Bull Market

Only HIV wins in twice-daily-Crixivan wars

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Drug companies are very aware of the AIDS-conference calendar and plan ahead to display research that best shows off their products. Through splashy presentations, they capture headlines and the attention of doctors and patients. But often their data are premature, at best. There are too few subjects and too few months of observation for meaningful conclusions, but the numbers look good.

Relentless evolution is the basic law of HIV behavior. This makes treating the virus very tricky: The drugs must block all replication; otherwise, HIV mutates and continues as if unchallenged. It's easy for conference attendees with data overload to lose sight of this uncomfortable truth.

In the race for protease-inhibitor sales, upstart Agouron's Viracept (nelfinavir) now attracts as many new people as does Merck's long-dominant Crixivan (indinavir). So Merck needs a public-relations breakthrough. Since one of Crixivan's drawbacks is that it's supposed to be taken every eight hours on a near-empty stomach, Merck has been looking into a twice-a-day dosing schedule to give Crixivan an edge. At the two most recent stellar events on the conference circuit, Merck unveiled the first results of its pilot trial (46 people for 20 weeks at last fall's ICAAC meeting; 28 for 32 by February's Retrovirus Conference). The results suggest that two times a day at 1,200 mg is as good as three times at 800.

Merck got the data it wanted, and by most accounts, doctors are increasingly prescribing this regimen. But should such a sweeping change be made based on the brief experience of a few dozen people? There are definite dangers in loosing twice-a-day Crixivan on hundreds of thousands: Above all, low drug levels between the two doses may promote virus not only resistant to Crixivan but cross-resistant to the other protease inhibitors.

It's standard practice to monitor drug levels during initial studies to determine whether insufficient or toxic amounts are getting into people's bodies. Merck, uniquely, says it never did this in its pilot study. The company insists that such measurements are irrelevant as long as the total daily dose is the same. But Merck's many critics still want the information, suspecting that the drug-level data would be discouraging indeed.

Meanwhile, sales of ritonavir (Norvir), Abbott's protease antagonist, have been lousy because of its

many side effects. Ironically, one of these—inhibition of the way the liver breaks down drugs—apparently makes combining ritonavir and Crixivan (400 mg each twice daily) an effective regimen. Abbott presented its very tentative trial—40 HIV negative volunteers on the combo for a single day after two weeks of ritonavir—at ICAAC. At the Retrovirus confab, the company privately released this additional piece of data: At the between-dose minimum, Merck's proposed 1,200 mg twice-a-day Crixivan regimen leaves levels well below the threshold needed to fully inhibit HIV, just as skeptics predicted.

People who follow Abbott's lead may find that ritonavir/Crixivan is less potent than its promoters promise. Merck, for its part, at least has data on actual viral suppression in real bodies. But thanks to the Abbott/Merck competition, we now know that twice-daily Crixivan has a reduced margin of safety and success depends on the combination's other drugs. Should HIV mutations or poor absorption weaken the meds' effect, the regimen is more likely to fail entirely.

Merck and Abbott are undertaking trials that promise more data. But at the upcoming World AIDS Conference and beyond, it will still be caveat emptor. We might get an answer to the simple question of whether twice-daily Crixivan or the ritonavir/Crixivan combo is more effective than three doses of Crixivan daily. But these companies' research will never tell us to what extent the new regimens breed resistant HIV over the long haul or, for that matter, how they compare to each other or anything else.

You may be able to fool an overwhelmed public from your podium, but you can't fool Mother Nature. As drug companies turn upbeat conference reports into glowing financial statements, the virus just keeps coldly capitalizing on our medical (and other) vulnerabilities.
