National AIDS Treatment Advocacy Project

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Note From the Publisher

I am the publisher and author of NATAP Reports and have been HIV+ for at least 12 years. This newsletter is an outgrowth of our ongoing treatment web site where more extensive information and on-site reporting from major AIDS conferences are available.

Encouraging information continues to emerge supporting the benefits of the new antiretroviral treatments. Data from several studies indicate that viral load reductions and CD4 increases can be sustained. So far, most of these studies are out to about 1.5 years. And ACTG 320 and Merck study 028 were recently stopped because indinavir combination therapy delayed disease progression and prolonged survival for study participants. However, we still need to measure the longer term durability of the efficacy and safety of these therapies. We also need to address the problem that treatments are failing many individuals while some are not responding at all.

Is Immune Reconstitution possible? Preliminary results from several small studies (and case studies) presented at the 4th Retrovirus Conference suggest that HAART (Highly Active Antiretroviral Therapy) may at least partially reconstitute the immune system for some individuals who respond well to therapy. In addition, preliminary results from several small studies suggest that the development of some OIs may be preventable. For example, of 52 patients with <50 CD4 treated with various antiretroviral combination regimens, 11 achieved a stable increase to >50 CD4. Of these 11 patients one developed a new OI while 14 of the 52 who did not respond to therapy with increases in CD4 developed new OIs (abstract #358, R Kaspar et al).

Other studies suggest that immune reconstitution may be responsible for the resolution of certain opportunistic infections. Preliminary data for 15/27 evaluable patients with chronic microsporidiosis and cryptosporidiosis, showed that diarrhea disappeared in 12, weight increased a mean of 2.1 lbs, and all but 2 patients had no identifiable parasites. All patients had identifiable microsporidiosis or cryptosporidiosis for a mean of 10 months prior to starting HAART. The mean CD4 increase was from 56 to 115 cells. Viral load decreased for 9 evaluable patients from 312,745 copies/ml to 5,788 copies/ml (abstract #357, Y Benhamou et al). Case studies reported significant improvements for individuals with cryptosporidiosis, PML, wasting, and Kaposi's Sarcoma.

However, data presented at the conference also showed that some individuals developed CMV shortly (4-10 weeks) after starting HAART . In addition, underlying mycobacterial avium complex infection (MAC) was reported to be "unmasked" (symptoms of infection surfaced) for some individuals after initiation of therapy with HAART, suggesting that individuals with advanced HIV should be evaluated for the presence of unrecognized MAC prior to starting HAART. The unmasking may be due to "enhanced immune response".

For those individuals who have not responded well to HAART, additional therapies are in development that may prove beneficial and are reviewed inside this issue of NATAP Reports: 1592U89, PMEA, PMPA, DMP-266, hydroxyurea.

We don't understand all of the reasons why therapy may not succeed for certain individuals, but non-compliance is a factor. It is crucial to take medications on schedule, follow dietary and hydration instructions, not to reduce or miss doses and not to take drug holidays. NATAP has published a compliance manual called Protease Inhibitor Users Guide. It outlines all the compliance requirements for all the protease therapies.

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Good luck

Jules Levin

Nevirapine, Ritonavir+Saquinavir, DMP-266

On May 10, 1997 at NYU Medical Center, NATAP organized its Third Free Community Education Forum with the support of many local community organizations entitled Current Issues in HIV Treatment. Leading researchers presented the latest data on antiretroviral therapies. Discussion included combining NNRTIs with protease inhibitors, new 44-week DMP-266 data and new 76-week nevirapine data, which follows. This data was reported for the first time at the forum.

Nevirapine: 76-Week Data Update

Previously reported were 52 weeks of CD4 and viral load changes for participants in BI study #1046. A more detailed review of the 52-week data, as well as other reports on nevirapine, are available on the NATAP web site. This article includes information and data reported at the NATAP forum by Maureen Myers, PhD of Boehringer Ingelheim.

In study #1046, 151 treatment naive individuals were randomized to be treated with the triple drug combination of nevirapine+AZT+ddI, AZT/ddI or nevirapine+AZT. The mean baseline CD4 count was 376 cells, and the mean HIV RNA (viral load) was 4.41 log (25,704 copies/ml); 96-98% of study participants were asymptomatic. The treatment dosing was the standard dose escalation method for nevirapine - 200 mg once daily for two weeks followed by a maintenance dose of 200 mg taken twice daily (this dose escalation regimen is recommended because it has been found to lessen the frequency of rash). For AZT it was 200 mg 3 times daily. For ddI it was 125 or 200 mg twice daily. Nevirapine can be taken with or without food, and with ddI or antacids.

Following is a review of the data previously reported up to 52 weeks for those study participants receiving the triple therapy of nevirapine (NVP)+AZT+ddI, and the new data extended to 76 weeks for that group. It includes mean changes in CD4 count and HIV RNA from baseline; percent undetectable as measured by both the Roche Amplicor test (lower limit of detection of 200 copies/ml) and the Roche Ultra Direct test (lower limit of detection of 20 copies/ml).

Mean Changes in CD4 Count and HIV RNA at 76 Weeks

NVP+AZT+ddI	**28 wks**	**52 wks**	**68 wks**	**76 wks***
CD4	+120	+140	+150	+100
HIV RNA (200)	-1.65 log	-1.3 log	-1.3 log	-1.4 log
HIV RNA (20)	-2.2 log	-1.8 log	-1.8 log	-2.1 log
% undetect (200)	70%	60%	60%	80%
% undetect (20)	60%	51%	45%	70%
N	35-40	25-35	15-25	10-12

* The data at 76 weeks is based on a small number of study participants and may not accurately predict the changes at that point after more individual's data are analyzed; the 68 week data is reported here because the data analysis is based on a greater number of participants and may be more reliable.

For those individuals randomized to receive AZT+ddI alone, their mean increase in CD4 counts from baseline were +70, +30, +30 cells at weeks 28, 52, and 76, respectively; their mean reduction in HIV RNA (lower limit of detection of 200 copies/ml) was -1.3 log, -0.9 log, -0.7 log at weeks 28, 52, and 76, respectively. The percent undetectable at weeks 28, 52, and 68 weeks (200 copy test) was 30%, 15-20%, and 10%, respectively.

For those individuals randomized to receive nevirapine+AZT alone, their mean change in CD4 was +10, 0, and -10 cells at weeks 28, 52, and 68 weeks, respectively; their mean reduction in HIV RNA (200 copy test) was -0.4 log, -0.3 log, and -0.2 log at weeks 28, 52, and 68, respectively. The mean change for both groups (AZT+ddI and nevirapine+ AZT) was based on visual observation of line graphs and are approximations.

Safety. Safety data from studies have been recently updated. The rate of incidence of certain side effects are: a rash developing due to nevirapine therapy is 16% (for additional discussion see delavirdine article, safety section), Stevens-Johnson Syndrome is 0.3%, increases in LFTs (liver function tests) are 3%, hepatitis is 1%. Other nevirapine related side effects are fatigue, fever, headache, nausea, and somnolence.

CSF penetration. Although it has not yet been confirmed with data from studies and is theoretical, a number of researchers feel that the important factor in judging whether or not an antiretroviral drug has a positive effect on an HIV-related infection or virus in the brain and the CNS is the percentage of free drug in the blood that penetrates the CSF. So, if only 2% of a drug in the blood is free-drug (not protein bound), but 100% of that 2% penetrates the CSF then that may be beneficial. However, we need additional research to explore this theory and to better understand the effect of antiretroviral therapies in the CSF.

At the NATAP forum, Dr. Myers related information regarding (CSF) cerebral spinal fluid penetration. She said, a certain percentage of the amount of a specific drug in your blood can be protein bound. The percentage that is protein bound in your blood does not penetrate your CSF. The amount that is not protein bound can enter your CSF and is called free drug. 45% of nevirapine is not protein bound and is free drug in the blood. Preliminary animal and human data indicates that 100% of the free-drug of nevirapine in the blood penetrates the CSF.

She went on to say that 60% of AZT is free drug in the blood and that 94% of that penetrates the CSF; 55% of d4T is free drug in the blood and 55% of that penetrates the CSF; 20% of ddC is free drug in the blood and 20% of that amount penetrates the CSF; 21% of ddI is free drug in the blood but she did not have data for what percentage penetrates the CSF. She did not have data on how much drug penetrates the CSF for 3TC, or protease inhibitors.

Research in this area of HIV-related CSF or brain disease, and antiretroviral drug penetration of the CSF and the brain has not been well developed. Because of the effectiveness of the new therapeutic regimens in suppressing viral activity in the peripheral blood, more attention should be devoted to research in this area. There is ongoing research exploring the effect of antiretroviral therapy in semen and lymph tissue, but the subject of HIV and the CNS/CSF and the brain and the effects of therapy are particularly complicated and need special attention.

Combination brain therapy: a therapeutic approach currently being suggested is to use two drugs in your combination that are both expected to have good penetration of the CSF.

Interactions with Protease Inhibitors

Preliminary studies have been conducted exploring the pharmacokinetic interactions of nevirapine with saquinavir, indinavir and ritonavir; a preliminary interaction study of nevirapine with nelfinavir is just beginning.

The Cmax is the peak or highest level of drug reached after a particular dose is taken. Cmin is the lowest level of drug during the dosing period. The AUC (area under the curve) represents the amount of drug concentration in blood over a fixed period of time such as 8 or 12 hours. The AUC is generally referred to as the measure of the overall blood levels for a particular drug during the dosing period (for example, 8 hrs for indinavir, 12 hours for ritonavir).

The following table represents the mean change in Cmax, Cmin, and AUC of 3 protease inhibitors when taken in combination with nevirapine. It is important to note that these type of interaction studies usually provide preliminary information upon which future clinical studies can be based, and they provide dosing information so proper dosing regimens can be explored and confirmed in future clinical studies.

Changes in Blood Levels of Protease Inhibitors from Preliminary Interaction Studies

NVP/Protease interactions	**Saquinavir**	**Indinavir**	**Ritonavir**
Cmax	-29%*	-11%*	-10%
Cmin	NA	-38%*	-9%
AUC	-27%*	-28%*	-11%
# of evaluable patients**	22	19	14

* Statistically significant
** Evaluable patients represents the number of individuals upon which the data is based.

This study found there was no effect of any of the 3 protease inhibitors on nevirapine blood levels. The mean change in ritonavir blood levels are not significant based on regimens using limited dosing and changes in ritonavir dosing is not recommended. The effect on saquinavir and indinavir blood levels are statistically significant. But, nevirapine's effect on indinavir blood levels may or may not be clinically significant.

Ritonavir and Saquinavir

Saquinavir blood levels were decreased when taken with nevirapine (See Table 13). Since the current formulation of saquinavir has low bioavailability, it is not recommended to combine nevirapine with saquinavir. Combining nevirapine with the double protease combination of ritonavir+saquinavir may be effective, but it has not yet been studied. Participants in the ongoing Abbott and Roche study of ritonavir+saquinavir will be permitted to add nevirapine so some data will be available in the future.

Indinavir

At the 4th Retrovirus Conference in January 1997, Marianne Harris, MD reported preliminary data of 20 weeks for 21 individuals with CD4 <50 receiving the open-label triple combination of

nevirapine+indinavir+3TC. Participants were indinavir and nevirapine naive, but heavily pretreated with NRTIs including 3TC. The median baseline CD4 and viral load were 30 cells and 150,000 copies/ml. After 20 weeks, CD4 increases ranged from 75-100 cells and the median viral load reduction from baseline was 3.12 log using the Roche Ultra-Direct test with a lower limit of detection of 20 copies/ml. 55% were below the level of detection when using the 500 copies/ml test, and 20% were undetectable when using the Ultra-Direct 20 copy test.

The preliminary results from this study relate to the issue of which dose of indinavir should be used. In this study, the dosing of indinavir is 800 mg every 8 hrs and some physicians are using the 800 mg dose of indinavir. Although nevirapine's effect on indinavir blood levels may be significant (as mentioned above), that effect may not be relevant to practical or in so-called clinical use, if the therapy adequately suppresses viral load and sustains it. However, as a safeguard, other physicians are increasing the indinavir dose to 1000 mg every 8 hrs because of concerns that the decreases in indinavir blood levels may cause indinavir resistance (see table 13). Apparently insurers will reimburse for the additional drug.

Nelfinavir

A study has just started exploring the effect of nevirapine on nelfinavir blood levels, and the effect of nelfinavir on nevirapine blood levels (Cmax, Cmin, AUC) when the 2 drugs are used in combination. The study will also explore the efficacy of this combination with d4T in HIV infected individuals who are nucleoside experienced. Twenty-four individuals will be recruited at two sites: Roger Williams Hospital at Brown University in Providence, R.I., investigator, Gail Skowron, MD, and St Francis Memorial Hospital in San Francisco, CA, investigator- Gifford Leoung, MD. It is premature to use nelfinavir and nevirapine together until we are more certain about which doses of each drug will be appropriate.

Ritonavir+Saquinavir: New 48 Week Data

Previously reported at the 4th Retrovirus Conference in January 1997 and in NATAP Reports' February issue were data out to 24 weeks for this double protease combination. This issue reports the very latest data extended to 48 weeks.

About 140 individuals were randomized in this open-label pilot study to one of four dose regimens (about 35 to each treatment arm) of these two protease inhibitors.
Group A received 400 mg ritonavir every 12 hours + 400 mg saquinavir every 12 hours; Group B received 600 mg ritonavir every 12 hours + 400 mg saquinavir every 12 hours; Group C received 400 mg ritonavir every 8 hrs + 400 mg saquinavir every 8 hrs; and group D received 600 mg ritonavir every 12 hrs + 600 mg saquinavir every 12 hrs.

The following report contains efficacy data (CD4 and HIV RNA) only for groups A and B because the regimens used for groups C and D are not normally recommended for several reasons: study participants in groups C and D generally experienced a higher incidence of side effects including a higher incidence of elevated liver related blood tests - AST/ ALT, GGT, and triglycerides; CD4 increases and viral load reductions were no better in Group D than in groups A and B, and individuals in Group C receiving a tid regimen were switched to a bid regimen.

The median baseline CD4 for both groups were about 270 cells; the median baseline HIV RNA for group A was 4.58 log (about 38,000 copies/ml) and the median HIV RNA for group B was 4.72 log (about 53,000 copies/ml). The study participants were protease naive but were asked to discontinue other antiretroviral therapy prior to receiving study medications.

After 6 months, median CD4 increases from baseline were about 120 cells for group A and B; median viral load decreases from baseline for both groups were 3 to 3.3 log. Although the Roche Amplicor test with a lower limit of detection of 200 copies was used to evaluate viral load reductions, the 3 to 3.3 log reduction was based on the actual values reported (see explanation in

the DMP-266 article). 80% in group B were undetectable (below 200 copies/ml); 90% in group A were reported below detection.

After 48 weeks, median changes from baseline for CD4 count, HIV RNA, and percent of patients with HIV RNA undetectable (<200 copies/ml):

CD4, Viral Load, and % Undetectable After 48 Weeks

Ritonavir + Saquinavir	**CD4**	**HIV RNA**	**% undetect (<200 copies)**
Group A (400+400 bid)	>100	-3 to -3.3 log	90%
Group B (600+400 bid)	>100	-3 to -3.3 log	90%

n=22 to 26 for each of the groups, this is number of study participants upon which the analysis of this data is based.

After 6-months, it was reported that 7 participants added d4T/3TC for failure to achieve or maintain viral load <200 copies/ml, and that 6/7 fell to and remained below 200 copies for a follow-up period of 4-16 weeks. A total of 12 individuals among the 140 study participants, including the 7 mentioned above, have added nucleoside(s) during the course of the study. Some of them were undetectable but chose to add the additional therapy for assurance.

Safety

Liver status prior to treatment with study drugs indicates a potential for elevation of liver enzymes. Study participants with elevations of liver enzymes (LFTs), 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. If you have any of these liver conditions prior to starting therapy, you should closely monitor your LFTs starting within a week after beginning therapy. Participants in groups C and D had a higher incidence of elevated LFTs, other side effects, and more discontinuations than the participants in groups A and B.

Side effects from ritonavir+saquinavir can include diarrhea, vomiting, taste perversion, malaise, and tingling around mouth area. Some individuals experience difficulty with the side effects, and some do not. The side effects may be diminished with dose escalation and a special diet. The dose escalation method is outlined in NATAP's New Protease Inhibitor Users Guide, or you can speak to your doctor about it. The Users Guide is available by contacting NATAP. Eating large high fat meals when taking the pills has been effective for some in reducing the side effects. Some individuals find it helpful to eat large portions of ice cream or high fat yogurt.

DMP-266: New 42 Week Data

In our last issue of NATAP Reports, we reported the latest preliminary data on DMP-266 from study #003, which at that time was out to 26 weeks. After a two-week lead-in period during which 30 study participants received indinavir monotherapy, the participants were randomized to continue indinavir monotherapy (n=9) or add 200 mg DMP-266 taken once per day to indinavir

(n=21). The mean baseline CD4 cell count was 269 cells and the mean baseline viral load was 4.97 log, about 93,300 copies/ml (HIV RNA).

For review, for those taking DMP-266+indinavir, after 26 weeks mean CD4 increases from baseline were +100 cells. The mean viral load reduction from baseline was -2.4 log when using the 400 copy test (a value of 200 copies was assigned to a test result below 400 copies). When using data that represents the actual number of copies reported (down to 0) from the Amplicor test, the mean reduction from baseline was -4.04 log.

The Roche Amplicor test measures viral load to a lower level of detection of 400 copies/ml, below which is called "undetectable" or non-quantifiable. The Chiron bDNA test measures viral load as low as 500 copies/ml, below which is considered "undetectable" or non-quantifiable. A test result below 400 or 500, depending on which test you use, is not necessarily considered precise and therefore may not be reliable, which is why it is not generally reported to you. An actual value of, for example, 50 copies is reported to you as "undetectable," although the actual value, 50, can be reported. The viral load reduction of 4.04 log reported here is the difference between the baseline value and the actual number of copies detected.

If your viral load test result is below 400 or 500 copies and you are told your viral load is undetectable, you still may have say 20 or 150 copies and virus still present in your blood. Remember, undetectable does not mean there is no virus in your blood. Safer sex is still required.

Recently updated preliminary studies based on a small number of individuals extended to 42 weeks was reported at the NATAP forum by Alan Goldberg, PhD of DuPont Merck.

Mean Changes in CD4 Count and HIV RNA at 42 Weeks

DMP-266 + indinavir	**26 wks**	**42 wks**
CD4	+100	+140
***HIV RNA**	-2.4 log (n=17)	-2.4 log (n=15)
****** **HIV RNA**	-4.04 log	-4.26 log
% undetectable[1]	82%	80%

The differences in viral load between the 26 and 42-week data are not statistically significant.

*these reductions in viral load were measured by the Roche Amplicor test with a lower limit of detection of 400 copies; when below 400 copies, a value of 200 copies was assigned.
**these reductions were based on the actual number of copies reported.
[1] The % undetectable was measured by the 400 copy test

We also reported in the last issue of NATAP Reports that those taking indinavir monotherapy (n=9), in this study, experienced a -1.5 log reduction in viral load from baseline at 26 weeks (n=7) when using the 400 copy test, and -2.2 log when using the actual number of copies. At 24 weeks these individuals added d4T+DMP-266. The preliminary data for these study participants is based on a small number of individuals. The updated mean changes from baseline in HIV RNA, viral load, and CD4 count after 42 weeks of study medications are indicated in the following table:

Mean Changes in CD4 Count and HIV RNA at 42 Weeks

Indinavir	26 wks	42 wks- IDV/d4T+DMP-266
CD4 [2]	>100	>140
***Viral load**	-1.51 log (n=7)	-2.47 log (n=6)
** **HIV RNA**	-2.19 log (n=7)	-4.39 log (n=6)
% undetectable[1]	43%	83%

[2] The updated reports of data indicate a mean increase from baseline in CD4 of 157 cells at 26 weeks, and an increase at 42 weeks of 237 CD4 from baseline. These increases in CD4 are based on only 6 or 7 individual's data and may not accurately predict the mean increase in CD4 count after more individual's data are analyzed.

At the NATAP forum, DuPont Merck reported that in a small 14-day monotherapy study (11 study participants received DMP-266 and 5 received placebo), viral load was reduced by -1.7 log from baseline after 14 days.

DMP-266 lowers indinavir blood levels about 35%, therefore investigators raised the indinavir dosing for study participants in study #003 to 1000 mg every 8 hrs from the usually recommended 800 mg every 8 hrs, but DuPont Merck reported that no additional incidence of kidney stones has been detected from using the elevated dosing of indinavir.

Safety. Reported incidence of drug-related rash from study 003 was the following: during initial 2-week indinavir monotherapy period 1/30 experienced rash; during the combination therapy period 4/21 taking DMP-266+indinavir experienced a rash, and 1/9 taking indinavir alone experienced a rash. There have been 2 discontinuations from the group taking DMP-266+indinavir due to adverse clinical events, 1 due to rash and 1 due to elevated LFTs (liver function tests).

Dosing. The dosing regimen used in study #003 was 200 mg once per day. A dose of 600 mg once per day is being explored. Company officials believed that this high dose will be tolerable. Preliminary research suggests DMP-266 may achieve good CNS penetration when clinically used; therefore company officials believe the 600 mg once per day dose would be very suppressive on pre-existing or potential NNRTI resistance in both the peripheral blood and the CNS/CSF.

This all remains to be confirmed in future studies. Although the potential for a higher incidence of rash is a concern at the higher dosing level, DuPont Merck researchers report that they have not yet observed a higher incidence of rash in individuals who have received the 600 mg dose.

Some CNS related side effects such as slight dizziness and antihistimine-like side effects have been detected at higher doses, but experience so far indicates these symptoms usually last only several hours and seem to dissipate over time. So that within a few weeks of initiating medication, few individuals report any CNS side effects. If this side effect continues to be a concern, they believe it can be addressed by adjusting the dosing regimen by taking the 600 mg dose before bedtime, by taking 300 mg twice per day, or if that's not tolerable by lowering the dose to 400 mg once per day taken at bedtime.

Future studies will include exploration of interaction with a variety of drugs including protease inhibitors and OI medications. As well, larger scale phase II/III studies are underway.

Delavirdine

The approval process for delavirdine has been a difficult and controversial one because some felt the efficacy data was not convincing. The FDA AIDS Drug Advisory Committee (ADAC) held their hearing to consider recommendation of approval for delavirdine in late Fall 1996. The NATAP web site contains a report of the committee hearing. It was agreed between the committee and the FDA that the viral load results from ACTG (AIDS Clinical Trials Group) study #261 (see below), which were not yet available, would be the basis for granting approval.

On April 4, 1997, the FDA granted accelerated approval to Pharmacia & Upjohn to market delavirdine (Rescriptor). Delavirdine is a non-nucleoside reverse transcriptase inhibitor (NNRTI). NNRTIs are the third class of antiretroviral drugs approved for treating HIV and AIDS. Delavirdine comes in 100 mg tablets and is to be taken at a dose of 400 mg three times per day. Upjohn says it can be taken with or without food.

CD4 increases and viral load reductions associated with delavirdine in studies so far conducted have indicated slight benefits when compared to the other treatment groups in the studies; but data shows delavirdine has an antiviral effect demonstrated by an initial 1 to 1.3 log reduction that was observed in a monotherapy study.

As with all NNRTIs, resistance develops quickly, faster than both protease inhibitors and nucleosides, and the initial viral load reduction rebounds quickly. A NNRTI needs to be used in a carefully selected regimen designed to adequately suppress viral load so that resistance is delayed or prevented. There are two key studies that demonstrate such use with nevirapine. A key to the approval of nevirapine were the CD4 increases and viral load reductions shown in study #1046. It examined the use of nevirapine in a triple drug combination (with AZT+ddI) in individuals who were treatment-naive. The data extended to 76 weeks is in this issue. The preliminary results from the Vancouver study of indinavir+nevirapine+3TC for individuals with <50 CD4 also indicated efficacy. (See Study Results, Page 13)

Unfortunately, these types of crucial studies using delavirdine have not yet been conducted by Pharmacia & Upjohn. In each of the 3 delavirdine studies below, there was some prior drug experience among the participants, but none of the studies were designed for treatment-naive individuals. Upjohn is now planning a number of such studies, but results will not be available for a while. Following are reports of the data from three studies of delavirdine submitted to the FDA.

Study 0017. This trial compared delavirdine+ddI to ddI alone. Mean baseline CD4 was 142 cells and mean baseline viral load was 5.77 log (about 590,000 copies/ml). About 80% of study participants had no prior ddI-experience, about 20% had <4 months prior ddI-experience. The average prior AZT-experience was 13 to 14 months.

Mean CD4 changes from baseline

	8 weeks	24 weeks	52 weeks
DLV + ddI	+30 CD4 (n=494)	+10 CD4 (n=368)	+15 CD4 (n=154)
ddI	+15 CD4 (n=498)	+10 CD4 (n=401)	+10 CD4 (n=165)

Mean Changes in Viral Load (HIV RNA) from Baseline

	4 weeks	24 weeks	52 weeks
DLV + ddI	-0.9 log	-0.5 log	-0.5 log
ddI	-0.5 log	-0.5 log	-0.6 log

The number of study participants (n) evaluated at each time point was about the same as it was for the CD4 evaluations at the same time points.

Study 0021. This study of 718 individuals compared delavirdine+AZT to AZT alone. The mean baseline CD4 was 334 cells, and the mean baseline viral load was 5.25 log (about 178,000 copies/ml). Sixty percent were treatment-naive and 40% had less than 6 months AZT experience. At weeks 2, 24 and 52 the mean CD4 increases from baseline for the delavirdine+AZT group were +47, +13 and +28, respectively. For the AZT alone group the mean changes from baseline at weeks 2, 24, and 52 were +40, +9, and -37.

Mean Changes in Viral Load (HIV RNA) From Baseline

	4 wks	8 wks	16 wks	32 wks	52 wks
DLV + AZT	-1 log	-0.63 log	-0.60 log	-0.57 log	-0.48 log
AZT	-0.5 log	-0.46 log	-0.37 log	-0.32 log	-0.33 log

The number of study participants (n) at 4, 8, 16, 32, and 52 weeks were about 151, 152, 134, 126, and 60.

Study ACTG 261. Because the vote on whether or not to recommend approval at the committee hearing was deadlocked it was agreed that the decision on approval should rest upon the viral load results from this study. 544 participants were randomized to one of 4 treatment arms: delavirdine+AZT, delavirdine+ddI, delavirdine+AZT+ddI, or AZT+ddI. Parti-cipants were either treatment-naive or had less than 6 months of either prior AZT or ddI experience (but not both). Thirty-seven percent reported previous experience (196 with AZT and 6 with ddI). The mean baseline CD4 was 296 cells, and the mean baseline viral load was 4.45 log (28,260 copies/ml).

Mean Changes in CD4 From Baseline

	4 wks	12 wks	24 wks	32 wks	48 wks
DLV+AZT+ddI	+35	+75	+60	+75	+60
DLV+AZT	+25	+20	+10	0	-20
DLV+ddI	+40	+30	+30	+35	+20
AZT+ddI	+40	+65	+70	+60	+40

The CD4 measures were obtained by visual observation of a graph line chart and so are approximations.

Mean Changes in Viral Load (HIV RNA) From Baseline

	4 wks	12 wks	24 wks	32 wks
DLV+AZT+ddI	-1.25 log	-1.1 log	-0.88 log	-0.91 log
DLV+AZT	-0.65 log	-0.3 log	-0.22 log	-0.37 log
DLV+ddI	-0.90 log	-0.7 log	-0.71 log	-0.70 log
AZT+ddI	-1.0 log	-0.8 log	-0.68 log	-0.70 log

The viral load measures were obtained by visual observation of a graph line chart and so are approximations.

Side Effects and Toxicities

Rash. The potential for development of a skin rash is a side effect concern associated with NNRTIs. A skin rash attributable to delavirdine (taking 400 mg tid) has occurred in 18% of study participants receiving combination therapies in phase II and III trials. In these trials, 4.3% discontinued treatment due to rash, and dose escalation did not significantly reduce the incidence of rash. The skin rash was more common for those with lower CD4 counts and usually occurred within 1 to 3 weeks. Rash classified as severe (grade II or IV) that was treatment related occurred in 3 to 4% of study participants in 0017 and 0021. In most cases the duration of the rash was 5 to 14 days and did not require dose reduction or discontinuation. Upjohn reports that of those who experienced a rash, 85 to 90% were able to continue or stop and rechallenge. If a treatment interruption was required due to rash, most were able to resume therapy upon rechallenge with delavirdine. Stevens Johnson Syndrome was rarely seen but resolved after discontinuing delavirdine. For comparison, the incidence of rash in studies due to nevirapine (Viramune) is

reported at 16%; of that 16%, 4.1% were grade III and 1.1% were grade IV. 5.9% discontinued from studies with the presence of any degree of rash, 4.8% discontinued with a grade 3 or 4 rash.

Upjohn suggests the following guideline for treatment of a rash due to delavirdine: continue drug, take Benadryl or Atarax for itching, don't get sunburned, be aware that if the rash is to become severe it does so in the first three days (of continued dosing despite rash), and watch the rash closely. Relief from symptoms can be seen with medications and usually resolves within 5 to 14 days.

Anyone experiencing severe rash accompanied by symptoms such as fever, blistering, oral lesions, sores involving the mucous membrane (sores in mouth, eyes, or vagina), conjunctivitis, swelling, muscle or joint aches "should discontinue delavirdine and call their doctor." After one month of therapy, it is unlikely that a rash should appear unless their have been prolonged treatment interruptions.

Liver Function Tests (LFTs). In clinical studies the incidence rate of elevated LFTs appears to be 1.5% due to delavirdine therapy. Other side effects associated with delavirdine that have been reported but at a low incidence rate are headache, fatigue, nausea (1.5-4.2%), diarrhea, and vomiting.

Cross-resistance. It appears as though NNRTIs have common resistance mutations and that resistance to one may cause cross-resistance to others.

Drug Interactions. Delavirdine is processed through the liver in a similar way as protease inhibitors and other NNRTIs. It is crucial to be aware of potential interactions with other drugs you take with delavirdine. Consult with your doctor regarding this.

Interactions with Protease Inhibitors

Only preliminary studies have been conducted exploring the dosing levels when combining delavirdine with any protease inhibitor. The studies reviewed below were conducted in healthy volunteers as opposed to HIV-infected individuals. Before making any treatment decisions we highly recommend consulting with a knowledgeable physician.

Indinavir. Preliminary data is available from a study (n=14) which indicates that delavirdine inhibits the metabolism of indinavir. The delavirdine package insert says, a 400 mg single dose of indinavir with delavirdine (400 mg 3x/day) resulted in an indinavir AUC value slightly less than that observed following taking an 800 mg dose of indinavir alone, which is the recommended dose of indinavir. Area under the curve refers to overall blood level, see nevirapine article section on interactions with protease inhibitors for additional discussion. At the NATAP forum, William Freimuth MD from Upjohn, related the preliminary results of combining 400 mg delavirdine (3X/day) with a single dose of 400 mg indinavir when compared to taking a single dose of 800 mg indinavir. When taking both drugs the AUC was "basically equivalent", the Cmax or peak drug level was reduced by almost one half, and the indinavir trough (Cmin) at 8 hrs was about 2-fold higher.

The package insert says, a 600 mg dose of indinavir taken with delavirdine (400 mg 3X/day) resulted in indinavir AUC values approximately 40% greater than those observed following taking an 800 mg dose of indinavir alone. At the forum, Dr. Freimuth related that the peak or Cmax of indinavir when taking this dosing regimen (600 mg indinavir), compared to the 800 mg indinavir dose, is reduced but not nearly as much as with the 400 mg indinavir dose. He said, the AUC of indinavir is increased by about 50% from taking the combination when compared to the AUC resulting from an indinavir dose of 800 mg; an increase in the trough of indinavir of about 4-fold results from the combination compared to the trough for the 800 mg indinavir dose. Upjohn has not yet conducted this experiment combining 800 mg indinavir with 400 mg tid delavirdine. However, Freimuth speculated that the peak would be comparable or slightly higher, and the

trough level would be 5-10 fold higher than the trough level normally seen with the usual indinavir dose of 800 mg. A single dose of indinavir had no effect on delavirdine blood levels.

Saquinavir. Preliminary data is available from a study of the current formulation of saquinavir at the approved dose of 600 mg every 8 hrs combined with the normal dose of delavirdine (400 mg 3X/day). The AUC (overall drug concentration in the blood) of the currently approved saquinavir as well as the Cmin or trough were increased about 5-fold compared to the levels normally achieved by the current formulation of saquinavir. Dr. Freimuth said these concentrations of saquinavir were similar to those achieved by using a daily total dose of 7200 mg of saquinavir. There was a modest reduction of about 15% in delavirdine Cmin or trough, which Dr. Freimuth said was not significant. Reversible elevations in LFTs were observed in 13% of the study participants, and 6% had grade 3 or 4 LFT elevations; therefore, Upjohn recommends frequent monitoring of LFT levels. Roche has submitted an application for approval to the FDA for the new more bioavailable soft-gel capsule (SGC) saquinavir. It is expected to be available during 4th quarter 1997.

Ritonavir. No studies have yet been conducted of delavirdine and ritonavir at their recommended doses. Preliminary results of studying delavirdine 300 mg ritonavir bid (twice/day) with delavirdine 400 mg to 600 mg bid indicated no evidence of an interaction.

CAUTION. Currently, there are no safety and efficacy data available from the use of the combination of delavirdine with indinavir, ritonavir or nelfinavir; but if considering the combination of indinavir with delavirdine, Upjohn suggests a dose reduction of indinavir to 600 mg every 8 hrs should be considered. There is limited safety data for combining saquinavir with delavirdine but no efficacy data. Using incorrect doses can cause resistance or harmful side effects to occur. It is expected that eventually we will learn the appropriate dosing regimens for combining delavirdine with all of the protease inhibitor therapies.

1592U89 Compassionate Use Program

Glaxo Wellcome announced on April 29, 1997 that a compassionate use program will be started for children, adults with severe dementia and for adults with advanced HIV in the United States, Canada, Europe and Australia. Drug for 2,500 individuals will be available for the entire program encompassing the three groups described above and the three geographical areas. It is anticipated that about 500 individuals will apply for the pediatrics and dementia programs. The remaining drug supply will be apportioned by the incidence of HIV in the three geographical areas. The pediatrics program is expected to begin in June, and its preliminary entry criteria is viral load >100,000, CD4 <15%, and person has failed at least one NRTI. For the AIDS Dementia Complex Program, the preliminary criteria are severe dementia (to be defined), diagnosed by a neurologist, and prior treatment with AZT. For the adult program, a starting date in July is being planned. The preliminary entry criteria are viral load >50,000 copies/ml, CD4 <100, and failed two NRTIs and one protease inhibitor. Preliminary plans are that Glaxo Wellcome will run the program through geographically dispersed centers which will include the major cities for incidence of HIV-infection. In addition, Glaxo announced that a larger expanded access program is expected to start in early 1998.

It is important to remember two points. Adding any one new drug to a failing regimen is usually considered a set-up for the quick development of resistance. For example, if you are taking Crixivan +AZT/3TC and your viral load is 50,000, you are failing that regimen, merely adding 1592 may not be an optimal use of 1592. Even if your viral load initially is reduced to undetectable after adding 1592, you are risking that within months resistance might emerge and your viral load will rebound because you may already be resistant to any of the other drugs in that combination due to virus replication. If your viral load rebounds or doesn't get reduced at all after starting 1592 you may have lost the potential benefit from 1592. It is recommended that when starting a new drug, that at least 2 new drugs are started together, and preferably 3 new drugs.

Second, we have limited information about cross-resistance between 1592 and other nucleosides. Much more information on how to best use 1592 will be available next year when Glaxo applies to the FDA for approval. You will be better equipped with information at that time and will be better able to know how 1592 might be best used for you.

Glaxo Wellcome will announce an 800 number for the program before the end of June. NATAP will provide the 800 number and further details on our web site or you can call our office for more information.

A number of ACTG and industry studies are being planned now for individuals whose treatment is failing them. A number of novel or unique drug combinations some of which will include 1592, as well as PMEA and DMP-266, will be utilized in these studies. These trials are expected to start rolling out soon. See your local study sites for information.

1592 Editorial. 1592U89 is a NRT inhibitor like AZT and d4T. It is the only new nucleoside at this time. Based on preliminary data it appears to be very potent. Individuals who have exhausted most viable treatment options and have advanced HIV may be able to benefit greatly from 1592. The only data available is based on about 30 individuals who received 1592 for 12 weeks. The drug reduced their viral load about 2 log and increased their about CD4 75 to 100 cells.

Community activists have been holding discussions with Glaxo Wellcome about this program for some time now and have expressed dissatisfaction to the company about its limited size. The company says they are unable to increase supply at this time, and they are not certain about the safety and efficacy of this drug for those who would access it through this program.

The purpose of a compassionate access program is to provide a potentially life saving opportunity to individuals who may have exhausted available treatment options or have few remaining, and have advanced HIV due to having developed resistance to protease inhibitors and/or other available drugs. I believe the number of individuals in the USA who would fall into this situation exceeds the size of the program. All available resources should be devoted to increasing the size of the program to assure that such individuals who want to enter this program can do so.

NUCLEOSIDES

D4T+3TC: For Treatment-Naive and Experienced

At the 4th Retrovirus Conference in January '97, results were reported from several studies of the double nucleoside combination of d4T+3TC. They are the first data reported from an official study of this double nucleoside combination. These studies indicate that the combination of d4T/3TC can be an effective antiviral therapy for both treatment naive and experienced.

A group from the Netherlands, including Dr. Joep Lange, reported preliminary results from a small (31 participants) open-label study comparing AZT/3TC to d4T/3TC as a therapy for individuals who were treatment-naive (no prior anti-HIV therapy). Twelve weeks of blood HIV-RNA and CSF HIV-RNA were reported. The mean reduction in blood HIV-RNA at 12 weeks was 1.24 log for those receiving AZT/3TC (baseline RNA was 4.61 log, or about 40,000 copies/ml) and 1.35 log for those receiving d4T/3TC (baseline 4.19 log, or about 15,500 copies/ml).

Similar reductions were seen in CSF (Cerebral Spinal Fluid) viral load. All participants had detectable CSF HIV-RNA at baseline (prior to receiving study drugs) with a mean of 3.57 log, and all had declined to undetectable by 12 weeks. The authors concluded from the preliminary data of this small ongoing study, "that from a CNS (Central Nervous System) perspective AZT/3TC and d4T/3TC were equivalent nucleoside analogue combinations."

A group from Vancouver, Canada which included Dr. Julio Montaner reported results from a study assessing the short-term antiviral effect and tolerability of d4T/3TC for 48 individuals who were

unable to tolerate AZT or displayed disease progression despite AZT therapy. Median baseline CD4 and HIV RNA were 135 cells and 4.7 log (about 50,000 copies/ml). An antiviral response was defined as a reduction of 1 log or greater by week 8. Twenty participants had such a response. Study participants with prior d4T experience or prior 3TC experience were less likely to respond with a 1 log or greater antiviral reduction; those with higher baseline CD4 were more likely to respond with a 1 log or greater antiviral effect. The authors reported that the length of time of prior AZT experience was not predictive of a viral load response. A median peak 1.5 log reduction was observed at week 2. At week 8, the median RNA reduction was 0.97 log. The authors concluded that participants with no prior experience with d4T or 3TC and with higher CD4 at baseline were more likely to have an antiviral effect.

Dr. Christine Katlama of France, reported 6 months of data from an open-label study called Altis I and II, where both treatment-naive and treatment-experienced individuals received d4T+3TC. The study was designed for those with CD4 count between 50-400 and viral load above 15,000. The d4T dose was either 40 or 30 mg bid (twice per day), and the 3TC dose was 150 mg bid. After 6 months of treatment, the Altis Plus Study began where participants in Altis I and II with HIV RNA above 3,000 were permitted to add ritonavir (n=39). Those with HIV RNA below 3,000 remained on d4T/3TC (n=35). Follow-up data will be reported. Exclusion criteria included, neuropathy above grade 2 and liver enzymes greater than 5 times normal.

Individuals in Altis I had no prior antiretroviral treatment. While, those in Altis II had experience using AZT, ddI, or ddC either as monotherapy or in combination. In Altis II, 49% had experience with monotherapy, while 51% had combination experience: 34% with AZT/ddC, 17% with AZT/ddI. The median duration of prior treatment-experience for those in Altis II was 35 months.

Of the Altis II participants (n=41), 41% were asymptomatic and 59% were classified as CDC Group II-III (more symptomatic). Of the Altis I participants (n=42), 71% were asymptomatic and 29% were classified as CDC Group II-III.

The median baseline characteristics and changes in CD4 and viral load:

	Altis I	**Altis II**
CD4		
baseline	258 CD4 count (n=42)	172 CD4 count (n=41)
increase at 24 weeks	+108 CD4 (n=42)	+46 CD4 (n=40)
HIV RNA		
baseline	76,500 copies/ml (4.88 log)	91,255 copies/ml (4.96 log)
peak decrease by wk 4	(n=42)	(n=41)
decrease at 24 weeks	-2.0 log (n=42)	-1.30 log (n=40)
	-1.66 log (n=42)	-0.66 log (n=40)
% below 3000 copies	57%	22%
% below 200 copies	21%	5%

In Altis I, 95% of participants had greater than a 0.6 log reduction from baseline. The analysis in the following table suggests that baseline viral load may have some predictive value of how low one's viral load might be reduced. It also indicates that more extensive previous nucleoside experience for the participants in this study may be a factor in the response to the study therapy.

Predictive Factors For Antiviral Response

Altis I	**% with HIV RNA below 3000 copies/ml**
baseline HIV RNA (copies/ml):	
above 120,000	29%
40-120,000	64%
below 40,000	79%

Altis II	
prior treatment experience:	**% with HIV RNA reduction greater than 0.60 log**
combination experience	22%
monotherapy experience	78%

At the Conference, Dale Kempf of Abbott Labs and others reported results from a study they conducted titled The Duration of Viral Suppression is Predicted by Viral Load During Protease Therapy, a retrospective analysis of individuals in 3 ritonavir clinical studies whose viral load rebounded. A retrospective study means that the study was not designed to answer the question your asking.

The authors concluded that the durability of response did not correlate with baseline viral load, initial viral load decline, baseline CD4, or magnitude of CD4 increase, while the data in Table 2 suggests that baseline RNA may predict how low one's viral load may be reduced. Kempf et. al. concluded that they observed a strong relationship between the lowest level of viral load achieved from therapy and the durability of that maximal suppression of viral load, that "the degree of suppression of viral replication is highly predictive of the durability of response."

In the Kempf study those with viral load suppression to undetectable exhibited greater durability of viral load suppression. More details of the study are available on the NATAP web site.

The entire adverse events profile for participants in Altis I and II is available on the NATAP web site. Briefly, moderate or grade 1/2 adverse events included a 36% incidence rate of elevated liver enzymes, a 6% incidence rate for increased CPK, incidence rate of 21% for increased LDH, a 9.6% incidence rate for increased amylase/lipase, 9.6% increase in incidence rate for a neurological symptom called parasthesias, and a 7.2% incidence rate for rash. There was a grade 3/4 adverse events incidence rate of 7.2% for elevated liver enzymes. Two individuals discontinued study treatments due to adverse events.

D4T+DDI: Treatment Naive and Experienced

The data reported below is the first available from an official study of this double-combination.

Treatment Naive. In April 1997 at the 10th International Conference on Antiviral Research (ICAR) in Atlanta, Dr. Richard Pollard reported an early final analysis of a small open-label study of the double nucleoside combination of d4T+ddI in relatively healthy treatment-naive individuals.

Resistance to both d4T and ddI has been relatively slow to develop. The development of specific mutations responsible for d4T resistance have been difficult to identify, and it has not been clearly identified what may be other reasons for d4T failure. (See article on nucleoside resistance on the NATAP web site)

The study. Ninety four participants were randomized, 86 received therapy and for purposes of study analysis 66 had baseline viral loads " 1,000. All participants were treatment-naive with median baseline CD4 counts of about 330 cells and HIV-RNA of about 25,000 to 31,600 copies/ml (4.4 - 4.5 log). Participants were randomized to following dose regimens (doses adjusted for weight):

- group A- ddI 100 mg/bid + d4T 10 mg/bid;
- group B- ddI 100 mg/bid + d4T 20 mg/bid;
- group C- ddI 100 mg/bid + d4T 40 mg/bid;
- group D- ddI 200 mg/bid + d4T 20 mg/bid;
- group E- ddI 200 mg/bid + d4T 40 mg/bid.

The full dose of ddI is normally 200 mg bid and the full dose of d4T is normally 40 mg bid.

Mean change from baseline in CD4 counts and HIV-RNA (viral load-VL)

	CD4 24 wks	CD4 51 wks	VL 24 wks	VL 51 wks
groups A & B	+85	+60	-1.2 log	-1 log
groups C, D, & E	+85	+160	-1.2 log	-1.3 log

The changes in viral load are for those individuals with at least 1,000 copies/ml at baseline, while changes in CD4 are for all participants. At week 51, n=44 for the CD4 data and at week 51 n=30 for the VL data. Both CD4 and viral load values in table were taken by visual observation of line graphs, so they are approximations.

Pollard stated that the viral load and CD4 differences between the two groups in the table are statistically significant. He is recommending full dose of both drugs for use in treatment based on the CD4 and viral load changes and the low incidence of peripheral neuropathy in this group of less advanced and treatment-naive individuals, but persons with more advanced HIV and more treatment-experience tend to develop peripheral neuropathy more easily and Pollard has narrowly defined peripheral neuropathy.

AZT+3TC.

It is usually accepted that it is difficult to compare results between studies because study populations are different. However for a reference, the NUCA 3001 study sponsored by Glaxo Wellcome examined treatment-naive individuals (< 4 weeks previous AZT use). Those receiving AZT (200 mg 3X/day) + 3TC (150 mg 2X/day) had median baseline CD4 of 364 cells, and median baseline viral load of 4.4 log (about 25,000 copies/ml). The Roche PCR test with a lower limit of detection of 200 copies/ml was used. Within the first 4 weeks of the study, peak reductions from baseline in viral load were achieved. They were: -1.19 log by the 3TC monotherapy arm (300 mg 2X/day), which returned to a -0.5 log reduction from baseline at week 24 and about -1.6 log for those receiving AZT/3TC (150 mg 3TC 2x/day). After 52 weeks for those taking AZT/3TC (150 mg bid), CD4 increases were about 69 cells, and viral load reductions from baseline were about -0.8 log.

In a subgroup of 224 study participants with baseline viral load " 20,000 copies/ml, the mean maximum reduction was -2.11 log. In this group the percentage of participants with at least one viral load measure while receiving study treatment that showed a 2 log or greater reduction was 61.

Serious Adverse Events (d4T/ddI study). Peripheral neuropathy: 2 cases - one in group A and one in group C. The one in group C developed a grade 3 neuropathy, drug was stopped and restarted 4 weeks later with reduced doses (50 mg/bid ddI - 20 mg/bid d4T). Diarrhea: 3 cases- one each in groups B, C and D. Abdominal pain: 3 cases- 2 in group D, 1 in group E. Lipase elevations: 2 each in groups A and D, 3 in group B. Liver enzyme elevations: 3 each in groups A and B, 2 each in groups D and E. Neutropenia: 1 each in groups A, B, and E.

There were no discontinuations from study drugs. Dr. Pollard defined peripheral neuropathy as the development of pain. Less severe symptoms such as tingling or numbness were not defined as neuropathy. As such, Pollard concluded that the combination is generally well-tolerated. The combination of d4T+ddI is being evaluated in several other studies exploring a variety of treatment strategies for both treatment-naive and experienced in combinations utilizing protease inhibitors and NNRTIs.

Treatment-Experienced

At the 4th Retroviral Conference in January 1997, the preliminary results of two small open-label studies of d4T+ddI in treatment-experienced individuals were presented. These study results show that this combination can be effective for individuals with prior treatment experience. In the first study (Table 4) 25 individuals were treated with the standard doses of both drugs, 18 of whom were experienced with AZT, 3 with ddI, 2 with ddC, 1 with AZT/ddC and 1 had no prior treatment-experience. Mean baseline CD4 counts was 116 cells and viral load was 5.3 log (199,790 copies/ml).

Preliminary Mean changes in HIV RNA and CD4:

	mean viral load	% undetect (< 500 copies)	mean CD4
4 weeks	-1.0 n=21	7 (33%) n=21	+57 n324
12 weeks	-0.9 n=21	7 (33%) n=21	+45 n=21

24 weeks	-0.7 n=13	4 (33%) n=17	+38 n=17

No AIDS defining events were reported during the study.

Safety. 4 persons discontinued from the study: 2 due to grade 2 peripheral neuropathy- complete recovery one month after d4T stopped; 1 due to grade 3 neuropathy- complete recovery three months after d4T stopped; 1 person developed asymptomatic grade 3 amylase - complete recovery I month after therapy. Although its incidence of occurrence is low, a potential toxicity associated with use of ddI is pancreatitis. Elevations in amylase and lipase are standard blood lab test which signals concern for this potential.

In the second study (Table 5), 60 individuals who had > 3 months prior NRTI-experience with the exclusion of ddI and d4T received open label d4T (40 mg bid) and ddI (200 mg bid).

Their prior treatment experience consisted of an average of 25 months AZT-experience and 11 months ddC-experience. Their mean baseline CD4 count was 217 and their HIV RNA was 5.0 log (100,000 copies/ml).

Preliminary Mean Changes in CD4 and Viral Load (undetectable is <500 copies)-

	mean HIV RNA	**> 1 log**	**> 2 log**	**< 500 copies**	**mean CD4**
4 weeks	-1.0 log	18 (53%)	7 (21%)	5 (15%)	+71
	n=34	n=34	n=34	n=34	n=53
12 weeks	-1.0 log	18 (51%)	7 (20%)	3 (9%)	+41
	n=35	n=35	n=35	n=35	n=44
24 weeks	-1.0 log	14 (42%)	4 (12%)	5 (15%)	+37
	n=33	n=33	n=33	n=33	n=33

Safety. 22/60 (37%) individuals experienced adverse events. Grade 2 peripheral neuropathy- 3 persons at weeks 12, 18, and 19; 2 discontinued therapy before week 24; all 3 improved off drug. Parasthesia (tingling and/or numbness) with subnormal neurological exam: 4 persons at weeks 3, 9, 11, and 12; 1 person reduced their d4T dose (80 to 60 mg daily) but did worse; 3 others continued therapy. Gastrointestinal (abdominal pain, flatulence, diarrhea): 10 persons but only 3 were related to study drugs and there was no modification of therapy required. Liver enzyme elevations (>5x upper limit of normal): 3 persons; 1 at week 12- d4T+ddI interruption; 1 person at week 24- d4T+ddI interruption; 1 person at week 18 continued drugs and improved at week 24. There were 6 persons (10%) who withdrew from the study by week 24: 4 due to side effects and 2 due to non-compliance with taking study drugs.

CNS Penetration. According to Bristol-Myers:

"After a single d4T 40 mg dose in 12 healthy subjects, CSF and simultaneous plasma

concentrations were determined. Mean CSF concentration was 40% of mean simultaneous plasma concentrations. Mean CSF concentration 4 to 5 hours post dose was 63.1 ng/ml (0.28 um). These results demonstrate that d4T does penetrate into the CSF and produces CSF concentration which exceed the ED50 of HIV clinical isolates."

It is generally conceded that d4T penetrates the CSF, but additional studies need to be conducted confirming the nature and extent of this CNS penetration. (See the discussion of CNS penetration in the Nevirapine article above.)

Protease Inhibitors

Nelfinavir (Viracept): New 10 Month Data and Cross-Resistance

As you may know by now, nelfinavir received FDA approval in March 1997 "for treatment of HIV when antiretroviral therapy is warranted." The approval was based upon changes in CD4 and viral load for participants in studies submitted to the FDA. There is no data yet on the effect of nelfinavir on HIV disease progression and survival but such a study comparing nelfinavir+nucleosides to ritonavir+nucleosides is ongoing.

In the last issue of NATAP Reports, we reported the results of nelfinavir study #511, in which 297 treatment-naive individuals (no prior experience using anti-HIV drugs, AZT, protease inhibitors, etc.) were randomized to receive nelfinavir in combination with AZT+3TC, or AZT/3TC alone.

Prior to receiving study drugs, the mean CD4 counts and viral load for the participants were 288 CD4 cells and 153,044 copies/ml, respectively. Two dose regimens of nelfinavir were studied--750 mg 3 times per day and 500 mg 3 times per day, but only the 750 mg tid dose received FDA approval.

For review, after 6 months, when using the 500 copies/ml viral load test those receiving 750 mg nelfinavir tid + AZT/3TC achieved a 2 log reduction in HIV RNA from baseline. When using the assay with sensitivity of 100 copies/ml the reduction achieved was 2.4 log. Those taking AZT/3TC achieved a 1.4 log reduction regardless of which test was used, and 20% were below the level of detection when using the 500 copy test.

10-Month Nelfinavir (NLF) Data

On April 7, 1997 at the 10th International Conference on Antiviral Research (ICAR) in Atlanta. Dr. Sharon Chapman of Agouron Pharmaceuticals reported preliminary 10-month (40 weeks) follow-up data for study 511.

Mean changes in HIV RNA and CD4 at 40 Weeks

	Mean CD4	**Mean viral load***	**% undetect (500 copies)**
NLF (750)+AZT/3TC (n=62)	+173	-2 log	84%
NLF (500)+AZT/3TC	+174	-1.8 log	60%

(n=39)			
AZT/3TC [#]	na	na	na

* The log reduction in viral load was calculated using the bDNA viral load test with a lower limit of detection of 500 copies. Some of the numbers in this table were taken by visual examination of a graph line chart, and so were approximated.

The participants receiving AZT/3TC alone were permitted additional therapy after the initial 6 month trial period.

Cross-Resistance

Agouron has preliminary data suggesting that if nelfinavir is the first protease inhibitor taken, and resistance develops, you could successfully switch to another protease inhibitor without cross-resistance developing. There is an unsettled difference of opinion over this issue. Others consulted believe cross-resistance will occur. What is the truth here? I do not know. This is one of many issues of about protease inhibitor cross-resistance that remain in dispute. Additional research and data is necessary to address cross-resistance concerns.

A related concern is how to treat persons who have developed resistance to protease inhibitors. A number of ACTG and industry sponsored trials are being planned to address this question. Several of these studies are expected to begin soon.

Is it possible to prevent cross-resistance?

Several researchers I have consulted with suggest that if you are using nelfinavir or any other protease inhibitor therapy and can quickly detect changes in viral load (suggesting resistance) by, for example, taking monthly viral load tests, it is possible that you may still be able to prevent cross-resistance by stopping your current therapy regimen immediately after detecting such a change (and confirming it with a 2nd test) and switching to a different regimen. At this point this is a theory which has not been explored.

A basis for this statement is that if resistance (mutations) begins to develop continuing the same drug will allow for additional resistance to develop which will increasingly encourage cross-resistance. However, they suggest if an individual is testing their viral load every several months it may not be possible to detect resistance soon enough to prevent cross-resistance.

However, according to Emilio Emini, PhD, Vice President of Antiviral and Vaccine Research, at Merck Research Labs:

"Cross-resistance may be inevitable once resistance to a protease inhibitor develops. Although you may be able to detect a viral load rebound quickly, background mutations may be developing to the extent where only extremely potent new therapy may be able to suppress the resistant virus."

The NATAP web site has a 9-page report on nelfinavir, which contains more extensive information regarding-- drug interactions, side effects, dosing, and more.

Double-Protease Studies

You should be warned that it is preliminary to experiment with any of the protease-protease combinations discussed below before proper dosing information is available from studies. Using wrong doses could result in the development of resistance to either one or both drug's or developing potentially harmful side effects. Preliminary information is available regarding changes

in blood levels for the double protease combinations described below, but this information is based on limited dosing experience. This data is generated from only one or several doses given to test subjects. Results from such studies are preliminary and may not reliably predict appropriate dosing. Subsequent human trials are necessary to test the safety, efficacy and proper dosing of double protease inhibitor combinations.

The remainder of 1997 and 1998 will be an interesting time because some results from the following studies will be forthcoming.

Indinavir + Nelfinavir

A pilot study has recently started exploring the combination of these two protease inhibitors. Currently, nelfinavir is taken 3X/day and indinavir is taken every 8 hours. Preliminary data indicates that when used in combination each drug generates increases in the blood levels of the other. The first goal of this study is to establish the safety of using this combination. The study will explore a bid dosing regimen, where each drug is taken twice daily or every 12 hours, with a light fat-free low protein meal for example, dry toast with jelly, apple juice, or skim milk. Essentially, this is the light meal recommended by Merck that can be taken with indinavir as an alternative to fasting before and after taking it. Participants in this study will be followed closely for safety, antiviral effect and the dynamics of the interactions between the two drugs. Whether or not future studies will be conducted hinge upon the results from this study.

Ritonavir + Indinavir

A small group of HIV-negative individuals are receiving several different dosing combinations of these two drugs to explore safety, efficacy and pharmacokinetics (changes in blood levels of each drug caused by using it in combination with the other). Study participants are receiving ritonavir and indinavir every 12 hours at dose levels well below the currently recommended doses for both drugs. As you may know, ritonavir increases the blood levels of other protease inhibitors. In combination with saquinavir, blood levels of saquinavir increase at least 20-fold. Again, the planning of future studies will hinge on the establishment of safety and adequate antiviral activity. Initial results indicate that ritonavir slightly lowered the peak (Cmax) blood levels of indinavir and raised the trough levels of indinavir. By early 1998, studies in HIV infected individuals should begin.

Nelfinavir + Ritonavir

The combination of these two protease inhibitors may also be promising and dosing could be twice a day. Preliminary data indicates that ritonavir increases nelfinavir blood levels favorably but that ritonavir blood levels may not be increased by nelfinavir. A study of this combination has not yet started but is soon expected.

141W94

This is a new protease inhibitor being developed by Glaxo Wellcome. Recently, a study began exploring it in combination with indinavir, nelfinavir and saquinavir. In preliminary studies 141W94 has a unique mutation profile. It is possible that virus resistant to some other protease inhibitors may be sensitive to 141. This unique mutation profile may also aid in synergistically combining it in double protease combinations.

Nelfinavir + Saquinavir

In March 1997 at the International Society for Antiviral Research Conference in NYC, Steve Kravcik (from the Ottawa General Hospital, Ontario) reported an update of preliminary data for the combination of nelfinavir and saquinavir.

Fourteen individuals (CD4 - 25-500, HIV RNA->20,000) received the double protease therapy.

Kravcik reported that the impact of 750 mg nelfinavir given tid (3 times/day) on a single dose of 1200 mg SGC saquinavir was an overall 5-fold increase in blood levels of saquinavir. Saquinavir SGC did not significantly affect nelfinavir blood levels (increased 18%).

The doses selected for the participants in the nelfinavir-saquinavir study were a regimen of nelfinavir 750 mg tid (the FDA approved nelfinavir dose regimen), with a saquinavir SGC dose of 800 mg tid. Prior to starting study drugs, the participants' baseline median CD4 was 327 cells and their viral load was 40,000 copies/ml. Previously, 12-week data had been reported at the 4th Retroviral Conference in January 1997. Now, Kravcik reported 5 month preliminary data for 13 individuals.

The median viral load reduction at 20 weeks was about -2 log and their CD4 increase was >70 cells. 7/13 were "undetectable" (<500 copies). 2/13 had to temporarily stop study meds due to OI-related concerns; 1/13 had a viral load level of 500-1000. 1/13 had a viral load level of 1000. 2/13 had higher viral loads. Kravcik reported study drugs were well-tolerated, without grade 3 or 4 medication related adverse events or lab abnormalities. These study results are preliminary, based on a small number of individuals. Several additional studies are underway or being planned exploring this double protease combination.

Indinavir Trials Stopped: ACTG 320, 028

Within the last few months, two clinical endpoint studies of indinavir were stopped. In ACTG (AIDS Clinical Trials Group) 320, indinavir+AZT (or d4T) +3TC was compared to AZT (or d4T) +3TC. The study was halted because those receiving indinavir plus the 2 nucleosides had less disease progression and deaths than those receiving the 2 nucleosides alone. This study included 1,146 individuals with <200 CD4. Participants were protease inhibitor naive, had < 7 days of 3TC experience, and > 3 months prior AZT experience. Merck's study 028 was conducted in Brazil for 996 individuals and was designed for treatment-naive persons with CD4 between 50 to 250. The study began in April 1995 and participants received indinavir+AZT, indinavir alone, or AZT alone. ACTG 320 began around January 1996.

Summary Table of Disease Progression and Death in ACTG 320

	AZT (or d4T) + 3TC	**IDV+AZT (or d4T) + 3TC**
Total (n=1,146)	*n=579*	*n=577*
1st Clinical Event(AIDS/death)	63 (11%)	33 (6%)
Death	18 (3%)	8 (1.4%)
Entry CD4 <50	*n=220*	*n=219*
1st Clinical Event (AIDS/death)	44 (20%)	23 (11%)
Death	13 (6%)	5 (2.3%)
Entry CD4 >50 to 200	*n=359*	*n=358*

1st Clinical Event	19 (5%)	10 (3%)
Death	5 (1.4%)	3 (.84%)

Those who were AZT intolerant at study entry were permitted to substitute d4T. Those who experienced nucleoside related toxicities or disease progression short of a protocol defined AIDS event were permitted to change their 2 nucleoside drugs. Only 3 participants started the study using d4T instead of AZT, and a total of 106 changed their nucleosides prior to developing an AIDS defining event: 69 who were initially taking AZT+3TC and 37 who were initially taking indinavir+AZT/3TC.

In ACTG 320, there was a 28% dropout rate in the double nucleoside arm versus 11% in the indinavir 3-drug arm. About 50% of these premature withdrawals were because subjects wanted open-label protease inhibitor therapy and/or were concerned about a high viral load. If not for this occurrence the differences in progression rates between the two study arms might be even greater.

The data analysis in the table below of study 028 is preliminary. The Crixivan monotherapy arm reduced the risk of development of an AIDS-defining event by 61% when compared to the AZT arm. The Crixivan+AZT arm reduced this risk by 70% when compared to the AZT arm. There were a total of 107/996 participants who experienced protocol defined clinical events (opportunistic infections, cancer, or death). The average median follow-up was

58 weeks (12-102 weeks).

Study 028 Summary

	HIV RNA	**CD4**	**500 copies**	**risk**	**#clinical events**
Crix+AZT	-1.03 log	+112	42%	70%*	6% (20)
Crixivan	-0.76 log	+103	34%	61%*	7.8% (26)
AZT	-0.25 log	+21	9%	-	18% (61)

* Both Crixivan arms demonstrated statistical significance compared to the AZT arm. But, the difference between the two Crixivan arms were not statistically significant.

It is widely accepted that Crixivan or any protease inhibitor in combination with only one approved nucleoside is a sub-optimal therapy. Such a regimen is not designed to lower and sustain a viral load below detection.

New FDA Proposal For Viral Load and Clinical Endpoint Studies

On May 16th at the FDA, officials from the agency hosted a small meeting for community advocates where they previewed an outline of their tentative plans for changing the criteria by which a new drug would be judged for both accelerated approval and full approval.

Currently, to receive accelerated approval, a new AIDS drug is judged by its effect on changes in CD4 and viral load. To receive full approval a new drug must prove that it delays disease progression and improves survival. ACTG 320 and study 028 were designed to address the regulatory requirements for receiving full approval. Some feel participants in those studies suffered disease progression and death unnecessarily. Others feel traditional clinical endpoint studies are necessary, although they admit such studies may no longer be feasible to conduct. I feel it is unethical to ask prospective study participants to risk randomization to what may be for them a sub-optimal treatment arm.

In addition to current criteria of CD4 and viral load changes, the FDA is proposing to use the percentage of participants in a study whose viral load is undetectable as a new criteria for accelerated approval. For full approval the FDA proposes to use CD4 and viral load changes in addition to measuring how may remain undetectable and for how long rather than measuring survival and disease progression; but a drug company would not be prohibited from conducting a traditional clinical endpoint study. A public joint meeting in July of the FDA and the Antiviral Drug Advisory Committee will explore this question. A more detailed report on the May 16th meeting is available on the web site.

An important concern to many is the use of a sub-optimal treatment arm in a clinical study or for that matter use of sub-optimal therapy in real practice. It is a complicated issue and at the May 16th meeting the FDA said they could not dictate which control arms should be used in a study.

A number of AIDS researchers maintain that any therapy regimen that is not designed to completely suppress viral replication to undetectable (below 50 copies/ml may be preferable) is sub-optimal. For example, if your viral load is 70,000 a double-nucleoside regimen (for example, AZT/3TC or d4T/ddI) is unlikely to lower your viral load to undetectable. If viral load is not suppressed to undetectable more active viral replication is permitted which may in turn allow resistance to develop to the drugs that you're taking. Once resistance to a drug develops you may have lost its value in the future.

Other researchers say there are additional considerations suggesting that suppressing viral load to undetectable may not be necessary or feasible for everyone with HIV. Some of these reasons are: saving treatment options; the possibility that maintaining viral load at a low level, say 5,000, may suffice in the long run, but some experts feel viral activity at any level above undetectable will allow viral load to rebound quickly; difficulty for some patients to be compliant over a long period of time; the at times difficult tolerability of some protease inhibitor side effects; the cost and access difficulties associated with protease inhibitors for some people.

ABT-378

In the last issue of NATAP Reports we discussed this new protease inhibitor which is in an early stage of development by Abbott Labs. It is currently still being studied in HIV negative volunteers to obtain as much pharmacokinetic information as possible before proceeding to the next stage of study in HIV-positive individuals. As we stated previously, enhancement of ABT-378 blood levels is very sensitive to low levels of ritonavir and were so well sustained in pre-clinical research that once-a-day dosing will be explored. Doses of between 50-200 mg of ritonavir will be explored in combination with ABT-378. If successful, Abbott may develop one capsule combining both drugs. ABT-378 has displayed much more potency than ritonavir in its early laboratory and animal studies. It has shown an ability to suppress ritonavir resistant virus. However, it is important to reserve judgment because in such early stages of development a number of obstacles can still emerge. Safety, toxicity, and efficacy remain to be explored in HIV positive individuals.

Roche Submits New Drug Application to FDA for SGC Saquinavir

The currently available saquinavir formulation is the hard-gel capsule. Studies have been ongoing of the new SGC (soft-gel capsule) formulation of saquinavir. Roche has just submitted an application for approval of the SGC to the FDA. The overall exposure of the SGC is increased 8 to 10-fold over that of the hard-gel capsule which has a low bioavailability of only 4%. The dose that Roche is using in their SQV-SGC studies is 1200 mg 3x/day (3600 mg total daily dose). This dose gives exposure similar to 7200 mg(total daily dose) of the older (hard-gel capsule) formulation of saquinavir. The SGC saquinavir is expected to be available during the 4th quarter of 1997. In a monotherapy trial (n=22) of SGC saquinavir the peak viral load reduction reported at 8 weeks was 1.43 log. Preliminary data from a small number of treatment-naive individuals who received the SGC-saquinavir with AZT/3TC over only an 8-week period appears encouraging, but more extensive data available in the near future should be more revealing.

New Bristol Myers Protease Inhibitors

On June 9, 1997, Bristol Myers Squibb announced they had acquired rights to two Ciba Geigy protease inhibitors, CGP 61755 and CGP 73547. CGP 61755 is now called BMS 234475, and CGP 73547 is named BMS 232623. The latter is in an earlier stage of development but the former, BMS 234475, is now entering a phase II clinical trial in Amsterdam in June. Thirty-two treatment-naive individuals will receive either indinavir+ d4T/3TC or one of two doses of BMS 234475 with d4T/3TC. Two weeks of monotherapy with BMS 234475 will be followed by 10 weeks of triple therapy to examine safety and efficacy.

Bis-Pom PMEA

Bis-Pom PMEA, also known as adefovir dipivoxil, is an inhibitor of reverse transcriptase but belongs to a new class of antivirals called nucleotides, which appear to have a different mechanism of action than nucleosides. Bis Pom PMEA is taken in a tablet once a day with or without food, but must be taken with oral L-carnitine 500 mg once per day because PMEA is associated at high doses with a decrease in serum (blood) carnitine levels. L-Carnitine is a food supplement available over-the-counter. PMEA is a broad spectrum antiviral which means it may have application against other viruses such as herpes, CMV and hepatitis B. Preliminary clinical results and in vitro studies suggest that the development of resistance may not be as great a concern as it has been with protease inhibitors, NNRTIs and nucleosides.

Another feature of PMEA is that the drug does not exit quickly from the cell it enters; a reservoir of drug is established within the cell. This may be responsible for its long half-life and the once-a-day dosing.

A phase II trial enrolled 72 individuals randomized to 125 mg once per day (n=24), 250 mg (n=24) once per day or to placebo (n=24); participants were not taking any other anti-HIV drugs. They had CD4 >200 and viral load >10,000 copies/ml. After an initial phase of 12 weeks, the median reduction in HIV-RNA (viral load) was 0.5 log (n=20) from baseline for the 125 mg once per day dose; in fact, the 250 mg dose RNA reduction was slightly less. Subsequent studies are using a dose of 120 mg once per day. The average increase in CD4 counts after week 12 was 57 cells. Five individuals had high-level resistance to AZT prior to receiving study drug and did have a decrease in viral load after the 12 weeks of Bis-Pom PMEA monotherapy, though not as great as those individuals without high-level resistance.

After the initial phase of the study, the maintenance phase began in which individuals received Bis-Pom PMEA 125 mg once per day, but were permitted to add nucleosides. Data so far analyzed for 30 participants completing 6 months of maintenance phase therapy indicate a median 0.6 log reduction in HIV-RNA. Gilead Sciences, the developer of Bis-Pom PMEA, says that preliminary data suggest that resistance does not emerge readily after 6 months of therapy or

longer. Gilead reports that during the maintenance phase, those who were not responsive due to significant AZT-resistance appeared more responsive after additional therapy was permitted. It remains uncertain how responsive a person will be to PMEA if they have significant AZT-resistance.

Several large trials have started or are about to begin for the purpose of accumulating data for approval. A number of smaller studies are planned to explore the use of PMEA in a variety of multi-drug combinations for individuals at several stages of HIV disease progression (early, intermediate and advanced HIV). As well, ACTG 359 is planning to study PMEA in combination with ritonavir+saquinavir+ delavirdine in individuals for whom indinavir is failing. Preliminary results from the initial study of its application to hepatitis B are encouraging. Additional studies for hepatitis B are ongoing and planned.

Although not as potent as a protease inhibitor or a NNRTI, adefovir could play an important role in combination therapy because it will present a new treatment option for those who've exhausted nucleoside or other therapies. With the possible exception of those with extensive AZT resistance, based on the limited data available prior nucleoside experience does not yet appear to limit its effectiveness. It may prove to be even more valuable if it is established that resistance to PMEA does not easily develop.

Observed side effects so far include mild to moderate gastrointestinal complaints (diarrhea, nausea), fatigue, elevated creatinine, protein in urine, and elevated liver enzymes (n=8/219, usually grade 3 which is 5-10 times upper limit of normal). It is preliminary to draw conclusions about the future efficacy and safety of Bis-Pom PMEA until further data is compiled and analyzed.

PMPA: First Human Data

In April 1997, at the 10th International Conference on Antiviral Research in Atlanta, Gilead Sciences reported data from the first human study of PMPA after 8 days of treatment. Both PMPA and Bis Pom PMEA (see accompanying report) are nucleotide analogues being developed by Gilead. This class of reverse transcriptase inhibitors have a different mechanism of action than a nucleoside RTI (AZT, d4T, etc). Gilead Sciences, the developer of both PMPA and PMEA, says that unlike nucleoside analogues, nucleotide analogues are already activated; they can enter uninfected cells and form a reservoir of drug that pre-arms the cell against the virus; in contrast, AZT and drugs in its class work only in cells that have the machinery to activate the drug.

Up until now, the only data available for PMPA has been from animal studies and the laboratory. Previously it was reported that PMPA has a long intracellular half life of 35 hours in monkeys and 30 hours in human cells in vitro. It is hoped that this long half-life will allow for relatively less frequent dosing than with the administration of currently used antiretrovirals.

Animal Data

Data was published in Science, November 1995 from a study of PMPA given in two different doses subcutaneously to 25 macaque monkeys either before or after exposing the monkeys to S.I.V. The monkeys received once daily injections of PMPA for 4 weeks, beginning either 48 hours before, four hours after or 24 hours after inoculating the monkey with SIV. The monkeys were followed regularly for 56 weeks, but no evidence was found of SIV, SIV DNA, or SIV-specific antibodies in the plasma or peripheral blood mononuclear cells (PBMC). From three weeks post-exposure onward, all 10 placebo-treated monkeys became infected with SIV. Each monkey also had a groin lymph node biopsied 16 to 26 weeks after SIV exposure. None of the treated monkeys, but all that received placebo, showed evidence of SIV infection in the biopsied tissues. Gilead reported there were no adverse side effects caused by PMPA.

The results of this study imply application of PMPA to post-exposure HIV prevention and may have implications for use in preventing maternal transmission of HIV to a newborn.

At the Ninth International Conference on Antiviral Research in Fukushima, Japan during May of 1996, Gilead presented data on two additional applications of PMPA in monkeys infected with SIV.

In one study, ten monkeys that had been infected with SIV for at least 19 weeks were treated with once-daily injections of PMPA for four weeks. After 2 or fewer weeks of treatment, PMPA (30 or 75 mg/kg/day) reduced SIV levels by more than 99% or approximately 2 to 3 logs; some levels decreased below the limit of detection. In the two control monkeys who did not receive PMPA, SIV viral load did not decrease. After the 4 weeks of PMPA treatment ended the SIV viral load rebounded within two weeks back to their baseline levels. It was reported that PMPA was well tolerated in the 30 mg/kg/day dose group. In the 75 mg/kg/day dose group, no clinical toxicities or side effects were observed but chemical changes in blood markers were seen (red blood cell, phosphate and hemoglobin counts went down but these effects were reversible).

In the other study, PMPA was administered in a topical gel intravaginally, and prevented the transmission of SIV to female monkeys exposed intravaginally to the virus. All of the PMPA treated monkeys showed no signs of SIV transmission or infection throughout an eight-week follow-up period. The control monkeys who did not receive PMPA showed signs of SIV transmission and infection within two weeks of exposure to the virus.

New Human Data

Twenty study participants (16 received PMPA and 4 placebo) were treated with a single intravenous dose of PMPA on day 1 followed by a 7 day washout period and then 7 consecutive days of once daily intravenous doses. Two dose levels (1.0 and 3.0 mg/kg/day) were evaluated. The median baseline CD4 counts and HIV-RNA (viral load) were 496 cells and about 50,000 copies/ml (4.7 log) for the low dose group, 239 cells and about 126,000 copies/ml for the higher dose group. For the 4 persons receiving placebo, the baseline CD4 and HIV-RNA were 804 cells and about 20,000 copies/ml (4.3 log).

After completion of 8 days of dosing (single IV dose on day one followed by 7 consecutive days off drug, and then followed by 7 consecutive days of dosing), the median change in HIV RNA from baseline was -1.1 log (n=8) for the higher dose, -0.6 log for the lower dose (n=8), and +0.1 log for the placebo (n=4). The CD4 count increases were about 40 cells for those receiving PMPA after day 14, and for those receiving placebo the CD4 counts decreased about 10 cells.

David Ho's widely accepted theory of HIV kinetics, based on his research and that of others, is that there is a two day half life of productively infected cells, which means that every two days there can be a 2-fold (50%) decrease in HIV in blood as a result of effective antiviral therapy. Based on the mathematics of this theory, Gilead officials said, the -1.1 log reduction achieved by PMPA in the study reported was the maximum that could be achieved in 8 days.

During PMPA treatment, viral load decreased continuously until completion of dosing. After 8 days of dosing, when treatment was stopped, the viral load decrease of -1.1 log for the higher dose was sustained for another 7 days, whereupon it started to rebound and approached baseline within about 1 week. The viral load reduction of -0.6 log achieved for the lower dose group was not sustained following stopping of drug, but immediately started rebounding after drug was stopped. Gilead reported that the potential maximum dose has not yet been reached, and that PMPA is cleared renally (through the kidney) and not through the P450 liver enzyme system. Protease inhibitors and NNRTIs (non-nucleoside reverse transcriptase inhibitors) are metabolized by the P450 liver enzyme system which often is associated with difficult to deal with drug interactions.

Safety

Gilead reported that there were no lab test abnormalities, but side effects were reported of the 16 persons who received PMPA: headache (5), dizziness (5), fatigue (4), protein in urine (1),

neutropenia (0). The 4 persons receiving placebo experienced: headache (2), dizziness (1), fatigue (0), protein in urine (1), neutropenia (1). Gilead characterized PMPA as safe and well-tolerated. It is important to remember that PMPA is still in very early stages of development. As human trials proceed and more individuals gain experience using PMPA, unforeseen toxicities or side effects can emerge. Therefore, high expectations should be constrained.

Resistance

In previous research in SIV infected monkeys on treatment with PMPA, over 1 year, resistance to PMPA was not detected, whereas AZT resistance in monkeys has been detected. In vitro, AZT resistant virus was sensitive to PMPA. Generally, animal and in vitro resistance data is preliminary and may not apply to humans. In vitro, the only identified resistance mutation found associated with PMPA is the K65R which caused a 3-fold reduction in sensitivity. In vitro, this same mutant caused a 10-fold reduction in sensitivity in to PMEA. However, a K65R mutation was introduced to SIV and a monkey was infected with that mutant SIV; that monkey had a full antiviral response to subsequent PMPA therapy.

Oral PMPA Study Starts

Gilead has an orally administered pro-drug for PMPA called Bis Poc PMPA which is expected to be taken with or without food. A Phase I/II study of oral PMPA started in May 1997. It is a double-blind, placebo controlled, dose-escalation trial in HIV-infected individuals which will evaluate safety, tolerability, antiviral activity and pharmacokinetics. Several dosing levels will be explored. The goal is to reach a maximum dose considering safety and tolerability.

It could be expected that a pro-drug may be more potent than an intravenous formulation. Initially once a day dosing will be explored. The first study will include continuous dosing for one month, and for safety's sake drug administration will stop at that point. It is not expected that resistance associated with PMPA would be an issue for a one-month course of treatment based on its mechanism of action and what we know so far about resistance associated with PMPA. Brief dose escalation studies will follow to attempt to reach a maximum dose considering safety and tolerability. It is expected that by the end of 1997 a dose should be selected and large scale studies will begin. Current plans are to explore PMPA alone and in combination with other anti-HIV drugs.

Hydroxyurea: a Novel Approach to HIV Therapy

Over the course of the last year data has been reported from several studies examining hydroxyurea in combination with ddI. At the 4th Retrovirus Conference in Washington in January 1997, data was reported from the first two studies examining hydroxyurea in combination with d4T+ddI.

Hydroxyurea has been used as a treatment for several types of cancer for many years, but at significantly higher doses than is being used in its application to HIV disease. The use of hydroxyurea in combination with a nucleoside(s) presents a novel concept to HIV therapy. That is, the simultaneous attack of a host (human) enzyme and a viral enzyme. Nucleoside analogues, non-nucleosides and protease inhibitors attack or exploit a virus enzyme, while hydroxyurea attacks a host enzyme, ribonucleotide reductase. This enzyme regulates the synthesis of the building blocks for DNA allowing for the reproduction information needed for reproducing HIV. Nucleoside analogues such as AZT, d4T, ddI, ddC, 1592U89 and 3TC work by replacing the building blocks for DNA and thereby inhibit the process by which an HIV infected cell reproduces new virus. The inhibition of the host enzyme (ribonucleotide reductase) by hydroxyurea increases the chances for nucleosides to incorporate themselves into the DNA and inhibit viral reproduction. As well, Bristol-Myers Squibb, the manufacturer of Hydrea, reports that hydroxyurea (generic name) penetrates the CNS well.

However, there are several concerns about using this therapy for HIV. Individuals initiating hydroxyurea therapy with low white blood cell counts (WBCs) may not tolerate the therapy well. Second, studies so far conducted have indicated that even when there is a significant viral load reduction, CD4 counts may not show the expected proportional increase. In the study discussed below (Tables 20 and 21, on Page 20) of hydroxyurea+ddI+d4T, the baseline CD4 counts for the study participants were 363 cells, but those receiving hydroxyurea combination therapy exhibit slight CD4 increases.

In the Jorge Vila study presented at Vancouver (see report on web site), 25 participants receiving ddI+hydroxyurea had higher baseline CD4 counts of 482 cells. They experienced a greater increase in CD4 of 163 to 575 cells. We do not understand the implications of no increases in CD4 or the effect of hydroxyurea. The study of this drug is in its early stages, so the amount of available research upon which to base treatment decisions is limited. Its use in therapy for HIV prior to more extensive research is experimental.

Study Results Reported at 4th Retroviral Conference, January 1997

In a small open label study of 35 individuals, participants were treated with hydroxyurea (1 gram per day--usually prescribed as 500 mg twice daily) and d4T+ddI at full doses. The mean CD4 and viral load for the participants prior to beginning the study therapy was 226 CD4 and 81,000 copies/ml. Prior to the study, seventeen were on antiretroviral monotherapy (AZT, ddI, or d4T) and two were on combination therapy (AZT/ddI, d4T/ddI). The mean increase in CD4 at 12 weeks for 6 patients was 12 cells. Viral load decreased by 1.5 log at 2 weeks, "a little more than 1 log at 4 weeks," and for 5 patients at 12 weeks there was a 2 log reduction from baseline. Neutropenia to absolute neutrophil count (ANC) below 700/ul developed in four patients entering study with ANC baselines below 1,700/ul. Neutropenia was reversible upon withdrawal of hydroxyurea and ANC was maintained at pretreatment levels during continued ddI and d4T dosing in three patients.

In a second study (see tables below) reported at the Conference, 142 individuals were randomized to either d4T+ddI or hydroxyurea+d4T+ddI. The daily doses used in the study were: 500 mg hydroxyurea twice daily, 40 mg d4T twice daily, 200 mg ddI twice daily. Participants were d4T and hydroxyurea-naive, but were either ddI-naive or with between 2 and 6 months ddI-experience. Prior to beginning study medications, the mean CD4 count for the participants was 363, CD4 % was 21.7. It appears as though this study group is healthier and less advanced in disease progression than the participants in the first study discussed in the previous paragraph.

Mean Changes in Viral Load (HIV RNA) from Baseline

HIV RNA	week 4		week 12		% undetectable
200 copy test	placebo	-1.6 log	placebo	-1.6 log	32%
	Hydrea	-1.5 log	Hydrea	-1.9 log	55%
20 copy test	placebo	-1.6 log	placebo	-1.8 log	na
	Hydrea	-1.5 log	Hydrea	-2.2 log	na

The placebo arm were those receiving ddI+d4T. The hydrea arm were those receiving

hydroxyurea+d4T/3TC. When using the more sensitive Roche PCR test (20 copies), the log reduction is greater because the limit of detection is lower. By direct visual observation of graph, it appeared as though there were about 8-10 individuals below 20 copies.

Mean CD4 changes from baseline

CD4	week 4	week 12
d4T+ddI	+104	+91
hydrea+d4T+ddI	+43	+10

Although preliminary data indicate an enhanced antiviral effect by adding hydroxyurea to d4T/ddI therapy, there is some concern about the effect of hyroxyurea on overall HIV disease because CD4 counts do not increase much. Hydroxyurea is cytostatic at the doses being investigated for HIV disease, that is it keeps cells from replicating. HIV infected as well as non-infected cells that are activated and ready to replicate are shut down but not eliminated. All of the studies referred to in this article are reported in greater detail on the NATAP web site. Also reported on the web site are interesting results of a resistance study for those taking ddI and hydroxyurea. The authors reported that despite the detection of ddI resistance mutation(s), a consistent viral suppression was sustained for many of the participants in this study without rebound for over 1 year. The authors say this is because of the mechanism of action of hyroxyurea. Individuals who may not be tolerant to protease inhibitors or may have developed resistance to protease inhibitors may want to consider hydroxyurea therapy subject to the concerns discussed in this article. Before starting an experimental therapy such as this, it is advisable to have a full discussion about it with a knowledgeable physician.

FDA Receives Reports of Diabetes-Like Symptoms

Eighty-three cases have been reported to the FDA of individuals who are taking protease inhibitor therapy and who have experienced manifestations of diabetes or diabetes like symptoms, including severe elevated blood sugar. The symptoms were reported to occur weeks or months after therapy began. The reports included individuals who may have had previous experiences with diabetes which may have resurfaced or individuals with diabetes whose situations may have worsened. This alert should not alarm individuals but

merely alert them to pay attention to this concern and report any incidents of this development to the FDA.

The 83 reports were proportionately distributed between all of the protease inhibitors, representing a fraction of 1% of the total taking protease inhibitors in the USA. The FDA has no evidence to suspect that the diabetes like reactions are causally related to taking protease inhibitors. Currently, there is no known mechanism of action that would cause such a reaction. The FDA emphasized that this development in and of itself should not deter individuals from taking or to discontinue protease inhibitor therapy.

The FDA wants to urge health care providers to report any cases of diabetes or hyperglycemia. They will send a letter to HIV treating healthcare professionals to alert them to watch for this potential development. For further information call the FDA at 1-800-FDA-1088, or more

extensive information is available on the FDA web site at - <http://www.fda.gov>.

Corrections

Indinavir

NATAP Reports' February issue did not contain this 68-week data. At the 3rd Retroviral Conference in January 1996, Merck reported 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 copies/ml, respectively. Following is the data for a small number of individuals extended to 68-weeks reported by Dr. Joe Wong of UCSD at the Fourth Retroviral Conference in January 1997.

Median reductions in viral load* and % below detection (<500 copies/ml and <50 copies/ml):

Table	#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.

DMP-266

In our previous issue, in the section reporting 26 week data for DMP-266, it was misprinted that when taken together DMP-266 increases the blood levels of indinavir. In fact, DMP-266 decreases the blood levels of indinavir by about 35%. It was evident to some readers by the context of the article, but we want to correct this error.