National AIDS Treatment Advocacy Project

Report from ACTG Meeting--July 31, 1996: Nelfinavir Resistance Profile, studies of eradication and immediate vs. deferred use of protease inhibitor therapy

We are indeed living in an exciting new frontier of treatment and research of HIV, as new developments are unfolding very quickly. This report discusses new developments: the first is from Agouron regarding a their resistance profile for nelfinavir; followed by a discussion of eradication and immediate vs. deferred protease inhibitor therapy.

Nelfinavir resistance profile
Agouron Pharmaceuticals' Amy Patick, PhD, reported first at the 5th International HIV Drug Resistance Workshop in Vancouver British Columbia (just prior to the Int'l. Conference), and again here at this meeting, of a finding that may indicate a unique mutation profile for their protease inhibitor, nelfinavir. Dr. Patick reported that nelfinavir-resistant HIV isolated from 5 patients was tested for susceptibility to indinavir, saquinavir, ritonavir and 141W94; it was found that the nelfinavir resistant virus was susceptible to each of the other 4 drugs. It is premature to apply Agouron's findings too broadly, but it is important to be aware of and to follow this development.

Agouron reported results from both an in vitro study and the one described above. Resistance was created by taking a laboratory HIV-1 strain and subjecting it to increasing amounts of nelfinavir after starting with a sub-optimal dosing regimen. That is a standard way researchers create in vitro resistance to examine the mutation profile that results. Bear in mind these resistance patterns need confirmation, and further studies to this end are both ongoing and planned.

In the other study, virus from humans (clinical isolates) that had become resistant to nelfinavir from previously conducted dose ranging studies were examined.

The results of both studies were comparable. From the in vitro study, after the lab strain had been passaged 22 times (the virus was subjected 22 times to nelfinavir, at increasing doses), and the virus was 8 fold resistant to nelfinavir, this virus was not cross-resistant to ritonavir, indinavir or saquinavir; the mutations that occurred after 22 passages were at positions 30 and 71. After 28 passages, and 32 fold resistance to nelfinavir emerged, resistance to ritonavir was 11 fold, indinavir 9 fold, and saquinavir 5 fold. Generally, 4-5 fold is considered resistant.

From analysis of clinical isolates of 17 study subjects who particpated in the human dose ranging study, the predominant mutation change in those that were resistant to nelfinavir was at position 30. This muation was stably maintained during the time period of the study (28 weeks). Other changes were also observed but at a lower incidence at positions--35, 36, 46, 71, 77, and 88. Mutations described for other protease inhibitors were never observed--48 (saquinavir) and 84 (indinavir and ritonavir); rarely observed was a mutation at 90 (saquinavir). One subject had a mutation at 82, but also had a change at 48 at baseline and was using surreptitously using saquinavir.

The clinical isolates which exhibited a reduction in susceptibilty to nelfinavir contained the same mutation at 30, while all clinical isolates which were sensitive to nelfinavir did not. Viruses containing this 30 mutation and having a 5 to 100 fold reduction in susceptibility to nelfinavir were fully susceptible to saquinavir, indinavir, ritonavir and 141W94 (Glaxo Wellcome protease inhibitor).

This is a unique resistance profile, as the 30 mutation has not been associated with resistance to the three approved protease inhibitors. This is suggestive that after treatment with nelfinavir, if resistance to nelfinavir develops, treatment with other protease inhibitors may be effective. However, the opposite would not necessarily apply; that is, if resistance develops from prior treatment with ritonavir, saquinavir, indinavir or 141W94, it would not necessarily follow that then the resistant virus would be susceptible to nelfinavir. Agouron would have to study viruses resistant to other protease inhibitors from initial treatment and subsequently expose that virus to nelfinavir and, of course, that study needs to be conducted.

In Vancouver, this information created some controversy. Some observers said they were suspect of this data. Another prominent researcher said "the data are the data." Although it is too soon to place much stock into this information, it is important to closely follow this development, as it may be crucial.

Eradication of HIV in the Infected individual

For background on this subject, please see the article on eradication. This has become a very controversial subject, that everyone is discussing and about which a good deal is being written. Because of the development and availability of new potent drugs--protease inhibitors, and nevirapine--we can for the first time, begin to address this question. Please bear in mind, the possibility of eradication of HIV from the infected person may be remote. Please do not yet place too much stock in this possibility, as many questions remain to be addressed in trials. But, the good news is that plans for clinical trials exploring the possibility of eradication, or the possibility of turning HIV into a chronic manageable disease, are being currently discussed.

The results of small pilot studies of triple-drug therapy in chronically infected treatment-naive individuals, as well as in sero-converters (recently infected individuals) reported in Vancouver have contributed to the discussion of the possibility of eradicating the virus. Viral RNA in plasma in these study subjects has been reduced below levels of 100 or possibly even 25 RNA copies/ml; as well, other studies have contributed to the thinking that it may be possible to eradicate HIV from the infected person, or turn HIV into a chronic manageable disease. But, viral reservoirs in other "compartments" (including lymph nodes, testes, central nervous system) may be difficult to drain; in fact, some researchers think these reservoirs may be sanctuaries that may be impossible to drain. If we can't drain the virus from these compartments, eradication may not be possible; but, the alternative may still remain, of turning HIV into a long-term manageable disease. These questions will have to be addressed in studies. Until we have results from these studies, the potential for eradication is a merely a hypothesis, but obviously it is vitally important to initiate this research.

Studying this hypothesis is a most pressing issue, and plans to study it are in fact on a fast

track. Proposals for such studies are circulating within the ACTG. To explore and confirm whether or not eradication can be accomplished, the concept of induction therapy followed by maintenance therapy needs to be studied. Individuals would be administered a potent 3-drug combination (including a potent protease inhibitor) for a pre-determined period of time called the induction phase. The maintenance phase would follow, where some individuals would start peeling away drugs. At key points in time during the study, certain "compartments" should be assessed for virus--lymph nodes, CSF, testes, etc.-- to explore whether or not the reduction in virus in the plasma is paralled with reductions in virus in these other hard to reach "compartments".

Immediate vs. Deferred Potent Therapy

Another cutting edge crucial issue, that everyone is talking about is when should an individual begin a potent therapy. This controversial subject is discussed in detail in NATAP's report--"Perspectives on Viral Load (HIV RNA) and When To Initiate Therapy", in the section entitled-- When To Initiate Therapy. More aggressive AIDS researchers are recommending an HIV infected individual should "hit early and hit hard". Other more conservative AIDS treating physicians are recommending initiating therapy with a 2-drug nucleoside combination (or ddI monotherapy) which would be followed by a potent 3-drug therapy after an individual progresses.

The plan is to address this issue in studies examining immediate vs. deferred therapy with a potent 3-drug treatment. Essentially, individuals would be randomized to either the immediate arm, where they would receive a potent 3-drug therapy, or to the deferred group which would initiate individuals on a nucleoside therapy (the regimen could be a nucleoside combination or ddI monotherapy).

Whether or not an individual should initiate therapy with a regimen of nucleoside(s), and hold the big guns for later (a potent 3-drug therapy), or initiate the potent therapy first, is a controversial subject addressed in the NATAP booklet on Perspectives on Viral Load. Many treating physicians and AIDS researchers are taking the approach that an individual should first initiate therapy with a nucleoside regimen, followed by a potent protease inhibitor therapy if and when disease progression occurs. The Journal of the American Medical Association (JAMA) published, in their issue of July 10, 1996, recommendations from a panel of AIDS doctors and researchers. These recommendations were first determined in January 1996 and revisisions were incorporated by group consensus during the February-May period of time. Briefly, they recommend initiating therapy with a nucleoside regimen to be followed by a protease inhibitor regimen after disease progression.

At the other end of the spectrum, other AIDS researchers have called for a "hit hard and early" approach, where they recommend initiating therapy with a potent 3-drug therapy. The rationales for both sides are discussed in the NATAP published booklet referred to above--"Perspectives on Viral Load and When to Initiate Therapy" (available by contacting NATAP).

Of course, individuals can stake out their own position on this controversial issue. But, the ACTG is planning to address this question with a study of immediate vs. deferred protease inhibitor therapy. Discussions are ongoing for the design of such a study.