccines be deployed against SARS-CoV-2. Do you foresee these platforms being applicable to other vaccine development efforts?

The 1990s, in retrospect, were a time of scientific exploration that changed the world of vaccines. In the 1990s, as you say, nucleic acid research was just beginning, both for DNA and for RNA, and for viral vectors. I remember very well at Sanofi we were testing poxvirus vectors for HIV. And although they didn’t work out, it nevertheless made the point that you could use a non-replicating viral vector to carry genes from other agents and as time went on, that became more and more feasible.

People talk about how quickly the mRNA vaccines were made but they don’t take into account the 20 years of research that went into that field before it became practical. My memory of the 1990s is that there was really a lot of excellent basic research which allowed us to do things in 2020 that were not possible before. Fortunately, for us. I would say that if you could forget about the death, destruction, and economic impact, the last two years have been the best years for vaccine research since the polio days.

Do you think the flu vaccine will be improved using the mRNA platform?

I certainly hope so! If we’re honest, we are lucky when the flu vaccine protects 50% or so of people. Although the existing flu vaccines work pretty well in children, they are only moderately effective as far as adults are concerned. Some years they’re really not terribly useful, so yes, I have great hopes for improving influenza vaccines.

What are the areas of basic research that should be prioritized now?
One point is that we need a lot more information about preventing mucosal replication. I think that is a weak point of our vaccines.

Another point is that we are always looking for neutralizing antibodies, and that’s obviously important, but, in a way, it is an artificial test. We take a measured amount of virus with a measured amount of anti-serum, and we put that together and see how much virus comes out. That doesn’t really mimic what happens in nature. My point here is that we are discovering immune functions that were not obvious or visible before — immune functions that don’t depend on this test tube neutralization but are biological means by which the body tries to deal with the invasive agents, so-called Fc-effector antibodies and cellular responses, which are not simply proliferation of cells in the presence of an antigen. My prediction, which is sort of obvious, is that we will eventually be testing many more immune responses that play a role in protection than we do now. And that will enable us to improve our vaccines.

I have been one of many that have been working on immune correlates of protection for COVID vaccines and that work has basically shown that neutralizing antibodies are an excellent correlate for protection, but as I always say when I talk about this subject, there is a hierarchy. Clearly, neutralizing antibodies are number one. But there are other things going on that add to that protection. If you have high antibodies, it doesn’t matter. But if you have low antibodies, those other functions help. The immune system has been designed to be redundant. We try to simplify things, but that doesn’t mean there aren’t other things going on that are more difficult to measure.

In 2015, Jeremy Farrar, Adel Mahmoud, and I wrote an article proposing the development of an agency that would deal with diseases that don’t have commercial prospects. Eventually that led to CEPI [the Coalition for Epidemic Preparedness Innovations], which was designed to deal with epidemics and with Disease X — that is whatever disease that would come along that we don’t know about. CEPI is now sponsoring a number of COVID vaccines, but is also still looking at the unknown, SARS-3, so to speak. I think that is also an extremely important area of research in the world of vaccines.

We’re living through a disaster but, on the positive side, I think it’s safe to predict that the knowledge that is being generated will help us deal with many other diseases.
Focus on Access

The global stakes for vaccine access

COVID-19 has made stark inequities in global access to vaccines, drugs, and diagnostics more visible and alarming than ever.

By Michael Dumiak

After nearly two years of a pandemic propelled by a novel and deadly airborne pathogen — for which vaccines were developed at astounding speed — agreements are only now in place to manufacture the new vaccines on the African continent.

On an optimistic timetable, construction will start on plants capable of manufacturing mRNA-based COVID-19 vaccines and other products in the middle of 2022. It’s not clear when actual production will start.

This comes as the world’s poorest countries struggle to obtain vaccine supply. Out of 5.5 billion doses of COVID-19 vaccines delivered, only 0.6% have gone to low-income countries. Only a quarter of African nations have enough vaccine to reach 10% of their populations. The goal of distributing two billion COVID vaccines to developing countries this year will fall short by perhaps 500 million shots. And in some countries where vaccines are available, it has proven challenging to distribute them quickly. As of now, more booster shots have been administered in high-income countries than the total number of first doses distributed to low-income countries, an imbalance drawing sharp criticism.

This was a few weeks before the new Omicron variant of SARS-CoV-2 was identified by South African scientists, causing several countries to shut down travel connections to southern African nations, with Japan and Israel both closing down all international flights.

The fight over access isn’t new, but its stark inequity was made acutely visible with the COVID-19 pandemic, which has killed 5 million people and infected 252 million. Tedros Ghebreyesus, head of the WHO, considers vaccine equity the challenge of our time. “One we are failing,” he told a ministerial meeting earlier this year.

Ensuring faster and more equitable access will require overcoming obstacles in development, production, and financing and distribution of vaccines, therapeutics, and diagnostics. These obstacles are substantial. But public health experts insist they can and must be solved, not just for COVID-19 but for long-running epidemics like tuberculosis and HIV, and for the daunting prospect of future emerging pathogens.

From sequencing the novel SARS-CoV-2 virus in January 2020 to emergency use of new vaccines less than a year later, the astounding pace and success of COVID-19 vaccine development is by now well documented. But access lags far behind the science.

Peter Hotez, dean of Baylor College of Medicine’s National School of Tropical Medicine, says vaccine access, and not just efficacy, needs to be considered from the very beginning of the vaccine development effort. For some time now Hotez has backed vaccine designs that can be used in resource-poor settings, where most of the world’s population lives.

In the crisis of the current pandemic the emphasis has been on speed and innovation, and it produced some of the most effective...
vaccines we have now: the Pfizer/BioNTech and Moderna mRNA-based COVID-19 vaccines, and the AstraZeneca/Oxford and Janssen/Johnson & Johnson adenovirus vector-based shots.

But vaccinating the world against COVID-19 requires billions of doses, and now additional booster doses on top of that. “As any engineer can tell you, with new technology there is a learning curve. We simply cannot go from zero to six or nine billion doses with mRNA and adenovirus-vectored vaccine,” Hotez says. “Innovation is great, and you can rapidly immunize millions of people with mRNA vaccines and adenovirus vaccines. But to scale it to the nine-billion level, it’s necessary to balance the portfolio with some old-school vaccines that we know we can scale up now.”

To do this, Hotez and his colleagues raised millions in private financing to fund development of their protein-based antigen, developed by the Texas Children’s Hospital Center for Vaccine Development at Baylor, for which he and Baylor microbiologist Maria Elena Bottazzi are co-directors. The vaccine is in advanced clinical trials in India, where it is known as Corbevax (the technology is already also licensed to developers in Indonesia and Bangladesh with a different name). It is a recombinant protein vaccine employing the SARS-CoV-2 spike receptor binding domain: in India the antigen is formulated in aluminum hydroxide and coupled with a Dynavax TLR-9 agonist adjuvant.

Hotez hopes this candidate will be available soon for emergency use in India and Indonesia. Baylor has already transferred the technology to Biological E, a vaccine manufacturer in Hyderabad, India, and facilities are being prepared to produce 100 million doses a month if it is authorized for emergency use, with an advance purchase of 300 million doses from the Indian government. Hotez describes this approach as a “people’s vaccine,” and says there are ongoing tech transfers in process with multiple other Asian and African countries.

Jason McLellan at the University of Texas in Austin and colleagues at the nonprofit PATH Center for Vaccine Innovation and Access have also collaborated on a pathway to a cheaper and more easily produced and distributed COVID-19 vaccine. This one can be manufactured in chicken eggs, similarly to the way flu shots are made and using the same manufacturing facilities. This candidate employs McClellan’s technique for stabilizing the SARS-CoV-2 spike protein antigen along with a viral vector used by researchers at the Icahn School of Medicine at Mount Sinai for multiplying the antigen in chicken eggs. It’s been reported that a single egg could yield five to 10 doses of COVID-19 vaccine. Clinical safety trials concluded successfully in September and Phase II trials are now ongoing.

Another protein-based candidate from the U.S. company Novavax is already in use in Indonesia and the Philippines and is currently under review by European regulators. This candidate is reported to have 89.7% efficacy against COVID-19, with higher rates against the original virus strain.

Mark Dybul, chief executive of Enochian BioSciences, former director of the Global Fund to Fight AIDS, Tuberculosis and Malaria, and an IAVI board member, says additional vaccines are one way to ensure broader access and will be needed in the future, both for SARS-CoV-2 variants and emerging pathogens. But he doesn’t see why new technologies — like the mRNA platform — can’t be instead made to work more broadly around the world.

“You could do protein-based vaccines, but why?” he questions, when the mRNA technologies offer flexibility and are highly effective. “We’re going to need new vaccines anyway, so why not invest in those systems. Then we’ll have them available for the next virus.”

Dybul says vaccine production should occur “all over the world in a decentralized way,” even for mRNA vaccines, by using manufacturing facilities with modular closed-system bioreactors. These employ single-use components for sterile processing, thereby saving on fixed costs and providing security against contamination.

A recent New York Times report suggests there are 10 potential mRNA manufacturers in low- and middle-income countries, none of which are ready to start producing vaccine right now. And timing is an issue.

COVID-19 continues to circulate unabated in large numbers of unvaccinated people in low- and middle-income countries (LMICs): this is at a terrible human cost, but also gives the virus more of a chance to evolve, giving rise to new variants. Currently more than 303 million doses have been dis-
tributed from wealthier countries to LMICs, with the U.S. alone pledging to buy and donate another 1.1 billion mRNA shots. They are starting to ship but the logistics are daunting and the ultra-cold chain required for storing mRNA-based shots is a big challenge. China says it will donate 600 million doses of its vaccines, with another 400 million to be made in joint production between Chinese companies and African countries.

“Here in the United States and in Europe the discourse is primarily focused on giving additional boosts to people who are fully vaccinated. While that probably is beneficial, when 7% of Africa is vaccinated, the health disparities are stark,” says Dan Barouch, who directs a virology and vaccine research program at the Harvard Medical School’s Beth Israel Deaconness Medical Center and at the Ragon Institute of Massachusetts General Hospital, MIT and Harvard. “We need more vaccines to go to Africa and some vaccine platforms are just going to be better at it than others. I think the vectors and the proteins are going to be much better at getting to remote areas in Africa because they don’t require a frozen cold chain.”

As SARS-CoV-2 emerged, the Coalition for Emerging Pandemic Innovations (CEPI) divided vaccine development in the face of the pandemic into four quadrants: speed, cost, scalability, and stability. “It’s fair to say you cannot do everything quickly,” CEPI’s head of vaccine research and development, Melanie Saville, said in describing these choices at the Berlin meeting. She said that when the COVID-19 pandemic began, there wasn’t time to think about thermal stability and related implications of rollout, par-

### COVID-19 vaccine access

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<th>High-income countries: 1 in 2 people, or 64.94% have been vaccinated with at least one dose as of Dec. 1, 2021</th>
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<th>Low-income countries: 1 in 12 people, or 8.06% have been vaccinated with at least one dose as of Dec. 1, 2021</th>
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Source: World Health Organization Coronavirus Dashboard
CEPI, which launched in the wake of the West African Ebola epidemic, is charged with forward thinking as part of its remit. Even while grappling with the ongoing waves of COVID-19, it has an eye to a potentially scary future. The organization is now promoting a 100-day target plan for novel vaccine development in future health emergencies as part of its ongoing US$3.5 billion funding drive.

The idea is to compress timelines and enable an effective response in under 100 days to a novel pathogen — the next Disease X — and to rank vaccine prototypes in terms of cost, thermostability, and manufacturing ease to determine which of these can be built quickly and deployed broadly when need arises. It now also explicitly links research and access. Making sure vaccines and other countermeasures are developed that meet the needs of all segments, of all populations, in all geographies, will now be part of the organization’s core mission.

But that won’t be easy. Financing the purchase and distribution of these vaccines will likely remain an issue long after COVID-19. Many lessons will likely be learned from the COVAX vaccine distribution facility that is meant to be the global pool for purchasing and distributing SARS-CoV-2 vaccines. COVAX was the brainchild of CEPI chief executive Richard Hatchett and Seth Berkley, the head of GAVI, the Vaccine Alliance (and former head of IAVI; see p. 4).

COVAX is administered by GAVI, CEPI, and the WHO, with support in supply and distribution from UNICEF (the United Nations Children’s Fund). The idea was to pool COVID-19 vaccine purchases under a single umbrella where high-income countries would funnel at least part of their vaccine purchases. That would give COVAX the means to negotiate bulk vaccine purchases from pharma manufacturers: participating payers in COVAX would gain some leverage in bidding for doses, while another arm of COVAX would subsidize shots and funnel them to 92 LMICs with the goal of vaccinating 20% of those populations by the end of 2021.

It has not been a smooth ride. Wealthy countries were able to pre-order vaccine doses and pay for them, at risk, long before anyone knew if or how effective the different vaccines would prove to be. Those orders were vast. In some cases, countries purchased three times the number of doses they would need to vaccinate their entire population. COVAX funding also came in slowly as events accelerated.

Like Hotez hopes to with the Baylor vaccine, COVAX turned to Indian manufacturers to secure large amounts of future supply: a move that looked to be logical, as India has vast vaccine manufacturing capabilities, and the country was doing better in weathering the pandemic in early 2021. Until suddenly it was not. When India succumbed to a terrible pandemic wave in April, New Delhi banned exports of shots in order to cope with the virus at home. This put a huge dent in COVAX supply that it is only now recovering from. Even poorer nations scrambled to set up bilateral deals outside COVAX; an arrangement with China is one of the first steps Ecuador took to being one of the most vaccinated nations in the region.

Public health experts agree that COVAX — or something like it — is vital to ensure equitable and timely access to public health interventions, while at the same time, there are glaring flaws in the results produced by the current system. It has a chorus of critics. Financing and producing global vaccines were prime subjects at the recent special World Health Assembly, weighted by heavy disapproval of donor-funded financing — even though there’s no clear vision for alternatives. Another line of criticism is that when massive public monies underwrite risky initial vaccine development, those funds should come with contract-bound measures to ensure better access.

A bevy of voices are still calling for intellectual property to be shared and patents and licenses to be lifted on COVID-19 vaccine technologies. But even if the strings on mRNA vaccines were as free as Linux’s systems or Hotez’s proteins, manufacturing would remain a vexing issue. It takes more than a free-use recipe to churn out vaccine in bulk — manufacturing at industrial scale is incredibly complex.

At the Berlin meeting, Rino Rappuoli, GlaxoSmithKline’s chief scientist and head of external research and development, was thinking big, outlining robotic workstations in remote
parts of the world for vaccine assembly. For now, nascent production facilities in Senegal and Rwanda may be a start.

Germany’s BioNTech, developer of the antigen and mRNA construction used in the COVID-19 vaccine produced along with Pfizer, inked agreements with the Rwandan government and Senegal’s Institute Pasteur de Dakar to construct and eventually handover turnkey manufacturing lines for mRNA-based vaccine doses. BioNTech will staff, own, and operate the facility to start with, but plans to eventually transfer the capacities and know-how to local partners. The company is also in talks to expand its partnership with Cape Town-based Biovac, which is part of the Pfizer-BioNTech COVID-19 vaccine manufacturing network.

Some are critical of the BioNTech agreements with Rwanda and Senegal because they say intellectual property issues will persist even if the buildings are in lower-income nations. But Dybul is cheered by this type of investment because it’s not just based on a single vaccine, but for the mRNA technologies themselves. “We tend to invest only in the product, not in the production technology,” Dybul says. But there is potential to create technology hubs in Africa, Asia, and Latin America. “It would totally disrupt our current sclerotic approach to research and development.”

And it should be possible to make these products at lower cost, too. Dybul says there’s much to learn from experience in the HIV epidemic. Access issues still loom large there, but the global situation is dramatically improved. “We’re actually at affordable products. But it took many years to get there,” he says. “I don’t know how sustainable it is because it’s heavily dependent on external resources. But we do have widespread access. It’s not universal, but it’s pretty available.”

A turning point in the HIV pandemic came with low-cost antiretroviral treatment, much of which came courtesy of large-scale generic manufacturing. As of now this seems one of the promising and proven paths to access.

Yet even the HIV field is likely to keep facing obstacles to access. Emphasis in the future may shift to newer technologies and preventive, where access pathways are less clear. “We don’t have widespread access to PrEP [pre-exposure prophylaxis]. We certainly wouldn’t have widespread access to novel technologies,” Dybul says. “There are going to be new approaches, including cell and gene-based therapies. If we start working on it now, by the time we have them we could actually already have R&D and production capacity.”

Ayesha Sitlani, associate vice president of antibody strategy at IAVI, is encouraged by advances in monoclonal antibody research and the prospect of using them as an HIV prevention approach, work IAVI is deeply involved in. And she and others at IAVI are planning for access to these potential products now, long before they’ve been proven to work. “The same access principles of acceptability, price, and the health care systems that allow delivery — all of those aspects need to be front and center of our minds,” she says.

These problems won’t be solved quickly. But global access to vaccines, diagnostics, and therapeutics is definitely at the fore in a way it was not before COVID-19. Pharmaceutical companies are also paying attention: after Merck and Pfizer recently developed oral antiviral drugs against COVID-19 they took steps to ensure equitable access (even though wealthier countries have already also put in advance orders for the pills). Ahead of authorization they are granting royalty-free licenses to the UN’s Medicines Patent Pool (MPP), a United Nations-backed agency which issues sub-licenses to certified generic manufacturers to make and market their own versions. The MPP has agreements with several HIV antiretroviral patent-holders, as well as agreements pertaining to a tuberculosis drug and hepatitis C antivirals.

Patent and technology-sharing platforms aren’t always the answer, however, as shown by the WHO’s COVID Technology Access Pool (C-TAP). Launched in May 2020 to foster open sharing of COVID-19 product-making know-how and data, no vaccine developers participated in it.

Industry, research organizations, and public-health bodies are also considering other strategies to improve access, including tiered pricing structures. None of these approaches on their own will likely be the answer, but as the COVID-19 pandemic grinds on, and new variants such as Omicron continue to emerge, the world is being forced to reconsider the consequences of inequitable distribution of vaccines and therapies.

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