National AIDS Treatment Advocacy Project

The following is the first edition of NATAPs newsletter, NATAP Reports. It is a nineteen page newsletter covering the 4th Conference on Retroviruses and Opportunistic Infections. Further more detailed and comprehensive reports from the conference will be posted to this web site and additional editions of NATAP Reports will be posted to a Newsletter section on our home page.

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Special Issue
Report of 4th Conference on Retroviruses and Opportunistic Infections
prepared and written by Jules Levin

The information in this newsletter is only for educational purposes. Before making any treatment decisions one should consult with their doctor(s).

Table of Contents

The annual conference was held in Washington, D.C. from January 22 through the 26th. This premiere issue of our newsletter is an outgrowth of the NATAP web site on the internet, and will review information and data reported at the conference. More comprehensive reports of data from specific studies or for particular therapies are on our web site because more space is available.

Sobering Statistics for Global AIDS Pandemic
In the opening session of the conference, Dr. Peter Piot, of the UN AIDS Project, delivered a series of sobering statistics graphically depicting, that unlike here in the US,

the course of the AIDS pandemic globally is unrelenting in its rate of increased incidence.

- There are 8,500 new infections everyday.
- 1,000 of them are in children under 15 years of age
- 90% are in developing countries and over 40% are women.
- Last year 3.1 million became infected
- 5.2 million are infected in South and Southeast Asia
- 14 million are infected in Sub-Saharan Africa, and infection rates are increasing quickly in Eastern Europe, East Asia, the Pacific and South America

To make matters worse, there is little hope of protease inhibitors being made available in the near future in poor undeveloped nations.

Viral Activity in Semen, CSF, and Lymph Tissue
Now that we are capable of suppressing viral load (HIV RNA) in the blood to "undetectable" levels while raising CD4 cell counts, it was realized earlier in 1996 that viral activity in other "compartments", or other sections of the body, must be investigated. We want to know if potent antiretroviral therapy which renders virus to undetectable levels in peripheral blood can achieve similar effects in these other compartments. There is concern that virus can find sanctuary in such places, and be hard to adequately reach with therapy. Following are a review of selected information (abstracts) reported at this conference.

Commentary: The characterizations of results of the semen studies from Drs. Ho and Markowitz as well as lymph node studies from them, Dr. Wong and Drs. Nottermans, Danner and Haase appear straight forward enough; but, the results of the CSF research discussed below appears difficult to interpret with much certainty. This may be a reflection of the difficulty in correlating disease progression in CNS with blood; and, that disease progression in CNS is not well characterized or understood, and appears to be more complicated.

Semen
D. Ho and M. Markowitz, of the Aaron Diamond AIDS Research Center in NYC, discussed their findings of HIV RNA activity in semen. They studied 5 patients who were participants in their small pilot study of individuals with acute infection receiving triple therapy for 7 to 16 months. Nearly all study participants have had their blood viral load rendered below 100 copies/ml. (Extensive data from this study available on NATAP web site). They were unable to detect replicating virus in the cellular compartment (inside the cell) in the subject's semen. The results are preliminary and studies are ongoing. Proviral DNA was detectable in all of the participants; however, cultures of blood and semen suggested that not all the DNA was infectious, but were non-infectious. DNA was decaying, but at a slower rate; so, continuing follow-up cultures will be examined to assess if DNA continues to decay. One way to determine if DNA is infectious would be

to stop therapy and see if replication is re-ignited. Participants who continue to have undetectable blood RNA will be asked if they are willing to stop therapy after a certain time point.

Other studies are ongoing where participants will be asked to stop therapy (ACTG 343 % 344); the concept of induction and maintenance therapy will be explored. In these studies, participants will be treated with potent multi-drug (induction) antiretroviral combination therapy, and at varying time points drug(s) will be removed (maintenance on fewer drugs) for some participants, while for others therapy will be completely stopped. Viral activity will be monitored in blood and other compartments for potential sanctuaries for the virus.

A group at the University of Pittsburgh including Drs. P. Gupta, J. Mellors and others used the NASBA technique to quantify HIV RNA in semen and blood plasma of 34 individuals at different stages of disease. Study investigators reported their findings: seminal viral load was 10 to 100 fold higher than previous estimates; seminal viral load was strongly correlated with blood plasma viral load, but not with CD4; they did not find a relationship between seminal viral load and the rate of disease progression. Perhaps most important, investigators found that both seminal and blood plasma viral load decreased markedly following initiation of potent antiretroviral therapy.

Commentary: Investigators said they did not find a correlation between seminal viral load and disease progression; but, if seminal viral load correlates with blood plasma viral load, and blood plasma viral load correlates with disease progression, and therapy reduces both seminal and blood plasma RNA, it might be fair to presume that seminal viral load might also correlate with disease progression.

CSF (Cerebral Spinal Fluid)
Another small study from a French group, including Drs. V. Calvez, C. Katlama and others, evaluated 19 subjects with AIDS. Using the RT-PCR Monitor Roche Assay, they found HIV RNA levels in plasma and CSF were significantly correlated, but results from previous studies of this potential correlation have been controversial. They found no correlation between the degree of neurocognitive decline and HIV RNA load in CSF nor plasma. They concluded that the correlation between HIV RNA load in plasma and CSF suggests either a blood-brain transfer of the virus, or a synchronization of viral replication in plasma and brain. The absence of correlation between RNA levels in CSF and plasma and degree of dementia suggests that AIDS dementia may not be directly related to the extent of brain infection.

Commentary: Others have suggested that there is at least some compartmentalization between the blood and the brain, that disease progression in the brain has a separate or distinct course than disease in the blood. On the other hand, it is suggested that virus traffics between the brain and blood and effective potent antiretroviral therapy in the blood may have a positive effect on viral activity in the brain. It is suspected that this positive effect may occur only in the earlier stages of HIV-related neurological disease. Once such disease progresses to a certain point, more direct therapy may be necessary. Dr. Justin McArthur, a neurologist at Johns Hopkins University, said at the conference that there is a reversible phase if neurological disease is diagnosed early enough and

treated properly, and there is also an irreversible phase, so adequate monitoring is advisable. In difference with the abstract from Calvez et al, preliminary findings from Marty St. Clair of Glaxo Wellcome and McArthur suggest that CSF HIV RNA correlates with neurocognitive decline.

In an ongoing small open-label study, AZT/3TC (n=15) was compared with d4T/3TC (n=16) in treatment-naive individuals with regards to CSF and blood plasma HIV RNA levels (viral load). Baseline CD4 and blood plasma viral load were about equal for the 2 treatment groups. A group from the University of Amsterdam including Drs. N. Foudraine, J. Lange and others measured blood and CSF RNA levels at weeks 0 and 12. The mean reductions in blood plasma RNA were 1.24 log for those taking AZT/3TC and 1.35 log for those taking d4T/3TC. Similar declines were seen in the CSF. All had detectable RNA in CSF at baseline (mean 3.57 log, about 3700 copies), which was "remarkable because all patients were asymptomatic with high CD4s (300)", and had declined to undetectable at 12 weeks. The authors concluded that from a CSF RNA perspective AZT/3TC and d4T/3TC were equivalent nucleoside analogue combinations; that d4T/3TC was as effective in reducing CSF RNA as AZT/3TC, and Foudraine hypothesized that both combinations would have effect in preventing AIDS dementia complex (ADC).

A report from G Pailoux, F Clavel and others with the Institut Pastuer in Paris, described one patient who had a history of Kaposi's sarcoma, CMV retinitis, colitis and microsporidiosis. He presented with neurological disorder--vacuolar myelopathy probably due to HIV. A lumbar puncture revealed 12 white blood cells. The CD4 and blood RNA were 20 cells and 100,000 copies/ml respectively. Combination therapy with indinavir/AZT/3TC was started in early June. By the end of August, his CD4 was 105, blood RNA was below 200 copies, but the CSF RNA was 1,262,653 copies/ml. In August, he was admitted to hospital: lumbar puncture yielded normal CSF; stains, PCR, and cultures of CSF were negative. Authors concluded that preliminary observation of polyneuropathy and vacuolar myelopathy related to HIV suggests that the CSF can play a role of sanctuary for HIV.

Commentary: These results are from one person and some of the CSF research above suggests that blood plasma RNA levels may not reflect CNS HIV-related impairment in later stages of HIV disease or after CNS disease may have advanced. We need to determine if the CNS is a sanctuary for HIV, if potent therapy can be effective in the CSF as it can be in the peripheral blood; there appears to be some difference of opinion about whether or not CSF viral load correlates with the degree of cognitive impairment; HIV related neurological disease does not appear to be well understood.

We need better research to resolve these questions. Boehringer Ingelheim, the manufacturer of nevirapine, presented information at the conference that nevirapine may be effective in human HIV-related CNS disease. Further human research is needed to explore and confirm the potential for nevirapine, d4T and other drugs which promise such efficacy. It is presumed that drugs penetrating human CSF also penetrate the brain, but this is not confirmed; lumbar punctures are not routinely done. When selecting a personal treatment regiment, it is suggested that you may want to consider combination therapy that may benefit the CNS not just the blood RNA; i.e., including two drugs that

are expected to penetrate the CSF.

Lymph Tissue

Ho and Markowitz examined the gut associated lymph tissue (GALT) of 5 treatment-naive participants in their seroconverter studies (patients were judged to be within 90 days of infection), who were receiving potent therapy with indinavir or ritonavir along with 2 nucleosides.

Participants have been taking therapy for about between 7 to 16 months and have generally maintained blood plasma RNA at least below 100 copies (some were able to be measured as being below 25 copies), increases in CD4, and increases towards normalization of CD4/CD8 ratios. For selected patients studied, a lack of CTL and antibody responses indicate that the immune system may not be getting presented with viral antigen. The lymph tissue was biopsied from the rectum, sigmoid and descending colon (and analyzed by in situ hybridization, HIV culture and RNA % DNA PCR); and, there was negative culture, in situ hybridization was negative, and no evidence of replicating RNA; but again proviral DNA was detected. In 2 subjects, residual viral RNA was found; this is likely RNA associated with long-lived cells such as macrophages or FDC-associated virus.

In November at the 3rd Int'l. Congress on Drug in HIV Infection in Birmingham, England, this study was first presented by D. Nottermans and S. Danner of the Academic Medical Center in Amsterdam, A. Haase of the University of Minnesota, Dr. R. Mills of Abbott Labs, and others. At this Retrovirus Conference, Dr. W. Cavert of the University of Minnesota presented data examining lymph tissue of tonsil biopsies from 10 treatment-naive study participants treated for 6 months with ritonavir/AZT/3TC. (A previous discussion of the report from the Birmingham data is available on the NATAP web site).

Cavert reported an initial quicker than expected decline in the FDC-associated virus (follicular dendritic cells) along with a rapid decline in the mononuclear cell (MNC) frequency in tonsil lymph tissue. After 6 months of therapy the mean decline in FDC-associated virus was greater than 3.4 log, while the MNC frequency declined greater than 2.2 log. As with blood plasma, the investigators noted a 2 phase decay in both FDC and MNC. Still, after 6 months residual HIV RNA virus was detectable but low in 9/10 participants.

In Birmingham, Nottermans reported that in the 6 patients they had so far examined out to 6 months, they were all below the level of detection of the Chiron 2.0 generation test used (below 500 copies). Cavert reported here that at 6 months, one individual had no detectable HIV RNA by exhaustive in situ hybridization (lower limit of detection was less than 300 cells/gram for cells with greater than 1 copy/cell) or by a sensitive RT-PCR test. However, again residual proviral DNA was detectable in all ten participants after 6 months; the test used was not quantifiable but it appeared that proviral DNA decreased. Cavert reported that it appeared there were "architectural improvements in the germinal center" of the lymph tissue. In Birmingham, questions were raised regarding the methodology used in this study. Some investigators said the results were promising, but the techniques used to collect the data needed refinement.

Drs. J Wong and D Havlir of UCSD, A Haase of Univ. of Minnesota, Dr. E Emini of Merck, and others studied viral load and proviral DNA, and characterized resistance in blood and inguinal (groin) lymph nodes for 9 participants in Merck protocol 035 (AZT-experienced, both indinavir % 3TC-naive) who received 36 to 52 weeks of indinavir/AZT/3TC, indinavir alone, or AZT/3TC. Of the 5 participants receiving indinavir/AZT/3TC, 2 sustained suppression of HIV RNA after therapy: below detection (20 copies/ml) in blood plasma, and negative PBMC and lymph node cultures.

However, a low level of virus was still detectable: 50-100 copies of HIV RNA/mg of tissue were detectable in lymph node in these 2 participants, although greater than 3.5 log reduction in lymph tissue was achieved.

Commentary: the findings in this study are similar to those reported by Notternmans in the above discussed ritonavir-AZT/3TC tonsil lymph node study, that viral burden is reduced by effective potent antiviral therapy, but residual virus remains in lymph tissue. It may be predictable after only 6 months of therapy that there is residual virus. Again, the important question--not just the detection of virus, but is there viral replication ongoing?

One participant on triple therapy and 1 on indinavir alone had low blood plasma RNA (viral load) levels of 120 to 720 copies/ml, and low levels of 150 to 220 copies/mg of HIV RNA in lymph node. Two had detectable but relatively low HIV RNA levels of 2,000 to 8,000 copies/ml in blood plasma, but their lymph nodes contained 40,000 to 230,000 copies/mg and they had positive lymph nodes (2) and PBMC cultures (1). Of note, these 2 subjects has multiple medication interruptions, and virus with indinavir and 3TC resistance mutations had emerged. Subjects on AZT/3TC had higher virus levels in blood plasma of 19,000 to 58,000 RNA copies/ml, also in lymph nodes of 3,600 to 230,000 copies/mg, and by in situ hybridization. They all were culture positive and had 3TC resistance.

In summary, these study results are preliminary but promising. The initial indications suggest that potent antiretroviral therapy reduces virus replication inside cells in semen, in lymph tissue examined, and in CSF. Still needing further investigation is: the full measure of suppression in these compartments, the durability of effect in these compartments as well as in the peripheral blood, the longer-term safety of protease inhibitors and other antiretroviral drugs, the meaning of detectable proviral DNA, potential viral activity in other compartments (or organs), confirmation of the findings so far, and as previously mentioned a better understanding of HIV-CNS disease is needed. All conference research reports are available in abstract form on the web at http://www.retroconference.org

Treatment Highlights

Nelfinavir: Cross-Resistance, and FDA Approval
Nelfinavir (brand name Viracept) is being reviewed by the FDA for accelerated approval at the time of this writing. It is expected that approval will be forthcoming very soon. Agouron is expected to be prepared for the drug to be in the pharmacy available for purchase within 2 days after official notice of FDA approval. In 3 phase II/III studies

submitted to the FDA, 696 participated and 484 received nelfinavir. 297 individuals participated in study 511, which was designed for treatment-naive individuals with any CD4 count, and were randomized to AZT/3TC (n=101), or 2 different doses of nelfinavir: nelfinavir 500 mg tid/AZT/3TC (n=97) or nelfinavir 750 mg tid/AZT/3TC (n=99). The baseline CD4 cell counts and viral load are composite numbers for all 3 studies--283 CD4 cells and 152,000 HIV RNA copies/ml.

Mean changes after 24 weeks of treatment from baseline for CD4[1], viral load (HIV RNA)[2], % undetectable[3](<500 copies/ml):

TABLE 1A	AZT/3TC	500 mg NFV/3TC	750 mg NFV/AZT/3TC
CD4 increase	+105	+161	+155
HIV RNA decrease	-1.38 log	-2.32 log	-2.48 log
% undetectable			
>100,000 baseline viral load*	15%	45%	80%
<100,000 baseline viral load*	27%	82%	81%

[1]The amount of CD4 increases in the above table are for the individuals who remained on the same treatment regimens on which they started the study. For example, if they changed therapy because they weren't doing well, their CD4 increases were slightly less: about 90, 135, 145, respectively.
[2]Viral load for all study participants was measured by 2 different tests: for one test, the lower level of detection was 500 copies, and by the other test the lower level of detection was 100 copies. The viral load decreases in Table 1A were based on the results of the test measuring down to 100 copies. By using the 500 copy test, the log reductions are less.
[3]For the proportion of individuals who were undetectable, the 500 copy test was used. If the 100 copy test were used, the proportion undetectable might be less.

* The study was not designed or powered (statistically) to look for this data, this was a retrospective (look-back) analysis after the data from the study was completed. Therefore, the data may not support use of only 500 mg dose for those with <100,000 copies/ml viral load.

Cross-resistance. In Vancouver, at ICAAC and again at this conference, Agouron has reported preliminary data indicating that nelfinavir has a unique mutation profile from other protease inhibitors. This data was the result of in vitro (test tube) analysis of clinical isolates (blood samples taken from individuals resistant to nelfinavir). These resistant virus isolates were exposed to ritonavir, indinavir, saquinavir, and 141W94. Investigators found that a mutation of D30N was present in all cases of nelfinavir-resistant virus, but

did not occur when the virus remained sensitive (not resistant) to nelfinavir (unchanged at position 30 in the protease enzyme); and, that this resistant virus is not cross-resistant to other protease inhibitors. The opposite cannot be concluded from this data. That is, if you develop resistance to a protease inhibitor other than nelfinavir, they are not saying you will be sensitive or not cross-resistant to nelfinavir. They are collecting data to address that question.

A question remaining is what happens if therapy continues with nelfinavir (after D30N develops) and additional mutations occur? Some researchers said that in that case they believe cross-resistance should occur. In general, the development of cross-resistance between protease inhibitors is not well understood and needs further research; i.e., more conclusive evidence is needed from in vivo (in humans) not from in vitro research. The real answers regarding cross-resistance will come from the collection of data from humans who start with 1 protease inhibitor, develop resistance and then switch to another.

Safety. Study investigators characterized nelfinavir as being well-tolerated. Investigators characterized the rate of discontinuation in the studies (11%) as low. Diarrhea appears to be the only main side-effect concern. The 511 study data reports about 20% taking 750 mg nelfinavir/AZT/3TC experience grade 2 or worse diarrhea; the rate was 10% for those taking 500 mg nelfinavir/AZT/3TC. It was found in studies that Imodium can be helpful with diarrhea. A more extensive report of nelfinavir data will be available on the NATAP web site including data and discussion of nelfinavir interactions with other drugs including other protease inhibitors.

Administration of Nelfinavir. It's uncertain at this point whether recommended dosing will be tid (three times per day) or every 8 hours and nelfinavir is taken with food. FDA recommendations on dosing will be available after review.

Ritonavir/saquinavir.
Prior reports of data for this first protease-protease combination to be researched were made by Abbott and Roche at Vancouver, ICAAC, and Birmingham. Reviews of all these are available on the NATAP web site for examination.

Here in Washington, John Mellors presented the 24 week efficacy and safety data. About 140 were enrolled in this open-label pilot study with 4 treatment arms (about 35 per arm) each with differing dosing regimens. The Group A regimen is 400 mg bid ritonavir + 400 mg bid saquinavir; Group B- 600 mg bid ritonavir + 400 mg bid saquinavir; Group C- 400 mg tid ritonavir + 400 mg tid saquinavir; Group D- 600 mg bid ritonavir + 600 mg bid saquinavir; bid means twice per day (ritonavir is taken every 12 hours), while tid means three times per day (every 8 hrs).

Study participants are treatment-experienced, with no prior protease inhibitor experience. For Group A, the median baseline CD4 cell count and HIV RNA were 277 and about 38,000; group B- 264 CD4, about 53,000 RNA; Group C- 300 CD4 and 30,000 RNA; Group D- 266 CD4 and 43,000 RNA.

Changes from baseline for CD4, viral load* (HIV RNA), and proportion undetectable (<

200 copies/ml) Table 1B:

Table 1B	CD4 cells/mm^3	≠ HIV RNA Ø (log)	% undetect. (<200 copies)
Group A 24 weeks	+125	-3.20 log	90%
Group B 24 weeks	+115	-3.20	80
Group C 20 weeks	+125	-3.20	85
Group D 20 weeks	+ 75	-3.20	67
*The viral load reduction was measured similar to the way it was done with nelfinavir, by a more sensitive test which measures down to, in this case, 20 copies. With nelfinavir, 100 copies was the lower level of the test.Numbers are approximations because they were taken off a line graph.			

Safety. Group C (tid dosing) had a higher rate of discontinuations than the other regimens; study participants are abandoning the tid regimen for a bid regimen. Group D participants are experiencing higher rates of side effects, and of more concern is the higher rate of elevated liver enzymes for those in Group D (600 mg bid of each drug). So far, Group A (400/400 bid) has indicated equal efficacy to Group B (600/400 bid), but with less incidence of practically all side effects. Liver status prior to treatment with study drugs indicate the potential for elevations of liver enzymes. Participants with elevations of liver enzymes, positive hepatitis B antigen or positive hepatitis C antibody prior to taking study medications were more likely to experience grade 3/4 elevations of liver enzymes while taking study medications. Discontinuations: 8 in Group C, 1 in Group A, 5 in Group B, 3 in Group D. 7 participants added d4T/3TC for failure to achieve or maintain viral load <200 copies/ml; 6/7 fell to <200 copies/ml, and remain there for a follow-up period of 4-16 weeks so far. Again, more extensive reporting of data will be available on NATAP web site. Study investigators reported data indicating that compliance is highly correlated with treatment response in this study: 90% of compliant participants were <200 copies after 24 weeks, while only 66% of non-compliant were <200 copies/ml. Side effects from ritonavir/saquinavir can include: diarrhea, vomiting, taste perversion, malaise, tingling around mouth area.

Indinavir. At last January's conference, Merck presented 24 week data from study 035, in which 97 AZT-experienced, 3TC- and protease inhibitor-naive individuals were randomized to treatment with AZT/3TC, indinavir alone, or indinavir/AZT/3TC. Median baseline CD4 cell count and viral load were 142 cells and 43,190 RNA, respectively.

Follow-up data out to 68 weeks was reported by Dr. Joe Wong, UCSD. Median reductions in viral load* and % below detectability (<500 copies/ml and <50 copies/ml)

were reported (Table 1C):

Table 1C	#pts/24 wks	#pts/36 wks	#pts/52 wks	#pts/68 wks
IDV/AZT/3TC				
<500 copies/ml	27/30 (90%)	23/29 (79%)	23/28 (82%)	18/21 (86%)
<50 copies/ml	20/29 (69%)	22/29 (78%)	21/27 (79%)	10/14 (71%)
HIV RNA log reductions*	-2.20	-2.00	-2.30	n.a. yet
*These values were obtained by using the less sensitive viral load with a lower level of detection of 500 copies. If the more sensitive test (20 copies) were used, log reductions may have been increased.				

CD4 increases have previously been reported for a small number of individuals out to 48 weeks and generally ranged from about 100 to 140 cells. CD4 increases continue to be followed and will be reported. Generally, individuals have been experiencing similar CD4 increases from potent antiretroviral therapy of 100-150 CD4 after approximately up to 1-1.5 years of successful therapy.

Commentary: We are anxiously waiting to see the durability of CD4 increases, viral load reductions and clinical benefits from potent antiretroviral therapy including protease inhibitors and NNRTIs; some researchers have said they expect CD4 increases may be leveling off but will start increasing again after a period of time; this remains to be seen. Of course a great concern is the capacity for immune reconstitution that may result from potent therapy. We do not yet understand the answer to this question; it appears that successful potent therapy may have a positive effect on opportunistic infections, with possible exceptions, which may depend on which infection, the degree of infection that mat have existed, and the timing of the infection. It is widely recommended that individuals who increase their CD4 counts as a result of therapy, continue to take their medications for prophylaxis of opportunistic infections (PCP, etc.) until results are available from studies exploring this question.

Safety
Data from clinical trials prior to accelerated approval reported approximately a 4% incidence of nephrolithiasis (defined as flank pain, blood in urine or kidney stones) in those studies. Side effects (>2% incidence) can be nausea, abdominal pain, headache, diarrhea, weakness/fatigue, insomnia, taste changes, acid regurgitation and back pain. Asymptomatic hyperbilirubinemia (when a blood lab test of bilirubinemia indicates levels at or above 2.5 mg/dl) has occurred in approximately 10% of those treated with indinavir. In less than 1% of them, this was associated with elevations in liver enzymes. As with all

protease inhibitors, drug interactions can potentially occur, because one drug can change the blood level of another. Dose reductions or increases are sometimes recommended for the protease inhibitor or the other drug. NATAP publishes a Protease Inhibitor Users Guide, which is a compliance or adherence manual outlining drug interactions and other important adherence concerns for all approved protease inhibitors; it is available by contacting us; or you can obtain a Package Insert from your pharmacist which should specify all drug interaction concerns. In addition, you should always discuss potential interactions with your doctor(s).

Indinavir for advanced HIV, <50 CD4. Dr. M Hirsch, of Harvard Medical School, reported 24 week data from study 039 of 320 individuals with <50 CD4, >6 months AZT-experience, who were 3TC- and protease inhibitor-naive, and randomized to receive AZT/3TC, indinavir alone or indinavir/AZT/3TC. Median baseline CD4 and viral load were 15 cells and 89,500 RNA copies/ml. The following table shows the % below detectability for viral load (<500 copies), blood HIV RNA log reductions of viral load, and CD4 cell count increases (Table 1D):

Table 1D	**#pts/24 wks**	**log Ø-24 wks**	**CD4**
IDV/AZT/3TC	55/85 (65%)	-2.19	+84
IDV	2/81 (2%)	-0.15	+65
AZT/3TC	0/80 (0%)	-0.20	0
After 24 weeks, the approx. n=81, 85, and 62 for IDV/AZT, IDV, AZT/3TC, respectively.			

Investigators reported at least 60% of those participants taking triple therapy experienced at least a 2 log reduction from baseline, and about 78% had increases in CD4 of at least 50 cells. In Birmingham, similar results were reported from a similar study using ritonavir or indinavir in a 3-drug combination in a similar group with advanced HIV and low CD4. These study results indicate that many individuals with advanced HIV can respond to potent antiretroviral therapy if used properly. In 039, study participants were treated with two drugs they had never before used--3TC, indinavir--although they had previous AZT experience. Merely adding a potent protease inhibitor onto therapy that a person has been taking for a while may be like taking protease inhibitor monotherapy; such an approach to therapy is likely to fail with viral load decreases rebounding and cross-resistance developing to other protease inhibitors.

Safety
Investigators reported 75 discontinuations (320 initially enrolled) in total for all 3 treatment arms; 17 discontinuations for those taking indinavir/AZT/3TC: 7 due to clinical adverse event; 1 due to lab adverse event; 1 lost to follow-up; 6 pts. withdrew; 2 for other reasons.

Seroconverters treated with indinavir/AZT/3TC. Previously, Ho and Markowitz have reported promising preliminary data of potent triple therapy using ritonavir or indinavir in newly infected individuals; as well, they have reported promising preliminary data from treating chronically infected treatment-naive individuals with nelfinavir potent 3-drug therapy. In both studies study participants' viral load were rendered below 100 RNA copies/ml, with increases in CD4 and trends toward normalization of CD4/CD8 ratios. Detailed results of these studies are available on the NATAP web site. At this conference, L Perrin and M Markowitz reported follow-up preliminary data from an ongoing small open-label study of 36 newly infected treatment-naive individuals treated with indinavir/AZT/3TC. Baseline median CD4 and viral load were 525 cells (range 216-940) and 81,280 RNA copies/ml (range 500-4,786,300 copies/ml), respectively.

Results: At one site, after 3 months of treatment, 11/11 participants lowered blood plasma HIV RNA to <100 copies; 2/8 lowered blood plasma HIV RNA to <20 copies. At the other site, after 6 months of treatment, 5/5 participants lowered blood plasma HIV RNA to <500 copies/ml; after 3 months, 2/5 participants lowered blood plasma HIV RNA to <20 copies/ml. After 3 months, median increases in CD4 cell counts were 111 cells. After 3 months 16/20 had lowered blood plasma HIV RNA to below 500 copies; after 6 months 16/16 were below 500 copies/ml. CD4/CD8 ratios trended towards normalization. There were 3 participants with drug-induced adverse events who reduced dosage; and 2 drop-outs, one due to non-compliance, another due to intolerance to treatment. Investigators concluded that triple drug potent therapy is a promising approach for newly infected individuals.

DMP-266.
S Riddler, Univ. of Pittsburgh, reported preliminary findings of this NNRTI (non-nucleoside reverse transcriptase inhibitor) studied in combination with indinavir. In this small randomized, controlled, double-blind study, after 2 weeks of indinavir monotherapy, 30 individuals were randomized to treatment with indinavir+DMP-266 (n=20) or continuing indinavir monotherapy for an additional 24 weeks. DMP-266 when taken with indinavir decreases blood levels (AUC) of indinavir by 35%; therefore, between 8-12 weeks into the study those receiving the combination treatment had their dosing of indinavir increased from the normally recommended dose of 800 mg every 8 hrs to 1000 mg every 8 hrs. In this study the dose of DMP-266 was 200 mg once per day. Study participants were both symptomatic/asymptomatic and nucleoside experienced/naive. Mean baseline CD4 cell counts and viral load were 247 cells and 85,113 copies/ml for the combination arm; and, 224 CD4 and 131,825 copies/ml for the indinavir alone arm.

After 26 weeks, the changes from baseline for CD4, viral load[1] and % undetectable[2]:

Table 1E	**CD4 cells/mm^3**	**HIV RNA (log)[1]**	**%undetect.[2]**
DMP-266+IDV	+100	-3.70 log/-2.40	78%

n=21			
IDV n=9	+100	-2.20/-1.50	45%
1 The first log reductions listed of -3.7 and -2.2 represent a higher reduction in viral load because a more sensitive test was used which has a lower limit of detection and therefore allows for detection of viral load to lower level. The second listed values of -2.4 and -1.5 were obtained when using the less sensitive test whose lower limit of detection was 400 copies/ml. When below 400 copies, a value of 200 copies was assigned. 2 The values obtained here were from using the test with lower limit of detection of 400 copies/ml.			

Additional phase II/III studies are ongoing where once per day dosing of both 400 mg or 600 mg of DMP-266 are being explored. In these studies, indinavir dosing of both 1000 mg or 1200 mg every 8 hrs are being explored. DMP-266 in combination with only AZT/3TC will be explored as a potential alternative to protease inhibitor therapy.

Safety
Investigators characterized DMP-266 as generally well-tolerated. Two participants receiving combination treatment discontinued: 1 due to rash (NNRTIs generally can cause rash), 1 due to grade 4 liver enzyme elevation; in the combination arm (n=21), the frequency of more common adverse clinical events were: # with Adverse Clinical Events=20; 8- rash, 6- headache; 6- diarrhea; 6- pharyngitis (inflammation of the pharynx); 5- URI; 5- sinusitis-; 5- dry skin; 4- depression. Of the 8 experiencing rash, 4 were mild and 4 were moderate to severe; investigators said 3 were not related to treatment. Three suspended usage of DMP-266 due to rash, with 1/3 discontinuing to due rash.

141W94+1592U89.
141W94 is a protease inhibitor and 1592U89 is an NRTI (nucleoside reverse transcriptase inhibitor). Dr. R Schooley, at Univ. of Colorado, reported preliminary 4 week findings regarding the safety, tolerability and antiviral activity of this 2-drug combination in a small number of individuals. Individuals with no prior protease inhibitor experience, and with median baseline CD4 of 223 and viral load of about 15,000 copies/ml were treated with 900 mg bid 141W94 and 300 mg bid 1592U89. 141W94 is being studied at a dose of 1200 mg bid in other trials; after 4 weeks of the 2-drug combination for 6 evaluable participants, there was a median reduction of about 2 log from baseline; 5/6 lowered viral load to undetectable (below 400 copies/ml) but the starting baseline viral load was low--only 15,000 copies (2 log decrease lowers level to 150 copies) for 7 evaluable participants, and the median CD4 increase was +79 from baseline. The combination was characterized by investigators as being well-tolerated with incidences of a few rashes and some gastrointestinal toxicities (nausea in 3 patients). Two patients discontinued prematurely: 1 due to nausea; dysarthria (pain in joints) were reported as serious by the

other patient who withdrew from study. Phase II/III studies are planned for both drugs in combinations with a number of other drugs.

Nevirapine. Dr. J Montaner, at Univ. of British Columbia, reported 20 week data from this ongoing open-label small study (n=21) of the triple combination of indinavir/nevirapine/3TC in individuals with advanced HIV (<50 CD4), who were heavily pre-treated with NRTIs but indinavir and nevirapine naive (and were 3TC experienced). The usual dose escalation method was used for nevirapine. The median baseline CD4 cell count, and viral load were 30 cells, about 150,000 copies/ml. The dosing regimen of indinavir is an important subject because nevirapine reduces blood levels of indinavir when the two drugs are used together (mean reduction in indinavir AUC --blood levels--of 28%, 11% reduction in peak indinavir level, and 38% reduction in indinavir trough level). In this study, the normally recommended dose of indinavir (800 mg every 8 hrs) was used. When nevirapine and indinavir are being used in combination, some physicians are using the 800 mg dose while others are increasing the dose to 1000 mg every 8 hrs. The concern about raising indinavir dosing is the potential for raising the potential incidence of nephrolithiasis (which can result in kidney stones), which has a 4% rate of incidence in clinical studies. The concern about not raising indinavir dosing is that you may end up with sub-optimal therapeutic levels of indinavir, which might eventually result in resistance.

The median changes from baseline (30 CD4, 150,000 copies/ml) in CD4, viral load* and % undetectable (as measured by both 500 copies and 20 copies/ml):

Table 1F	**CD4 cells/mm^3**	**viral load***	**%undetect.**
IDV/NVP/3TC 20 weeks data	+100	-3.00	55% (<500 copies) 20% (<20 copies)
*The ultra-sensitive test with a lower limit of detection of 20 copies was used. If the test with a lower limit of 400 copies were used, the log reduction would have been less.			

Commentary: Although, using the 800 mg dose of indinavir, viral load was still reduced to low levels. However, the fuller durability of the benefits in this study has yet to be measured. Additionally, could the antiviral effect seen in this study be even stronger with a 1000 mg dose of indinavir?

Boehringer's study 1046 of nevirapine/ddI/AZT for treatment-naive individuals indicates that a 3-drug nevirapine regimen without a protease inhibitor may be an effective initial therapy for those who want to delay or save protease therapy (see NATAP web site

article: "Nevirapine--recommended for accelerated approval" for a comprehensive discussion of the data from that study.) But, it is important to remember that this approach applies to individuals who have no prior treatment-experience.

Nevirapine with ritonavir or saquinavir. For the first time the manufacturer reported preliminary initial results from an interaction study of these two drugs in 19 HIV-infected study participants. The blood levels of ritonavir were generally reduced about 10% when used with nevirapine: Cmax (peak blood level) was reduced 10%, Cmin was reduced 9%, and AUC was reduced 11%. Investigators characterized this as not being clinically significant. In other words, no changes in dosing for ritonavir is being suggested. It is suggested that nevirapine dosing remains the same when combining it with indinavir or ritonavir, as changes in nevirapine blood levels are not significant. Nevirapine generally decreases saquinavir blood levels significantly. Boehringer has been urged to conduct an interaction study of nevirapine in combination with ritonavir/ saquinavir.

ABT-378. More than 8 posters and additional oral presentations were devoted to this new protease inhibitor still in very early testing being developed by Abbott Labs; it is currently being studied for safety and pharmacology in normal volunteers (phase I). ABT-378 is being studied for use in combination with ritonavir, which as you may know by now increases blood levels of other drugs because of its potent suppressive effect on the metabolism of other drugs. That is a premise for the combination of saquinavir and ritonavir. In the next phase of studies, expected to begin within several months, ABT-378 will be explored in HIV-infected individuals with low dose regimens of ritonavir expected to vary from 50-200 mg per day. Data from pre-clinical studies indicate that enhancement of ABT-378 blood levels is very sensitive to even low levels of ritonavir. A low dose of ritonavir administered to rats in combination with ABT-378 produced high blood levels of ABT-378 well sustained above the levels needed for efficacy for at least 8 hours. As a result, the potential for once per day dosing will be explored. Preliminary pre-clinical and in vitro data indicate that ABT-378 "displays potent activity against" virus resistant to ritonavir. This suggests that in humans ABT-378 may be effective against virus resistant to ritonavir and possibly other protease inhibitors. Of course this is preliminary and remains to be explored in human studies. However, it is imperative to remember that this drug is in very early stage of development; any number of obstacles might emerge that could prevent further development. For example, we have yet to test for potential toxicities or efficacy in HIV-infected humans.

Nelfinavir/d4T/ddI. Dr. L Pednault, of Bristol-Myers Squibb, reported preliminary data from small open-label ongoing pilot study designed to assess the safety, tolerability and antiviral activity of this triple combination in 22 individuals with no prior experience with these 3 drugs, no CD4 limit and baseline viral load >10,000 copies/ml. Baseline median CD4 cell count was 315 cells (range 70-709), and viral load about 56,000 copies/ml (range approx. 10,000-380,000). A number of study participants were non-adherent which was defined as missing dosing of 1 or more study drug(s) for >7 days out of any 4-week period. Therefore, results were reported separately for both adherent and all participants which includes adherent and non-adherent.

For all study participants, after 12 weeks, the median CD4 cell count increase was about 100 cells (n=18); their median viral load reduction from baseline peaked at about -1.70

log at 4 weeks and rebounded to a reduction of about -1.40 log at 12 weeks (n=16).

The median changes in CD4, viral load, and % undetectable (<500 copier/ml) for study participants who were adherent :

Table 1G	CD4≠-8 wks/ 12 wks	viral load -8 wks/	12 wks	%undetect (<500 copies) 8 wks	12 wks
NFV/d4T /ddI	+150/200 (n=8,7)	-2.00 log	-2.25 (n=8,6)	50%	83% (n=8,6)

These results are based upon small numbers of study participants and are preliminary; larger follow-up studies are planned.

Safety. d4T in combination with ddI has been the subject of a pilot study exploring different dosing combinations in a group of individuals with no prior drug experience and with less advanced HIV. The incidence of peripheral neuropathy is not expected to be high in such a group of healthy drug-naive individuals. The incidence and severity of peripheral neuropathy can be expected to be more problematic in an advanced group with extensive prior drug-experience. However, 12 weeks is to early to accumulate any data regarding peripheral neuropathy. Investigators reported most subjects had mild to moderate "loose stools", not requiring dosing interruptions (a potential side effect of nelfinavir); loose stools was characterized as--3 loose stools per day. There was 1 case of grade 3 allergic reaction to nelfinavir; one case of grade 3 neutopenia+grade 4 liver enzyme elevation; 4 participants experienced mild fatigue.

Pediatrics and perinatal transmission.
Progress is being made for treatment of children; the study and use of more potent therapy including protease inhibitors for children and in perinatal transmission is progressing. A nelfinavir study for 41 children (3 months of age 13 yrs+) has been ongoing since Summer '96. It appears as though a dosing regimen has been selected with equivalency to adult blood levels; preliminary data reported at this conference for two children (one received nelfinavir for 4 weeks and the other for 6 weeks) indicates initial "significant" antiviral activity, and favorable tolerability; nelfinavir's pediatric form is a palatable tasting powder, and its pediatric application for FDA approval is being currently reviewed parallel to the adult application. Agouron (in San Diego, 619-622-3000) has an ongoing expanded access program through which children can access nelfinavir for free until FDA approval. Ritonavir has been in an ongoing pediatrics trial (phase I/II-for children 2 yrs+, enrolling 40 children at the NCI-National Cancer Institute) for longer than nelfinavir so there is more data available. Abbott has submitted a pediatric application to the FDA for capsules and liquid for children. As with adult use, there is more incidence of side effects--elevated cholesterol, triglycerides, liver-related function tests--but investigators characterize the side effects as not clinically significant. "Nice" CD4 increases and "sustained" viral load decreases were reported, as multiple dose

regimens were explored. Although the liquid suspension used for children is less palatable than the nelfinavir powder, investigators reported that if a child is able to tolerate ritonavir liquid for initial 2 weeks, then tolerance should be good. Mothers and doctors used innovative ways to facilitate tolerance. Some coated the mouth of the child with peanut butter before taking the ritonavir liquid. Also, the use of chocolates and other sweets were helpful.

A number of ACTG (AIDS Clinical Trial Group) studies will explore protease inhibitor therapy during pregnancy to prevent transmission. Several studies are about to begin using various drug combinations for women in pregnancy. We don't know yet if protease inhibitors cross the placenta, but apparently AZT and 3TC do. Among these drug combinations that will be explored: indinavir/AZT/3TC will be given to mothers in pregnancy, babies won't receive indinavir because of a concern about potential bilirubin elevations; nelfinavir/AZT/3TC will be given to mothers in pregnancy and babies after birth; ritonavir/AZT/3TC will be given to mothers in pregnancy and infants after birth; as well, 1592U89/AZT/3TC will be given to mothers and babies.

ACTG 250, an exciting study, will explore a single-dose of nevirapine during labor followed by a single-dose for the infant within 2-3 days after birth. That single dose in the newborn is expected to produce high antiviral activity sustained for 1 week. During pregnancy, the mother can be treated with whatever therapy the women's doctor wants to use. Investigators expect to enroll over 800 women, and hopefully some data will be available in 1997.

Editorial 1592U89, 141W94: Expanded Access. Two years ago monotherapy was common, and practical use of combination therapy consisted primarily of 2 nucleosides; that is, treatment options were much less complicated, and our understanding of drug resistance has greatly changed since then. It is widely accepted now that when switching to a new therapeutic regimen it may be advisable to begin with at least 2 and preferably 3 drugs you've never before taken. This notion along with several other factors have changed the context for expanded access programs. The availability and use of protease inhibitors and a number of other drugs recently made available also change the circumstances. The time it takes from phase I/II human trials to FDA accelerated approval has been shortened and this too changes circumstances. An expanded access program where an individual is encouraged to merely add the new drug to their ongoing existing therapy should be avoided. For myself and others, that is how we generally used 3TC when it was available in expanded access and after its approval.

It is in this context that expanded access programs for both of these new drugs are being designed by the developer, Glaxo Wellcome (GW). 1592 is a nucleoside reverse transciptase inhibitor, similar to AZT, but preliminary data from ongoing clinical studies indicates 1592 has more antiviral activity than AZT, d4T or ddI--CD4 rises of about 80-100 and viral load reductions of 1.5 to 2.0 log, similar to that seen from a protease inhibitor (see NATAP web articles for more extensive data reports). An important question which is not yet fully resolved is the potential benefit from 1592 to individuals who have extensively used other NRTIs and are or may be resistant to these other drugs--AZT, 3TC, d4T, ddI, ddC. The 184 mutation that causes 3TC resistance may also cause 1592 resistance, although GW researchers don't think that will occur. GW initiated a

study this past Fall of individuals with prior NRTI experience to try and measure their responsiveness to 1592, but the results are not yet available. The answer to this question is an important element in deciding how and when to use 1592. Even if there is some measure of cross-resistance, you still may want to use it, but in such a scenario it becomes all the more important to use it along with drug(s) you've never before used in a combination that is most likely to maximally suppress viral load.

The antiviral activity data available for 141 is limited to preliminary data of 4 weeks indicating about a 2 log reduction when used in the highest dose experimented with in that study--1200 mg bid; and, from the 4-week data outlined above when used in combination with 1592. Preliminary in vitro resistance data for 141 indicates that the major important sites for potential mutations exist at positions 46, 47, and 50. This is a relatively unique profile and offers the potential for benefit to those who may be resistant to other protease inhibitors. GW has just begun a protease-protease study examining 141 in combination with saquinavir, indinavir or nelfinavir. In vitro data indicates 141 resistant virus may be responsive to saquinavir therapy and saquinavir resistant virus may be responsive to 141. Future opportunities for 141's use have yet to be fully explored. All the more reason for being prudent when considering how and when to use 141. You would not want to prematurely develop resistance to 1592 or 141 without knowing the ways in which they may be most useful for you to use.

So, questions do remain to be answered as the amount of data from these two drugs is relatively limited. However, expanded access is supposed to offer an opportunity to individuals who have few or no other treatment options remaining; the nelfinavir expanded access program began in September '96 for individuals with <50 CD4 and resistance or intolerance to approved protease inhibitors. Recently, Agouron raised the CD4 criteria to 100. Over 1000 individuals have enrolled in this program. By early March '97, nelfinavir should be available in your pharmacy. Considering GW says that limited production and supply will be a factor initially in designing a 1592 protocol, some form of limited distribution may be proposed by GW. Community sources have suggested an idea for expanded access-- an initial program for those with <50 CD4 or viral load above 40,000 who have failed approved RTIs and at least one protease inhibitor; other community sources have suggested that as more supply begins to become available for 1592/141, GW should initiate a protocol "that would be in effect a large simple trial that would randomly assign participants to one of 3 arms, 1592, 141 or the combination of both", and all would be free to add additional therapy.

Ideally, CD4 cell count should not be a decisive inclusion/exclusion criteria, but such criteria should more soundly be based upon whether or not an individual has adequate remaining treatment options; but, if drug supply is a decisive issue, a fair cut-off may have to be selected, in which case I think 150 CD4 is fair; 50 CD4 is too restrictive. Inadequate remaining treatment options could be defined as: not necessarily having exhausted NRTI options remaining, or resistant or intolerant (refractory) to protease inhibitors. Although there are exceptions, individuals who are not doing well and who have few if any remaining viable options usually have relatively low CD4.

The purpose, as I see it, for expanded access is to make sure the drug(s) get to the patient as quickly and as easily as possible. Too much administration and paperwork will

discourage doctors from enrolling their patients in the program. A large randomized "trial" would be too cumbersome to implement, create too much bloodwork and paperwork for GW and the doctor, and delay quick access to the drug. An intent of such a large randomized trial is to create a large safety database for the drugs. I think that is unnecessary. Participants will be taking multiple other drugs so no matter how you design the program, there will be limitations on how much we can learn from the data. I think we could obtain safety data just as well by simply following all participants in the program for as long as possible. Because so many drugs are now available it is difficult to sort out safety information for one drug when individuals are using multiple drugs at once.

I think anyone who qualifies for expanded access may be in the position of needing access to both 141 and 1592; they should not be put in the position of risking randomization to an arm that excludes access to one or the other drug for the purpose of possibly acquiring useful safety data; it should be their option, if possible, to access both drugs if there is a need.

Frankly, as a person with AIDS myself, I would prefer delaying using 1592 or 141 until there is more data, until I understand more about how to use them properly, and until I may have actual need for them. Of course, it is a personal decision as when you feel you can no longer wait before using a therapy. However, to use them improperly or too soon may compromise future benefit from them.

Protease-Protease Studies: Preliminary Data from Nelfinavir/Saquinavir
Ritonavir/saquinavir was the first double protease combination to be researched and now is in limited clinical use. In 1997, many other double protease combination studies are planned. Already ongoing is a study of 141W94 in combination with indinavir, nelfinavir or saquinavir, but not yet with ritonavir. Glaxo Wellcome, the manufacturer of 141W94, has delayed including ritonavir. In a preliminary early study, the potential combination of nelfinavir and saquinavir was explored. Investigators found the following: nelfinavir increased AUC (area under the plasma-concentration time curve) of the new soft gel EOF saquinavir almost 5-fold, and increased its maximum concentration by almost 3-fold; saquinavir had little effect on blood levels of nelfinavir; after 12 weeks of therapy with nelfinavir (750 mg tid) and the new EOF saquinavir (1200 mg tid), HIV RNA was reduced by about 2 log and CD4 increased by about 100 cells in 13 protease-naive participants with a median baseline viral load of 39,900 copies/ml and CD4 of 327 cells. Additional studies are planned to begin soon.

At the conference, John Mellors discussed this subject and reported increases in blood levels (AUC) that have been seen from preliminary interaction studies: ritonavir increases nelfinavir AUC by 2.5 fold (we know from previous more in-depth research that saquinavir AUC in increases >20 fold from ritonavir); indinavir increases nelfinavir AUC by 1.8 fold; nelfinavir increases indinavir AUC by 1.5 fold and saquinavir Enhanced Oral Formulation (EOF)--the new saquinavir more potent formulation-- by 5 fold. Early studies will explore the tolerability of some of these combinations; as well, previously used dosing regimens of 3 times per day may be reduced to 2 times per day, for some of these protease inhibitors, because of changes in blood levels and the ability to remain adequately above trough levels when in combination with another protease inhibitor.

1997 should be an interesting year for HIV antiretroviral research. By 1998, results from studies examining new possibilities should be available. Because of limitations of space in this newsletter, the NATAP web site will contain more detailed and comprehensive reports of the therapies discussed in this newsletter as well as additional reports on therapies discussed at the conference. http://www.aidsnyc.org/natap

Free Viral Load Access Program.
Roche Diagnostics and Chiron Corp. make and distribute to labs the viral load testing kits. Both companies have set up separate programs to provide free viral load testing to individuals without reimbursement. The Roche Amplicor PCR test was FDA approved last June; the Chiron bDNA test is currently being reviewed by the FDA for approval. The Roche program is available regardless of where you live, offers 2 free baseline tests, and up to 5 tests over the next year to those who qualify . Your doctor may have an application form, but you can call toll-free for information: 1-888-Test-PCR. The Chiron program is currently offered only in 3 cities--San Francisco, Boston, Chicago--but Chiron has promised to expand the program to other cities. For information on the Chiron program, you can call toll-free: 1-888-HIV-LOAD; or, in Boston- 617-534-5285 (contact: Daniel Shapiro); in Chicago, at Rush Hospital--312-633-3005 (contact-Renslow Sherer), or at Cook Hospital (contact-Ron Lollar, Mary Hayden)- 312-942-6246.