The Duration of Viral Suppression is predicted by Viral Load During Protease Therapy

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Dale Kempf, of Abbott Labs, et al conducted a retrospective analysis of data from a total of 32 patients on 3 different treatments regimens (ritonavir monotherapy, ritonavir/AZT, and ritonavir/saquinavir) in three different clinical studies who eventually developed resistance. They wanted to identify why viral load rebounds. The durability of response was assessed from the initiation of therapy to the time of initial rebound of viral load.

The following criteria were used to qualify individuals for this study:

- rebound in viral load from the point or points of maximal suppression
- were on drug(s) during time of initial rebound from maximum suppression
- documented ritonavir-associated mutations following rebound at 1 or more of following positions in HIV protease: 20, 33, 36, 46, 54, 54, 71, 82, 84, 90
- viral load was measured at least every 6 weeks on therapy prior to rebound

They concluded that the durability of response did not correlate with baseline viral load, initial viral load decline, baseline CD4, or magnitude of CD4 increase. They concluded that they observed a strong relationship between the lowest level of viral load achieved from therapy and the durability of that maximal suppression of viral load, that "the degree of suppression of viral replication is highly predictive of the durability of response".

Commentary: It appears as though many researchers believe that when initiating therapy the goal should be to maximize the suppression of viral load; the level of viral load prior to the initiation of therapy (or when switching regimens) may be an important consideration in trying to select a therapy that is most likely to achieve such maximal suppression; you may need more suppressive value from a therapy regimen if your viral load is high. In contrast, several researchers are suggesting that to achieve benefits that may be more sustained, it may not be necessary to suppress viral load below "detection". They hypothesize it may suffice to maintain viral load at a lower level (the value of that level is not determined, but it has been suggested variously as 2,000, 10,000, or maybe even 20,000). They suggest we need studies to explore this question. They claim there are certain problems that compel us to explore this treatment approach: (1) certain difficulties in taking protease inhibitors are cited--compliance with proper hydration and eating, storage, strict dosing regimens; non-adherence to these requirements can cause resistance and cross-resistance to develop; side effects and drug interactions can complicate adherence; (2) the expense of taking a protease inhibitor limits access for many

individuals; (3) if maintaining a low viral load (rather than maximal suppression to below detection) is acceptable, then it may be reasonable to save protease inhibitor therapy. If you use protease inhibitor therapy initially, and develop resistance relatively quickly, you may not have adequate options remaining. To be fair, this issue requires a more extensive discussion of additional considerations. The NATAP booklet called "Perspectives on Viral Load and When To Initiate Therapy", addresses these concerns in more detail. It is available on this web site or you can order printed booklet by contacting our office.

The analysis included only patients whose viral load rebounded while on therapy not those who experienced continued suppression (below 200 copies/ml), or whose viral load rebounded because of treatment interruption.

The following table is a depiction of their conclusion.

Mean Duration of Maximal Response for Groups of Patients Whose Viral RNA Rebounded on Protease Inhibitor Therapy		
No. of Patients	Viral Load at lowest level achieved by therapy	Duration of Maximal Response (days)
16	above 1,000	60 ± 26
9	200 - 1,000	102 ± 25
7	below 200	207 ± 81

The authors concluded that rebound in viral load is due to the "the outgrowth of mutant HIV as a consequence of incompletely suppressed viral replication".

Commentary: There may be additional factors involved in why full suppression of viral load is not achieved or maintained. There are limitations to the interpretation of a retrospective analysis: the study was not designed to examine this question, but the general conclusion is one that some leading virologists would agree with. Although, there is some disagreement about when is the best time to start therapy for the first time, when starting therapy or initiating a new therapeutic regimen you should aim for the maximum suppression of viral load that is possible; to fall short of "full suppression" will encourage the development of viral replication, consequent resistance and treatment failure (viral load rebound) in time. They believe the best hope for sustaining suppression of viral load and for treatment success (preventing replication, consequent resistance and viral load rebound) is to suppress viral load below "detection". Again, a number of other researchers believe studies should be conducted to explore whether or not it is necessary to rely on that treatment approach to achieve long-term benefit from therapy.