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AIDS researchers emphasize new drug combinations

Despite changes in AIDS incidence and some decline in death rates, experts insist that coping with human immunodeficiency virus (HIV) infections remains a major, mostly unmet challenge. And if the growing class of HIV protease inhibitors (PI) is the main reason for flashes of optimism among researchers and AIDS patients, difficulties in administering these antiviral drugs and suggestions of viral resistance quickly offset any tendency toward complacency. Basic and clinical researchers attending the recent Fourth Conference on Retroviruses and Opportunistic Infections in Washington in late January say they continue to welcome new antiviral drugs and drug candidates but point out that ever more sophisticated care is required in using them.

Several sets of guidelines for treating HIV-infected patients will soon be made public, and they are expected to "include strong recommendations for starting patients with triple-drug therapy," according to Douglas Richman of the University of California, San Diego, cochair of the conference. Although none of the guidelines will spell out precisely how or which drugs to administer, the underlying message to clinicians is to "be more aggressive" in trying to control HIV infections. That advice, which has clear implications for drug developers and producers, reverses earlier beliefs that led several major pharmaceutical companies to quit this field, he notes.

Another part of the message is that treating such patients is not a task for the "casual care giver," Richman adds. "Specialists in HIV chemotherapy can provide more intelligent use of available drugs. This is an area of very special expertise, and those experienced in it provide care with better outcomes."

Triple drug combinations often include two HIV reverse transcriptase (RT) inhibitors, which block the viral enzyme that converts its RNA genome into DNA, and a PI, which interferes with an enzyme that splits a large precursor protein of the virus into usable components. Even though clinical use of PIs is recent, and several such drugs have seen use only in clinical trials, clinical isolates of HIV already show resistance to members of this drug class.

Nonetheless, resistance to one PI does not necessarily bring resistance to the class. For instance, resistance to nelfinavir, a nonpeptide PI being developed by Agouron Pharmaceuticals (La Jolla, CA), involves an amino acid substitution at position 30 of this viral enzyme but does not confer resistance to other PIs, according to a team of researchers from Agouron, the Aaron Diamond AIDS Research Center (New York), and the University of Colorado Health Sciences Center (Denver, CO). Conversely, viral isolates that are not susceptible to other PIs often retain sensitivity to nelfinavir. Such complexity is challenging for physicians and their patients, but it also provides them with a growing number of treatment options.

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Other promising PIs are under development. For instance, a team from Abbott Laboratories (Abbott Park, IL) has designed and is testing one such inhibitor, ABT-378, that is 10- to 50-fold more potent than other PIs, according to Abbott's Hing Sham. Tested in vitro, this candidate drug retains activity against HIV isolates that are "highly resistant" to other licensed members of this class. Moreover, its activity in rodents is "greatly enhanced" when it is coadministered with ritonavir, another PI, whose availability is reduced because of binding to plasma proteins. Preliminary tests indicate these effects are also seen clinically, Sham says.

Not all hopes for helping AIDS patients are pegged to antiviral treatments. For instance, 24 weeks of controlled treatment with Filgrastim, Amgen's (Thousand Oaks, CA) recombinant version of granulocyte colony stimulating factor, improved immune responsiveness, reduced bacterial infections, and shortened hospital stays among a group of HIV-infected individuals compared within those in a similar group who did not receive this treatment and, instead, tended to develop neutropenia (depression of neutrophils in the blood). There were no unexpected or new adverse events associated with this treatment, according to the research team from the University of Colorado, George Washington University (Washington, DC), the University of Toronto (Toronto, Canada), San Francisco General Hospital (San Francisco, CA), and Amgen.

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