# POZ Insider

Who’s moving and what’s shaking in treatment activism

October 1, 1994 By Mike Barr

---

**Protease, inhibited**

Beware getting overexcited about the results of Hoffmann-La Roche’s new study comparing its protease inhibitor saquinavir in combination with AZT to the two combined with ddC; which was then compared to AZT with ddC. Saquinavir holds promise but the study results should be viewed with caution. New York-based Treatment Action Group (TAG), for one, has many concerns about the design of the trial and its power to effectively compare the study arms.

First, the study did not determine the best dose of the drug. Roche tested a 600 mg dose for pragmatic reasons but so far, the highest dose ever tested has not been associated with significant side effects. It remains unknown whether a higher dose will perform better or delay (or accelerate) development of resistance.

Second, the three study arms were tested at the whim of Roche, rather than for compelling scientific reasons. The study did not have the power to compare the two control arms, AZT with saquinavir and AZT with ddC. This implies, then that it also lacked the power to do the more important comparison, AZT plus ddC plus saquinavir against the two two-drug combinations, because each arm had an equal number of participants.

Thus, the differences between them, while statistically significant, can be regarded as tarted-up anecdotes. Even so, they are bizarre. AZT with saquinavir induced a higher CD4 cell rise for a longer time than AZT with ddC, but AZT with ddC levels of virus in blood and plasma more than than AZT with saquinavir. Conversely, AZT with saquinavir reduced p24 antigen levels more than did AZT with ddC.

Other significant technical problems exist as well. The current scuttlebutt has it that Hoffmann-La Roche has already applied for accelerated approval for saquinavir based on the CD4 cell count and virological marker changes seen in the study. But in an attempt to answer some of the many lingering questions concerning the clinical use of saquinavir, TAG has asked the FDA to hold off on regulatory approval for saquinavir. Instead of accelerated approval, TAG members have approached the FDA with a plan for a large placebo-controlled comparative trial that would enroll up to 18,000 people and last from two to five years. While more meetings between TAG and the

FDA ensue -- as well as meetings with Roche, Merck, Searle and other protease developers -- the future of what would be the first protease to make it to market gently unfolds.

**Vaccine flip-flop**

The Pentagon should take note: Federal AIDS research advisers showed amazing efficiency recently when -- with a single vote -- they torpedoes several opportunities to advance our knowledge of HIV vaccines and how the virus eludes our immune defenses.

The shot was fired at a recent joint meeting of two federal AIDS advisory committees. Members recommended that the National Institute of Allergy and Infectious Diseases (NIAID) overturn a previous recommendation to move forward with large trials of two vaccines based on the HIV envelope protein gp120.

If the decisions stands -- which it won't, predicts vaccine researcher Don Francis, who was portrayed by hair-throb Matthew Modine in last year's HBO movie *And The Band Played On* -- the government has simultaneously jettisoned opportunities to 1) test the "soluble envelope" concept of vaccine design; 2) develop a marketable vaccine within a decade; 3) advance understanding of antibody-based immunity to HIV; and 4) learn whether an envelope-based vaccine could prompt immunity in mucous membranes, a key site of HIV transmission.

*Nature* reporter Colin Macilwain's summation is sober: "The decision leaves AIDS with no immediate prospects for either a preventive vaccine, a therapeutic vaccine or a satisfactory drug therapy."

**Switch or hitch?**

Perhaps it was just the romance of good guys and bad guys but it was definitely the big story out of the Amsterdam AIDS conference, summer of 1992 -- the TH1-TH2 switch. An immune-system theory seductive in its simplicity, the TH1-TH2 switch works like this: The immune system has two main weapons -- one dominated by antibodies (TH2) and one dominated by immune-system cells (TH1). Each weapon (also called a response) is orchestrated by its own set of cytokines, tiny immune-system messengers. And, most important, the two responses are more or less mutually exclusive; as one response grows stronger, the other grows proportionately weaker, effectively switching places.

If correct, the theory explains a number of arcane mysteries of how HIV causes disease that had long eluded researchers. As applied to AIDS, the theory held that cytokines associated with antibodies were bad and cytokines associated with cell-mediated response were good. In a vacuum forged out of treatment quandaries and failed paradigms, the TH1-TH2 dogma offered itself up as something of a life raft to frustrated scientists.

The theory has many high-level enthusiasts and some impressive supporting research. But before the ink could dry on the flurry of treatment newsletters reporting the supposed advancement, a

phalanx of opposing scientists began attacking the theory, NIAID’s Anthony Fauci leading the charge, and either could not reproduce pro-switch research or found evidence against it.

The TH1-TH2 paradigm has not been invalidated as one part of how HIV may cause AIDS. But, consistent with every other shout of “Eureka” tied to an AIDS discovery, this theory that once seemed to hold the answer now just seems full of holes.

---