Drugs to Watch in 2009

Experts think we're about to enter a dry spell in terms of new HIV treatments, with no truly novel compounds available for treatment-experienced patients likely for the next several years. They remain hopeful, however, that new technologies and avenues of research could spark the next great leap forward.

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The science of HIV has been a mixed bag. The search for an effective vaccine has experienced one setback after another, and it has often seemed that we're no closer to a cure today than we were when the virus was first discovered more than 25 years ago. But with treatment—drugs to achieve long-term management of the disease—we've hit the jackpot. Within the same 25 years, the U.S. Food and Drug Administration (FDA) has approved 20 different drugs, four of them in the past three years.

Now, however, that run of riches has hit a snag. No completely innovative new treatment is in a stage of research beyond the earliest point in human testing—which means it will be several years before such a drug can be prescribed for highly treatment-experienced HIV-positive individuals who need them most.

Experts who've been watching HIV drug development for nearly two decades universally expressed concern about the state of AIDS research and the possibility of no new drugs being available in the short term. They stated that the path to FDA approval has become more challenging for HIV treatments, compounded by the fact that the market has become more crowded with drugs that generally work quite well for many years.

This doesn't mean that researchers, or drug companies, have completely given up on HIV. Activists and researchers contacted by AIDSmeds say there are reasons to remain hopeful. It's just that the treatments that look most interesting at this point are far from a sure bet, especially in an industry where most drugs that look promising in early studies don't pan out in advanced clinical trials.

Despite such a dreary short-term outlook, people do have hope for the future. The following is a roundup of experimental treatments—and novel ways to use some existing treatments—that several researchers and AIDS treatment activists identified as the most exciting drugs to watch in 2009.

Closest to the Finish Line

A handful of drugs that could work for heavily treatment experienced patients have made it over the hurdles of early drug development. They include two entry inhibitors known as ibalizumab and PRO 140; a nucleoside analogue reverse transcriptase inhibitor (NRTI) called amdoxovir; and bevirimat, a maturation inhibitor. All have made it through early Phase I testing and are either in clinical trials or entering studies to determine preliminary dosing, safety and effectiveness. IDX-899, purchased earlier this month by GlaxoSmithKline for further development, is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with potential for patients with HIV resistance to current NNRTIs.

Old Dogs, New Tricks

Bob Huff, who's in charge of antiretroviral (ARV) advocacy at the Treatment Action Group (TAG) in New York City, says he's most interested in "watching research on new strategies in antiretroviral treatment, chief among them combinations that do not use drugs from the nucleoside analogue [NRTI] class, or 'nuke-sparing regimens.'"

Huff points to studies that are either currently recruiting or about to get started that substitute either an integrase inhibitor like Isentress (raltegravir) or an entry inhibitor like Selzentry (maraviroc) for NRTIs like Truvada (tenofovir plus emtricitabine). He reasons that such drugs may be less likely to have long-term side effects, given the fact that NRTIs may actually damage cellular DNA.

An avenue of research that excites Steven Becker, MD, an AIDS researcher and consultant to the pharmaceutical industry from Seattle, is new drug delivery technology. One in particular that he feels has promise is a special way of formulating the NRTI Viread (tenofovir) so that it is much more readily absorbed by the fat molecules on the surface of CD4 cells. This new formulation is being developed by Chimerix in cooperation with Viread's maker, Gilead Sciences, and could allow doctors to use significantly lower doses of the drug, which could potentially reduce side effects.

Becker also sees a great deal of promise in nanotechnology, which several companies are exploring as a way to make drugs that only have to be taken weekly or once a month.

Bob Munk, a longtime treatment activist from New Mexico, says he is intrigued by a new immune-boosting drug that also has a novel delivery mechanism—through the skin. The drug, called DermaVir, is given via a transdermal patch similar to nicotine patches. It is currently in Phase II studies. Researchers hope that DermaVir can help train people's CD4 and CD8 cells to more effectively fight HIV.

New Supporting Characters

Another type of drug that could breathe new life into some old standbys—as well as some newer drugs in the wings—is called a pharmacokinetic (PK) enhancer. These drugs are used solely to boost the blood levels of other drugs. Right now, the only drug of that type in use is Norvir (ritonavir), which also unfortunately boosts cholesterol and triglyceride levels—even at lower doses.

Reported at the 16th Conference on Retroviruses and Opportunistic Infections that took place just last week in Montreal are two new PK enhancers, one from Gilead Sciences and the other from Sequoia Pharmaceuticals. Both companies presented data on their PK boosters from Phase I studies in HIV-negative volunteers. The studies were conducted to provide an early look at safety and proof that the drugs do what they are supposed to do. Gilead reports it'll be developing its booster, called GS 9350, in tandem with its integrase inhibitor, elvitegravir (which currently requires Norvir boosting), and will package both in a four-in-one pill that also includes Truvada. It is possible that the Sequoia drug, called SPI-452, might also be coformulated with other HIV drugs that depend on a booster.

Reversing Viral Sabotage

The human immune system actually has a number of effective methods for controlling viral infections. One of these is a protein called APOBEC-3G. In recent years, scientists have discovered that APOBEC-3G is quite remarkable at stopping many viruses in the lentiviral family, which includes HIV, from reproducing. Such viruses have had to evolve their own proteins, called VIF proteins, to disable APOBEC-3G.

David Margolis, MD, an AIDS researcher from the University of North Carolina in Chapel Hill, thinks that drugs that could counteract VIF have a lot of promise in the long term. He says he'll be eagerly following research on APOBEC-3G and VIF in the coming year.

Elite Control

Another recent discovery is the role of a cell receptor called programmed cell death 1, or PD-1, in long-term survivors with HIV. Scientists think the receptor—which, when stimulated causes cells to self-destruct—is a vital component in protecting the body from diseases that cause the immune system to attack a person's own body. It's presence on virally infected cells, however, appears to have negative consequences, leading to a syndrome called T-cell exhaustion. In such cases the immune system can no longer adequately control the viral infection.

A set of researchers who've been examining the characteristics of a group of people who manage to control HIV reproduction for long periods of time without ARV drugs—called elite controllers—found a characteristic in common: Their CD4 and CD8 cells tend not to have very many PD-1 receptors on their surface compared with people who do not control the virus well.

Richard Jefferys, who heads up immune and vaccine research advocacy at TAG, is eager to see what will happen with a treatment that blocks PD-1. Just last year, researchers at Emory University in Atlanta found that the immune cells of monkeys infected with simian immunodeficiency virus (SIV) were far more effective when the monkeys were given an antibody that blocks PD-1. What's more, the monkeys who got the antibody lived longer than monkeys who did not.

Jefferys concedes that it's a long way from monkeys with SIV to humans with HIV, but he's hopeful about companies such as Medarex that are developing PD-1 antibodies for use against HIV and other diseases.

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