National AIDS Treatment Advocacy Project

Thursday in Vancouver July 11

This Conference was extremely upbeat and exciting as data from protease inhibitor studies continue to grab the limelight with promising findings. This is the last day of the Conference and most packed with data. This data is the highlight of the Conference and will be the subject of newspaper and TV headlines worldwide. Yesterday, Abbott and Roche held a press conference to announce their 6 weeks of data on the combination of ritonavir and saquinavir. Today, Merck presented their updated data for the 3-drug study of indinavir and AZT/3TC. Data from an important trial of nelfinavir/AZT/3TC in a previously unstudied population (treatment-naive individuals) was presented suggesting that treatment of HIV should be "early and hard." The importance of viral load in predicting disease progression was underscored here. Announced to the world was the end of monotherapy treatment of HIV, as the era of combination therapy is being ushered in.

These promising results follow the discussion of the talks by David Ho and Giuseppe Pantaleo regarding HIV pathogenesis. Additionally, there was extensive discussion about the potential for "eradicating" the virus or making HIV a chronic, manageable disease. These latter concepts created controversy, but it was clearly and repeatedly underscored that these concepts are theoretical at this point, concepts that need and will get further attention.

Ho said we now have a new understanding of viral dynamics, which sheds new light on our understanding of HIV. He is referring to the discovery and understanding of the high production rate of viral replication by himself, George Shaw, and others. From the very beginning after infection, HIV replicates very productively. Within 3-9 months an individual's immune system creates an "equilibrium" or balance between viral replication and their own immune system. Through the work of Ho, Shaw and others we have come to understand the rates of viral production.

Ho and Pantaleo both agreed that viral factors are not the sole determinant of the course of HIV progression, but they serve as the "engine" for the virus; HIV is a viral disease, not some poorly characterized syndrome. He said constant viral replication causes constant CD4 destruction and increased replication causes faster progression. However, viral factors are not the only determinant in HIV status or progression.

Repeated references have been made here about what measures of virus need to be done aside from RNA: lymph nodes, latently or chronically infected cells and macrophages, the CNS, and the testes were indicated by David Ho as compartments that need exploration. He said CNS penetration is a concern because many drugs don't penetrate that compartment, and the ones that do may not do so adequately.

Indinavir/AZT/3TC
Roy Gulick of NYU presented the data update for the Merck study #035 which created excitement at the Human Retrovirus Conference in Washington in January 1996. This trial compares AZT/3TC and indinavir (IDV) to IDV monotherapy and AZT/3TC. The participants had extensive AZT pre-treatment but were protease inhibitor naive and, importantly, 3TC-naive. It is important to consider the number of evaluable study subjects for the 3-drug combination: 28 at baseline, 27 at 24 weeks, 24 at 36 weeks and only 9 at 48 weeks.

- RNA: Average RNA reductions at 24 and 36 weeks were 2 log and at 48 weeks were 2.3 log (n=9)

- The proportion of patients with undetectable virus: at 24 weeks for IDV/AZT/3TC group--90%; IDV monotherapy--40%; at 36 weeks--82% for IDV/AZT/3TC and 40% for IDV monotherapy; at 48 weeks--84% for 3-drug group and 55% for monotherapy group

- CD4: The CD4 increases were about 130 cells at 36 weeks; although the increases at 44 weeks were significantly higher (220 cells) Gulick cautioned that this number is for only 9 patients

Ritonavir and Saquinavir: combination study
This trial breaks new ground in the research of treatment of HIV because it is the first study of combining two protease inhibitors. William Cameron from the University of Ottawa presented 6 weeks of preliminary efficacy and safety data for this ongoing effort. Four different dosing regimens are being studied in a treatment-experienced study group. This initial data is based on two dose-regimen groups: 400 mg./bid (every 12 hrs) ritonavir (RTN) combined with 400 mg/bid saquinavir (SAQ); and 600 mg/bid ritonavir combined with 400 mg/bid saquinavir.

- RNA: The baseline RNA was just under 100,000 for this collective group. At 6 weeks, in the 600 mg/RTN-400 mg/SAQ group: the average RNA reduction for both groups collectively was about 2.5 log; about 65% were below the level of detection (200 copies by PCR); about 85% were either undetectable or had a 2 log reduction in RNA. On the graph the RNA was still trending down.

- CD4: The average baseline CD4 was 200-300 cells. At 6 weeks the CD4 increases were 80-100 cells. On the graph the CD4 was trending up at 6 weeks.

The combination so far appears to be safe, which was of primary importance to explore in this study.

Both William Cameron and Martin Markowitz cautioned that this data is preliminary because it is only 6 weeks, and we don't yet know either the longer-term safety of this combination nor the longer-term durability of this combination. However, both Cameron and Markowitz spoke of the fact that, in the real world, both drugs were approved and that both doctors and patients were experimenting with this combination without the benefit of even this preliminary data. They also spoke of the importance for this

combination to individuals with extensive treatment experience and possibly without any other viable treatment options.

That is why I've been strongly urging Merck, Roche and Abbott for two years now to more quickly assess the combination of 2 protease inhibitors. Unfortunately, we have had to wait for this still preliminary data. Other combination protease inhibitor studies are still in planning stages. For a further discussion of this subject see these 2 articles on NATAP web-site: "Pre-Vancouver Protease Inhibitor Update" and "We Need Protease Inhibitor Combination Studies."

I will have more detailed data to present on this study upon returning to NYC.

Nelfinavir and AZT/3TC
Another important trial examines 12 treatment-naive and chronically infected subjects (11 subjects remain in study, as one withdrew). This open-label trial addresses the hypothesis that treatment of HIV with a potent triple therapy should begin early in the course of progression of HIV disease. A vital controversial question that remains even with the following positive results from this study: how early is early?

- RNA: Baseline: mean- 209,011 RNA copies; median- 81,270 RNA copies; range- 17,990-864,900;

  At 8 weeks, viral load reached undetectable levels after a decline of about 2.6 log (below 500, as measured by bDNA-2nd generation test). At 16 weeks, the RNA remains undetectable for subjects. In fact, the RNA levels of all study subjects is under 25 copies as measured by a very sensitive test available only in the lab. All 11 subjects had achieved negativity in PBMC co-cultures by 12 weeks of therapy, with a mean RNA reduction of 2.62 log

- CD4: Baseline CD4: mean 258, median 253, range 37-557; increases in CD4 cells are about 100 cells at 16 weeks.

Following the predicted 2.0 log reduction in plasma RNA in the first 2-3 weeks, the "second phase" of viral decay was slower. David Ho estimated the second phase of viral decay may take about 3 weeks and then viral load is reduced to undetectability.

Future studies of these individuals are being actively planned, to determine the viral levels in other "compartments" after plasma becomes very low in plasma; lymph node biopsies will be conducted to assess viral levels in this "compartment."

ddI and Hydroxyurea (HU)
A 1-year study of these two drugs was presented, which the presenter said confirmed their synergistic effect. The dosing regimen: 400 mg ddI/day and 15/mg/kg/day of HU (500 mg/BID). The trial examines tolerance, viral RNA and CD4. Study design: 25 asymptomatic adults, over 200 CD4, treatment-naive, follow-up at 180 and 360 days. The presenter characterized the tolerance of the treatment as good overall with no treatment interruptions.

- CD4 Changes: CD4 increased by an average of 163 cells (from 482 to 575).

Individuals who managed to achieve undetectable RNA had better CD4 improvement, averaging over 200 cell increases.

- RNA Changes: Average baseline RNA was 29,396 but those with lower RNA at baseline were more able to achieve undetectable RNA as measured by PCR. At 180 days, 13/24 had undetectable RNA, and the other 11/24 had average RNA of 1,914. After 360 days, 10/20 had undetectable RNA, and the other 10/20 averaged 2,440 copies.

The presenter, Jorge Vila, commented that HU may slow CD4 response; he suggested a lower dose may be useful.

Lymph nodes were studied at 360 days:

- 5/6 study subjects had no infectious virus in lymph node mononuclear cells,
- 5/6 had no infectious virus in the lymph node CD4 cells,
- 5/6 were undetectable (2) or slightly above the threshold of detectability for HIV RNA.
- 1/6 had positive infectious virus in PBMC and CD4 cells, and had clearly positive HIV RNA (268,696 copies).

In the Conference abstract for this study it refers to only 10 patients at 360 days, probably because the data on 20 was accumulated after publication. The abstract says: 4/10 showed an average reduction in plasma viremia of 1.69 log (from 85,838 to 4,330 copies), with an average increase in CD4 of 53 cells (from 325 to 378). The six patients with undetectable virus at 360 days also were undetectable at 180 days.

ddI/d4T
This trial has been ongoing as data was presented at the January Human Retrovirus Conference. This presentation updates the data. Richard Pollard said ddI/d4T are additive to synergistic in vitro. Study design: 75 treatment-naive individuals, 200-500 CD4, 52-week study.

Five different dosing combinations were explored, which I will detail in a post-Vancouver report. As well, then I will discuss all the details of this study.

- Baseline CD4s were about 330 cells; after 52 weeks the CD4 increases were about 70 cells.
- RNA reductions were 1.2 log for all dosing groups collectively at 4 weeks, and this reduction was sustained at about 1.4 log out to 52 weeks. There were only 15 individuals in each dose regimen group, so therefore out to 52 weeks the number of individuals upon which this data is based is small in number.

  At 28 weeks, based on data for 36 evaluable subjects, 10 subjects had at least a 1 log reduction in viral RNA; and 6 subjects had a reduction of at least 2 log.

1592U89

See the article on the NATAP web-site which comprehensively discusses the data for this nucleoside analogue up to this point: "1592U89: An Important New Anti-HIV Drug." In that prior report, data was available only for one dose-regimen group, that is 200 mg/tid. Significant RNA and CD4 improvements were indicated both as monotherapy and in combination with AZT. Utilizing the higher dosing regimens of 300 mg/bid and 400 mg/tid, dose dependent improvements in CD4 and viral load were observed. In combination with AZT, RNA reductions were sustained at 1.7 to 2.5 log after 12 weeks of therapy. As well, for those individuals taking 1592 monotherapy RNA and CD4 improvements were sustained after 12 weeks of therapy: RNA--1.5 to 2.2 log.

CD4 benefits were sustained with increases of 80-100 cells for all groups after 12 weeks of therapy.

Further details will be forthcoming on this study in Conference reports after I return from Vancouver. Because it's 8 pm and I'm tired and now I have to leave to meet a group for dinner.

See you all back in the USA.