Merck Study 028 Stopped, Preliminary Data

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Within the past month, it was announced that this clinical endpoint study in Brazil was stopped by the Data and Safety Monitoring Board because the data available was convincing that indinavir+AZT significantly reduced disease progression when compared to either AZT alone or indinavir alone. The study began in April 1995 as a randomized, double-blind phase III study comparing AZT monotherapy to AZT+indinavir and indinavir monotherapy. About one year later the option of adding 3TC to the AZT arms was offered to participants. It certainly isn't an eye-opener that both Crixivan monotherapy and Crixivan+AZT (or 3TC+Cixivan+AZT) are clinically superior to AZT (or AZT+3TC). In March 1997, ACTG 320 was stopped for the same reasons. Unfortunately, participants in both studies were subjected to disease progression and death in order to prove a point that is readily accepted. (see NATAP article on ACTG 320, on our web site).

In study 028, 996 antiretroviral-naive individuals participated with between 50-250 CD4 (baseline CD4- 147 cells), and baseline HIV RNA of 30,051 copies/ml. This analysis of data is preliminary. The Crixivan monotherapy arm reduced the risk of development of an AIDS-defining event by 61% when compared to the AZT arm. The Crixivan+AZT arm reduced this risk by 70% when compared to the AZT arm. There were a total of 107/996 participants who experienced protocol defined clinical events (opportunistic infections, cancer, or death). The average median follow-up was 58 weeks (12-102 weeks).

	HIV RNA	**CD4**	**500 copies**	**risk**	**#clinical events**
Crix+AZT	-1.03 log	+112	42%	70%*	6% (20)
Crixivan	-0.76 log	+103	34%	61%*	7.8% (26)
AZT	-0.25 log	+21	9%	-	18% (61)

* Both Crixivan arms demonstrated statistical significance compared to the AZT arm. But, the difference between the two Crixivan arms were not statistically significant.

commentary: It is widely accepted that combining any protease inhibitor with one other

nucleoside (AZT, d4T, 3TC, etc.) is inadequate therapy. This has been displayed in several studies conducted by Agouron, Abbott, Roche and Merck. Generally, such a two-drug regimen is not adequately reliable in reducing viral load to "undetectable" and in sustaining that reduction. Undertaking such a therapeutic approach is too risky. Once you decide to begin a potent protease inhibitor therapy, or a properly designed NNRTI regimen (non-reverse transcriptase inhibitor), it is generally recognized that the goal of undertaking such a strategy should be to suppress viral load to "undetectable". Since the only viral load tests available to most persons only measure as low as 400 or 500 copies, that is the only available criteria. But, it is becoming increasingly recognized that viral load should be suppressed to as low as possible. Tests measuring viral load down to as low as 50 or 25 copies/ml are available to researchers. In the near future, these tests will likely be available to consumers. Roche is expected to soon apply to the FDA for approval of such a test. It is also generally recognized that lowering viral load to under 50 or 25 will probably be the new goal of potent multi-drug therapy. It appears as though such a goal will be the best way to delay or prevent resistance and to sustain CD4 increases and viral load suppression.

There are many doubts being raised today about the feasibility, ethics or necessity of conducting these traditional clinical endpoint studies where the ultimate measure of success is how many sicknesses or deaths do or do not occur. It is generally agreed that these types of studies cannot be conducted any more. Some believe they are necessary to assess a drug but are no longer feasible; others believe they are just plain too unethical. Many believe we should use viral load changes as an endpoint for FDA approval. A minority of others believe we don't yet know enough about the reliability of viral load in predicting outcome of disease progression, nor do viral load changes offer enough information regarding safety of a new therapy. Others believe that safety information is in fact important but can be attained by means other than clinical endpoint studies..

The reality is that it appears to be near impossible to conduct this type of clinical endpoint study anymore. There are many drugs (10 approved, 5 more may be approved by mid-'98) available which when used properly in combination are capable of significantly lowering viral load and increasing CD4 that there is very little reason to remain in a study in which you do not receive adequate treatment options. The FDA, ACTG and the pharmaceutical industry face the challenge of designing trials that are at once ethical, fair, feasible, able to fairly recruit participants, and ultimately able to obtain the data or information we need to adequately judge treatments.