



KP-1461: A Novel Anti-HIV Drug in Limbo?

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The path of an experimental drug from the laboratory to U.S. Food and Drug Administration (FDA) approval is typically long, rocky, and uncertain. It is especially so for a drug that turns common wisdom on its head.

Take KP-1461, a new type of antiretroviral drug from Koronis Pharmaceuticals in Seattle. Unlike all of the currently approved anti-HIV drugs, which aim to reduce the amount of virus in the body by blocking viral replication, KP-1461 was designed not to inhibit replication, but rather to force newly created HIV to become less able to infect human cells.

Despite this intriguing mechanism of action, clinical trials of the experimental drug were put on hold in 2008 due to unexpected results in laboratory studies, and they have yet to restart. The concerns were not about safety, but whether the drug is able to adequately shut down HIV production, as well as problems with recruiting trial participants. Some insiders remain optimistic about the drug, but the obstacles are substantial.

“I think that the potential is there, but we do have challenges in formulation and delivery,” said Jim Mullins, PhD, researcher and key independent adviser to Koronis for the drug. “Furthermore, the virus is incredibly resilient.”

Mullins, a professor of microbiology and medicine at the University of Washington in Seattle, is an expert in the area of viral mutagenesis—in other words, how viruses mutate, or change over time. He has been studying a particular theory of viral mutation called lethal mutagenesis. If a drug like KP-1461 works as planned, it will create so many mutations in HIV’s genetic code that the virus will be rendered unable to survive, replicate, and infect new cells.

Understanding Lethal Mutagenesis

Every living creature carries genetic instructions that enable it to reproduce and carry out the functions necessary to grow and sustain life. One of the strengths of viruses, including HIV, is that very little of the original genetic blueprint must be conserved from one generation to the next.

Another advantage is that viruses reproduce rapidly and in large numbers. This means that mutations take place quickly and many of them can occur without harming the virus population too much. Ultimately, despite the body’s best attempts

to control HIV, the virus mutates to overcome everything the immune system can throw at it. It also mutates to escape the effects of antiretroviral drugs, leading to drug resistance.

Mullins and others have been working on a way to turn these particular strengths into an Achilles’ heel. Rather than shutting down HIV by blocking its replication or stopping mutations from occurring, the researchers hope that a drug might be used to stimulate even more mutations—but these mutations would harm rather than help the virus.

“The idea of lethal mutagenesis really follows from the theory of what’s been called ‘error catastrophe,’” explained Robert Smith, PhD, an assistant research professor at the University of Washington. Simply put, the theory of error catastrophe suggests that only so many errors can be introduced into HIV’s genetic blueprint before those instructions fail and the virus can no longer produce viable copies.

Under normal circumstances, numerous errors occur as HIV rapidly makes more copies of itself. In fact, a large proportion of the new virions (viral particles) created through replication are defective and incapable of infecting human cells. But because so many new virions are produced, and because so little of the viral genetic code must be conserved, the high mutation rate actually works in HIV’s favor.

Experts think that all these mutations bring HIV perilously close to the error catastrophe state. If too many harmful mutations build up and the rate of error keeps increasing, the virus can lose its ability to copy itself and infect additional cells.

Carmen Ruiz-Jarabo, PhD, from Universidad Autonoma de Madrid in Spain and colleagues offered proof for this theory. In the journal *Virology* in 2003, they reported on the successful use of a mutagenic drug called 5-fluorouracil

(5-FU) to induce lethal mutagenesis of lymphocytic choriomeningitis virus (LCMV) in mice.

The study found exactly what the theory predicted: 5-FU caused a massive increase in the mutation rate of LCMV to the point where the virus could no longer sustain itself. Similar experiments have been carried out in cell cultures of the viruses that cause polio and foot-and-mouth disease.

Enter KP-1461

The success of inducing lethal mutagenesis in other viruses sparked hope that the same result could be accomplished with HIV. In 2005, Smith published a paper in *Virus Research* pointing out the promise of lethal mutagenesis in HIV and describing the conditions that would have to be met by a drug designed to induce error catastrophe in this virus. He pointed to two *in vitro* experiments with mutagenic drugs that prompted HIV to mutate at an accelerated rate, which led to impaired replication.

According to Smith and his co-authors, one of the potential problems of a mutagenic anti-HIV drug would be the risk of causing damage to mitochondria in host cells. Mitochondria are the energy-producing powerhouses of all cells, converting fats and sugars into the energy cells need in order to function.

Several existing antiretroviral drugs in the nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) class were found—after approval—to significantly damage mitochondria. The consequences of this mitochondrial toxicity include fat loss in the limbs, face, and buttocks (called lipoatrophy) and nerve damage that causes pain and tingling in the hands and feet (called peripheral neuropathy; see “Understanding and Managing Peripheral Neuropathy,” page 27). The data Smith reviewed suggested that an NRTI aimed at lethal mutagenesis, rather than termination of the viral life cycle, could likewise cause mitochondrial toxicity.

Also in 2005, Kevin Harris, PhD, a scientist with Koronis, published the first data on KP-1461 in *Antiviral Research*. The report described the potential of KP-1461, or rather its active form, KP-1212. Further down the line, Koronis found a way to boost blood levels of KP-1212 by using the body’s metabolic processes to transform a small amount of the prodrug KP-1461 into a larger amount of KP-1212.

Like the NRTIs, KP-1212 has a structure similar to that of natural nucleosides, the building blocks of genetic material that exist in the body. HIV uses these building blocks to produce new DNA copies of its own genetic material. Because KP-1212 looks like a normal nucleoside, the virus can mistakenly incorporate the drug into its DNA. Given its flexible structure, it can pair up with multiple nucleoside bases, leading to mutations in the genetic code. But unlike NRTIs—which act as defective building blocks that prevent

HIV from completing new DNA strands—KP-1212 allows the virus to continue constructing its now-mutated DNA.

Harris’s team showed that in cell cultures, KP-1212 accelerated HIV’s mutation rate to such a degree that it ultimately “burned out” the infection, eradicating the virus in laboratory tests.

What’s more, KP-1212 did not force HIV to create drug-resistance mutations, either to itself or to any of the approved antiretroviral drugs. Instead, HIV exposed to KP-1212 became even more sensitive to that drug, as well as to approved NRTIs, including AZT (zidovudine; Retrovir) and d4T (stavudine; Zerit). Contrary to the concerns raised by Smith and his co-authors, KP-1212 also did not harm the genetic workings of host cells or mitochondria.

Early Clinical Trials

At the 45th Annual Meeting of the Infectious Disease Society of America in 2007, Koronis presented data from a 14-day Phase Ib clinical trial comparing several doses of KP-1461 versus placebo in treatment-experienced HIV positive participants. In that study, investigators found the drug to be safe and well tolerated at doses up to 1,600 mg taken every 12 hours.

In mid-2007, Koronis initiated a longer, 124-day, Phase IIa study of KP-1461 in heavily treatment-experienced people with HIV. In this trial, the target enrollment was 40 participants and the dose of KP-1461 was scheduled to escalate over time as more safety data became available. Midway through enrollment, however, researchers encountered the first obstacles.

A set of laboratory studies designed to assess the potential for the development of drug-resistance mutations ran parallel with the Phase I/II trial program. These studies produced an anomalous result: Unlike previous *in vitro* tests, in which multiple doses of KP-1461 in cell cultures substantially reduced and eventually eliminated HIV, these new studies failed to eradicate the virus. This finding, along with difficulty enrolling participants, put the clinical trial on hold.

“The trial investigators were coming back to me and saying, ‘I no longer have patients who are multi-class resistant, because of the new drugs that have been recently coming out onto the market,’” explained Jeff Parkins, Vice President of Clinical Development at Koronis. The inability to enroll an adequate number of trial participants, combined with the alarming *in vitro* data, brought research on KP-1461 to a standstill.

Starting Over Again

According to Parkins, Koronis Pharmaceuticals is now working on a new formulation of KP-1461 that will produce sufficient concentrations in the blood and cause enough damage to HIV’s genetic material to trigger lethal mutagenesis.

The data Koronis analyzed from the halted Phase II study

did not show a statistically significant difference in viral load reduction between people receiving KP-1461 and a group of control participants who took other antiretroviral drugs. One of the main reasons for this disappointing finding may have been inadequate blood plasma concentrations of the drug; in short, too little KP-1461 made its way to HIV-infected cells.

Still, there were reasons to be optimistic. Mullins notes that there were significant increases in the frequency of HIV mutations in participants taking KP-1461 compared with the control group. This increased mutation rate is a sign that the goal of stimulating lethal mutagenesis is possible, according to Parkins. “I’ve talked with some of our clinicians who participated in the Phase II study, and they’re very excited over the increased mutation [rate],” he said. Based on early data, the experimental drug was also considered safe and well tolerated.

Figuring out how to keep studying KP-1461 is not an easy task. Koronis must convince the FDA that moving forward with clinical trials is safe and fills an unmet need. Given the challenge of finding people who have not fared well on other therapies—and the potential safety risk of having them take KP-1461 by itself—Parkins said that investigators have begun to look at testing the drug at the other end of the spectrum, in people who have not yet started HIV treatment.

“Ultimately, this may be a drug that may be best positioned as an up-front therapy in a newly diagnosed, treatment-naïve patient,” Parkins explained. Such a strategy “would put them on something that would not take away from the potential for any downstream treatment with standard antiretrovirals. Rather, they could continue on [KP-1461] treatment with an undetectable viral load for an extended period of time, and ultimately defer or eliminate the need to go on something else somewhere down the road.”

Mullins, however, thinks KP-1461 should still be tested in treatment-experienced people before trying it in those who have not yet taken antiretroviral drugs. “I don’t think we’re presenting enough viral suppression to make [KP-1461] viable as a first shot,” he said. Rather, Mullins anticipates that KP-1461 will “push the greatest likelihood of error catastrophe” in the presence of drugs to which the virus is already resistant.

Mullins’s view corresponds with the thinking of one of the world’s top HIV virologists, John Coffin, PhD, Professor of Molecular Biology and Microbiology at Tufts University.

“My thinking on this is that [KP-1461] is another mechanism that should be considered on a level playing field with other antivirals,” said Coffin, who has no official ties to Koronis. “It has the advantage that the mechanism is likely to be different enough from other antivirals that there’s a good chance there won’t be cross-resistance. So I see this as [part of] another class of antiviral drugs that has interesting properties, but not necessarily completely unique ones.”

HIV Eradication: The Holy Grail

Another potent antiretroviral agent that would work even in the face of existing drug resistance would be welcome, but it is the possibility for lethal mutagenesis—and the resulting eradication of HIV—that got people most excited about KP-1461 in the first place.

Researchers once thought that existing antiretroviral drugs would be potent enough to eradicate HIV if viral replication could be suppressed. But this goal has been impeded by the existence of “sanctuary sites” (such as the brain) and latent immune cells that persistently harbor HIV and can release new virions even when viral load in the blood drops to levels that are nearly immeasurable using the best available technology. Accessing and eradicating HIV in these sites has become the life’s work of several top AIDS researchers.

When asked whether a drug like KP-1461 has unique properties that might allow it to overcome the problem of viral reservoirs, Coffin and Mullins do not agree. Coffin says no; Mullins, however, thinks that the experimental drug’s mechanism of action—inducing increasingly less-fit virus—should lend itself just as well to reducing viral fitness within reservoirs as it does in more easily accessed circulating blood and tissues.

With the current downturn in the U.S. economy, biotechnology companies are having a much harder time securing the funding they need to make new antiretroviral therapies a reality. Whether or not KP-1461 has the potential to accomplish the goal of eradicating the virus from the body, its novel approach to fighting HIV makes it an experimental treatment worth watching.

David Evans is currently a senior editor with *AIDSmeds.com* and *POZ* magazine. In addition to writing, he has been an AIDS treatment educator and activist for nearly 20 years.

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