Carl W. Dieffenbach – Director of the Division of AIDS (DAIDS), NIH National Institute of Allergy & Infectious Diseases (NIAID)



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The US National Institutes of Health (NIH) is the largest public investor in HIV/AIDS research globally. This means that, as Director of the Division of AIDS (DAIDS) at the NIH's National Institute of Allergy & Infectious Diseases (NIAID) Dr Carl Dieffenbach oversees a global HIV/AIDS research portfolio of more than USD one billion. In an exclusive conversation with PharmaBoardroom, Dr Dieffenbach explains the crucial role that DAIDS-funded research has played in the development of antiretroviral therapies and long-acting formulations, helping move the needle for those living with HIV. He also highlights some of the biggest ongoing challenges in HIV research, including developing an effective HIV vaccine and achieving a cure, emphasising the importance of collaboration, shifting from competition to partnership in the field, and the ongoing importance of addressing structural barriers to equitable healthcare access.

How did you first enter the field of HIV/AIDS research?

I earned my PhD in 1984 with a focus on virology, specifically human responses to viruses, and especially interferon and interferon-induced genes. People like Ian Kerr and George Stark were leaders in the field at that time, and it was becoming clear that harnessing existing systems could have a global impact on viruses.

During my postdoc, my university had a small amount of funds set aside for HIV research, which I applied for and won. Within two years of starting a postdoc, I was promoted to assistant professor, an extremely unusual occurrence! At that point I was working on flu, coronavirus, and HIV. My lab cloned a cellular receptor for mouse hepatitis virus, which is a coronavirus, and was one of the first virus receptors ever cloned.

At that point, in 1989/1990, it became clear that HIV was the single biggest threat to humankind, as it still is today. I therefore turned my lab over to working exclusively on HIV. Then, due to funding issues, my university was under threat of closure and I was faced with a difficult decision. I could either stay and continue my work there in a diminished capacity or – because I was based in Bethesda, Maryland – jump across the street and join NIAID. In 1992 I chose the second option, heading up the 'Developmental Therapeutics' group and setting a path towards finding countermeasures to treat HIV.

How has your research on HIV science evolved over the past 30 years?

Back in the early 1990s we were already thinking about prevention as well as treatment. This included working on antivirals, which was still a relatively unknown field at the time although Gertrude Elion had been able to develop antiviral for the herpes viruses.

As we went through the discovery of these agents, we would test each one in a prevention model using non-human primates. Then in 1995/1996, we discovered that only one of the existing nucleotide analogues could prevent acquisition in non-human primates. This was a drug called PMPA [later referred to as tenofovir], which was then taken by John Martin and Norbert Bischofberger and derivatised into tenofovir disoproxil fumarate. This became a very potent agent that, when paired with the drug emtricitabine, became Truvada.

From the very beginning, the question was: could drugs be used for prevention and treatment? There were, of course, significant concerns about drug resistance if used in treatment, which Doug Richman, Brendan Larder and others demonstrated in the mid-90s.

At that time, the core of my research was on antiretrovirals. Once you become a science leader at NIH, you transition from conducting personal research to facilitating research by others. This shift led to the development of the START and SMART trials run by the INSIGHT network, as well as the HPTN 052 study, which tested and proved the U=U concept (Undetectable = Untransmittable).

Then, around 2010 and 2011, we began to explore the potential of long-acting formulations, which was crystalised at the 2012 International AIDS Conference (AIDS 2012) in Washington DC. Only one company – ViiV Healthcare – was exploring this alternative to oral pills, and we ended up partnering with them.

All in all, my goal has been to try to develop strategies and approaches that – when implemented at scale – could really have an impact on HIV incidence.

And there *has* been an impact – something that was a virtual death sentence for patients in the 1980s and 1990s is now a manageable chronic disease for many. How did we get here and what needs to be done next?

We have definitely changed the course for people affected by and living with HIV although there are still tremendous challenges with delivery and reaching populations. Then there are governments around the world that say the right things, but don't do them. The United States, for example, is not the best place in the world to be living with HIV, particularly in the American South if you are young, black, and gay.

As we get quality tools, the question becomes: how do we implement them and take them to scale equitably? Oftentimes the structural barriers that we are dealing with – such as a lack of affordable health insurance and a pricing structure that is, in my opinion, contrary to public health here in the US – are difficult to overcome.

In the meantime, as researchers, we will continue to search for truly innovative solutions that help move the needle for people. Currently, this means broadly neutralising antibodies (bNAbs), new long-acting formulations of novel molecules, cure research, and continuing work on HIV vaccines. I became director of the division in 2007-2008 and, we have made progress across all.

From a pure research perspective, there are two major challenges left. One is the development of a safe, durable, and effective HIV vaccine. Once we have that, we then must figure out how to take it to scale. The second is a cure. I do not care whether it is a "true" cure, in which the virus is cleared from the body, or a functional cure, in which the body can control HIV off therapy, but it should be something that stops people's disease from progressing, ensures their safety, and means that they are free to love who they want.

Given the rash of late-stage HIV vaccine research failures, how optimistic are you that new approaches like germline targeting that generate bNAbs can eventually lead to a vaccine?

There are several labs, both in the US and Europe, exploring these kinds of approaches. The field has evolved from competitive to collaborative with a focus on sharing not just data, but innovative tools for vaccine evaluation in the preclinical space. That has changed the nature to very friendly competition with different actors driving each other to do better.

Antibodies *will* end up being part of the next vaccine we test. My concern is that we still do not know the required concentration of neutralising antibodies that target one of the five sites of vulnerability on HIV in a person who is vaccinated to achieve protection. Based on the AMP (Antibody Mediated Prevention) trial [a major clinical study designed to test whether infusing bNAbs directly into individuals can prevent HIV infection – Ed.] the concentration needed is a rather high level. The caveat "this will be good, but…" is what we need to pay attention to. By vaccination, will we be able to achieve concentrations antibodies directed against the sites of vulnerability of at least three broad neutralising antibodies in people who have been vaccinated for enough time for the vaccine to have a protective effect?

Additionally, we need to improve how we utilise T-cells alongside these antibodies. So far, the T-cell responses measured in vaccines have been ineffective. Although we can measure multifunctional gamma interferon and IL-2 producing cells, they lack cytotoxic capability. Drawing from our experience with antivirals and barrier methods, which protect target cells from HIV acquisition, we understand the importance of direct protection strategies. Similarly, for a T-cell vaccine to be effective, it needs to either neutralise the virus or prevent its interaction with target cells. This is akin to the natural protection observed in individuals with the Delta 32 CCR5 double deletion, where the virus cannot recognise or bind to the cells.

Some might consider this perspective reductionist, but simplifying our focus teaches us about what we need to do: protect the body from initial HIV acquisition in the tissue. Then, if there is any virus acquisition, the T-cells must be capable of eliminating those cells containing HIV.

This issue is complex and multifaceted. We are making progress in inducing broadly neutralising antibodies and have achieved significant advances with at least two epitopes. The third epitope, the MPER (Membrane Proximal External Region) and the fusion peptide, are also advancing quickly. Within the next three to four years, we may have all the necessary components. The challenge then becomes how to effectively combine them. It may be that our first vaccine is something of a

Rube Goldberg machine [a contraption which performs a simple task in an indirect and overly complicated way – Ed.]. How do we deliver that? How do we then take that to scale? How do we reduce it to practice?

In the meantime, we still face challenges in triggering a CD8 T-cell response that is cytotoxic. Currently, we lack methods to effectively induce such a response, regardless of which marker – such as porphyrin or granzyme – we aim to use. This aspect must be developed further, and then all these components must be integrated into a practical form of delivery, such as a syringe or a patch. While this integration poses a complex engineering challenge, there are many talented individuals in this field who are capable of making significant advances.

What are some of the challenges and opportunities of this move from competition to collaboration in HIV vaccine research? Taking just one of these projects, there are seven different partners (Moderna, IAVI, Scripps Research, the Gates Foundation, NIAID, PEPFAR, and USAID), which seems like a lot of moving parts to coordinate…

One of the greatest strengths of those partnerships is the democratisation of where the research gets done. What USAID brings to the table is world-class labs on the continent of Africa. The HIV Vaccine Trials Network brings their lab in South Africa as well. Andrew Ward at Scripps can use the microscope to determine the shape and structure of every antibody that binds to an HIV envelope within days of identifying it. Moderna can quickly make vaccine constructs that can go into preclinical for evaluation. The whole process is tightly iterative with immunogens being swapped between different groups around the world. These groups can take an immunogen which is known to induce a specific epitope, modify it slightly, and maybe add another epitope to another site on it.

Additionally, knock-in (KI) mice technology, enhanced by CRISPR-Cas editing, allows us to engineer mice with human immune system components. This enables us to test specific immunogens directly in a controlled environment. With this approach, we can assess whether an immunogen behaves as expected, which is a significant improvement over past methods.

This ecosystem of everybody knowing what everybody else is doing and then going to each other’s meetings and sharing the unpublished data is very positive. There will be friendly competition, because that is an essential element in science, but it can be done in a way that is still collaborative.

Has your own organisation's approach to partnering with the pharmaceutical industry changed over the years?

The mission of our division is to transform the practice of HIV medicine globally. Success is measured by our ability to produce results that lead to changes in medical guidelines, not just in the US, but worldwide. While it is possible to conduct discovery and advance molecules through Phase II trials independently, progressing to large-scale clinical trials and eventual market production requires the involvement of a pharmaceutical partner. Such partnerships are essential for mass-producing a vaccine or drug and conducting the efficacy studies or further research needed to bring a product to market.

In Europe, for example, the EMA now approves the use of injectable Cabotegravir for HIV prevention. With backing from the US FDA, EMA, and WHO, we are poised for full-scale implementation. The first step is gaining approval from global regulators. Then, companies must determine how to produce the treatment at scale. This involves companies like ViiV licensing their technology to generic manufacturers capable of producing it at a feasible cost and scale.

That's what was achieved with the combination of tenofovir, FTC, and dolutegravir, now globally recognised as TLD. This combination is cost-effective, with a year of therapy priced at less than USD 100. This approach contrasts sharply with charging over USD 50,000 per year for a drug, a practice still prevalent in the treatment of hepatitis C. Despite the availability of a cure, the cost remains too high for a 12-week treatment course, making it inaccessible for widespread use in curing hepatitis C. The ideal solution would be a long-acting, single-dose treatment, which could significantly advance public health and potentially lead to the eradication of hepatitis C within a few years.

The pattern observed in HIV treatment – starting with multiple daily doses, progressing to once-daily pills, and eventually developing long-acting formulations administered every few months – illustrates the trajectory we aim for. Drug discovery and development are fraught with challenges, particularly concerning unforeseen toxicities. Issues like neutropenia or neuropathy are serious concerns, impacting cells that either rapidly regenerate or do not regenerate at all, potentially causing severe damage to the mitochondria or nerves

To what extent do downstream questions of access and delivery play into your work at NIAID?

One of our major challenges is effectively integrating these aspects from the onset of drug development. It is crucial to identify and collaborate with the right partners starting from Phase I trials. Although it is difficult to engage in discussions about a drug at such an early stage, thinking about implementation before reaching the licensure stage is essential. This is a practice our field – including myself and the NIAID – has historically overlooked.

In the US this means collaborating with organisations like the Centers for Disease Control and Prevention (CDC) on prevention strategies, as well as healthcare delivery agencies like the Health Resources and Services Administration (HRSA), Centers for Medicare & Medicaid Services (CMS), and the Department of Veterans Affairs (VA).

It is also imperative to have these discussions with pharmaceutical partners, though this poses challenges due to their interest in patent protection and pricing strategies. Working with the Gates Foundation has been beneficial in this regard, as they enforce pricing clauses that help direct our approach towards more equitable access.

CROI 2024 was held in Colorado this April, bringing together the latest research on HIV and related conditions. Which projects or approaches stood out to you as most exciting?

There are two significant directions to discuss. The first is the continued improvement in the care of people living with HIV, particularly regarding chronic immune activation and its consequences. A notable breakthrough was the use of semaglutide to reduce metabolic dysfunction-associated steatotic liver disease, a widespread chronic liver disease. While the finding that it worked at all was not entirely unexpected, the fact that it worked as well as it did was a very pleasant surprise.

The second involves Deborah Persaud and her team at the IMPAACT network, who are advancing a study known as P1115. This study builds on the phenomenon first observed over a decade ago in ‘the Mississippi baby,’ a child who – after being treated with antiretroviral therapy experienced a treatment interruption and still showed no detectable virus. This virus free period lasted 27 months. In P1115, a large cohort of babies were initially treated; the study then narrowed to a subset who, with ethical considerations, parental consent, and community support, underwent a treatment interruption.

Results varied: some children experienced viral rebound almost immediately, while others remained virally suppressed for an extended period. This research marks a significant advancement in defining a public health approach to treating infants born to HIV-positive mothers,

focusing on early and sustained antiretroviral therapy.

Additionally, Debbie and the IMPAACT team have innovated by incorporating a monoclonal antibody into their treatment regimen. Although this aspect might not have received much attention, it represents a significant step forward in exploring new therapeutic possibilities for infant HIV treatment.

Moreover, the science around health during and after pregnancy is evolving and there are a lot of public health and scientific opportunities in this field. While access to HIV treatment and prevention is essential for all people with or affected by HIV, respectively, we need to support the use of these interventions during and after pregnancy, throughout the entire lactating period, to prevent vertical HIV transmission and address the enhanced biological susceptibility to HIV acquisition that people experience postnatally. Studies are starting to look at how to optimize care during this crucial time.

Elsewhere, HIV cure research is undergoing significant evolution, expanding beyond North America to include studies on the African continent. The aim is to truly internationalise this research, extending it to South America and Asia. However, the success of these studies hinges on the availability of scientists to develop and drive them. Investment in the global South is beginning to effect change.

Our collaboration with the Gates Foundation supports this expansion by focusing on research initiatives within these regions rather than limiting them to the US or Europe. To effectively address HIV globally, it is essential to have tools and technologies that are effective against all HIV clades. Currently, many assays are developed primarily for B-clade; however, we expect final CLIA certifications for other clades within a month. With the right tools, capacity, and intellectual firepower, I anticipate significant advancements in HIV research in the global South soon

What are you most looking forward to achieving in the next few years?

I am looking forward to a time when we can develop an injectable therapeutic that lasts six months and combines two agents. Currently, the drugs in Cabenuva – Rilpivirine and Cabotegravir – are effective for two months. There is a significant challenge in many countries with the use of non-nucleoside reverse transcriptase inhibitors like nevirapine, which was widely used early on for preventing vertical HIV transmission.

This might seem like a niche issue, but with advancements in long-acting formulations, we anticipate seeing monoclonal antibody cocktails that also last for six months. While it is not certain that a monoclonal antibody cocktail that lasts for six months could match the potency of antivirals because of coverage issues, we need to ask the question to determine whether it is worth pursuing.

Just as importantly, we need to improve the implementation of the tools we already have for communities that face structural barriers to accessing healthcare. A peculiar challenge in the US is that we have 50 states with different laws, including deeply blue states and deeply red states. The American South faces specific challenges due to some of these laws. For example, to access healthcare, one might need to demonstrate employment, but the reporting requirements are so stringent that a minor mistake can result in being disqualified from healthcare access. It feels almost punitive. We need to support each other rather than imposing additional hardships on those who are less fortunate.

Nationally, we need to understand how to reach all people. The ‘Ending the HIV Epidemic in the US’ (EHE) program is a good example of what can be done, piloting very small-scale initiatives and leveraging the strengths of implementation science, to focus on local solutions. What works locally? Can we analyse what has worked in various jurisdictions and, through collaboration among implementation science experts, identify strategies that could be scaled nationally?

To achieve this, we need to involve programs like the Ryan White HIV/AIDS Program [a US federal initiative that provides a comprehensive system of care for people living with HIV who are uninsured or underinsured – Ed.] that have a mission centred on implementation. However, it must be tied to health departments and community organisations. It cannot be left solely to academics; it must be owned by the groups that will ultimately be responsible for their success.

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