Rescue 3-8-7

PWAs need salvage therapy, and Abbott's new protease fits the bill. If only?

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People with HIV have little to fall back on when therapy fails. Because HIV easily develops cross-resistance to all drugs within a class, each person really has only four effective anti-HIV drugs—two nucleoside analogs, one NNRTI and one protease inhibitor—before their virus becomes resistant to all. For the first time, though, several protease inhibitors in the pipeline show potential for evading cross-resistance. By far the most advanced is Abbott Laboratories' ABT-378.

In devising ABT-378, Abbott selected a very sticky molecular structure that adheres to its target site on the HIV protease, even in the presence of mutations that defeat other protease inhibitors. And ABT-378 is less likely to stick to blood proteins, a problem that blocks other protease inhibitors from entering cells. Another trick is to combine ABT-378 with small amounts of Abbott's other protease, ritonavir (Norvir), which reduces the rate at which the liver metabolizes ABT-378. The result is a product relatively easy to take—three capsules twice a day.

These qualities suggest that ABT-378 has an immediate role as a salvage, or rescue, therapy for people doing poorly on other drugs. Abbott first unveiled ABT-378 more than three years ago, and progress has been slow. Last winter, a group of treatment activists (including me) lost patience and decided to pressure Abbott to hurry up, already. We asked the company to expedite testing ABT-378 as a rescue agent and begin planning an expanded access program for people who lack other treatment options. More than 100 organizations and individuals endorsed a consensus statement by the Coalition for Salvage Therapy.

But Abbott insists on going slow. Eugene Sun, head of the firm's Antiviral Venture, says: "We can't release this drug on top of the other useless drugs people are taking. If we do things with haste, ABT-378 will be as useless as all the other drugs on expanded access." ABT-378 is not so unconventional: Like all protease inhibitors, it needs the support of other drugs to suppress the virus' evolutionary response to therapy.

Abbott now has a single ongoing study of ABT-378 as a second-line therapy cautiously designed to meet the company's concerns. The trial includes 70 people whose first protease inhibitor proved unable to control their virus and who previously tried no NNRTIs. They take ABT-378 along with the NNRTI Viramune and two nucleoside analogs, at least one of which must be new. Their median viral load at the start was only 10,000, and most dropped rapidly to undetectable levels and

stayed there. A preliminary study in people more protease experienced is due this spring.

Meantime, more and more people are in dire straits, burning through treatment options and getting sick. “I have had probably seven deaths in the last year among this group of patients,” says Colin Kovacs, MD, a Toronto HIV specialist with some 450 patients. To help those who are failing, he proposed over a year ago a trial combining ABT-378 with other experimental agents. Abbott rejected this plan as premature.

The Coalition for Salvage Therapy has resurrected Kovacs’ proposal and has also begun building bridges between Abbott and other drug firms. Twenty-person pilot studies of ABT-378 with T-20 or PMPA (two other unapproved candidates for rescue therapy) should be up and running by early next year.

For all those who cannot enter these trials, Abbott officials pledged at a March community meeting to begin an expanded-access program by 2000. But the specifics remain nebulous, and many people cannot afford to wait for Abbott’s deliberations. As they use up drugs to fight the fast-changing virus, they run out of effective drugs to combine with ABT-378. By 2000, their viral loads, their cell counts and perhaps even their physical condition will have worsened, making successful treatment still less likely. New Yorker Fred Labow is already approaching the point of no return. “I’ve gone through everything, and nothing works anymore,” he says. “I’m sitting here with 10 T-cells waiting for new drugs that aren’t coming.”

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