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Original Article/Research

The repeated setbacks of HIV vaccine development laid the groundwork for SARS-CoV-2 vaccines

Jeffrey E. Harris

Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA
Eisner Health, Los Angeles, CA 90015, USA



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ABSTRACT

The decades-long effort to produce a workable HIV vaccine has hardly been a waste of public and private resources. To the contrary, the scientific know-how acquired along the way has served as the critical foundation for the development of vaccines against the novel, pandemic SARS-CoV-2 virus. We retell the real-world story of HIV vaccine research – with all its false leads and missteps – in a way that sheds light on the current state of the art of antiviral vaccines. We find that HIV-related R&D had more than a general spillover effect. In fact, the repeated failures of phase 2 and 3 clinical trials of HIV vaccine candidates have served as a critical stimulus to the development of successful vaccine technologies today. We rebut the counterargument that HIV vaccine development has been no more than a blind alley, and that recently developed vaccines against COVID-19 are really descendants of successful vaccines against Ebola, MERS, and SARS. These successful vaccines likewise owe much to the vicissitudes of HIV vaccine development. We then discuss how the failures of HIV vaccine development have taught us how adapt SARS-CoV-2 vaccines to immune escape from emerging variants. Finally, we inquire whether recent advances in the development of vaccines against SARS-CoV-2 might in turn further the development of an HIV vaccine - what we describe as a reverse spillover effect.

Introduction

Scientists and policymakers have been fretting for decades about our failure to develop an effective, workable vaccine against human immunodeficiency virus (HIV). The basic science is extraordinarily complex, many researchers have rightly noted [1]. Antiretroviral drugs were the path of least resistance, others have cogently observed [2].

The principal conclusion of this review article is that the decades-long effort to produce a workable HIV vaccine has hardly been a failure. To the contrary, the scientific know-how acquired along the way has served as the critical foundation for the development of vaccines against the novel, pandemic SARS-CoV-2 virus. While it is already widely acknowledged that HIV-related research has had substantial spillover effects [3,4], our thesis is more pointed. We find that the repeated failures of HIV vaccine clinical trials have served as a critical stimulus to the development of successful vaccine technologies today.

Our methodology is primarily historical. We retell the story of HIV vaccine research in a way that sheds light on the current state of the art of antiviral vaccines. The manifold scientific reasons why it is so difficult to engineer an HIV vaccine were simply unknown when the U.S.

Secretary of Health and Human Services announced in a famed April 1984 press conference that a preventive vaccine would be ready for testing within two years [5,6]. As researchers encountered a succession of unanticipated obstacles, they tried out new models of vaccine delivery that ultimately failed to overcome HIV but turned out to have wide application to the control of COVID-19 and other infectious diseases.

Learning by doing, knowledge externalities

On February 4, 2020, the U.S. National Institute of Allergy and Infectious Diseases announced that it was halting its clinical trial of yet another candidate vaccine against HIV [7]. The trial, called Uhambo, tested a vaccine based on canarypox, a live bird virus that can infect human cells without causing disease. The canarypox virus had been genetically altered to induce infected human cells to manufacture several key proteins of the HIV virus [8]. These proteins, it was hoped, would then stimulate the vaccine recipient's immune system to protect against future infection by HIV.

The Uhambo trial had been conducted in 14 sites across South Africa, enrolling over 5,400 HIV-negative participants 18–35 years old. More

E-mail address: jeffrey@mit.edu.

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than half-way through the study, researchers had unsealed the data to find that the intervention and control groups had about the same number of new cases of HIV. “While we are obviously disappointed in the results,” commented Winnie Byanyima, Executive Director of UNAIDS, “important science has been learned that can be carried forward to future trials.” [9]

Byanyima’s comment was precisely on target. Large-scale, complex scientific and technological research enterprises, including the task of developing and testing a vaccine against HIV, involve what economists call *learning by doing* [10]. It is not simply that the research team becomes more efficient at producing the candidate vaccine or carrying out a trial on human subjects. Researchers gain insights from their mistakes. The suspension of Uhambo was just the latest in a decades-long series of failures to find a vaccine against HIV and, in the process, to learn by trying, failing, rethinking, and trying again (Table 1).

A great many of the candidate HIV vaccines that have been tested over the last three decades were originally developed by private firms and protected by patents. The private firms holding these patents have been competing for a very valuable prize. If a candidate vaccine turns out to be effective, its patent holder wins big. But when the candidate vaccine fails, all the competitors in the vaccine field – not just the patent holder – learn from the mishap. The patent holder can reap the rewards of success, but it cannot fully capture the gains from its mistakes. We thus have a positive externality, specifically a *knowledge spillover* [19, 20]. An HIV vaccine trial ending in failure may still have an extraordinarily large social benefit even if its private benefit turns out to be vanishingly small, or even negative.

The conventional approaches were too risky

Before the HIV epidemic of the 1980s, vaccines were made primarily through two conventional methods. First, *inactivated whole virus vaccines* were produced by heat or chemical treatment of the infectious organism (Fig. 1). The Salk polio vaccine was produced by treating the poliovirus with formaldehyde [21], a component of embalming fluid. Second, *live attenuated virus vaccines* were produced by repeatedly passing the infectious organism through animals, cell lines, or unfavorable conditions in order to induce mutations that would render it harmless but still infectious (Fig. 2). The original measles vaccine was made by passing the measles virus through cell cultures of human organs and chick embryos, as well as embryonated hen’s eggs [22]. It wasn’t clearly known why these two approaches worked, but they were enormously successful in combating not only polio and measles, but also rabies, mumps and rubella [23,24]. Still, when it came to the novel problem of combating a virus that lay dormant in an infected person’s body for years before it emerged as deadly AIDS, these conventional technologies were considered too risky.

Table 1
Key Clinical Trials of HIV Vaccines

Trial	Protocol
AIDSVAX B/B [11] ^a	gp120 purified protein derived from HIV subtype B
AIDSVAX B/E [12] ^a	gp120 purified protein derived from HIV subtypes B & E
Merck STEP Trial [13] ^a	Ad5-based viral vector vaccine
RV144 ^b [14]	Canarypox vector (ALVAC) + gp120 from AIDSVAX B/E
HVTN 505 [15] ^a	Plasmid DNA + Ad5-based viral vector
Uhambo (HVTN 702) [7, 16] ^a	Canarypox vector (ALVAC) + gp120 purified protein
Imbokodo (HVTN 705) [17] ^a	Ad25-based viral vector + gp140 purified protein
Mosaico (HVTN 706) [18] ^c	Ad25-based viral vector + gp140 purified protein

^a Failed to provide protection against HIV.

^b Provided 31.2% protection against HIV in a modified intent-to-treat analysis.

^c In progress.

The inactivated virus vaccine model was frowned upon chiefly because there was a material risk that the virus would not be completely inactivated [31]. In fact, inactivated whole virus vaccine candidates that advanced to the point of evaluation in human subjects have been rare. One such vaccine candidate named REMUNE, developed by a biotech company cofounded by Jonas Salk in 1986, was ultimately abandoned in 2007, apparently because the chemical treatment required for inactivation also stripped the virus of a key molecule that stimulated immunity [32]. In a subsequent attempt to produce a workable whole virus vaccine, HIV was first genetically modified to knock out some of the genes responsible for its infectivity and then chemically inactivated. The vaccine candidate, named SAV001 developed by SumaGen Canada, a member of the Seoul-based Curo Group [33], was evaluated in a phase 1 human clinical trial in 2013 [34], but has not advanced further.

Serious safety concerns likewise surrounded the application of the live attenuated virus model to the development of an HIV vaccine [35]. At least early on, it wasn’t known what mutation was responsible for rendering the virus harmless. If the virus had been attenuated as a result of an unknown mutation, there was a genuine possibility that it could revert to its more virulent form as a result of a back mutation, or perhaps a separate compensatory mutation [36]. Added to this concern was the possibility that supposedly attenuated viruses might still cause disease in patients whose immune system had been weakened by HIV. Finally, there was the concern that the attenuated virus could recombine with a virulent, wild form of HIV.

HIV was different

Cellular immunity – not just humoral immunity – was critical

Humans and other animals have evolved a dual, partly complementary and partly redundant system of defenses against noxious infectious agents [37]. Under *humoral immunity*, the defending animal produces antibodies that claw onto and neutralize molecules called antigens. Under *cellular immunity*, a specialized army of cells, including certain white blood cells called killer lymphocytes, work in concert to destroy the offender. The distinct roles of humoral and cellular immunity are especially important in the host’s defenses against latent viruses such as varicella zoster virus (VZV). Both the humoral and cellular systems are involved in the initial response to chickenpox caused by a VZV infection. A shingles outbreak occurs when cellular immunity is later weakened [38].

From the start of the HIV epidemic, there was growing evidence that the host’s defenses against the virus were especially dependent on cellular immunity. As early as 1985, it was known that HIV stimulated the development of neutralizing antibodies in most infected people, who then became “HIV-positive,” but that those antibodies alone were insufficient to confer protection against disease [39,40]. When an individual was initially infected, it was found, the killer lymphocytes – not the antibodies – were responsible for tamping down the spread of the virus [41–44]. In fact, progression of HIV infection to AIDS was associated with escape from killer lymphocyte control [45]. Studies of individuals called elite controllers, who were chronically infected but never seemed to progress to AIDS, even without treatment, confirmed they were shielded by their cellular immune system [46,47].

HIV mutated rapidly

Viruses are microscopic organisms consisting of a nucleic acid – either DNA or RNA – surrounded by a protein shell. Viruses are parasites. They cannot reproduce on their own. Instead, they infect host cells and then use the infected cell’s machinery to produce more viruses.

While both SARS-CoV-2 and HIV are RNA viruses, they act very differently once they have infected a host cell. SARS-CoV-2, like other coronaviruses, uses the genetic instructions in its viral RNA to directly make copies of itself in the host cell cytoplasm. HIV, on the other hand,

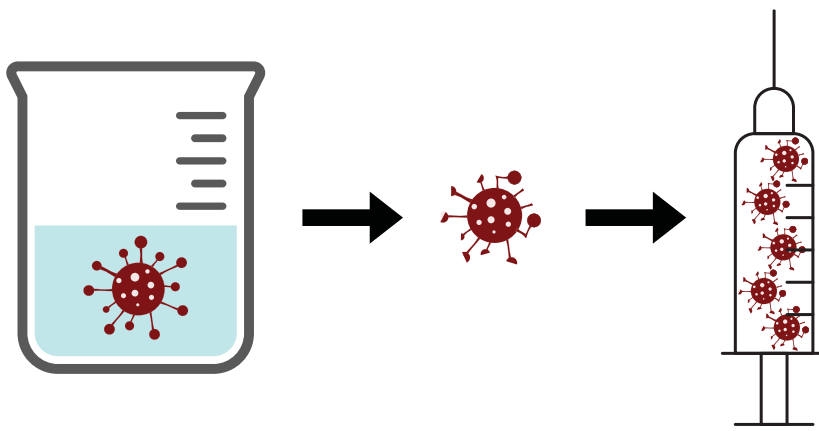


Fig. 1. Inactivated Whole Virus Vaccine. The virus is chemically treated (left) so that it is unable to infect host cells (center) but can still stimulate an immune response when injected (right) into the recipient. Inactivated virus vaccines against SARS-CoV-2, including those manufactured by Sinovac [25], Sinopharm [26], and Bharat [27], are produced by treating the virus with beta propiolactone (BPL). Because the inactivated virus cannot by itself infect cells and thus stimulate cellular immunity, inactivated virus vaccines need to be administered with a mixture of aluminum salts called an adjuvant [28,29]. All figure credits: the author.

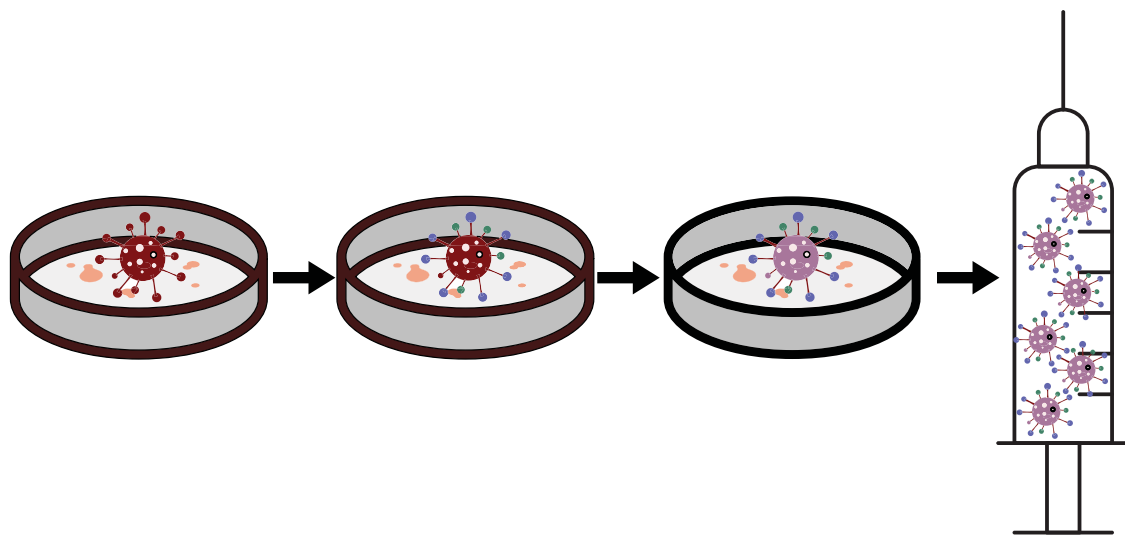


Fig. 2. Live Attenuated Virus Vaccine. The virus is repeatedly passed through unfavorable conditions in order to induce mutations that render it harmless but still infectious. Currently, hepatitis A vaccine is available in both inactivate virus and live attenuated virus forms [30]. As of February 15, 2022, two live attenuated virus vaccine candidates against SARS-CoV-2 were in phase 1 or 2 clinical trials, but none was currently marketed. See Table 2 below.

relies upon a more roundabout process to convert its viral RNA back to viral DNA, which then gets imported into the host cell nucleus and integrated into the host's own DNA, where it can remain latent for years [48]. This roundabout process is extremely prone to error and thus results in extraordinarily high rates of viral mutation.

We are by now accustomed to the fact that SARS-CoV-2 undergoes mutation, and that these mutations can result in the emergence of new viral variants [49]. We are likewise accustomed to the mutation-induced variations of influenza virus strains that require repeated seasonal flu vaccinations [50]. But the *mutability* of HIV turned out to be an order of magnitude greater – so much greater that HIV's genetic signature varied significantly not only across infected individuals, but also over the course of infection within the same individual.

In what later became known as the transmitted founder effect, a single virus was almost always found to be involved in the initial transmission of an HIV infection from one person to another [51]. But within months, the transmitted founder was replaced by mutated viruses that did not react to antibodies developed by the infected person and thus might escape humoral immune control [52]. By one estimate, the genetic diversity of HIV within a single infected patient exceeded the worldwide diversity of influenza virus during an entire season [53].

HIV's massive sugar-coated shield

In addition to the basic protein shell encasing the inner nucleic acid, many viruses have an extra envelope containing glycoproteins, which are proteins coated with sugary molecules called glycans. Among these enveloped viruses are Ebola, hepatitis C, the Epstein-Barr virus, the coronaviruses SARS and SARS-CoV-2, and HIV. In each virus, one of these glycoproteins functions as the key to unlock the hatch on the host cell membrane and thus allow the virus to invade the cell. But the viral envelope also contains a multitude of other glycans that help the virus evade the host's humoral immune system.

In the Ebola virus, for example, these other glycans serve as decoys, diverting the host's antibodies away from the key glycoprotein that causes disease [54]. The glycans in the envelope of SARS-CoV-2 shield about 40 percent of virus' protein surface, not enough to keep antibodies from clawing onto the spike glycoprotein that we have come to recognize as the virus' key to invading host cells [55]. The glycoprotein envelope of HIV, by contrast, was loaded with far more glycans than that of any other enveloped virus, making up about half of the weight of the entire virus particle [56]. HIV's *glycan shield*, researchers learned, seemed to be constantly evolving as the virus repeatedly mutated [57].

A successful vaccine may not mimic the natural immune response

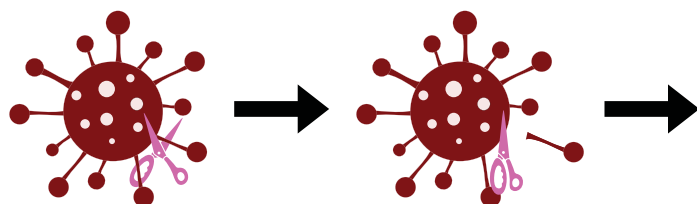
Under the conventional, pre-HIV model of vaccination, the main strategy was to mimic the natural process of acquiring immune protection against the infectious agent. If contracting an infection naturally protected someone against getting it again, then the idea was to develop a vaccine that would make the blood of the vaccine recipient look like the convalescent serum of a recovered individual. HIV rendered this classical idea meaningless. The problem was that we didn't – and still don't – have a crystal-clear notion of what it means to naturally recover, and thus become naturally immune, to HIV [58].

As HIV vaccine researchers began to work on the most effective combination of stimulants to both humoral and cellular immunity, a novel reevaluation of the basic paradigm was in order. Protection and natural recovery from infection may be different [37,59]. That could mean, for example, that a sufficiently large stimulus to humoral immunity could confer protection even though the levels of antibodies seen in naturally infected individuals didn't appear to be sufficient. The same could apply to a sufficiently large stimulus to cellular immunity, much larger than among people naturally infected by HIV.

gp120 and the AIDSVAX vaccines

Through detailed analysis of HIV's molecular structure, researchers determined that the key molecule in the virus' envelope unlocking host cell membranes was a glycoprotein named gp120. This discovery led the way to a new model for potentially achieving immunity. Instead of using a whole virus to stimulate an immune response – as in the case of inactivated and live attenuated viruses – the approach would be to make a vaccine out of pure gp120. The goal was to artificially stimulate a sufficiently strong humoral antibody response to the pure glycoprotein molecule, even if that sort of response did not occur during natural infection (Fig. 3).

Two vaccine candidates adhering to this new model of a *purified viral protein vaccine* advanced to the point where they were evaluated in large clinical trials on volunteer, HIV-negative human subjects. Both were produced by VaxGen, a relatively small U.S. biotechnology company spun off from the larger firm Genentech in 1995. One of the candidate vaccines was AIDSVAX B/B, based upon the purified form of gp120 encountered in HIV subtype B, which circulated in countries where man-to-man sex and the sharing of injection equipment were the main routes of transmission. The other candidate was AIDSVAX B/E, based on purified forms of gp120 seen in subtype B and in a hybrid-viral subtype circulating in Southeast Asia, where heterosexual transmission was more prevalent. A US\$ 122 million joint venture with South Korean investors to manufacture more than 200 million doses of AIDSVAX vaccines annually was in the works [60].



Why AIDSVAX failed: immune escape

Unfortunately, AIDSVAX B/B failed to curb HIV in a study of over 5,400 volunteers in the U.S and the Netherlands [11], while AIDSVAX B/E performed no better in a study of over 2,500 injection drug users in Bangkok, Thailand [12]. The failures of these two candidate vaccines became the focus of a substantial research effort. Both vaccines did indeed stimulate a humoral response against gp120, but that alone did not offer protection against infection [67].

Researchers acquired a growing appreciation of the phenomenon of *immune escape* [68]. As we enter the third year of the COVID-19 pandemic, we have become keenly aware that mutations of SARS-CoV-2 can result in new variants that at least partially evade the immune responses induced by vaccines or naturally acquired infection [69]. By the early 1990s, researchers were already aware that, as a result of mutation, neutralizing antibodies against one isolated sample of HIV did not necessarily cross-neutralize other isolated samples [70]. They recognized that HIV could escape antibody neutralization by repeatedly mutating even within the same infected individual [71]. A key takeaway from the AIDSVAX failures was that immune escape was not simply the means by which the virus overcame an individual's weak natural antibody response, but it was going to be a critical impediment to effective vaccine development.

Reanalysis of the AIDSVAX data offered some evidence of a correlation between the protective effect and the cellular immune response to the vaccine, but the results were inconclusive [72]. Still, the findings brought home the possible key role of cellular immunity in the prevention of HIV infection. The idea was that an effective HIV vaccine would differ fundamentally from the smallpox vaccine, which generated enough antibodies to block viral entry entirely – what we now call *sterilizing immunity*. Instead, transient infection would be permitted, but the virus would be cleared by the cellular immune system – what we now call *infection-permissive immunity* [73]. Having lived through the Omicron wave of SARS-CoV-2, we are now acutely aware that the cellular immune response to vaccines may help stave off the severe consequences of COVID-19 without blocking acute infection [74]. Back then, however, it was no more than a hypothesis.

Live viral vectors become the new model

The STEP trial of the Ad5 viral vector

In the face of the failure of the AIDSVAX candidate vaccines to stimulate adequate humoral immunity against the key molecule gp120, and with growing evidence of the role played by cellular immunity in the defense against HIV infection, vaccine researchers turned to radically different models for conveying the immune stimulus [75].

During the 1980s, a research team had managed to genetically

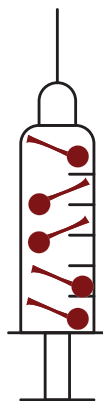


Fig. 3. Purified viral protein vaccine. A protein on the outer coat of the virus that stimulates the immune response is isolated (left and center), and the purified protein is then injected into the vaccine recipient (right). The schematic omits an alternative process of producing the purified protein, known as recombinant technology, which involves identification of the viral genome that codes for the protein and then transferring the genetic code to a bacterial or mammalian cell that serves as a biological factory for producing the protein. The AIDSVAX B/B [11] and AIDSVAX B/E [12] trials of purified forms of gp120 failed to prevent HIV. Purified protein vaccines against SARS-CoV-2 in current use include those produced by Anhui Zhifei Longcom Biopharmaceutical [61] and Vektor State Research Center of Virology and Biotechnology [62,63]. Other vaccine candidates derived from a purified form of the SARS-CoV-2 glycoprotein, developed by Novavax [64,65] and by Sanofi and GSK [66], have demonstrated efficacy in phase 3 clinical trials and are seeking regulatory approval.

engineer a live smallpox virus to produce a key protein from the surface of another virus – the hepatitis B virus. Chimpanzees infected with this modified smallpox virus turned out to be immune against hepatitis B [76]. Of course, no one contemplated infecting a human being with smallpox in order to immunize him against hepatitis B. But the finding raised the possibility that a benign virus, once modified, could act as a live vector to produce immunogenic proteins from HIV (Fig. 4).

Efforts focused on a common-cold virus called adenovirus 5 (or Ad5) as a potential live vector [81–84]. Evidence had accumulated, in particular, that a genetically engineered version of Ad5, once it naturally infected the cells of the vaccine recipient, could activate its newly acquired genes to boost anti-HIV cellular immunity [85].

In the STEP vaccine trial, the pharmaceutical manufacturer Merck made a major, multimillion-dollar investment to test this concept [60]. Almost 3,000 participants were recruited from 34 sites where subtype B was prevalent, including Australia, Brazil, Canada, the Dominican Republic, Haiti, Jamaica, Peru, Puerto Rico and the United States. Participants were given one injection with each of three Ad5 viruses modified to contain three different HIV genes.

Unfortunately, Merck's Ad5-based vaccine did not fully live up to expectations. While the vaccine stimulated cellular immunity [86], it showed no reduction in HIV incidence compared to a placebo vaccine [13]. What's more, a participant's prior immunity to the Ad5 virus turned out to at least double the risk that he would come down with HIV during the trial [13]. As a result, the Phambili trial of the same vaccine in South Africa was cancelled [87–89], while PAVE-100, another Ad5-based trial proposed for Africa and the Caribbean was put on hold [90].

There were two competing explanations for the failure of Merck's STEP vaccine. One was that the whole concept of using a virus vector was flawed. The other was that adenovirus 5 simply wasn't the right vector. Perhaps vaccine recipients preferentially developed antibodies against the native proteins of Ad5, and not just against the artificial HIV proteins inserted into the vector's genetic code [85]. While Ad5 had been engineered to infect the host cells of the vaccine recipient without itself multiplying [91], even this so-called replication-defective adenovirus 5 still stimulated a strong immune reaction in humans. In fact, a

significant proportion of participants in the Merck STEP study already had antibodies to Ad5.

The RV144 trial of a combination vaccine

To help sort out why the Merck STEP vaccine failed, the RV144 trial, conducted by the U.S. Military HIV Research Program, tested a *combination vaccine* on over 16,400 supposedly HIV-negative volunteers in Thailand [14]. The *primer* vaccine, based on a canarypox viral vector, a proprietary product acquired by Sanofi Pasteur named ALVAC, was administered at 0, 4, 12 and 24 weeks. In addition, two *booster* doses of AIDSVAX B/E were administered at 12 and 24 weeks. Even if this new vaccine protocol were to have commercial value, it would come too late for VaxGen's stockholders, as the company had negotiated the rights to AIDSVAX to a nonprofit foundation in 2008.

In a December 2009 intent-to-treat analysis of the RV144 data – which included all participants – scientists reported a statistically insignificant “trend” toward HIV prevention with an estimated efficacy of 26.4%. The findings looked more promising (up to 31.2%) when the researchers excluded 7 participants who were discovered to be already HIV-positive at the time they were enrolled in the trial, or when they analyzed only those participants in the intervention group who received all vaccine doses [14]. Still, the problem was that an efficacy of about 31 percent simply wasn't enough to make the vaccine realistically useful for HIV prevention.

Waning efficacy and extra booster doses

A leading explanation for the weak protection offered by RV144 was that the canarypox-based primer and AIDSVAX-based booster, administered together during the first 6 months of the trial, were inadequate to sustain a strong immune response over 3.5 years of follow-up. Post-hoc analysis of the trial data indicated that regimen had an initial efficacy of about 60% during the first year but waned rapidly during the next two years [14,92,93].

To explore that possibility, a public-private collaborative team called the Pox-Protein Public-Private Partnership (or P5) initiated Uhambo in

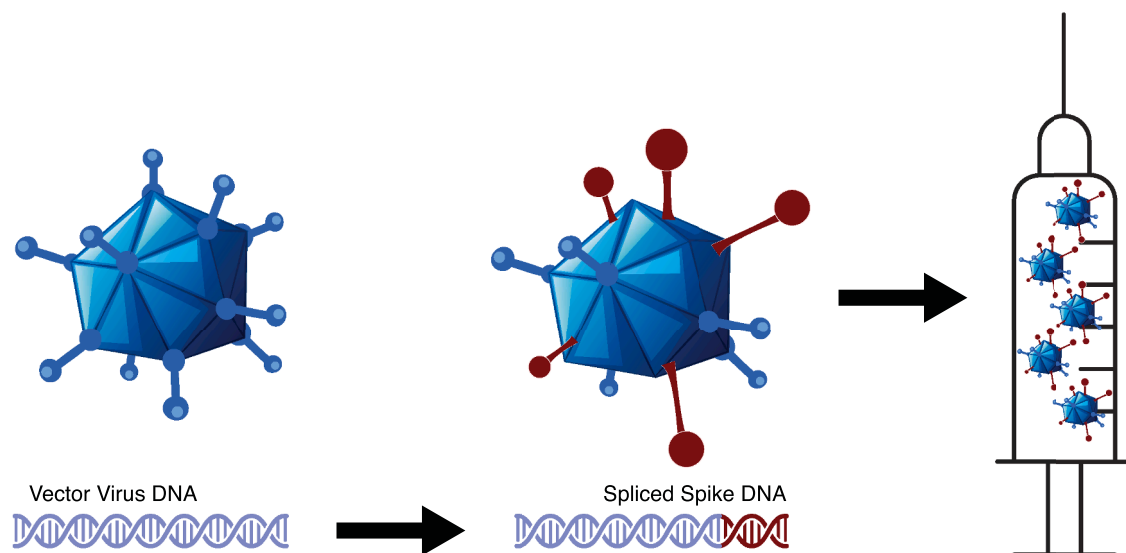


Fig. 4. Viral vector vaccine. The DNA from a benign virus such as adenovirus (left) is spliced together with DNA coding for the spike protein of the offending virus (center). The genetically modified, live infectious virus, when injected into the vaccine recipient (right), expresses the spike protein on its surface and thus stimulates immunity against the offending virus. The Merck STEP trial, which tested a combination of three Ad5-based viruses modified to express HIV genes *gag*, *pol* and *nef*, respectively, failed to prevent HIV infection [13]. Currently marketed viral vector vaccines against COVID-19 include those developed by Janssen (based on Ad26) [77,78] and AstraZeneca and Oxford University (based on Ad5) [79]. Gem-COVID-Vac/Sputnik V, developed by Gamalaya Research Institute, is based upon a priming dose with an Ad26 vector and a booster dose with an Ad5 vector [29,80].

2016, using the combination of the canarypox ALVAC primer from Sanofi Pasteur at weeks 0 and 4, along with three booster doses at weeks 24, 24 and 52 of a different purified form of gp120 from GlaxoSmithKline (GSK) adapted to HIV subtype C, which is more prevalent in South Africa [16]. We already know that Uhambo was called off in February 2020 [7,9].

Uhambo, however, was not the only variation of the vector-based prime-boost strategy designed to extend the partially successful results of RV144 [90]. An alternative strategy was to combine immune-stimulating antigens from a variety of subtypes of HIV within the same viral vector. The Imbokodo trial in women (HVTN 705), sponsored by Janssen in collaboration with a consortium of global partners, used an adenovirus 26 vector encoding proteins from a *mosaic* of different HIV subtypes in a series of four primer doses 6 months apart, along with purified gp140, another key protein on HIV's envelope, as booster doses 12 months apart [17]. In August 2021, Imbokodo was discontinued when the vaccinated and placebo groups showed no significant difference in HIV rates during 24 months of follow-up [94]. The Mosaico trial in men (HVTN 706), also sponsored by a Janssen-led consortium and still in progress, is relying up the same vector-based primer with a different gp120-based booster [18].

Nucleic acid vaccines

The fabrication of vector-based vaccines entailed multiple laborious steps: extracting the critical sequences of RNA from key HIV genes, then converting these RNA sequences into DNA sequences, and then inserting these DNA sequences into the genome of a DNA-based vector virus (Fig. 4). Would it be more efficient to copy the key HIV gene sequences into *messenger RNA* (or mRNA), the form of RNA that cells naturally use to crank out multiple copies of proteins? If not mRNA, then why not at least work with the corresponding sequences of DNA?

The use of freestanding nucleic acids, it was understood, might be vastly easier than inactivating or attenuating a whole virus, or inserting a gene into another vector virus. Those vaccine technologies had to be customized for each virus and, in some cases, each strain of each virus. When the 2009 H1N1 pandemic hit, vaccine developers took six months just to switch the strain of influenza virus to be covered – too late for the second wave that hit the U.S. in the fall of that year [95]. But the

technology for developing nucleic acid-based vaccines could be more readily standardized, and thus take advantage of significant economies of scale and scope [96].

By 1990, investigators working with mice found that naked DNA or RNA, when injected directly into muscle, could result in the expression of the encoded protein [97]. By 1993, in another mouse-based study, naked DNA coding for a protein from one influenza virus had been found to stimulate the immune response to a related but distinct influenza virus [98]. While naked nucleic acids appeared to be too unstable to be used alone, other investigators were able to package a water-based solution containing RNA inside globules lined with fat molecules [99].

These initial advances in the use of nucleic acid vaccines offered a scientific basis for moving forward with further research. What's more, preliminary evidence suggested that nucleic acid vaccines for HIV more closely mimicked the form of infection that would adequately stimulate both immune systems [59,100–102]. Still, a critical stimulus to the search for a nucleic acid vaccine was the repeated difficulties in getting the live virus vector model to work for HIV.

HVTN 505 and the path to mRNA

Researchers began work on a vaccine made from plasmid DNA, a naked, circular loop of double-stranded DNA that naturally exists in bacterial cells. Their efforts culminated in HVTN 505, a phase 2b trial that tested a combination of two components (Fig. 5): a primer dose of a plasmid DNA-based vaccine expressing six HIV genes, followed by a booster dose of an Ad5 vector containing the same genes [15]. Unfortunately, after two years of follow up, the intervention and placebo groups had indistinguishable rates of HIV infection [15].

Once again, failure led to further research to explain the failure. One explanation was that the prime-boost DNA-Ad5 combination used in HVTN 505 likewise stimulated weak antibodies against the Ad5 vector rather than against HIV [105]. To address this possibility, a DNA-AIDSVAX prime-boost combination vaccine is now under evaluation [106]. Another possibility was that a DNA-based vaccine was unlikely to work because the plasmid DNA had too hard a time passing into the target cell nucleus [96]. This stimulated further interest in mRNA-based vaccines, which only had to get into the host cell cytoplasm to do their job.

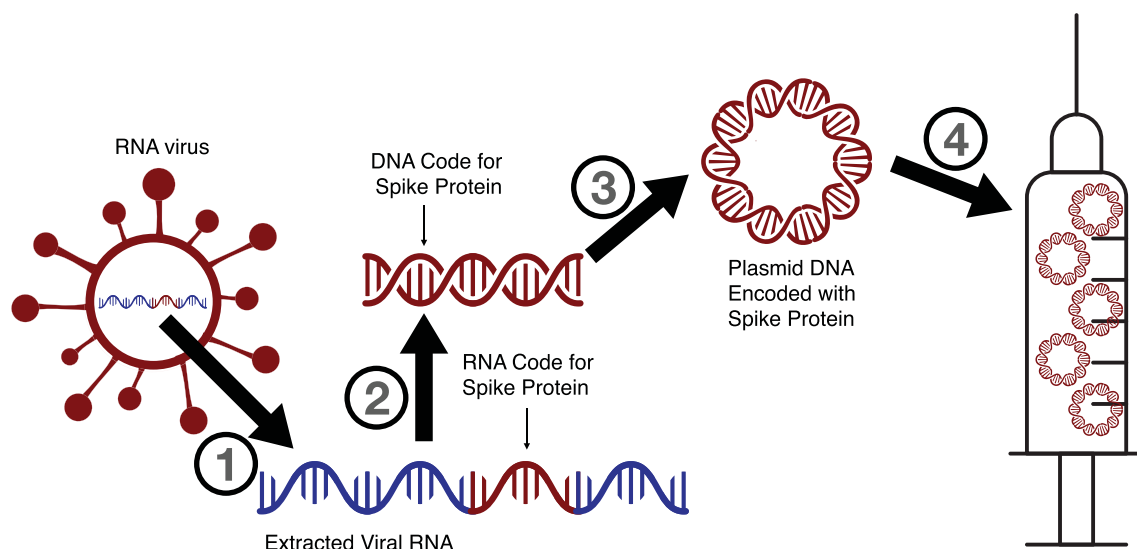


Fig. 5. Plasmid DNA vaccine. (1) The RNA is extracted from the offending virus and the code for the spike protein is isolated. (2) The RNA code for the spike protein is converted into DNA. (3) The DNA code for the spike is incorporated into plasmid DNA, a naked, circular loop of double-stranded DNA that exists naturally in bacterial cells. In the failed HVTN 505 clinical trial, a plasmid DNA vaccine expressing six genes of HIV was followed by a booster dose an Ad5-based viral vector containing the same genes [15]. As of February 15, 2022, sixteen vaccine candidates against COVID-19 using DNA technology were in clinical trials (Table 2). Of these, one DNA-based vaccine developed by Zydus Cadila, delivered by skin patch rather than injection, has applied to the Indian government for emergency use authorization [103,104].

But mRNA-based vaccines faced a critical obstacle: mRNA itself stimulated an immune response. That problem was solved in 2005 by chemically tinkering with the natural bases that make up RNA's molecular backbone [107,108]. A further advance was the development of self-amplifying mRNA (or SAM) (Fig. 6). In one study, researchers created an SAM, splicing the mRNA encoding HIV's envelope protein into the mRNA from the alphavirus, then wrapped the hybrid mRNA in a lipid particle [109].

mRNA Models for Therapeutic HIV Vaccines

As we've already learned, scientists understood that boosting cellular immune defenses was essential to keeping an HIV-infected person healthy without having to take lifelong antiretroviral medication. To that end, vaccine developers pushed ahead with human trials of mRNA prototypes not just for prevention, but also for HIV treatment. In one phase 1 trial, investigators injected an mRNA vaccine encoding 16 key fragments of HIV RNA into the lymph nodes of human volunteers who were already chronically infected with HIV. At the highest dose, the vaccine appeared to stimulate the cellular immune response [114].

By 2019, just months before SARS-CoV-2 was about to enter the world stage, mRNA had reached the forefront of vaccine research, with experimental tests of vaccines against influenza, Zika, and Ebola virus as well [96]. With many of the problems of packaging mRNA out of the way, and with the possibility of streamlined fabrication of mRNA vaccines on demand, it has become clear in retrospect that if mRNA vaccines really worked, they would be the first out of the starting gate in the race for a SARS-CoV-2 vaccine.

SARS-CoV-2 vaccines

The spike glycoprotein as a vaccine target

By the time of the SARS-CoV-2 outbreak in Wuhan, China, in December 2019, researchers already knew that other human coronaviruses such as SARS and MERS had their own envelope spike glycoprotein that facilitated invasion into human lung cells [115,116]. With the publication of the complete genetic code of SARS-CoV-2 a month later

[117–121], researchers quickly confirmed that the spike glycoprotein of this novel coronavirus would play a similar role [122,123]. Just as the gp120 envelope glycoprotein had become a critical target in the search for an HIV vaccine that began more than three decades earlier, researchers understood that the spike glycoprotein could serve as the critical target for vaccines against SARS-CoV-2.

HIV vaccines as progenitors

As of February 15, 2022, the World Health Organization's COVID-19 *Candidate Vaccine Landscape and Tracker* reported 143 candidate vaccines undergoing human clinical trials or already in use, and 195 additional candidates in preclinical development [124]. Among the 143 candidates in the clinical phase, 119 (or 83 percent) involved technologies that could be traced back to prototypes tested in HIV vaccine trials, while only 24 (17 percent) were based on inactivated virus, live attenuated virus, or other models.

Table 2 shows the specifics. The largest category – nearly one-third of vaccine candidates undergoing clinical testing – is based on the purified viral protein model (Fig. 3). Just as the AIDSVAX vaccines were made from purified gp120 of HIV, so these vaccines are made from the purified spike protein of SARS-CoV-2. Two of these candidates, developed by Novavax [64,65] and by Sanofi and GSK [66], have demonstrated efficacy in phase 3 clinical trials and are being submitted for regulatory review.

The STEP trial relied on the Ad5 virus. When that trial failed, the RV144 and Uhambo trials switched to a canarypox viral vector. And when those trials failed, the Mosaico and Imbokodo trials switched to the Ad26 virus. To date, 16 percent of the vaccines against SARS-CoV-2 in Table 2 are based upon the viral vector model (Fig. 4). Among these vaccines are: the vaccine developed by Janssen and Beth Israel Deaconess Medical Center, which is based upon the Ad26 vector [77, 78]; the vaccine developed by AstraZeneca and Oxford University, based upon the Ad5 vector [79]; and the Sputnik V vaccine developed by Gamalaya Research Institute, based upon a priming dose with an Ad26 vector and a booster dose with an Ad5 vector [29,80].

As further shown in Table 2, 28 percent of SARS-CoV-2 vaccine candidates in clinical trials are based upon the RNA or DNA nucleic acid

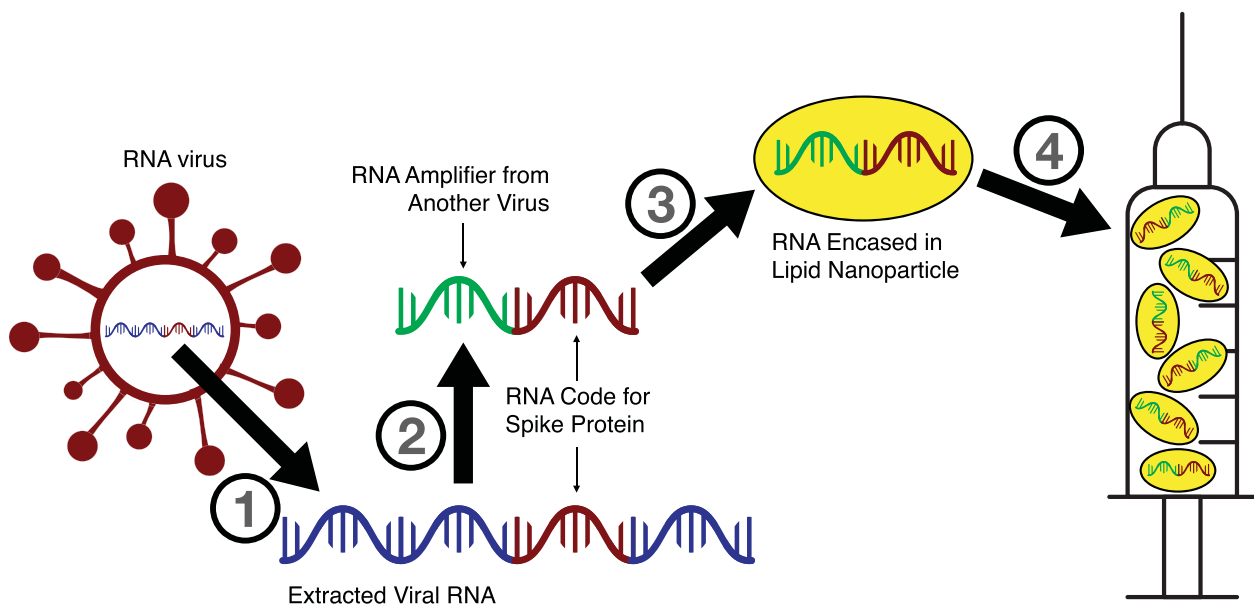


Fig. 6. mRNA vaccine. (1) The RNA is extracted from the offending virus and the code for the spike protein is isolated. (2) The section of RNA coding for the spike protein is spliced onto RNA amplifier code from another virus, thus creating self-amplifying mRNA (SAM) [110,111]. (3) The SAM, with the natural bases in its backbone modified to reduce its inflammatory potential, is encased in a lipid nanoparticle to enhance its stability. (4) The SAM nanoparticles are injected into the vaccine recipient. mRNA vaccines currently in use include those manufactured by Pfizer-BioNTech [112] and Moderna [113].

Table 2
HIV Vaccine Progenitors of SARS-CoV-2 Vaccine Candidates in Clinical Trials^a

Vaccine Model	SARS-CoV-2 Candidates		HIV Vaccine Progenitor ^b
	Number	Percent	
Purified Viral Subunit	47	32.9%	AIDSVAX [11]
Nucleic Acid ^c	40	28.0%	HVTN 505 [15]
Viral Vector ^d	23	16.1%	Merck STEP [13]
Inactivated Virus	21	14.7%	–
Virus-Like Particle	6	4.2%	[125–127]
Viral Vector + DC ^e	3	2.1%	[128–131]
Attenuated Virus	2	1.4%	–
Other ^f	1	0.7%	–

^a Among 107 SARS-CoV-2 vaccine candidates in clinical trials identified by WHO as of July 9, 2021 [124]. These include vaccines currently approved or reported to have completed phase 3 trials [29]: Pfizer-BioNTech (nucleic acid); Moderna (nucleic acid); Oxford-AstraZeneca (viral vector); Johnson & Johnson (viral vector); Gamaleya-Sputnik V (viral vector); CanSino Biological (viral vector); Novavax (purified viral subunit); Sinovac (inactivated virus); Sinopharm (inactivated virus); Bharat (inactivated virus); and Medicigo-Glaxo Smith Kline (virus-like particle).

^b Not all progenitors identified. For example, other progenitors of the Purified Viral Subunit model included the booster doses in the RV144, Uhambo, Mosaico and Imbokodo trials.

^c Includes vaccines based on plasma DNA and messenger RNA. d. Includes vaccines based on replicating and non-replicating viral vectors.

^e DC = dendritic cell. WHO refers instead to antigen-presenting cells (APCs).

^f Bacterial antigen-spore expression vector.

platforms (Figs. 5 and 6). These include not only the mRNA-based vaccines from Pfizer-BioNTech [112] and Moderna [132,133], already approved in the United States and other jurisdictions, but also plasmid DNA-based and other mRNA-based vaccines in development.

Counterargument: other viruses deserve the credit

One counterargument to our hypothesis is that our experiences with other deadly coronaviruses – the SARS outbreak in 2002-2003 and the continuing reintroduction of MERS on the Arabian Peninsula a decade later [134] – are what really prepared us scientifically for the arrival of SARS-CoV-2. Vaccines against SARS and MERS, based upon the technologies described in Table 2, were already in development, and a few candidates had entered clinical trials [135,136].

Quite apart from SARS and MERS, the counterargument continues, our experience with other non-corona viruses contributed to our scientific know-how. The Ebola vaccine, to take one example, is based upon a viral vector derived from the vesicular stomatitis virus (VSV). A critical step in vaccine development was the creation of a genetically engineered VSV that expressed the Zaire Ebola virus (ZEBOV) glycoprotein [137–139]. The resultant vaccine (rVSV-ZEBOV) was approved in Dec. 2019 [140]. Subsequently, the European Medicines Agency approved a separate viral vector vaccine for the Zaire strain of Ebola (commercially called Zabdeno) based upon a combination of two vectors, Ad26 and Modified Vaccinia Ankara [141].

A mere reference to the development of other vaccines, however, is hardly enough to rebut our principal hypothesis. One would have to contend that these vaccines were developed along tracks independent from and unaided by the search for an HIV vaccine. That would not fit the facts. To the contrary, the successful Ebola vaccines and the unsuccessful HIV vaccines drew from a common knowledge base. The first experimental Ebola virus vaccine to protect nonhuman primates involved an adenovirus 5 vector [142], the same vector that served as the prototype for the Merck STEP vaccine. It would be a stretch to contend that we have an ample menu of candidate vector virus vaccines against SARS-CoV-2 today because we managed to develop rVSV-ZEBOV for Ebola just in time.

Private losses, public gains

A massive R&D spillover

Within the first 15 months of the COVID-19 epidemic, public sector funding of R&D for COVID-19 vaccines already reached \$18 to \$23 billion [143], and that did not count at least \$70 billion in advanced purchasing agreements [144]. Private sector funding of R&D for COVID-19 vaccines has been more difficult to gauge, as most firms report only total R&D spending without project-specific breakdowns [145,146] and some of their reported R&D spending was publicly funded [147]. For the full year 2020 and the first quarter of 2021 combined, total R&D spending by Moderna, the developer of one of the currently marketed mRNA vaccines, amounted to \$1.7 billion [145,146].

By contrast, cumulative undiscounted R&D spending on HIV vaccines from 2000 to 2019 (the last year for which data are available) amounted to US\$ 15.3 billion, about 80 percent of which came from the public sector, about 11 percent from philanthropic sources, and the remaining 9 percent from private, commercial firms [148,149]. This relatively modest investment spread over two decades on an apparently unsuccessful enterprise laid the foundation for a subsequently successful enterprise that saved an estimated 1.1 lives through November 2021 in the U.S. alone [150].

How do firms learn from others' failures?

This massive R&D spillover took place in an economic environment where innovations in vaccine development have been tightly guarded by intellectual property protections. Consider some of the private entities investing in HIV vaccine development that appeared, at least facially, to have sustained losses: VaxGen, the relatively small U.S. biotechnology company that originally owned the rights to the AIDSVAX vaccine; the South Korean investors who entered into a US\$ 122 million joint venture with VaxGen to manufacture more than 200 million doses of AIDSVAX vaccines annually; Merck, the pharmaceutical firm that made a multimillion-dollar investment in the STEP Ad5 viral vector vaccine; Sanofi Pasteur, the pharmaceutical firm whose proprietary canarypox vector ALVAC was tested in the RV144 trial; GlaxoSmithKline (GSK), whose purified gp120 adapted to HIV subtype C was used in the Uhambo trial; and Janssen, whose proprietary AdVac adenovirus 26 vector was tested in the Imbokodo trial.

The failures of these private entities to capitalize on their intellectual property rights were ultimately translated into substantial gains in immunology, virology, molecular biology, and vaccine design generally. The question remains: How exactly did other competitors benefit from these failures?

There is certainly no paucity of economic research examining how one firm learns from other firms' *successful* innovations [151–153]. Nor is there any denying that organizations learn from *their own failures* [154]. During the launch of the *Atlantis* orbiter in October 2002, a piece of foam insulation broke off, damaging a ring holding a rocket booster but not interfering with the mission. During the launch of *Columbia* in January 2003, a piece of foam insulation similarly broke off, damaging the left wing, and ultimately resulting in the disastrous disintegration of the orbiter upon reentry and the demise of seven crew members. The response of the National Aeronautics and Space Administration to the *Columbia* failure, it has been noted, stood in stark contrast to its response to the *Atlantis* accident, which was perceived as a success [155].

Phase 2 and 3 clinical trials as the catalysts for knowledge leaks

Here, however, our focus is on the responses of firms and other organizations to the *failures of others*, particularly in the pharmaceutical and biotechnology sectors. The available evidence supports the proposition that publicly disclosed, phase 2 and 3 clinical trials have been the critical catalysts for knowledge leaks surrounding negative results

[156–158]. In the present context, the failed trials enumerated in Table 1 served as key pathways for the diffusion of know-how that prepared us for SARS-CoV-2 vaccines.

Anecdotal evidence from the therapeutic class of lipid-altering agents brings home the point. In December 2006, Pfizer abruptly halted its phase 3 trial of torcetrapib, a next-generation drug intended to increase blood concentrations of HDL (the “good”) cholesterol, on which the firm had already invested US\$ 800 million, when interim data showed the intervention group had 82 deaths while the control group had only 51 [159]. The failure appears to have motivated competitor Merck to design a scaled-back trial in patients at highest cardiovascular risk to assess whether its own candidate drug anacetrapib posed the same risks as Pfizer’s torcetrapib [160] and, in fact, Merck’s larger phase 3 trial of anacetrapib was delayed by about 4 years [161]. Competitor Roche, by contrast, apparently motivated in part by molecular differences between its own candidate dalcetrapib and Pfizer’s torcetrapib, went forward with its phase 3 trial [161,162].

The roles of the public and nonprofit sectors

Our emphasis on the critical catalytic function of clinical trials should not detract from supporting roles of the public and nonprofit sectors. These sectors have made far and away the largest contribution to HIV vaccine R&D over the last two decades [148,149]. The Uhambo, Imbokodo and Mosaic trials were conducted as collaborations between public, private nonprofit and commercial partners. While VaxGen, the developer of the AIDSVAX version of purified gp120, exited the market, the firm negotiated its intellectual property rights to a nonprofit foundation in 2008. AIDSVAX and related glycoproteins were subsequently employed as boosters in the RV144, Uhamabo, Mosaico and Imbokodo trials.

That said, we still need to acknowledge that a substantial majority of vaccines currently in use – and of vaccine candidates that have failed – have been developed by private firms taking advantage of their patents and trade secrets. These private firms ultimately had to learn from each other’s failures.

SARS-CoV-2 Variants: what we’ve learned and already forgotten from HIV

Hypermutability within immunocompromised hosts

Increasingly potent variants of SARS-CoV-2 have been emerging worldwide. By July 2021, the Delta variant (B.1.617.2) had rapidly become the dominant strain in many countries, including the United States [163,164]. Delta was approximately 60 percent more transmissible than the Alpha variant (B.1.1.7) that had previously dominated the United Kingdom, or about 2.4 times more transmissible than the ancestral strain [165]. The Omicron variant (B.1.1.529), which has swept through the world since its first appearance in late November 2021, appears to be about twice as transmissible as Delta [166], though mutations in its spike glycoprotein have made it more prone to attack the upper airways of the human respiratory system rather than the deep lung [167].

Each new variant-driven wave seems to blindside medical gurus and public policymakers, who are forced to hastily retract their rosy forecasts that the denouement was finally upon us. Yet in a real sense, we are observing no more than a scientific replay of the ongoing struggle to find a vaccine against HIV.

While SARS-CoV-2 mutates at a lower rate than HIV, the COVID-19 pandemic has now extended far enough and lasted long enough that mutations producing these new variants have inevitably emerged. Aside from the sheer volume and scope of infections as a mutation driver, there is evidence that immunocompromised individuals who do not rapidly clear their infection may serve as long-term reservoirs for a cascade of viral mutations [168,169]. In fact, the strikingly distinct genetic

signature of 30 bundled mutations in the spike glycoprotein of the Omicron variant quite likely arose from long-term SARS-CoV-2 infection in an individual with untreated HIV [170].

In a sense, we have come full circle. The recurrent waves of new SARS-CoV-2 variants have been driven not so much by random mutations among distinct infected individuals as by clustered, serial mutations within the same infected individual. And the irony is that the most important way to dampen the waves of SARS-CoV-2 may be to get nearly everyone with HIV on antiviral therapy or, better still, finally come up with a vaccine against HIV [170].

Currently available, effective SARS-CoV-2 vaccines are infection-permissive

The extraordinarily high rates of efficacy against symptomatic infection from the ancestral strain of SARS-CoV-2, observed in the phase 3 clinical trials of the two mRNA vaccine candidates [112,113], created the illusion that these vaccines might come close to providing sterilizing immunity. Genuine sterilizing immunity against SARS-CoV-2, however, would require a high-level immune response at the virus’ point of entry through the nose and mouth [171,172], just as sterilizing immunity against HIV would require a comparable response at the mucous membranes of the vagina and rectum [173,174]. When it was first noted that vaccinated individuals were becoming infected with the Delta variant [175,176], these cases were misleadingly labeled *breakthrough infections*.

In fact, we have every reason to think that currently available, effective vaccines against SARS-CoV-2 adhere instead to the infection-permissive model of protection. These vaccines did not prevent infection entirely, but rather shifted the distribution of severity backward to the point where a very substantial proportion of those infected had no symptoms. Strictly speaking, they were all breakthrough infections. With the subsequent advent of Delta and Omicron, the distribution of severity has shifted forward somewhat, so that these vaccines are less effective against symptomatic infection but still offer powerful protection against hospitalization and death [177]. We could have anticipated all this from our string of failures to develop an HIV vaccine but seem to have forgotten much along the way.

Immune escape all over again

Our struggle with HIV vaccines taught us about immune escape. The halving of the efficacy of the RV-144 vaccine from 60 percent at one year to 30 percent after 3 years [14,92,93] showed us that immune escape could be as much a consequence of waning immune defenses as it was a result of viral hypermutability. We have now relearned that the degradation of the humoral antibody response to SARS-CoV-2 began soon after the most recent dose of mRNA vaccine [178,179], and that the immune escape observed with the recent Delta and Omicron variants was not entirely due to their spike glycoprotein mutations [180,181]. Yet when data from Israel, where the Pfizer mRNA vaccine had been in widespread use, first signaled a marked waning in vaccine effectiveness [182] to the point where a booster dose was recommended [183], the news was received as a lightning bolt.

Combination vaccine redux

The string of HIV vaccine failures also taught us a lesson about combination vaccines. Here, we do not refer to the classic combinations against measles, mumps, and rubella, or against diphtheria, tetanus and pertussis, where the components work independently to prevent distinct diseases. Instead, we focus on the combination vaccines where the components are intended to act synergistically to achieve immune protection against the same disease. Early evidence that the Oxford-AstraZeneca viral vector vaccine could be combined with the Pfizer-BioNTech mRNA vaccine was greeted with fanfare [184]. Yet in the

RV144, Uhamabo, Imbokodo, and Mosaico trials, a viral vector had already been combined with a purified protein vaccine. In HVTN 505, a nucleic acid-based vaccine had already been combined with a viral vector vaccine [15].

Prospects for an HIV vaccine: reverse spillover effects

The economic incentive to develop an HIV vaccine depends on the extent of the market. By 2020, the incidence of newly acquired HIV infections worldwide had dropped to 1.5 million annually, down 30 percent since 2010 [185]. This figure is dwarfed by the more than 400 million cases of COVID-19 reported worldwide since late 2019 [186]. Still, the number of persons at high risk for contracting HIV is likely to be at least two orders of magnitude higher than the current incidence, that is, around 150 million [187]. If we consider the possibility of a therapeutic vaccine to halt the natural progression of HIV – as a substitute to a lifetime of antiviral chemotherapy – then we should also include the 37.6 million people living with HIV [185]. That would put the potential market for an HIV vaccine in the range of at least 200 million consumers.

The more interesting question, however, is whether recent advances in the development of vaccines against SARS-CoV-2 will further the development of an HIV vaccine – what one might call a *reverse spillover effect*.

The most obvious area of reverse spillover is the application of new mRNA technology to the development of HIV vaccines. The spike protein of SARS-CoV-2 not only serves as the key to unlocking the host cell membrane, but it has also turned out to be an ideal immunogen. While scientists have long known that the gp120 glycoprotein molecule is the corresponding key on HIV, there is still considerable uncertainty as to what HIV-specific molecules are the most immunogenic. The AIDSVAX trials demonstrated early on that pure gp120 by itself was not enough [11,12]. Thus far, a significant obstacle in HIV vaccine development has been the enormous investment in time and resources required to develop and test the handful of potential immunogens other than gp120 that have gone into the booster shots of the RV144, Uhambo, Mosaico and Imbokodo trial vaccines [8,14,17,18,188,189]. In this sense, the learning-by-doing process in HIV vaccine development has become a numbers game. In the face of so many subtypes of HIV, how many different surface glycoproteins and structural proteins can we cram into a single booster?

That's where the economies of scale and scope inherent in mRNA technology may come into play. Investigators have been able to construct model mRNA vaccines that contain a wide variety of surface glycoproteins and structural proteins from various subtypes of HIV. Some of these mRNA prototypes have already been tested in animal models [190]. Phase 1 trials of two mRNA-based candidate vaccines against HIV are now in the recruiting phase [191].

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