The Benefits of HIV Research? Let Us Count the Ways

HIV work has helped shape the FDA, provided drugs for other infections, changed health systems globally and more, say Fred Hutch experts.

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You may not realize you've benefited from HIV research. But if you've received a treatment that was approved through a recent clinical trial, received a CAR T cell for your cancer, or even just taken Paxlovid, you have.

As highlighted in a recent commentary in Nature Medicine, co-authored by Fred Hutch Cancer Center virologist and past president and director Larry Corey, MD, the impact of HIV research has been wide-ranging, contributing to advances in areas from immunology to cardiovascular disease, from vaccine development to the genetic engineering strategies that have made recent advances in cellular cancer immunotherapy possible.

This World AIDS Day, Fred Hutch HIV experts spoke about a few of the many ways that HIV science and the investment of funds and effort have benefited people around the world, even those who will never become infected with HIV.

"HIV research draws on science and investigators from a really wide range of fields: biology, public health and epidemiology, evolutionary biology and mathematics," said Fred Hutch computational biologist Daniel Reeves, PhD, a principal staff scientist in the Vaccine and Infectious Disease Division (VIDD), and affiliate assistant professor at UW who studies the HIV reservoirs that are the main barrier to cure. "HIV science is a standard-bearer for interdisciplinary and high-quality work."

Inspiring patient-centered science

"One of the absolute most important things is that the world of HIV really brought activists into the conversation about science," said Adrienne Shapiro, MD, PhD, an infectious disease physician at Fred Hutch and the University of Washington and associate medical director of the Seattle Vaccine Trials Unit (VTU). "They really lived the philosophy of nothing about us without us."

HIV activists worked to set the research agenda and ensure they played active roles in clinical trials, making community advisory boards with input into protocol design and population representation the standard, Shapiro said.

“Including women in research, including minorities — that was not solely an aspect of HIV research, but HIV research was a major contributing push to that and even thinking about how we talk about participants in clinical trials,” she said. “Now we recognize their contributions, that they’re not patients, they’re not subjects: they are volunteers, they are participants, they are the drivers of research success.”

This continues in the HIV Vaccine Trials Network (HVTN), said James Kublin, MD, PhD, who is the HVTN’s executive director and medical director of the Seattle Malaria Clinical Trials Center.

“We’re very reliant on community connections to inform the direction of all of our research,” Kublin said. “Indeed, I think the biomedical social research that we do within the network, the implementation and outcomes science research that we do … is as crucial as the more exclusively biomedical research that we do to interrogate immune responses that these vaccines are eliciting.”

This philosophy is now established in many other biomedical research fields, including cancer research. The National Institute’s Specialized Centers of Excellence, or SPOREs, include patient advisory boards that give input on research directions.

HIV community engagement teams “have really written the book about how to do this,” said Fred Hutch biostatistician Holly Janes, PhD, who heads the Biostatistics, Bioinformatics and Epidemiology Program within VIDD.

So much so, that she asked them to teach the class on it.

Janes was teaching students in the University of Washington School of Public Health about clinical trials.

“It covers a very broad array of topics involved in doing clinical trials, everything from ethics to data safety monitoring boards to statistics to selecting trial sites,” she said. “One of the topics that I noticed was not covered was community engagement. This is especially important for prevention science, where you’re recruiting healthy participants from the community. How do you recruit them to participate in a trial and how do you inform the community about the results of the trial?”

To educate her students, Janes was able to bring in members of the community engagement team at Fred Hutch, which headquarters the HVTN and the VTU.

Fred Hutch biostatistician Deborah Donnell, PhD, who designs and analyzes HIV prevention trials, also pointed to the community-building as a model pioneered in HIV work that can be applied elsewhere.

“I do think the prevention work that I do for HIV is being carried over to STI [sexually transmitted disease] prevention,” said Donnell, who is also involved in a trial of a vaccine against gonorrhea. “You have to identify the people who don’t have the disease, but who are at risk. You have to work within the context of the community who truly understand the elements of risk.”

HIV activists shaped our clinical trials, drug approval processes

“Activists became very knowledgeable about the science, and as a result of activists driving a survival agenda, this resulted in better clinical trials,” Shapiro said. “It resulted in new pathways that changed how the FDA approves drugs.”

Our ability to access experimental medications in early development if there are no other treatment options for a disease, and the pathway that accelerates trial timelines using surrogate endpoints, can be traced to HIV activism, Shapiro said.

A surrogate endpoint is an effect that may act as a biomarker for a therapeutic benefit, such as improved survival. Using a validated surrogate endpoint can allow scientists to get answers with fewer trial participants in a shorter time frame.

These processes have shaped clinical trials of all stripes. Cancer researchers, for example, can test new therapies faster using surrogate endpoints like progression-free survival or time to progression.

Vaccine trials have also benefited: Correlates of immune protection are an important surrogate endpoint that, if properly statistically validated, can tell researchers if the vaccine is likely to work.

“That’s a particular sort of scientific question you can ask, and there’s particular methodology associated with answering that question,” Janes said. “And it basically came out of HIV, I would say.”

Honed by Fred Hutch biostatistician Peter Gilbert, PhD, and others working on vaccines to prevent HIV, correlates of protection are used in vaccine trials for many other infections, from SARS-CoV2 to dengue to tuberculosis.

They’ve also been adapted to measure efficacy of monoclonal broadly neutralizing antibodies developed to protect against HIV and other infections, such as dengue.

Another type of analysis that was essentially generated by the HIV field but has broad applicability is what’s known as sieve analysis, Janes said.

In a trial comparing a vaccine to a placebo in which some people in both groups become infected, “sieve analysis is comparing the genotypic properties of that virus in the people who were vaccinated and became infected versus the people who received placebo and became infected.”

Sieve analysis can tell you whether the vaccine reduced the rate of infection for viruses with certain characteristics, or perhaps those most akin to the vaccine itself. Understanding what a vaccine can and cannot protect against can help improve the design of future vaccines.

The success of PrEP, or pre-exposure prophylaxis, has also influenced clinical trial design in ways that have implications for other biomedical fields, Shapiro said. As new PrEP modalities (daily oral

pill, monthly injectable, long-acting injectable and now an experimental monthly pill) get developed, the way that scientists design trials testing HIV prevention approaches must shift.

“Because PrEP works so well, it’s no longer ethical to compare a new prevention treatment to a placebo,” Shapiro said. “That really changes how you design a prevention trial, in terms of how many people you enroll and what kind of surrogates you use. How do you really measure the impact? What kind of statistical techniques do you use to estimate that? These are things that really arose in HIV medicine but have implications throughout medicine.”

“This legacy of HIV research has carried into other diseases, other conditions and shaped how the FDA as a whole works with clinical trials,” Shapiro said.

Blazing the path for other viruses

Many researchers pointed to Operation Warp Speed, which piggybacked on HIV research infrastructure and expertise to fast-track development and testing of a vaccine against SARS-CoV-2, as a clear example of how investment in HIV research and researchers has broad impacts.

“When COVID hit, we had all this HIV research infrastructure in place and we basically took the genetic information of SARS-CoV-2 and plugged that into our research ‘kitchen’ that was completely fully equipped with the most state-of-the-art equipment and that allowed us to make a vaccine and monoclonal antibodies in less than a year,” said Huub Gelderblom, MD, PhD, MPH, who directs strategic partnership for the HVTN. “If that hadn’t been in place, it probably would have taken two or three years to make a vaccine.”

The globe-spanning network grew out of the need for large, coordinated clinical trials, said Fred Hutch HIV cellular and molecular immunologist Nathifa Moyo, PhD, a senior staff scientist in the McElrath Lab who works in the discovery medicine pipeline for the HIV vaccine. “The rapid development and testing of COVID-19 vaccines and treatments contributed to ending the COVID-19 pandemic.”

The relative ease with which COVID-19 vaccines were developed highlights how complex HIV is compared to other pathogens, said Gelderblom, who works on the clinical development of broadly neutralizing antibodies for HIV prevention.

“What that tells you is that HIV is a much more difficult target, because how can it be that we made a COVID vaccine with all that infrastructure, but we still don’t have an HIV vaccine? Well, HIV is just more difficult to address,” he said.

Paxlovid is another example of how HIV innovation fast-tracked our response to SARS-CoV-2. Ritonavir, one of Paxlovid’s components, was first developed against HIV. It’s not the only HIV antiretroviral drug that has been repurposed.

“There has been a sophisticated approach to developing antiretroviral drugs for HIV, and that has also been applied to create highly effective treatments for other viral diseases,” Moyo said. The

development of direct-acting antivirals have effectively cured disease from the hepatitis C virus, one of the leading causes of liver cancer, she said.

Hepatitis C, like hepatitis B, is a virus-caused liver disease (in this case the hepatitis B virus, or HBV) and can also lead to cirrhosis (chronic liver disease) and liver cancer. Some drugs against HIV (like tenofovir) also have activity against HBV.

Our understanding of HIV and related viruses has been adapted in other ways, too, Moyo said.

“HIV research provided a really deep understanding of lentiviruses, which are related to HIV,” Moyo said. “They’re both retroviruses, and this knowledge allowed scientists to adapt lentiviruses into vectors to safely deliver gene therapies and develop vaccines for other diseases.”

HIV work provided insights into how central immune cells called T cells are in fending off infections and cancer. This has implications for vaccine design, and has been leveraged against cancer to develop cellular immunotherapies.

Chimeric antigen receptor, or CAR, T cells are a cellular immunotherapy in which T cells are genetically engineered to carry a scientist-designed molecule (the CAR) that can help them seek out and destroy target cells. Several have been approved against various blood cancers and researchers are working to develop more against solid tumors.

CAR T cells are genetically engineered using lentiviral vectors (honed using knowledge gleaned from the study of HIV) and were initially tested against HIV, Moyo noted.

The innovations from HIV research have positively impacted the treatment of other viral infections and cancer, she said.

“I think the idea of a cure of latent, lifelong viruses is also something that, philosophically, emerged from HIV research,” Reeves said. “This dream for curing HIV has been real for a while, and hepatitis C is one that actually did get a cure developed.”

Reeves noted other cure work by Fred Hutch scientists in particular, such as research aimed at curing herpes simplex and hepatitis B infections.

The field of viral dynamics, in which scientists study how viruses and other pathogens wax and wane in the body, originated in HIV, he said. Seminal papers using a mathematical approach to studying how treatment changed viral patterns in people were performed in the late 1990s for HIV.

“The formalisms and mathematics developed for HIV ballooned into a whole field of viral dynamics where people now use these models to examine all kinds of different viruses and bacteria,” Reeves said.

Much HIV work underpins our understanding of how broadly neutralizing antibodies, which are

critical immune proteins that can protect against a wide swath of pathogen strains, arise in the body. Monoclonal antibodies are being used against a growing list of viruses, including, for a time, SARS-CoV-2. The AMP trials for HIV laid the groundwork for future antibody cocktails to stave off immune evasion of wilier viruses like HIV, said Gelderblom.

HIV investment buoys treatment of other diseases

Tuberculosis, or TB, is another disease that has benefited from investment in (and knowledge gleaned from) HIV science, Shapiro said. The two infections are deeply intertwined: people living with HIV are at very high risk for contracting TB and it's their leading cause of death.

The World Health Organization reports that of the 690,000 deaths from HIV in 2019, about 30% of these could be attributed to TB. And these deaths made up about 15% of the 1.23 million deaths from TB that year.

"It's much harder to treat TB in people living with HIV," said Shapiro, who describes TB as her 'originating passion.' "It's harder to diagnose — everything is worse."

At first, HIV care and treatment were delivered separately from longstanding TB programs, even in areas where many patients needed care from both systems, she said. And despite the existence of cheap, effective drugs to prevent TB, getting them to people living with HIV was not a priority.

"Through (again) a lot of activism, but also creative science and recognition that these two diseases were very co-linked, there was a de-siloing of HIV and TB and an increasing move to treat them together," Shapiro explained. "And in many places that was a precursor towards decentralized medical care in general."

This included developing more-comprehensive primary health care systems that encompassed both HIV and TB as well as primary care activities such as diabetes care and antenatal (prenatal) care, she said.

Some of this can be traced to PEPFAR, the United States President's Plan for AIDS Relief.

"PEPFAR made one of its metrics the proportion of people living with HIV who started TB-preventive therapy, and in the space of a year or two years, the number of people with HIV starting TB-preventive therapy increased by orders of magnitude," Shapiro said.

This relationship between TB and HIV is not, unfortunately, unique, said Kublin. HIV also makes people more susceptible to malaria — and malaria in turn raises the risk of contracting HIV.

"On a population level, on an epidemiologic level, that really highlights the need for a more horizontal public health and infectious disease control approach rather than one that's vertically focused on each individual infection alone," Kublin said.

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