

Need for Novel Approaches to Treating HIV Still Exists

Special Report

Patricia F. Dimond, Ph.D.

Drug companies continue to make HIV drugs more convenient for patients by pursuing novel combination strategies, which is also aimed at avoiding inevitable drug resistance. Close to half of HIV-infected patients who initially respond to treatment, however, develop drug-resistant strains and stop responding within 8 to 10 months. An additional 20% to 40% have drug-resistant strains when first diagnosed.

While over 30 different formulations, reformulations, or coformulations of antiretroviral drugs are now in use, this combination strategy has not prevented resistance, and the need for something completely different still remains. Some drugs in currently in development are aimed at as yet unexploited characteristics that enable the virus' seemingly endless adaptability and escape artistry.

On the Market

Current anti-HIV drugs work by several mechanisms, like reverse transcriptase inhibitors (RTIs) that prevent DNA copies of the virus from being made following its integration into the host cell genome. These drugs include nucleoside analog RTIs (NRTIs), nucleotide analog RTIs, and non-nucleoside RTIs (NNRTIs). The first two drug classes are analogs of naturally occurring deoxynucleotide components. As these modified DNA components become incorporated into the growing DNA chain by reverse transcriptase, they block further addition of naturally occurring deoxynucleotides, thereby terminating DNA chain growth. The first approved HIV drug, Zidovudine, is an NRTI.

Other types of marketed HIV drugs include protease inhibitors such as [GlaxoSmithKline's](#) Lexiva and Amprenavir that interfere with viral protein processing by the virus-specific protease enzyme. This prevents mature viral particle formation in infected cells.

Integrase inhibitors, on the other hand, prevent viral insertion into cellular DNA. [Merck & Co.'s](#) Isentress®, which received FDA approval in October 2007, is the only such currently available medication. [Gilead Sciences](#) is also developing an integrase inhibitor called eltegravir, which is in Phase III trials.

Yet another class of drugs blocks HIV access into susceptible cells like healthy CD4 cells. Two entry inhibitors have been approved by the FDA: [Roche's](#) Fuzeon, sanctioned in March 2003, targets the gp41 protein on HIV's surface, and [Pfizer's](#) Selzentry, [green-lighted in August 2007](#), targets the CCR5 protein on the T-cell surface.

To circumvent resistance, combination HIV drugs consisting of as many as five different compounds have been developed. These medications are theoretically supposed to prevent the virus from becoming resistant to one or more drugs. To reduce the number of pills that must be taken, many of these medications are combined in one capsule or tablet. Such drugs include Gilead's Truvada comprising Viriad (tenofovir) and emtricitabine, both of which are RTIs.

The potential utility and profitability of new combinations of old drugs and old drugs coupled with investigational new drugs in a similar class as the old drug has driven a significant number of deals. Most recently Gilead and [Tibotec decided to work together](#) to combine Gilead's Truvada and Tibotec's investigational NNRTI called TMC278 to create a three-drug combination consisting of two different drug classes. If approved, the product will be the second complete antiretroviral treatment regimen for HIV

available as a single, once-daily tablet. The first such therapy, Atripla, consisting of efavirenz, emtricitabine, and tenofovir and marketed by [Bristol-Myers Squibb](#) and Gilead, was approved by the FDA in 2006.

New Approaches to Tackling Resistance

The strategy behind drug combinations, whether from the same class or different classes, is to lower viral levels to the point where not enough replication occurs to sustain the development of mutants. That means the drugs work only temporarily until the virus achieves enough critical mass to break through the mutant barrier and start replicating with its usual relentless efficiency.

One example of a new technique is a therapy being developed by [Koronis Pharmaceuticals](#), which exploits the virus' greatest survival mechanism, its rapid mutation rate. Koronis' scientific founders, Larry Loeb, M.D., and Jim Mullins, Ph.D., propose that by presenting HIV with an error-inducing nucleoside analog, as opposed to a termination-inducing analog, the viral genome mutation rate could be pushed beyond its allowable limits of diversity. Koronis' lead drug candidate, KP-1461, is a nucleoside that can reportedly accelerate HIV mutation to such an extent that the virus becomes permanently disabled and replication incompetent, a phenomenon known as terminal mutagenesis or error catastrophe.

Jeff Parkins, Koronis vp of clinical and regulatory affairs, differentiates the firm's drug from other nucleosides by saying, "Our drug is a cytidine analog, but it is not a planar structure and undergoes constant conformation change, or tautomerization. So it can act as either cytidine or thymidine and become incorporated into the complimentary strand of the viral DNA copy, thereby producing base-pair mismatches."

Since the host cell has repair mechanisms like excision repair, the virus is unlikely to affect its DNA. Mitochondrial toxicology studies have supported this view. Additionally, during a Phase II study at a lower dose of the drug administered over four months, "We didn't see any increase in resistance nor have we seen any known resistance to standard antiviral drugs due to KP-1461," Parkins states.

He also notes that a complicated paradigm shift must be dealt with from a clinical trial perspective to show efficacy: the use of viral load reduction as an endpoint. "Because our drug passively creates mutations, it doesn't have a fast action against the virus. It takes time for mutated viral forms to accumulate, so the clinical gold standard of rapid viral load reduction may be an inappropriate endpoint for this drug. Our idea is that over a more extended time frame, based on what we have seen in our early clinical studies, we may be able to really knock out the virus permanently and get rid of any reservoir of replication-competent virus."

[Myriad Pharmaceuticals](#), a spinout of Myriad Genetics, is also developing a new class of HIV treatments called maturation inhibitors. MPC-4326, which has fast-track designation, binds to the capsid/SP1 cleavage site on the Gag protein. This inhibits the ability of the virally encoded protease to release the capsid protein and complete the viral maturation process. The resulting immature virus particles are structurally defective and noninfectious. MPC-4326 is expected to enter a Phase IIb trial later this year.

It is hoped that these and other efforts will put new drug weapons in the hands of doctors and patients to arm them in the life and death struggle against HIV.

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