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THE REPEATED SETBACKS OF HIV VACCINE DEVELOPMENT LAID THE
GROUNDWORK FOR SARS-COV-2 VACCINES

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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 HIV vaccine trials 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, SARS-CoV-1 and human papillomavirus. These successful vaccines likewise owe much to the vicissitudes of HIV vaccine development.

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The Repeated Setbacks of HIV Vaccine Development Laid the Groundwork for SARS-CoV-2 Vaccines

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March 19, 2021

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 HIV vaccine trials 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, SARS-CoV-1 and human papillomavirus. These successful vaccines likewise owe much to the vicissitudes of HIV vaccine development.

Key Words: COVID-19, coronavirus, human immunodeficiency virus, clinical trials, R&D

JEL Codes: H41, I18, O31

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1. 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. Antiretroviral drugs were the path of least resistance, others have cogently observed.

The principal contention of this 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.

The chronicle of repeated, unsuccessful efforts to develop an HIV vaccine is in some ways a parable about the leakiness of scientific knowledge. It is also a take-home lesson in the undervaluation of scientific and technological research. The supreme irony of the previous generation's checkered attempts to overcome HIV is that in trying so hard to do so, it has ultimately facilitated the next generation's conquest of another virus now ravaging the globe.

It is already widely acknowledged that HIV-related research and, in particular, HIV vaccine-related research, have had substantial spillover effects.¹ Our thesis is more pointed. We contend that the repeated *failures* of HIV vaccine trials have served as a critical stimulus to the development of successful vaccine technologies today.

How could one possibly test the principal contention of this article? Obviously, we cannot rerun the tape on a counterfactual world deprived of a decades-long HIV vaccine initiative to see what would have happened to our technical capabilities. What we can do, however, is 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.

The main rejoinder to our hypothesis is that HIV vaccine development was no more than a blind alley, an unsuccessful bystander to more fruitful lines of research. Recently developed vaccines against COVID-19, it might be contended, are really descendants of successful vaccines

¹ As one group of reviewers put it, “In gaining this understanding, research progress in HIV-1 vaccine development has catapulted forward the fields of non-human primate and human immunology, retroviral biology, structural biology, genetics of the immune response, viral drug development, and vector development of gene delivery—all accomplishments that are benefitting many non-HIV-1 areas of research.” (Haynes et al. 2016) As another group of scientists noted, the attempt to develop an HIV vaccine “has been the inspiration for much research in vaccine technology, resulting in improved tools for induction of both T cell and antibody responses.” (Andersson, Schwerdtfeger, and Holst 2018)

against Ebola, MERS, SARS-CoV-1, human papillomavirus, and influenza (Li et al. 2020). Our response is that these successful vaccines likewise owe much to the vicissitudes of HIV vaccine development. Beginning in the 1980s, the inadequacies of tried-and-true models for making vaccines repeatedly pushed HIV vaccine research beyond conventional boundaries and into the forefront of scientific understanding. These general advances were subsequently translated into specific innovations in the development of workable, effective antiviral vaccines today.²

A secondary counterargument is that it has simply been a matter of adequate financing. 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 (Resource Tracking for HIV Prevention R&D Working Group (RTWG) 2019, 2020). By contrast, the U.S. government's Operation Warp Speed has spent about \$10 billion in a matter of months (Ball 2021), and total investment in SARS-CoV-2 vaccine R&D and distribution has been already projected at \$39.5 billion (Cornish 2020).

The response to the latter counterargument is that it doesn't really prove or disprove our hypothesis about the critical role of HIV vaccine development. If anything, it reinforces the contention that we'd be a lot farther along in the search for an HIV vaccine if we had devoted adequate resources to the task, especially to the formation of public-private partnerships (Harris 2009). It reinforces the view long held by economists that science doesn't simply march forward by fortuitous accident. Science is endogenous (Romer 1990, Azoulay 2002).

2. 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 (NIAID 2020). 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 (Bekker et al. 2018). These proteins, it was hoped, would then stimulate the vaccine recipient's immune system to protect against future infection by HIV.

² "Things like this give a real shock to a field, and the field makes a major advance. It's just great, because, thanks to HIV, we were much better prepared – at least scientifically – for this virus, if not the level of boots on the ground, where we were not prepared at all. But scientifically, we're ready for this." (Yewdell 2020)

The Uhambo trial had been conducted in 14 sites across South Africa, enrolling over 5,400 HIV-negative participants 18–35 years old. More than half-way through the study, researchers had unsealed the data to find that the intervention group, composed of persons who got the candidate vaccine, and the control group, composed of persons who got an inert placebo vaccine, 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.” (UNAIDS 2020)

Byanyima’s comment was right on target. Even the simplest, small-scale production process involves what economists call learning by doing (Arrow 1962). Let’s say you’re a restaurant chef learning to make clafoutis, a French dessert with fruit and a custard-like creamy filling. If you bake it too little, the dessert is runny and tastes like eggs. If you bake it too much, your patrons won’t appreciate the chalky custard. You’ve got to make clafoutis several times to really get the hang of it. To take a more complex example, once an organ transplant team has worked together on hundreds of cases, the transplant surgery goes faster, there are fewer complications, and the organ recipient’s long-term survival is improved.

The same goes for large-scale, complex scientific and technological research enterprises, including the task of developing and testing a vaccine against HIV. It’s not simply that the research team becomes more efficient at producing the candidate vaccine or carrying out a trial on human subjects. What matters even more is that 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.

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 cannot fully capture the gains from its mistakes. We thus have a positive externality, specifically a knowledge spillover (Griliches 1992, Aghion and Jaravel 2015). 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.

3. The Conventional Approaches Didn't Work.

3.1. *Inactivated and Live Attenuated Vaccines*

Before the HIV epidemic of the 1980s, vaccines were made primarily through two conventional methods. First, inactivated vaccines were produced by heat or chemical treatment of a virus or other infectious organism. The Salk polio vaccine, for example, was produced by treating the poliovirus with formaldehyde (Juskewitch, Tapia, and Windebank 2010), a key component of embalming fluid. Second, live attenuated 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. The original measles vaccine, for example, was made by passing the virus through cell cultures of human organs and chick embryos, as well as embryonated hen's eggs (Stokes, Hilleman, and Weibel 1961). It wasn't clearly known why these two approaches worked, but they were enormously successful in combating not only polio and measles, but also smallpox, rabies, mumps and rubella (German measles) (Zhang et al. 2019, Hicks, Fooks, and Johnson 2012). Currently, hepatitis A vaccine is available in both inactivate virus and live attenuated virus forms (WHO 2020).

Unfortunately, these previously successful, conventional approaches to vaccine development bumped headlong into two critical features of the natural course of HIV infection.

3.2. *Cellular Immunity – Not Just Humoral Immunity – Was Critical.*

From the start of the HIV epidemic, there was abundant evidence that combating the virus would require not only humoral immunity, but also cellular immunity. Humans and other animals have evolved a dual, partly complementary and partly redundant system of defenses against noxious infectious agents (Plotkin 2010). Under humoral immunity, the defending animal produces antibodies that claw onto and neutralize the offending antigen. Under cellular immunity, certain white blood cells called killer lymphocytes attack and destroy other white blood cells that have lassoed the offender.³

As early as 1985, it was known that HIV stimulated the development of neutralizing antibodies in most infected people, but that those antibodies alone weren't enough to confer

³ In the humoral system, helper (CD4+) lymphocytes recognize mostly large, exogenous molecules and present them to B lymphocytes, which in turn make antibodies to neutralize these antigens. In the cellular system, dendritic cells (and other antigen-presenting cells) recognize mostly small, endogenous molecules and present them to killer (CD8+) lymphocytes, which in turn destroy them. For example, both humoral and cellular immunity are involved in the body's response to the chickenpox virus. A shingles outbreak occurs when cellular immunity is later weakened.

protection against disease (Robert-Guroff, Brown, and Gallo 1985, Weiss et al. 1985). By the 1990s, it was also known that HIV could transfer directly from an infected cell to another cell, thus avoiding humoral antibodies that roamed in extracellular fluids (Girard 1990). When an individual was first infected, it was subsequently found, the killer lymphocytes – not the antibodies – were responsible for tamping down the spread of the virus (Borrow et al. 1994, Koup et al. 1994, Price et al. 1997, Heeney and Plotkin 2006). In fact, progression of HIV infection to AIDS was associated with escape from killer cell control (Goulder et al. 1997). Later on, studies of elite controllers – chronically infected people who never seemed to progress to AIDS even without treatment – confirmed they were shielded by their cellular immune system (Genovese, Nebuloni, and Alfano 2013).⁴

3.2. *HIV Mutated Rapidly.*

HIV is a single-stranded RNA virus enclosed in an envelope. The RNA is positive-sense, which means it can immediately use the machinery in the infected cell's cytoplasm to make viral protein.⁵ The only viral proteins that HIV immediately makes are an enzyme called reverse transcriptase, which converts the viral RNA to complementary viral DNA, and an integrase, which then integrates the viral DNA into the host cell DNA, where it then can remain latent for years. The initial process of reverse transcription, however, is extremely error-prone and subject to mutation. And, as the scientific community soon found out, there's the rub.

The hypermutability of HIV played havoc with some of the basic ideas underlying vaccine development. Neutralizing antibodies against one isolated sample of the virus, it was found, did not necessarily cross-neutralize other isolated samples (Girard 1990, Wei et al. 2003). 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 (Keele et al. 2008). But within months, the transmitted founder was replaced by mutated viruses

⁴ “Given the accumulation of evidence that cell-mediated immune responses play a substantial role in containment of primary HIV infection and suppression of viral replication, it is likely that a component of an effective vaccine is the ability to elicit HIV-specific T cells.” (Dubey et al. 2007)

⁵ RNA is ribonucleic acid, while DNA is deoxyribonucleic acid. Both are nucleic acids. A double-stranded DNA molecule has positive-sense and anti-sense strands. Positive-sense viral RNA is similar to a host cell's own messenger RNA (mRNA) in that both are complementary to the anti-sense strand of DNA and thus can be immediately translated into protein once inside the cell. The RNA from HIV and coronaviruses is positive-sense. Influenza viruses have negative-sense RNA and thus need an extra packaged enzyme to make positive-sense RNA.

that did not react to antibodies developed by the infected person and thus might escape humoral immune control (Derdeyn et al. 2004).

These two critical features of HIV infection – the central role of cellular immunity and the hypermutability of the virus – posed serious problems for conventional vaccine technology.⁶ For one thing, inactivated virus vaccines appeared to stimulate the humoral system to make antibodies, but since they could not infect host cells, they did not stimulate the cellular immune system. To be sure, live attenuated virus vaccines did appear to stimulate the cellular system (Zhang et al. 2019). However, 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 (Whatmore et al. 1995). 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. And then there was the possibility that the attenuated virus could recombine with a virulent, wild form of the virus. The live attenuated virus model was, at least for the meantime, off the table, too.

4. 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 tossed this classic idea out the window. 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 (Desrosiers 2004).

We're not talking about the elite controllers who let HIV enter through the front door and then cohabit with their new guest indefinitely. To the contrary, we're talking about a model of immunity in which HIV can't even get past the front door – sometimes called sterilizing immunity (Dutta et al. 2016). At least for heterosexual transmission, that would mean an immune response that keeps the virus from traversing the mucous membranes involved in sexual contact

⁶ “The human immunodeficiency virus (HIV) is the best-studied virus for which an established technology is unlikely to yield an effective vaccine. Like influenza virus and HCV [hepatitis C virus], HIV mutates at an extraordinarily rapid rate, allowing it to evade a neutralizing antibody response.” (Letvin 2007)

at the very moment of infection. Achieving this level of immunity turned out to be even more challenging, as there was evidence that HIV itself may be able to disable those front-door defenses (Morrow et al. 2007, Letvin 2007).

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 (Plotkin 2010, Liu 2010). 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.

4.1. gp120, Viral Receptors, and the AIDSVAX Vaccines

Through detailed analysis of HIV's molecular structure, researchers determined that the outer skin (or envelope) of the virus contains a key molecule named gp120, where "gp" is short for glycoprotein, which is basically a sugar-coated protein. This key molecule protrudes outward from the viral envelope and fits like a key into a viral receptor on the surface of a target cell in the victim's body. Upon attachment of the key to the receptor, the viral envelope fuses with the target cell membrane, thus effectively opening the lock and permitting viral invasion of the cell. As it turned out, gp120 fit onto the viral receptor of a white blood cell called CD4+ lymphocyte that is critical in maintaining the body's cellular immunity. What's worse, the gp120 key also fit on viral receptors of other types of cells, including the nervous system.

The discovery of gp120 as the key molecule that attaches the host's receptor 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 strong humoral antibody response to the pure glycoprotein molecule, even if that sort of response did not occur during natural infection.

Two vaccine candidates adhering to this new model 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 (Harris 2009).

Unfortunately, AIDSVAX B/B failed to curb HIV in a study of over 5,400 volunteers in the U.S and the Netherlands (Flynn et al. 2005), while AIDSVAX B/E performed no better in a study of over 2,500 injection drug users in Bangkok, Thailand (Pitisuttithum et al. 2006). The failures of these two candidate vaccines became the focus of a substantial research effort. Both vaccines did indeed stimulate a humoral response against the gp120 stimulus, but that alone did not confer immunity (Gilbert et al. 2005). There was some evidence of a correlation between the protective effect of the gp120 vaccines and antibody-dependent cell-mediated immunity, but again, the findings were inconclusive (Forthal et al. 2007).

Even at this point in the narrative, the connections to SARS-CoV-2 vaccine development should be evident. The research on gp120 as the key molecule on the surface of HIV attaching to receptors on CD4+ lymphocytes and other tissues was the forerunner of subsequent research on the spike protein as the key molecule on SARS-CoV-2 attaching to ACE2 receptors in the lungs and other organs. But we're getting ahead of our story.

5. Live Viral Vectors Become the New Model.

5.1. The STEP Trial of the Ad5 Viral Vector

In the face of the failure of the AIDSVAX candidate vaccines to stimulate protective 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 (Benmira, Bhattacharya, and Schmid 2010).

During the 1980s, a research team had managed to genetically 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 (Moss et al. 1984). Of course, no one contemplated infecting a human being with smallpox in order to immunize him against hepatitis B. But if we could instead find a benign

virus to act as a live vector, then perhaps we could similarly engineer it to produce immunogenic proteins from HIV.

Efforts focused on a common-cold virus called adenovirus 5 (or Ad5) as a potential live vector (Downey et al. 1983, Rodrigues et al. 1997, Rodrigues et al. 1998, Patterson, Papagatsias, and Benlahrech 2009). 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 (Sekaly 2008). Even if the Ad5 vaccine could not completely block HIV infection, perhaps it would stave off the progression of the infection to AIDS.

In the STEP vaccine trial, the pharmaceutical manufacturer Merck made a major, multimillion-dollar investment to test this concept (Harris 2009). 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 the HIV genes *gag*, *pol* and *nef*, respectively.

Unfortunately, Merck's Ad5-based vaccine did not fully live up to expectations. While the vaccine stimulated cellular immunity (McElrath et al. 2008), it showed no reduction in HIV incidence compared to a placebo vaccine (Buchbinder et al. 2008). 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 (Buchbinder et al. 2008). As a result, the Phambili trial of the same vaccine in South Africa was cancelled (NIAID 2007, Gray, Buchbinder, and Duerr 2010, Moodie et al. 2015), while PAVE-100, another Ad5-based trial proposed for Africa and the Caribbean was put on hold (Day and Kublin 2013).

5.2. *The RV144 Trial*

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 polyreactive antibodies against many Ad5 proteins, including its native proteins, and not just against the artificial HIV proteins inserted into the vector's genetic code (Sekaly 2008). While Ad5 had been engineered to infect the host cells of the vaccine recipient without itself multiplying (Wold and Toth 2013), even this replication-defective adenovirus 5 stimulated a strong immune reaction in

humans. What's more, a significant proportion of participants in the Merck STEP study already had antibodies to Ad5.

To help sort out these two possibilities, the RV144 Trial, conducted by the U.S. Military HIV Research Program (MHRP), tested a two-component vaccine on over 16,400 supposedly HIV-negative volunteers in Thailand. The first component – a primer– was based instead on the canarypox vector, a proprietary product acquired by Sanofi Pasteur named ALVAC. The second component – a two-dose booster– was AIDSVAX B/E. Even if this new vaccine protocol were to have commercial value, it would ultimately come too late for VaxGen's stockholders, as the company 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 – MHRP scientists reported a statistically insignificant “trend” toward HIV prevention with an estimated efficacy of 26.4%. The findings looked more promising when the researchers tossed out 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 followed through with all vaccine doses (Rerks-Ngarm et al. 2009). Still, the problem was that an efficacy of about 26 percent simply wasn't enough to make the vaccine realistically useful for HIV prevention.

One possible reason that RV144 gave only weak protection against HIV was that the two booster doses with AIDSVAX B/E were inadequate. To explore that possibility, a public-private collaborative team called the Pox-Protein Public-Private Partnership (or P5) initiated Uhambo in 2016, using the combination of the canarypox ALVAC vaccine from Sanofi Pasteur along with multiple booster doses at one year and 18 months of a different purified form of gp120 from GlaxoSmithKline (GSK) adapted to HIV subtype C, which is more prevalent in South Africa.

We already know that Uhambo was called off in February 2020. But those findings have in turn led scientists to test other variations of the vector-based prime-boost strategy to achieve adequate immunity against HIV.⁷ The Imbokodo trial in women (HVTN 705) and the Mosaico trial in men (HVTN 706), both sponsored by Janssen, used an adenovirus 26 vector encoding proteins from a mosaic of different HIV subtypes, along with a purified gp140, another key

⁷ In a 2013 review entitled “Lessons Learned from HIV Vaccine Clinical Efficacy Trials,” one pair of commentators wrote, “Moreover, valuable information has emerged from RV144 and the other completed efficacy trials and is serving to guide vaccine discovery efforts.” (Day and Kublin 2013)

protein on HIV's envelope, as a booster (U.S. National Library of Medicine 2020b, a). Both Mosaico and Imbokodo are ongoing.

5.3. *Virus-Like Particles*

If a significant proportion of vaccine recipients already had antibodies against naturally occurring viral vectors such as Ad5 and Ad26, was there any way to create an artificial viral vector to which recipients would be immunologically naïve? That's where the idea of virus-like particles (VLPs) came into play (Doan et al. 2005, Young et al. 2006). In this novel vector system, a purified viral glycoprotein was not directly administered to the recipient, as was the case with purified gp120 in the AIDSVAX trials and purified gp120 and gp140 in the booster doses of the RV144, Imbokodo, and Mosaico trials. Instead, an amalgam of viral glycoproteins was assembled into a particle that resembled a real virus but did not have any nucleic acid and thus could not reproduce (Zhao, Ao, and Yao 2016). While work has continued on a VLP-based vaccine against HIV, other vaccines based on the VLP platform are already in use against human papillomavirus (HPV), hepatitis B, and malaria (Fuenmayor, Godia, and Cervera 2017).

5.4. *DC Therapeutic Vaccines*

As we've already learned, researchers became increasingly convinced that cellular immunity was critical to mounting an effective defense against HIV. They further understood the long-term maintenance of cellular immune defenses would be essential to keeping an HIV-infected person healthy without having to take lifelong antiretroviral medication. Boosting cellular immunity was thus the key not only to HIV prevention, but also to its treatment.

There was a growing scientific consensus that those vaccines most closely mimicking a natural viral infection had a greater propensity to boost cellular immunity. Live attenuated virus vaccines were in that category, but as we've noted, the risk of a back mutation to virulent HIV, or of recombination with the virulent form, was just too great. They had learned from the Merck STEP trial that live viral vectors could stimulate cellular immunity, but multiple clinical trials with that vaccine model had so far not succeeded.

In the cellular immune system, a dendritic cell (DC) – or another antigen-presenting cell (APC) such as a macrophage – engulfs an antigen molecular and then presents the antigen to a killer CD8+ lymphocyte, which gobbles it up. (See note 3 above.) The acquired knowledge of the detailed workings of the cellular immune system led to the idea of creating a vaccine consisting of an individual's own DCs loaded with HIV antigens, HIV antigen-expressing viral

vectors, HIV antigen-containing VLPs, or HIV antigen-encoding RNA (Kundu et al. 1998, Lu et al. 2004). By 2016, seventeen clinical trials had been undertaken to see whether the DC-based approach could be employed as a therapeutic strategy in HIV-infected patients (Zhao, Ao, and Yao 2016). Unfortunately, the DC vaccine approach has thus far not proved to be consistently effective (Gandhi et al. 2016), but efforts to refine this strategy continue (da Silva et al. 2018).

6. Nucleic Acid Vaccines

If vaccine designers were going to all the trouble of extracting the 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 replication-defective DNA-based vector virus, then why not just skip the vector altogether and work directly with the HIV-derived RNA from start? Why not copy the key HIV gene sequences into messenger RNA (or mRNA), the form of RNA that cells naturally used as an amplifier to crank out multiple copies of proteins? Or if not mRNA, then why not work at least 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.⁸ But the technology for developing nucleic acid-based vaccines could, at least in principle, be more readily standardized, and thus take advantage of significant economies of scale and scope (Maruggi et al. 2019).

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 (Wolff et al. 1990). 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 (Ulmer et al. 1993). While naked nucleic acids initially appeared to be too unstable to be used alone in a workable vaccine, other investigators were able to package a water-based solution containing RNA inside globules lined with fat molecules, a drug delivery device called a liposome (Martinon et al. 1993).

⁸ 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 (Amanat and Krammer 2020).

These initial advances in the use of nucleic acid vaccines offered a scientific basis for moving forward with further research. Still, the critical added stimulus to the search for a nucleic acid vaccine was the repeated failure to get the live virus vector model to work for HIV. What's more, there remained significant uncertainty about the respective roles of humoral and cellular immunity in mounting an effective defense against HIV, and preliminary evidence suggested that nucleic acid vaccines for HIV more closely mimicked the form of infection that would adequately stimulate both immune systems (Mascola et al. 2005, Allen et al. 2000, Amara et al. 2001, Liu 2010).

6.1. HVTN 505 and the Path to mRNA

Then came the HVTN 505 trial, which tested a vaccine combining two components: a primer dose of a DNA-based vaccine expressing six HIV genes, followed by a booster dose of a replication-defective Ad5 vector containing the same genes (Hammer et al. 2013). The primer dose of the DNA-based vaccine was made from plasmid DNA, a naked, circular loop of double-stranded DNA that exists naturally in bacterial cells. Unfortunately, after two years of follow up, 27 of the 1,253 individuals randomized to receive the two-component vaccine came down with HIV, compared to 21 of the 1,251 individuals randomly assigned to receive a placebo (Hammer et al. 2013).

Once again, failure led to further research to explain the failure. One suggested explanation was that the prime-boost DNA-Ad5 combination used in HVTN 505 likewise stimulated weak, polyreactive antibodies against the Ad5 vector (Williams et al. 2015). The other possibility was that a DNA-based vaccine was simply not going to work, in part because the plasmid DNA had too hard a time passing into the target cell nucleus (Maruggi et al. 2019). This stimulated further interest in mRNA-based vaccines, which only had to get into the host cell cytoplasm to do their job.

Still, mRNA vaccines still faced significant obstacles. One of the trickiest problems was that mRNA itself stimulated an immune response. That's not what vaccine researchers wanted. The whole point was to stimulate the immune response to the protein that the mRNA encoded, not the mRNA itself. That problem was ultimately solved in 2005 by chemically tinkering with the natural bases that make up RNA's molecular backbone (Kariko et al. 2005, Kariko et al. 2008). But even with that problem out of the way, experimental HIV vaccines based on mRNA

provoked other inflammatory responses that tended to counteract their effectiveness (Pollard et al. 2013).

To address these problems, researchers worked on more sophisticated systems for delivering mRNA to the vaccine recipient. One important advance was the development self-amplifying mRNA (or SAM). The idea was to take the section of mRNA that codes for a particular immunogenic protein and splice it onto another section of mRNA that contains the code for amplification of the RNA and expression of the protein (Pardi et al. 2018, Moyo et al. 2019). 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 (Bogers et al. 2015).

Nor were HIV vaccine researchers deterred from pushing ahead with human trials of RNA vaccine prototypes. 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, thus raising the hope that it could ultimately be used as therapy for those already infected (Leal et al. 2018).

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 (Maruggi et al. 2019). 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 actually worked, they would be the first out of the starting gate in the race for a SARS-CoV-2 vaccine.

7. SARS-Cov-2 Vaccines

7.1. They Knew It Was Coming.

The SARS-CoV-1 outbreak in 2002-2003 and the continuing reintroduction of MERS-CoV on the Arabian Peninsula a decade later (Lee 2015) sent a clear message to the public health and scientific communities well before the December 2019 outbreak of SARS-CoV-2 in Wuhan, China. At any minute, a novel, lethal respiratory coronavirus could emerge with the potential for pandemic human-to-human spread (Cockrell et al. 2018, Maruggi et al. 2019). Piggybacking on the major advances in virology, immunology and molecular biology achieved during the

scientific confrontation with HIV, researchers already knew that human coronaviruses were positive-sense RNA viruses with a key spike glycoprotein that protruded from viral envelope. They already knew that the spike glycoprotein could bind to viral receptors on host target cells. The spike glycoprotein of SARS-Cov-1, they knew as well, could bind a receptor called ACE2 in human lungs (Cockrell et al. 2017, Cockrell et al. 2018). They knew it was coming and, at least from the scientific point of view of vaccine development, they were ready.

7.2. Pivotal Knowledge Leak

Within a month after the initial outbreak in Wuhan, China, the complete genetic code of SARS-CoV-2 was published (Wu et al. 2020a, b, Zhou et al. 2020, Zhu et al. 2020, Lu et al. 2020), an unimaginable, lightning-paced feat in comparison to the decade it took for the genome of HIV to be unraveled (Bachmann et al. 1994). This disclosure – no doubt the pivotal knowledge leak of the entire COVID-19 pandemic – led quickly to confirmation that the spike glycoprotein SARS-Cov-2 would likewise bind to the ACE2 receptor in human lungs (Lan et al. 2020, Wrapp et al. 2020). By February 3, 2020, the day that the Ohambu HIV vaccine trial was cancelled, almost precisely the day when SARS-CoV-2 had jumped from Hubei to Italy (Worobey et al. 2020), scientists in the know had already arrived at an important conclusion. Just as the gp120 envelope glycoprotein had played a key role in the search for HIV vaccines that began more than two decades earlier, the spike protein could serve as an immune stimulus for potential vaccines against SARS-Cov-2 (Lan et al. 2020, Wrapp et al. 2020).

The importance of this knowledge leak cannot be overemphasized. With multiple vaccine-development groups on the ready to respond to a new pandemic threat, it is doubtful that any single firm could have capitalized on its private knowledge of the SARS-CoV-2 genome for long. Still, if there had been even a few weeks delay until investigators outside China acquired viral samples and sequenced the viral RNA, we would not be where we are today.

7.3. HIV Vaccines as Progenitors

As of March 5, 2021, the World Health Organization's COVID-19 *Candidate Vaccine Landscape and Tracker* reported 78 candidate vaccines undergoing human clinical trials or already in use, and 181 additional candidates in preclinical development (World Health Organization 2021). Among 78 candidates in the clinical phase, 68 (or 86 percent) involved technologies that could be traced back to prototypes tested in HIV vaccine trials, while only 11 (14 percent) were based on inactivated virus and a live attenuated virus.

Table 1 shows the specifics. The largest category – nearly one-third of vaccine candidates undergoing clinical – was based on the purified viral protein model. We have already seen how the glycoprotein gp120 on the surface of HIV was found to be the key molecule unlocking the receptors on human host CD4+ lymphocytes. The purification of gp120 led to the development of AIDSVAX B/B and AIDSVAX B/E. While both of these vaccine candidates failed in clinical trials (Flynn et al. 2005, Pitisuttithum et al. 2006), purified gp120 and related viral glycoproteins served as the booster shots in the RV144, Uhamabo, Mosaico and Imbokodo trials (Rerks-Ngarm et al. 2009, Bekker et al. 2018, Abakuks 1973, U.S. National Library of Medicine 2020b, a, Cohen 2020). With the exception of Mosaico and Imbokodo, which are ongoing, these trials likewise failed to produce an effective, workable HIV vaccine.

Table 1. HIV Vaccine Progenitors of SARS-CoV-2 Vaccine Candidates in Clinical Trials*

<i>Vaccine Model</i>	<i>SARS-CoV-2 Candidates</i>		<i>HIV Vaccine Progenitor</i> †
	<i>Number</i>	<i>Percent</i>	
Purified Viral Subunit	25	32.1%	AIDSVAX (Flynn et al. 2005)
Nucleic Acid ‡	20	25.6%	HTN 505 (Hammer et al. 2013)
Viral Vector §	16	20.5%	Merck STEP (Buchbinder et al. 2008)
Inactivated Virus	10	12.8%	–
Virus-Like Particle	3	3.8%	(Young et al. 2006)
Viral Vector + DC ¶	3	3.8%	(Kundu et al. 1998, Lu et al. 2004)
Attenuated Virus	1	1.3%	–

* Among 78 SARS-CV-2 vaccine candidates in clinical trials identified by WHO as of March 5, 2021 (World Health Organization 2021). These include vaccines currently approved or reported to have completed phase 3 trials (Kyriakidis et al. 2021): 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 Medicago-Glaxo Smith Kline (virus-like particle).

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

‡ Includes vaccines based on plasma DNA and messenger RNA.

§ Includes vaccines based on replicating and non-replicating viral vectors.

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

Yet the entire line of research laid the scientific foundation for subsequent identification of the spike protein as the key molecule on SARS-CoV-2 unlocking ACE2 receptors in the human lungs and other organs. It further laid the foundation for the use of purified versions of the spike protein in vaccine candidates currently under development against SARS-CoV-2. One of these candidates is NVX-CoV2373, under development by Novavax, produced high titers of neutralizing antibodies in a phase 1/2 trial (Keech et al. 2020) and has been under phase 3 investigation since September 2020.

The model employed for the priming dose in the STEP, RV144, Unambo, Mosaico and Imbokodo trials of HIV vaccine candidates was a viral vector. The STEP relied on the Ad5 virus. When that trial failed, the RV144 and Uhambo trials switched to a canarypox viral vector. When those trials failed, the Mosaico and Imbokodo trials switched to the Ad26 virus. Now, one-fifth of the vaccines against SARS-CoV-2 in Table 1 are based upon the viral vector model. Among these vaccines is the Ad26.COVS candidate, developed by Johnson & Johnson and Beth Israel Deaconess Medical Center and recently approved for emergency use in the United States and based upon the Ad26 vector (Sadoff et al. 2021, National Institute of Allergy and Infectious Diseases 2021).

Other SARS-CoV-2 vaccines based upon the viral vector model include AZD1222, developed by AstraZeneca and Oxford University, based upon the Ad5 vector (van Doremalen et al. 2020), and Gem-COVID-Vac/Sputnik V, developed by Gamalaya Research Institute, based upon a priming dose with Ad26 vector and a booster dose with the Ad5 vector (Sputnik V 2020, Kyriakidis et al. 2021). It is not just the case that the HIV vector vaccine trials predated these SARS-CoV-2 vaccines. The knowledge gained from these failed progenitor trials – particularly a greater understanding of the role of preexisting antibodies against the viral vectors themselves – contributed directly to the design of their more successful progeny.

As shown in Table 1, about one in four SARS-CoV-2 vaccine candidates in clinical trials is based upon the nucleic acid platform. These include not only the mRNA-based vaccines from Pfizer-BioNTech (Polack et al. 2020) and Moderna (Anderson et al. 2020, Widge et al. 2021), already approved for emergency use in the United States and other jurisdictions, but also plasmid DNA-based and other mRNA-based vaccines in development. While a phase 1 trial of a plasmid DNA-based HIV vaccine was launched as early as 2002 (Graham et al. 2006), only one nucleic acid-based vaccine against HIV has advanced as far enough to undergo evaluation in a phase 3

clinical trial. In the HTVN 505 trial, as we've already noted, a priming dose with a plasmid DNA-based vaccine was combined with an Ad5 vector-based booster (Hammer et al. 2013). That's not a whole lot of progenitors.

But this is not about keeping a box score of the number of DNA-based and RNA-based vaccines against HIV. The critical issue is that the repeated failure of vector-based vaccine candidates against HIV provided the momentum to press forward with nucleic acid-based models. And the further failure of the plasmid DNA-based vaccine in HTVN 505 enhanced the incentive to investigate mRNA-based vaccines as alternatives. After all, DNA was known to be more stable than RNA, but RNA only had to enter the host cell cytoplasm to do its job, while DNA had to go one step further and get into the cell nucleus. So, if a DNA-based vaccine didn't work, then researchers would have to figure out how to deliver a more stable RNA-based vaccine.

Table 1 shows us that fewer SARS-CoV-2 candidates have exploited the virus-like particle and the dendritic cell models. Still, the same underlying paradigm applies. The failure of the viral vector model to yield an effective vaccine against HIV expanded the search for other models that mimicked viral infection and thus stimulated an adequate cellular immune response.

8. Counterarguments

8.1. *What About Inactivated Virus Vaccines?*

The first counterargument comes directly out of Table 1. A total of 14 percent of SARS-CoV-2 vaccine candidates in clinical trials have been based on conventional models that predated the search for an HIV vaccine. These include inactivated viral vaccines developed by Sinovac (Zhang et al. 2021), Sinopharm (Xia et al. 2021), and Bharat (Ella et al. 2020), which are now in use in several countries worldwide.

The inactivated vaccine model may appear to be so primitive that its successful application does not even require knowledge of the SARS-CoV-2 genome. Just marinate the virus in formaldehyde – or, more recently, in the alkylating agent beta propiolactone (BPL) – and it's ready for prime time. But that is far from the reality of modern vaccine development.

It has been long been known that an inactivated virus cannot on its own infect host cells and thus adequately stimulate cellular immunity. That could lead to a weaker, shorter-lived immune response and thus require higher doses and repeated boosters. To get around this

limitation, inactivated virus vaccines had to be administered with a mixture of aluminum salts called alum, which acts as an adjuvant (Christensen 2016). In fact, all three of the inactivated virus vaccines currently in use against SARS-CoV-2 are administered along with alum or another aluminum salt (Kyriakidis et al. 2021).

The use of vaccine adjuvants is hardly new. What is new is the regulatory framework for demonstrating that a vaccine candidate is effective. It is no longer enough for a developer to submit data that a virus was inactivated with BPL and then combined with alum. Developers now have to show that the BPL disables the viral RNA without also knocking out the surface glycoproteins that stimulate the host's immune response (Fan et al. 2017). They now have to demonstrate during phase 1/2 trials that their proposed candidate adequately stimulates cellular immunity as well as humoral immunity, especially in view of the evidence that natural infection with some coronaviruses evokes only limited-duration protection (Choe et al. 2017). Had it not been for advances in virology and immunology achieved through HIV research in the 1980s and 1990s, one wonders whether inactivated viral vaccines against SARS-CoV-2 would have cleared these significantly higher, modern-day regulatory hurdles.

As we've already learned, the search for an HIV vaccine focused researchers' attention on the importance of the cellular immune response to infection, and not just the humoral immune response. Scientists had learned that the first step in the infection of a CD4+ cell, also called a T-helper (or Th) cell, was the attachment of key glycoprotein gp120 (Fauci 1988). They further determined that there were actually two types of Th cells.⁹ Resistance to HIV infection, it was found, was associated with a strong response of type-1 T-helper cells (Th1), which mediated the cellular immune response. By contrast, progression of HIV infection to AIDS was associated with a switch to type-2 T-helper cells (Th2), which mediated the humoral immune response (Romagnani et al. 1994).

Knowledge about the nature of virus-host molecular interaction and the cellular immune response – acquired from the confrontation with HIV – ultimately helped to resuscitate conventional vaccine technologies. In phase 1/2 trials, each one of three inactivated virus

⁹ Immunologists now regard Th1 and Th2 as distinct phenotypes of both CD4+ and CD8+ cells, but the complete scheme had not been worked out when the Th1 → Th2 switch hypothesis was first elaborated.

candidates (Sinovac, Sinopharm, Bharat) was able to demonstrate a dominance of Th1 over Th2 activation.¹⁰

8.2. SARS-CoV-1, MERS-CoV, and Other Viruses Deserve the Credit Instead.

The second counterargument is that outbreaks of other deadly coronaviruses – SARS-CoV-1 in 2002-2003 and MERS-CoV – are what really prepared us scientifically for the arrival of SARS-CoV-2. By the time that the latter virus arrived in late 2019, as we've acknowledged, virologists already knew that coronaviruses were single-stranded, positive-sense RNA viruses, that the outer shell was adorned with spike proteins, that the spike protein of SARS-CoV-1 locked onto the ACE2 receptor of the host cell. They even understood the conformational change in the spike's S molecule required to fuse with host cell membrane (Masters 2006). Vaccines against SARS-CoV-1 and MERS-CoV, based upon the technologies described in Table 1, were already in development, and a few candidates had entered clinical trials (Enjuanes et al. 2016, Li et al. 2020). There is little doubt that the acquired knowledge about SARS-CoV-1 and MERS-CoV set the stage for the extraordinarily rapid emergence of workable, efficacious SARS-CoV-2 vaccines in 2020.

Quite apart from SARS-CoV-1 and MERS-CoV, didn't research on other unrelated viruses also contribute to our scientific know-how? Take Ebola virus. The Ebola vaccine 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 (Garbutt et al. 2004, Jones et al. 2005, Feldmann et al. 2007). The resultant vaccine (rVSV-ZEBOV) was approved in Dec. 2019 (Monath et al. 2019).

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 (European Medicines Agency 2020).

Human papillomavirus (HPV) is a major cause of cervical cancer and other diseases. The HPV vaccines in current use are virus-like particles (Kirnbauer et al. 1992, Kirnbauer et al. 1993, Harro et al. 2001, Koutsky et al. 2002). And we've already acknowledged that a vaccine based on the virus-like particle technology is currently in use against hepatitis B (Fuenmayor, Godia, and Cervera 2017). What's more, those vaccines were successes, not failures.

¹⁰ It has also been suggested HIV trials in South Africa have created the necessary infrastructure for subsequently conducting SARS-CoV-2 trials (Miller 2021). We will not pursue this line of inquiry here.

The principal response to this multifaceted counterargument is that the foregoing observations about other vaccines are accurate but shortsighted. For any one of these vaccines – call it vaccine X – we could have adapted this article with a modified title: *The Repeated Setbacks of HIV Vaccine Development Laid the Groundwork for Vaccine X*.

It is not enough merely to cite the development of some other viral vaccine X as a counterexample. One would have to argue that vaccine X was developed along a track independent from and unaided by the search for an HIV vaccine. That would not fit the facts.

To the contrary, the successful search for a human papillomavirus (HPV) vaccine shared common techniques of virology and molecular biology with the failed search for an HIV vaccine. Attempts to exploit the virus-like particle model go back to the early years of the HIV epidemic (Gheysen et al. 1989, Delchambre et al. 1989, Wagner et al. 1998, Buonaguro et al. 2002). The successful Ebola vaccines and the unsuccessful HIV vaccine likewise drew from a common knowledge base. The development of the VSV viral vector used in the Ebola vaccine did not come out of nowhere. In fact, the first experimental Ebola virus vaccine to protect nonhuman primates involved an adenovirus 5 vector (Sullivan et al. 2000), the same vector that served as the prototype for the Merck STEP vaccine.

To reiterate, the development of viral vector vaccines for HIV and for Ebola shared common techniques of virology and molecular biology. 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 just in time and that prior work on vector virus vaccines for HIV was an irrelevant bystander doesn't fit the facts.

9. Private Losses, Public Gains

If we dare to accept the principal contention of this article, then we are confronted with a truly massive R&D spillover. A relatively modest investment of about US\$ 16 billion spread over two decades on an enterprise that, on its face, has been unsuccessful actually laid the foundation for a subsequently successful enterprise that may end up saving the world from the brutal endgame of the plagues (Cohn 2008, Alfani and Bonetti 2019). This singular case study, with a sample size of one, would appear to be so important that we ought to think hard about what, if anything, it teaches us about the economics of innovation.

9.1. *How Do Firms Learn from Failures?*

Let's enumerate 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; and GlaxoSmithKline (GSK), whose purified gp120 adapted to HIV subtype C was used in the Uhambo trial. The apparent failures of these private entities to capitalize on their intellectual property rights to specific vaccine platforms were counterbalanced by enormous social gains in immunology, virology, molecular biology, and vaccine design generally.

There is certainly no paucity of economic research examining how one firm learns from another firm's innovation (Jaffe 1986, Bernstein 1988, Ornaghi 2006). Neither is there a lack of data on the ripple effects of an apparently narrow innovation in one product market on the state of the art in other product markets. The discovery of froth flotation, for example, initially implemented in the refining of sulfide ores, ended up benefiting firms in mineral processing generally, waste water treatment, and paper recycling (Lynchagin et al. 2016). Nor is there any denying that firms don't always gain from R&D spillovers (Bloom, Schankerman, and Van Reenen 2013). Nor has it been lost on economists that the social returns to R&D are in the aggregate a multiple of the private returns (Lucking, Bloom, and Van Reenen 2019). Still, the case where a sustained string of private R&D failures has been associated with substantial social gains has received little attention.

There is an interesting literature on how organizations react to *their own failures* (Desai 2016). 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 (Madsen and Desai 2010).

Here, however, our focus is on the responses of firms and other organizations to the *failures of others*. 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 (Tanne 2006). 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 (Cannon et al. 2010). The failure of torcetrapib ultimately delayed Merck’s larger phase 3 trial of its own anacetrapib by about 4 years (News Analysis 2011). 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 (News Analysis 2011, Schwartz et al. 2009).

Case studies of this sort have led investigators to hypothesize that the phase 3 clinical trial is the critical catalyst for knowledge leaks of negative results in bio-pharmaceutical R&D (Magazzani, Pammolli, and Riccaboni 2012, Chiou et al. 2016). In our study, this hypothesis points the finger at AIDSVAX, Merck STEP, RV144, Uhambu, and other failed phase 3 HIV vaccine trials as key pathways for the diffusion of know-how that prepared us for SARS-CoV-2 vaccines. Still, there is evidence that phase 2 trials have been just as instrumental in opening up knowledge leaks (Krieger 2021).

More than a few economists have suggested that patents on existing innovations may inhibit subsequent scientific research and product development (Galasso and Schankerman 2015). Whether this phenomenon – well documented in the case of the human genome project (Williams 2013) – applies just as well to the development of HIV and other antiviral vaccines is less clear. Intellectual property rights to adenovirus 5 (Ad5) based viral-vector vaccines did not stop Sanofi Pasteur from developing a canarypox viral-vector based vaccine. Nor did patents on purified gp120 stop GlaxoSmithKline (GSK) from developing another form of the purified glycoprotein adapted to an HIV subtype more prevalent in South Africa.

Still other researchers have distinguished between the R&D spillover effects of complete failures and near failures (Kim and Miner 2007). A study of the disk drive industry suggested that a firm’s complete exit from a market has a considerably greater inhibitory effect on knowledge diffusion than less-than-total failure with survival (Hoetker and Agarwal 2007). This

distinction, however, may not have been critically important in the diffusion of knowledge generated by HIV vaccine research. 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 clinical trials. This observation suggests that the nonprofit sector may have been a critical vehicle in transferring otherwise doomed technical know-how from a failed firm to successors.

Why isn't it simply the case that the public sector kept the search for an HIV vaccine alive, even in the face of a string of failures of private vaccine candidates? After all, the public sector has made far and away the largest contribution to HIV vaccine R&D over the last two decades (Resource Tracking for HIV Prevention R&D Working Group (RTWG) 2019, 2020). The Pox-Protein *Public-Private Partnership* (or P5) initiated the Uhambo trial in 2016. Public regulation of pharmaceuticals created the framework that requires conducting the phase 2 and 3 clinical trials that were undoubtedly instrumental in promoting knowledge leaks. 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 intellectual property rights. These are the firms that ultimately have to learn from each other's failures.

Whatever the underlying mechanisms that transformed the succession of failed HIV vaccines into the growing list of successful SARS-CoV-2 vaccines already in use today, we need to take a broad view of the returns to HIV-related research and development. A narrow view that focused myopically on the string of setbacks of HIV vaccine development would vastly understate its contribution to our social welfare.

References

- Abakuks, Andris. 1973. "An Optimal Isolation Policy for an Epidemic." *Journal of Applied Probability* 10 (2):247-262.
- Aghion, Philippe, and Xavier Jaravel. 2015. "Knowledge Spillovers, Innovation and Growth." *Economic Journal* 125 (March):533–573. doi: 10.1111/eoj.12199.
- Alfani, G., and M. Bonetti. 2019. "A survival analysis of the last great European plagues: The case of Nonantola (Northern Italy) in 1630." *Popul Stud (Camb)* 73 (1):101-118. doi: 10.1080/00324728.2018.1457794.
- Allen, T. M., T. U. Vogel, D. H. Fuller, B. R. Mothe, S. Steffen, J. E. Boyson, T. Shipley, J. Fuller, T. Hanke, A. Sette, J. D. Altman, B. Moss, A. J. McMichael, and D. I. Watkins. 2000. "Induction of AIDS virus-specific CTL activity in fresh, unstimulated peripheral blood lymphocytes from rhesus macaques vaccinated with a DNA prime/modified vaccinia virus Ankara boost regimen." *J Immunol* 164 (9):4968-78. doi: 10.4049/jimmunol.164.9.4968.
- Amanat, F., and F. Krammer. 2020. "SARS-CoV-2 Vaccines: Status Report." *Immunity* 52 (4):583-589. doi: 10.1016/j.immuni.2020.03.007.
- Amara, R. R., F. Villinger, J. D. Altman, S. L. Lydy, S. P. O'Neil, S. I. Staprans, D. C. Montefiori, Y. Xu, J. G. Herndon, L. S. Wyatt, M. A. Candido, N. L. Kozyr, P. L. Earl, J. M. Smith, H. L. Ma, B. D. Grimm, M. L. Hulsey, J. Miller, H. M. McClure, J. M. McNicholl, B. Moss, and H. L. Robinson. 2001. "Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine." *Science* 292 (5514):69-74. doi: 10.1126/science.1058915.
- Anderson, E. J., N. G. Roupael, A. T. Widge, L. A. Jackson, P. C. Roberts, M. Makhene, J. D. Chappell, M. R. Denison, L. J. Stevens, A. J. Pruijssers, A. B. McDermott, B. Flach, B. C. Lin, N. A. Doria-Rose, S. O'Dell, S. D. Schmidt, K. S. Corbett, P. A. Swanson, 2nd, M. Padilla, K. M. Neuzil, H. Bennett, B. Leav, M. Makowski, J. Albert, K. Cross, V. V. Edara, K. Floyd, M. S. Suthar, D. R. Martinez, R. Baric, W. Buchanan, C. J. Luke, V. K. Phadke, C. A. Rostad, J. E. Ledgerwood, B. S. Graham, J. H. Beigel, and R. N. A. Study Group m. 2020. "Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults." *N Engl J Med* 383 (25):2427-2438. doi: 10.1056/NEJMoa2028436.
- Andersson, A. C., M. Schwerdtfeger, and P. J. Holst. 2018. "Virus-Like-Vaccines against HIV." *Vaccines (Basel)* 6 (1). doi: 10.3390/vaccines6010010.
- Arrow, Kenneth J. 1962. "The Economic Implications of Learning by Doing." *Review of Economic Studies* 29 (3):155-173. doi: 10.2307/2295952
- Azoulay, Pierre. 2002. "Do Pharmaceutical Sales Respond to Scientific Evidence?" *Journal of Economics & Management Strategy* 11 (4):551-716. doi: <https://doi.org/10.1111/j.1430-9134.2002.00551.x>.
- Bachmann, M. H., E. L. Delwart, E. G. Shpaer, P. Lingenfelter, R. Singal, and J. I. Mullins. 1994. "Rapid genetic characterization of HIV type 1 strains from four World Health Organization-sponsored vaccine evaluation sites using a heteroduplex mobility assay. WHO Network for HIV Isolation and Characterization." *AIDS Res Hum Retroviruses* 10 (11):1345-53. doi: 10.1089/aid.1994.10.1345.

- Ball, Philip. 2021. "The lightning-fast quest for COVID vaccines — and what it means for other diseases." *Nature* 589:16-18.
- Bekker, L. G., Z. Moodie, N. Grunenberg, F. Laher, G. D. Tomaras, K. W. Cohen, M. Allen, M. Malahleha, K. Mngadi, B. Daniels, C. Innes, C. Bentley, N. Frahm, D. E. Morris, L. Morris, N. N. Mkhize, D. C. Montefiori, M. Sarzotti-Kelsoe, S. Grant, C. Yu, V. L. Mehra, M. N. Pensiero, S. Phogat, C. A. DiazGranados, S. W. Barnett, N. Kanesa-Thasan, M. Koutsoukos, N. L. Michael, M. L. Robb, J. G. Kublin, P. B. Gilbert, L. Corey, G. E. Gray, M. J. McElrath, and Hvtm Protocol Team. 2018. "Subtype C ALVAC-HIV and bivalent subtype C gp120/MF59 HIV-1 vaccine in low-risk, HIV-uninfected, South African adults: a phase 1/2 trial." *Lancet HIV* 5 (7):e366-e378. doi: 10.1016/S2352-3018(18)30071-7.
- Benmira, S., V. Bhattacharya, and M. L. Schmid. 2010. "An effective HIV vaccine: A combination of humoral and cellular immunity?" *Curr HIV Res* 8 (6):441-9. doi: 10.2174/157016210793499286.
- Bernstein, Jeffrey I. 1988. "Costs of Production, Intra- and Interindustry R&D Spillovers: Canadian Evidence." *Canadian Journal of Economics* 21 (2):324-347. doi: <https://www.jstor.org/stable/135304>.
- Bloom, Nicholas, Mark Schankerman, and John Van Reenen. 2013. "Identifying Technology Spillovers and Product Market Rivalry." *Econometrica* 81 (4):1347-1393. doi: <https://www.jstor.org/stable/23524180>.
- Bogers, W. M., H. Oostermeijer, P. Mooij, G. Koopman, E. J. Verschoor, D. Davis, J. B. Ulmer, L. A. Brito, Y. Cu, K. Banerjee, G. R. Otten, B. Burke, A. Dey, J. L. Heeney, X. Shen, G. D. Tomaras, C. Labranche, D. C. Montefiori, H. X. Liao, B. Haynes, A. J. Geall, and S. W. Barnett. 2015. "Potent immune responses in rhesus macaques induced by nonviral delivery of a self-amplifying RNA vaccine expressing HIV type 1 envelope with a cationic nanoemulsion." *J Infect Dis* 211 (6):947-55. doi: 10.1093/infdis/jiu522.
- Borrow, P., H. Lewicki, B. H. Hahn, G. M. Shaw, and M. B. Oldstone. 1994. "Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection." *J Virol* 68 (9):6103-10.
- Buchbinder, S. P., D. V. Mehrotra, A. Duerr, D. W. Fitzgerald, R. Mogg, D. Li, P. B. Gilbert, J. R. Lama, M. Marmor, C. Del Rio, M. J. McElrath, D. R. Casimiro, K. M. Gottesdiener, J. A. Chodakewitz, L. Corey, M. N. Robertson, and Team Step Study Protocol. 2008. "Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial." *Lancet* 372 (9653):1881-1893. doi: 10.1016/S0140-6736(08)61591-3.
- Buonaguro, L., L. Racioppi, M. L. Tornesello, C. Arra, M. L. Visciano, B. Biryahwaho, S. D. Sempala, G. Giraldo, and F. M. Buonaguro. 2002. "Induction of neutralizing antibodies and cytotoxic T lymphocytes in Balb/c mice immunized with virus-like particles presenting a gp120 molecule from a HIV-1 isolate of clade A." *Antiviral Res* 54 (3):189-201. doi: 10.1016/s0166-3542(02)00004-9.
- Cannon, C. P., S. Shah, H. M. Dansky, M. Davidson, E. A. Brinton, A. M. Gotto, M. Stepanavage, S. X. Liu, P. Gibbons, T. B. Ashraf, J. Zafarino, Y. Mitchel, P. Barter, Efficacy Determining the, and Investigators Tolerability. 2010. "Safety of anacetrapib in patients with or at high risk for coronary heart disease." *N Engl J Med* 363 (25):2406-15. doi: 10.1056/NEJMoa1009744.

- Chiou, Jing-Yuan, Laura Magazzani, Fabio Pammolli, and Massimo Riccaboni. 2016. "Learning from successes and failures in pharmaceutical R&D." *Journal of Evolutionary Economics* 26:271-290. doi: 10.1007/s00191-015-0439-z.
- Choe, P. G., Rapm Perera, W. B. Park, K. H. Song, J. H. Bang, E. S. Kim, H. B. Kim, L. W. R. Ko, S. W. Park, N. J. Kim, E. H. Y. Lau, L. L. M. Poon, M. Peiris, and M. D. Oh. 2017. "MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015." *Emerg Infect Dis* 23 (7):1079-1084. doi: 10.3201/eid2307.170310.
- Christensen, D. 2016. "Vaccine adjuvants: Why and how." *Hum Vaccin Immunother* 12 (10):2709-2711. doi: 10.1080/21645515.2016.1219003.
- Cockrell, A. S., A. Beall, B. Yount, and R. Baric. 2017. "Efficient Reverse Genetic Systems for Rapid Genetic Manipulation of Emergent and Preemergent Infectious Coronaviruses." *Methods Mol Biol* 1602:59-81. doi: 10.1007/978-1-4939-6964-7_5.
- Cockrell, A. S., S. R. Leist, M. G. Douglas, and R. S. Baric. 2018. "Modeling pathogenesis of emergent and pre-emergent human coronaviruses in mice." *Mamm Genome* 29 (7-8):367-383. doi: 10.1007/s00335-018-9760-9.
- Cohen, Jon. 2020. "Another HIV vaccine strategy fails in large-scale study." *Science* (February 3). doi: doi:10.1126/science.abb1480.
- Cohn, S. K., Jr. 2008. "Epidemiology of the Black Death and successive waves of plague." *Med Hist Suppl* (27):74-100.
- Cornish, Lisa. 2020. *Funding COVID-19 vaccines: A timeline*. <https://www.devex.com/news/funding-covid-19-vaccines-a-timeline-97950>: Devex, August 21.
- da Silva, L. T., B. T. Santillo, A. de Almeida, Ajds Duarte, and T. M. Oshiro. 2018. "Using Dendritic Cell-Based Immunotherapy to Treat HIV: How Can This Strategy be Improved?" *Front Immunol* 9:2993. doi: 10.3389/fimmu.2018.02993.
- Day, T. A., and J. G. Kublin. 2013. "Lessons learned from HIV vaccine clinical efficacy trials." *Curr HIV Res* 11 (6):441-9. doi: 10.2174/1570162x113116660051.
- Delchambre, M., D. Gheysen, D. Thines, C. Thiriart, E. Jacobs, E. Verdin, M. Horth, A. Burny, and F. Bex. 1989. "The GAG precursor of simian immunodeficiency virus assembles into virus-like particles." *EMBO J* 8 (9):2653-60.
- Derdeyn, C. A., J. M. Decker, F. Bibollet-Ruche, J. L. Mokili, M. Muldoon, S. A. Denham, M. L. Heil, F. Kasolo, R. Musonda, B. H. Hahn, G. M. Shaw, B. T. Korber, S. Allen, and E. Hunter. 2004. "Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission." *Science* 303 (5666):2019-22. doi: 10.1126/science.1093137.
- Desai, Vinit. 2016. "Learning to learn from failures: the impact of operating experience on railroad accident responses." *Industrial and Corporate Change* 25 (2). doi: 10.1093/icc/dtq019.
- Desrosiers, R. C. 2004. "Prospects for an AIDS vaccine." *Nat Med* 10 (3):221-3. doi: 10.1038/nm0304-221.

- Doan, L. X., M. Li, C. Chen, and Q. Yao. 2005. "Virus-like particles as HIV-1 vaccines." *Rev Med Virol* 15 (2):75-88. doi: 10.1002/rmv.449.
- Downey, J. F., D. T. Rowe, S. Bacchetti, F. L. Graham, and S. T. Bayley. 1983. "Mapping of a 14,000-dalton antigen to early region 4 of the human adenovirus 5 genome." *J Virol* 45 (2):514-23.
- Dubey, S., J. Clair, T. M. Fu, L. Guan, R. Long, R. Mogg, K. Anderson, K. B. Collins, C. Gaunt, V. R. Fernandez, L. Zhu, L. Kierstead, S. Thaler, S. B. Gupta, W. Straus, D. Mehrotra, T. W. Tobery, D. R. Casimiro, and J. W. Shiver. 2007. "Detection of HIV vaccine-induced cell-mediated immunity in HIV-seronegative clinical trial participants using an optimized and validated enzyme-linked immunospot assay." *J Acquir Immune Defic Syndr* 45 (1):20-7. doi: 10.1097/QAI.0b013e3180377b5b.
- Dutta, A., C. T. Huang, C. Y. Lin, T. C. Chen, Y. C. Lin, C. S. Chang, and Y. C. He. 2016. "Sterilizing immunity to influenza virus infection requires local antigen-specific T cell response in the lungs." *Sci Rep* 6:32973. doi: 10.1038/srep32973.
- Ella, Raches, Siddharth Reddy, Harsh Jogdand, Vamshi Sarangi, Brunda Ganneru, Sai Prasad, Dipankar Das, Dugyala Raju, Usha Praturi, Gajanan Sapkal, Pragya Yadav, Prabhakar Reddy, Savita Verma, Chandramani Singh, Sagar Vivek Redkar, Chandra Sekhar Gillurkar, Jitendra Singh Kushwaha, Satyajit Mohapatra, Amit Bhate, Sanjay Rai, Samiran Panda, Priya Abraham, Nivedita Gupta, Krishna Ella, and Balram Bhargava. 2020. *Safety and immunogenicity clinical trial of an inactivated SARS-CoV-2 vaccine, BBV152 (a phase 2, double-blind, randomised controlled trial) and the persistence of immune responses from a phase 1 follow-up report*. <https://www.medrxiv.org/content/10.1101/2020.12.21.20248643v1>: December 22.
- Enjuanes, L., S. Zuniga, C. Castano-Rodriguez, J. Gutierrez-Alvarez, J. Canton, and I. Sola. 2016. "Molecular Basis of Coronavirus Virulence and Vaccine Development." *Adv Virus Res* 96:245-286. doi: 10.1016/bs.aivir.2016.08.003.
- European Medicines Agency. 2020. *Zabdeno*. <https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno>: July 23.
- Fan, C., X. Ye, Z. Ku, L. Kong, Q. Liu, C. Xu, Y. Cong, and Z. Huang. 2017. "Beta-Propiolactone Inactivation of Coxsackievirus A16 Induces Structural Alteration and Surface Modification of Viral Capsids." *J Virol* 91 (8). doi: 10.1128/JVI.00038-17.
- Fauci, A. S. 1988. "The human immunodeficiency virus: infectivity and mechanisms of pathogenesis." *Science* 239 (4840):617-22. doi: 10.1126/science.3277274.
- Feldmann, H., S. M. Jones, K. M. Daddario-DiCaprio, J. B. Geisbert, U. Stroher, A. Grolla, M. Bray, E. A. Fritz, L. Fernando, F. Feldmann, L. E. Hensley, and T. W. Geisbert. 2007. "Effective post-exposure treatment of Ebola infection." *PLoS Pathog* 3 (1):e2. doi: 10.1371/journal.ppat.0030002.
- Flynn, N. M., D. N. Forthal, C. D. Harro, F. N. Judson, K. H. Mayer, M. F. Para, and H. I. V. Vaccine Study Group rgp. 2005. "Placebo-controlled phase 3 trial of a recombinant glycoprotein 120 vaccine to prevent HIV-1 infection." *J Infect Dis* 191 (5):654-65. doi: 10.1086/428404.

- Forthal, D. N., P. B. Gilbert, G. Landucci, and T. Phan. 2007. "Recombinant gp120 vaccine-induced antibodies inhibit clinical strains of HIV-1 in the presence of Fc receptor-bearing effector cells and correlate inversely with HIV infection rate." *J Immunol* 178 (10):6596-603. doi: 10.4049/jimmunol.178.10.6596.
- Fuenmayor, J., F. Godia, and L. Cervera. 2017. "Production of virus-like particles for vaccines." *N Biotechnol* 39 (Pt B):174-180. doi: 10.1016/j.nbt.2017.07.010.
- Galasso, Alberto, and Mark Schankerman. 2015. "Patents and cumulative innovation." *Quarterly Journal of Economics* 130 (1):317-370. doi: <https://www.jstor.org/stable/10.2307/26372601>.
- Gandhi, R. T., D. S. Kwon, E. A. Macklin, J. R. Shopis, A. P. McLean, N. McBrine, T. Flynn, L. Peter, A. Sbrolla, D. E. Kaufmann, F. Porichis, B. D. Walker, N. Bhardwaj, D. H. Barouch, and D. G. Kavanagh. 2016. "Immunization of HIV-1-Infected Persons With Autologous Dendritic Cells Transfected With mRNA Encoding HIV-1 Gag and Nef: Results of a Randomized, Placebo-Controlled Clinical Trial." *J Acquir Immune Defic Syndr* 71 (3):246-53. doi: 10.1097/QAI.0000000000000852.
- Garbutt, M., R. Liebscher, V. Wahl-Jensen, S. Jones, P. Moller, R. Wagner, V. Volchkov, H. D. Klenk, H. Feldmann, and U. Stroher. 2004. "Properties of replication-competent vesicular stomatitis virus vectors expressing glycoproteins of filoviruses and arenaviruses." *J Virol* 78 (10):5458-65. doi: 10.1128/jvi.78.10.5458-5465.2004.
- Genovese, L., M. Nebuloni, and M. Alfano. 2013. "Cell-Mediated Immunity in Elite Controllers Naturally Controlling HIV Viral Load." *Front Immunol* 4:86. doi: 10.3389/fimmu.2013.00086.
- Gheysen, D., E. Jacobs, F. de Foresta, C. Thiriart, M. Francotte, D. Thines, and M. De Wilde. 1989. "Assembly and release of HIV-1 precursor Pr55gag virus-like particles from recombinant baculovirus-infected insect cells." *Cell* 59 (1):103-12. doi: 10.1016/0092-8674(89)90873-8.
- Gilbert, P. B., M. L. Peterson, D. Follmann, M. G. Hudgens, D. P. Francis, M. Gurwith, W. L. Heyward, D. V. Jobes, V. Popovic, S. G. Self, F. Sinangil, D. Burke, and P. W. Berman. 2005. "Correlation between immunologic responses to a recombinant glycoprotein 120 vaccine and incidence of HIV-1 infection in a phase 3 HIV-1 preventive vaccine trial." *J Infect Dis* 191 (5):666-77. doi: 10.1086/428405.
- Girard, M. 1990. "Prospects for an AIDS vaccine." *Cancer Detect Prev* 14 (3):411-3.
- Goulder, P. J., R. E. Phillips, R. A. Colbert, S. McAdam, G. Ogg, M. A. Nowak, P. Giangrande, G. Luzzi, B. Morgan, A. Edwards, A. J. McMichael, and S. Rowland-Jones. 1997. "Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS." *Nat Med* 3 (2):212-7. doi: 10.1038/nm0297-212.
- Graham, B. S., R. A. Koup, M. Roederer, R. T. Bailer, M. E. Enama, Z. Moodie, J. E. Martin, M. M. McCluskey, B. K. Chakrabarti, L. Lamoreaux, C. A. Andrews, P. L. Gomez, J. R. Mascola, G. J. Nabel, and Team Vaccine Research Center 004 Study. 2006. "Phase 1 safety and immunogenicity evaluation of a multiclade HIV-1 DNA candidate vaccine." *J Infect Dis* 194 (12):1650-60. doi: 10.1086/509259.
- Gray, G., S. Buchbinder, and A. Duerr. 2010. "Overview of STEP and Phambili trial results: two phase IIb test-of-concept studies investigating the efficacy of MRK adenovirus type 5 gag/pol/nef subtype B HIV vaccine." *Curr Opin HIV AIDS* 5 (5):357-61. doi: 10.1097/COH.0b013e32833d2d2b.

- Griliches, Zvi. 1992. "The Search for R&D Spillovers." *Scandinavian Journal of Economics* 94:S29-S47. doi: 10.2307/3440244
- Hammer, S. M., M. E. Sobieszczyk, H. Janes, S. T. Karuna, M. J. Mulligan, D. Grove, B. A. Koblin, S. P. Buchbinder, M. C. Keefer, G. D. Tomaras, N. Frahm, J. Hural, C. Anude, B. S. Graham, M. E. Enama, E. Adams, E. DeJesus, R. M. Novak, I. Frank, C. Bentley, S. Ramirez, R. Fu, R. A. Koup, J. R. Mascola, G. J. Nabel, D. C. Montefiori, J. Kublin, M. J. McElrath, L. Corey, P. B. Gilbert, and Hvtm Study Team. 2013. "Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine." *N Engl J Med* 369 (22):2083-92. doi: 10.1056/NEJMoa1310566.
- Harris, J. E. 2009. "Why we don't have an HIV vaccine, and how we can develop one." *Health Aff (Millwood)* 28 (6):1642-54. doi: 10.1377/hlthaff.28.6.1642.
- Harro, C. D., Y. Y. Pang, R. B. Roden, A. Hildesheim, Z. Wang, M. J. Reynolds, T. C. Mast, R. Robinson, B. R. Murphy, R. A. Karron, J. Dillner, J. T. Schiller, and D. R. Lowy. 2001. "Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine." *J Natl Cancer Inst* 93 (4):284-92. doi: 10.1093/jnci/93.4.284.
- Haynes, B. F., G. M. Shaw, B. Korber, G. Kelsoe, J. Sodroski, B. H. Hahn, P. Borrow, and A. J. McMichael. 2016. "HIV-Host Interactions: Implications for Vaccine Design." *Cell Host Microbe* 19 (3):292-303. doi: 10.1016/j.chom.2016.02.002.
- Heeney, J. L., and S. A. Plotkin. 2006. "Immunological correlates of protection from HIV infection and disease." *Nat Immunol* 7 (12):1281-4. doi: 10.1038/ni1206-1281.
- Hicks, D. J., A. R. Fooks, and N. Johnson. 2012. "Developments in rabies vaccines." *Clin Exp Immunol* 169 (3):199-204. doi: 10.1111/j.1365-2249.2012.04592.x.
- Hoetker, Glenn, and Rajshree Agarwal. 2007. "Death Hurts, But It Isn't Fatal: The Postexit Diffusion of Knowledge Created by Innovative Companies." *Academy of Management Journal* 50 (2):446-467. doi: <https://doi.org/10.5465/amj.2007.24634858>.
- Jaffe, Adam B. 1986. "Technological Opportunity and Spillovers of R & D: Evidence from Firms' Patents, Profits, and Market Value." *American Economic Review* 76 (5):984-1001. doi: <https://www.jstor.org/stable/1816464>.
- Jones, S. M., H. Feldmann, U. Stroher, J. B. Geisbert, L. Fernando, A. Grolla, H. D. Klenk, N. J. Sullivan, V. E. Volchkov, E. A. Fritz, K. M. Daddario, L. E. Hensley, P. B. Jahrling, and T. W. Geisbert. 2005. "Live attenuated recombinant vaccine protects nonhuman primates against Ebola and Marburg viruses." *Nat Med* 11 (7):786-90. doi: 10.1038/nm1258.
- Juskewitch, J. E., C. J. Tapia, and A. J. Windebank. 2010. "Lessons from the Salk polio vaccine: methods for and risks of rapid translation." *Clin Transl Sci* 3 (4):182-5. doi: 10.1111/j.1752-8062.2010.00205.x.
- Kariko, K., M. Buckstein, H. Ni, and D. Weissman. 2005. "Suppression of RNA recognition by Toll-like receptors: the impact of nucleoside modification and the evolutionary origin of RNA." *Immunity* 23 (2):165-75. doi: 10.1016/j.immuni.2005.06.008.

- Kariko, K., H. Muramatsu, F. A. Welsh, J. Ludwig, H. Kato, S. Akira, and D. Weissman. 2008. "Incorporation of pseudouridine into mRNA yields superior nonimmunogenic vector with increased translational capacity and biological stability." *Mol Ther* 16 (11):1833-40. doi: 10.1038/mt.2008.200.
- Keech, C., G. Albert, I. Cho, A. Robertson, P. Reed, S. Neal, J. S. Plested, M. Zhu, S. Cloney-Clark, H. Zhou, G. Smith, N. Patel, M. B. Frieman, R. E. Haupt, J. Logue, M. McGrath, S. Weston, P. A. Piedra, C. Desai, K. Callahan, M. Lewis, P. Price-Abbott, N. Formica, V. Shinde, L. Fries, J. D. Lickliter, P. Griffin, B. Wilkinson, and G. M. Glenn. 2020. "Phase 1-2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine." *N Engl J Med* 383 (24):2320-2332. doi: 10.1056/NEJMoa2026920.
- Keele, B. F., E. E. Giorgi, J. F. Salazar-Gonzalez, J. M. Decker, K. T. Pham, M. G. Salazar, C. Sun, T. Grayson, S. Wang, H. Li, X. Wei, C. Jiang, J. L. Kirchherr, F. Gao, J. A. Anderson, L. H. Ping, R. Swanstrom, G. D. Tomaras, W. A. Blattner, P. A. Goepfert, J. M. Kilby, M. S. Saag, E. L. Delwart, M. P. Busch, M. S. Cohen, D. C. Montefiori, B. F. Haynes, B. Gaschen, G. S. Athreya, H. Y. Lee, N. Wood, C. Seoighe, A. S. Perelson, T. Bhattacharya, B. T. Korber, B. H. Hahn, and G. M. Shaw. 2008. "Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection." *Proc Natl Acad Sci U S A* 105 (21):7552-7. doi: 10.1073/pnas.0802203105.
- Kim, Ji-Yub (Jay), and Anne S. Miner. 2007. "Vicarious Learning from the Failures and Near-Failures of Others: Evidence from the U.S. Commercial Banking Industry." *Academy of Management Journal* 30 (3):687-714. doi: <https://doi.org/10.5465/amj.2007.25529755>.
- Kirnbauer, R., F. Booy, N. Cheng, D. R. Lowy, and J. T. Schiller. 1992. "Papillomavirus L1 major capsid protein self-assembles into virus-like particles that are highly immunogenic." *Proc Natl Acad Sci U S A* 89 (24):12180-4. doi: 10.1073/pnas.89.24.12180.
- Kirnbauer, R., J. Taub, H. Greenstone, R. Roden, M. Durst, L. Gissmann, D. R. Lowy, and J. T. Schiller. 1993. "Efficient self-assembly of human papillomavirus type 16 L1 and L1-L2 into virus-like particles." *J Virol* 67 (12):6929-36.
- Koup, R. A., J. T. Safrit, Y. Cao, C. A. Andrews, G. McLeod, W. Borkowsky, C. Farthing, and D. D. Ho. 1994. "Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome." *J Virol* 68 (7):4650-5.
- Koutsky, L. A., K. A. Ault, C. M. Wheeler, D. R. Brown, E. Barr, F. B. Alvarez, L. M. Chiacchierini, K. U. Jansen, and Investigators Proof of Principle Study. 2002. "A controlled trial of a human papillomavirus type 16 vaccine." *N Engl J Med* 347 (21):1645-51. doi: 10.1056/NEJMoa020586.
- Krieger, Joshua L. 2021. "Trials and Terminations: Learning from Competitors' R&D Failures." *Management Science* ePub February 15. doi: <https://doi.org/10.1287/mnsc.2020.3775>.
- Kundu, S. K., E. Engleman, C. Benike, M. H. Shaper, M. Dupuis, W. C. van Schooten, M. Eibl, and T. C. Merigan. 1998. "A pilot clinical trial of HIV antigen-pulsed allogeneic and autologous dendritic cell therapy in HIV-infected patients." *AIDS Res Hum Retroviruses* 14 (7):551-60. doi: 10.1089/aid.1998.14.551.

- Kyriakidis, N. C., A. Lopez-Cortes, E. V. Gonzalez, A. B. Grimaldos, and E. O. Prado. 2021. "SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates." *NPJ Vaccines* 6 (1):28. doi: 10.1038/s41541-021-00292-w.
- Lan, J., J. Ge, J. Yu, S. Shan, H. Zhou, S. Fan, Q. Zhang, X. Shi, Q. Wang, L. Zhang, and X. Wang. 2020. "Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor." *Nature* 581 (7807):215-220. doi: 10.1038/s41586-020-2180-5.
- Leal, L., A. C. Guardo, S. Moron-Lopez, M. Salgado, B. Mothe, C. Heirman, P. Pannus, G. Vanham, H. J. van den Ham, R. Gruters, A. Andeweg, S. Van Meirvenne, J. Pich, J. A. Arnaiz, J. M. Gatell, C. Brander, K. Thielemans, J. Martinez-Picado, M. Plana, F. Garcia, and Hivarna consortium i. 2018. "Phase I clinical trial of an intranodally administered mRNA-based therapeutic vaccine against HIV-1 infection." *AIDS* 32 (17):2533-2545. doi: 10.1097/QAD.0000000000002026.
- Lee, S. I. 2015. "Costly Lessons From the 2015 Middle East Respiratory Syndrome Coronavirus Outbreak in Korea." *J Prev Med Public Health* 48 (6):274-6. doi: 10.3961/jpmph.15.064.
- Letvin, N. L. 2007. "Correlates of immune protection and the development of a human immunodeficiency virus vaccine." *Immunity* 27 (3):366-9. doi: 10.1016/j.immuni.2007.09.001.
- Li, Y. D., W. Y. Chi, J. H. Su, L. Ferrall, C. F. Hung, and T. C. Wu. 2020. "Coronavirus vaccine development: from SARS and MERS to COVID-19." *J Biomed Sci* 27 (1):104. doi: 10.1186/s12929-020-00695-2.
- Liu, M. A. 2010. "Immunologic basis of vaccine vectors." *Immunity* 33 (4):504-15. doi: 10.1016/j.immuni.2010.10.004.
- Lu, R., X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, W. Wang, H. Song, B. Huang, N. Zhu, Y. Bi, X. Ma, F. Zhan, L. Wang, T. Hu, H. Zhou, Z. Hu, W. Zhou, L. Zhao, J. Chen, Y. Meng, J. Wang, Y. Lin, J. Yuan, Z. Xie, J. Ma, W. J. Liu, D. Wang, W. Xu, E. C. Holmes, G. F. Gao, G. Wu, W. Chen, W. Shi, and W. Tan. 2020. "Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding." *Lancet* 395 (10224):565-574. doi: 10.1016/S0140-6736(20)30251-8.
- Lu, W., L. C. Arraes, W. T. Ferreira, and J. M. Andrieu. 2004. "Therapeutic dendritic-cell vaccine for chronic HIV-1 infection." *Nat Med* 10 (12):1359-65. doi: 10.1038/nm1147.
- Lucking, Brian, Nicholas Bloom, and John Van Reenen. 2019. "Have R&D Spillovers Declined in the 21st Century?" *Fiscal Studies* 40 (4):561-590. doi: <https://doi.org/10.1111/1475-5890.12195>.
- Lynchagin, Sergey, Joris Pinske, Margaret E. Slade, and John Van Reenen. 2016. "Spillovers in space: Does geography matter?" *Journal of Industrial Economics* 64 (2):295-335.
- Madsen, Peter M., and Vinit Desai. 2010. "Failing to Learn? The Effects of Failure and Success on Organizational Learning in the Global Orbital Launch Vehicle Industry." *Academy of Management Journal* 53 (3):451-476. doi: <https://doi.org/10.5465/amj.2010.51467631>.
- Magazzani, Laura, Fabio Pammolli, and Massimo Riccaboni. 2012. "Learning from Failures or Failing to Learn? Lessons from Pharmaceutical R&D." *European Management Review* 9 (1):45-58. doi: <https://doi.org/10.1111/j.1740-4762.2012.01027.x>.

- Martinon, F., S. Krishnan, G. Lenzen, R. Magne, E. Gomard, J. G. Guillet, J. P. Levy, and P. Meulien. 1993. "Induction of virus-specific cytotoxic T lymphocytes in vivo by liposome-entrapped mRNA." *Eur J Immunol* 23 (7):1719-22. doi: 10.1002/eji.1830230749.
- Maruggi, G., C. Zhang, J. Li, J. B. Ulmer, and D. Yu. 2019. "mRNA as a Transformative Technology for Vaccine Development to Control Infectious Diseases." *Mol Ther* 27 (4):757-772. doi: 10.1016/j.ymthe.2019.01.020.
- Mascola, J. R., A. Sambor, K. Beaudry, S. Santra, B. Welcher, M. K. Louder, T. C. Vancott, Y. Huang, B. K. Chakrabarti, W. P. Kong, Z. Y. Yang, L. Xu, D. C. Montefiori, G. J. Nabel, and N. L. Letvin. 2005. "Neutralizing antibodies elicited by immunization of monkeys with DNA plasmids and recombinant adenoviral vectors expressing human immunodeficiency virus type 1 proteins." *J Virol* 79 (2):771-9. doi: 10.1128/JVI.79.2.771-779.2005.
- Masters, P. S. 2006. "The molecular biology of coronaviruses." *Adv Virus Res* 66:193-292. doi: 10.1016/S0065-3527(06)66005-3.
- McElrath, M. J., S. C. De Rosa, Z. Moodie, S. Dubey, L. Kierstead, H. Janes, O. D. Defawe, D. K. Carter, J. Hural, R. Akondy, S. P. Buchbinder, M. N. Robertson, D. V. Mehrotra, S. G. Self, L. Corey, J. W. Shiver, D. R. Casimiro, and Team Step Study Protocol. 2008. "HIV-1 vaccine-induced immunity in the test-of-concept Step Study: a case-cohort analysis." *Lancet* 372 (9653):1894-1905. doi: 10.1016/S0140-6736(08)61592-5.
- Miller, Benjamin. 2021. *Can the World Learn From South Africa's Vaccine Trials?* <https://www.nytimes.com/2021/03/13/world/africa/south-africa-vaccine-virus.html>: New York Times, March 13.
- Monath, T. P., P. E. Fast, K. Modjarrad, D. K. Clarke, B. K. Martin, J. Fusco, R. Nichols, D. G. Heppner, J. K. Simon, S. Dubey, S. P. Troth, J. Wolf, V. Singh, B. A. Coller, J. S. Robertson, and Group Brighton Collaboration Viral Vector Vaccines Safety Working. 2019. "rVSVDeltaG-ZEBOV-GP (also designated V920) recombinant vesicular stomatitis virus pseudotyped with Ebola Zaire Glycoprotein: Standardized template with key considerations for a risk/benefit assessment." *Vaccine X* 1:100009. doi: 10.1016/j.jvax.2019.100009.
- Moodie, Z., B. Metch, L. G. Bekker, G. Churchyard, M. Nchabeleng, K. Mlisana, F. Laher, S. Roux, K. Mngadi, C. Innes, M. Mathebula, M. Allen, C. Bentley, P. B. Gilbert, M. Robertson, J. Kublin, L. Corey, and G. E. Gray. 2015. "Continued Follow-Up of Phambili Phase 2b Randomized HIV-1 Vaccine Trial Participants Supports Increased HIV-1 Acquisition among Vaccinated Men." *PLoS One* 10 (9):e0137666. doi: 10.1371/journal.pone.0137666.
- Morrow, G., L. Vachot, P. Vagenas, and M. Robbiani. 2007. "Current concepts of HIV transmission." *Curr HIV/AIDS Rep* 4 (1):29-35. doi: 10.1007/s11904-007-0005-x.
- Moss, B., G. L. Smith, J. L. Gerin, and R. H. Purcell. 1984. "Live recombinant vaccinia virus protects chimpanzees against hepatitis B." *Nature* 311 (5981):67-9. doi: 10.1038/311067a0.

- Moyo, N., A. B. Vogel, S. Buus, S. Erbar, E. G. Wee, U. Sahin, and T. Hanke. 2019. "Efficient Induction of T Cells against Conserved HIV-1 Regions by Mosaic Vaccines Delivered as Self-Amplifying mRNA." *Mol Ther Methods Clin Dev* 12:32-46. doi: 10.1016/j.omtm.2018.10.010.
- National Institute of Allergy and Infectious Diseases. 2021. *Janssen Investigational COVID-19 Vaccine: Interim Analysis of Phase 3 Clinical Data Released (News Release)*. <https://www.nih.gov/news-events/news-releases/janssen-investigational-covid-19-vaccine-interim-analysis-phase-3-clinical-data-released>: January 29.
- News Analysis. 2011. "Learning lessons from Pfizer's \$800 million failure." *Nature Reviews Drug Discovery* 10 (March 1):163-164.
- NIAID. 2007. *Clinical Alert: Immunizations Are Discontinued in Two HIV Vaccine Trials* https://www.nlm.nih.gov/databases/alerts/hiv_step_study.html: National Institute of Allergy and Infectious Diseases, Last accessed May 26, 2020.
- NIAID. 2020. *News Release: Experimental HIV Vaccine Regimen Ineffective in Preventing HIV*. <https://www.niaid.nih.gov/news-events/experimental-hiv-vaccine-regimen-ineffective-preventing-hiv>: National Institute for Allergy and Infectious Disease, February 3, 2020.
- Ornaghi, Carmine. 2006. "Spillovers in product and process innovation: Evidence from manufacturing firms." *International Journal of Industrial Organization* 24:349–380. doi: 10.1016/j.ijindorg.2005.07.002.
- Pardi, N., M. J. Hogan, F. W. Porter, and D. Weissman. 2018. "mRNA vaccines - a new era in vaccinology." *Nat Rev Drug Discov* 17 (4):261-279. doi: 10.1038/nrd.2017.243.
- Patterson, S., T. Papagatsias, and A. Benlahrech. 2009. "Use of adenovirus in vaccines for HIV." *Handb Exp Pharmacol* (188):275-93. doi: 10.1007/978-3-540-71029-5_13.
- Pitisuttithum, P., P. Gilbert, M. Gurwith, W. Heyward, M. Martin, F. van Griensven, D. Hu, J. W. Tappero, K. Choopanya, and Group Bangkok Vaccine Evaluation. 2006. "Randomized, double-blind, placebo-controlled efficacy trial of a bivalent recombinant glycoprotein 120 HIV-1 vaccine among injection drug users in Bangkok, Thailand." *J Infect Dis* 194 (12):1661-71. doi: 10.1086/508748.
- Plotkin, S. A. 2010. "Correlates of protection induced by vaccination." *Clin Vaccine Immunol* 17 (7):1055-65. doi: 10.1128/CVI.00131-10.
- Polack, F. P., S. J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G. Perez Marc, E. D. Moreira, C. Zerbini, R. Bailey, K. A. Swanson, S. Roychoudhury, K. Koury, P. Li, W. V. Kalina, D. Cooper, R. W. Frenck, Jr., L. L. Hammitt, O. Tureci, H. Nell, A. Schaefer, S. Unal, D. B. Tresnan, S. Mather, P. R. Dormitzer, U. Sahin, K. U. Jansen, W. C. Gruber, and C. Clinical Trial Group. 2020. "Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine." *N Engl J Med* 383 (27):2603-2615. doi: 10.1056/NEJMoa2034577.
- Pollard, C., J. Rejman, W. De Haes, B. Verrier, E. Van Gulck, T. Naessens, S. De Smedt, P. Bogaert, J. Grooten, G. Vanham, and S. De Koker. 2013. "Type I IFN counteracts the induction of antigen-specific immune responses by lipid-based delivery of mRNA vaccines." *Mol Ther* 21 (1):251-9. doi: 10.1038/mt.2012.202.

- Price, D. A., P. J. Goulder, P. Klenerman, A. K. Sewell, P. J. Easterbrook, M. Troop, C. R. Bangham, and R. E. Phillips. 1997. "Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection." *Proc Natl Acad Sci U S A* 94 (5):1890-5. doi: 10.1073/pnas.94.5.1890.
- Rerks-Ngarm, S., P. Pitisuttithum, S. Nitayaphan, J. Kaewkungwal, J. Chiu, R. Paris, N. Prensri, C. Namwat, M. de Souza, E. Adams, M. Benenson, S. Gurunathan, J. Tartaglia, J. G. McNeil, D. P. Francis, D. Stablein, D. L. Birx, S. Chunsuttiwat, C. Khamboonruang, P. Thongcharoen, M. L. Robb, N. L. Michael, P. Kunasol, J. H. Kim, and Moph-Taveg Investigators. 2009. "Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand." *N Engl J Med* 361 (23):2209-20. doi: 10.1056/NEJMoa0908492.
- Resource Tracking for HIV Prevention R&D Working Group (RTWG). 2019. *HIV Prevention Research & Development Investments 2018: Investing to end the epidemic*. <https://www.avac.org/resource/hiv-prevention-research-development-investments-2018-investing-end-epidemic>: Issued July 2019, Last accessed March 3, 2021.
- Resource Tracking for HIV Prevention R&D Working Group (RTWG). 2020. *HIV Prevention Research & Development Investments*. <https://www.hivresourcetracking.org/>: Last accessed March 3, 2021.
- Robert-Guroff, M., M. Brown, and R. C. Gallo. 1985. "HTLV-III-neutralizing antibodies in patients with AIDS and AIDS-related complex." *Nature* 316 (6023):72-4. doi: 10.1038/316072a0.
- Rodrigues, E. G., F. Zavala, D. Eichinger, J. M. Wilson, and M. Tsuji. 1997. "Single immunizing dose of recombinant adenovirus efficiently induces CD8+ T cell-mediated protective immunity against malaria." *J Immunol* 158 (3):1268-74.
- Rodrigues, E. G., F. Zavala, R. S. Nussenzweig, J. M. Wilson, and M. Tsuji. 1998. "Efficient induction of protective anti-malaria immunity by recombinant adenovirus." *Vaccine* 16 (19):1812-7. doi: 10.1016/s0264-410x(98)00181-9.
- Romagnani, S., G. Del Prete, R. Manetti, A. Ravina, F. Annunziato, M. De Carli, M. Mazzetti, M. P. Piccinni, M. M. D'Elia, P. Parronchi, and et al. 1994. "Role of TH1/TH2 cytokines in HIV infection." *Immunol Rev* 140:73-92. doi: 10.1111/j.1600-065x.1994.tb00865.x.
- Romer, Paul M. 1990. "Endogenous Technological Change." *Journal of Political Economy* 98 (5):S71-S102. doi: <https://www.jstor.org/stable/2937632>.
- Sadoff, J., M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A. M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P. J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K. E. Stephenson, S. C. De Rosa, K. W. Cohen, M. J. McElrath, E. Cormier, G. Scheper, D. H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, and H. Schuitemaker. 2021. "Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine." *N Engl J Med*. doi: 10.1056/NEJMoa2034201.
- Schwartz, G. G., A. G. Olsson, C. M. Ballantyne, P. J. Barter, I. M. Holme, D. Kallend, L. A. Leiter, E. Leitersdorf, J. J. McMurray, P. K. Shah, J. C. Tardif, B. R. Chaitman, R. Duttlinger-Maddux, J. Mathieson, Outcomes Committees dal, and Investigators. 2009. "Rationale and design of the dal-OUTCOMES trial: efficacy and safety of dalcetrapib in patients with recent acute coronary syndrome." *Am Heart J* 158 (6):896-901 e3. doi: 10.1016/j.ahj.2009.09.017.

- Sekaly, R. P. 2008. "The failed HIV Merck vaccine study: a step back or a launching point for future vaccine development?" *J Exp Med* 205 (1):7-12. doi: 10.1084/jem.20072681.
- Sputnik V. 2020. *Second interim analysis of clinical trial data showed a 91.4% efficacy for the Sputnik V vaccine on day 28 after the first dose; vaccine efficacy is over 95% 42 days after the first dose.*
<https://sputnikvaccine.com/newsroom/pressreleases/second-interim-analysis-of-clinical-trial-data-showed-a-91-4-efficacy-for-the-sputnik-v-vaccine-on-d/>: December 14.
- Stokes, J., Jr., M. R. Hilleman, and R. E. Weibel. 1961. "Efficacy of Live, Attenuated Measles-Virus Vaccine Given With Human Immune Globulin." *New Engl J Med* 265 (11):507-513.
- Sullivan, N. J., A. Sanchez, P. E. Rollin, Z. Y. Yang, and G. J. Nabel. 2000. "Development of a preventive vaccine for Ebola virus infection in primates." *Nature* 408 (6812):605-9. doi: 10.1038/35046108.
- Tanne, J. H. 2006. "Pfizer stops clinical trials of heart drug." *BMJ* 333 (7581):1237. doi: 10.1136/bmj.39059.438044.DB.
- U.S. National Library of Medicine. 2020a. *A Study of Heterologous Vaccine Regimen of Adenovirus Serotype 26 Mosaic4 Human Immunodeficiency Virus(Ad26.Mos4.HIV), Adjuvanted Clade C gp140 and Mosaic gp140 to Prevent HIV-1 Infection Among Cis-gender Men and Transgender Individuals Who Have Sex With Cis-gender Men and/or Transgender Individuals (MOSAICO).*
<https://clinicaltrials.gov/ct2/show/NCT03964415>: ClinicalTrials.gov, Last updated May 12, 2020.
- U.S. National Library of Medicine. 2020b. *A Study to Assess the Efficacy of a Heterologous Prime/Boost Vaccine Regimen of Ad26.Mos4.HIV and Aluminum Phosphate-Adjuvanted Clade C gp140 in Preventing Human Immunodeficiency Virus (HIV) -1 Infection in Women in Sub-Saharan Africa.*
<https://clinicaltrials.gov/ct2/show/NCT03060629>: ClinicalTrials.gov, last updated May 13, 2020.
- Ulmer, J. B., J. J. Donnelly, S. E. Parker, G. H. Rhodes, P. L. Felgner, V. J. Dwarki, S. H. Gromkowski, R. R. Deck, C. M. DeWitt, A. Friedman, and et al. 1993. "Heterologous protection against influenza by injection of DNA encoding a viral protein." *Science* 259 (5102):1745-9. doi: 10.1126/science.8456302.
- UNAIDS. 2020. *Press Statement: HVTN 702 clinical trial of an HIV vaccine stopped.*
https://www.unaids.org/sites/default/files/20200204_PS_vaccine_en.pdf: February 4, 2020.
- van Doremalen, Neeltje, Teresa Lambe, Alexandra Spencer, and et al. 2020. *ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques.*
<https://www.biorxiv.org/content/10.1101/2020.05.13.093195v1.full.pdf>: bioRxiv preprint, May 13, 2020.
- Wagner, R., V. J. Teeuwesen, L. Deml, F. Notka, A. G. Haaksmas, S. S. Jhaghoorsingh, H. Niphuis, H. Wolf, and J. L. Heeney. 1998. "Cytotoxic T cells and neutralizing antibodies induced in rhesus monkeys by virus-like particle HIV vaccines in the absence of protection from SHIV infection." *Virology* 245 (1):65-74. doi: 10.1006/viro.1998.9104.
- Wei, X., J. M. Decker, S. Wang, H. Hui, J. C. Kappes, X. Wu, J. F. Salazar-Gonzalez, M. G. Salazar, J. M. Kilby, M. S. Saag, N. L. Komarova, M. A. Nowak, B. H. Hahn, P. D. Kwong, and G. M. Shaw. 2003. "Antibody neutralization and escape by HIV-1." *Nature* 422 (6929):307-12. doi: 10.1038/nature01470.

- Weiss, R. A., P. R. Clapham, R. Cheingsong-Popov, A. G. Dalgleish, C. A. Carne, I. V. Weller, and R. S. Tedder. 1985. "Neutralization of human T-lymphotropic virus type III by sera of AIDS and AIDS-risk patients." *Nature* 316 (6023):69-72. doi: 10.1038/316069a0.
- Whatmore, A. M., N. Cook, G. A. Hall, S. Sharpe, E. W. Rud, and M. P. Cranage. 1995. "Repair and evolution of nef in vivo modulates simian immunodeficiency virus virulence." *J Virol* 69 (8):5117-23.
- WHO. 2020. *International Travel and Health: Hepatitis A Vaccine*. <https://www.who.int/ith/vaccines/hepatitisA/en/>: World Health Organization, Last accessed May 28, 2020.
- Widge, A. T., N. G. Roupael, L. A. Jackson, E. J. Anderson, P. C. Roberts, M. Makhene, J. D. Chappell, M. R. Denison, L. J. Stevens, A. J. Pruijssers, A. B. McDermott, B. Flach, B. C. Lin, N. A. Doria-Rose, S. O'Dell, S. D. Schmidt, K. M. Neuzil, H. Bennett, B. Leav, M. Makowski, J. Albert, K. Cross, V. V. Edara, K. Floyd, M. S. Suthar, W. Buchanan, C. J. Luke, J. E. Ledgerwood, J. R. Mascola, B. S. Graham, J. H. Beigel, and R. N. A. Study Group m. 2021. "Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination." *N Engl J Med* 384 (1):80-82. doi: 10.1056/NEJMc2032195.
- Williams, Heidi L. 2013. "Intellectual Property Rights and Innovation: Evidence from the Human Genome." *Journal of Political Economy* 121 (1):1-27. doi: <https://www.jstor.org/stable/10.1086/669706>.
- Williams, W. B., H. X. Liao, M. A. Moody, T. B. Kepler, S. M. Alam, F. Gao, K. Wiehe, A. M. Trama, K. Jones, R. Zhang, H. Song, D. J. Marshall, J. F. Whitesides, K. Sawatzki, A. Hua, P. Liu, M. Z. Tay, K. E. Seaton, X. Shen, A. Foulger, K. E. Lloyd, R. Parks, J. Pollara, G. Ferrari, J. S. Yu, N. Vandergrift, D. C. Montefiori, M. E. Sobieszcyk, S. Hammer, S. Karuna, P. Gilbert, D. Grove, N. Grunenberg, M. J. McElrath, J. R. Mascola, R. A. Koup, L. Corey, G. J. Nabel, C. Morgan, G. Churchyard, J. Maenza, M. Keefer, B. S. Graham, L. R. Baden, G. D. Tomaras, and B. F. Haynes. 2015. "HIV-1 VACCINES. Diversion of HIV-1 vaccine-induced immunity by gp41-microbiota cross-reactive antibodies." *Science* 349 (6249):aab1253. doi: 10.1126/science.aab1253.
- Wold, W. S., and K. Toth. 2013. "Adenovirus vectors for gene therapy, vaccination and cancer gene therapy." *Curr Gene Ther* 13 (6):421-33. doi: 10.2174/1566523213666131125095046.
- Wolff, J. A., R. W. Malone, P. Williams, W. Chong, G. Acsadi, A. Jani, and P. L. Felgner. 1990. "Direct gene transfer into mouse muscle in vivo." *Science* 247 (4949 Pt 1):1465-8. doi: 10.1126/science.1690918.
- World Health Organization. 2021. *Candidate Vaccine Landscape and Tracker*. <https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines>: Last accessed March 5.
- Worobey, Michael, Jonathan Pekar, Brendan B. Larsen, and et al.. 2020. *The emergence of SARS-CoV-2 in Europe and the US*. <https://www.biorxiv.org/content/10.1101/2020.05.21.109322v1>: BioRxiv, May 23, 2020.
- Wrapp, D., N. Wang, K. S. Corbett, J. A. Goldsmith, C. L. Hsieh, O. Abiona, B. S. Graham, and J. S. McLellan. 2020. "Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation." *Science* 367 (6483):1260-1263. doi: 10.1126/science.abb2507.
- Wu, F., S. Zhao, B. Yu, Y. M. Chen, W. Wang, Z. G. Song, Y. Hu, Z. W. Tao, J. H. Tian, Y. Y. Pei, M. L. Yuan, Y. L. Zhang, F. H. Dai, Y. Liu, Q. M. Wang, J. J. Zheng, L. Xu, E. C. Holmes, and Y. Z. Zhang. 2020a.

- "Author Correction: A new coronavirus associated with human respiratory disease in China." *Nature* 580 (7803):E7. doi: 10.1038/s41586-020-2202-3.
- Wu, F., S. Zhao, B. Yu, Y. M. Chen, W. Wang, Z. G. Song, Y. Hu, Z. W. Tao, J. H. Tian, Y. Y. Pei, M. L. Yuan, Y. L. Zhang, F. H. Dai, Y. Liu, Q. M. Wang, J. J. Zheng, L. Xu, E. C. Holmes, and Y. Z. Zhang. 2020b. "A new coronavirus associated with human respiratory disease in China." *Nature* 579 (7798):265-269. doi: 10.1038/s41586-020-2008-3.
- Xia, S., Y. Zhang, Y. Wang, H. Wang, Y. Yang, G. F. Gao, W. Tan, G. Wu, M. Xu, Z. Lou, W. Huang, W. Xu, B. Huang, H. Wang, W. Wang, W. Zhang, N. Li, Z. Xie, L. Ding, W. You, Y. Zhao, X. Yang, Y. Liu, Q. Wang, L. Huang, Y. Yang, G. Xu, B. Luo, W. Wang, P. Liu, W. Guo, and X. Yang. 2021. "Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial." *Lancet Infect Dis* 21 (1):39-51. doi: 10.1016/S1473-3099(20)30831-8.
- Yewdell, John Wilson. 2020. *TWiV 620: Antibodies and T cells in COVID-19 patients*. <https://www.microbe.tv/twiv/twiv-620/>: This Week in Virology, May 27, 2020, at 1:28.
- Young, K. R., S. P. McBurney, L. U. Karkhanis, and T. M. Ross. 2006. "Virus-like particles: designing an effective AIDS vaccine." *Methods* 40 (1):98-117. doi: 10.1016/j.ymeth.2006.05.024.
- Zhang, C., G. Maruggi, H. Shan, and J. Li. 2019. "Advances in mRNA Vaccines for Infectious Diseases." *Front Immunol* 10:594. doi: 10.3389/fimmu.2019.00594.
- Zhang, Y., G. Zeng, H. Pan, C. Li, Y. Hu, K. Chu, W. Han, Z. Chen, R. Tang, W. Yin, X. Chen, Y. Hu, X. Liu, C. Jiang, J. Li, M. Yang, Y. Song, X. Wang, Q. Gao, and F. Zhu. 2021. "Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial." *Lancet Infect Dis* 21 (2):181-192. doi: 10.1016/S1473-3099(20)30843-4.
- Zhao, C., Z. Ao, and X. Yao. 2016. "Current Advances in Virus-Like Particles as a Vaccination Approach against HIV Infection." *Vaccines (Basel)* 4 (1). doi: 10.3390/vaccines4010002.
- Zhou, P., X. L. Yang, X. G. Wang, B. Hu, L. Zhang, W. Zhang, H. R. Si, Y. Zhu, B. Li, C. L. Huang, H. D. Chen, J. Chen, Y. Luo, H. Guo, R. D. Jiang, M. Q. Liu, Y. Chen, X. R. Shen, X. Wang, X. S. Zheng, K. Zhao, Q. J. Chen, F. Deng, L. L. Liu, B. Yan, F. X. Zhan, Y. Y. Wang, G. F. Xiao, and Z. L. Shi. 2020. "A pneumonia outbreak associated with a new coronavirus of probable bat origin." *Nature* 579 (7798):270-273. doi: 10.1038/s41586-020-2012-7.
- Zhu, N., D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G. Wu, G. F. Gao, W. Tan, Investigating China Novel Coronavirus, and Team Research. 2020. "A Novel Coronavirus from Patients with Pneumonia in China, 2019." *N Engl J Med* 382 (8):727-733. doi: 10.1056/NEJMoa2001017.