Optimism invades HIV conference

New protease inhibitors, with combination drug therapy, and early intervention to reduce 'viral load' show real promise in treating AIDS.

After years of watching their patients deteriorate and die, AIDS clinicians suddenly find themselves with powerful new prognostic tools and effective anti-HIV weapons. After years of hearing positive HIV test results as a decree of death, some AIDS patients can now expect longer life. This new optimism, which permeated the Third Annual Conference on Retroviruses and Opportunistic Infections held January 28 through February 1 in Washington, DC, rests on the twin pillars of data from trials of experimental HIV protease inhibitors (*Nature Medicine* **1**, 285; 1995) and data correlating the quantity of virus in plasma (*Nature Medicine* **1**, 980; 1995) with clinical end points. Studies of protease inhibitors have been so promising that Abbott and Merck have filed New Drug Applications with the Food and Drug Administration (FDA) for their protease inhibitors ritonavir and indinavir, respectively, which the FDA will consider on March 1. Rapid approval is expected, as was given to saquinavir (a protease inhibitor made by Hoffman–La Roche) last December on the basis of preliminary data (see box). And at least four other promising protease inhibitors are also in clinical trials.

The emergence of the new protease inhibitors and the significance of viral load evolved together over the past few years. The significance of viral load in HIV disease was discovered in the course of treatment with experimental protease inhibitors (described, by David Ho of the Aaron Diamond AIDS Research Center in New York and George Shaw of the University of Alabama at Birmingham, in *Nature* 373, 117; 1995), which demonstrated that the so-called "latent" period of HIV infection is a period of incredible viral and host immune cell ($CD4^+$ T cell) turnover. Treatment with protease inhibitors uncoupled the two processes, leading to a decrease in viral load and a corresponding increase in $CD4^+$ T cells.

Protease inhibitors, such as Merck's indinavir, bind to HIV protease.

Although it was clear from this work that the new protease inhibitors could lower viral load, especially in combination with other antiviral drugs (such as AZT and the recently approved nucleoside analogue 3TC), it wasn't as clear that a lower viral load meant a delay or even arrest of the onset of AIDS and death. John Mellors and his collaborators at the University of Pittsburgh Medical Center demonstrated a strong correlation between viral load and progression to AIDS and death in a cohort of patients dating back to 1985. Other studies support Mellors' work, adding weight to the growing consensus that viral load is an earlier and more accurate marker for disease progression than the currently used $CD4^+$ T-cell count.

"We are looking at a paradigm shift in the way we approach treatment decisions," said Emilio Emini of Merck during a presentation of data on indinavir. "The goal

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Saquinavir: Too early to market?

Saquinavir, the protease inhibitor manufactured by Hoffman–La Roche, and the only protease inhibitor approved to date by the FDA for treatment of HIV disease, shows extremely low bioavailability and, therefore, generated less enthusiasm among clinicians. But even more responsible for the notable lack of interest is the perception that Hoffman–La Roche "jumped-the-gun" by seeking — and gaining — FDA approval for what several researchers call a "suboptimal" dose of the drug. Research presented at the meeting suggests that treatment with low doses can lead to the rapid appearance of resistant virus and, although unproven, viral strains at least partially resistant to other protease inhibitors. This puts Hoffman–La Roche in the awkward position of again having an anti-HIV compound that, at least initially, does not appear as effective as others in its class (Hoffman–La Roche's FDA-approved nucleoside analogue, ddC, is widely regarded to be less effective than similar compounds, including ddI, AZT, and 3TC).

Miklos Salgo, director of virology clinical research for Hoffman–La Roche, says that company scientists are testing a new formulation of saquinavir that will have a bioavailability three times that of the original, but that studies have to be completed showing the safety and activity of the new formulation. However, Salgo also denies that the current formulation is ineffective, pointing out that after one year on combined saquinavir, AZT and ddC therapy, viral load is reduced in most patients, and the percentage of patients demonstrating resistance is between 31 and 38 percent (meaning that between 60 and 70 percent of patients still have "wild-type" virus, presumably sensitive to other treatments, including a higher dose of saquinavir). Salgo also argues, correctly, that the issue of cross-resistance is "unresolved."

Ironically, saquinavir — and Hoffman–La Roche's investment — may be rescued by further cross-resistance studies. Initial results indicate a different viral resistance profile for saquinavir versus the similar profiles for indinavir and ritonavir, suggesting that combination treatment of saquinavir with either ritonavir or indinavir may be potent and effective. "I think we are in the situation now with protease inhibitors that we were a few years ago with nucleoside analogues," say Salgo. "We know how they work individually, but need to think about using them together." Abbott has announced an interest in doing just that, and Merck will likely follow suit in the near future.

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