THE LONG SHOT

An injectable HIV drug with a novel mechanism shows remarkable ability to prevent infection

By **Jon Cohen**

The drug lenacapavir (yellow) binds to HIV's capsid proteins, preventing the capsid cone from passing through pores into the nucleus of a human cell.

Despite decades of progress, HIV still infects more than 1 million people a year, and a vaccine remains stubbornly out of reach. But this year the world got a glimpse of what might be the next best thing: an injectable drug that protects people for 6 months with each shot.

A large efficacy trial in African adolescent girls and young women reported in June that these shots reduced HIV infections to zero—an astonishing 100% efficacy. Any doubts about the finding disappeared 3 months later when a similar trial, conducted across four continents, reported 99.9% efficacy in gender diverse people who have sex with men.

Many HIV/AIDS researchers are now hopeful that the drug, lenacapavir, will powerfully drive down global infection rates when used as pre-exposure prophylaxis (PrEP). "It has the potential, if we can do it right, which means going big and getting it out there," says Linda-Gail Bekker, an infectious disease specialist at the University of Cape Town who led one of the two efficacy trials for the drug's maker, Gilead Sciences.

But that's not the only reason *Science* has named lenacapavir its 2024 Breakthrough of the Year. The off-the-charts success of the drug as PrEP sprang from a basic research advance: a new understanding of the structure and function of HIV's capsid protein, which lenacapavir targets. Many other viruses have their own capsid proteins, which form a shell around their genetic material, so this drug's triumph raises the exciting prospect that similar capsid inhibitors could fight other viral diseases.

Great strides have been made in HIV treatments since the bad old days, when an infection meant horrific wasting, a decimated immune system leading to other rampant infections, and an early death. In 1996, researchers showed that powerful cocktails of drugs could fully suppress HIV and stave off development of AIDS—*Science*'s breakthrough that year. Current antiviral drugs are even better, allowing millions to live normal life spans with a chronic but manageable disease. Treated people whose virus is suppressed also rarely infect others, a discovery that led *Science* to declare "treatment as prevention" the 2011 Breakthrough of the Year. As more people around the world gained access to the drugs, new global infections plummeted from 2.1 million in 2011 to 1.3 million last year.

Help also came from prevention tools such as condoms, male circumcision, needle exchanges, and education, as well as from "oral PrEP." First approved in the United States in 2012, PrEP pills offer powerful protection—if people take them. In men who have sex with men, they helped drive new HIV infections to near-zero in San Francisco, Sydney, and Amsterdam. But years passed before poorer countries could even access generic versions of the drugs. And in many African countries, young girls and women took the pills only intermittently because of obstacles including stigma and relationship dynamics. In 2021, a PrEP drug called cabotegravir came to market that only requires shots every 2 months. But it, too, has been held back by high costs and limited interest.

Progress has stalled, leaving the world far from the goal set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) of cutting new HIV infections to below 370,000 next year and less than 200,000 in 2030. But lenacapavir might break the impasse. It upended the PrEP world in June with news that in a blinded study in more than 5000 cisgender women and adolescent girls in South Africa and Uganda, not a single person who received the injections became infected. In September, a second lenacapavir PrEP trial only had two infections in more than 2000 cisgender men, transgender men and women, and nonbinary people who had sex with men in South America, Asia, Africa, and the U.S.

"You don't see data like this every day," says Mitchell Warren, who heads AVAC, a nonprofit that began as the AIDS Vaccine Advocacy Coalition and has increasingly made PrEP its main focus.

Unlike mainstay HIV drugs that disrupt viral enzymes by binding to the "active sites" that allow them to function, lenacapavir interacts with the capsid proteins that form a protective cone around the viral RNA. At first, researchers did not see capsid as a particularly "druggable" target. In the 1990s and early 2000s, researchers had shown that the cone interacts with cellular proteins to perform a series of important functions during the early stages of infection. Drugmakers assumed blocking those interactions would require many drug molecules, each one binding to several capsid proteins.

But new findings rewrote the playbook on how capsid works by showing that the cone consists of a stable but flexible lattice of five- and six-molecule groups. This new picture intrigued Gilead chemists and eventually led to the creation of lenacapavir. Later, researchers found that the cone does not immediately fall apart when HIV enters a cell, as previously thought, but remains intact and can even squish through pores in the nuclear membrane to deliver its payload of viral genes. Lenacapavir, it turns out, not only blocks capsid's interactions with the cellular proteins, but also makes the cone rigid, apparently preventing it from slipping into the nucleus. And even if it fails to block this step and the cell produces HIV proteins, the drug similarly stiffens the freshly minted capsid subunits, interfering with the formation of new cones and viral particles.

There was a hitch, though: Lenacapavir is relatively insoluble, and the body has trouble absorbing it. But when Gilead's team developed an injectable form of the molecule, this weakness became its superpower, giving the drug an extraordinarily long life in the body.

Injectable lenacapavir has been on the market for 2 years as a "salvage" treatment for people living with the virus who have failed other drugs. Now, it may have a new life as the most effective form of PrEP.

Whether lenacapavir PrEP will become widely used and speed the end of the HIV/AIDS epidemic depends on access, delivery, and, of course, demand. Regulatory approval isn't expected until the middle of 2025 at the earliest. The price, still unannounced, will determine who can afford it. Gilead has cut a deal with six generic manufacturers to produce low-cost versions for 120 developing countries, but so far there's no discount for middle-income countries such as Brazil, which has South America's largest number of people living with HIV. And resource-strapped governments might not have the budget even for discounted product. Overburdened health care systems, social unrest, extreme weather events, and transportation challenges could all hamper delivery. And people must be willing to get the shots every 6 months.

Powerful as it is, lenacapavir PrEP is no substitute for a vaccine, says Jeanne Marrazzo, head of the U.S. National Institute of Allergy and Infectious Diseases. Marrazzo is optimistic the drug could help "dramatically reduce HIV incidence in our most challenging areas." But a vaccine could be given to everyone, not just people at high risk; cost only a few dollars to make; and last for many years with a few shots. "We must continue to search for an intervention that will create durable individual immunity if we really want to end HIV."

Although injectable lenacapavir may not be enough to achieve the goals set by UNAIDS, it holds the potential to protect millions from infection. It is a potent addition to the series of spectacular biomedical breakthroughs that—as they reach the people who need them most—are steadily moving HIV/AIDS away from being a disease that upends entire communities and turning it into a rare malady. ■

VIDEO AND PODCAST
More about the development of lenacapavir: https://www.science.org/boty2024

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