National AIDS Treatment Advocacy Project

NIH Panel to Define Principles of Therapy of HIV Infection: proceedings of Nov. 13-14 panel meeting in Washington, D.C.

This is Jules Levin reporting from my Delta shuttle leaving Washington, D.C. on Nov 14 after attending the two-day meeting called the "NIH Panel to Define Principles of Therapy of HIV Infection". A series of about 30 AIDS academic researchers, practitioners and pharmaceutical industry researchers were invited to present information on a variety of related subjects. Researchers presented the latest data for approved drugs and those in development. This panel was convened to issue a set of guiding principles, or commonly called a "standard of care" for the treatment of individuals with HIV or AIDS. Doctors and HIV+ individuals will look to these principles for guidance. Two separate government sponsored initiatives may be undertaking a similar effort in the next several months.

At this meeting, discussion essentially focused on: when to start treatment, what to start treatment with, when and with what therapy to transition into after prior therapy. We do not yet know enough information or data to make many definitive recommendations, but this panel was convened to review the data and information available and attempt to issue helpful guidelines. It remains to be seen how instructive and guiding the guidelines will be.

Plasma, CSF and lymph tissue RNA. The first day's hearing started with Dr. David Ho reviewing the findings of his work and that of others regarding HIV replication dynamics. As you may know (you can read about on NATAP web site--"Perspectives on Viral Load....."), prior thinking was that there was a prolonged period of relative virus latency; this has been replaced with the thinking that ongoing, high-level viral replication takes place from the time of initial infection. As many as 10 billion new HIV virions are produced per day.

Dr. Ashley Haase, of the University of Minnesota, said you can measure the number of infected cells in lymphoid tissue, as well as the number of CD4 cells in lymph tissue. 1% of the body and its organs is composed of lymph tissue, but it is an important depository, reservoir and source of HIV for the peripheral circulation. The lymph node RNA data presented in Birmingham (see NATAP Birmingham Report 2) for the ritonavir/AZT/3TC study used a tonsillar biopsy to obtain lymph tissue. Haase said the tonsil is reasonably representative and easier to work with on an outpatient basis. Question has been raised about whether or not the methodolgy used in this study will yield the full extent of

information that we can obtained from other methodolgy.

We are still uncertain of the full effect of potent 3-drug therapy on the lymph tissue viral reservoir, even in individuals treated during primary infection (immediately after infection). Ongoing and planned research will address this concern.

We have not yet adequately addressed the effect of potent 3 or 4 drug antivretroviral therapy on the CSF, brain and other potentially relevant compartments. The protease inhibitors so far available don't appear to penetrate the brain well. Studies exploring this are planned. There appear to be mixed opinions about the ability to adequately effect the CSF and the brain by the potent 3-drug protease inhibitor therapies.

Dr. Lisa Dunkle, of Bristol-Myers, said at steady-state, CSF concentration of d4T was 16-72% of serum concentration (blood levels) 2 hours after dosing.

In Birmingham, it was stressed that a neuro-protective drug should be a component of a multi-drug combination therapy. There is data confirming AZT's effectiveness on neuroloigcal HIV-associated problems. For those who may be AZT-resistant, it is uncertain whether or not AZT may remain effective for such purposes; resistance in the brain may develop more slowly than in the blood. Although, such efficacy data for d4T is lacking, there appears to be some agreement that d4T should be effective since it does penetrate the CSF. CSF fluid does enter into the brain.

Re-constitution of the immune system. Dr. Ronald Gress, of the NIH, said non-thymic generation of CD4 that comes from the periphery lacks the ability to regenerate naive CD4. Age may correlate with the ability to regenerate naive CD4. The potential of the thymus to regenerate naive CD4 is better for children and decreases with age. My report from the Surrogate Marker conference of November 18-19, where Dr. Mario Roederer spoke on this issue, will further discuss and explain this concern.

At best, there were mixed opinions about the ability of the immune system to reconstitute itself. It appears it will be difficult to reconstitute the immune system. It was generally agreed that the best opportunity to reconstitute the immune system was with the earliest possible treatment with potent therapy--hitting hard and early. The earlier you are in the disease stage, the more intact is your immune system; you have more naive CD4 and a wider repertoire of CD4; treatment during primary infection may be the most effective on virus burden in lymph tissue. In late stage disease, antiviral activity of CD8 is lost.

Of course, there are problems associated with taking treatments so early, including: healthy individuals may not be compliant; if therapy is not successful and resistance develops, treatment options may be limited due to cross-resistance; insurance re-imbursement may be a concern; compliance may be difficult, if it is necessary to maintain treatment for many years. However, studies are expected to start soon exploring induction therapy of indinavir/AZT/3TC followed by a maintanance therapy of 0, 1 or 2 drugs.

The standard of care recommendations emanating from this NIH-OAR (Office of AIDS Research) effort should fully explain all these options to doctors without prejudice.

Dr. Anthony Kelleher, of Australia, was a ritonavir study investigator. He said if you can suppress viral load low enough for a long enough period of time, there may be some immune system repair, which could get around the loss of repertoire; the evidence seems to argue against that increases in CD4 are just a redistribution of CD4, although Mario Roederer thinks they are due to re-distribution.. In Dr. Kelleher's research, he has found memory cells to increase as you see increases in absolute numbers of CD4. He agreed with others that therapy should start early.

Double nucleoside therapy in primary infection. Dr. Luc Perrin, of Switzerland, discussed a small study of treatment with AZT/ddI for individuals in primary infection. After 6 months of therapy, 8/12 had undetectable plasma RNA (under 200 copies/ml); after 12 months 8/12 remained undetectable. During the period of 7-10 months, lymph node biopsies were conducted on 5 patients; 4/5 were negative for RNA (in situ). Dr. Perrin agreed therapy should begin as early as possible. But he suggested you could begin therapy with a nucleoside regimen; Dr. Julio Montaner, the principal investigator of the nevirapine/AZT/3TC-naive study #1046, suggested starting with a nevirapine 3-drug regimen.

Dr. Martin Markowitz, of the Aaron Diamond AIDS Research Center in NYC, said double nucleoside therapy for those with chronic infection (those with at least some disease progression), was not adequate. He said, only 8/12 were rendered undetectable in the AZT/ddI study. In other words, if your goal is to fully suppress viral load, you take the risk that the double nucleoside therapy may not be successful for all. As reported in the NATAP Birmingham Reports, Drs. Richman, Lange and Emini agreed that treatment with the most potent available therapy should start as early as possible. (see NATAP Birmingham Reports for details).

Early vs. late. In the NATAP Birmingham Reports 1 and 2, I reported that Dr. Joep Lange said he would treat individuals with the most potent therapy if they had any viral load, even 100 copies. At this NIH conference, Dr. John Mellors, of the University of Pittsburgh, and some others said it may not be necessary for early intervention for some individuals. They suggested if an individual presents themselves with high CD4 and low viral load (under 5,000), you could monitor them, and delay treatment if the values remain stable.

Dr. Alvaro Munoz, of Johns Hopkins University, discussed some data from the MACS study which correlated baseline viral load with disease progression (see NATAP article "Perspectives on Viral Load"). The initial blood samples for this study were taken over 10 years ago; because of blood processing and storage problems, the following RNA values are about one-half of their true estimate. Of 53 individuals who showed no disease progression, there average RNA value at baseline was 2,071 copies/ml; this group was divided into 2 sub-groups: the non-progressors had an average of 1,627 RNA copies; and, the late progressors averaged 5,049 copies. The 55 moderate decliners had an average RNA copy number of 3,791; and, the 55 fast decliners had an average of 12,720 copies.

Protease inhibitor failure and cross-resistance. Ronald Swanstrom, Ph. D. of the University of North Carolina, showed a slide of two individuals who failed ritonavir therapy at different time points and added saquinavir to the ritonavir therapy. The first

person added saquinavir after failing ritonavir at 25 weeks of therapy, and their RNA remained suppressed. The other person failed ritonavir after 70 weeks and then added saquinavir; their viral load initially went down but rebounded relatively quickly.

The fact that a number of individuals are already protease inhibitor resistant was discussed. As yet, it is uncertain how to treat someone who may be resistant to ritonavir or indinavir. Dr. Bob Anderson, of Agouron Pharmaceuticals, discussed their study #522, where they are collecting viral blood samples from individuals resistant to protease inhibitors other than nelfinavir. They are subjecting these resistant viruses to nelfinavir in vitro. Agouron has previously reported preliminary findings that treating first with nelfinavir may not produce cross-resistance to other protease inhibitors. Study #522 is intended to explore if nelfinavir may be effective in suppressing virus that is already resistant to other protease inhibitors. Preliminary results may be available in early 1997. Availability to nelfinavir in the expanded access program is restricted to individuals who've failed other protease inhibitors. Hopefully, some data will emerge from the expanded access program..

A number of physicians are treating protease inhibitor-resistant individuals with the combination of ritonavir+saquinavir. The benefits of treatment with this combination could be due to the high levels of saquinavir. It could be that the antiviral activity of this combination is from the higher blood levels of saquinavir alone.

Some participants from the early indinavir trials who rendered their viral load to undetectable have had their viral load rebound, but their CD4 has remained elevated. Without viable alternative treatments to switch to, many are remaining on indinavir therapy. There is speculation that the CD4 remain elevated because the resistant or mutant virus is less virulent, defective, or not as fit for replication. It is not yet well understood why this occurs.

If using saquinavir in combination with nucleosides, and resistance to saquinavir develops, you may have success treating with ritonavir, indinavir or ritonavir/saquinavir. Merck says pre-treatment with saquinavir, with or without the development of saquinavir resistance, is likely to cause the premature development of resistance to indinavir. Roche claims the chances of that are less likely.

Noel Roberts, PhD of Roche Labs, presented the following cross-resistance data. Cross-resistance was defined as a 4-fold loss of sensitivity to another protease inhibitor. After 1 year of saquinavir treatment with nucleosides: 86% remained fully sensitive to saquinavir; 10/12 have complete or some remaining sensitivity to other protease inhibitors; 5.25% have some reduced sensitivity to all protease inhibitors; 3.5% have reduced sensitivity to all other protease inhibitors.

For individuals who in fact developed the L90M mutation from saquinavir treatment, 5/9 were saquinavir resistant, 2/9 were indinavir resistant, 2/9 were ritonavir resistant and 2/9 were VX-478 resistant. It is rare to develop the G48V mutation along with the 90 mutation, but for those who did--3/3 were saquinavir resistant, 2/3 were indinavir resistant, 3/3 were ritonavir resistant and 0/3 were VX-478 resistant. Roche says other mutations occur besides those at 48 and 90, but they are not significant in leading to

saquinavir resistance nor indinavir cross-resistance; Merck disagrees, they claim the saquinavir mutation profile, including these other additional mutations, will contribute to reduced sensitivity to subsequent indinavir treatment. More conclusive information may be expected from data of individuals who have been indeed treated with saquinavir and then switched to indinavir. ACTG 333 was the first sudy designed to address this issue. Some preliminary results should be available in early 1997.

A question was raised about whether resistance develops more easily from the use of a potent protease inhibitor than from use of a NRTI. Emilio Emini, of Merck, said the protease inhibitor exerts more pressure on the protease enzyme than a NRTI exerts on the reverse-transcriptase enzyme. Therefore, resistance by the protease enzyme is likely to develop more easily.

Saquinavir absorption and eating. If an individual is taking saquinavir in combination with nucleosides, eating an adequate meal prior to taking saquinavir is required for proper absorption of saquinavir. According to the saquinavir package insert a large fatty meal is recommended for maximal absorption. When ritonavir is used in combination with saquinavir, the blood levels of saquinavir are greatly increased. That is the reason for combining the two drugs. An important question is, do you still need to eat before taking your medication of saquinavir with ritonavir, and if so how much? Roche says they are now researching this question, but for now they recommend eating an "adequate" meal before taking the two protease inhibitors. In fact, although Abbott says it's not absolutely necessary, a sandwich sized meal is recommended prior to taking ritonavir medication, also for absorption.

New sero-converter update. Dr. Martin Markowitz presented some additional data since the Vancouver presentations, on the small pilot studies of sero-converters. For the ritonavir/AZT/3TC study of sero-converters, in Vancouver data was presented for 1 patient out to 10 months, 3 patients out to 4 months and 1 patient each out to 8, 7 and 6 months (see NATAP article "Newly Infected Individuals: ritonavir/AZT/3TC", in the post-Vancouver drug development section). All patients in the study had undetectable viral load (plasma HIV RNA) by these time points.

Dr. Markowitz explained how at baseline there was a variety of viral load values: one individual had a 5 million RNA value, another's was 1 million, and a third person had a 20,000 RNA copy number. He presented here that 10/11 study patients were at least out to 7 months and remained undetectable. One patient's RNA was 140 copies at 9 months. Six patients were out to 10 months and were still undetectable. Four patients were out to 12 months and still undetectable; and, 1 patient was out to 15 months and undetectable.

Twelve sero-converters were receiving treatment with indinavir/AZT/3TC in a separate pilot study. All patients were between 3 to 8 months on study treatment and all but one was under 100 RNA copies. That one patient had a value of 291 copies. All 12 were culture negative. Investigators expect to conduct rectal lymph tissue biopsies, because it's difficult to get consent for lymph node biopsies; for those remaing undetectable, they will be asked if they're willing to discontinue treatment; future studies are planned where they might increase viral turnover with therapy. Treatment during primary or acute infection may be the most effective therapy, and may offer the best hope of eradication. Some

researchers do not believe eradication is possible with the currently available therapies; several researchers expressed here that early treatment with a protease inhibitor therapy may jeopardize adequate future treatment options.

Recommendations. Clearly, there is a diversity of opinions regarding when to initiate therapy and with what. There are some who feel strongly that the best approach is to treat as early as possible wuth as potent a therapy as possible; the immune system is still relatively intact (naive CD4 population has not depleted); the lymph nodes may not yet be beyond salvation; it may be the best opportunity for immune reconstitution and eradication. There are some who suggest starting therapy as soon as possible with 2 nucleosides; compliance will be easier; therapy options can be saved. Others recommend if an individual initially presents themselves with high CD4 and low viral load (below 5,000 was a cutoff raised at this meeting), the person should be monitored closely and at the first sign of progression double nucleoside or potent 3-drug therapy could be started. The potent 3-drug therapy could consist of nevirapine/AZT/ddI or protease inhibitor therapy/nucleoside(s).

Editorial: I testified that the guidelines should not be restrictive but should remain flexible to allow doctors and patients to make their own decisions of whether to treat early and with what type of treatment. Adequate insurance re-imbursement may depend on sufficiently flexible recommendations. It is equally important to educate doctors of all the treatment options and the pluses and minuses for each decision. It is clear, that as of this point in time, opinions are mixed as to precisely when to begin therapy and what is the optimal treatment to start therapy with--whether it be hitting hard and early with 3-4 drug therapy or starting with double-nucleoside therapy. Treatment decisions should be personal, individualized and between doctor and patient.

But, adequate education of all doctors and treating professionals is a major obstacle. Good treatment today is more complicated than previously, when AZT-monotherapy for those with under 500 CD4 was first recommended. Many doctors will be aware of the latest information and treatment options, but many will not. Will over-burdened clinic and HMO doctors take the time to be adequately informed? Will the federal government be able to undertake an effective program for such education. The stakes are higher now because of the greater-than-ever promise for improved health due to protease inhibitors; and, the equal potential to ruin the promise due to resistance from improper treatment and compliance. Is the NIH and our medical establishment up to this challenge?

It is advisable that doctors and patients plan treatment strategies into the future. You should plan ahead to your next 2 or three moves, like in a chess match. Consider which drugs are currently available and which will become available and when; consider potential cross-resistance, and plan for alternatives if a particular strategy doesn't work out.

The NIH panel will meet again privately in December before issuing recommendations after January 1, 1997.