National AIDS Treatment Advocacy Project

IDSA

T-20. At the recent IDSA meeting, preliminary data was reported from a phase I/II dose escalating study of T-20. T-20 inhibits fusion of HIV with host cells (CD4s). Although the following data is encouraging, it is preliminary and is from early stages of research in humans. Further studies are needed to evaluate T-20's efficacy and safety. Fusion inhibition's approach to HIV therapy is different than any other currently approved HIV antiviral.

16 treatment-naive or experienced (off drugs for 15 days prior to starting T-20) individuals received doses of 3, 10, 30 or 100 mg of T-20 every 12 hours for 14 days.

T-20 was administered by bolus intravenous infusion.

Investigators reported no drug-associated adverse events and a dose dependent decrease in plasma viral load and increase in CD4. The investigators concluded they saw significant anti-HIV activity.

DOSE q12hrs	Mean Viral Load			Mean CD4		
	Day 0	D 14	change	D 0	D 14	change
3 mg	4.82	4.71	-0.11	248	207	-41
10 mg	5.12	5.06	-0.06	357	344	-13
30 mg	4.95	4.47	-0.48	410	431	+21
100 mg	4.20	<2.70	-1.50	322	374	+52

All 4 participants receiving the 100 mg dose were <500 copies/ml (undetectable).

Follow-up studies are necessary to confirm preliminary findings. Sub-cutaneous administration is expected to be explored in a forthcoming study.

Nelfinavir: 12 month data report

This is a brief preliminary report of the important information reported in this abstract. A more extensive report will follow. This report contains the data out to 12 months for participants in nelfinavir study #511 which compared 750 mg nelfinavir three times per day plus AZT/3TC, 500 mg nelfinavir 3X/day plus AZT/3TC and AZT/3TC alone.

The 750 mg 3x/day dose regimen of nelfinavir is the only one approved by the FDA and in fact produced superior results in this study to the 500 mg dose.

297 individuals were randomized to one of the 3 arms. About 100 were randomized to the nelfinavir 750 mg 3x/day regimen. The participants were treatment naive. Their baseline CD4 and viral load were 283 cells and 4.83 log (about 67,000 copies/ml), respectively. After 12 months the viral load reduction for this arm was about 2 log, 80% were undetectable (<500 copies/ml), and CD4 increases were about 170 cells from baseline.

The investigators did some additional research relevant to the current treatment environment. The higher a participant's CD4 was at baseline the higher the likelihood to reach undetectable and sustain it. For those with >300 CD4 at baseline, 83% were undetectable. The lower a person's viral load was at baseline the more likely they would be successful with treatment. For participants whose baseline viral load was <50,000 copies/ml, 95% were undetectable at 12 months. This scores a point in favor of early aggressive treatment for HIV.

DMP-266

48 week efficacy data was reported for participants in this study which compared two arms. One group received DMP-266, a new NNRTI from DuPont Merck, plus indinavir

in a two drug combination. The other group received indinavir monotherapy. After 12 weeks those taking indinavir monotherapy were permitted to add d4T+DMP-266.

The baseline viral load and CD4 was about 5 log (100,000 copies/ml) and 283 cells. 71% of the participants had some level of prior NRTI experience but were protease inhibitor and NNRTI naive.

After 48 weeks (n-47), the individuals in the DMP-266+indinavir arm had a reduction in HIV RNA from baseline of about 2.4 log, 88% were undetectable (<400 copies/ml), and their increase in CD4 was +245 from baseline. After 48 weeks (n=31), the individuals who were in the other group had a reduction in viral load of 1.89 log, 68% were undetectable, and had a CD4 increase of +150 cells.

There were 11 premature discontinuations in the DMP-266/indinavir arm and 9 in the other arm.

Tolerability **-** Rash Summary

Toxicity Grade	**DMP-266+indinavir**	**Indinavir**
I	19/84 (22.6%)	11/42 (26.2)
II	9/84 (10.7%)	1/42 (2.4%)
III	0/84	1/42
IV	28/84 (33.3%)	13/42 (31%)

1st Report of Highlights From ICAAC

Tuesday, 1997, Toronto, Canada.

This is an initial report of important treatment highlights from the 37th annual ICAAC conference in Toronto.

At the opening session Sunday evening, Dr Robert Siliciano of Johns Hopkins University discussed his findings of a viral reservoir of post integrated proviral DNA persisting in resting CD4 memory t-cells. These cells are in a reversible state of non-productive infection but can be capable of producing infectious virus if stimulated by antigen. He said that the frequency of these cells and their decay rate are important to evaluating the effect on the potential for eradication.

Using a sensitive assay he found the frequency of these cells to be extremely low. The replication competent integrated proviral DNA was found in <.01% of resting CD4+ t-cells. He took a lymph node biopsy of 14 individuals from the Ho studies and found

significantly that the frequency of these cells are not different in the blood and the lymph node. This is important because it allows researchers to access this compartment just by taking a peripheral blood sample. He ran an independent assay, a virus culture, because there was thinking that all the DNA was not competent to reproduce virus. His findings were confirmed.

In order to determine the decay rate of these cells Siliciano entered into a collaboration with clinical researchers to see if this reservoir persists in individuals who have been on long term highly active antiretroviral therapy (HAART). For this study, he selected patients who were likely to maintain a high level of compliance to the regimens; who were on three or four drugs at least one of which was a protease inhibitor; who had a rapid response to therapy (who became undetectable within 2-3 months); and, who remained undetectable (200 copies/ml) with multiple measurements for the period of study including the times for which they took blood to look for latently infected cells.

Replication competent proviral DNA was found in resting CD4+ t-cells in essentially all the individuals (18/18), including those who were on therapy for up to 30 months, and it can persist for a while. In four patients they were unable to get enough resting CD4 t-cells to conduct proper tests. Unfortunately, he concluded that the frequency of these cells in the study individuals was not reduced by being on therapy for a longer period of time. The frequency for those who were on therapy the longest was not much different for those individuals who were on therapy for a short period of time. He said we will have to conduct studies following individuals over time to try and determine the decay rates of these cells.

For comparison sake, it has been generally accepted that free virus only persists for minutes or hours. Cells that produce most of the virus last only a day or two. Cells with unintegrated DNA retain the ability to produce virus for only a few days. Extracellular virus particles bound to follicular dendritic cells (in the lymph tissue) last for about two weeks. Although we have less information on chronically infected macrophages, their half-life appears to be about two weeks. The half-life of resting CD4+ t-cells with integrated proviral DNA could be a 5 to 7 months. This is consistent with the fact that these are memory t-cells and their biological function is to persist. Some researchers have said to me that memory cells can last for a number of years.

After being on HAART for a period of time, an individual may experience a partial restoration of the immune system. If the CD4 cells increase appreciably in conjunction with some immune restoration it is possible that the immune system could control any virus that could be produced by the activation of these resting cells. This can only be determined by following individuals over time.

David Ho and the ACTG are planning to conduct studies of strategies designed to target these cells. Stay tuned.

CSF (Cerebral spinal fluid) Viral Load Measurement of Individuals receiving Ritonavir+Saquinavir

Dr Charles Farthing of the AIDS Healthcare Foundation in Los Angeles presented this report. 13 individuals were selected from the study# 462 (ritonavir+saquinavir) to participate in this substudy. These were individuals with undetectable HIV RNA (<200 copies) for at least 8 weeks after one year of therapy. None of these individuals added RTIs, they were only receiving ritonavir+saquinavir. Their baseline CD4 and viral load were about 50,000 copies/ml and 234 CD4. 6/13 were taking 400 mg bid of both drugs. However, there was no baseline CSF viral load measurement, so there was no basis for comparison, and they did not measure for CSF levels of ritonavir or saquinavir. Still, the following results are encouraging but need to be followed with additional studies better designed to form more definitive conclusions. Abbott said such a study is in progress.

In this substudy 12/13 had CSF viral load <400 copies/ml. One patient on ritonavir+saquinavir had plasma viral load <200 copies/ml but had a CSF viral load equal to 650 copies/ml.

***IDSA Report* - CSF Viral Load for individuals taking Indinavir plus Nucleosides**

This was reported at the IDSA meeting earlier in September but I thought it would fit nicely here. Dr Anne Collier of the University of Washington reported this information. She found indinavir drug levels in the CSF and the CSF to plasma ratio of HIV RNA was higher later in the dosing interval of 8 hours. That is because the plasma indinavir levels decline towards 8 hours but the CSF indinavir level remains the same.

Data from two groups of individuals were reported. In group A, 9/10 individuals had <200 copies/ml CSF HIV RNA. Only 4/10 had plasma HIV RNA <200 copies/ml. These 10 individuals were taking indinavir plus two nucleosides. No baseline measure of CSF HIV RNA were done.

In group B, 9 individuals had CSF and plasma viral load measures at baseline and week 8. At baseline, 0/9 were <200 copies/ml in plasma and 2/9 were <200 copies/ml in CSF viral load. At week 8, 1/9 was <200 copies/ml in plasma and 6/8 were <200 copies/ml in CSF viral load.

Collier said this was an initial observational pilot study. The results are preliminary as are the results from the ritonavir+saquinavir study.

Indinavir Twice-A-Day Dosing Study

Dr Bach-Yen Nguyen of Merck Research Labs reported the results of a preliminary pilot study exploring dosing indinavir every 12 hours compared to the standard dosing of every 8 hours. The objective is to see if indinavir can be successfully dosed every 12 hours to make it a more convenient regimen for individuals. Three arms were compared: indinavir 800 mg every 8 hrs, indinavir 1000 mg every 12 hours and indinavir 1200 mg every 12 hours. AZT+3TC was taken with indinavir in each arm. This is a 36 week study. Preliminary 24 week data was reported. Participants are 3TC and protease inhibitor naive, but can be AZT experienced. The median baseline CD4 ranged from 264 to 294 in the 3 arms. The median baseline viral load ranged from about 38,000 copies/ml to about

54,000 copies/ml in the 3 arms.

Nephrolithiasis--3 in the 800 tid arm; 2 in the 1000 bid arm; 5 in the 1200 bid arm.

Pts with serious adverse events: 1 in the 800 tid arm; 0 in the 1000 mg tid arm and 4 in the 1200 mg tid arm. The investigators characterized the bid regimens as well tolerated as the tid regimen.

Although the number of participants out to 24 weeks is small, the viral load reductions, proportion undetectable, and the CD4 increases were about the same in all 3 arms.

24 week median changes from baseline

	CD4	**HIV RNA**	**<500 copies**	**<50 copies**
IDV 800mg tid+AZT/3TC	100+	-1.5 log (n=9)	40% (13)	40% (9)
IDV 1000mg bid+AZT/3TC	75	-2 log (n=15)	70% (17)	60% (13)
IDV 1200mg bid+AZT/3TC	75	-2 log (n=11)	70% (16)	70% (10)

Although you can see differences between some of the arms, the number of evaluable participants is too small at 24 weeks to draw conclusions about comparisons between the different arms. The best assessment, at this point, is that all three arms appear comparable. Further research is needed to confirm these results. Merck is planning a large study of 400-500 individuals to begin soon. Merck is also planning a study of individuals currently taking the tid regimen of indinavir and switching them to the bid regimen. Because the data is so preliminary, it may be premature to use the twice daily dosing regimen.

Study 035, Indinavir+AZT/3TC- 2 Years Follow-up

Dr Roy Gulick of New York University Medical Canter reported 100 week data for individuals taking indinavir+AZT/3TC in study #035. This study of 97 individuals compared the triple regimen to AZT/3TC alone, and indinavir monotherapy. Participants were 3TC and protease inhibitor naive, and AZT experienced (average 2.4 years). 80% of participants had taken other nucleosides prior to the study including ddI, ddC or d4T. The median baseline CD4 and viral load were 144 cells and 43,190 copies/ml.

Previous results have been reported showing the superior viral load reductions, CD4

increases and % undetectable for those taking the triple regimen. Between 24 and 52 weeks, individuals in the study receiving AZT/3TC or indinavir monotherapy started to switch to the triple therapy.

After 100 weeks of therapy those receiving the triple therapy from the start of the study had a % undetectable (<500 copies) of 79% (22/28); the median CD4 increase from baseline was 230 cells; and, the median viral load reduction was 2.12 log. About 60 to 70% achieved <50 copies/ml which continued through 100 weeks.

Those originally receiving AZT/3TC showed an initial viral load reduction which trended back towards baseline. After adding indinavir after 6 months the viral load remained about 1 to 1.5 log below baseline out to 100 weeks.

Those participants randomized to indinavir monotherapy achieved an initial reduction in viral load of about 1.5 log but also started to trend back to baseline. After adding AZT/3TC the viral load reductions appeared to remain the same out to 100 weeks.

In both of these other groups they had only 30-40% at <50 copies through the 100 weeks.

Very few AZT experienced individuals who merely added 3TC had undetectable viral load after 6 months. After adding indinavir the best they achieve is 40% at <500 copies/ml which does continue through the 100 weeks. The indinavir monotherapy group initially achieved 40% at <500 copies ml through the first 6 months. After adding AZT/3TC the group maintained the 40%.

Five participants randomized to the triple regimen discontinued from the study early. Two had increasing RNA during the trial and discontinued study medications. Two required treatment for OIs. One dropped out for nausea. Larger numbers of participants dropped out of the original indinavir monotherapy arm or the AZT/3TC arm due to various reasons, most commonly due to rising viral load.

Ritonavir+Saquinavir Studies

A major subject of importance in today's treatment environment is how to treat individuals who have failed a protease inhibitor. The following reports included studies using the double protease inhibitor combination of ritonavir+saquinavir to treat individuals for whom a protease inhibitor therapy has failed. Although, in general, the preliminary results from the studies are mixed there is some encouraging data. These studies fall short of using the most potent regimens available. None of these studies include in the regimens: a NNRTI (nevirapine, DMP-266, delavirdine), PMEA, or 1592U89. Studies including these drugs are being planned in the ACTG and by the industry but are very slow in starting.

The studies presented here used a regimen composed of ritonavir+saquinavir usually combined with recycled nucleosides because most individuals were extensively pretreated with a variety of nucleosides.

Ritonavir/Saquinavir+d4T/3TC: with protease experience and nucleoside experience abstract I-200

G Kauffman reported data results from a small study of 58 individuals who had relatively advanced HIV with baseline CD4 of 170 and baseline viral load of about 100,000 copies/ml and prior drug experience. The following table will give you a sense of their prior drug experience. 67% of study participants had prior protease inhibitor experience, mostly with saquinavir. Resistance studies are ongoing to analyze the effect of saquinavir resistance.

Prior Drug Experience of Study Group

n-58	**All**	**AZT/3TC (n-18)**	**d4T/3TC (n-40)**
pretreated w/ nukes	23%	na	na
treatment naive	10%	12%	8%
protease inh naive (exp)	33% (67%)	29%	33%
SQV exp (avg 19 wks)	50%	47%	52%
RTV exp	14%	18%	12%
IDV exp	3%	6%	3%
prot inh weeks	19	22	17
RTV/SQV dose-600/400mg bid	39%	44%	37%
400/600mg bid	61%	56%	63%

na - not available

% Undetectable (<500 copies/ml)

week 12 33% (n-56)
week 24 60% (n-51)

week 36 49% (n-35)
week 48 28% (n-19)

The initial viral load of about 5 log (100,000 copies/ml) rapidly dropped to undetectable, but 7 patients at week 24, 13 at week 36, and 18 a week 48 stopped treatment due to treatment failures and are not included in this analysis.

For individuals who responded well to therapy, CD4 counts increased appreciably (from 170 to 450 cells by the end of the observation period). Adverse events occurred frequently: 33% experienced diarrhea and 12% experienced nausea. 2 individuals experienced peripheral neuropathy due to d4T. In 1 person a rash occurred. 17% of participants were incomplete responders and 10% were non-responders. 10% stopped study therapy due to adverse events. D4T experienced individuals had a response rate of 34% while d4T naive persons had a response rate of 50%, although this difference was not statistically significant.

The author concluded that good initial responses were experienced but after 7 months treatment failures occurred more frequently probably due to reduced compliance or drug resistance developing.

Commentary. The conditions for success were not optimal in this study. Although the overall response rate wasn't very good, 28% (n=19) did in fact maintain a good response out to 48 weeks, which probably could have been improved with the addition of a NNRTI and/or PMEA to the regimen. 50% of the participants had an average prior exposure to saquinavir of 19 weeks. For a person failing saquinavir, a better salvage therapy might include indinavir/a NNRTI/PMEA.

Ritonavir + Saquinavir for Indinavir Failures for those with Advanced HIV abstract I-201

L Ruiz from Barcelona reported the data from this small study of 11 individuals where the objective was to assess the efficacy of switching to ritonavir/saquinavir at 24 weeks in persons with advanced HIV; and, to evaluate the correlation of genotypic and phenotypic resistance to saquinavir with subsequent response.

Commentary. Although the study is small, the responses appear to me relatively favorable.

11 individuals who failed indinavir were switched to ritonavir/saquinavir combination therapy which included 2 nucleosides. But not all participants changed the RTIs they were taking prior to switching from indinavir to ritonavir/saquinavir. The 11 participants belonged to a cohort of 50 persons with an initial median CD4 count of 50 (range: 34-81 cells). 8 persons were included in the genotypic analysis. The dose regimen was 400 mg bid ritonavir and 600 mg bid saquinavir.

Patients had been treated with indinavir monotherapy (n=4) or indinavir in combination

with nucleosides: (n=7) ddC, AZT+3TC, AZT+ddI+3TC, AZT+ddC+3TC.

Patients were classified as responders or non-responders. Responders had >1 log reduction in viral load at 24 weeks (n=5). Non-responders did not have >1 log reduction in VL at any time point during the follow-up period (n=3).

The baseline CD4 and viral load were 50 cells and 5.5 log (about 316,000 copies/ml).

8 patients (73%) completed the 24 week period. 3 remaining patients dropped out. 1 developed a new AIDS event during the follow-up period and 2 dropped out due to non-compliance. Ruiz characterized the combination of ritonavir/saquinavir as well tolerated.

At week 24, the mean increase in CD4 was 60 cells (range: 17-248), and the mean decrease in plasma viral load was 1.3 log.

Results. In all persons in this study, genotypic and phenotypic baseline resistance mutations were detected. In 2 persons, classical mutations to saquinavir were detected (L90M or G48V). 2 out of 3 non-responders had a saquinavir mutation. Interestingly, 1 of the responders had resistance to all 3 protease inhibitors at baseline.

At week 24, 5 out of 8 persons completing 24 weeks had achieved a viral load reduction from baseline of >1 log. In 4/5, viral load was <2,000 copies/ml. 2 persons achieved undetectable viral load.

All responders also changed at least one RT inhibitor, d4T and/or 3TC, at start of this study. The absence of a baseline saquinavir mutation was associated with a good clinical and virological (viral load reduction) response.

Safety and Efficacy of Ritonavir+Saquinavir Added to AZT/3TC abstract I-202

This was an open-label study of 16 persons who were pretreated with >9 months with nucleosides and at least the last 3 months with AZT/3TC. They merely added ritonavir+saquinavir at the dose of 600 mg bid ritonavir and 400 mg bid saquinavir; they had 47 months (range 20-90) prior nucleoside experience.

The baseline CD4 and viral load were 60 cells (range 10-200) and 4.86 log (about 72,400 copies/ml), (range: 10,000-562,000 copies/ml).

Results. At week 24, for 16 participants, when using the 20 copy viral load test the mean decrease in VL was 2.36 log, and the median decrease was 3.02 log.

10/16 were <200 copies/ml. 5/16 <20 copies/ml. The mean CD4 increase was 93 cells (range 0-300). 9/16 had >3 log decrease.

9/12 of the study defined compliant participants were <200 copies/ml at week 24. 11/12 were <1,000 copies/ml at week 24. 1 non-compliant person was <200 copies and 1 non-compliant person was <1,000 copies.

Tolerance. *Of the 16 participants:*

9 decreased ritonavir dose: 6 to 500 mg bid, and 3 to 400 mg bid

2 persons stopped therapy: 1 for intolerance - severe GI, the other for non-compliance, who was also experiencing minor side effects.

Adverse Events.	
Grade 3	**N**
Diarrhea	11
Nausea	8
Circumoral Parasthesia	7
Flushing	7
Fatigue	6
Vomiting	4
Lab Abnormalities	
Grade 3	N
Triglycerides increase	15
Cholesterol increase	5
ALT (LFTs) increase	5
CPK increase	2

Ritonavir+Saquinavir with d4T in Patients with Advanced HIV; correlation with blood drug levels abstract I-203

56 patients received 600 mg bid saquinavir and 400 or 600 mg bid ritonavir, with d4T (30-40 mg bid). Preliminary data of the first 9 weeks (phase 1) was reported for this study. Only 2 patients had any prior nuke experience, all were d4T and protease inhibitor naive.

Median baseline CD4 was 80 cells (0-231), and baseline viral load was about 5 log (100,000 copies/ml).

Results. After 5 weeks the median viral load drop was 2 log, after 9 weeks the preliminary median viral load drop was 2.7 log. There were 7 premature discontinuations before week 9: 2 due to fatigue, I person experienced a liver toxicity, and 2 requested to be withdrawn. 49 were still receiving treatment at week 9.

Of the 49 persons who completed phase I (9 weeks)

- 36/49 (73%) had >2 log reduction in viral load
- 33/49 (67%) had undetectable viral load
- 42/49 (86%) fulfilled either criteria

The median CD4 increase was 100 at week 9. CD8 cells increased from a mean of 643 to 923.

Protease Inhibitor Blood Levels. Saquinavir blood levels were measured in 16 patients who reached week 9. Ritonavir was within normal limits in all 16 patients measured. In 1 patient saquinavir levels were unchanged. In remaining 15 patients saquinavir levels were 10-100 times elevated with a mean of 46 times elevation, and a median of 40 times elevation. All 16 patients who finished the first phase were responders.

Safety and Tolerability (n-16). No adverse events (A/E) related to study medications were seen. 6 patients had 11 A/Es rated moderate to severe: 1 was unrelated to medications; 2 A/Es led to 2 premature discontinuations and to one dose adjustment.

A/Es experienced were fatigue, circumoral paresthesia, diarrhea, and 1 grade III rise in LFTs (liver function tests) which was transient.

There were no relevant mutations at baseline--at positions 48, 90 or 82. The authors concluded that a very nice full response to therapy was seen in the initial phase of this study: 79% by intent to treat and 86% by those actually completing first 9 weeks (7 premature discontinuations). Saquinavir given in a dose of 400 to 600 mg bid in combination with 400 mg bid ritonavir in combination with d4T was well tolerated in the majority of patients.

Experience with a Ritonavir+Saquinavir Based Regimen for the Treatment of HIV Infection in Subjects Developing Increased Viral Loads While Receiving Nelfinavir abstract -204

This report was well anticipated and discussed before, during and after the presentation. As you know there is much concern about cross-resistance between protease inhibitors. The concern is as follows: if you fail one and have resistance your ability to benefit from subsequent protease inhibitor therapy could be little or none. Research is ongoing to explore a variety of different potent regimens that could be effective for an individual after developing resistance to a protease inhibitor.

Some of the different drugs that are or will be explored in the near future in different combinatorial arrangements include: ritonavir+saquinavir, nelfinavir+saquinavir, indinavir+nevirapine, indinavir+delavirdine,141W94+indinavir, 141W94+nelfinavir, PMEA, 1592U89, DMP-266, nevirapine, delavirdine, ABT-378. All of these drugs are reviewed the July issue of our newsletter, *NATAP Reports*, which is on our web site.

The regimen that may work for any given individual may vary according to their history of antiretroviral use. As with all treatment regimens, they need to be tailored to the

individual's needs and experiences.

Prior to the St. Petersburg International Workshop on Resistance this June 1997, many predicted and were concerned about cross-resistance between protease inhibitors. At the workshop studies were presented which reinforced these concerns and the likelihood of cross-resistance. However, researchers are designing potent multi-drug combinations which will include new drugs. As I mentioned above, studies will explore the possibility that protease resistant virus can be suppressed by these regimens.

"One of the important questions not resolved at the workshop in St. Petersburg is whether the risk for development of cross-resistance to other protease inhibitors is lower when nelfinavir is used first", Joep Lange and Douglas Richman, Antiviral Therapy, Vol 2, Number 3. We need hard data from well designed studies to answer that unresolved question.

However, this study is a first step in addressing the question. The study took individuals who failed nelfinavir therapy in 3 different nelfinavir studies (506, 511 and 525). They were treated with ritonavir+saquinavir+d4T+3TC. Keith Henry, the author, cautioned that the data resulting so far is preliminary (follow-up to 16 weeks), the key is the durability of the results; and, the participants did not switch over early or immediately after first failing nelfinavir. Some researchers suspect that if you can detect a viral load rebound immediately after its occurrence; and if you make adequate therapy changes, you may be able to durably suppress viral load. All the patients, in this study, had high viral loads immediately prior to initiating the ritonavir/saquinavir regimen.

Additionally, all the participants had an average time of pretreatment with 3 or 4 nucleosides of 1.8 years. They all had prior experience with d4T and 3TC; and in a sampling of 16 persons for genotypic mutations 7/11 had 3TC resistance prior to receiving the switch over 4-drug regimen. The study results may have been further improved by using drugs in combination with ritonavir/saquinavor which the patients had never seen like PMEA, or a NNRTI.

19 patients who failed nelfinavir as participants in one of three nelfinavir studies (studies 506, 511, and 525) were participants in this study. 11 were participants in 506, 1 from 511, and 7 from 525. All participants received ritonavir+saquinavir (400 mg bid of both)+3TC 150 mg bid+d4T 40 mg bid.

Participants in 506 received nelfinavir+d4T. Their prior RTI experience included: AZT, 3TC, ddI, ddC, delavirdine. 5 participants from 506 and 1 from 511 had not previously taken 3TC. Participants in 511 received nelfinavir+AZT+3TC, but were treatment-naive, they had no prior drug experience. Henry reported that the 525 participants had extensive prior nucleoside experience. The study design for 525 was nucleoside experienced individuals (AZT, 3TC, d4T, ddI, ddC) randomized to either add nelfinavir to their existing nucleoside regimen or to switch nucleosides and add nelfinavir.

The baseline characteristics as reported by Henry

	506/511	525
mean HIV RNA prior to NFV (bDNA)	130,646 (14,670-499,600)	263,027 (9681-1,600,000)
mean CD4 prior to NFV	208 (63-463)	65 (<10-135)
mean prior NFV use	41 (20-56)	30 (20-40)
mean HIV RNA prior to RTV/SQV	60,948 (1075-146,400)	233,667 (11990-1,186,000)
mean CD4 prior to RTV/SQV	226 (82-448)	109 (13-217)
mean # prior RTIs used	3	4
mean prior RTI use	1.8 (0.1-5.8)	(0.3-6.9)

numbers in parenthesis are a range

The following table shows that resistance to nelfinavir was broadly present, by the presence of a mutation at D30N. Agouron has reported that D30N is the mutation predominantly responsible for resistance developing to nelfinavir. L90M is a mutation that can occur from resistance developing to saquinavir, or in some cases from use of other protease inhibitors. I84V is a mutation that can occur from resistance to ritonavir or indinavir. M184I/V is a mutation from 3TC resistance. This data suggests there was more broad 3TC resistance in the 25 group.

Genotypic Changes Prior to Substudy

Change	506/511	525
D30N	9/11	4/5
L90M	2/11	0/5
I84V	0/11	0/5
M184I/V (3TC)	2/6	5/5
Other RTI mutations	4/6	4/5

Data from Merck Research Labs

There was a difference in response between the participants from 506/511 and those from 525. As you can see from the baseline characteristics, those from 525 had more advanced HIV (higher viral load, lower CD4). For the 12 participants in this substudy who came from 506/511, their approximate mean viral load reduction from baseline after initiating the substudy 4-drug regimen was: -1.6 log (n-10) at 4 weeks, -1.7 log at 8 weeks (n-11), -1.6 log at 12 weeks (n-8), and -1.4 log at 16 weeks (n-7).

12/12 (100%) of the participants from the 506/511 study were able to initially suppress their viral load <500 copies/ml (undetectable by bDNA test). At 16 weeks, 6/7 individuals were undetectable, <500 copies/ml. Henry reported that there is one person out to 12 months with undetectable viral load. He also reported 2/6 had <20 copies/ml at 16 weeks. The CD4 increases were about 80 cells.

The response for the 7 individuals from the 525 study were not as encouraging. 3/7 (43%) were undetectable (<500 copies/ml) at 16 weeks. 4 persons rebounded. 1 person was non-compliant, another's viral load fell to 593 copies/ml but then rebounded.

One person, who was non-compliant, received directly observed therapy and reduced their viral load by 1.5 log.

Following are the positions at which genotypic changes occurred for two selected patients (pt# 4 and pt# 1) from the 525 study group after the switch in therapy:

Experience with a Ritonavir+Saquinavir Based Regimen for the Treatment of HIV Infection in Subjects Developing Increased Viral Loads While Receiving Nelfinavir - abstract 204

pt #	**Before Switch, After 36 wks NFV Use**	**After Switch, 12 wks on RTV/SQV**
525 -4	D30N, A71A/V	D30N, L33F/L, A71T, I84V, N88D,L90M, I72I/v
525 -1	D30N, K45K/R, M46I, A71A/T, N88D	M46I, A71V, I84V, N88D, L90M

The first two 525 failures who failed RTV/SQV had suboptimal blood levels for both drugs. 2/16 had the L90M mutation after nelfinavir failure, but both reduced viral load to undetectable.

The author concluded (1) maintaining a high level of suppression may be a challenge and partly due to the extent of prior RTI experience and disease stage, and (2) nelfinavir failure was most often associated with D30N in conjunction with M46I, A71V, and N88D.

I want to remind readers that the author, Keith Henry, cautioned listeners that this information is preliminary. The study is small and the durability of the benefits are the true test. Although encouraging results came from the 506/511 group, 16 weeks is not enough time to judge the durability. Follow-up is ongoing and will be reported. Again, a more potent regimen than used in this substudy may be more successful in durably suppressing viral load.

Fortovase- the new formulation of saquinavir

The dosing regimen for the new saquinavir (SGC) will be 1,200 mg three times per day (tid). Based on recent studies, it's been reported that 1,200 mg tid of saquinavir SGC has resulted in increased drug blood levels that are 10-fold higher than that of Invirase, the older formulation of saquinavir.

Reports of data from several different studies examining the new saquinavir were presented both at the ICAAC conference and at meetings outside the conference in Toronto. Following is a consolidation of highlights of the data.

The **SUN Study** was an open-label non-comparative examination of the triple regimen of saquinavir SGC (soft-gel capsule), Fortovase, plus AZT and 3TC. 42 treatment-naive individuals were enrolled with mean baseline and HIV RNA and CD4 of 4.8 log (about 63,000 copies/ml) and 419 cells, respectively. The study is ongoing and the following data is preliminary.

The investigators reported that after 20 weeks, the reduction in viral load for 23 evaluable study participants was 3.34 log. However, the investigators used a more sensitive viral load test (20 copies/ml), which can report (although accuracy can be inconsistent) viral load reductions down to a lower level than you'll get from using the 400 copy test. 91% were <400 copies/ml (undetectable), and 60% had a viral load at <20 copies/ml. 19/42 participants had withdrawn from the study by week 20 and were not included in the analysis: 2 due to adverse events, 3 due to non-compliance, 4 due to refusal of treatment, 6 lost to follow-up, 1 missed week 16th visit. After 16 weeks the mean CD4 increase was 170 cells.

Safety. Investigators characterized the triple combination as well-tolerated. The most frequent side effects related to study drug, less than 5%, was nausea, vomiting, diarrhea, and headaches. 1 person had a grade III AST/ALT (liver function tests) at week 4 which resolved after discontinuing study treatment. 1 person had a grade IV AST/ALT at week 12 associated with acute hepatitis A. An approximate 20% incidence of diarrhea has been reported associated with saquinavir SGC in a different study.

The **CHEESE Study** compares saquinavir SGC plus AZT/3TC to indinavir plus AZT/3TC in 43 treatment-naive individuals. Participants were 3TC and protease inhibitor naive. The baseline CD4 and viral load were about 300 cells and 74,000 copies/ml, respectively.

At week 8, the median reduction in viral load was to below detection with at least about a

2 log reduction for both groups. This median change was sustained out to 24 weeks for both groups where the n=3 for each group. At week 16 n=8 for the SQV SGC group and 7 for the indinavir group. The CD4 increases were substantial for both groups.