June 5th marked 35 years since the first official reporting of the virus that would become known as HIV. This was for all intents and purposes when the AIDS pandemic began and when researchers, doctors, and scientists began fighting it. One of those scientists, Robert Gallo, director of the Institute of Human Virology at the University of Maryland School of Medicine, would become one of the co-discoverers of HIV and he has, in one way or another, been battling HIV ever since. But his lab only recently reached the point when one of its vaccine candidates became ready for Phase I clinical trials in humans.

The reason Gallo is still hammering away at HIV is because he thinks it is worth pursuing a vaccine—even with all the disappointing results, the array of treatment and prevention options that are now available, and the daunting scientific challenges that are yet to be overcome. He’s not alone in his persistence. There is still broad agreement in what is now a varied field that it will be a vaccine, and only a vaccine, that finally puts an end to AIDS.

“I might criticize the vaccine research effort as, to my mind, there’s a little bit of a herd mentality at work and it could use a bit more creativity. But I certainly would not give up on vaccines,” Gallo says.

**Prevention and persistence**

In the long and still ongoing march to solve one of the most difficult and mutative viruses in human history, there are numerous success stories. Among them are the cadre of highly effective antiretroviral drugs (ARVs) that allow HIV-infected individuals who can access them to live relatively long lives. Newer prevention strategies are also coming to bear. The prospect of effective and convenient use of what’s called pre-exposure prophylaxis (PrEP)—using ARVs to ward off infection in healthy people—is one of these new prevention strategies that is garnering attention.

The only licensed PrEP drug available now is Truvada. Truvada is a combination of the ARVs emtricitabine and tenofovir and is delivered via a once-a-day blue pill. The pharmaceutical company Gilead first launched Truvada for the treatment of adults affected with HIV more than a decade ago, in 2004. Based on preliminary results in the field, the US National Institutes of Health’s National Institute of Allergies and Infectious Diseases (NIAID) in 2007 started examining whether Truvada could be used before exposure to HIV to prevent the virus from establishing infection. This led to a series of studies that showed the efficacy of this approach, and in 2012 the US Food and Drug Administration (FDA) approved Truvada as the first oral PrEP drug. The World Health Organization then recommended it for all high-risk people. As the drug has gained acceptance and wider use, Truvada has shown itself to reduce the risk of HIV infection in people who are at high risk by up to 92 percent, according to the US Centers for Disease Control and Prevention.

There are also other prevention efforts in the pipeline. For years researchers have been pursuing different kinds of ARV-based microbicides administered either as a topically applied gel or released from a ring which would work somewhat similarly to the vaginal ring used for contraception.

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Earlier this year, initial findings were released from studies testing a vaginal ring containing an experimental ARV called dapivirine. Efficacy was as high as 56 percent in certain age groups, with an overall efficacy between 27 and 31 percent, and much lower efficacy in women aged 18 to 21. These studies showed that adherence is a problem even with the vaginal rings: if women don’t use it, it doesn’t work.

Thirty-five years into the pandemic and researchers are still battling human behavior. One approach being pursued to avoid the problems with adherence is long-acting ARVs. The benefits for HIV treatment are obvious, but researchers think these drugs might also offer a long-acting means of HIV prevention. The goal is to create a single-dose therapy that could last a year or longer and perhaps also be used for PrEP.

Where does this leave vaccines?

Earlier this year NIAID head Anthony Fauci penned an op-ed in the Washington Post with the headline, No more excuses. We have the tools to end the HIV/AIDS pandemic. Fauci’s essay ran with a photo of Lisa Sterman, a doctor who runs an AIDS clinic in the Castro section of San Francisco, holding up a Truvada pill. Sterman prescribed Truvada off-label to her patients at high risk for HIV even before the FDA approved it for that purpose, according to a report from National Public Radio in the US.

“Why does this global pandemic continue to rage?” Fauci asked in his essay. “It’s not that we lack the medical advances and interventions to end the pandemic. It is that our proven tools have not been implemented adequately or uniformly.” The NIAID director goes on to tick down the list of the advances in the struggle against the virus: the development of combination ARV therapy, treating HIV-infected patients as quickly as possible after exposure, and the development of PrEP among them. “Even in the absence of an effective HIV vaccine,” Fauci writes, “which would be the final nail in the coffin of the pandemic, we have the tools to end the HIV/AIDS epidemic in the United States and globally.”

This is, Fauci effectively concedes in an interview, a complex statement to make. He makes a distinction between what he calls a ‘durable end’ and “ballgame over.”

“If you have optimal implementation globally of the tools that we have at our disposal—namely, diagnosing essentially everyone, hopefully more than 90 percent of the people who are infected; getting the overwhelming majority, more than 90 percent of those on treatment; and keeping them on treatment. By that mechanism alone not only would you save the lives of people, but you will make it extremely difficult for them to transmit the infection to their sexual or other partners,” Fauci says. Superimpose that on to the gaining widespread use and understanding of PrEP, he adds, and then you are at least on the path, if not quite all the way there, to the durable end. “You can do the mathematical modeling and see that you would have ultimate transformation of the kinetic curve of infection. So the epidemic essentially dispels itself.”

This logic, though, contains a lot of contingencies. Funding is one obstacle. Altering human behavior so that treatment and PrEP are used correctly and consistently is another. “Knowing the difficulty with getting resources to implement this to the extent I’m describing, knowing human nature, it is unlikely this is going to happen expeditiously. It might, but I can’t rely on it,” Fauci says. “That’s the reason I can say in the same breath that we have the tools to end the epidemic, but that I still believe strongly that we need a vaccine. Those are not incompatible statements.”

Adding a vaccine to the scenario Fauci describes makes the path to ending AIDS more feasible. “A vaccine with a reasonable amount of efficacy, I’m not talking 95 percent like measles because if that were the case it would be ballgame over, that would be the end,” he says. “It has to be better than the 31 percent in the RV144 trial [a clinical trial of an HIV vaccine conducted in Thailand by the US Army]. Something moderately better: 55 or 60 percent.” That would help fill the gaps left by treatment and PrEP.

This is also what some modeling studies have born out. Modeling is harder than it seems, as any meteorologist, banker, or political pollster will attest. But it still can quantify huge data sets and present it in a way that is easier to grasp. A team from the International AIDS Vaccine Initiative, Avenir Health, and AVAC recently used an epidemiological model to measure the potential health impact and cost-effectiveness of an AIDS vaccine in lower- to middle-income countries as part of a framework overseen by the Joint United Nations Programme on HIV/AIDS. The model shows an exponential decrease in the number of new infections over decades following the introduction of a theoretical new vaccine with 70 percent efficacy starting in the year 2027 (PLoS ONE 11, e0146387, 2016). If the vaccine came in three doses, gave five years of protection, and enjoyed a strong uptake, the model shows new infections decreasing by 44 percent by 2037, 65 percent by 2052, and by 78 percent in 2070.

These are impressive numbers: they not only show how effective a vaccine could be,
but they also show how entrenched the HIV pandemic has become. A 78 percent decrease in infection by 2070 would still mean that 144,000 people would become newly HIV infected that year in developing countries. Just last year, 2.1 million people were newly infected with HIV around the world and 1.1 million died of AIDS-related causes.

**Beyond Truvada**

Earlier this year Maple Leaf Medical Clinic HIV specialist David Knox reported that a man had contracted HIV even though he’d been taking Truvada regularly as directed for PrEP. This underscored that 92 percent protection, while exceptional, is not the same as 100 percent. It prompted Noah Sather, an immunologist and assistant professor at the Center for Infectious Disease Research in Seattle, to write an opinion essay in Wired magazine with this headline: Preventive Treatment like Truvada Won’t Stop HIV. Only a Vaccine Can.

“I’ve been thinking about it a lot,” Sather says. “What it illustrates is that even at the best case scenario where you have a subject who’s fully adherent, there are still ways people can get infected. I don’t think it’s correct to consider any treatment foolproof.” The Seattle immunologist points to potential adaptation or resistance from the virus to ARVs used for prevention as another potential risk that could compromise future treatment options.

“To be clear, I’m in no way, shape, or form against Truvada or pre-exposure prophylaxis,” Sather says. After the Wired story came out, he received criticism from some readers who thought his opinions hampered efforts now underway to boost access to Truvada for PrEP. “The major point is that I don’t think it replaces the vaccine,” he says. “I think pre-exposure prophylaxis is the best tool we have now, and should be rolled out in the best way possible,” Sather says. “I understand growing frustrations, and the sentiment that you have in hand a treatment already that can prevent HIV. But long term, a vaccine is going to be far more economically viable and it’s going to have a much greater impact in the long run.”

Robin Shattock, an Imperial College of London immunologist, agrees. He has been working on combination microbicides for the last several years for potential use against HIV. “A protective vaccine will still be essential to ending the epidemic,” he says. “The new intervention approaches all have an important role and may prevent many infections, but it is wishful thinking that they alone will be sufficient.” Again, it comes down to behavior and the consistent use of therapies. “Each of the current interventions require individuals to recognize they are at risk and take steps to reduce their risk. It is as clear as day that recognizing risk and acting on it constantly is the Achilles heel for most risk-reduction strategies,” he says. And this is compounded because HIV is associated with marginalized and often highly mobile individuals that have little or infrequent contact with healthcare providers or for a variety of reasons can’t regularly access or use preventive methods, such as PrEP. “Until we have an effective vaccine that can be rolled out in endemic countries and given to all, we will only be able to suppress the epidemic.”

While many researchers agree a vaccine is still necessary, the path to a vaccine is still difficult. There have been hundreds of different AIDS vaccine trials conducted since 1984, according to the journal Science. But so far only four HIV vaccine concepts have gone through to advanced efficacy studies, with six of these trials all told. “The issue with a vaccine is less a burdensome resource issue than it is a scientific challenge. It’s a misinterpretation that you need billions and billions of dollars to develop a vaccine. The real challenge is that there are significant scientific obstacles,” Fauci says.

These obstacles are something Gallo, who’s spent over three decades working on HIV and vaccine research, knows well. He is optimistic about his lab’s vaccine candidate, now six months into clinical evaluation, but he still recognizes the numerous and tough challenges posed by developing an HIV vaccine. “I like our vaccine candidate. I like it better than anything that’s gone forward before. Will it be better? I hope so,” Gallo says. “Will it be a home run? Absolutely not.”

He, like many others, know that there is much more left to do.

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

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**GLOBAL NEWS**

**Ending AIDS: Reach Vulnerable Populations or Risk Erasing Gains Made Against HIV**

Groups consistently pushed to society’s fringes aren’t receiving the support they need to successfully prevent or treat HIV infection, health officials and advocates declare during the United Nations (UN) High-Level Meeting on Ending AIDS in New York City last week. From China and Russia to Malawi and Middle Eastern countries, intravenous drug users, sex workers, prisoners, and men who have sex with men are key populations in which the spread of HIV continues in many regions.

And while AIDS has moved from a fatal diagnosis to a treatable, chronic disease in many parts of the world, protecting vulnerable and isolated populations will be key to achieving the ambitious goal set by the UN as part of the Sustainable Development Goals to end the AIDS epidemic by 2030. “For now, we’ve been sneaking condoms under the doors of prisoners,” said Namibian health and social services minister Bernhard Haufiku during the meeting, which took place June 8-10. “But I’ve been talking with the commissioner of the corrective service to change that policy, which dates back to the apartheid era. Other marginalized groups are starting to get access to more services—sex workers, truck drivers, and more.”
Such efforts by Haufiku and other health officials around the world to support these populations come at a critical time in the decades-long struggle to contain the spread of HIV. The world has clearly made huge strides. Since 2000, the number of new annual infections has fallen by 30 percent. This is largely due to the extraordinary scale-up of antiretroviral treatment since 2010. An estimated 17 million people were receiving therapy by the end of 2015, according to the latest report issued by the Joint United Nations Programme on HIV/AIDS (UNAIDS) just days before the UN meeting opened. More than 2 million people gained access to life-saving antiretroviral therapy since the previous year alone. Availability of these drugs has pushed down annual AIDS-related deaths by 43 percent since 2003. Yet these advances remain on fragile ground. UNAIDS reports that the number of new HIV infections globally has plateaued, with around 2 million people becoming newly infected every year for more than five years despite unprecedented investment in HIV treatment programs. Even more troubling, Eastern Europe and Central Asia saw a 57 percent increase in new HIV infections over a five-year period ending in 2015. “Declines in new HIV infections among adults have slowed alarmingly in recent years, with the estimated annual number of new infections among adults remaining nearly static,” write the authors of the 2016 UNAIDS Global AIDS Update. “Beneath this global figure lie multiple disparities—across regions, within countries, between men and women and young and old, and among specific populations being left behind. These disparities must be addressed in order to achieve the reductions required to end the AIDS epidemic as a public health threat by 2030.”

Remembering the forgotten

Experts warn that the reluctance by authorities to reach the most vulnerable populations is fueling HIV’s spread. Through criminalizing and stigmatizing same-sex relationships, transgender people, sex work, and drug use, those who fall into these categories get locked out of education and are also less likely to benefit from HIV prevention or treatment programs. Marginalized people accounted for more than 90 percent of new HIV infections in 2014 in Central Asia, Europe, North America, the Middle East, and North Africa, and for 20 percent of new infections in sub-Saharan Africa, the UNAIDS data reveals. A Chinese AIDS activist at the High-Level Meeting said stigmatization of gay men was fueling a rising infection rate among that demographic. Pavel Aksenov, the director of Esvero, the Russian Harm Reduction Network, said antipathy from his country’s officials toward these ostracized groups is translating into real problems. “Russia dropped support for necessary programs by 75 percent, leaving many without funds overnight,” he said, the strain in his voice making clear his deep frustration. “The question is how can you work with people when you do not recognize their existence in the first place.”

Indeed, to many at the UN meeting it has become clear that not engaging these groups doesn’t just risk stalling advances made in controlling HIV, it also threatens the global commitment to rid the world of AIDS. Switzerland’s Ambassador for Global Health, Tania Dussey-Cavassini, said much progress has been made, but it is important to remember that around 37 million people are currently living with the disease and that number could easily grow. “If we continue to do the same thing, we will achieve nothing more than what we’ve already accomplished today,” she said. “We all must work constructively outside of our comfort zones.”

New financing

Many meeting attendees called for the same prescription to reach key populations and take the global AIDS response into its next phase: more money. Indeed, donors and middle- and low-income countries will need to increase investment in AIDS programs significantly to meet 2020’s US$26.2 billion target, which UNAIDS projects is the necessary amount to scale up ART treatment and prevention sufficiently to end AIDS by 2030. Outside analysts calculate that the program would cost $54 billion over the next 10 years. Advocates and officials hailing from middle-income countries, whose relatively stronger economies exclude them from some of the stream of donor funds going to the poorest nations, voiced concerns that they would be unable to reach the key populations at risk of HIV within their borders. “So far, funding most programs for key populations has come from international sources,” said Lorena Castillo de Varela, the First Lady of Panama and a UNAIDS Special Advocate for AIDS in Latin America. “There needs to be a transition to domestic, sustainable funding for these people. And we still must help countries that don’t have the capacity to do it.”

To that end, during the meeting the US announced that it would bolster efforts around the world to reach these vulnerable groups with a $100 million Key Populations Investment Fund. The money is meant to fund community-based groups directly providing HIV prevention and treatment services to sex workers, gay men and other men who have sex with men, injection drug users, transgender people, and prisoners. Another goal of the fund is to reduce stigma and discrimination suffered by these individuals. Jeffrey Sachs, a renowned economist and director of the Earth Institute at Columbia University who spoke about financing the end of AIDS, said that any hand wringing about the cost to get the job done should be brushed off. “This is not so hard, honestly,” he said. “It’s a matter of just a little bit of money. How much is needed? A rounding error so small—maybe another $5 to $10 billion a year. We’re talking small change.” — Michael Keller

Michael Keller reports from the frontiers of science, technology, and international affairs. His writing has appeared online and in newspapers, magazines, and books, including the graphic novel Charles Darwin’s On the Origin of Species.