

Double Protease Combinations

Reported by Jules Levin, Executive Director of NATAP, (March 6, 1998)

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Ritonavir + Saquinavir: 60 week update

DW Cameron, of Ottawa General Hospital, and others reported a 60 week update from the open label Abbott protocol #462 on the safety, tolerability and antiviral activity of this double protease inhibitor combination. While Invirase was used in this study, in another study, when ritonavir was combined with the same dose of Invirase or Fortovase, the actual mean plasma exposures were not significantly different (ref: Fortovase package insert). 141 participants were randomized to one 2 groups. There were 4 possible dosing regimens. All participants were protease inhibitor naive and were required to discontinue NRTIs at least two weeks prior to starting study drugs. Initially, participants received only ritonavir+saquinavir.

Group 1:

Treatment arm A: 400 mg bid RTV + 400 mg bid SQV (n=35), every 12 hours

B: 600 mg bid RTV + 400 mg bid SQV (n=35), every 12 hours

Group 2:

C: 400 mg tid RTV + 400 mg tid SQV (n=33), every 8 hours

D: 600 mg bid RTV + 600 mg bid SQV (n=37), every 12 hours

The median number of antiretroviral drugs previously used was 2 for each of the 4 treatment groups. The median baseline plasma HIV RNA ranged from 4.5 log (31,600 copies/ml) to 4.7 log (50,100 copies/ml) for each of the 4 groups. The baseline median CD4 counts ranged from 266-300 for each of the 4 groups.

Table 1. Patient Disposition

The two arms: 400/400 bid and 600/400 bid- were both more tolerable than the other two arms

	400/400 bid	600/400 bid	400/400 tid	600/600 bid
# randomized	35	36	33	37
<i>Prematurely Disct</i>	5	9	12	11
for adverse event	1	6	9	6
<i>Continued on Study</i>	30	27	21	26
On randomized doses	29	16	12	11
On reduced doses	0	10	9	14
Other	1	1	0	1

Table 2. Viral Load and CD4 Changes from Baseline

The week 60 data includes only individuals who remained on study drugs. Study dropouts were not included. It is important to bear in mind that a number of the participants originally randomized to Groups C or D changed their dosing regimens to A or B. The actual number of such changes follow the table. 27 participants added up to 2 NRTIs (usually d4T/3TC) after week 12 (see Table 6). Although data is reported for all 4 arms, it is generally recommended that the dosing regimens to be used are those used in arms A or B. The incidence of side effects is higher in arms C and D. Also, arms C and D do not appear to be any more efficacious than arms A and B, but noncompliance may have been higher in arms C & D.

	%<200 copies/ml	CD4	HIV RNA
400/400 bid (A)	80%	+210	3.0 to 3.5 log
600/400 bid (B)	90%	+150	3.0 to 3.5 log
400/400 tid (C)	89%	+175	3.0 to 3.5 log
600/600 bid (D)	89%	+160	3.0 to 3.5 log

This is the actual dose regimens participants were receiving:

	week 24	week 48	week 60
RTV 400 bid + SQV 400 bid	n=46	n= 50	n=51
RTV 600 + SQV 400 bid	21	17	16
RTV 400 + SQV 400 tid	13	12	12
RTV 400 + SQV 400 tid	17	13	11
other	10	11	10
Total	107	103	100

As you can see almost half of participants were randomized or switched to 400/400 bid by week 24. By week 60, 51% had switched to 400/400 bid.

Ultrasensitive Viral Load

All participants who were on study at week 48 and had sufficient stored plasma available had HIV RNA measured by the Roche Ultrasensitive test (lower limit of detection 50 copies/ml). 86% (66/80) who were <200 copies/ml by the standard assay also were <50 copies/ml using the Ultrasensitive test.

CSF Sub-study

15 participants who were <200 copies/ml for at least 8 weeks after about 1 year on ritonavir-saquinavir alone and did not add NRTIs had CSF evaluations. Although this data is encouraging, CSF viral load was taken only once which was after being on therapy for >1 year. There was no CSF evaluation taken prior to study entry. Therefore there was no baseline measure taken to compare to the measure taken during therapy, and to see if there was an actual change and to measure the change. 14/15 (93%) had CSF <400 copies/ml. 1 person on RTV-SQV 600-600 bid had a plasma viral load <200 copies/ml but had a CSF viral load of 650 copies/ml. In the Prometheus Study, both baseline and during therapy CSF measures were taken for individuals on RTV/SQV and RTV/SQV plus nucleosides. That data is below.

Table 3. Safety and Tolerability

Safety data is only through week 48. Most common (>5%) adverse events at least moderate in severity and with possible, probable, or unknown relationship to study drugs.

Adverse Event	400/400 bid	600/400 bid	400/400 tid	600/600 bid
Circumoral parasthesia*	1	3	1	4
Diarrhea	4	11	5	12
Asthenia*	2	3	8	10
Nausea	4	7	4	11
Depression	1	3	1	4
Dizziness	1	0	5	4
Peripheral parasthesia*	1	4	1	2

* Circumoral parasthesia is a tingling and numbness around the mouth area. Asthenia is general fatigue. Peripheral parasthesia is numbness and tingling in peripheral parts of body such as hands or feet.

The experience of side effects can be reduced by the dose escalation method recommended by Abbott and Roche. Certain dietary recommendations can reduce side effects. Eating high calorie and hi-fat meals at the time of taking the pills can reduce side effects. Over time the severity and incidence of side effects tend to diminish for many individuals, and a return to a more normal diet is acceptable.

The incidence of all side effects including those related to the liver were increased for those receiving the dose regimens in arms C and D. For that reason, the dose regimens in arms A and B are recommended. Abbott prefers to recommend the arm A dose regimen of 400/400 bid because of the lowest incidence of side effects compared to the other dose regimens; and, because the CD4 increases and viral load reductions appear equal to those of the other dose regimens.

Commentary: The 600/400 bid regimen (Group B) has certain pharmacokinetics characteristics you may want to consider. Because you are taking 50% more ritonavir (vs 400/400 bid regimen), the peak, trough and AUC blood levels for both ritonavir and saquinavir are higher compared to if you were taking 400/400 bid. Is that an advantage? I think it offers some potential benefits. If you were taking ritonavir without saquinavir, 400 mg ritonavir would be suboptimal. However, the 60 week data shows that 400/400 bid was equivalent to 600/400 bid as measured by CD4, viral load reductions and percent below detection. But, having higher trough levels of a drug at the end of a dosing period creates a comfortability or cushion, but tolerability and consideration of long term effects are factors.

Table 4. Hepatic Transaminases (Liver Enzymes)

10 of the 14 participants experiencing the following lab events had at least one of the following abnormalities prior to starting study drugs: baseline SGPT above the upper limit of normal; Hepatitis B serum antigen positive; or, Hepatitis C antibody positive. Study investigators concluded that liver status prior to treatment with study drugs indicates a potential for elevation of liver enzymes during treatment with study drugs. Individuals with any of the 3 conditions mentioned above (hep B antigen+, hep C antibody+, or elevated LFTs) were more likely to experience grade 3/4 elevations of liver enzymes while taking study drugs. Individuals with such background should closely monitor LFTs during therapy.

Grade 3 or 4	400/400	600/400 bid	400/400	600/600 bid

	bid		tid	
-elevated SGOT (AST) and/or SGPT (ALT)	2*	2	2	8

* one patient developed serologically proven Hepatitis A; one patient increased ritonavir dose in violation of protocol

Commentary: Some individuals, soon after starting ritonavir+saquinavir regimen, may develop significant elevations in LFTs to the 500-600 level. Rather than immediately discontinuing therapy over concern about those elevations, trying to work through the elevations while continuing on same regimen with very close monitoring may be successful. The elevations may peak and slowly decrease over time to a manageable level.

Triglycerides

- 11% (16/141) of patients developed grade 3 or 4 (1500 mg/dl) elevations in triglycerides levels
- 6/16 were treated with antihyperlipidemic agents (drugs that may lower triglyceride levels)
- No cases of pancreatitis have been observed

Table 5. Effect of Antihyperlipidemic Agents on Triglyceride Levels

pt #	Treatment Arm	Antihyperlipidemic Drug Used	Pre-Intervention Max Trig Level	Post-Intervention Trig Level
1048	A	Atromid	2000	636
1031	B	Clofibrate	2870	815
1066	B	Atromid-S	3570	626
2030	C	Lopid	1762	877
2020	D	Lopid	2568	1821
2031	D	Lopid	2085	1392

At week 48, the mean increase from baseline in triglyceride levels for each of the 4 dose regimens were about: +175 for both Groups A and B (400/400 bid, 600/400 bid); +290 for Group D (600/600 bid); +260 for Group C (400/400 tid). The suggestion is that the regimens in A & B are less likely to cause greater increases in triglycerides.

Table 6. Treatment Intensification

- 27 patients added up to 2 NRTIs after week 12 for virologic failure or incomplete suppression
- d4T/3TC were the most common pair used
- 23/27 (85%) were <200 copies/ml after intensification and remained at that level at week 60

	400/400 bid	600/400 bid	400/400 tid	600/600 bid
# adding NRTI for incomplete incomplete suppression	8	5	4	10
added d4T/3TC	8	5	2	8

other	0	0	2	2
# with plasma HIV RNA <200 copies/ml after intensification	7/8	5/5	3/4	8/10

Correlation of Compliance with Treatment Response at Week 24

In the week 24 data report (see the [Double Protease Combination](#) report on the NATAP website) the investigators reported a compliance assessment of participants up to week 24. They concluded compliance is highly correlated with treatment response. At week 24, 90% of those defined as being compliant were <200 copies/ml; 97% of those defined as compliant were <1000 copies/ml. Only 66% defined as noncompliant were <200 copies/ml and only 73% were <1000 copies/ml. See the actual report for the investigators definition of compliance.

Viral Load Reduction at Week 12 Predicts Treatment Response at Week 24

This report also was issued at week 24 and is discussed in the above mentioned report on the NATAP website. Investigators showed data that of individuals with <1001 copies/ml at week 12, 98% had <200 copies at week 24; of individuals with >1000 copies/ml at week 12, only 25% had viral load <200 copies/ml. If an individual's viral load was <201 copies/ml at week 12, 93% were <200 copies/ml at week 24. At the Chicago Retrovirus Conference, Lisa Demeter reported that data from ACTG 320 indinavir clinical endpoint study indicates that early viral load reductions also predict treatment response in that study.

The Effect on CSF Viral Load of RTV/SQV and RTV/SQV+d4T

NATAP reported preliminary data from the Prometheus Study that was presented at the Hamburg AIDS Conference. See the report on [Double Protease Combinations](#) on this website for details. A 24 week update was reported in Chicago. Investigators reported CSF viral load changes between week 0 and week 12 for 8 individuals receiving RTV/SQV alone and for 9 individuals receiving RTV/SQV+d4T. Unlike the CSF data above, this has a comparison between two time points (weeks 0 and 12).

- 138 participants were randomized in this open label study to receive either RTV/SQV (400 mg bid of both) or RTV/SQV+d4T
- there were 7 discontinuations; adverse events experienced were mild/moderate diarrhea (50%); oral parasthesia (50%)- tingling and numbness around mouth; elevated liver enzymes (28%) - more common in RTV/SQV/d4T arm; elevated triglycerides (25%)
- mean baseline CD4 was 273 and 251 for protease alone and d4T arms, respectively; mean baseline HIV RNA was 4.3 log (about 20,000 copies/ml) for both arms; 54% in protease alone arm had previous NRTI experience while 48% in d4T arm had previous NRTI experience
- at week 24, 64% taking RTV/SQV alone and 87% taking RTV/SQV/d4T were <400 copies/ml (total # of evaluable patients at week 24 is 111)
- if viral load did not reach undetectable by week 18, intensification was permitted; 6 patients in the RTV/SQV arm intensified with d4T/3TC and all 6 were undetectable by week 36
- mean CD4 increase was about +145 for both arms

Table 7. CSF Substudy

28 patients volunteered for the substudy and 17 completed 12 weeks. Lumbar punctures were performed before the start of study (week 0) and after 12 weeks (week 12).

PT #	Treatment	Prior Drug x	Week 0 Serum	CSF	Week 12 Serum	CSF
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1	RTV/SQV	naive	+	17,700	-	3,188
2	RTV/SQV	experienced	+	1,136	-	489
3	RTV/SQV	naive	+	24,118	+*	-
4	RTV/SQV	naive	+	5,357	+	22,178
5	RTV/SQV	naive	+	1,645	+	11,536
6	RTV/SQV	exp	+	-	-	-
7	RTV/SQV	exp	+	-	-	-
8	RTV/SQV	naive	+	-	-	-
9	R+S/d4T	exp	+	18,149	-	-
10	R+S/d4T	exp	+	868	-	-
11	R+S/d4T	naive	+	13,788	-	-
12	R+S/d4T	naive	+	655	-	-
13	R+S/d4T	exp	+	3,872	-	1,233
14	R+S/d4T	naive	+	-	-	-
15	R+S/d4T	naive	+	-	-	-
16	R+S/d4T	naive	+	-	-	-
17	R+S/d4T	naive	+	-	-	-

+ HIV RNA is detectable (400 copies/ml is the lower limit of detection)

- HIV RNA is undetectable

*serum (blood) HIV RNA was 624 copies at week 12, and undetectable at week 24

Commentary: As you can see, of the patients with detectable VL in serum and CSF at week 0, and undetectable VL in serum at week 12 1/3 on RTV/SQV has an undetectable VL in CSF at week 12, as compared to 4/5 in the RTV/SQV/d4T arm. The results from this study are preliminary; it may be too soon to draw conclusions and too small a number of patients at this point to draw conclusions. Week 12 may be too soon to evaluate the effect of a therapy on CSF viral load. In the CSF evaluation discussed above where 14/15 had undetectable CSF viral load, the CSF viral load levels were assessed after one year of therapy. The authors said that neither ritonavir nor saquinavir was found to penetrate the CSF well in 9 patients as measured by RTV or SQV CSF drug levels. But, ritonavir is 99% protein bound in blood, and if you were looking for unbound ritonavir in blood you may not be able to find it.

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Nelfinavir + Saquinavir

There were updated reports from two studies of this combination at the Retrovirus Conference. [NATAP Reports January 1998 issue](#) reported the updates that were presented at the European AIDS Conference Hamburg in November 1997. The following report provides the latest information which was made available in Chicago. The Kravick study is a small open label evaluation of 14 individuals receiving NFV

750 mg tid (3X/day) and SQV 800 mg tid (3X/day). Nelfinavir increases SQV SGC AUC (blood levels) by 5 fold. Saquinavir does not significantly effect NFV blood levels. SQV 800 mg tid was selected by Roche for both of the studies discussed here. Participants in this study were both NRTI naive (n=3) and experienced (n=11) but protease naive; some took NRTIs with the NFV/SQV therapy while others received only the NFV/SQV combination. The initial part of the study was a pharmacokinetic evaluation following which all participants were maintained on NFV 750 mg tid + SQV SGC 800 mg tid with the possible addition or continuation of up to 2 NRTIs .

No participants had current opportunistic infections at study entry. The median baseline HIV RNA was 39,917 copies/ml (range 19,496 - 109,065). The median CD4 count was 327 cells (range 19-621).

The investigators reported that from genotypic analysis of isolates drawn from all subjects in weeks 15-22 and weeks 20-35 no occurrence of the D30N mutation was observed. At month 12, the median decrease in HIV RNA was about 2.4 log (n=9) and the median increase in CD4 was about 100 (the increase at month 11 was 172), n=9. The percent <500 copies/ml was 80% at month 12 (n=9) and 90% at month 11. As you can see, the data is based on a small number of individuals.

Table 8. Treatment Related Adverse Events

Investigators reported there were no clinically significant drug related lab abnormalities.

Adverse Event	Moderate (Grade 2)	Severe (Grade 3)
Abdominal pain/cramps	2	0
Asthenia	1	0
Ataxia	1	0
Diarrhea	6*	0
Dyspepsia	1**	0
Ear Pain	1	0
Flatulence	2*	0
Headache	3	0
Pain in the legs	1	0

* 5 patients tested positive for intestinal parasites which may have contributed to gastrointestinal adverse events

** patient diagnosed with H. Pylori which may have contributed to dyspepsia

Table 9. Individual Patient Summary

You will see in table that at some time points it just says PCR neg without mutation changes. When a person is PCR neg you cannot detect mutations. DC@ M6 means discontinued at month 6. BLD means viral load is below the level of detection. There are 4 discontinuations noted below.

Pt#	Study	Baseline	Week	Genotypic Changes	HIV RNA	CD4	NRTI	On Study
	Status	HIV RNA			@12mo	@12mo	Exp	NRTIs

1	on study	31,284	1	41,60	+0.80 log*	+152	yes	AZT
1			18	PCR neg				
1			26	41				
2	DC@ M6	61,284	1	41,60,63	-2.10	-174	yes	na
2			18	60,62,63,71,84, 90				
2			22	60,63,71,73,84, 90				
3	on study	41,008	1	35,63,77,93	-2.44	+323	no	none
3	BLD		18	PCR neg				
3			22	63,77,93				
4	on study	19,847	1	70,71,72,77,93	-1.93	-133	yes	d4T/3T C
4	BLD		22	PCR neg				
4			35	PCR neg				
5	DC@ M2	102342	nd		-0.38	-64	yes	na
6	on study	38,825	1	63,72	-2.36	+101	yes	3TC
6	BLD		21	63,72				
6			25	PCR neg				
7	on study	98,679	1	63	-2.46	+432	yes	none
7	BLD		21	63				
7			25	63				
8	on study	27,155	1	63,71	-2.39	+191	yes	ddl
8	BLD		17	63,71				
8			21	PCR neg				
9	on study	71,650	1	35,36,63	-2.40 log	+12	no	d4T/3T C

9	BLD		17	35,36,48,54,63				
9			21	35,36,48,54,63,82				
10	DC@M8	183929	1		-0.85	+126	yes	na
10			21	48,74				
10			26	48,54,74				
11	on study	22,124	1	41,71,93	-1.17	+11	yes	none
11			17	PCR neg				
11			21	PCR neg				
12	on study	19,496	1	63,72,77	-1.91	+172	yes	AZT
12	BLD		15	PCR neg				
12			20	PCR neg				
13	DC@M8	109065	1	63	-0.11	+35	yes	na
13			16	36,63,71,88,90				
13			20	36,63,71,88,90				
14	on study	37,682	nd		-2.15	+100	no	none
14	BLD							

* at a subsequent visit this person was BLD

For many of the participants there were more mutations than I noted in the table above but there was limited space, so I noted the mutations and changes I thought might be relevant.

The second study called **SPICE** was reported by M Opravil and others and is a pilot randomized study enrolling 157 individuals comparing 4 treatment arms; the number randomized to each arm in parenthesis:

- SGC SQV 1200 mg tid + 2 NRTIs (A), (26)
- NFV 750 mg tid + 2 NRTIs (B), (26)
- SQV SGC 800 mg tid + NFV 750 mg tid + 2 NRTIs (C), (51)
- SQV SGC 800 mg tid + NFV 750 mg tid without NRTIs (D), (54)

Crossovers to other arms were permitted for intolerance or virological failure. Participants had to be able to start at least 1 new NRTI. The study investigators said the data should be considered preliminary until formal analysis at week 48.

Table 10. Baseline Characteristics

	SQV+2 NRTIs (A)	NFV+2 NRTIs (B)	SQV/NFV+2 NRTIs (C)	SQV/NFV (D)
N	26	26	51	54
% female	31%	8	10	15
% non-white	4	0	14	13
Mean HIV RNA	63,000	63,000	50,000	63,000
Mean CD4	334	305	300	301
% Treatment naive	54%	54%	53%	56%
#(%) treatment exp & starting 2 new NRTIs	3 (25%)	2 (17%)	6 (25%)	na

Table 11. Concomitant NRTIs

	AZT/3TC	d4T/3TC	d4T/ddI	AZT/ddC	other
SQV+2 NRTIs (A)	21%	26%	26%	6%	3%
NFV+2 NRTIs (B)	37%	38%	10%		
SQV+NFV+2 NRTIs (C)	26%	36%	15%	5%	3%

Table 12. Discontinuations and Crossovers

	SQV+2 NRTIs	NFV+2 NRTIs	NFV+SQV+2 NRTIs	NFV+SQV	Total
	26	26	51	54	
Discontinuations-					
Adverse event/intercurrent ill.	3	1	4	3	11
Treatment Failure	1	1	1	4	7
Withdrawn consent	-	1	1	-	2
Lost to followup	-	-	2	1	3
TOTAL	4	3	8	8	
Crossover for toxicity	1	1	1	3	6

Crossover for virologic failure	2	5	0	11	18
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Table 13. Disposition of Virologic Failures

All crossovers were to NFV+SQV+2 NRTIs.

(N)	Virologic Failure	Crossover	Remaining on Regimen	Study Withdrawal
SQV+2 NRTIs (26)	5	2	2	1
NFV+2 NRTIs (26)	9	5	3	1
SQV+NFV+2 NRTIs(51)	4	-	2	2
SQV+NFV (54)	18	11	4	3

Serious Adverse Events

Of 16 reported serious AEs, 4 were considered possibly treatment related:

- unstable diabetes (SQV+NRTIs)
- renal colic (SQV/NFV+NRTIs)
- diarrhea and cachexia (SQV/NFV no NRTIs)
- fever (SQV/NFV no NRTIs)

Table 14. Preliminary Week 32 Changes in Viral Load and CD4 from Baseline

By 32 weeks, 24 patients crossed over to NFV+SQV+2 NRTIs (C): 6 for toxicity and 18 for virologic failure (2 from arm A, 5 from arm B, and 11 from arm D). The authors said 11 additional patients were defined as virologic failures but had not yet crossed over at the time of this analysis. The following analysis of data was based on individuals remaining on the therapy to which they were originally randomized (crossovers and discontinuations were not included). The number of evaluable patients are in parenthesis.

	SQV+2 NRTIs	NFV+2 NRTIs	SQV+NFV+2 NRTIs	SQV+NFV
starting # of pts	26	26	51	54
HIV RNA (all pts)				
<400 copies/ml	-1.96 log	-1.77 log	-1.75 log	-1.86 log
Ultrasens <50 copies	-2.48 log	-2.23 log	-2.46 log	-2.39 log
CD4 (all pts)	+92	+73	+134	+161
%<400 (all pts)	70% (20)	55% (20)	83% (40)	69% (36)
%<50 (all pts)	55% (20)	50% (20)	70% (40)	39% (36)

Naive %<400 copies	60% (12)	60% (11)	80% (20)	60% (20)
Exp %<400 copies	70% (8)	40% (9)	80% (20)	70% (16)

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Indinavir + Nelfinavir

In preliminary studies conducted by Agouron they found that in a single dose study drug blood levels to both indinavir and nelfinavir increased compared to monotherapy with each drug. In the interest of potentially increasing potency and decreasing dosing from three times per day to two times per day (for both drugs) this pilot study of combining IDV with NFV was initiated.

21 patients were initially enrolled. They were protease naive, CD4 (100, HIV RNA (30,000 copies/ml. The median baseline viral load was 50,500 copies/ml (range 9000-316,170); the median baseline CD4 was 259 (range 120-568); 58% had no prior anti-retroviral experience and the remaining 42% were NRTI experienced.

Group A received NFV 500mg every 12 hrs + IDV 1000 mg every 12 hrs (q12h) for one week. Starting in the second week they received NFV 750 mg q12h + IDV 1000 mg q12h. Group B started with NFV 750 mg q12h + IDV 1000 mg q12h.

Based on the data from Agouron's single dose studies it was expected by some that those effects seen in that study (increased IDV AUC by 51%-single dose of IDV; increased NFV AUC by 83%-single dose of NFV) would be seen when combining NFV with IDV. The investigators in this study did not observe those PK responses reflected in this study. This indicates that you cannot generally rely upon single or limited dosing studies to predict drug interactions and optimal dosing regimens. To do so is risky. It is safer to wait for additional research identifying adequate dosing regimens.

Investigators in this study found that when combining 1000 mg IDV q12h with 750 mg NFV q12h: indinavir blood levels were similar to indinavir taken at the standard dosing of 800 mg every 8 hours; that indinavir did not increase NFV steady state blood levels, resulting in low NFV trough levels. At week 8, 7/10 study participants were <500 copies/ml, and 9 patients had a mean increase in CD4 of 156 cells. Treatment was discontinued in 1 person for rash; other adverse events included: diarrhea/loose stools (6), bloating (2), and nephrolithiasis (1); nephrolithiasis can lead to kidney stones.

Because of the low NFV trough levels, a higher dose of nelfinavir was investigated. All participants raised their dose of nelfinavir from 750 to 1000 mg q12h while maintaining IDV dosing at 1000 mg q12h.

For an explanation of terms like trough, AUC, Cmax and pharmacokinetics (PK) , see the report titled [Primer on PK](#) on the web site. Without understanding these terms it is difficult to understand the considerations that go into selecting dosing, and to understand the following tables and much of the other information in NATAP's reports.

Table 15. 8 Week PK (pharmacokinetics) Data on 11 Patients Compared to Historical IDV & NFV Monotherapy Data; this table describes the blood levels obtained using the initial dosing of NFV 750 mg q12h co-administered with IDV 1000 mg q12h, and compares it to blood levels seen when taking NFV or IDV at the standard monotherapy dosing

	Trough	Est AUC 24 hrs	Cmax
IDV 1000mg every 12 hrs	205 nM	99.8 uM*hr	14.3 uM
IDV 800mg every 8 hrs	251 nM	92.1 uM*hr	12.6 uM

NFV 750mg every 12 hrs	<i>0.7 mg/L</i>	<i>50 mg hr/L</i>	3.5 mg/L
NFV 750mg every 8 hrs	1.5 mg/L	56 mg hr/L	3.5 mg/L

As you can see the trough and AUC (italics) for the NFV 750 q12h dosing regimen was not increased by the addition of IDV, compared to the trough and AUC values for taking NFV monotherapy every 8 hrs (trough- 0.7 vs 1.5 mg/L, AUC- 50 vs 56 mg hr/L).

Table 16. PK of 5 Patients at 1000 mg q12h dose of NFV Compared to the NFV 750 mg q12h Dose; this table displays the changes in AUC, trough and Cmax that occurred as a result of raising the NFV dose to 1000 mg q12h co-administered with IDV 1000 mg q12h

Patient #	750 mg Trough mg/L	1000 mg Trough mg/L	750 mg AUC 12h mg*h/L	1000 mg AUC 12h mg*h/L	750 mg Cmax mg/L	1000 mg Cmax mg/L
2	0.356	0.447	16.9	19.6	2.43	2.63
4	0.461	0.386	20.8	21.8	3.09	4.07
1	0.359	0.131	13.4	13.2	2.36	2.86
13	2.530	4.78	56.3	76.5	6.20	8.18
14	0.255	0.618	9.5	18.9	2.00	2.80

The investigators reported the mean percent change resulting from increase in NFV dose of 750 mg q12h to 1000 mg q12h in AUC, Cmax and trough for these 5 patients was 31%, 27%, and 35%, respectively.

10/21 (47%) had undetectable HIV RNA by the Roche Amplicor viral load test (<400 copies/ml). 6 of these 10 were undetectable using the Roche ultrasensitive test (<50 copies/ml). Three study participants added NRTIs to their regimen after at least 12 weeks either for virological (viral load) failure or to increase antiviral effect to prevent virological failure. The median increase in CD4 from baseline (12-32 weeks) was 133 cells. There were 5 discontinuations.

Table 17. Individual HIV RNA Data on 21 Patients

Patient #	Baseline HIV RNA	Study Week	HIV RNA	<50 copies/ml (week)	Comments
1 (A)	112,932	32	20,371	364 (12)	
2 (A)	102,240	32	neg	neg (28)	
3 (B)	123,067	24	neg	80 (20)	
4 (A)	153,425	32	neg	neg (28)	

5 (B)	94,003	20	62,738	na	
6 (B)	48,456	16	neg	neg (12)	
7 (A)	36,440	28	neg	neg (24)	
8 (A)	53,440	32	neg	neg (28)	add d4T @ wk33
9 (A)	92,444	32	neg	210 (24)	add ddl/d4T @ wk37
10 (B)	100,705	24	neg	67 (20)	
11 (B)	74,130	24	3994	na	add ddl/d4T @ wk21
12 (B)	27,501	12	7072	na	
13 (A)	170,384	28	neg	64 (24)	
14 (A)	49,459	24	1088	822 (4)	
15 (B)	57,466	16	<400	na	
16 (B)	77,049	12	neg	neg (8)	
<i>Discontinued</i>					
17 (A)	44,322	28	546	219 (20)	on NFV only; rash (IDV/NFV) & back pain
18 (B)	202,260	24	193,422	na	d/c for viral load failure
19 (A)	118,196	20	10,849	na	d/c for viral load failure
20 (A)	72,606	na	na	391 (8)	d/c for non-compliance
21 (A)	61,811	28	3916	224 (12)	d/c for non-compliance

na- not available

The antiviral activity or potency of the combination might improve if the dosing of indinavir and/or nelfinavir were increased to the dosing regimens used in their bid studies (1200mg bid for NFV and 1250mg bid for IDV). A potential concern might be the increase of side effects such as diarrhea from NFV or nephrolithiasis from IDV. Authors concluded the optimal role of IDV/NFV twice daily dosing will be clarified by ongoing studies using additional dosing regimens and potential future studies evaluating the addition of NRTIs and NNRTIs to this combination.

Table 18. Adverse Events

Event	Number of Patients	Dose Limiting
	total n=21	
Rash	1	0
Gastrointestinal Symptoms*		
Diarrhea	6	0
Bloating/Cramps	4	0
Nephrolithiasis	2**	0

* Grade 2 or higher

**One of these 2 subjects had 2 episodes

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Ritonavir+Nelfinavir

Testing of this combination is in early stages. Two small initial pilot studies are ongoing, exploring different dosing regimens of these two protease inhibitors. One study is exploring 400 mg ritonavir bid + 1000 mg nelfinavir + d4T/3TC, and has just started so it will be a while before data will be available. Investigators are examining the effect of therapy on CSF and lymph tissue, as well as performing immunological evaluations.

In Chicago, JE Gallant and C Flexner of Johns Hopkins and others reported preliminary findings from a small open-label, dose escalating, non-randomized trial in 20 individuals. Participants were protease inhibitor naive while 10 were NRTI experience and 10 were NRTI naive, but all were permitted to add NRTIs after week 12 at the discretion of the investigator.

The study is an initial assessment of safety, pharmacokinetics and antiviral activity of two dosing regimens (400mg RTV bid+500mg NFV bid, 400mg RTV bid+ 750mg NFV bid). Some reasons offered by the investigators for this combination being attractive include:

- Differing primary resistance patterns - D30N for nelfinavir and V82A for ritonavir
- Convenience of twice daily dosing
- Known enhancement of pharmacokinetics of NFV by RTV. RTV slows the metabolism of other protease inhibitors, increasing blood levels and prolonging half-life, because of its potent inhibition of the CYP3A system in the liver which metabolizes protease inhibitors as well as other drugs. It is my understanding RTV increases NFV blood levels by 2 to 2.5 fold but PK data from this study are currently being analyzed
- Since both drugs are highly protein bound, one drug may displace the other from its protein binding sites, especially on alpha1-acid glycoprotein

Baseline Characteristics. Assessment of antiviral activity is based on use of Roche Amplicor Monitor test (400 copies/ml detection limit) and the Roche Ultrasensitive Amplicor test (20 copies/ml detection limit). The median baseline HIV RNA and CD4 for all 20 patients were 32,459 (range 4,118->750,000 copies/ml) and 325 cells (range 23-941), respectively.

The 20 participants were divided into two groups: group 1 received 500mg NFV bid with 400mg RTV bid while group 2 received 750mg NFV bid with 400mg RTV bid. Each group dose escalated for several days

before reaching the full dose regimens.

Group 1 mean baseline HIV RNA was 58,045 copies/ml (range 4,912 to 279,938); mean baseline CD4 was 335 (range 29-1042). 5 persons in Group 1 were treatment naive and 5 were experienced.

Group 2 mean baseline HIV RNA was 135,300 copies/ml (range 7,756-939,794); mean baseline CD4 was 329 (range 186-578). 5 persons in Group 2 were treatment naive and 5 experienced.

Current Status of Group 1 (500mg NFV):

6/10 achieved <400 copies/ml and 2/10 were <20 copies/ml before adding NNRTIs-

- 4 patients discontinued because of virologic failure (>1 log increase in viral load on 2 consecutive visits). Failures occurred during weeks 6 to 8 for 1 person, weeks 12 to 14 for 1 person, and weeks 16 to 20 for 2 persons
- 3 patients with low, but detectable viral load (HIV RNA 20-400 copies/ml) added two NRTIs (d4T/3TC for one, AZT/3TC for two) at weeks 16 (n=1) and 20 (n=2)
- 1 person with undetectable viral load (HIV RNA <20 copies/ml) added AZT/3TC at week 24
- 1 person with low but detectable viral load (HIV RNA 20-400 copies/ml at weeks 20 and 24) remained on RTV/NFV without adding NRTIs person is temporarily off the study due to incarceration, but had HIV RNA <20 copies/ml at week 12 (prior to treatment interruption)
- 1 person is temporarily off the study due to incarceration, but had HIV RNA <20 copies/ml at week 12 (prior to treatment interruption)

Current Status of Group 2:

6/10 achieved <400 copies/ml and 3/10 were <20 copies/ml before adding NRTIs or NNRTI-

- 2 persons with undetectable viral loads (HIV RNA <20 copies/ml) added NRTIs at week 16 (d4T/3TC for one, NVP/3TC for other)
- 3 persons with low but detectable virus (HIV RNA 20-400 copies/ml) added NRTIs at week 16 (n=3): AZT/3TC for 2 and d4T/3TC for 1)
- 3 persons with detectable viral load (HIV RNA >400 copies/ml) added NRTIs at week 16: d4T/ddI in 2, d4T/3TC in 1)
- 1 person with undetectable viral load (HIV RNA <20 copies/ml) at week 16 remained on NFV/RTV without adding NRTIs.
- 1 person with 2 episodes of noncompliance and alcohol abuse (4 day drug holiday at week 10 and 3 day drug holiday at week 16) has withdrawn from study

Genotypic mutations are being assessed in persons experiencing failure.

Table 19. Adverse Events

9/20 persons experienced moderate-to-severe diarrhea

	Group 1- 500 NFV/400 RTV	Group 2- 750 NFV/400 RTV	Total
	n=10	n=10	n=20
Diarrhea	4	5	9
Nausea	3	1	4
Asthenia*	2	1	3

*Asthenia is fatigue and is associated with ritonavir

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141W94 (Amprenavir) in Combination with NFV, SQV or IDV

Joe Eron of UNC reported on the preliminary findings from PROA2001, a small phase II open label study whose goal as stated by Eron is:

- to evaluate the efficacy of 141 in combination with other protease inhibitors for the purpose of identifying which combinations to explore further
- to examine steady state pharmacokinetics for each combination. Data from previous research from which investigators have characterized a preliminary range for increases in Cmax of 16-31% and in AUC of 22-64% for 141 when used with indinavir. They reported no appreciable change in indinavir blood levels when used with 141. *commentary:* These increases, if confirmed in further studies, may contribute to the potency and effectiveness of the combination of 141+indinavir; as possibly reflected by the 3.75 log reduction seen with 141+IDV in the table below.
- to assess safety and tolerability.

Participants are protease naive but could be NRTI experienced. If so they washed out prior to receiving study drugs. CD4 cells >200; HIV RNA >10,000 copies/ml.

Table 20. Treatment Regimens

Dose Group	141 Dose	other PI Dose
A	800 mg tid*	SQV SGC 800 mg tid*
B	800 mg tid	IDV 800 mg tid
C	800 mg tid	NFV 750 mg tid
D	800 mg tid (alone for 3 wks)*	na

*The usual dose of 141 is 1200mg bid. But, 800 mg tid amounts to the same daily dose. The usual SQV SGC dose is 1200 mg tid. After three weeks, participants in Group D added AZT/3TC.

After 12 weeks patients can add NRTIs if their viral load is >400 copies/ml but so far no one has exercised that option. The first 3 weeks included intensive PK. Patients tolerating study drugs could continue out to 48 weeks.

Baseline Characteristics

- Median CD4 - 393 (n=33)
- Median HIV RNA - 4.63 log, n=33 (about 42,600 copies/ml)
- 21 patients had prior NRTI experience in past 6 months
- most patients had none or minimal symptoms

Preliminary Viral Load Data

This analysis was using the 20 copy limit of the ultrasensitive assay. The number of patients starting therapy in each arm is small and the number of evaluable participants at week 16 is even smaller so the results are preliminary. The number of evaluable patients is smaller at week 16 than the number of patients starting in each group not because of dropouts but it represents the numbers moving towards the 16 week endpoint. There were 2 serious adverse events resulting in two dropouts. Because the number

of participants are so small it is difficult to distinguish significant differences between the arms and it is difficult to draw many conclusions.

Table 21. Reductions in Viral Load From Baseline

the number of patients is in parenthesis. Again, after 3 weeks AZT/3TC was added to 141 monotherapy in 4th arm.

	Base VL	Week 2	Week 4	Week 8	Week 16	<400 copies	<20 copies
141+SQV	40,700 (8)	-1.83 (7)	-2.53 (5)	-2.17 (6)	-2.94 (5)	5/5	2/5
141+IDV	67,600 (9)	-2.18 (9)	-2.23 (9)	-2.21 (8)	-3.75 (6)	5/6	4/6
141+NFV	53,700 (7)	-1.78 (6)	-2.04 (6)	-2.29 (6)	-1.84 (6)	3/6	3/6
141+AZT/3TC	12,300 (9)	-1.53 (8)	-1.49 (7)	-2.44 (3)	-2.79 (3)	2/3	2/3

Table 22. Most Common Adverse Events

9/34 patients discontinued study drugs due to consent withdrawal, lost to follow-up, or in two cases serious adverse events.

Event	# pts	Mild	Moderate	Severe
	(n=26)			
Diarrhea	17	14	3	0
Perioral tingling/numbness	10	10	0	0
Nausea/vomiting	9	8	1	0
Headache	8	7	1	0
Abdominal pain/flatulence	7	6	1	0
Cutaneous adverse events	6	4	2	0

Table 23. Adverse Events by Regimen (no. of patients)

Event	141+SQV	141+IDV	141+NFV	141+AZT/3TC
	n=7	n=8	n=7	n=4
Diarrhea	5	3	5	2
Perioral tingling/numbness	1	4	3	2
Nausea/vomiting	3	3	1	2
Headaches	3	3	0	2

Abdominal pain/flatulence	3	2	0	2
Cutaneous adverse events	2	1	1	2

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Treating Protease Resistant Virus-- A Commentary

This brief commentary will address some of the potential options expected to be available for individuals who've failed protease inhibitor(s). Cross-resistance between protease inhibitors is a serious concern. Many experts believe you should choose the most potent regimen for your initial therapy because they believe your first shot is your best shot. In other words, they are saying your first therapy has the best chance for being the most potent and durable. If you fail your initial potent therapy, it lessens the capacity of future therapy to maximize potency. There is some hope that 141W94's resistance profile may be unique enough so that individuals with protease resistant virus might respond to 141: at this point it is uncertain if 141 can have such an effect but there is basis for hope: 141's different resistance profile. But treatment with 141, for those who've failed a protease inhibitor(s), may have to consist of a potent regimen including additional drugs. An example of such a potent regimen might be: 141+IDV+1592+efaveirenz+(PMEA and/or recycled NRTIs). If a person has failed IDV or RTV possibly substituting SQV or NFV for IDV would be preferable. Shortly, it is expected that a couple of new studies may begin for protease failures incorporating 141 into the study regimens.

Additionally, Abbott's second generation protease, ABT-378, is currently in phase II in HIV infected individuals. ABT-378 appears to have a relatively unique resistance profile, based on in vitro research done to date. It did not appear to have a mutation at position 82, which is important for IDV and RTV resistance. ABT-378 will be used with a small dose of RTV because the addition of ritonavir greatly enhances the PK profile of ABT-378. In vitro ABT-378 appears to suppress virus with some limited degree of ritonavir resistance (possibly up to 25 fold RT resistance). As soon as possible, Abbott hopes to start trials with ABT-378 for individuals who've failed protease therapy. As well, Upjohn's new protease, PNU-140690, may offer some effectiveness against protease resistant virus. Upjohn has just started recruiting for a small study evaluating the effectiveness of PNU-140690 in individuals who have failed protease therapy. In one arm indinavir or ritonavir failures will receive PNU140690. The second arm is for individuals who have experience with multiple protease inhibitors. Individuals will receive PNU140690 if they've failed their current protease therapy and had previous protease therapy. The objective is to make a preliminary observation if individuals who've failed protease inhibitors will be sensitive to PNU140690. If all goes well, the hope is that by this Summer a larger study will begin exploring PNU140690's effectiveness for individuals who have failed protease therapy.

At the recent Chicago Retrovirus Conference, preliminary data from Gilead Science's new drug called PMPA showed a -1.22 log reduction over the course of a 30 day study in HIV infected. PMPA is from a new class of drugs called nucleotides. It is not expected that PMPA would be at all cross-resistant with protease inhibitors. Although the development for PMPA in the early stages it is hopeful that it will prove effective.

In the [January 1998 newsletter, NATAP Reports](#), we reported the findings of Dr Cassy Workman from Australia. She used a 6-drug regimen for individuals who failed protease inhibitors. She recycled previously used NRTIs for 12 individuals. The 12 persons had previously used all available nucleosides and 3 protease inhibitors (indinavir, ritonavir and saquinavir). But, they were naive to nevirapine and nelfinavir. The 6-drug regimen was-- d4T, 3TC, ddl, NVP, NFV, and SQV. 3 individuals were intolerant to components to the therapy that they had previously been intolerant to. But, 9/9 individuals had undetectable viral load (<400 copies/ml) at week 12. 12 weeks is too soon to draw conclusions but follow-up information will be reported.

Hydroxyurea (HU) is a potential option for therapy. Studies have shown that in combination with ddl, reductions in viral load can be significant. Hu has been studied with ddl, ddl+d4T, and with ddl+a protease inhibitor. The actual results of these studies were reported in the January NATAP Reports and

separately on this web site. There is no cross-resistance between HU and protease inhibitors. There are 3 concerns attached to using HU therapy: (1) HU can lower the WBC (neutropenia), (2) it may have a negative effect on platelet count, and (3) although viral load may be reduced, proportionate increases in CD4 do not occur; CD4 increases may be blunted; for a discussion of this see the [HU reports](#) on the web site.

According to Franco Lori, the researcher pioneering the research into HU application in treating HIV, neutropenia may be a concern only for individuals who already have a problem regarding their WBC. The same may be true for platelets. If your CD4 is already low, the HU component to a therapy may not raise your CD4 count. But using HU in conjunction with other drugs may have the effect of raising your CD4 count. Consult with a knowledgeable physician before making treatment decisions. Within the next few months several studies will start for individuals who've failed protease inhibitors.

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