

## National AIDS Treatment Advocacy Project

4th Retroviruses & Opportunistic Infections Conference - 2nd Report  
from Jules Levin

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### TREATMENT HIGHLIGHTS

Now that we are able to render viral load to undetectable levels in the blood, we need to study the effects of potent therapy on other "compartments" where virus will be. This was recognized and discussed in Vancouver and at ICAAC earlier this year. Researchers are fulfilling their promises to conduct this research. Studies have been initiated exploring these areas. Early results were reported at this conference from studies examining the effects of potent therapy on virus activity in these other compartments or potential virus sanctuaries--semen, lymph nodes, CSF. The report from David Ho, which I discussed in the Day 1 Report, is such an example. I hope to address further the additional reports from this conference on this subject in my follow-up articles.

Nelfinavir+d4T/ddI. Louise Pednault, of Bristol Myers Squibb, reported 12 weeks data from an open-label pilot study of this triple combination in treatment-naive individuals. The dosing regimen used: d4T- 40 mg bid (every 12 hrs, 2x daily) + ddI- 200 mg bid (every 12 hrs, 2x daily) and nelfinavir 750 mg 3 times per day.

A significant portion of the patient group in this study were not compliant. The viral load is reported for all patients and separately for only adherent patients.

For all patients, after 12 weeks (n=16) the viral load reduction from baseline was 1.4 log. For only adherent patients in this study, after 12 weeks (n=6) the viral load reduction from baseline was 2.25 log. For all adherent patients, 83% (n=6) were below the level of detection of viral load (500 copies).

SAFETY. There was 1 case of a grade 4 elevation of liver enzymes. Most subjects had mild to moderate "loose stools", none of whom required dose modifications. The investigator described this grade I experience as merely 3 stools per day which were loose, which is associated with nelfinavir treatment. 4 patients experienced mild fatigue.

Ideally, Agouron recommends that nelfinavir be taken every 8 hrs, but 3 times per day is considered adequate by Agouron. Nelfinavir should be taken with food, as blood levels may diminish otherwise.

Ritonavir or indinavir with nevirapine--interaction data. Previously, the interaction of taking nevirapine with indinavir or saquinavir has been characterized and reported on this web site (for indinavir/nevirapine interaction, see recent article in Drug Development section). Essentially, nevirapine reduces the blood levels of indinavir: the peak levels (C-max) of indinavir is reduced by 11%; the AUC is reduced by 28%; the trough level (C-min) of indinavir is reduced by 38%.

In the [first Report](#) from this conference, I report the findings of the Canadian group using the triple combination of nevirapine with indinavir and 3TC in an advanced population. The normally recommended dose of indinavir of 800 mg every 8 hrs was used in the study. To compensate for the 28% reduction in AUC (blood levels) Boehringer Ingelheim and Merck suggest considering increasing the dose of indinavir to 1000 mg every 8 hrs. There is a difference of opinion about this concern; you must balance the increase of potential for the side effect of kidney stones from the higher dose of indinavir with the potential for proper dosing so that the maximal efficacy of the 3-drug therapy is realized. It was reported at this conference that an informal survey of doctors produced a mix of opinion: when combining nevirapine with indinavir, some support using 800 mg indinavir while others prefer using 1000 mg indinavir.

Today, for the first time publicly, the manufacturer of nevirapine, Boehringer Ingelheim, revealed the early preliminary results from the interaction study of ritonavir and nevirapine. They found that the ritonavir peak levels (C-max) were reduced by 10%; that the trough level (C-min) was reduced by 9%; and, the AUC (blood levels) were reduced by 11%. They characterized these reductions as not being significant, and therefore no dose changes were necessary for either drug. In other words, both nevirapine and ritonavir could be taken together at full dose. Consultation with your physician about these questions is recommended before making decisions about treatment.

Protease-protease studies. 1997 will be the year for a number of protease-protease studies to begin. I have been prodding the drug manufacturers for two years to conduct this research; with the exception of this ritonavir/saquinavir research, it has taken the manufacturers til now to get to this point. The following protease-protease studies have either recently started or will soon begin: ritonavir+nelfinavir; nelfinavir+indinavir; nelfinavir+new more potent formulation of saquinavir (EOF); and a recently started study initiated by Glaxo Wellcome will explore their new protease inhibitor, 141W94, in combination with saquinavir, indinavir or nelfinavir.

John Mellors, MD, of the University of Pittsburgh, yesterday presented that ritonavir increases the AUC (blood levels) of nelfinavir by 2.5 fold, indinavir increases the blood levels of nelfinavir 1.8 fold, nelfinavir increases the blood levels of indinavir 1.5 fold and EOF saquinavir AUC is increased 5 fold by nelfinavir. The reciprocal relationship between nelfinavir and indinavir may allow for both drugs to be taken twice a day as opposed to their currently recommended dosing of three times per day. Combining ritonavir with nelfinavir may also allow nelfinavir to be taken twice a day. Twice a day dosing regimens are the direction of treatment and research as it makes taking treatment much easier and improves compliance.

Ritonavir/saquinavir combination data. John Mellors reported the latest follow-up data for the ongoing open-label pilot study of this first double protease study-- after 24 weeks, the CD4 and viral load improvements are sustained. At the Birmingham, England conference in November (reported on this web site), Abbott reported after 20 weeks: a 3.2 log reduction of viral load from baseline, about 80% of study participants were below the level of detection (200 copies), and an increase from baseline of about 100 CD4 for those taking either dosing regimen of 600 mg ritonavir-400 mg saquinavir bid or 400 mg ritonavir-400 mg saquinavir bid. Reported at this conference is that after 24 weeks, 90%

of study participants are below the 200 copy level, the median 3.2 log reduction is sustained, and the median CD4 increase from baseline remains about 100. Additional data on immune reconstitution related to this treatment is being reported Sunday and will be relayed to you in my follow-up report from this conference. The thrust of the 24-week safety data reported here is not much different than reported in Birmingham, but will also be addressed in my follow-up report.

Hydroxyurea + d4T/ddI. At various conferences since this past Summer, data was reported for the use of the combination of hydroxyurea (hydrea) and ddI (see reports on this web site). At this conference, there were two abstracts reporting results from studies of hydrea in combination with d4T and ddI. Oliver Rutschmann, MD, of University Hospital in Geneva, reported early data from an ongoing study of 142 patients randomized to ddI+d4T+placebo or ddI+d4T+hydrea 500 mg bid. After 12 weeks (n=92), the viral load reduction from baseline (about 33,000 copies/ml) was 2.2 log, 22% were below 200 copies/ml (lower level of detection), and the CD4 increase from baseline was 10 cells. The investigators suggested that the lack of effect on CD4 could be explained by hydrea-induced lymphopenia. 20 study participants stopped study therapy--10 due to reported side effects, 10 due to patient's decision.

The 2nd study reported here showed similar findings and will be reported in my follow-up.

Pediatrics therapy and vertical transmission. Yesterday, early preliminary data was reported from ongoing pediatric studies of nelfinavir powder and ritonavir oral suspension for children. Nelfinavir powder appears well tolerated and the early data shows efficacy for children participating in the study. Different dosing regimens have been explored in this study and Agouron Pharmaceuticals has submitted an application for approval to the FDA for use of nelfinavir for children along with their application for approval for adults. Preliminary viral load data for two children was reported. One child had a 2.1 log reduction in viral load after 4 weeks and the other had a 1.5 log reduction after 6 weeks. Agouron (located in San Diego, California) has established an expanded access program where nelfinavir is available free prior to approval; for further information speak to your doctor or contact the company at tel # 619-622-3000. However, you may be better advised to wait for more data to accumulate before initiating therapy.

Abbott presented preliminary follow-up data from their phase I/II pediatric study at the NCI. They have submitted an application to the FDA for approval for pediatric use of the oral suspension of ritonavir. It is not as well tolerated but the data presented at this conference as well as in Birmingham indicated efficacy with improvements in CD4 and viral load. Again, different dosing regimens are being explored.

Today on Sunday in the late-breakers session, reporting will include: DMP-266 data updates for this promising NNRTI; preliminary data from a small number of individuals taking 141W94 in combination with 1592U89; lymph node and CSF data; data from the study of individuals with under 50 CD4 taking indinavir/AZT/3TC; and other reports.

Post-conference follow-up reports will be published on this web site. As well, we will

publish our first printed newsletter reporting conference information; contact our office at tel # 212-219-0106 to be placed on the mailing list.

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