Improving Treatment For HIV

KU Leuven

Imagine receiving a diagnosis for a life-threatening disease and then learning that treatment will require taking dozens of pills each day, with terrible side effects, for the rest of your life. For years, this was the plight of patients infected with HIV (human immunodeficiency virus). Now they have a better treatment option: a single pill, taken once a day. That pill includes a vital compound called tenofovir, the product of collaboration between researchers at the Rega Institute for Medical Research (at KU Leuven), the Institute for Organic Chemistry and Biochemistry (IOCB) at Prague's Academy of Sciences and Gilead Sciences. During the past decade, tenofovir has emerged as a medical breakthrough for HIV, providing treatment that gives patients more life — in both quantity and quality.

Grappling With a Difficult Disease

By the end of 2012, the estimated number of people infected worldwide by HIV exceeded 34 million. That's roughly

equivalent to the entire population of Canada.

During the early 1980s, researchers identified HIV as the virus that can devastate the human immune system and lead to AIDS (acquired immunodeficiency syndrome). Years ago, an HIV diagnosis was akin to a death sentence. The first treatment, AZT (azidothymidine), came on the market in 1987 and was soon joined by other medications targeting HIV. These drugs could extend patients' lives, but at a cost. Patients suffered debilitating side effects like nausea, fatigue and muscle pain. What's more, the virus would often mutate and develop resistance to the drugs, rendering them ineffective.

The treatment itself required an onerous regimen. "In the past, patients had to take multiple pills, three to five times a day. It was almost a handful of medication," says Patrick Chaltin, Ph.D., a former senior intellectual property officer at KU Leuven Research & Development (LRD) and currently managing director of the Centre for Drug Design and Discover (CD3).

Disabling the Copy Machine

When the first AIDS case was documented in 1981, it caught the attention of Jan Balzarini, Ph.D. "It was a new infection, something that was very mysterious and affecting a lot of people," says Balzarini, who currently heads KU Leuven's virology laboratory. "More and more, it became clear that this would become one of the most serious pandemics in the world." Balzarini has conducted research in KU Leuven's virology laboratory for more than three decades. During most of that time, he worked for the previous head of the lab, Erik De Clercq, M.D. (who retired in 2006).

To treat this mysterious virus, De Clercq and Balzarini tested a category of compounds called nucleoside analogues. Since they mimic the structure of natural building blocks for DNA synthesis, they can enter the host cells of the virus and block the enzyme HIV needs to replicate. It's like throwing a wrench in the virus copy machine.

After a nucleoside analogue enters a virus's host cell, it can't immediately disable the copy machine. It must undergo a three-step chemical process within the cell, and sometimes that process can break down, hindering the treatment's effectiveness.

The first clinically used anti-HIV drugs (like AZT) were nucleoside analogues. But De Clercq and Balzarini focused on a unique group of nucleoside compounds, called nucleoside phosphonates. It was Antonin Holý, Ph.D., along with Hana Dvoráková, Ph.D., at the IOCB in Prague who synthesized the nucleoside phosphonates and sent them to De Clercq's lab for investigation. "That was a crucial part — bringing together the disciplines of biology and chemistry, and collaborating to make a huge discovery," says Chaltin.

One of the compounds turned out to have several benefits that made it more effective against HIV compared to other nucleoside compounds. The nucleoside phosphonate didn't need a three-step chemical process to disable HIV's copy machine. It only required two steps — and the compound had a more stable chemical structure — which helped ensure its ability to block the virus from replicating.

The researchers were also struck by the compound's staying power. Other nucleoside compounds can disable HIV's copy machinery for a few hours — requiring patients to take drugs up to five times a day. Notably, the nucleoside phosphonate blocked HIV's ability to replicate for up to 24 hours.

"This property became important many years later for the success of tenofovir, because it allowed IOCB and Gilead Sciences to make a drug that you only have to take once a day," says Balzarini. "That's extremely important for a disease that you have to treat not in one week, or one month, but for many years."

They tested many variations of nucleoside phosphonate compounds and found one with minimal side effects — which became known as tenofovir. Balzarini points out there are compounds closely related to tenofovir that have bad side effects. "The distinction is often very subtle, with one small chemical group that can make an enormous difference."

With early treatments, HIV drug resistance was a big problem. Balzarini, De Clercq and their collaborators speculated that the resistance risk would drop significantly if they used a compound that mimicked DNA's building blocks as closely as possible. If the virus couldn't detect an artificial compound, then it wouldn't create mutations to build up resistance. That was the hunch, and it proved correct.

"The virus sees this molecule as almost natural, so the resistance level is quite low and takes a long time to develop," says Balzarini — noting that resistance to tenofovir is as much as 100 times lower than some other HIV drugs.

Entering the Marketplace

Tenofovir was initially licensed to Bristol-Meyers in the late 1980s, but the company lost interest in the compound after merging with Squibb Corp. in 1989 and subsequently returned the intellectual property to IOCB and KU Leuven. One person at Bristol-Myers did not lose interest, however: John Martin, Ph.D., who went on to become CEO of Gilead Sciences. While at Bristol-Myers, Martin served as a head chemist on the tenofovir project.

"He understood the importance of the compound," says Balzarini. After Martin left Bristol-Myers-Squibb to join California,-based Gilead Sciences, he contacted De Clercq and Holý to see if Gilead could obtain the license to tenofovir.

IOCB and KU Leuven licensed the technology to Gilead Sciences in 1991. At that time, the KU Leuven's technology transfer office (TTO) was relatively small, but that's changed, says Balzarini. "Our TTO these days is doing a fantastic job at the university to support scientists who have inventions, in terms of patent filing, defending patents, making contacts with pharmaceutical companies and negotiating to get the best deal for the university and inventors," he says.

Gilead successfully developed a form of tenofovir that could be taken orally (called tenofovir disoproxil fumarate) and began selling it in 2001 under the brand name Viread. When used with other antiretroviral drugs, it helps keep the virus suppressed. Viread is now an active ingredient in three single-tablet HIV treatments sold by Gilead: Atripla, Complera and Stribild.

The benefits of a once-a-day pill extend beyond mere convenience for patients.

"It combines a full, multidrug course of HIV therapy into a single tablet — making it easier for patients to take their medicine on a consistent basis, which helps improve treatment outcomes," says Norbert Bischofberger, Ph.D., executive vice president of research and development and chief scientific officer for Gilead Sciences. "These Viread-based single-tablet regimens have become standards of care in HIV therapy." He notes that today, 4.4 million patients worldwide are receiving tenofovir (the active ingredient in Viread), making it the most widely prescribed molecule in HIV therapy.

"Today, thanks to improved therapies, many individuals who are diagnosed with HIV early in the course of the disease can look forward to a near-normal lifespan," says Bischofberger.

The drug's minimal side effects make a big difference for patients too. "Now they can do things that other people do," says Chaltin. "They can more or less live their lives until they die of other diseases, not HIV."

Expanding Access to Treatment

HIV represents a worldwide problem, but the epidemic is most severe in the developing world. When Viread was approved in 2001, only about 240,000 patients in low- and middle-income countries had access to HIV therapy, says Bischofberger. "The few HIV drug-access programs that existed at the time were inadequate and unsustainable, so the company innovated its own model and established its treatment access programs in 2003."

These efforts included providing Viread — and medicines containing it — at steeply discounted prices in low- and middle-income countries. Gilead established licensing agreements with Indian manufacturers that enable them to produce and sell high-quality, low-cost generic versions of Gilead HIV medicines in more than 100 developing countries (including all of Africa). According to Gilead, approximately 3.5 million people in the developing world are receiving HIV medications manufactured by the company and its Indian partners.

Gilead also provides licenses for tenofovir-based drugs to the Medicines Patent Pool, a United Nations-supported initiative to improve treatment access through patent sharing.

A Role in Treating Other Viruses

Viread's usefulness extends beyond HIV. In 2008, it received approval as a treatment for chronic hepatitis B virus infection, the most common serious liver infection in the world. "It is now one of the most prescribed treatments for that disease," says Bischofberger.

In 2012, sales for Viread (the brand name for tenofovir) reached about $845 million, and sales for Truvada, Atripla, Complera and Stribild (which contain tenofovir) totaled about $8.14 billion. The financial success of those drugs may help fuel further breakthroughs from Balzarini and his colleagues, as tenofovir licensing royalties come back to the universities and the virology lab.

> *"It gives us the opportunity to further expand our research group and to be flexible in our research," says Balzarini. "We now have the freedom to develop new compounds for HIV, or other viruses, or cancer."*

The funding from licensing income provides a more efficient way to work, he says — as opposed to research grants, which can constrain researchers' ability to follow a hunch or a new development. Instead, the money from tenofovir's licensing enables Balzarini and his team to pursue the unexpected: "If a new virus comes out tomorrow, we can, in a very dynamic way, more easily address emerging problems."

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