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Glaxo may be selling its newest nuke short—and wrong.

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Just days before the standard six-month review period ran out, the Food and Drug Administration (FDA) approved Glaxo Wellcome's abacavir (the drug formerly known as 1592; brand name: Ziagen). The close call is a sign of the agency's doubts about its own 1997 rule permitting accelerated approval based on less than six months' data showing reduced viral loads. The looser requirement has tempted companies to run very quick trials that emphasize a drug's power without clarifying its role as a real-world therapy. In the case of abacavir, Glaxo found that this shortcut can have its pitfalls.

Pilot studies of abacavir in people without previous treatment found exciting decreases in HIV levels that surpassed the combined effect of Glaxo's other two nucleoside analogs, AZT and 3TC. But rather than look at ways to use abacavir to supplant these older drugs, Glaxo gambled on four fast studies that would show abacavir's utility when *combined* with AZT and 3TC. This strategy yielded frustrating results that nearly torpedoed abacavir's FDA filing.

One Glaxo study tested an AZT/3TC/abacavir combo against AZT plus 3TC as initial therapy in 173 volunteers for a mere 16 weeks. No one was surprised that three drugs together proved much better than two in driving HIV loads below detectable levels. Many other studies have illustrated this point. But the trial also yielded perplexing data: Seemingly contradicting this viral load difference, the two-drug combo resulted in a rise in CD4 cell counts twice that of the three-drug combo. More long-term data suggest that the CD4 result was a fluke, but these data were not solid enough for the FDA to rule out some hidden toxicity.

A second trial in 205 treatment-experienced children found a slight effect against HIV with the triple-drug regimen and an even smaller one with AZT/3TC. Abacavir, it turns out, is a lightweight when it comes to HIV that has resisted other nukes, especially AZT and 3TC. Information on this cross-resistance only became available after the children's trial began.

A third trial tested abacavir's effect on AIDS dementia by adding it or a placebo to current treatment in 99 people. Since abacavir penetrates the brain exceptionally well, this trial seemed to offer another easy way to demonstrate the drug's advantages. But lo and behold, both groups in the study showed similar improvement in neuropsychologic function at 16 weeks. Again, abacavir failed to distinguish itself in people doing poorly on prior therapy.

To bolster its weak case, Glaxo at the last moment produced preliminary data from an ongoing more-comprehensive trial comparing its three-nuke AZT/3TC/ abacavir combo to a more standard regimen containing AZT, 3TC and the protease inhibitor Crixivan. The 48-week trial is following 562 adults without previous treatment. At least at 16 weeks, both combos performed nearly the same in terms of viral load and CD4 count. Still, the trial is marred by a high and as-yet-unanalyzed dropout rate, which may skew the results.

Abacavir could well find its best role in simplifying therapies, improving patient adherence and reducing toxicity. Abacavir-containing double combos could replace the standard triple combos that include two nukes, which contributes mightily to side effects (especially when one is AZT). Abacavir alone plus a protease inhibitor performed remarkably well in early tests. Yet instead of following up on such “drug sparing” therapies, the pharmaceutical is devoting its efforts to an all-Glaxo, all-nuke “protease sparing” combos. But AZT/3TC/ abacavir raises its own durability and toxicity issues, particularly the potentially lifethreatening allergic reaction it occasionally triggers.

Glaxo may have overlooked HIVers’ best interests in how it tested abacavir, but the company apparently took their concerns into account when pricing the drug. The recent protests over the unexpectedly high cost of DuPont’s Sustiva reportedly made an impression on the company. Glaxo officials took the unprecedented step of discussing abacavir’s price at a small community meeting. It was feared that abacavir would come to market with a two-nuke price tag. Instead, it is just a fifth more expensive than AZT.

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