

National AIDS Treatment Advocacy Project

2nd Report of the 3rd Intl. Conference on Drug Therapy in HIV Infection - November 12, 1996

Information reported from the meeting:

1. When and with what to begin therapy: "[genetic misadventure](#)" or [saving your aces](#); protease inhibitor cross-resistance.
2. To the FDA and drug industry: are traditional clinical endpoint studies necessary any more? "[Clinical endpoints are surrogate markers of an antiviral effect](#)"; Drs. Joep Lange and Robert Schooley address this question.

Data from studies of important treatments:

1. [Nevirapine: updated viral load data](#)
2. [Ritonavir+saquinavir combination](#): the latest update--20 weeks of CD4 and viral load data from the ongoing study of the double-protease combination.
 - eating recommendations for ritonanir/saquinavir
 - 4-drug study: sero-converters, chronic infection
3. [Ritonavir+AZT/3TC](#): for treatment-naive, immediate vs. delayed triple therapy--24 weeks of CD4, viral load data;
 - virus levels in lymphoid tissue in the tonsil for 6 patients
4. [Ritonavir+AZT/ddC](#): French study in treatment-naive; update of 72 weeks CD4, viral load data.
5. [Ritonavir in children](#): 6 months to 18 years of age.
6. [Nelfinavir in combination with d4T/ddI](#): pilot study in treatment/naive.

"Genetic mis-adventure" or saving your aces.

Dr. Doug Richman, a virologist at UCSD, characterized sub-optimal viral suppression as a "genetic mis-adventure".

AIDS is an infectious disease; scientists stated at this conference, as they have previously, when treating other infectious diseases or cancer it is standard to treat upon detection with the most potent therapy. Other researchers have taken a different position; they are concerned that using the most potent option immediately, in treating HIV, could leave an individual without adequate options if the first therapy fails (see NATAP web site article "[Perspectives on Viral Load and When To Initiate Therapy](#)", for a lengthy

discussion of this important subject). If resistance develops from use of a protease inhibitor, which could result in a broad array of mutations (a genetic mis-adventure), there is potential for resulting cross-resistance to limit or prevent future benefit from subsequent protease inhibitor therapy. That is, if resistance developed from therapy with a potent three drug therapy including indinavir or ritonavir, there is concern about the level of cross-resistance that could develop with other protease inhibitors available now or in the future.

Drs. Richman, Emini, and Lange agree if treatment is initiated with a therapy that does not maximally suppress the virus to below detection, resistance will eventually develop. As alluded to in the 1st report from Birmingham, in the Darwinian evolution section, Dr. Richman said once resistance emerges, the genetic make-up of the protease enzyme changes forever. This could diminish the virus' sensitivity to currently available protease inhibitors; and to others now in clinical or pre-clinical development. Several drug company programs are in pre-clinical development with additional protease inhibitors that may have limited or no cross-resistance with the currently available inhibitors. But, it is too soon to determine or speculate if that will occur.

It appears as though the currently approved protease inhibitors (saquinavir, ritonavir, indinavir) have at least some measure of overlapping mutation profiles. The significant mutations that can result from resistance to one protease inhibitor can overlap with those of another. For example, ritonavir and indinavir appear to be fully cross-resistant. If you develop resistance to one, it is unlikely you can benefit from the other. Agouron has reported preliminary information indicating that nelfinavir has a unique mutation profile; they reported D30N as the predominant mutation responsible for resistance; the preliminary indication is that if you use nelfinavir prior to other protease inhibitors you may still be sensitive to the other protease inhibitors, if resistance to nelfinavir develops. It is important to remember that the true measure of cross-resistance is actual experiences; that is, when larger numbers of individuals actually are taking a drug and switching therapies after resistance develops.

Treatment choices also have a personal aspect. If you have exhausted some or all nucleoside options, selecting a maximally potent or suppressive therapy becomes difficult. It is crucial to plan the future course of your treatment strategies. Look ahead to the drugs that will be available in the future, consider your current options and map out a strategy.

As discussed in the 1st Report from Birmingham, an individual must be willing to commit to the adherence or compliance necessities of taking the potent 3-drug protease inhibitor therapy. If a person starts therapy with AZT/3TC alone without sustained maximal suppression, resistance will eventually emerge and that person has forever lost the full benefit of the AZT/3TC combination. However, as newer drugs come along,-- such as 1592U89, possibly Lubovcavir from Bristol-Myers, DMP-266 (NNRTI from DuPont Merck)--the possibility of exhausted AZT/3TC may not be as significant.

It appears crucial that at least when initiating a new therapy for the purpose of maximal suppression, you need at least two drugs you never before used; at least one of these two ought to be a potent antiretroviral, such as a potent protease inhibitor. Adding a protease inhibitor on top of 1 or 2 nucleosides that you've been taking for a prolonged period of

time lessens your chances of achieving maximal suppression, and is like taking protease inhibitor monotherapy. In this scenario, you should be prepared for the possibility that resistance may emerge and your viral load may come back up.

Some individuals are able to render their viral load to undetectable with indinavir or ritonavir monotherapy, or a combination of 2 drugs. It is less risky and more advisable to use a 3-drug combination composed of drugs from different classes. Different classes of drugs may be able to enter different types of cells or different compartments. This should help suppress replication better and increase ability to avoid resistance. Overall results of a number of indinavir studies indicated about 40% of those taking indinavir monotherapy were able to sustain viral load below detectability of the test used after a prolonged period; but, that is misleading as 40% is a mean or median. Many participants in those studies did not lower their viral load to undetectable or were not able to sustain it, developed resistance and thereby lost the opportunity to benefit from indinavir and possibly ritonavir forever.

Soon, we may have a better understanding of how to combine a protease inhibitor with a NNRTI. Some individuals are already combining indinavir with nevirapine because they've exhausted other treatment options, but the interaction data of combining these two drugs is preliminary; both are processed through the cytochrome p450 liver system, which alters blood levels of the drugs being taken; you could end up with blood levels of a drug that are either too low or too high, and this could cause toxicity or resistance. It may not yet be advisable to combine them, unless you have no other alternatives. NNRTIs have the potential for cross-resistance. The development of resistance to a NNRTI may limit benefit from another NNRTI. As well, if taking ritonavir and saquinavir in combination, you should add 1 or 2 nucleosides.

In earlier indinavir studies where some individuals viral load has rebounded, possibly due to taking indinavir monotherapy, their CD4 has remained elevated. The reason for this is not understood. It is thought that their virus has become debilitated, possibly non-infectious, defective, and less virulent. The implications of such a development are not understood, but it may be a positive outcome.

Today and tomorrow, November 13 and 14, the NIH is conducting a conference in Washington, D.C. to address establishing an updated standard of care; hopefully, a good document will emerge. Researchers and community advocates gathered to observe and participate. On the first day, several researchers agreed that if an individual presented themselves with high CD4 and low viral load (for example, 500 CD4 and 2,000 plasma RNA), and was not a sero-converter, they would not necessarily recommend therapy. They would monitor their CD4 and viral load closely for any changes unless the individual insisted on starting treatment.

Nevirapine: updated viral load data. In the Boehringer Ingleheim trial #1046, triple therapy of nevirapine/AZT/ddI was studied. After 28 weeks, there was a CD4 rise from baseline of about 150 cells , and a plasma RNA decline of 1.65 to the lower limit of detection. 73% of study participants receiving this triple therapy had undetectable viral load (the Roche PCR test was used --200 RNA copies/ml was the lower limit of detection). After 52 weeks, the proportion that remained undetectable was 57%. See the

two articles on NATAP web site: Post-Vancouver Nevirapine Update and Nevirapine Approval Recommended; these two articles comprehensively review #1046 and other information.

At this conference, BI presented for the first time, findings from the Roche ultra-sensitive viral load test (whose lower level of detection is 20 copies). After 52 weeks, 51% were below the limit of detection. The reliability of the Roche ultra-direct (20 copies/ml) test is still in development. The development of resistance may be a factor in the decline from 73% undetectability to 57%. Although, the data is for a smaller number of individuals, in the Merck study #035, where participants were AZT-experienced and 3TC-naïve (see Post-Vancouver Indinavir/AZT/3TC Update on web site), the viral load reductions and the proportion of individuals remaining undetectable (lower limit of detection is 500 copies) appear to be more durable. As well, the latest results described below from ritonavir triple combination studies may indicate better durability. Preliminary interaction data is available of nevirapine used with saquinavir; preliminary interaction data of its use with indinavir and ritonavir is expected in November and December, respectively. But, more time is needed to better understand how to combine nevirapine with indinavir and ritonavir. Nevirapine reduces saquinavir blood levels, so that is a questionable combination.

The report of the first day from this conference, also discussed opinions expressed at this meeting in support of starting potent therapy as soon as possible, with the intent of lowering viral load to zero.

The International AIDS Society (IAS) convened a panel of AIDS doctors and researchers and said: "any decision to initiate therapy for individuals with over 500 CD4 must be tempered by the fact that there is no available data to support treatment in such an early stage of the disease". Some of the considerations that might influence the decision to delay therapy include: (1) a concern about tolerance and toxicities; the potential side effects of protease inhibitors may discourage individuals from starting therapy when they feel healthy; some individuals may be concerned about toxicities from longer-term treatment; (2) the cost of protease inhibitor therapy may be prohibitive; (3) the possibility of developing drug resistance and consequent protease inhibitor cross-resistance may be a deterrent; (4) if an individual isn't compliant, it may be better to delay starting therapy until they are prepared to be compliant.

However, the IAS has also said, ideally, therapy should be initiated before any immunological damage occurs. Data from John Mellors MACS study shows individuals with CD4 of 787 and high viral load progress significantly more quickly than individuals with CD4 of 787 but who have low viral load. The IAS has recommended considering starting therapy with a double nucleoside regimen, i.e. AZT/ddI, AZT/3TC, d4T/ddI, AZT/ddC, d4T/3TC; which could be followed by more potent therapy, particularly if treatment failure develops. It is rumored that the IAS may be convening to revise these recommendations, but have yet to do so. I hope an awareness of both sides of the discussion is helpful. Treatment choices are complex, personal and have consequences.

"Clinical endpoints are surrogate markers of an antiviral effect"; to the FDA: are traditional clinical endpoint studies necessary anymore?

Traditional clinical endpoint studies are where individuals are randomized to receive the drug, which is the object of the study, or not to receive it. On top of the new drug or placebo, they may be permitted, to take other approved drugs. These studies are now usually reserved for individuals with low CD4 (under 100 or 200). The purpose is to examine the rate of the development of opportunistic diseases and deaths for each of the two treatment arms. If the individuals in the treatment arm receiving the new drug, which is the object of the study, live longer and develop OIs less quickly or in less quantity (as compared to the individuals in the other treatment arm not receiving the study drug), then the drug is approved. Are the individuals in the placebo or control group receiving sub-optimal treatment?? Should they receive sub-optimal therapy? These are crucial questions, that are being hotly discussed at this changing time in AIDS drug development.

There is some important information derived from such studies: safety and some measure of durability of the drug's effect on disease progression. However, it has been suggested that this information could be obtained by long-term observational studies where all volunteers would receive open-label drug; they would simply be followed for an extended period (3, 5 or possibly 10 years) to study the durability of benefits and potential toxicities; but, it is suggested that a one-year randomized clinical endpoint study gets answers more quickly and allows us to have a better basis more quickly for treatment decisions. Randomization to roughly equivalent treatment arms is another approach. For example, one arm could be indinavir with two nucleosides of your choice vs. nelfinavir with two nucleosides of your choice. Either arm has appeal, without sacrificing an individual to a sub-optimal therapy. Additional alternative approaches have been suggested. Again, answers from such a study would probably take longer to accrue than a traditional endpoint study.

A relevant question in this debate about the usefulness of traditional clinical endpoint studies is: can we use a drug's effect on viral load as an adequate measure of its ability to delay progression and prolong survival? If so, then safety and durability remain to be addressed. But, how would we detect whether a potential toxicity from long-term use results from the drug or from HIV without randomization? The FDA is not yet convinced that viral load is an adequate measure of clinical progression.

Joep Lange said at this meeting, "as you may know, I'm not of the opinion that clinical endpoint studies are the holy grail of antiretroviral therapy. They are in fact, surrogate markers of an antiviral effect.....There appropriate role in developing new drug therapies are often misunderstood and/or abused by regulatory authorities, health care providers, governments and pharmaceutical companies.....I do not condone the use of sub-optimal therapies in clinical endpoint studies". However, Dr. Lange may approve of a clinical endpoint study that doesn't randomize one to a sub-optimal therapy.

Dr. Robert Schooley, who heads the ACTG (AIDS Clinical Trials Group), said we need to radically change our approach to clinical trials, as he addressed the future of clinical endpoint studies. Most trials have been designed up til now to see if you can slow down the rate at which individuals may develop an HIV related infection, with the addition of one new drug to existing available therapies. These types of trials are set up to wait for patient failure. He said, we cannot continue to do this for every new drug coming along; such trials aimed at gaining regulatory approval cost \$50-100 million.

Schooley went on to say, today successful patient management requires individualized attention and strategy, which is not possible in the way trials are currently designed. We need trial design that allows both treatment arms to stay with a regimen that allows for maximal viral suppression and without clinical progression; and, that allows for changes in therapy that may be necessary to accomplish that goal.

Schooley continued, we need clinical endpoint studies, but they should be focused on: (1) treatment sequencing strategies and paradigms; for example, is complete suppression of the virus the way we need to go?; if so, how do we best do that? (2) longer term trials should address specific questions such as to better understand resistance, cross-resistance and how to prevent it; which drugs may be better to combine pharmacologically; which drugs may be better in specific populations; (3) a trial should simultaneously address its affect on viral replication, the development of opportunistic infections and immune function.

Finally, he said, patients entering a clinical trial should expect to be treated at least as well and hopefully better than they would in a practitioner's office; and, they should receive real-time viral load testing results.

Again, do we need randomization to detect if a potential toxicity from longer-term therapy is drug-related or due to HIV?

Author's commentary: It is high-time for the FDA and drug companies to get creative. It is crucial that the FDA be flexible, progressive and quickly adapt to the new developments in research and treatment. I call on the FDA and the industry to give immediate consideration to these questions. Resources for clinical trials are limited, as measured both by dollars and patient participation; we cannot use these resources unwisely, because we need adequate resources devoted to developing more and better drugs.

Ritonavir and Saquinavir in combination. Dr. William Cameron, of the University of Ottawa, presented the latest data available from the ongoing open-label pilot trial comparing 4 different dosing regimens in this first study of a protease-protease combination therapy. Previously, at ICAAC in September, 12 weeks of data were presented. For prior background data and information see the NATAP articles reviewing data presented at Vancouver (6 weeks) and ICAAC.

As you may already know, study participants have been randomized to one of 4 treatment arms: (1) 400 mg bid (every 12 hrs) ritonavir + 400 mg bid saquinavir; (2) 600 mg bid ritonavir + 400 mg bid saquinavir; (3) 400 mg tid (every 8 hrs) ritonavir + 400 mg tid saquinavir; (4) 600 mg bid ritonavir + 600 mg bid saquinavir. Cameron presented 20 weeks of data for the 1st two groups, and 12 weeks of data for the 3rd and 4th groups, as group 3 and 4 started therapy after the first two groups.

Cameron reported, after 20 weeks, those in group 1 taking 400 mg RTN bid+400 mg SQV bid had median reductions in RNA of 3.21 log and median increases in CD4 of 75, from baseline. By comparison, at 12 weeks this group experienced a median reduction in RNA of 2.74 log and a median increase in CD4 of 91, from baseline. Their median

baseline RNA and CD4 were about 43,000 (4.63 log) and 277, respectively.

Those from group two taking 600 mg RTN bid+400 mg SQV bid had a median reduction in RNA of 3.17, and a median increase in CD4 of 120. By comparison at week 12, this group had a median reduction of 3.06 log, and a median increase in CD4 of 113. Their median baseline RNA and CD4 were about 53,000 (4.72 log) and 264, respectively. The number of study participants upon which the data is based for both groups is 51. The improvements for both groups 1 and 2 appear to be leveling off.

The Roche PCR test with a lower limit of detection of 200 was used in this study. About 80% of the 51 individuals from both groups were below the limit of detection of 200 copies/ml. At 12 weeks, for groups 1 and 2, the proportions were 75% and 70%, respectively. Approximately a 2 log decline in RNA for all 4 groups reduces their viral load to the 200 copy level. The remaining reduction is below the 200 level.

After 12 weeks, those from group 3 taking 400 mg RTN tid+400 mg SQV tid, experienced a median reduction in RNA from baseline of 2.68 log, and a median increase from baseline in CD4 of about 100. By comparison at week 6, their RNA reduction was 2.09 and CD4 increase was 74. Their median baseline RNA and CD4 were about 27,000 (4.43 log) and 302 cells, respectively.

After 12 weeks, individuals in group 4 taking 600 mg RTN bid+600 mg SQV bid, experienced a median reduction in RNA of 2.73 log, and a median CD4 increase of 120. By comparison at week 6, this group's RNA reduction was 2.19 log, and CD4 increase was 88. The % undetectable for groups 3 and 4 were reported as 80% and 60%, respectively. Their baseline median RNA and CD4 were about 43,000 (4.63) and 251. The data for groups 3 and 4 are based on 44 evaluable study participants.

The differences in RNA and CD4 responses between treatment groups are not statistically significant. It is still uncertain which of the dose regimens may be superior. In the future, different dose regimens may be studied. However, the tid regimen appears to be less tolerable, and may be the least preferable. For groups 1 and 2, it doesn't appear as though the side effect profile is any different than that for ritonavir. For group 4, there were several incidences of elevated LFTs (liver enzyme levels). It is my understanding there were a few discontinuations or interruptions in treatment due to that side effect.

We do not know the longer term durability of this drug combination; it was the first study of combining two protease inhibitors. Cameron cautioned listeners not to draw too many conclusions from the data. Merck is now planning a protease-protease study of combining indinavir with the "EOF" saquinavir (enhanced oral formulation-the new more bio-available form). It may be advisable that a regimen of ritonavir+saquinavir should include nucleoside therapy of one or possibly two drugs. The combination of two protease inhibitors is still experimental. Although, it may render viral load undetectable, the durability of this reduction may be more secure with additional nucleoside(s) therapy. With more advanced AIDS or higher viral load, it may be more difficult to keep a viral load reduction sustained..

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.

4-drug combination studies. At the conference, David Ho reported preliminary information on the first study of 4-drug therapy. It is an open-label, non-randomized, multi-center study of ritonavir 600 mg bid+saquinavir 600 mg bid+AZT 300 mg bid+3TC 150 mg bid. Twenty-four patients--12 sero-converters and 12 with chronic infection--are in study and "beginning to see a potent antiviral effect". After 6 weeks, the acutely infected individuals, who began with high viral loads have exhibited only a 1st phase decay of RNA decline; one, however, that is substantial and prolonged. Ho said, this is different from what one sees in chronic infection, where one sees a "bi-phasic decay", i.e. the 1st phase decay has a more steep decline in RNA, followed by the 2nd phase decay, characterized as a less steep decline in RNA ; in this study, and normally, the 2nd phase begins after 2 weeks.

Ritonavir/AZT/3TC: immediate vs delayed. Dr. Sven Danner, of the University of Amsterdam, presented preliminary data of this ongoing open-label, randomized two-arm study of anti-retroviral naive individuals, with CD4 counts greater than 50 and plasma RNA above 30,000. Tonsillar biopsies of lymphoid tissue were taken at 4 time-points to compare changes in plasma RNA with changes in tissue load.

Side effects experienced were nausea, vomiting, diarrhea, asthenia (tingling around the mouth) and malaise. Eight patients withdrew from the study. As well, there were dosage interruptions and reductions due to side effects.

Thirty-one individuals were randomized to begin the triple therapy (ritonavir 600mg bid+AZT 300mg bid+3TC 150mg bid) simultaneously or to the delayed group where ritonavir was initiated alone followed by the addition of AZT and 3TC three weeks later. In each arm, ritonavir was started at 300mg bid, gradually escalating to the full dose after 4 days. The immediate vs delayed comparison is to detect if there is difference in antiviral effect due to the three week delay in adding AZT/3TC. Group 1, the immediate group, had a median baseline RNA and CD4 of 5.27 log (about 187,000 copies/ml), and 177 cells, respectively. Group 2, which delayed AZT/3TC for 3 weeks had a median RNA and CD4 baseline of 5.37 log (about, 235,000 copies/ml), and 134 cells, respectively.

The RNA response for both groups, of about a 2.0 log reduction from baseline, was about the same at 3 weeks. At 24 weeks, the CD4 increases were 180 for the immediate group (9 evaluable patients) and 100 for the delayed group (12 evaluable patients). Dr. Danner said the difference could have been due to the difference in their baseline CD4 numbers.

After 12 weeks the decline in RNA appears to level off, at a reduction of 2.8 log from baseline, because, as Dr. Danner explained, a number of study participants were below the limit of detection of the assay. The Roche Amplicor test was used with a median lower level of detection of 238 copies/ml. After 24 weeks, with 10 evaluable participants in each of the two arms, the decline in plasma RNA was 2.8 log for both groups; there was no statistical difference between the two groups.

The following data does not include study participants who discontinued or interrupted therapy, that is only those who remained on full dose of study medications. In the immediate group, 100% were undetectable by week 16 and remained undetectable at week 24. By week 24, 100% of the delayed group were undetectable. This and other studies indicate that it can take as long as 24 weeks to achieve maximal suppression. As long as an initial adequate suppression of 1 to 2 logs is seen in the first few weeks after beginning therapy, you should be patient.

Dr. Danner said, the results obtained to date do not point to a difference in antiretroviral potential between the two treatment groups over the first three weeks. This suggests that the incomplete reduction in viral load seen after three weeks (when compared to the reduction after 16 weeks) is not due to lack of potency of the regimen, nor to rapidly developing resistance. Dr. Danner reported 2 patients had a A71 mutation at baseline; at day 22, 1 patient had a V82A, and another patient had a A71; one patient had a mutation at 41 and 215 but was still undetectable and another had a mutation at 82 after a few weeks, but was also still undetectable.

Lymphoid tissue. Dr. Daan Notermans, of the Academic Medical Center in Amsterdam, reported results from a study of the RNA load in the lymphoid tissue from tonsillar biopsies of 6 participants who continued on treatment in the ritonavir/AZT/3TC study. For each of the six, investigators have baseline and six months values. The tissue RNA load was measured with the Chiron ultra-sensitive bDNA assay. The lower limit of detection of the test is 500 copies; this calculates to 30,000 copies per gram of tissue (or 30 copies per mg of tissue) and is 1.84 log. Notermans reported that by week 24, in all of the six patients, the tissue RNA was below the limit of detection for the assay. Although below 500 copies, residual virus may still be present. Other researchers said more effective methodology, than was used in this study, for examining lymph tissue should be utilized and will in studies conducted in the very near future. The more effective methodology is expected to yield a more definitive understanding of virus activity in lymph tissue. The goal is to correlate virus activity in lymph tissue with virus activity in plasma (blood circulation), as measured by commercially available viral load tests, such as the PCR and bDNA tests. If that correlation can be established, it may not be necessary to measure viral burden in lymph tissue.

Notermans requested that standards for anti-retroviral therapy be re-set to include reducing HIV RNA levels in the lymphoid tissue in addition to reduction in the peripheral blood. He continued, "we need to follow-up to see how sustained the suppression is; and, we need to know other things, such as what happens to the level of pro-viral DNA in the lymphoid tissue. Even if we manage to suppress the virus strong and long enough, is reconstruction of the immune system possible?"

These results were encouraging, but more extensive lymphoid tissue studies will be necessary and are planned.

Ritonavir/AZT/ddC. Dr. Jean-Pierre Chauvin, of Abbott Labs-France, reported the findings of a pilot, open-label, non-randomized evaluation of this triple therapy in anti-retroviral naive individuals. See the Post-Vancouver report (60 weeks) on the NATAP web site for background information and previously reported data. The regimen used was 600 mg bid ritonavir, 200 mg tid AZT, and 0.75 mg tid ddC. Chauvin said ddC was chosen because 3TC was not available at the start of the study. Thirty-two individuals were initially enrolled with CD4 between 50-250. The oral solution of ritonavir was used at the start of the study, and after one year study participants were switched to the capsules.

Baseline characteristics were: median CD4 152 cells; median HIV plasma viral load 4.80 log (about 63,000 copies/ml; range about 1,200 copies to 246,000 copies).

The mean reduction in HIV RNA was 2.0 (n=27) at week 8; this was sustained at week 24 (n=21) and at week 72 with a reduction of 1.9 log in 17 patients remaining on triple therapy. After 72 weeks 12/17 patients (70%) had cellular viremia below the detectable level.

The mean CD4 was 170 at baseline, 280 at week 8 (n=26), 304 at week 24 (n=21), 338 at week 60 (n=17), and 328 at week 72.

During the first six months 11 patients discontinued; Chauvin said six of these were due to the oral solution of ritonavir, and compliance appeared to improve.

Ritonavir in children. Dr. Brigitta Mueller, of the National Cancer Institute, reported preliminary data from this phase I/II study. This trial is examining safety, tolerability, clinical effects, viral load in plasma, and CD4. Four dose levels (250 mg/m², 300 mg/m², 350 mg/m², and 400 mg/m² given orally) were evaluated using the liquid formulation in two age groups (six months to 2 years and greater than 2 years). The 2 years and above group was further sub-divided for analysis purposes into 2 groups: 2-12 years, 12-18 years. Ritonavir was dose escalated over 5 days to full dose. Ritonavir was given alone for the first 12 weeks and then in combination with AZT and/or ddI.

Dr. Mueller characterized ritonavir as "overall well-tolerated". There was an incidence of elevation in triglyceride levels. Several patients experienced nausea and vomiting at the two higher dose levels; there were a few incidences of elevated liver enzymes (not dose related); One LFT elevation was experienced by a child with hepatitis C. The mouths of some children were coated with peanut butter, while others drank chocolate milk before and after medication to help tolerance of the distasteful liquid.

As of September 30, 1996, 46 children have been enrolled. Thirty-seven had completed at least 12 weeks or had come off study and were included in this analysis.

By day 28, the median CD4 increase was 38 cells for those on the lowest dose and 148 for those on the highest dose. Plasma RNA decreased "rapidly" from baseline by 0.5-2.0 log and remained below baseline for at least 24 weeks.

After 12 weeks, preliminary CD4 increases were reported to be 50-100 cells. >From 12-24 weeks, when AZT and/or ddI were added, CD4 counts continued increasing. After adding the nucleoside therapy, RNA levels didn't continue to decline because some children were taking ddI at the same time as ritonavir. ddI is supposed to be taken on an empty stomach, while ritonavir is to be taken with food.

Meuller described one patient's positive response. Their CD4 was 50-60 at baseline; after 6 months of treatment the CD4 increased to 580 cells and later on to 900 cells. Mueller said there is a preliminary indication of a significant antiviral effect, and that limited data in children under 2 years of age indicate that a dose of 250-300 mg/m² given every 12 hours is well tolerated.

Enrollment is continuing and resistance, pharmacokinetics and CD4 repertoire studies will be conducted. There are plans to conduct studies of ritonavir for vertical transmission and neo-nates.

Nelfinavir + d4T/ddI. Dr. Louise Pedneault, of Bristol-Myers Squibb, reported preliminary data from this 12-week, pilot, open-label study of 22 individuals; all were naive to d4T, ddI and protease inhibitors, and received full dose of each drug. Dr. Pedneault outlined some reasons for exploring this combination: (1) the in vitro synergy between d4T and ddI; (2) ddI and d4T appear to have some favorable resistance characteristics; (3) preliminary resistance data from Agouron indicates nelfinavir may have a unique resistance profile; that is, treatment with nelfinavir prior to other protease inhibitors may not create cross-resistance to those other protease inhibitors.

This study was intended to evaluate safety, tolerance, and preliminary antiviral effect. Baseline CD4 and plasma RNA were 315 cells (range 70-700) and 4.75 log (about 56,000 copies/ml). Half of participants had a history of prior therapy and half were drug-naive.

After 8 weeks, the reduction in plasma RNA was 1.8 log (n=17) with a median increase in CD4 of 90-100 cells (n=19). Chiron's bDNA viral load test, with a lower limit of detection of 500 copies/ml, was used to measure plasma RNA. Considering that many study participants started the trial below 56,000 copies, an approximate 2.0 log reduction would render them undetectable by the assay; that may be a reason we see only a 1.80 log reduction for the 17 evaluable participants. Additionally, it can take longer than 8 weeks to realize the full effect of a potent therapy on plasma viral load.

It was found that ddI did not effect the pharmacokinetics of nelfinavir.

Dr. Patrick Yeni, of the Hopital-Bichat Claude Bernard-Paris, said "the triple combination was well-tolerated.....individual drug profiles suggest that there may be less drug resistance with this combination than with others."

New trials. Bristol-Myers is planning a 200-patient European trial of this triple combination. As well, they're initiating a trial comparing d4T+3TC+indinavir and d4T+ddI+indinavir with AZT/3TC+indinavir. See the NATAP web site post-Vancouver review of the preliminary data from the d4T/ddI trial. In that trial there was a low incidence of neuropathy, but the study participants were a relatively healthy group earlier in the disease stage. The incidence of neuropathy can be higher in a more advanced stage

of disease. The first public announcement was made by Roche and Agouron in Birmingham, of a 48-week trial of the combination of nelfinavir with saquinavir (the new EOF). An initial study of the combination found favorable pharmacokinetics and it was well-tolerated. This trial will take place in Europe only, and is expected to begin by the end of 1996. Four treatment arms are planned for comparison: saquinavir+nucleosides vs nelfinavir+nucleosides vs saquinavir+nelfinavir without nucleosides vs saquinavir+nelfinavir with nucleosides.

Stay tuned for 3rd Report from Birmingham and report from Surrogate Marker meeting of November 18-19