National AIDS Treatment Advocacy Project

Nelfinavir: general information, study results (CD4 and viral load), dosing schedule, eating instructions, drug interactions, combination with other protease inhibitors and NNRTIs, side effects, resistance, cross-resistance

Nelfinavir (Viracept) is the fourth protease inhibitor to be FDA approved for accelerated marketing and will be available in the pharmacy by March 20. It was approved "for the treatment of HIV infection when antiretroviral therapy is warranted. This indication is based on surrogate marker changes in patients who received Viracept in combination with nucleoside analogues or alone for up to 24 weeks. At present there are no results from controlled trials evaluating the effect of therapy with Viracept on clinical progression of HIV infection such as survival or the incidence of opportunistic infections."

Nelfinavir is to be taken three times per day with a meal. It does not necessarily need to be taken every eight hours.

You should take nelfinavir as prescribed. You should not alter the dose or discontinue therapy without talking to your doctor. If a dose is missed you should take the dose as soon as possible. If, for example, you realized you missed a dose 10 hours after taking the last dose, and you then take it, you should delay the next dose several hours to space them out properly. Nonetheless, you should take nelfinavir three times per day.

The most frequent side effect associated with nelfinavir is diarrhea. In nelfinavir clinical trials diarrhea was treatable with the non-prescription anti-diarrheal Imodium.

I've excerpted information from the Viracept package insert which I feel is most important and included that in this report together with my comments and thoughts.

Ritonavir, indinavir and saquinavir were evaluated in studies of survival and disease progression, and it was found that use of each of those three in a combination therapy reduced disease progression and prolonged survival; the results were statistically significant. The ritonavir study was conducted in those with advanced HIV. ACTG 320, which was just stopped and studied indinavir, examined individuals with under 200 CD4, and found that disease progression was delayed and survival prolonged. The saquinavir study also resulted in prolonged survival and delayed progression. Nelfinavir is the subject of an ongoing clinical study comparing nelfinavir+nucleosides to ritonavir+nucleosides.

Patient Assistance Program for Both Adults and Children. Agouron has established a Patient Assistance Program "to help patients find a way to pay for Viracept. Agouron will provide Viracept without charge to those patients whose need is greatest and who are least able to pay for the drug. In addition, Agouron will provide Viracept without charge to any child in the U.S. who is not covered by public or private insurance. For information for both adults and children, call toll-free 1-888-777-6637.

Hemophilia. There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B with protease inhibitors. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship has not been established.

Resistance: Patients from studies "were monitored for phenotypic (n=19) and genotypic (n=55) changes". Mutations of one or more were observed at positions 30, 35, 36, 46, 71, 77, and 88. "Of 19 patients for which both phenotypic and genotypic analysis was performed on clinical isolates, 9 showed reduced susceptibility (5- to 95-fold) to nelfinavir in vitro. All 9 patients possessed one or more mutations in the virus gene." The most frequent site of mutations appeared at position 30. "The clinical (for persons taking nelfinavir) relevance of phenotypic and genotypic changes associated with nelfinavir therapy has not yet been established."

Cross-resistance: Isolates obtained from 5 patients which were 5- to 93-fold resistant to nelfinavir in vitro did not demonstrate a similar increase in resistance to indinavir, ritonavir, saquinavir or 141W94, in vitro. However, "following ritonavir therapy, 6/7 clinical isolates with decreased ritonavir susceptibility (increased resistance) (8- to 113-fold) in vitro also showed decreased susceptibility to nelfinavir in vitro (5- to 40-fold). An HIV isolate obtained from a patient receiving saquinavir therapy showed decreased susceptibility to saquinavir (7-fold), but did not demonstrate a concordant decreased susceptibility to nelfinavir. Because the potential for cross-resistance between nelfinavir and other protease inhibitors has not been fully explored, it is unknown what effect nelfinavir therapy will have on the activity of coadministered or subsequently administered protease inhibitors."

Absorption. After single and multiple oral doses of 500 to 750 mg (2-3 250 mg tablets) with food, peak nelfinavir plasma concentrations were typically achieved in 2 to 4 hours.

Effect of Food on Oral Absorption. Maximum plasma concentrations and AUC (area under the plasma concentration-time curve) were 2- to 3-fold higher under fed conditions compared to fasting. The effect of food on nelfinavir absorption was evaluated in two studies (n=14, total). The meals evaluated contained 517 to 759 Kcal, with 153 to 313 Kcal derived from fat. Agouron recommends that "Viracept should be taken with a meal or light snack."

Hepatic or Renal Insufficiency. The pharmacokinetics of nelfinavir have not been studied in patients with hepatic or renal insufficiency; however, less than 2% of nelfinavir is excreted in the urine, so the impact of renal impairment on nelfinavir elimination should be minimal.

Table 1 - Effect of Nelfinavir on Coadministered Drug Plasma AUC and Cmax (Cmax is the peak level of drug concentration reached in blood after dosing).

	Coadministered Drug

Coadministered Drug	**Nelfinavir dose**	**N**	**AUC (95% CI)**	**Cmax (95%)**
3TC 150 mg single dose	750 mg q8h x 7-10 days	11	up 10% (1-20%)	up 31% (5-62%)
d4T 30-40 mg bid x 56 days	750 mg tid x 56 days	8	--	--
AZT 200 mg single dose	750 mg q8h x 7-10 days	11	down 35% (28-41%)	down 31% (8-49%)
Indinavir 800 mg single dose	750 mg q8h x 7 days	6	up 51% (25-83%)	--
Ritonavir 500 mg single dose	750 mg q8h x 5 days	10	--	--
Saquinavir 1200 mg (SGC) single dose	750 mg tid x 4 days	14	up 392% (271-553%)	up 179% (105-280%)
Ethinyl estradiol 35 ug qd x 15 days	750 mg q8h x 7 days	12	down 47% (41-63%)	down 28% (14-39%)
Norethindrone 0.4 mg qd x 15 days	750 mg q8h x 7 days	12	down 18% (12-27%)	--
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	up 207% (151-276%)	up 146% (112-186%)
Terfenadine 60 mg single dose	750 mg q8h x 7 days	12	see below	

"up" indicates increase
"down" indicates decrease
-- indicates no change
** Terfenadine and nelfinavir should NOT be coadministered (see warnings)--Terfenadine plasma concentrations were transiently measurable when coadministered with Viracept

Brief explanation of Cmax and Cmin and anti-HIV drugs. After you've taken your dose of a particular drug, the concentration level of that drug in your blood increases until it reaches its peak (Cmax) level of concentration in your blood. For example, after 4 hours ritonavir reaches its peak level of concentration in the blood. After reaching its peak, blood levels of a drug start declining towards the Cmin (or trough level), which is the lowest concentration (or level) of drug achieved in the blood given the drug dose and

dosing schedule. Every effort should be made to maintain the Cmin above the minimal effective level for maximum antiviral activity, that is above or equal to the lowest level of blood concentration it needs to still adequately suppress virus replication. The amount of time it takes to reach the trough level from the time you took the drug should equal the amount of time between dosing and varies between drugs. For example, Crixivan is taken every 8 hours because the scientists at Merck determined that sometime soon after 8 hours following taking Crixivan the drug concentration in your blood reaches (trough or Cmin) the point where it will fall below the level necessary to adequately suppress virus replication. Dosing schedules should be prescribed to prevent blood levels of a particular drug from falling below the level needed to adequately suppress viral replication. Viral replication causes resistance. Not adhering to a well-designed recommended dose schedule is an invitation for resistance.

Although nelfinavir is prescribed to be taken three times per day, it does not have to be taken every eight hours or every 12 hours (as with ritonavir) because it takes longer than 8 hours to reach the trough level. So, nelfinavir's dosing schedule is not strict and has flexibility; but, nelfinavir must be taken with food or absorption of the drug is much less.

The tables report the changes in AUC and Cmax, both of which may be important for assessing potential toxicities as well as maintaining adequate blood levels when combining a drug with nelfinavir. AUC (area under the curve) is the amount of drug in the blood detectable over a fixed period of time. Drugs can have the same AUC but different Cmax or Cmin. Possibly the most important consideration might be the effect on Cmin that might occur as a result of combining a drug(s) with nelfinavir or any other anti-HIV drug. You always want to maintain a drug's blood concentration level above the Cmin to prevent resistance. That's why dosing schedules should be based on how long it takes to reach the trough or Cmin. The time between dosing is scheduled prior to reaching the trough or Cmin.

Illustration of AUC, Cmax and Cmin

I've tried to keep this illustration simple, but it assumes equivalent potency of both drugs A & B. The first curve with the dashed line represents drug A. The second curve with a thicker line represents drug B. The straight line represents the blood level of drug below which suppression of viral load is inadequate. Keeping drug blood levels above the straight line is necessary to maintain enough adequate suppression of viral replication. The AUC (area under the curve) for either drug represents the total blood concentration over a fixed period of time. You can see how the dosing schedule for drug A & B might

differ.

Table 2 - Effect of Coadministered Drug on Nelfinavir Plasma AUC and Cmax

			Nelfinavir	
Coadministered drug	**Nelfinavir Dose**	**N**	**AUC (95% CI)**	Cmax (95% CI)
ddI 200 mg single dose	750 mg single dose	9	--	--
AZT 200 mg+3TC 150 mg single dose	750 mg q8h x 7-10 days	11	--	--
Indinavir 800 mg q8h x 7 days	750 mg single dose	6	up 83% (34-150%)	up 31% (13-52%)
Ritonavir 500 mg q8h x 3 doses	750 mg single dose	10	up 152% (86-242%)	up 44% (25-67%)
Saquinavir (SGC)1200 tid x 4 days	750 mg single dose	14	up 18% (5-33%)	--
Ketoconazole 400 mg qd x 7 days	750 mg q8h x 5-6 days	12	up 35% (21-49%)	up 25% (8-44%)
Rifabutin 300 mg qd x 8 days	750 mg q8h x 7-8 days	10	down 32% (10-48%)	down 25% (6-38%)
Rifampin 600 mg qd x 7 days	750 mg q8h x 5-6 days	12	down 82% (77-86%)	down 76% (67-83%)

Protease-Protease Interactions

The potential efficacy of protease-protease combination therapy is of keen interest. A pharmacokinetics (PK) study for the combination of nelfinavir+saquinavir has been conducted; the clinical study is supposed to be starting. However, the exploration of these other protease-protease combinations has yet to begin.

ritonavir+nelfinavir -- this appears to be a promising combination. Nelfinavir AUC is increased 152% (about 2.5 fold) by ritonavir, but ritonavir AUC appears unchanged by nelfinavir. The combination of these two drugs could make nelfinavir dosing two times per day rather than 3 times per day, in addition to the potential for increased overall efficacy. Abbott and Agouron do not appear to have scheduled a PK study to begin examining this combination. Community pressure could persuade them to do so.

indinavir+nelfinavir --this also appears to be a promising combination. Indinavir increases the AUC of nelfinavir by 83% (1.8 fold), and nelfinavir increases indinavir AUC 51% (1.5 fold). The combination of these two drugs could potentially convert both drugs to twice per day dosing regimens. Initial studies needs to begin.

nelfinavir+saquinavir -- saquinavir effect upon nelfinavir is negligible (increases AUC by 18%), but nelfinavir increases saquinavir AUC by 392% (4-fold). A PK study has already been conducted and a clinical trial is supposed to be starting.

141W94 -- Glaxo Wellcome recently announced the start of a study comparing the combination of 141 with saquinavir, nelfinavir or indinavir. Unfortunately, they excluded ritonavir from this study. I disagree with that decision; I think they should have been prepared to include ritonavir.

ritonavir+saquinavir -- as you should know the open-label trial of this combination has been ongoing for almost 1 year. Ritonavir increases saquinavir blood AUC by 20 to 50 fold. Four different dosing combinations have been explored with about 140 study participants. Six months data were reported at the 4th Retrovirus Conference in January 1997. The NATAP has a report of the data in our newsletter which is available by mail or on our web site (contact us for a copy).

NNRTIs (non-nucleoside reverse trancriptase inhibitors) and Nelfinavir -- We do not yet have interaction data available for combining nelfinavir with delavirdine or nevirapine. Although some individuals who have no remaining treatment options may want to combine delavirdine or nevirapine with nelfinavir, it is discouraged at least until we have basic interaction data. This basic data would describe the effect of blood levels (AUC) that delavirdine or nevirapine would have on nelfinavir and also the effect of nelfinavir on the NNRTI. Both Agouron and Beohringer Ingelheim (the manufacturer of nevirapine) are about to begin such a study. But, it could take several months to complete.

Results of studies

Study 511 compared nelfinavir+AZT+3TC to AZT+3TC. Two dosing regimens of nelfinavir were compared- 500 mg three times per day and 750 mg three times per day. The study participants were treatment-naive with baseline CD4 and viral load of about 290 cells and about 153,000 copies/ml. Briefly, there were about 300 study participants; those taking either dose of nelfinavir+AZT+3TC experienced an increase of about 125 CD4 from baseline (n=83 taking 750 mg nelfinavir); when viral load was measured by a sensitive assay (lower level of detection is 100 copies) it was reduced about 2.4 log from baseline; when the less sensitive assay was used (lower limit of detection of 500 copies) the viral load reduction was about 2 log. For those taking the 750 mg dose of nelfinavir+AZT/3TC, about 82% were below the level of detection (undetectable) for their viral load (500 copies was the lower limit of detection; the bDNA test was used). For those taking AZT/3TC (n=101), after 24 weeks: the viral load reduction was about 1.4 log (for both tests, 100 and 500 copies); the CD4 increase was about 100 cells; about 20% were below 500 copies (undetectable). The study data (CD4 and viral load changes out to 24 weeks) are reported in more detail in the NATAP newsletter which is available

on our web site or you can contact our office to mail a copy to you (ph: 212-219-0106, fx: 212-219-8473).

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

	Mean CD4 up	**Mean viral load* down**	**% undetect (500 copies)**
NLF (750)+AZT/3TC n=74	+173	-2 log	83%
NLF (500)+AZT/3TC n=65	+174	-1.8 log	60%
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. The 2 log reduction in viral load from baseline (for the NLF 750 arm) after 40 weeks was the same reduction achieved in this triple arm at 24 weeks when the same viral load test was used (with a 500 copy lower level of detection). Some of the numbers in this table were taken by visual examination of a graph line chart, and so were approximated.

The participants in this treatment arm were permitted additional therapy after the initial 6 month trial period.

Study 506 is a double-blind, randomized controlled trial comparing treatment with 2 doses of nelfinavir (500 mg tid and 750 mg tid)+d4T with d4T monotherapy in 308 participants. Sixty-one patients were treatment-naive (20%) and 237 (80%) had a mean duration of previous treatment-experience of 32 months. The mean baseline CD4 was 279 cells and the mean HIV RNA was 141,369 copies/ml. After 12 weeks, participants who were failing therapy (as measured mostly by surrogate marker response) were permitted to alter their study therapy. The failure rate in the d4T arm was much greater than in the arms receiving nelfinavir.

Changes From Baseline for CD4 and HIV RNA

	750mg NLF+d4T	**500mg NLF+d4T**	**d4T**
CD4 up at 12 wks	+120	+110	+35

CD4 up at 24 wks	+100	+100	+40
HIV RNA down at 2 wks	-1.4 log	-1.4 log	-0.6 log
HIV RNA down at 12 wks	-1.3 log	-1.2 log	-0.5 log
HIV RNA down at 24 wks	-1 log	-1 log	-0.6 log

the changes are approximations based on visual observation of line graphs

Drug Interactions

As with other protease inhibitors and NNRTIs (non-nucleoside reverse transcriptase inhibitors), nelfinavir is metabolized in part by CYP3A (the cytochrome P450 system in the liver). Coadministration of nelfinavir with other drugs metabolized through that system may increase or decrease blood levels of nelfinavir or the other drug. Potentially toxic side effects can result or underdosing can result. If the blood level of nelfinavir is decreased too much, you could in effect be taking a sub-optimal dose of nelfinavir and thereby encourage resistance. If the blood levels of the other drug is decreased too much, you could lose the therapeutic effect of that drug in addition to creating resistance. If blood levels of either drug are increased potentially dangerous side effects or toxicities could occur.

The following information is excerpted from the Viracept package insert and so are the recommendations from Agouron. Based on known metabolic profiles, clinically significant drug interactions are not expected between nelfinavir and: dapsone, trimethoprim/sulfamethoxazole, clarithromycin, azithromycin, erythromycin, itraconazole or fluconazole.

Drug Class	**Drugs Within Class Not to be Coadministered With Viracept**
Antihistimines	astemizole, terfenadine
Antimycobacterial agents	rifampin
Benzodiazepines	midazolam, triazolam
GI motility agents	cisapride

Agouron reports that anticonvulsants (carbamazepine, phenobarbital, phenytoin) may significantly decrease nelfinavir blood levels to the extent that nelfinavir may lose its efficacy.

rifabutin --Coadministration of rifabutin resulted in a 32% decrease in nelfinavir blood AUC and a 207% increase in rifabutin blood AUC. It is recommended that the dose of rifabutin be reduced to one-half the usual dose when administered with Viracept.

ketoconazole --Coadministration of ketoconazole with Viracept resulted in a 35% increase in nelfinavir blood AUC. The change was not considered clinically significant and no dose adjustment is needed when ketoconazole with Viracept is coadministered.

ddI --It is recommended that ddI be administered on an empty stomach; therefore, nelfinavir should be taken (with food) one hour after or more than 2 hours before ddI.

3TC or d4T --Little or no change in the pharmacokinetics of either drug was observed when Viracept was coadministered with 3TC or d4T.

AZT -- Coadministration of AZT and 3TC with Viracept resulted in a 35% decrease in AZT blood AUC. A dose adjustment is not recommended by Agouron when AZT is administered with Viracept.

Rifampin -- Coadministration of rifampin and Viracept resulted in an 82% decrease in nelfinavir blood AUC. Viracept and rifampin should not be coadministered.

Ethinyl estradiol and norethindrone (oral contraceptives) --Coadministration of Viracept with OVCON-35 resulted in a 47% decrease in ethinyl estradiol and an 18% decrease in norethidrone blood concentrations. Alternate or additional contraceptive measures are recommended during therapy with Viracept.

Percentage of Patients with Treatment-Emergent Adverse Events of Moderate or Severe Intensity Reported in >2% of Patients

	Study 511 - treatment naive			**Study 506 - treatment-experienced**		
Adverse Events	AZT +3TC	500mg tid NLF+AZT/3TC	750mg tid NLF+AZT/3TC	d4T	500mg tid NLF+d4T	750mg tid NLF+d4T
	n=101	n=97	n=100	n=109	n=98	n=101
Abdominal pain	1%	0	0	3%	2%	4%
Asthenia	2%	1%	1%	4%	3%	1%
Diarrhea	3%	14%	20%	10%	28%	32%
Nausea	4%	3%	7%	1%	3%	2%

Flatulence	0	5%	2%	4%	8%	3%
Rash	1%	1%	3%	0	4%	3%

As you can see, the only detectable adverse event of concern is diarrhea, which is treatable with Imodium.

Percentage of Patients by Treatment Group With Marked Laboratory Abnormalities in >2% of Patients (Marked laboratory abnormalities are defined as a grade 3 or 4 abnormality in a patient with a normal baseline value or a Grade 4 abnormality in a patient with a Grade 1 abnormality at baseline)

Study 511 - treatment naive				**Study 506 - treatment-experienced**		
	AZT +3TC	500mg tid NLF+AZT/3TC	750mg tid NLF+AZT/3TC	d4T	500mg tid NLF+d4T	750mg tid NLF+d4T
	n=101	n=97	n=100	n=109	n=98	n=101
Hemoglobin	6%	3%	2%	0	0	0
Neutrophils	4%	3%	5%	1%	1%	4%
Lymphocytes	1%	6%	1%	1%	1%	0
ALT (SGPT)	6%	1%	1%	1%	3%	2%
AST (SGOT)	4%	1%	0	0	3%	3%
Creatine Kinase	7%	2%	2%	4%	5%	6%

As you can see, from studies conducted and analyzed to date, changes in lab markers are not significant overall.