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You've Gotta Have HAART

For patients who have access to the latest retroviral therapies, HIV is no longer the sure killer it once was. The development of drug cocktails—three-drug combinations known as highly active antiretroviral therapies (HAART)—has made it possible to keep the virus at bay. But while dozens of drugs target specific stages of HIV's life cycle, only certain combinations of drugs suppress the virus effectively.

A new study led by Howard Hughes Medical Institute (HHMI) researchers, published June 15, 2008 in an advanced online publication of the journal *Nature Medicine*, reveals that this is true because three classes of HIV drugs inhibit the virus more than 10,000 times better than others. The findings stem from a new mathematical model of drug/virus interactions developed by graduate student Lin Shen and HHMI investigator Robert Siliciano. According to Siliciano, the findings have implications well beyond HIV treatment.

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- Robert F. Siliciano

"This applies to every drug [and vaccine] that operates against a virus," said Siliciano, who is at Johns Hopkins University School of Medicine. "It would also be a useful tool for picking which drugs would be most effective in fighting hepatitis C infections, or influenza—it's very general," he said.

Since no drug has been able to completely eliminate HIV from the body, treatment aims to keep the virus under tight control. The virus mutates rapidly, and each new life cycle provides an opportunity for HIV to evolve into a drug-resistant strain. When followed closely, HAART regimens prevent this by keeping drug levels high in the body throughout the day. The

drugs attack the virus at several stages of its life cycle—ensuring that even if the virus evolves to beat one drug, it won't run amok.

AZT was the first drug approved for combating HIV infection. AZT and similar drugs look like building blocks of DNA called nucleosides, but are in fact non-functional molecules. They jam the viral enzyme, reverse transcriptase, and prevent it from further copying HIV's RNA into DNA. Other classes of HIV drugs have since been developed, including different types of reverse transcriptase inhibitors, and protease inhibitors that prevent HIV's protease enzyme from cutting viral proteins into functional units.

HAART combines these classes of drugs. With their development, Siliciano says, “it finally became possible to suppress [the virus] down to undetectable levels.”

Experience has shown that HAART cocktails only work if they include either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor (NNRTI), along with two AZT-like drugs.

But why this should be so had remained a mystery, because the most commonly used mathematical models didn't take into account how much an increase in dosage would boost each drug's effect. “People had ignored this,” said Siliciano, because it was thought to be the same for all drugs—double the dose, and the drug is twice as effective. Siliciano, Shen, and their colleagues found that this wasn't true: the two most effective classes of HIV drugs (NNRTIs and protease inhibitors) actually become exponentially more effective with increasing dosage. Three protease inhibitors reduced viral replication by 10,000 times with only a 10-fold increase in dosage in test tube experiments.

That's important, said Siliciano, because in the world of HIV treatment keeping viral levels as low as possible is the name of the game. “It makes a huge difference whether you have 99 percent inhibition or 99.999 percent inhibition,” he noted.

Siliciano says that because the model is expected to apply to all antiviral drugs, it could be a powerful tool in developing drugs against a variety of pathogens. “You can do these measurements in a test tube, and clearly get a sense of whether a potential drug is good or not,” he said. The same might be true for some vaccines.

However, Siliciano and Shen cautioned that while their new mathematical model is a much better predictor of drug efficacy than previous versions, virus inhibition isn't the only factor that governs how a doctor chooses to treat a patient. Many drugs have side effects that affect patients differently, which may increase with rising dosage. In addition, some drugs, including some of the most effective, degrade quickly in the body, meaning that a missed dose is a much bigger problem than it is for less effective, but more stable, options.