National AIDS Treatment Advocacy Project

Notes From ICAAC--Wednesday Sept 18

The weather is very stifling in New Orleans. It is extremely hot and humid every day. Fortunately I mostly am in air-conditioning in either the convention center or the hotel. As is the usual when I travel to a conference, I have not had any chance to see or explore New Orleans at all; all I see is the hotel, a few restaurants, and the meetings. I discovered upon arrival that gambling is legal here. My hotel had a casino on a riverboat docked at the hotel. Of course, I played some slot machines and actually won $12.

The most significant treatment developments were reported at the Monday session, which was covered in the first report. Below, are some brief notes from today's presentations.

1. Indinavir in combination with IL-2
2. The FDA and the future of AIDS clinical studies
3. Hydroxyurea in combination with ddI
4. ACTG 152--pediatrics
5. Neonates--viral load and progression, early treatment
6. Indinavir + AZT--Implications for induction & maintenance therapy

Indinavir and IL-2

As you may know, research of treatment with IL-2 has been ongoing for several years. Treatment with IL-2 can significantly raise CD4 but has no effect on viral load. The initial response to IL-2 therapy is a transient rise in virus activity. Initially, trial results indicated that individuals with low CD4 counts wouldn't respond to IL-2 therapy.

An NIH study has been exploring the theory of treating individuals with IL-2 and indinavir. Ten study subjects had CD4 counts under 100 at baseline. It was previously thought, individuals with such low CD4 could not be responsive to IL-2 therapy with increases in their CD4 counts. 7/10 responded well to treatment with significant rises in CD4.

The remaining question about IL-2 treatment that has limited itd development and utility as HIV therapy is--are the CD4 rises resulting from IL-2 therapy meaningful?? Since CD4 rises but viral load doesn't, many have cast doubt upon the potential efficacy of this treatment. The answer to this problem is to conduct a clinical endpoint study, but not in the traditional approach of design to such studies.

The FDA and The Future of AIDS Clinical Studies

We are in a transitional period with regards to the design of studies for antiretroviral

AIDS drugs, and particularly with regards to clinical endpoints. There is strong consensus that it is no longer feasible to randomize individuals to control arms that are obviously significantly below standard and optimal available treatment. Nonetheless, new approaches to clinical endpoint studies will eventually be designed, and we can do the same for a study of IL-2.

The FDA must react much more quickly to this changing environment and reflect these changes in the requirements they place upon drug companies for studies of new drugs. From here on, any new study that attempts to randomize an individual with 200 CD4 to a treatment arm with sub-standard therapy is questionable in terms of ethics and the feasibility of conducting that study.

The NIH's AIDS Clinical Trial Group is currently conducting a study called ACTG 320. It is a clinical endpoint study comparing AZT/3TC to indinavir + AZT/3TC for individuals with under 200 CD4. The recruitment for this study is falling off and study participants already enrolled are dropping out. There is concern the study may not be adequately completed. Individuals can do viral load testing for themselves outside the study, and if they are progressing they can drop out of the study and obtain a protease inhibitor. Of course, individuals who cannot obtain access to a protease inhibitor are relegated to the treatment that many would consider sub-standard.

Abbott's clinical endpoint study of ritonavir randomized individuals with under 100 CD4 to either ritonavir or placebo in addition to continuing their current therapy. Many study participants progressed to AIDS or death to prove that ritonavir can delay death and progression. This study (#247) enrolled well because protease inhibitors were not yet approved and available; many individuals entered the study to gain access to ritonavir not to participate in a study.

The circumstances are different now. Firstly, 3 protease inhibitors are available; soon it will be 4 after Agouron's approval for nelfinavir. If an individual with 200 CD4 can access protease inhibitor therapy, why should they take the chance of being randomized to sub-standard therapy. If a newly started clinical endpoint study (but designed in the traditional sense) were to randomize individuals to any approved therapy plus or minus the new drug being studied, two problems will arise. The individuals randomized to current therapy plus placebo will be individuals with under 200 CD4 and they will be denied access to this new drug; and, because these individuals will be receiving standard treatment (which will include a protease inhibitor), it will take a long time before they progress to clinical endpoints or death. Either, they will be consigned to their current therapy and sit and wait for endpoints or they will change their therapies while on study. By changing therapies on study, the results of the study become much more uninterpretable.

The FDA, academic researchers and the drug companies fully realize this problem, and discussions are ongoing regarding it. People with AIDS cannot wait for the slow grinding wheels of bureaucracy to institute needed changes. We need to address these issues immediately and implement adjustments. New and important drugs are in various stages of development. We need to make these adjustments so the phase II and III studies for these drugs don't become mired in these problems. If we don't, the FDA will be held

accountable for the situation.

Hydroxyurea + ddI
As you may know, a number of studies have been conducted examining the efficacy of this unique combination of drugs; and a number of new studies are now beginning. In Vancouver, positive results of such a study were presented. The data is reviewed on the NATAP website. But there have been mixed results from the various studies. Here at ICAAC, such a mixed result study was presented.

About 27 individuals were grouped by baseline CD4 count. Group 1 comprised individuals with under 300 CD4 and a mean value of146. Group 2 comprised individuals with CD4 above 300 and a mean value of 380. For group 1, the mean viral load decrease from baseline was 1.59 log at week 48; for group 2, the mean viral load reduction from baseline was 0.90 log at week 12. But, there was a strong rise in CD4 count for group 2 (+124 cells), while there was no significant change in group 1. No serious toxicities were observed, although a grade II-III alopecia appeared in 3 subjects with very low CD4 cell counts. It is felt that, for some individuals, hydroxyurea may be toxic to CD4 and therefore prevent an increase in the CD4 count. At a recent AIDS conference in Barcelona, a French hydroxyurea researcher announced that he may have uncovered a sister drug to hydroxyurea that may not have this characteristic.

ACTG 152, Pediatrics
Those of you who follow pediatric data may already be familiar with this information. AZT/ddI was compared with ddI monotherapy. Study investigators have concluded ddI alone was as efficacious as AZT/ddI combination therapy, and that both therapies were superior to AZT alone for initial therapy of antiretroviral naive, symptomatic HIV-infected children. DDI recipients had fewer hematological toxicities; and in this study, it was found that those receiving AZT alone or with ddI did not have superior protection from the development of CNS complications, as compared to those receiving ddI alone. As a result, study investigators are recommending ddI as initial therapy for children. (Abstract #I150--Results of ACTG 152, A Randomized Comparative Trial of AZT, ddI, and AZT/ddI Combination Therapy in Symptomatic HIV-Infected Children).

Pediatric AIDS and Early Intervention
The investigators in this study found that RNA during primary infection for an infant is prognostic for progression to AIDS. Viral load (plasma HIV RNA) within 1 month after birth is predictive of progression to AIDS within one year's time; as well, viral load measured at 3 months was also predictive of progression to AIDS within a year.

This study was conducted in France; neonates with high viral load are treated with combination therapy of AZT/ddI/3TC. If the viral load is not high a less potent therapy is considered. But, it is difficult to administer these therapies to such young children. (Abstract #I154--HIV-1 Cell Viremia in Neonates is Predictive of Early AIDS.

As well, another presentation was made here at ICAAC addressing the same issue. The authors say their data suggests that the ability of the virus to replicate increases over time with the evolution of more "fit" virus. In infants who received early intervention (less than 6 months of age) and had a slow disease course over the next 3 years, the virus

isolated following treatment was less "fit". The authors suggested further studies should address whether early aggressive treatment may influence replicative properties. (Abstract #I70 --Changes In The In Vitro Replication Kinetics of HIV Primary Isolates Over Time in Perinatally Infected Children).

In the NICHD-NIH IVIG Clinical trial, children were prospectively studied to evaluate the association between baseline viral load, CD4% and survival in symptomatic HIV-infected children whose mean age at entry into study was 44 months. 184 children were eligible for inclusion in the study. About 14 months of follow-up was conducted, and16 (9%) died during follow-up. The authors concluded that baseline RNA as well as CD4% were independent predictors of survival among HIV-infected children enrolled in this trial. (Abstract #I101--Baseline HIV-1 RNA Copy Number & CD4 Lymphocyte Percent Independently Predict Mortality in HIV-Infected Children).

Indinavir+AZT: Implications for Induction & Maintenance Therapy
An interim analysis of pooled surrogate marker data from two ongoing studies (#028 & #033) of indinavir+AZT were analyzed. Among other observations, it was noted that for individuals in the lowest range of RNA at baseline, indinavir monotherapy was effective in maintaining efficacy. Merck is not yet sure how to utilize this information, but it may have application in exploring the possibility of induction followed by maintenance therapy. If an individual initiates therapy (induction phase) with a potent 3 or 4-drug therapy, this data suggests that after a period of time (possibly 12, 18, 24 or 30 months)) the individual could stop taking all the drugs in the regimen, except in this case for indinavir. This concept will be explored in future studies and has important implications. IF it is possible that such a treatment strategy is successful, cost for treatment would be reduced and compliance concerns would be relieved, because taking one drug a day is easier than taking 3 or 4. (Abstract # I109--Antiviral Activity of Indinavir Plus AZT Compared with That of Indinavir or AZT Alone in Antiretroviral Naive Patients).

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