Seeking for the Perfect Pill

Will two new meds solve the problem with protease?

October 1, 2005 By Ivan Oransky, MD

As HIV's powerful protease inhibitors (PIs) hit their 10th birthday, meet the two new kids who bring the PI class size to 10: Aptivus (tipranavir), FDA-approved in June, and TMC-114, heading for approval. Both have unique resistance profiles, battling HIV that evades other PIs. And a recent study suggests that combining TMC-114 and Norvir (ritonavir) downs HIV better than other Norvir-boosted PIs. "Both new drugs seem very powerful," says Howard Grossman, MD, executive director of the American Academy of HIV Medicine. "Efficacy against resistant virus is important." TMC-114 is being tested in both new and veteran med takers, while Grossman says Aptivus has targeted mostly "the deep salvage arena."

But the two pills are perfect examples of, well, the perennially imperfect PI class. Neither skirts the PI weakness of raising lipids (blood fats), and both need a boost from the handy PI helper Norvir—which comes with its own side effects. The body breaks down Norvir via the same liver enzyme as the other PIs, so adding Norvir forces the others to hang around and work longer. No HIVer who has benefited from a Norvir-boosted combo would knock it, but the capsule's chronic gastrointestinal (GI) and lipid issues leave some longing to lose it. Most PIs need 100 milligrams of Norvir once or twice daily, but Marshall Glesby, MD, of Cornell's Weill Medical College, says Aptivus needs a whopping 200 milligrams twice a day. And "even with Norvir," he says, "Aptivus will lower other PIs' levels," so don't combine it with other PIs (the drugmakers are working on that issue). Aptivus also caused liver toxicity in studies, so Glesby says to watch liver enzymes. On the bright side, Grossman calls the new PI's lipid profile "better than you'd think, considering you're boosting it with four Norvirs."

One solution to the Norvir problem would be to better the booster. A soon-to-be-released Norvir tablet may reduce the capsule version's GI effects. The new pill isn't expected to tackle lipid lifts, "but you never know," says Grossman. "Changing drug delivery [from cap to tab] can change absorption—and that can change lots of things." Good news for the many who take Kaletra—it's being refashioned as a tablet, too.

Some HIVers solve PI lipid problems with Reyataz (atazanavir). A recent study showed that switching from other PIs to Reyataz lowered lipids.

There are some other PIs in the pipeline, though most are in preclinical trials, and it's too early to

tell whether they will need boosting. Grossman says researchers aren't obsessed with finding the perfect PI. "I think we've decided to move on to other drug classes," he says. "Entry inhibitors—now available orally—are looking particularly good." Class is in session.

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