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Nelfinavir

A Review of its Therapeutic Efficacy in HIV Infection

Blair Jarvis and *Diana Faulds*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

A. Breckenridge, Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, England; ***C.C.J. Carpenter,*** Brown University, The Miriam Hospital, Providence, Rhode Island, USA; ***J. Gatell,*** Hospital Clinic Provencal, Barcelona, Spain; ***B.G. Gazzard,*** Chelsea and Westminster Hospital, London, England; ***S. Kravcik,*** Ottawa General Hospital, Ottawa, Ontario, Canada; ***P. Krogstad,*** Department of Pediatrics, UCLA School of Medicine, Los Angeles, California, USA; ***A. Pozniak,*** Department of Genitourinary Medicine, King's College School of Medicine and Dentistry, King's College, London, England; ***A. Rachlis,*** Sunnybrook Health Science Centre, University of Toronto, Toronto, Ontario, Canada; ***C. Terriff,*** College of Pharmacy, Washington State University, Spokane, Washington, USA; ***D. Zarowny,*** Canadian HIV Trials Network, Vancouver, British Columbia, Canada.

Data Selection

Sources: Medical literature published in any language since 1966 on nelfinavir, identified using AdisBase (a proprietary database of Adis International, Auckland, New Zealand), Medline and EMBASE. Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: AdisBase search terms were 'nelfinavir', 'AG-1343', 'AG-1346' and 'viracept'. Medline and EMBASE search terms were 'nelfinavir', 'AG-1343', 'AG-1346', 'viracept' and '159989-65-8'. Searches were last updated 28 May 1998.

Selection: Studies in patients with HIV who received nelfinavir. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: AG-1343, drug interactions, nelfinavir, pharmacokinetics, pharmacodynamics, therapeutic use.

Contents

Summary

Abstract

Nelfinavir is a selective inhibitor of HIV protease, the enzyme responsible for post-translational processing of HIV propeptides. In the presence of the drug, immature, noninfectious virus particles are produced.

Nelfinavir in combination with nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors and/or other protease inhibitors profoundly suppresses viral replication. Plasma HIV RNA levels (viral load) rapidly fall below the limit of detection (LOD; usually 400 or 500 copies/ml) in the majority of patients. When used in combination with NRTIs, nelfinavir 1250mg twice daily produced similar results to 3-times-daily nelfinavir at a range of total daily dosages. In an ongoing study >70% of adults receiving a nelfinavir-based combination regimen had plasma HIV RNA levels below the LOD (<400 copies/ml) after 84 weeks. In addition, 73% of paediatric patients receiving nelfinavir plus at least 1 new NRTI had viral loads below the LOD (<400 copies/ml) after 34 weeks. Furthermore, CD4+ cell counts generally increased in conjunction with reductions in viral load.

Combination therapy with nelfinavir and saquinavir results in higher saquinavir plasma concentrations, makes twice-daily administration of saquinavir feasible and may delay the emergence of resistant viral strains. A unique mutation at codon 30 (D30N) of the protease gene confers resistance to nelfinavir, but HIV with the D30N mutation remains fully susceptible to indinavir, ritonavir and saquinavir *in vitro*. Nonetheless, in clinical use, significant cross-resistance is seen with all currently available protease inhibitors.

Diarrhoea is the most frequently reported adverse event in patients receiving nelfinavir-based combination therapy and has been reported in up to 32% of nelfinavir recipients in randomised trials. Diarrhoea is generally of mild to moderate severity and does not result in weight loss. Rash, nausea, headache and asthenia were each reported in ≤5% of patients. Approximately 5% of patients enrolled in an expanded access programme in the US discontinued nelfinavir because of adverse events. Nelfinavir is metabolised by the cytochrome P450 system. Several clinically significant pharmacokinetic drug interactions between nelfinavir and other drugs (i.e. ketoconazole, rifabutin, rifampicin), including other protease inhibitors (i.e. indinavir, ritonavir, saquinavir) have been documented. As with other available protease inhibitors, hyperglycaemia, hyperlipidaemia and abnormal fat distribution have been reported, albeit infrequently, in association with nelfinavir.

Conclusion: Nelfinavir-based combination regimens are well tolerated and produce profound and prolonged suppression of HIV replication in adult and paediatric patients. Hence, nelfinavir is suitable for inclusion in antiretroviral regimens for initial therapy for HIV infection and, alternatively, in regimens for patients unable to tolerate other protease inhibitors.

Antiviral Activity

HIV protease cleaves viral propeptides [*gag* (p55) and *gag-pol* (p160)] to yield structural and enzymatic HIV proteins and is essential for the production of infectious virus particles. Nelfinavir is a selective, nonpeptidic, competitive inhibitor of HIV protease. Immature, noninfectious viral particles are produced after exposure of acutely and chronically infected cells to nelfinavir. The concentration of nelfinavir inhibiting 50% (EC_{50}) of reverse transcriptase production in several laboratory or clinical strains of HIV-1, including a zidovudine-resistant strain, was 10 to 60 nmol/L in acutely infected human cells. In human T lymphocytes

chronically infected with HIV-1, the EC_{50} was 39 nmol/L. Nelfinavir when combined with most other antiretroviral drugs has either synergistic or additive activity against HIV-1.

Nelfinavir resistance identified during dose-finding studies was predominantly associated with substitution of asparagine for aspartate at amino acid position 30 (D30N) of HIV protease. *In vitro* susceptibility to indinavir, saquinavir and ritonavir was unaffected in isolates with the D30N mutation. Significant cross-resistance is seen with all currently available protease inhibitors. In one study, 58 to 60% of clinical isolates resistant to indinavir, ritonavir or saquinavir were cross-resistant to nelfinavir. Conversely, the frequency of cross-resistance to nelfinavir-resistant isolates was 77% for indinavir, 79% for ritonavir and 64% for saquinavir.

Pharmacokinetic Properties

The time to maximum plasma concentration of nelfinavir was 3.4 to 4 hours after oral administration of a single 100 to 800mg dose. After a single 750mg dose, the maximum plasma concentration (C_{max}) was 3.23 mg/L and the area under the plasma concentration-time curve (AUC) was 15.32 mg/L • h. In children receiving nelfinavir 23 mg/kg, median values for C_{max} (3.8 mg/L) and AUC during the 8-hour dose interval (AUC_8) (19 mg/L • h) were similar to those in adults receiving a single 750mg dose. Absorption of nelfinavir is reduced by 27 to 50% in the fasting versus fed state.

In mice, tissue concentrations of nelfinavir generally exceed those in plasma. However, nelfinavir concentrations in mouse brain tissue are <10% of those in plasma.

The mean elimination half-life of nelfinavir is 3.5 to 5 hours. Nelfinavir is metabolised by hepatic cytochrome P450 enzymes; mainly cytochrome P450 3A4 (CYP3A4); and has an active metabolite.

Nelfinavir undergoes metabolic interactions with a number of drugs that are metabolised by CYP3A4 including other protease inhibitors. Ritonavir and, to a lesser extent, saquinavir decrease the metabolism of nelfinavir. Nelfinavir, in turn, impairs elimination of saquinavir and indinavir. The clearance of nelfinavir was considerably increased after administration with rifampicin or rifabutin. Conversely, the clearance of nelfinavir decreased when it was administered with ketoconazole.

Therapeutic Efficacy

Various combinations of nelfinavir and nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and/or other protease inhibitors have resulted in rapid, profound and prolonged reductions in plasma HIV RNA levels and increased CD4+ cell counts. In patients not previously treated with antiretroviral agents, nelfinavir plus 2 NRTIs suppressed plasma HIV RNA levels to a greater extent than the 2 NRTIs alone: >80% of patients receiving nelfinavir 750mg 3 times daily with zidovudine and lamivudine had plasma HIV RNA concentrations below the limit of detection (LOD; 400 or 500 copies/ml) after ≥28 weeks. In contrast 18% of patients receiving zidovudine, lamivudine and placebo achieved similar reductions. More than 70% of patients had viral loads below the LOD after 84 weeks on this triple therapy regimen. When used in combination with NRTIs, nelfinavir 1250mg twice daily produced similar results to 3-times-daily nelfinavir at a range of total daily dosages. Ultrasensitive plasma HIV RNA assays (LOD <50 copies/ml) show that nelfinavir-based combination regimens are capable of profound suppression of viral replication. The viral load was below the LOD (<400 copies/ml) after 34 weeks in 73% of

children (aged ≤13 years) who started nelfinavir 20 to 30 mg/kg 3 times daily and at least 1 new NRTI.

Mean reductions in plasma HIV RNA levels of ≥1.7 $\log_{10}$ copies/ml have been achieved in patients receiving nelfinavir plus saquinavir SGC combination regimens with viral loads below the LOD (<400 or 500 copies/ml) in >55% of patients after ≥24 weeks.

Tolerability

Diarrhoea, the most common adverse effect of nelfinavir, has been reported in up to 32% of patients receiving nelfinavir-based combination regimens in clinical trials. Diarrhoea is generally of mild or moderate severity and can often be controlled with antidiarrhoeal agents.

Diarrhoea was reported by 16% of a series of 1532 US patients who received nelfinavir because of contraindications to, or therapeutic failure or toxicity with other protease inhibitors. Rash, nausea, headache and asthenia were each reported by ≤5% of these patients. Approximately 5% of patients discontinued nelfinavir because of adverse events.

Hyperglycaemia, hyperlipidaemia and abnormal fat distribution have been infrequently reported in association with all available HIV protease inhibitors, including patients receiving nelfinavir therapy.

Dosage and Administration

The recommended dosage of nelfinavir in adult patients with HIV infection is 750mg 3 times daily. Children aged 2 to 13 years should receive oral nelfinavir 20 to 30 mg/kg 3 times daily. Nelfinavir should be taken with food.

Plasma glucose levels should be monitored at regular intervals in patients receiving nelfinavir. Coadministration of astemizole, amiodarone, cisapride, ergot derivatives, midazolam, quinidine, rifampicin, terfenadine or triazolam with nelfinavir is contraindicated because of the potential for drug interactions resulting in clinically significant adverse events.

1. Introduction

HIV protease is an aspartic protease which cleaves viral propeptides [*gag* (p55) and *gag-pol* (p160)] to yield structural and enzymatic proteins essential for HIV maturation and the production of infectious virus particles.[1,2] Inhibition of this enzyme has become a major strategy in the therapy of HIV disease (fig. 1). Protease inhibitors (fig. 2) can profoundly suppress plasma HIV RNA levels and, unlike reverse transcriptase inhibitors (RTIs), have activity against latent HIV infection. The use of protease inhibitors in combination with RTIs has been associated with impressive reductions in morbidity and mortality in patients with advanced (CD4+ cell counts <100/ml) HIV disease.[4,5]

Nelfinavir, a nonpeptidic competitive HIV protease inhibitor developed using protein structure-based design, was briefly reviewed in a previous issue of *Drugs*.[6] Nelfinavir does not significantly inhibit human aspartic proteases including pepsin, renin, gastricin, and cathepsins E and D.[7] In the presence of nelfinavir, immature, noninfectious viral particles are produced.

2. Antiviral Activity

2.1 *In Vitro*

2.1.1 Nelfinavir Alone

Nelfinavir inhibits purified HIV protease with an inhibition constant (K_i) of 1.7[7] or 2 nmol/L.[8]

In human T cell lines (CEM, CEM-SS, MT-2, MT-4), macrophages or peripheral blood mononuclear cells (PBMCs) with acute HIV-1 infection (various laboratory and clinical strains, including a zidovudine-resistant strain), the concentration of nelfinavir inhibiting 50% cell death (ED_{50}) or 50% reverse transcriptase (RT) activity (EC_{50}) ranged from 10 to 60 nmol/L.[7,8] The ED_{50} of nelfinavir

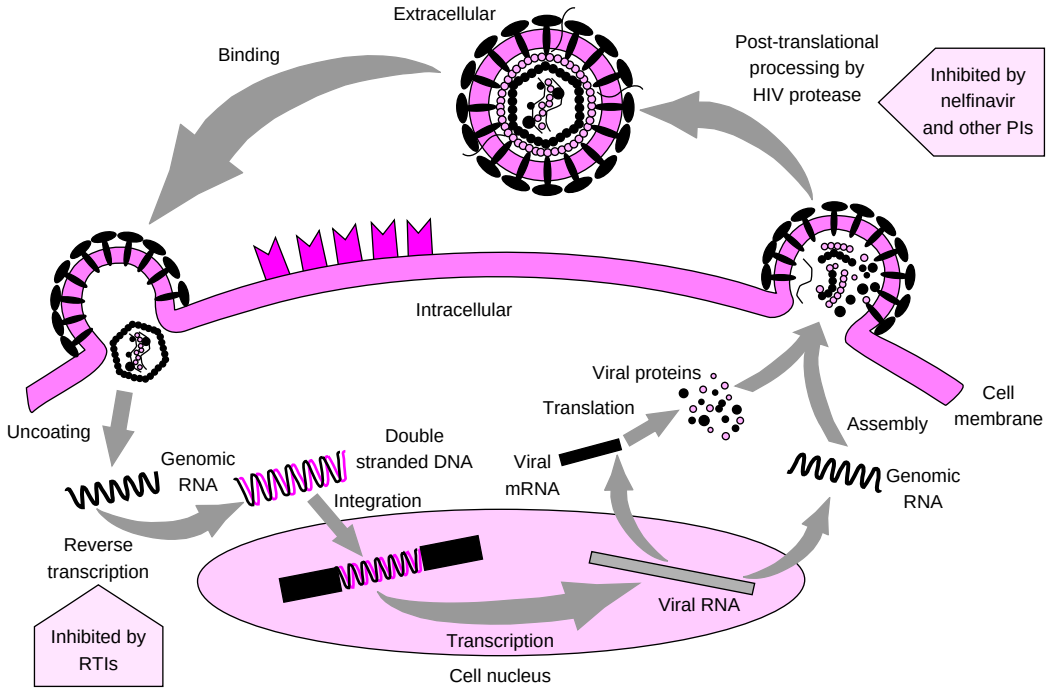


Fig. 1. The life cycle of HIV and the site of action of nelfinavir and other antiretroviral agents. **PI** = protease inhibitors (e.g. nelfinavir, amprenavir, indinavir, ritonavir, saquinavir); **RTI** = reverse transcriptase inhibitors (e.g. didanosine, lamivudine, stavudine, zalcitabine, zidovudine, adefovir, efavirenz, delavirdine, nevirapine). Adapted from Barry et al.[3] with permission.

in CEM-SS cells infected with HIV-2_{ROD} was 9 nmol/L.[7]

In CEM-SS cells with chronic HIV-1_{IIIB} infection nelfinavir had an EC_{50} of 39 nmol/L. Protease activity was only partially restored 36 hours after removal of nelfinavir from culture.[7]

Nelfinavir showed low cytotoxicity *in vitro* with 50% cell death in T cell lines occurring at drug concentrations 526- and 916-fold greater than the ED_{50}s against HIV-1-infected cells.[7]

2.1.2 Nelfinavir in Combination with Other Agents

Combination therapy with a protease inhibitor plus 2 RTIs has become the standard of care for patients with HIV infection, although optimal combinations have yet to be determined (section 7).[9-12]

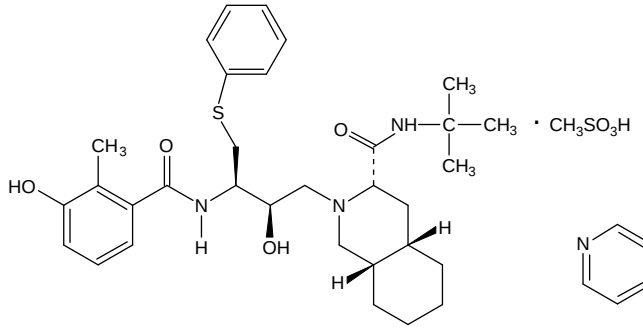
In an *in vitro* study (CEM-SS cells) nelfinavir in combination with various RTIs had synergistic (lamivudine, zalcitabine, zidovudine or lamivudine plus zidovudine) or additive (didanosine or stavudine) activity against HIV-1; combinations of nelfinavir with other protease inhibitors were additive (saquinavir), antagonistic (indinavir) or ambiguous (ritonavir) [table I].[13]

Nelfinavir showed mild to moderate synergistic anti-HIV-1 activity *in vitro* in combination with adefovir or 9-(2-phosphonomethoxypropyl)adenine (PMPA), 2 acyclic nucleoside phosphonate analogues.[14]

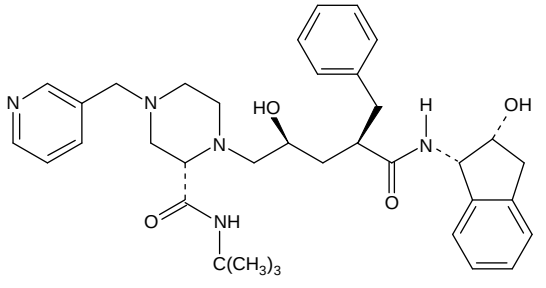
2.2 Resistance

2.2.1 Genotypic Resistance

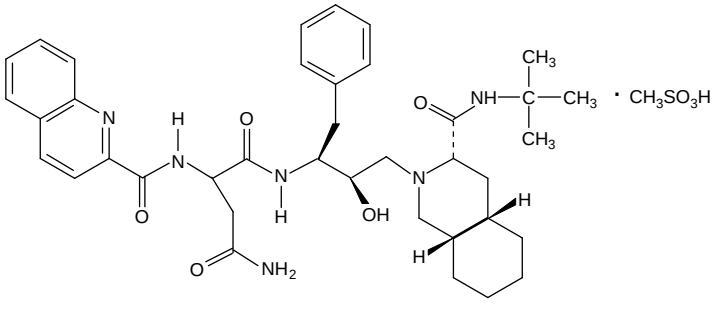
Characterisation of key viral mutations that result in resistance is important for the design of rational combination regimens and to guide therapeutic decisions once resistance arises.[15] The predominant mutation conferring nelfinavir resistance in viral isolates from patients enrolled in dose-finding studies was substitution of asparagine for aspartate at position 30 (D30N) of HIV protease.[16] Clinical isolates with the D30N mutation



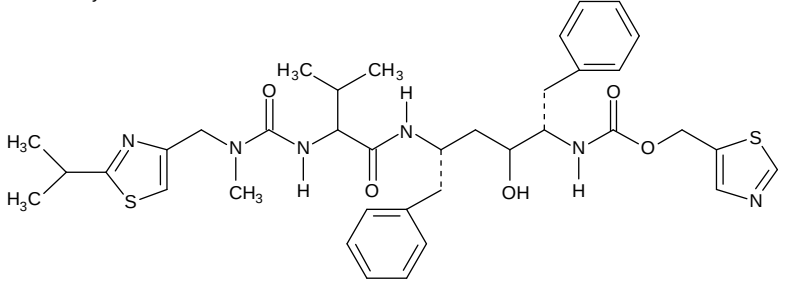
Nelfinavir mesylate



Indinavir



Saquinavir mesylate



Ritonavir

Fig. 2. Chemical structures of nelfinavir and some other protease inhibitors.

had reduced susceptibility (7 times lower) to nelfinavir; however, *in vitro* susceptibility to indinavir, saquinavir and ritonavir was unaffected. Furthermore, clinical isolates from patients receiving nelfinavir did not contain key mutations that confer significant resistance to other protease inhibitors (e.g. codon 82 and 84 for resistance to indinavir and ritonavir and codon 48 for saquinavir resistance) and viral mutants containing these point mutations remained susceptible to nelfinavir *in vitro*.[7,17] A mutation at codon 90 (L90M) that confers a low level of resistance to saquinavir (10- to 20-fold) has been rarely detected in nelfinavir recipients.[7]

In a clinical study in which genotypic analyses were performed after 15 to 22 weeks and again at

20 to 35 weeks, mutations were evident in HIV isolated from 6 of 14 patients receiving nelfinavir 750mg and saquinavir soft gel capsules (saquinavir SGC) 3 times daily; however, the D30N mutation was not detected.[18] Isolates from 4 patients (3 of whom were noncompliant and had increases in viral load) had mutations at codons 48 (G48V) or 90 (L90M) each of which confer low level resistance to saquinavir; however, no isolate had both G48V and L90M which, when combined, confer high level (≈ 100-fold) resistance to saquinavir.

In a further clinical study, 3 of 12 patients experienced loss of efficacy [defined as 2 consecutive measurable plasma HIV RNA levels following suppression below the limit of detection (LOD; <500 copies/ml)] after 7, 15 and 17 months of therapy with nelfinavir 750mg 3 times daily combined with zidovudine and lamivudine.[19] Genotypic analysis revealed mutations in reverse transcriptase [M184V (confers resistance to lamivudine) in all 3 patients] and protease sequences (D30N in 2 and L90M in 1 patient) in HIV isolated from all 3 patients. In another genotypic analysis, HIV with the D30N mutation was isolated from 13 of 18 patients (72%) in whom nelfinavir-based therapy had failed (defined as 2 consecutive viral loads >5000 copies/ml).[20]

2.2.2 Phenotypic Resistance

The data presented in section 2.2.1 suggest that a novel genotype alone confers resistance to nelfinavir and that there is limited cross-resistance between nelfinavir and other protease inhibitors; however, the clinical situation is less conclusive. Although unique genotypes may be associated with resistance to a given protease inhibitor, significant cross-resistance is seen with all currently available drugs in this class.[1,2,21-23] For example, of 365 clinical isolates resistant [defined as a >10-fold increase in EC_{50} compared with a control strain (HIV-1_{LAI})] to indinavir, ritonavir or saquinavir, 58 to 60% were cross-resistant (>4-fold increase in EC_{50}) to nelfinavir.[23] In the same study, the frequency of cross-resistance to nelfinavir-resistant isolates was 77% for indinavir, 79% for ritonavir and 64% for saquinavir. Genotypic analyses were not provided in this study. Furthermore, poor clinical responses (median increase in HIV RNA concentration of 0.05 $\log_{10}$ copies/ml) were obtained with nelfinavir in 23 patients with extensive treatment histories and low (<100 cells/μl) CD4+ cell counts who were not responding to, or were intolerant of, indinavir or ritonavir and had not previously received nelfinavir.[24] Poor responses were also seen in a series of patients who were switched to a second protease inhibitor-containing regimen after failing initial therapy with a nelfinavir-based regimen.[25] The viral load continued to increase in 4 patients and decreased modestly (mean decrease 0.64 $\log_{10}$ copies/ml) in 3 of 4 remaining patients. Hence, cross-resistant phenotypes, in which the susceptibility of HIV to protease inhibitors is reduced, may arise regardless of prior exposure to a particular drug or the presence of specific key mutations.

Table I. Effect of nelfinavir in combination with other antiretroviral drugs against acute HIV-1_{RF} infection in a human T cell line (CEM-SS)[13]

Drug(s) in combination with nelfinavir	Drug class	Effect
Didanosine	NRTI	+/++
Lamivudine	NRTI	++
Stavudine	NRTI	+/++
Zalcitabine	NRTI	++
Zidovudine	NRTI	++
Lamivudine + zidovudine	NRTI + NRTI	++
Indinavir	PI	–
Ritonavir	PI	–/+
Saquinavir	PI	+

NRTI = nucleoside reverse transcriptase inhibitor; **PI** = protease inhibitor; + indicates additive effect; ++ indicates synergistic effect; – indicates antagonistic effect.

Preliminary evidence suggests that combination therapy with saquinavir and ritonavir is effective in patients in whom nelfinavir resistance has been detected.[20,26]

3. Pharmacokinetic Properties of Nelfinavir

The pharmacokinetic properties of orally administered nelfinavir have been studied in healthy volunteers[27-29] and patients with HIV-infection.[30-32] Limited data are also available for children.[33]

In single-dose studies the time (t_{max}) to maximum plasma concentration (C_{max}) was 3.4 to 4 hours after oral nelfinavir 100 to 800mg.[29,30] The area under the plasma concentration-time curve (AUC) was 15.32 mg/L · h, and a C_{max} of 3.23 mg/L was observed after a single 750mg dose was taken with food.[30]

Absorption of nelfinavir is reduced in the fasting state. For example, AUC values were reduced 27 to 50% compared with the fed state when single doses of nelfinavir 400 or 800mg were administered to 6 fasted volunteers.[29]

Plasma drug concentrations exceeded the EC_{95} for HIV-1 (0.04 mg/L) for 8 and 24 hours, respectively, after single oral doses of nelfinavir 100 and 800mg taken with food.[29] A steady-state C_{min} value of >0.6 mg/L was reached after 4 days in healthy volunteers receiving 300mg every 8 hours.[29]

At the end of the dose interval, steady-state C_{min} was 1 and 0.7 mg/L in 21 patients receiving nelfinavir 750mg 3 times daily or 1250mg twice daily, respectively;[31] the time-averaged concentration over the dosage interval (C_{avg} = AUC/tau) was 1.9 and 2.1 mg/L.

Nelfinavir is extensively bound (98%) to plasma proteins.[34]

Nelfinavir is metabolised by at least 4 hepatic cytochrome P450 isoenzymes (3A4, 2C19, 2C9 and 2D6), with cytochrome P450 3A4 (CYP3A4) accounting for about 50% of the total.[28] Nelfinavir has 2 active metabolites: 1 with equivalent anti-HIV-1 activity and the other with 10 to 20% of the activity of the parent compound.[32] The mean AUC over the 8-hour dose interval (AUC_8) of nelfinavir and the most active metabolite were 13.9 and 4.8 mg/L · h in 10 patients after 28 days of nelfinavir 750mg 3 times daily. Concentrations of nelfinavir and its most active metabolite exceeded their respective *in vitro* EC_{50} values for HIV-1 by more than 10-fold throughout the 8-hour dose interval, which suggests that this metabolite contributes substantially to the therapeutic efficacy of the drug.

The mean terminal elimination half-life of nelfinavir is 3.5 to 5 hours.[34]

In mice, nelfinavir concentrations in colon, small intestine, kidney, spleen, liver and lung tissue exceeded those in plasma 4 hours after intravenous administration.[35] Concentrations in brain were <10% of those in plasma; however, in mice with a genetic disruption of the gene coding for the P-glycoprotein drug transporter, nelfinavir concentrations in brain increased 36-fold and were 2.6 times those in the plasma. This finding suggests that the P-glycoprotein is a substantial barrier to CNS penetration by nelfinavir.[35] CSF concentrations have not been quantified in humans receiving nelfinavir.

3.1 In Children

Clearance of nelfinavir was greater in children (adjusted for bodyweight) than in adults. Mean AUC and C_{max} values in 8 children (aged 2 to 13 years) after a single 10 mg/kg dose of nelfinavir were 20 to 40% of those in adults after a similar weight-adjusted dose.[36] Children (aged 3 months to 13 years) require nelfinavir doses (mg/kg) 2 to 3 times higher than adults to achieve similar plasma concentrations. Median steady-state C_{max} and C_{min} were 3.8 and 1.5 mg/L in 19 children (aged 3 months to 13 years) receiving 23 mg/kg 3 times daily; the corresponding median AUC_8 was 19 mg/L · h.[33] These values were similar to those seen in adults receiving a single 750mg dose. Powder and tablet formulations produced similar plasma nelfinavir concentrations in children.

3.2 Drug Interactions

Like all currently available nonpeptidic protease inhibitors, nelfinavir is metabolised to the greatest extent by CYP3A4 (see section 3), so the greatest potential for pharmacokinetic drug interactions is with other drugs metabolised by this isoenzyme.[37]

Dual protease inhibitor-based regimens are currently generating great interest (section 4.1.2). Metabolic interactions between agents in this class are potentially beneficial because they may increase plasma drug concentrations, reduce the required frequency of administration and delay the emer-

Table II. Pharmacokinetic drug interactions involving nelfinavir and other drugs

Coadministered drug dosage (no. of participants)	Nelfinavir dosage	Effect of coadministered drug on nelfinavir pharmacokinetics		Effect of nelfinavir on coadministered drug pharmacokinetics	
		C_{max}	AUC	C_{max}	AUC
In combination with other protease inhibitors					
Indinavir 800mg tid md[a][34]	750mg sd	↑31%	↑83%		
Indinavir 800mg sd[a][34]	750mg tid md			0	↑51%
Ritonavir 500mg bid md[a][34]	750mg sd	↑44%	↑152%		
Ritonavir 500mg sd[a][34]	750mg tid md			0	0
Saquinavir SGC 1200mg tid md[a][34]	750mg sd	0	↑18%		
Saquinavir SGC 1200mg sd[a][34]	750mg md			↑179%	↑392%
Saquinavir SGC 1200mg tid md (14[b])[38]	750mg sd		↑17%		
Saquinavir SGC 1200mg sd (14[b])[38]	750mg tid md				↑403%
Saquinavir HGC 600mg tid md (10[b])[39]	750mg tid md			↑680%	↑740%
Saquinavir HGC 1000mg bid md (10[b])[39]	1250mg bid md			↑890%	↑1150%
Saquinavir HGC 600mg tid md (6[bc])[40]	750mg tid md			↑376%	↑395%
In combination with reverse transcriptase inhibitors					
Delavirdine 400mg tid md (24[d])[41,42]	750mg tid md	↑81%	↑92%	↓34%	↓42%
Didanosine 200mg sd[a][34]	750mg sd	0	0		
Efavirenz 600mg od md(7[d])[43]	750mg tid md	↑17%	↑15%	↓9%	↓8%
Lamivudine 150mg sd[a][34]	750mg tid md			↑31%	↑10%
Nevirapine 200mg bid md (23[b])[44]	750mg tid md	0	0		
Stavudine 30 or 40mg bid md[a][34]	750mg tid md			0	0
Zidovudine 200mg sd[a][34]	750mg tid md			↓31%	↓35%
Lamivudine 150mg + zidovudine 200mg sd[a][34]	750mg tid md	0	0		
Stavudine 30 or 40mg + nevirapine 200mg bid md (12[b])[45]	750mg tid md	0	0	0	0
In combination with drugs used to treat opportunistic infections					
Ketoconazole 400mg od md (12[d])[27,34]	500mg tid md	↑25	↑35		
Rifabutin 300mg od md[a][34]	750mg tid md	↓25%	↓32%	↑146%	↑207%
Rifampicin 600mg (12[d])[28,34]	750mg tid md	↓76%	↓82%		

a Number and status of participants (i.e. patients or volunteers) was not specified.
b HIV-positive patients.
c All patients were receiving ongoing therapy with zidovudine 250mg plus lamivudine 150mg bid.
d Healthy volunteers.

AUC = area under the plasma concentration-time curve; **bid** = twice daily; **C_{max}** = maximum plasma concentration; **HGC** = hard gel capsule; **md** = multiple dose; **od** = once daily; **sd** = single dose; **SGC** = soft gel capsule; **tid** = 3 times daily.

gence of resistance.[21] Nelfinavir impairs the elimination of saquinavir and indinavir but not ritonavir; conversely, the metabolism of nelfinavir is inhibited by ritonavir and to a lesser extent by saquinavir (table II). In contrast to the results obtained with single doses of nelfinavir which showed a decrease in nelfinavir elimination (table II), indinavir did not affect nelfinavir steady-state concentrations in a multiple dose study.[46] Mean steady-state nelfinavir concentrations in patients receiving nelfinavir 750mg plus indinavir 1000mg twice daily were similar to historical control patients receiving nelfinavir 750mg twice daily alone.[46]

Nelfinavir has a lower propensity for drug interactions with currently available RTIs than with protease inhibitors (table II). However, the interaction between nelfinavir and delavirdine warrants further investigation. Substantial reductions in the AUC (42%), C_{max} (34%) and C_{min} (52%) of delavir-

dine occurred when it was administered with nelfinavir to healthy volunteers.[41,42] Whether this interaction will result in subtherapeutic plasma concentrations and will promote resistance to delavirdine in HIV-infected patients is unknown; however, a higher dose of delavirdine (600mg 3 times daily) in combination with nelfinavir is under investigation.[42,47] Nelfinavir also reduces the C_{max} and AUC of zidovudine by >30% (table II); however, intracellular concentrations of zidovudine triphosphate are unaffected by changes of this magnitude and dosage adjustments are not recommended.[2]

The clearance of nelfinavir is increased when given it is with rifampicin (rifampin) or rifabutin and decreased when it is given with ketoconazole; conversely, nelfinavir produces a substantial reduction in the clearance of rifabutin such that reduced dosages of rifabutin are recommended with this combination.[34] Nelfinavir also reduces the C_{max} and AUC of ethinyl estradiol by 28 and 47%. and the AUC of norethindrone by 18%.[34] Hence, the efficacy of combination oral contraceptives may be reduced by nelfinavir.

Nelfinavir may alter the metabolism of amiodarone, astemizole, cisapride, ergot derivatives, midazolam, quinidine, terfenadine and triazolam (see section 6).[34] Furthermore, the clearance of nelfinavir may be increased by coadministration of carbamazepine, phenobarbital or phenytoin.[34]

4. Therapeutic Efficacy

Morbidity and mortality are the primary endpoints for studies of antiretroviral therapy in HIV-infected persons; however, in therapeutic trials of short duration surrogate markers of disease progression are generally used as indicators of biological activity. The effect of nelfinavir on surrogate markers of disease progression [plasma HIV RNA concentrations (viral load) and CD4+ cell counts] has been reported mostly in abstracts or poster presentations. The effect of nelfinavir on clinical endpoints such as mortality or the incidence of opportunistic infections has not been established.

Nelfinavir has been evaluated in combination with a number of antiretroviral therapies in HIV-positive patients.[18,31,33,45,46,48-55] In general, patients had not previously received protease inhibitors,[18,33,45,46,49,51-54] had plasma HIV RNA levels ≥10 000 copies/ml (4 $\log_{10}$ copies/ml)[18,31,46,48-52,54] and had CD4+ cell counts ≥100/ml[45,46,48,52] when screened for inclusion. All trials were randomised but only 2 were double-blind.[31,49] Five trials enrolled only antiretroviral therapy-naive patients.[49,50,52,56,57]

Nelfinavir 900 to 3000 mg/day rapidly reduced plasma HIV RNA levels and increased CD4+ cell counts when administered alone to HIV-positive patients in short term, nonblind, dose-finding studies.[58-61] However, single agent therapy for HIV is strongly discouraged, as it produces only short term improvement because of the rapid emergence of drug resistance.[9,10,62]

4.1 Effect on Viral Load

4.1.1 In Combination with RTIs

Nelfinavir in combination with nucleoside RTIs (NRTIs) or non-nucleoside RTIs (NNRTIs) rapidly and consistently suppressed plasma HIV RNA concentrations for up to 52 weeks in clinical trials (table III). Mean (or median) reductions in plasma viraemia ranged from 1.6 to 2.4 $\log_{10}$ copies/ml in patients receiving nelfinavir-based combinations. Nelfinavir plus 1 or 2 NRTIs reduced plasma viraemia considerably more than 1 or 2 NRTIs without a protease inhibitor.[48-50] In studies involving patients not previously treated with antiretroviral agents, >80% of patients receiving nelfinavir 750mg 3 times daily with zidovudine plus lamivudine had undetectable plasma HIV RNA levels after ≥28 weeks (LOD <400[49] or <500 copies/ml[50]). In contrast, 18% of control patients treated with zidovudine plus lamivudine had an undetectable viral load.[50]

Reducing the frequency of administration of nelfinavir from 3 times to twice daily does not reduce its efficacy. Nelfinavir 750mg 3 times daily, or 1250mg twice daily, combined with 2 NRTIs produced similar mean reductions in viral load

Table III. Effect of nelfinavir (NFV) combined with reverse transcriptase inhibitors (RTIs) on surrogate markers in persons with HIV infection

Reference	Study design (duration of treatment [wk])	Baseline parameters (mean)		Treatment regimen (mg tid)[a] [no. of patients]	Results (mean change from baseline)		Patients below LOD for HIV RNA (%)
		plasma HIV RNA (log_{10} copies/ml)	CD4+ cell count (cells/μl)		HIV RNA (log_{10} copies/ml)	CD4+ cell counts (cells/μl)	
Combined with lamivudine (3TC) bid and zidovudine (ZDV) tid							
AVANTI 3[50]b	r, nb (28)	5.0c	279c	NFV750/3TC/ZDV [41]	↓1.85c*		83d
		4.8c	287c	3TC/ZDV [40]	↓0.98c		18d
Hecht et al.[57]b	nb (12)	4.9c	541c	NFV750/3TC/ZDV [10]			100d
Study 511[49,63-65]b	r, db, pc (52)	4.9	283	NFV500/3TC/ZDV [97]	↓2.2 (24wk) ↓1.9 (52wk)	↑140e (24wk) ↑192e (52wk)	62f (24wk) 54f (52wk)
				NFV750/3TC/ZDV [99]	↓2.3 (24wk) ↓2.3 (52wk)	↑150e (24wk) ↑198e (52wk)	81f (24wk) 76f (52wk)
				3TC/ZDV [100]	↓1.3 (24wk)	↑104 (24wk)	8f (24wk)
Combined with 3TC bid and stavudine (d4T) bid							
Study 542[31]g	r, db (32)	5.1	260	NFV750/3TC/d4T [65]	↓2.4	↑155	≈80f
		5.0	279	NFV1250h/3TC/d4T [176]	↓2.2	↑181	≈80f
Other combinations							
Freimuth et al.[47]	r, nb (4)	5.1	354	NFV750/DLV400/ddI/d4T [10]	↓2.1		
				NFV750/DLV600/ddI/d4T [10]	↓1.8		
Gathe et al.[48,66]	r, nb (4)	≥4.2	≥200	NFV500,750,1000/d4T [33]i	↓>2	↑80 to 195	75d
				d4T	↓0.9		
Martel et al.[67]jk	nb (8 to 17)	5.2c	32c	NFV/NRTIs [10]	↓1.8c	↑149c	20d
Mellors et al.[56]b	r, nb (4)	4.8c	≥100	NFV750/ACV [12]	↓2.1f		
Pedneault et al.[51,63]j	nb (8)	4.8c	315c	NFV750/d4T/ddI [8]	↓2.1c	↑218c	38d
Sension et al.[52,68]bg	nb (24)	4.8	392	NFV1000h/3TC/ZDV [22]i	↓2.2	↑152	100f
				NFV1250h/2 NRTIsl			100f
Skowron et al.[45,69]jm	nb (9)	4.5	372	NFV750/d4T/NVP [19]	↓1.6c	↑94	84f
Study 524[33]k	nb (34)	4.6		NFV/2NRTIs [18]			55f

a Unless otherwise indicated.
b Patients were antiretroviral therapy-naive.
c Median.
d LOD <500 copies/ml (Chiron bDNA assay).
e Values derived from graphs.
f LOD <400 copies/ml (Roche Amplicor® PCR assay).
g Adolescents aged >13 years were enrolled in this study.
h Nelfinavir administered bid.
i Combined number of patients in both arms of the trial.
j Patients had not previously received protease inhibitors.
k Children aged 3 months to 13 years were enrolled in these studies and received NFV 30mg/kg[65] or 20 to 30 mg/kg[32] tid.
l Patients received either 3TC plus ZDV or 3TC plus d4T.
m Patients were NNRTI-naive.

ACV = abacavir given bid; **bid** = twice daily; **db** = double-blind; **ddI** = didanosine given bid; **DLV** = delavirdine given tid; **LOD** = limit of detection; **nb** = nonblind; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **NVP** = nevirapine given once daily; **pc** = placebo controlled; **r** = randomised; **tid** = 3 times daily; ↓ indicates decrease; ↑ indicates increase; ≈ indicates approximate; ***p** <0.001 *vs* 3TC/ZDV.

(>2 log_{10} copies/ml) with ≥80% of patients achieving viral loads below the LOD (<400 copies/ml).[31] Less frequent drug administration may enhance patient compliance; nevertheless, the long term durability of viral load reductions with twice-daily nelfinavir-based regimens requires confirmation before such regimens can be widely recommended.

Nelfinavir-based triple therapy provides durable reductions in plasma viraemia. The mean reduction in plasma HIV RNA levels remained unchanged at 2.3 log_{10} copies/ml between weeks 24 and 52 in antiretroviral therapy-naive patients receiving nelfinavir 750mg 3 times daily with zidovudine plus lamivudine, and the viral load was below the LOD (<400 copies/ml) in >75% of patients after 52 weeks.[49] Of 54 patients completing 84 weeks on this regimen in a nonblind extension of the study, >70% continued to have plasma HIV RNA levels below the LOD.[49]

Ultrasensitive plasma HIV RNA assays (LOD <50 copies/ml) have shown that nelfinavir 750mg 3 times daily or 1250mg twice daily combined with 2 RTIs produces profound and prolonged suppression of viral replication.[19,49,57,68-71] When samples from patients in study 511 were reanalysed using an ultrasensitive assay, >60% of patients receiving nelfinavir 750mg 3 times daily combined with zidovudine plus lamivudine had viral loads below the LOD (<50 copies/ml) after 6 and 12 months (fig. 3).[49] When nelfinavir (500 or 750mg 3 times daily) was added to the control regimen (zidovudine, lamivudine and placebo) after 6 months, the percentage of patients with an undetectable viral load (<50 copies/ml) increased from 5 to 23% by the end of 12 months. This result suggests that the addition of a protease inhibitor to pre-existing NRTI therapy may be less effective than initiating triple therapy in antiretroviral therapy-naive patients.

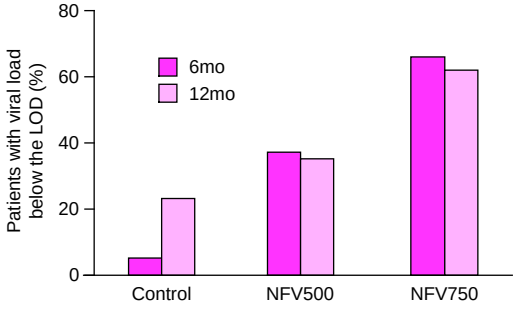


Fig. 3. Long term suppression of HIV in patients treated with a nelfinavir-based triple therapy regimen (study 511).[49] Percentage of antiretroviral therapy-naive patients with plasma HIV RNA levels below the limit of detection (LOD; <50 copies/ml) 6 and 12 months after starting therapy with nelfinavir 500mg (NFV500; n = 97) or 750mg (NFV750; n = 99) 3 times daily. All patients also received zidovudine (ZDV) 200mg 3 times daily and lamivudine (3TC) 150mg twice daily. At 6 months all patients in the control group (ZDV, 3TC plus placebo; n = 101) were started on NFV500 or NFV750.

Profound suppression of HIV RNA levels was correlated with the duration of response.[71] 89% of patients (n = 105) who achieved HIV RNA levels below the LOD (<50 copies/ml) during study 511 had viral loads below the LOD after 48 weeks of treatment. In contrast, only 5 of 39 patients (13%) who achieved HIV RNA levels below the LOD of the 'conventional' HIV RNA assay (<400 copies/ml), but not <50 copies/ml, continued to respond after 48 weeks.[71]

Nelfinavir is effective in paediatric patients aged ≤13 years. 55% of children receiving nelfinavir 20 to 30 mg/kg 3 times daily plus NRTIs had a viral load below the LOD (<400 copies/ml) after 34 weeks.[33] Furthermore, 73% of children who had started ≥1 new NRTI at the time nelfinavir was introduced had plasma HIV RNA levels below the LOD.

4.1.2 In Combination with Other Protease Inhibitors, With or Without RTIs

Combination regimens including 2 protease inhibitors (table IV) are currently generating much interest. Plasma concentrations of protease inhibitors can be increased by exploiting pharmacokinetic drug interactions between agents in this class (section 3.2). In several studies, nelfinavir combined with saquinavir SGC produced durable reductions in viral load. Patients receiving nelfinavir and saquinavir SGC experienced decreases in viral load ≥1.7 log_{10} copies/ml and ≥55% of patients had undetectable levels of HIV RNA (LOD <400 or 500 copies/ml) after ≥24 weeks.[18,55] In 1 study,

Table IV. Effect of nelfinavir (NFV) combined with other protease inhibitors, with or without reverse transcriptase inhibitors (RTIs), on surrogate markers in persons with HIV infection

Reference	Study design (duration of treatment [wk])	Baseline parameters (mean)		Treatment regimen (mg tid)[a] [no. of patients]	Results (mean change from baseline)		Patients below LOD for HIV RNA (%)
		plasma HIV RNA (log_{10} copies/ml)	CD4+ cell count (cells/μl)		HIV RNA (log_{10} copies/ml)	CD4+ cell counts (cells/μl)	
Combined with indinavir (IDV) bid							
Havlir et al.[46]b	nb (8)	≥4.5	≥100	NFV750[c]/IDV1000 [10]		↑156	70[d]
Combined with ritonavir (RTV) bid							
Gallant et al.[53]b	nb (16)	4.5[e]	325[e]	NFV750[c]/RTV400 [8]	↓2.7	↑	88[f]
				NFV500[c]/RTV400 [7]	↓2.1	↑	71[f]
Combined with saquinavir (SQV)							
SPICE[55]b	r, nb (24)	4.8	301	NFV750/2NRTIs [26]	↓1.8		53[f]
				SQV-SGC1200/2NRTI's [26]	↓1.7		63[f]
				NFV750/SQV-SGC800/2NRTIs [51]	↓1.7		86[f]
				NFV750/SQV-SGC800 [54]	↓1.8		55[f]
Study 534[54,72]g	r, nb (16)	4.9	343	NFV1250[c]/SQV-HGC1000[c]/d4T/3TC [20][h]	↓2.5[e]	↑225[e]	80[f]
		4.7	312	NFV750/SQV-HGC600/d4T/3TC	↓2.4[e]	↑256[e]	80[f]
Study 538[18]b	nb (44)	4.6	327	NFV750/SQV-SGC800 [10][i]	↓2.25	↑173	90[d]
Combined with amprenavir (APV) tid							
Eron et al.[73]b	r, nb (4)	4.9		NFV750/APV800 [4]	↓3.2[k]		
		4.3		APV800 [4][j]	↓1.7[k]		

a Unless otherwise indicated.
b Patients had not previously received protease inhibitors.
c Administered twice daily.
d LOD <500 copies/ml (Chiron bDNA assay).
e Median.
f LOD <400 copies/ml (Roche Amplicor® PCR assay).
g Only women were enrolled in this study.
h Combined number of patients in both arms of the trial.
i Patients were encouraged to take concomitant NRTI therapy.
j Patients received amprenavir alone for 3 weeks followed by the addition of zidovudine 300mg plus lamivudine 150mg bid.
k LOD <40 copies/ml.

3TC = lamivudine given bid; **bid** = twice daily; **d4T** = stavudine given bid; **HGC** = hard gel capsule; **LOD** = limit of detection; **nb** = nonblind; **NRTI** = nucleoside reverse transcriptase inhibitor; **r** = randomised; **SGC** = soft gel capsule; **SQV** = saquinavir; **tid** = 3 times daily; ↓ indicates decrease; ↑ indicates increase.

nelfinavir 1250mg plus saquinavir hard gel capsules (saquinavir HGC) 1000mg both twice daily and nelfinavir 750mg plus saquinavir HGC 600mg both 3 times daily provided similar results after 16 weeks in HIV-positive women.[54,72]

Studies of nelfinavir combined with ritonavir or indinavir (all drugs administered twice daily) without concomitant NRTIs are also ongoing. After 8 to 16 weeks ≥70% of patients achieved viral loads below the LOD (<400[53,74] or 500 copies/ml[46]).

Dual protease inhibitor regimens without RTIs are capable of producing profound suppression of viral replication, although inclusion of the latter appears to optimise results. In the SPICE trial 75% of patients receiving nelfinavir 750mg plus saquinavir SGC 800mg 3 times daily and 2 NRTIs had

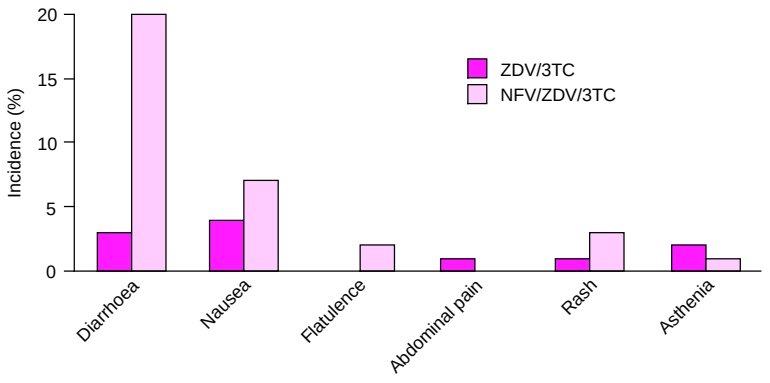


Fig. 4. Adverse events in patients receiving nelfinavir-based triple therapy.[34] Adverse events reported during the first 24 weeks of a randomised double-blind study of nelfinavir (NFV) 750mg 3 times daily, zidovudine (ZDV) 200mg 3 times daily and lamivudine (3TC) 150mg twice daily (NFV/ZDV/3TC; n = 100) or placebo, zidovudine and lamivudine (ZDV/3TC; n = 101) in previously untreated patients with HIV infection.

viral loads below the LOD (<20 copies/ml) after 24 weeks.[55] In contrast, only 27% of patients receiving nelfinavir 750mg plus saquinavir 800mg 3 times daily without NRTIs had similar results after 24 weeks.[55] Similarly, 8 of 21 patients (38%) receiving nelfinavir 750mg and indinavir 1000mg twice daily had undetectable HIV RNA levels (LOD <20 copies/ml) after 48 weeks.[46] Finally, 2 of 15 patients (13%) had undetectable HIV RNA levels (LOD <20 copies/ml) after 12 weeks of combined twice-daily nelfinavir 500 or 750mg and ritonavir 400mg.[53]

Three of 4 HIV-positive women with detectable levels of HIV RNA (≥400 copies/ml) in cervical lavage fluid before treatment with nelfinavir 1250mg, saquinavir HGC 1000mg plus 2 RTIs twice daily had undetectable levels after 3 months.[54]

4.2 Effect on CD4+ Cell Counts

Nelfinavir in combination with 2 RTIs produced mean (or median) increases in CD4+ cell counts of 80 to 218 cells/μl in patients after 4 to 52 weeks.[31,48,49,51,63,66-69] Dual protease inhibitor regimens that include nelfinavir have produced similar increases in CD4+ cell counts (85 to 173 cells/μl) after 4 to 44 weeks.[46,53,63,75]

5. Tolerability

Diarrhoea has been the most frequently reported adverse event associated with nelfinavir-based combination regimens in clinical trials (fig. 4). Indeed, diarrhoea was reported by up to 32% of patients receiving nelfinavir 750mg 3 times daily in combination with 1 or 2 NRTIs.[34] Nausea and flatulence (in <10% of patients) have also been associated with nelfinavir-based regimens (fig. 4).

Diarrhoea was also the most frequent adverse event (16%) reported by 1 532 HIV-infected adults receiving nelfinavir through an expanded access programme in the US, who were unable to take indinavir, ritonavir or saquinavir because of contraindications, therapeutic failure or toxicity.[76] In addition, rash, nausea, headache or asthenia were reported in ≤5% of patients in this series. Approximately 5% of patients enrolled in the programme discontinued nelfinavir because of adverse events.

The tolerability profile of nelfinavir in children appears to be qualitatively similar to that in adults. Mild transient diarrhoea was reported in 22% of paediatric patients in one series.[33] One patient (1.7%) withdrew from the study because of diarrhoea.

Diarrhoea is generally of mild to moderate severity and can often be controlled with antidiarrhoeal agents. Loperamide and psyllium husk have

been moderately effective in managing diarrhoea associated with nelfinavir.[77,78] Furthermore, a pancrelipase preparation (Ultrase® MT20) was effective, when given with meals and snacks, in controlling diarrhoea in 24 of 26 patients who did not respond to loperamide.[77]

Hyperglycaemia, hyperlipidaemia and abnormal fat distribution (e.g. cervical fat pads or 'buffalo hump') have been infrequently associated with all currently available nonpeptidic protease inhibitors including nelfinavir.[2,79-87] Whether 1 agent has an advantage over another in these regards and whether patients becoming hyperglycaemic on 1 agent will become hyperglycaemic on all agents in this class are unknown. However, serum glucose levels normalised in 5 of 8 patients, who had become hyperglycaemic (random blood glucose >10 mmol/L) on indinavir, after switching to nelfinavir.[88]

No abnormalities in hypothalamo-pituitary-adrenal axis function have been identified (e.g. 24-hour urinary cortisol excretion; response to dexamethasone suppression testing) in patients receiving protease inhibitors, which suggests that a mechanism other than hypercortisolaemia is responsible for these findings.[82,84-86] The authors of one case report speculate that a common mechanism – inhibition of proteases responsible for processing human proinsulin – may underlie protease inhibitor-induced hyperglycaemia.[79] Inhibition of low density lipoprotein receptor-like protein (a hepatic scavenger of plasma lipids that bears a 70% sequence homology with the catalytic site of HIV protease) by protease inhibitors has also been suggested to be the common mechanism underlying this phenomenon.[87]

Abnormal liver function test results have been documented in a small number of patients (≤3%) receiving nelfinavir-based combination regimens.[34] Acute hepatitis/cholangitis which recurred with rechallenge was documented in 1 patient receiving nelfinavir plus saquinavir in a clinical study.[39]

Haemarthrosis and skin haematomas have been reported in patients with haemophilia type A and B receiving protease inhibitors; therefore, close monitoring of such patients receiving nelfinavir is warranted.[34]

6. Dosage and Administration

Nelfinavir should be used in combination with other antiretroviral agents in patients with HIV infection. For optimal absorption, nelfinavir should be taken with food. In patients aged >13 years the recommended oral dosage is 750mg 3 times daily.[34] Children aged 2 to 13 years should receive oral nelfinavir 20 to 30 mg/kg (not to exceed 750mg) 3 times daily. In neonates a dosage of 10 mg/kg 3 times daily is under investigation.[12]

Nelfinavir powder contains 11.2mg of phenylalanine per gram and hence should be used with caution in patients with phenylketonuria.

Nelfinavir administration has not been associated with fetal abnormalities in animals.[34] However, there are no data available on human use during pregnancy. Nelfinavir is included in pregnancy category B in the US.[34]

Coadministration of nelfinavir and astemizole, amiodarone, cisapride, ergot derivatives, midazolam, quinidine, rifampicin, terfenadine or triazolam is contraindicated because of the potential for drug interactions (section 3.2) resulting in clinically significant adverse events.[34]

The pharmacokinetics of nelfinavir have not been studied in patients with severe renal or hepatic dysfunction. It is recommended that the drug be used with caution in those with hepatic dysfunction but dosage reductions are not warranted in patients with renal impairment, since less than 2% of a dose is excreted in urine.

The viral load, CD4+ cell count and plasma glucose levels should be monitored at regular intervals in all patients receiving nelfinavir-based regimens.

7. Place of Nelfinavir in the Management of HIV Infection

Intensive antiretroviral therapy with protease inhibitor-based regimens slows the progression of HIV disease and reduces morbidity and mortality in persons with HIV infection.[5,89,90] Profound suppression of HIV replication, as evidenced by

plasma viral load assays, is crucial to achieving control of HIV disease.

Plasma viral load assays provide insight into the dynamics of HIV infection that aid in the design of rational therapeutic regimens. It is clear that primary infection is not followed by a period of viral quiescence. Rather, primary infection results in prodigious HIV replication.[91,92] At steady state the average life-span of an infected T lymphocyte is 2.2 days, and 10 billion virions are produced each day.[92] Furthermore, HIV replication occurs with low fidelity and has the potential to give rise to multiple mutations at each locus daily.[91,92] Selection pressure in the form of drug therapy leads to the rapid development of drug-resistant mutants. Monotherapy may appear to be effective initially but does not produce a durable effect in this milieu. As the result of these insights, combination antiretroviral therapy is now mandated by various treatment guidelines.[9-11]

The goal of therapy for HIV infection is the prevention of disease progression and opportunistic infections and the prolongation of life. At present, the most likely way to achieve these goals is by reducing the viral load to the greatest extent possible for as long as possible.[89] The duration of viral suppression below the LOD has been shown to be directly proportional to the nadir in plasma HIV RNA concentration.[93] Furthermore, profound and prolonged suppression of viral replication may prevent the emergence of resistant viral strains.[94]

Protease inhibitor-dual NRTI combinations ('triple therapy') provide marked reductions in plasma HIV RNA concentrations that exceed those seen in patients receiving dual NRTI therapy. The efficacy of triple therapy is reflected in currently available guidelines for the treatment of HIV-infected persons. Triple therapy with a protease inhibitor and 2 NRTIs is recommended by US and Canadian authorities as initial therapy for HIV-infected adults[9,10] and by US authorities for HIV-infected children.[12] The British HIV association guidelines (currently under revision) also acknowledge that combination therapy with a protease inhibitor and 2 NRTIs is widely considered to be the current standard of antiretroviral care.[11]

Protease inhibitor-based therapies reduce morbidity and mortality in patients with advanced HIV infection. Mortality and the incidence of serious opportunistic infections declined by 75 and 73%, respectively, in a cohort of 1255 US patients with advanced HIV disease (CD4+ cell count <100/μl) who received antiretroviral therapy between 1994 and 1997.[4] The decrease in morbidity and mortality was directly proportional to the intensity of antiretroviral therapy, with patients receiving protease inhibitor-based regimens faring best. Furthermore, combination antiretroviral therapy that included protease inhibitors significantly increased survival in a cohort of patients with severe immunodeficiency (mean CD4+ cell count <15/μl) and cytomegalovirus retinitis.[5]

When to initiate therapy for HIV infection, what constitutes failure and when to switch therapy are contentious issues; the viral load, CD4+ cell count and clinical symptoms must be considered. The available guidelines recommend treating all symptomatic adult and paediatric patients; however, there is no common threshold for treatment initiation in asymptomatic patients.[9-12] US and Canadian guidelines recommend therapy for all asymptomatic adults with a viral load of 5000 to 10 000 copies/ml or CD4+ cell counts below a prescribed threshold (300 cells/μl in Canada; 500 cells/μl in the US).[9,10] In contrast, the British guidelines recommend treating adults with viral loads below 10 000 copies/ml only if the CD4+ cell count is falling.[11] In spite of these empiric recommendations, the guidelines acknowledge that there are no data that preclude initiating treatment at any stage of HIV infection and allow that combination therapy should be offered to all informed and motivated patients who are likely to be compliant with a complex regimen.

Combination antiretroviral therapy is recommended by US authorities for all infants <12 months of age.[12] In theory, early aggressive antiretroviral therapy in neonates and infants may pre-

serve immune function and prevent viral dissemination.[12]

Patients should be monitored for intolerance, noncompliance and therapeutic efficacy after initiating treatment. The viral load should be measured 4 to 8 weeks after initiating or changing therapy and, thereafter, every 3 to 4 months in conjunction with CD4+ cell counts.[9] A 1 $\log_{10}$ decrease in plasma HIV RNA concentration within 8 weeks of initiating therapy is indicative of success, although maximum reductions may take up to 24 weeks.[9-12] Therapeutic failure is evidenced by rising plasma HIV RNA levels, falling CD4+ cell counts and/or clinical disease progression.[10,12] Switching therapy may be considered when plasma HIV RNA levels rise and is strongly recommended should the viral load reach 5000 to 10 000 copies/ml.[9,10] The addition of a single drug to a failing regimen is discouraged, as this amounts to little more than sequential monotherapy with the attendant risks of rapidly acquired drug resistance. Hence, at least 2 new drugs should be used to replace a failing regimen.

Resistance and cross-resistance are crucial issues in the selection of antiretroviral regimens both initially and in response to treatment failure.[15] Indeed, resistance to all currently available antiretroviral drugs has been observed[95] as has cross-resistance between all currently available protease inhibitors.[1,2,21-23] Cross-resistant phenotypes can emerge in the absence of these key mutations and without prior exposure to a given drug. In the event that drug resistance does arise, there are data to suggest that patients with less extensive antiretroviral treatment histories and those with lower viral loads fare better when switched to a new regimen.[20] Hence, salvage therapy should be instituted in a timely manner.

Although available guidelines acknowledge the important role of protease inhibitors in therapy, they do not recommend specific agents. In the absence of specific recommendations, the selection of a particular agent should be guided by tolerability, the propensity for clinically relevant drug interactions and convenience of administration.

Diarrhoea has been the most frequently reported adverse event with nelfinavir. It is generally of mild or moderate severity, is not associated with weight loss and may be controlled with over-the-counter antidiarrhoeal agents.[95-98] Although clinical experience is limited, in comparison with other protease inhibitors nelfinavir has not been associated with nephrolithiasis, as has indinavir, or elevations in hepatic enzymes, circumoral paraesthesia and altered taste sensation, as has ritonavir.[96,98] Furthermore, ritonavir is associated with a broader spectrum of clinically significant drug interactions than are the other available protease inhibitors.[96,97]

Hyperglycaemia, hyperlipidaemia and abnormal fat distribution are adverse events common to all protease inhibitors.[2,81] Although hyperglycaemia may be severe, it may be controlled by insulin or oral hypoglycaemic agents. Blood glucose levels should be routinely monitored in all patients receiving protease inhibitors and patients should be educated as to the signs and symptoms of hyperglycaemia. Although the long term sequelae of protease inhibitor-induced hyperglycaemia are unknown, it seems logical that they are preferable to the sequelae of suboptimal control of HIV replication. Hence, control of blood sugar with, for example, insulin administration is preferred to discontinuation of the protease inhibitor.

All available protease inhibitors must be taken in multiple daily doses. Ritonavir is administered twice daily, but because it induces its own metabolism a dose escalation schedule is recommended to maintain plasma levels and minimise the frequency of adverse events.[2] Absorption of nelfinavir, saquinavir and ritonavir increases when they are taken with food. In contrast, food decreases absorption of indinavir; hence, it must be taken in the fasting state. Furthermore, to minimise the incidence of nephrolithiasis with indinavir, increased fluid intake is required. Administration of nelfinavir twice daily in combination with RTIs or other protease inhibitors appears to be as effective as 3 times daily administration and may enhance compliance.

In conclusion, nelfinavir, when used in combination with RTIs and/or other protease inhibitors, effectively reduces the viral load below the LOD in adults and children with HIV infection. The drug lacks some of the rare adverse events associated with indinavir and ritonavir[2] and appears to be effective when administered twice daily with RTIs and other protease inhibitors. These qualities make nelfinavir an effective component both in regimens used for initial therapy in antiretroviral therapy-naive patients and also in regimens for patients unable to tolerate other protease inhibitors.

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Correspondence: *Blair Jarvis*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand.
E-mail: demail@adis.co.nz